Orofacial Pain

A Guide to Medications and Management

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Preface

This book begins by describing the 30 most common conditions that a dentist or physician may encounter when patients present with orofacial pain and dysfunction (not due to a dental infection). Chapter 1 provides a short description of the clinical characteristics of these 30 conditions. The majority of these conditions are also described in greater detail along with recommendations about the best evidence-based treatment approach in Chapters 12 through 20. Chapter 2 introduces the 60 most common medications that are used by clinicians who treat orofacial pain. These medications and how they are used are then described in detail in Chapters 3 through 11.

In all instances we have attempted, where possible, to collect and present the scientific evidence that supports or refutes the use of a specific medication for a specific condition. Obviously this book has a clear focus on medications because so many of the pain disorders that occur in the orofacial region are treated with medications. However, this focus should not diminish the fact that there are several other options that should be used in combination with medications, including behavioral (psychosocial) and various physical medicine methods. These interventions can help a patient gain a sense of control over his or her pain and should be introduced early in the course of pain management.

The creation of a body of work such as this takes a good deal of time and effort. First we want to thank our spouses for the support and tolerance they have given us during this effort. Next we thank all of the chapter authors, all of whom are good friends and colleagues who trusted us to produce a book that they would be proud to have contributed to. Finally, at the end of Chapters 3–20 we provide a few key recommendations based on the content covered in these chapters. We have put all of the tables, figures, and end-of-chapter recommendations in a website maintained by Wiley (our publisher) for anyone who has enough curiosity to go to the website (www.wiley.com/go/clarkdionne). As an added benefit we have included a set of 187 questions and answers that should be valuable to the readers. We hope this website is considered a valuable addition to the book.

Glenn T. Clark
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Orofacial Pain

A Guide to Medications and Management

Chapter 1

The 30 most prevalent chronic painful diseases, disorders, and dysfunctions that occur in the orofacial region

Glenn T. Clark, DDS, MS

1.1 Introduction and definitions

Although there are many more than 30 orofacial pain conditions, this chapter focuses on the ones most commonly seen in clinical practice. The distinction between a disease, a disorder, and a dysfunction is somewhat arbitrary: The terms "disorder" and "dysfunction" are used more or less interchangeably to mean an ailment or impaired functioning of a bodily system The term "disease" implies a pathological condition of a part, organ, or system of an organism, resulting from various causes, such as infection, genetic defect, or environmental stress, and characterized by an identifiable group of signs or symptoms.[1] Regardless of how they are classified, these 30 conditions can be logically clustered into 7 subgroups. A clinician who can learn about these subgroups and distinguish between these 30 conditions will be a long way toward having the expertise required to properly manage patients with chronic orofacial pain. Toward this goal, the chapter begins with several tables that summarize information about the characteristics, appropriate diagnostic tests, age predilection, and known prevalence of these 30 conditions. These tables are accompanied by discussion of the process necessary to render a differential diagnosis for a patient with chronic orofacial pain complaints. Table 1.1 briefly describes the clinical characteristics of the 30 conditions considered in this chapter. Treatment of these 30 conditions is discussed, along with associated conditions, in various other chapters in this book and therefore is not covered here.

1.1.A Nociceptive versus neuropathic pain

When pain persists beyond the time expected for healing to occur, two explanations exist. First, long-standing chronic pain sensations may still be occurring via local disease inducing pain mediators (e.g., inflammatory cytokines). Second, long-standing pain might be due to a "neuropathic conversion" due to sensitization of the peripheral and central nerves. The following five-step pathophysiologic process can be used to explain how this conversion occurs: (1) local cellular and humoral inflammation develops where tissue damage or ischemic injury occurs; (2) this inflammation means there is an accumulation of pain-inducing endogenous chemicals within the pain site; (3) altered peripheral neurogenic tissues develop because of these chemicals; (4) these altered nerves have lowered thresholds and even spontaneous activation; and (5) central sensitization and plasticity of the pain pathways from trigeminal nucleus or spinal cord to the cortex develop. Additional discussion of specific neuronal changes that occur in the nervous system with neuropathic pain is provided in Chapter 6, which focuses on neurogenic pain and anticonvulsant medications. This dichotomous etiology indicates that, in addition to making a diagnosis, you must also understand whether the pain is a typical nociceptive pain or an atypical neuropathic pain, because they have different prognoses and are treated quite differently.

1.1.B Differential diagnosis and etiology of chronic orofacial pain

When a patient attends a physician's or dentist's office with a complaint of orofacial pain, they hope fervently that they will be given a diagnosis and an effective plan of treatment. Most physicians and dentists will perform an examination, take a careful medical history, and order appropriate tests. Based on this information, a diagnosis is usually rendered. For example, if a patient has pain on function, has limited mouth opening, and notices a crunching sound coming from one of the jaw joints, a diagnosis of localized osteoarthritis

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Table 1.1 The 30 most common orofacial-pain-related diseases and their distinguishing clinical features

Disease	Distinguishing clinical features
1 Myalgia	Subjective pain in the muscle on function Pain that can be replicated by muscle palpation No discernable taut band or trigger point with referring pain *Note:* It is necessary to distinguish primary from secondary myalgia. Secondary myalgia sources include direct trauma to the muscle (injections) and regional painful pathology such as arthritic joint disease or disk derangement.
2 Myofascial pain	Subjective pain in the muscle on function Pain that can be replicated by muscle palpation Discernable taut band in the affected muscles Trigger point in this band that causes pain to radiate on sustained compression *Note:* Myalgia is labeled *myofascial pain* only when taut bands and trigger points are present.
3 Fibromyalgia	Subjective pain in multiple sites aggravated by function Widespread pain involving more than three body quadrants Continuous symptoms (>3 months in duration) Strong pain on muscle palpation in at least 11 of 18 established body sites *Note:* Myalgia is labeled *fibromyalgia* only when these criteria are met.
4 TMJ DDWR	Single noise—click or pop—from the TMJ on a single movement Noise may be reciprocal (on both open and close) No restriction or deflection of jaw motion after click
5 TMJ DDNR	Sudden onset, continuous loss of full jaw motion Pain in the affected joint on wide open attempt Prior history of clicking in the affected joint that has now stopped *DxTest:* MRI shows DDNR in both closed and open positions
6 Local TMJ arthritis	Subjective pain in preauricular area aggravated by function Pain that can be replicated by TMJ capsule palpation Joint motion often produces crepitation sounds *DxTest:* erosive or remodeling-type joint-surface changes on CT imaging
7 Polyjoint OA affecting the TMJ	Subjective pain in preauricular area aggravated by function Pain that can be replicated by TMJ capsule palpation Joint motion often produces crepitation sounds Multiple joints affected with pain beyond TMJ *DxTest:* erosive or remodeling-type joint-surface changes on CT imaging *DxTest:* negative serology for autoimmune markers of rheumatoid disease
8 Rheumatic arthritis affecting the TMJ	Subjective pain in preauricular area aggravated by function Pain that can be replicated by TMJ capsule palpation Joint motion often produces crepitation sounds Multiple joints affected with pain beyond TMJ *DxTest:* erosive or remodeling-type joint-surface changes on CT imaging *DxTest:* positive serology for autoimmune markers of rheumatoid disease
9 Temporal arteritis	New headache pain of a constant nature Tender, thickened, and pulseless scalp vessels *DxTest:* positive serology for autoimmune markers of an inflammatory disease *DxTest:* confirmed by blood vessel biopsy showing giant-cell infiltrate *Note:* Markers are elevated ESR and a C-reactive protein.
10 Trigeminal sensory neuropathy	Unilateral or bilateral sensory loss of one or more trigeminal nerve divisions Usually, also presence of pain in these same areas *DxTest:* negative MRI for pathology involving the CNS or trigeminal nerve *DxTest:* confirming diagnosis of associated CTD *Note:* Most commonly associated with an autoimmune CTD such as mixed or undifferentiated CTD, scleroderma, Sjögren's syndrome, or lupus erythematosis. If so, there may also be complaints of Raynaud's phenomenon, polyjoint arthritis, and sometimes muscle weakness.
11 Migraine	Unilateral headache location Pulsatile severe headache that lasts multiple hours Nausea associated with the headache pain Photophobia and phonophobia associated with headache pain *DxTest:* negative MRI for pathology involving the CNS *Note:* Pain episodes may be preceded by aura such as "flashing lights or dizziness."

Table 1.1 (*Continued*)

Disease	Distinguishing clinical features
12 Cluster headaches	Rapid-onset intense paroxysmal headache pains One-sided retro-orbital, supraorbital, and temporal headache pains Pain episodes lasting from 15 to 180 minutes Headaches occur several times in a 24-hour period Pain that may occur at night, waking the patient from a sound sleep *DxTest:* negative MRI for pathology involving the CNS *Note:* Headache must be associated with ipsilateral autonomic signs, including conjunctival injection, ptosis, miosis, eyelid edema, facial flushing or blanching, forehead sweating, lacrimation, nasal congestion, and rhinorrhea.
13 Tension-type headaches	Dull aching bilateral, episodic pain of long-lasting duration (hours to days) Pain located in the suboccipital, temporal, and frontal regions Pain typically increasing slowly during the day to a later afternoon peak
14 Chronic daily headaches	Continuous or very frequent headache (4 or more days per week) Maybe with clinical features of both migraine and tension-type headache *DxTest:* negative MRI for pathology involving the CNS
15 Acute trigeminal neuritis	Injury- or infection-associated acute onset numbness or tingling Burning sensation in the affected nerve *DxTest:* CTs and MRI needed to check for pathology involving the involved nerve
16 Trigeminal neuroma	Movement- or touch-induced sharp often electric-like pain Pain occurring in an area of anesthesia that was induced after an injury or surgery that inadvertently transected a nerve
17 Trigeminal neuralgia	Sudden, usually unilateral, severe pain Brief (seconds), stabbing or electric-like pain Usually recurrent (multiple times a day) pain Pain occurring in one or at most two trigeminal nerve branches *DxTest:* MRI of trigeminal nerve and brain *Note:* In most (90%) cases MRI will not show pathology involving the trigeminal nerve; other cases will show CNS tumor or other pathology.
18 Chronic trigeminal neuropathy	Constant dental and gingival pain in a very focal oral region Usually, pain of unknown origin *DxTest:* negative radiographic finding indicative of pulpal pathology *DxTest:* negative endodontic thermal testing indicative of pulpal pathology
19 Postherpetic neuralgia	Burning, deep aching, tingling, itching, or stabbing pain of the skin Usually located on the V1 or V2 division Pain that is always located in area of prior viral infection where ulcerative lesion was located *Note:* Pain and preceding ulcerative lesion can be intraoral if it involves the V3 division.
20 Burning mouth (not related to hyposalivation)	Constant burning sensation of the anterior tissues of the mouth Pain often increasing throughout the day No clinically discernable oral pathology on examination
21 Pemphigus vulgaris	Blistering diseases of the skin and mucous membranes of the mouth *DxTest:* Biopsy will confirm the diagnosis of pemphigus.
22 Benign mucous membrane pemphigoid	Blistering diseases of the skin and mucous membranes of the mouth *DxTest:* Biopsy will confirm the diagnosis of BMMP.
23 Erosive lichen planus	Filamentous, white, lacy lines on the cheek or other oral tissues Erythema and ulceration of the mucosal tissues *DxTest:* Biopsy will confirm the diagnosis of LP. *Note:* LP becomes painful when it turns erythematous and erosive.
24 Mucositis	Painful inflammation and ulceration of the mucous membranes *Note:* This disorder almost always occurs as a result of chemotherapy and radiotherapy for cancer, although a severe allergic reaction to a medication or infection is possible.
25 Ulcerative disease of the mucosa	Ulcerative or severe inflammation of the mucous membrane *DxTest:* Biopsy will confirm the diagnosis of a nonspecific ulcerative disease. *Note:* Positive findings for the causative systemic or allergic disease
26 Cancer pain in the jaw	Trigeminal sensory disorder with variable presentation Neural deficit may be numbness or pain (continuous or episodic) *DxTest:* Positive MRI for cancer affecting trigeminal nerve

(*Continued*)

Table 1.1 (*Continued*)

Disease	Distinguishing clinical features
27 Orofacial dyskinesia	Repetitive abnormal movement disorder involving the jaw, lip, and tongue *DxTest:* Negative MRI for any CNS pathology
28 Orofacial dystonia	Involuntary briefly sustained contraction of involved muscle *DxTest:* Negative MRI for any CNS pathology
29 Bruxism	Sleep-state-related motor hyperactivity causing repeated brief motor activation of the jaw closers, usually with resulting side-to-side motion of the jaw and tooth attrition *DxTest:* Wear patterns on full arch acrylic splint can prove whether bruxism is active.
30 Habitual parafunction and secondary masticatory hyperactivity	Conscious tooth clenching, habitual cheek chewing, or habitual lip biting Consider medication-induced hyperactivity if taking SSRI or stimulant Elevated masticatory and cervical muscle stiffness evident on palpation *DxTest:* Stop suspected medications if patient is on stimulants or SSRIs.

AIDS, acquired immunodeficiency syndrome; BMMP, benign mucous membrane pemphigoid; CDH, chronic daily headache; CNS, central nervous system; CT, computed tomography; CTD, connective tissue disease; ddC, dideoxycytidine; ddI, dideoxyinosine; DDNR, disk displacement with no reduction; DDWR, disk displacement with reduction; DxTest, diagnostic test; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; LP, lichen planus; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; SSRIs, selective serotonin reuptake inhibitors; TMJ, temporomandibular joint.

is certainly probable. If the disease has progressed far enough, a radiograph of the temporomandibular joint (TMJ) will confirm and document the magnitude of the osseous changes. Unfortunately, simply reformulating the patient's complaint (painful, noisy joint) into medical nomenclature (osteoarthritis) is not sufficient. An expert clinician must strive to both find an etiology for the disease and understand the pathophysiologic basis for the pain itself, before this diagnosis is complete (Table 1.2). The discovery of the etiology is by far the most difficult part of the diagnostic process; later in this chapter and in several other chapters, we discuss what is currently known about the causation of most of the common orofacial pain disorders.

1.1.C Anatomic localization and age predilection

Another essential component of the differential diagnostic process is to fully understand and document the anatomic localization and extent of the pain site. In most cases this begins by having the patient outline the pain's outer borders and then pinpoint the pain's focal source (if one exists). The clinician must also palpate this source to verify it and see if, with simple pressure, the pain can be replicated. Based on the physical signs and symptoms as well as the anatomic location, pattern, and character of the pain, a list of diseases that cause pain in the orofacial region can usually be narrowed down to two or three likely pain disorders. This process is facilitated if, when creating the differential diagnosis list, the clinician has in mind the "age-based" predilections of the painful diseases that occur in the orofacial region. For example, trigeminal neuralgia is far more likely in someone over the age of 50 than under the age of 50.

1.1.D Diagnostic testing

Appropriate tests or diagnostic–treatment procedures may help narrow the list to the most likely diagnosis; however, due to the subjective nature of pain, there is no test that can measure the intensity of pain, nor any current clinically useful imaging device that can show pain. In most cases, clinicians must use the patient's own description of the type, duration, and location of the pain to get diagnostic clues. Certain pain-inducing pathologies are visible on a radiograph or a magnetic resonance image (MRI); however, because many are not, we must occasionally use innovative methods to confirm our diagnosis. These innovative methods are discussed in Chapter 10, but here we provide in table form the most frequently used diagnostic methods appropriate for the 30 diseases considered in this chapter (Table 1.3). More details on the pros and cons of these tests are provided in the various chapters where each disease entity is discussed.

1.1.E Prevalence of orofacial pain

Comparing the age predilection, the anatomic localization, and the character of the patient's problem with the known prevalence of orofacial pain disorders usually allows the clinician to make a reasonable diagnosis. The reported overall prevalence of general persistent pain in the adult population of the United States is quite high. For example, a Gallup survey of 2002 adults found that approximately 4 of 10 adults (42%) of those polled say they experience pain on a daily basis, while 89% admit to experiencing pain on a monthly basis.[2] These pains have diverse origins: chronic pain disorders such as arthritis, osteoporosis, diabetic neuropathy, migraine, and fibromyalgia; pain related to cancer;

Table 1.2 Probable etiologies associated with the 30 most common orofacial pain diseases

Disease	Etiology
1 Primary and secondary myalgia (all types)	Medications (stimulants or SSRIs) causing motor hyperactivity Stress (job or personal) causing muscular hypoperfusion and/or hyperactivity Waking and sleeping parafunctions (repetitive oral habits and behaviors) History of traumatic muscle injury (intramuscular local anesthetic injection) Local nonmuscle pathology (arthritis or derangement)
2 Myofascial pain (all types)	Common etiologies same as for myalgia Taut bands and trigger points, suggesting localized neuronal sensitization in muscle
3 Chronic widespread pain and fibromyalgia	Common etiologies same as for myalgia Multiple pain sites, allodynia, and mechanical hyperalgesia, suggesting central sensitization Unknown genetic susceptibility that predisposes to fibromyalgia
4 TMJ DDWR	Traumatically altered discal ligaments that attach it to the condyle Parafunction Joint hypermobility Acute macrotrauma to jaw
5 TMJ DDNR	Common etiologies that cause DDNR same as for DDWR
6 Localized TMJ arthritis	Trauma (either macrotrauma or repetitive microtrauma) A prior DDNR in the involved joint
7 Polyjoint osteoarthritis and TMJ	Idiopathic (but most likely genetic) Secondary polyjoint arthritis (e.g., psoriasis)
8 Rheumatic arthritis and TMJ	Autoimmune induced
9 Temporal arteritis	Giant-cell inflammation due to autoimmunity
10 Idiopathic trigeminal sensory neuropathy	Autoimmunity (seen with various CTDs such as Sjögren's syndrome, undifferentiated and mixed CTD, and scleroderma)
11 Migraine	Genetics
12 CH and autonomic cephalalgias	Genetics
13 Tension-type headaches	Stress
14 Chronic daily headaches	Neuronal sensitization due to frequent episodic headaches Genetic factors likely Stress factors likely Analgesic medication overuse may play a causative role in CDH.
15 Facial pain related to trigeminal neuritis	Viral-induced neural inflammation (e.g., HIV, *Cytomegalovirus*, *Poliovirus*, and hepatitis B or C infections) Trauma-induced neural inflammation Bacterial-induced neural inflammation (e.g., leprosy, diphtheria, Lyme disease, and trypanosomiasis) Diabetes may be involved if widespread Rare immune reactions (e.g., Guillain–Barré syndrome; chronic inflammatory demyelinating polyneuropathy; neuropathies associated with vasculitis) Metabolically induced and nutritional-imbalance-induced neuropathy (e.g., deficiency of vitamins B_{12}, B_1 [thiamine], B_6 [pyridoxine], and E) Renal-failure-induced polyneuropathy Toxin-induced polyneuropathy (e.g., alcohol and other toxins) Medication-induced neuritis (e.g., vincristine and cisplatinum; ddC and ddI in AIDS; and dapsone, used to treat leprosy)
16 Facial pain related to trigeminal neuroma	Surgical or trauma-induced nerve trunk transection
17 Facial pain related to trigeminal neuralgia	Vascular compression Multiple sclerosis Acoustic neuroma (tumor) induced compression CNS neoplasia
18 Facial pain related to a chronic trigeminal neuropathy	Inflammation or trauma to alveolar nerve (e.g., traumatic injury, periodontal surgery, pulp extirpation, endodontic therapy, apicoectomy, tooth extraction, implant insertion) Maybe genetic factors

(*Continued*)

Table 1.2 (*Continued*)

Disease	Etiology
19 Facial pain related to postherpetic neuralgia	Herpes zoster infection
20 Burning mouth symptoms (not related to hyposalivation)	Inflammation- or age-related trigeminal small fiber dysfunction or atrophy in tongue and lip region
21 Pemphigus vulgaris	Autoimmunity against keratinocyte cell surfaces
22 Benign mucous membrane pemphigoid	Autoimmunity
23 Lichen planus	Autoimmunity Lichenoid reactions, allergic responses to an allergen Medication induced (e.g., antihypertensive drugs, NSAIDs, tetracycline, and several sulfonamides)
24 Mucositis	Chemotherapy Radiation therapy Allergic reaction to medication
25 Other chronic (nonmalignant) ulcerative conditions of the mouth	Autoimmunity Trauma Systemic disease with oral manifestations (e.g., Behçet's disease, celiac disease, GVHD, Crohn's disease, ulcerative colitis, lupus erythematosus, and neutropenia)
26 Cancer pain in the jaw	Neoplasia invasion of trigeminal nerve or base of brain at foramen ovale Jaw bone cancer due to primary or malignant–metastatic neoplasia
27 Dyskinesia	Idiopathic dysfunction of basal ganglia Medication induced (e.g., neuroleptic medications)
28 Dystonia	Idiopathic dysfunction of basal ganglia
29 Bruxism	Disinhibition disorder involving the jaw motor system during sleep
30 Habitual parafunction and spontaneous and secondary hypertonicity	Idiopathic extrapyramidal system hyperactivity Medication-induced motor hyperactivity (e.g., SSRIs or psychostimulants) Stress

AIDS, acquired immunodeficiency syndrome; CDH, chronic daily headache; CH, cluster headache; CNS, central nervous system; CTD, connective tissue disease; ddC, dideoxycytidine; ddI, dideoxyinosine; DDNR, disk displacement with no reduction; DDWR, disk displacement with reduction; GVHD, graft-versus-host disease; HIV, human immunodeficiency virus; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors; TMJ, temporomandibular joint.

Table 1.3 Confirmatory or exclusionary diagnostic methods

Disease	Diagnostic testing
1 Localized myalgia	History, palpation findings
2 Myofascial pain	History, palpation findings
3 Fibromyalgia	History, palpation findings
4 TMJ DDWR	Auscultation, jaw ROM assessment
5 TMJ DDNR	Palpation, jaw ROM assessment, MRI
6 Local TMJ arthritis	Palpation, cone beam CT of TMJ
7 Polyjoint OA (affecting the TMJ)	Palpation, cone beam CT of TMJ, clinical review of all joints
8 Rheumatic arthritis (affecting the TMJ)	Cone beam CT, serologic testing (RF, ESR, ANA), clinical review of all joints
9 Temporal arteritis	Serologic testing (ESR, CRP), scalp vessel palpation, blood vessel biopsy
10 Trigeminal sensory neuropathy	MRI imaging (to rule out CNS pathology), serologic testing for CTDs (ANA, CRP)
11 Migraine	History, MRI (to rule out CNS pathology)
12 Cluster headaches	History, MRI (to rule out CNS pathology)

Table 1.3 (*Continued*)

Disease	Diagnostic testing
13 Tension-type headaches	History
14 Chronic daily headaches	History, MRI (to rule out CNS pathology)
15 Acute trigeminal neuritis	History, neurologic exam, MRI (to rule out CNS pathology)
16 Trigeminal neuroma	MRI (to rule out CNS pathology), neurologic exam, anesthetic testing
17 Trigeminal neuralgia	History, MRI (to rule out CNS pathology), neurologic exam
18 Chronic trigeminal neuropathy	History, dental radiographs, MRI, anesthetic testing
19 Postherpetic neuralgia	History, anesthetic testing
20 Burning mouth (not due to hyposalivation)	History, MRI (to rule out CNS pathology)
21 Pemphigus vulgaris	Clinical exam, biopsy
22 Benign mucous membrane pemphigoid	Clinical exam, biopsy
23 Lichen planus	Clinical exam, biopsy
24 Mucositis	History, clinical exam
25 Other ulcerative disease of the mucosa	History, clinical exam, serologic testing
26 Cancer pain in the jaw	MRI and CT
27 Orofacial dyskinesia	Brain MRI (to rule out CNS pathology)
28 Orofacial dystonia	Brain MRI (to rule out CNS pathology)
29 Bruxism	History and examination, occlusal appliance wear pattern
30 Oral parafunction and spontaneous and secondary hypertonicity	History, palpation

ANA, antinuclear antibody; CT, computed tomography; CNS, central nervous system; CRP, C-reactive protein; CTD, connective tissue disease; DDNR, disk displacement with no reduction; DDWR, disk displacement with reduction; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; RF, rheumatic factor; ROM, range of motion; SSRIs, selective serotonin reuptake inhibitors; TMJ, temporomandibular joint.

postsurgical pain; and pain caused by accidents and burns. Whether it is cancer pain or noncancer pain, opioid treatment of pain is common. For example, 73% of hospitalized patients receiving opioid therapy still reported moderate distress and 75% of postsurgical patients were in either moderate or marked distress.[3,4] When you look more closely at elderly patients (defined as over the age of 65), the prevalence of general persistent pain is much higher than in those under the age of 65. The prevalence of persistent pain in the elderly ranges from 25% to 88%, depending on the definition used and the subset of elderly patients being studied.[5,6] For example, another study conducted telephone interviews of community-dwelling north Floridians ($n = 1636$) who were over 65 years of age and found that 17.4% reported some form of current or recent (with the last year) orofacial pain.[7]

1.2 Facial pain related to muscle pain

Muscle pain comes in many forms, from the widespread types such as fibromyalgia to the local and regional forms of myalgia. Myofascial pain and the more generalized fibromyalgia syndrome (FMS) are common chronic pain problems that predominantly affect middle-aged women.[8–11] While local myalgia and myofascial pain are more prevalent in the middle aged, fibromyalgia increases with age and is substantially more evident in the elderly population. Each of the myalgia subtypes is discussed in the following subsections. A detailed discussion of these disorders and their appropriate management is presented in Chapter 16.

1.2.A Disease 1a: primary myalgia

Myalgia can be separated into local and regional, with a distinction between primary and secondary myalgia also made. The term "primary myalgia" indicates that if a biopsy were performed, there would be no microscopic evidence of inflammation. Histologically evident myositis is discussed in Section 1.2.B on secondary myaglia.[12,13] The pain-inducing changes seen in primary myalgia are most likely due to sensitization of muscle nociceptors.

Clinical criteria

When a direct muscle injury that explains the muscle pain cannot be found and the patient does not have another adjacent pathology in the area that would cause secondary muscle guarding effects (e.g., arthritis of the TMJ or internal derangement of the TMJ), then one of the criteria for a primary myalgia is satisfied. The actual diagnosis of myalgia (all types) requires the following additional criteria to be satisfied: (1) the patient is aware of pain in the muscle on function; (2) this pain must be replicated by palpation; and (3) there is no discernable taut band or trigger point in the muscle that causes pain to radiate on palpation.

Etiology

If a primary myalgia is suspected, the clinician must seek to find the etiology by asking about (1) medications, (2) stress, and (3) parafunctions (both waking and sleeping). If a patient is using psychological stimulant medication or is using a serotonin selective reuptake inhibitor (SSRI), then a medication-induced myalgia would be suspected. The various medications that can induce muscle pain are reviewed in Chapter 19 and are not discussed here. Second, a stress-associated myalgia should be suspected if a patient reports a prolonged increase in environmental (job or personal) stress levels. A discussion of how stress can induce muscle pain without the presence of histologically evident inflammation is given in Chapter 16. With regard to stress, psychological factors have been associated with chronic facial and jaw pain.[14] Third, a parafunction-induced myalgia should be suspected when a patient admits to repetitive oral habits or if such habits are observed. In this case the clinician will typically diagnose a primary myalgia due to parafunction. Sometimes the parafunction is very specific and the pain it produces in the jaw muscles is limited to one or two muscles. Oral parafunctions may be present both during waking and sleeping hours and during specific activities such as chronic gum chewing.[15]

Several studies have reported that there is a moderately strong positive association between self-reported clenching and chronic masticatory myofascial pain (MMFP).[16–18] Unfortunately, these studies do not specify whether the clenching is occurring during waking or sleeping periods because to do so accurately would require an actual recording of the jaw motor behaviors over moderately long periods of time (minimum 2 weeks). One study used a case–control design including 83 patients with MMFP, selected from the patients at a hospital dental service, and 100 concurrent controls. Using unconditional logistic regression analysis they found that self-reported clenching–grinding either in association with an elevated anxiety score (OR = 8.48) or an elevated depression score (OR = 8.13) was statistically associated with chronic MMFP. They concluded that tooth clenching, trauma, and female gender strongly contribute to the presence of chronic MMFP even when other psychological symptoms are similar between subjects. Interestingly, grinding-only behaviors, age, and household income and education were not related to chronic MMFP. This report showed no association between tooth grinding and chronic muscle pain, which is in conflict with other studies. For example, one study performed a questionnaire-based epidemiologic cross-sectional study and another used a clinically based case–control design.[19,20] These two studies found a positive relationship between self-reported nocturnal tooth grinding and self-reported jaw pain. This conflict will require additional data to resolve.

1.2.B Disease 1b: secondary myalgia due to active local pathology (e.g., temporomandibular joint disease)

Direct muscle injury is not common in the masticatory system, but when present it can produce a quite dramatic change in normal function causing strong focal pain and severely limited opening; this limitation is due to co-contraction of the openers and closers and is called trismus.[21]

Clinical criteria

The term "secondary myalgia" implies the presence of some extrinsic direct trauma or local (nonmuscle) pathology that is inducing myalgia.

Etiology

The two most common causes of a secondary myalgia are (1) a traumatic muscle injury and (2) a local nonmuscle pathology that induces a change in muscle function. The most common traumatic cause of a focal myositis in the jaw system is an inadvertent intramuscular injection of local anesthetic during dental treatment. In these cases, the nature of the injury is influenced by the amount of injected material, the type of anesthetic used, and more important, whether a vasoconstrictor such as epinephrine was included in the anesthetic solution. Several authors have described and documented the effect of an inadvertent anesthetic injection into muscle tissue.[22–25] In some cases, acute traumatic trismus can convert to chronic contracture of the involved muscle.[26] Other forms of local muscle injury can occur from trauma (e.g., neck musculature can be injured during a low-velocity rear-end collision) that produces a regional cervical muscle strain, which then causes a secondary cervical and sometimes even masticatory myalgia. Current data suggests that the jaw closing and opening muscles themselves are not overstretched or torn during a low-velocity rear-end motor vehicle collision,[27,28] but they may become involved when a guarding–trismus response develops in concert with the

injured craniocervical muscles.[29] If a direct muscle trauma is suspected as the etiology, then the traumatic event is usually easily identified in the history. Fortunately, most such traumatic injuries are self-resolving without long-term consequences.

When a local pain-inducing pathology is present, localized and even regional myalgia will develop in response. For example, acute TMJ arthritis can cause an associated muscle pain in the masseter and temporalis on the side ipsilateral to the involved joint. The pain in the muscle tissue is secondary, but it may generate an equal or greater degree of tenderness to palpation than elicited by palpating the involved joint. That the nociceptors inside a joint or even inside a tooth can induce a secondary motor reaction in the anatomically adjacent muscle has been clearly demonstrated in the literature.[30,31] The most likely secondary jaw and cervical motor activation occurs with a painful arthritis or internal derangement of the TMJ.[32] However, these reactions are also likely to occur with acute pulpal pain, osteomyelitis, or other mandibular bone or soft-tissue infections in the region. When a patient presents with one-sided muscle pain in the absence of trauma or a strong stress or parafunction history, the clinician should carefully examine the TMJ for local disease or dysfunction. When a patient presents with both a local pathologic process and muscle pain that seems to have developed after the pathology began, it would be appropriate to consider that the myogenous process is a secondary myalgia not a primary one. In these cases it is logical and appropriate to manage or minimize the local pathology first and then re-examine the myogenous pain for resolution or persistence.

1.2.C Disease 2: myofascial pain (focal or regional)

While many consider myalgia and myofascial pain to be similar, the International Association for the Study of Pain Subcommittee on Taxonomy has classified myofascial pain (MFP) as pain in any muscle with trigger points that are very painful to compression during palpation and cause referred pain sensations.[33] Essentially the term myofascial pain is used only when specific criteria are satisfied.

Clinical criteria

The criteria for myofascial pain are both subjective (history based) and objective (examination based). The three subjective criteria that patients should endorse are (1) spontaneous dull aching pain and localized tenderness in the involved muscle(s), (2) stiffness in the involved body area, and (3) easily induced fatigueability with sustained function. The four objective criteria are (1) a hyperirritable spot within a palpably taut band of skeletal muscle or muscle fascia, (2) reports by the patient, upon sustained compression of this hyperirritable spot, of new or increased dull aching pain in a nearby site, (3) decreased range of unassisted movement of the involved body area, and (4) weakness without atrophy and no neurological deficit explaining this weakness. Many have included the presence of referred autonomic phenomena upon compression of the hyperirritable spot and/or a twitch response to snapping palpation of the taut bands as additional diagnostic criteria.[34–38] However, inclusion of the last criterion is not endorsed by all since it is not a reliably present physical finding.[39]

Etiology

The common etiologies that cause myofascial pain are the same as those given for myalgia (see Secs. 1.2.A and 1.2.B).

1.2.D Disease 3: chronic widespread pain and fibromyalgia

Chronic widespread pain and fibromyalgia are quite similar conditions in that the patient has complaints of multiquadrant muscle pain, but only fibromyalgia has an accepted set of specific physical examination criteria. Fibromyalgia affects up to 2% of the population and can start at any age; it is at least 7 times more common in women than in men.[40] By the time the diagnosis is made, patients have often had symptoms for many years.

Clinical criteria

Patients with fibromyalgia complain of muscular and sometimes joint pain all over and, by definition, have pain on both sides of the body, above and below the waist, and in both the trunk and extremities. There are specific clinical history and examination criteria that must be met before a diagnosis of fibromylagia is rendered. These criteria, adopted by the American College of Rheumatology (ACR), specify that a diagnosis of fibromyalgia is made when there is widespread pain lasting for at least 3 months accompanied by tenderness at discrete locations.[41] According to the ACR criteria, patients must have at least 11 tender points of a possible 18 but, in practice, the diagnosis can be made in patients with fewer tender points if there is widespread pain and many of the other characteristic symptoms. Patients with fibromyalgia are often tender all over; the presence of tenderness other than at the classic locations does not exclude the diagnosis. These findings suggest and most researchers agree that an aberrant central pain processing mechanism produces a state of sensitized pain perception in FMS.[42] Because of the widespread muscle and joint pain, fibromyalgia patients usually have poor-quality nonrestorative sleep. They also frequently report irritable bowel syndrome and headaches. Because of

the negative effect fibromyalgia has on activities of daily living, it usually induces depression and anxiety, and it often accompanies other chronic painful disorders.[43]

Etiology

It is likely that patients who develop chronic widespread pain and/or fibromyalgia have a genetic factor that predisposes them to sensitization of the central nervous system (CNS). For the local factors that trigger pain, see Sections 1.2.A and 1.2.B; the common etiologies that cause fibromyalgia are the same as those given for myalgia.

1.3 Facial pain due to derangement and non-autoimmune arthritis or capsulitis of the temporomandibular joint

The second subgroup of conditions is facial pain due to joint and disk derangements as well as the non-autoimmune arthrogenous diseases. "Derangement" is a nonspecific term that means abnormal function of the intra-articular structures (displacement of the disk), but in this section we also include abnormal joint function (dislocation and locking), as described in Section 1.3.C. Disk derangement of the TMJ is more common in the 20- to 50-year-old population.[44] Localized osteoarthritis is characterized by focal degeneration of joint cartilage with osseous erosion and sclerosis; sometimes osteophyte formation at the joint margins occurs in an older cohort of patients.[45,46] In addition to osteoarthritis, there are a number of polyarthritic diseases in which the TMJ is involved in the arthrogenous process. These various conditions are described in Sections 1.3.D and 1.3.E and in the next subgroup of orofacial pain disorders (Sec. 1.4).

1.3.A Disease 4: disk displacement with reduction

Disk displacement with reduction (DDWR) is more of a dysfunction than a pain disorder, but if the joint tissue is inflamed, a click can be painful.

Clinical criteria

Evidence for disk displacement with reduction is transient jaw movement interference or clear joint noise, noted clinically as a single joint sound (usually described as a click or pop) emanating from one or both joints. A diagnosis of DDWR is not appropriate if the opening or closing movement noise is only an asynchronous eminence translation. If the click is associated with a clear loss of maximum opening ability or if the noises are a result of arthritic changes in the joint (i.e., crepitus or multiple noises in a single movement), then the diagnosis of disk displacement without reduction (DDNR, Sec. 1.3.B) or osteoarthritis will supersede the diagnosis of DDWR.

Etiology

For a TMJ disk to be displaced, the ligaments that attach it to the condyle must be stretched to such a degree that the disk has additional mobility. This process can occur from parafunction, joint remodeling, acute trauma, and joint hypermobility syndrome. These etiologies and how they cause DDWR and DDNR are discussed in Chapter 20.

1.3.B Disease 5: disk displacement with no reduction

Disk displacement with no reduction (DDNR) is definitely painful when the patient attempts to open wide in the early stages.

Clinical criteria

The appropriate historical evidence for DDNR is a clear TMJ movement restriction or hypomobility that began suddenly and has continued since that time without remission. The appropriate clinical evidence for this disorder is maximum passive stretch mouth opening (interincisal distance including overbite) of less than 38 mm. This opening is often accompanied by a deflection to the side that is locked during maximum opening. The patient will also have only a small limitation of lateral motion if any loss is evident. Finally, the affected joint often has a history of joint noises that stopped at the time of the movement restriction. If the acute onset hypomobility becomes chronic (i.e., greater than 6 months), the opening may increase by several millimeters (up to 42 mm) and crepitus noises may develop. Magnetic resonance imaging is needed to see the disk since it is a soft-tissue structure that cannot be seen on computerized tomography (CT).

Etiology

The common etiologies that cause DDNR are the same as those given for DDWR (see Sec. 1.3.A).

1.3.C Open dislocations and locking problems seen in the temporomandibular joint

Because they are relatively rare and generally unmistakable when present, these three TMJ internal derangement subcat-

egories are not included in this group of 30 most common disorders.

Clinical criteria

1. A *true open dislocation* is present when the condyle undergoes excessive translation, moving to a position that is well beyond where it would normally go to even with a very wide open movement. In this position the jaw will be unable to close and usually requires that manual manipulation of the jaw be performed to reduce the problem.
2. A *simple open locking* is often mistakenly diagnosed as a dislocation when the patient's jaw is actually only locked open and not truly dislocated. An open locking is present when the condyle becomes stuck or locked in a wide open position (condyle anterior to eminence) but is not in a position of excessive condyle translation. Similar to true dislocation, open locking is a situation in which the patient is unable to close, but most times the patient is able to self-reduce the locked jaw without assistance.
3. A *posterior disk displacement* of the TMJ disk causes an inability to fully close after opening or a partial-open locking. Actually this condition should not be confused with the prior problem of wide-open locking of the condyle. These patients complain of the inability to close their jaw after opening but the condyle is not anterior to the articular eminence. If only one joint is involved, the jaw may be in an extreme lateral position but again not in a wide open position. The likely cause of this condition is a posterior DDNR, preventing the condyle from returning to its original position or full closure. Spasm of the lateral pterygoid can also cause the posterior teeth not to articulate.

It should be noted that dysfunction, not pain, is clearly the main problem when derangements occur, because a disk derangement of the jaw (clicking, locking, and/or dislocation) is normally not painful when the jaw is not moving. On the other hand, osteoarthritis does cause spontaneous pain and certainly pain on function.

A detailed discussion of derangement-type disorders and their appropriate management is presented in Chapter 20.

Etiology

For a true dislocation to occur, the ligaments that restrict condyle motion (i.e., the TMJ ligament) must be stretched to such a degree that the condyle has additional mobility. For an open locking to occur, the various ligaments of the jaw do not need to be stretched or torn, but jaw elevator muscles must tighten (i.e., develop trismus) to such a degree that the joint is jammed anterior to the eminence. For a posterior disk displacement this dysfunction develops due to the same process as for anterior disk displacement, namely the disk ligaments are stretched. These etiologies and how they cause DDWR and DDNR are discussed in Chapter 20.

1.3.D Disease 6: local temporomandibular joint arthritis

As the name implies, arthritis of the TMJ is a painful inflammation of the joint. Osteoarthritis (OA) is the most common degenerative disease that affects the TMJ. It is considered a disease of the bone, cartilage, and supporting tissues and is the result of both mechanical and biologic events that destabilize the normal coupling of degradation and synthesis of articular cartilage and subchondral bone.[47]

Clinical criteria

A painful joint without any osseous changes is described as arthralgia, which is considered to be present when the joint tissues exhibit increased tenderness to palpation pressure. Other terms for arthralgia are capsulitis, retrodiscitis, synovitis, and joint effusion. When a crunching or grinding type of noise is produced by motion of the jaw and/or if TMJ radiographs confirm the presence of bony surface deterioration, then the diagnosis switches to localized OA. If the condition involves joints other than the TMJ, then it is called a polyarthritic osteoarthritis assuming no other arthritic disease process is identified. Osteoarthritis also requires the presence of joint pain confirmed by palpation and/or detectable crepitus coming from the involved joint. If only bony surface changes are present and normal function exists and no pain is elicited, this condition is described as osteoarthrosis. Radiographic findings that indicate degenerative arthrotic changes of the TMJ are loss of joint space, flattening of the articulating surfaces, bony spurs, sclerosis of bony surfaces, or discrete erosive bony lesions. Once pain, swelling, and dysfunction are found in other body joints beyond the TMJ, then polyarthritis is considered to be present. The polyjoint form of OA has no serologic markers but almost always there are clear radiographic indications (e.g., flattening, loss of space, spurs, erosive lesions, and sclerosis) of arthrotic changes of the TMJs.

Etiology

Localized OA is usually thought to be traumatic in nature (either macrotrauma or repetitive microtrauma) but could also be due to a rare infective arthritic disease. When an elderly patient attends a dentist's office with a complaint of jaw pain, the most likely diagnosis is localized arthritis

(assuming he or she does not exhibit polyjoint arthritic disease). This can usually be discovered with palpation, auscultation, and radiographic examination of the joint. When a patient has such complaints, is in his or her twenties or thirties, and there is no clear-cut traumatic injury to explain the localized arthritis, the most likely trauma is a prior DDNR of the involved joint. In a study based on a European population, the reported prevalence of OA was approximately 12% for subjects between 25 and 50 years of age, but in patients over 60 years this prevalence reached as high as 95%.[48] Osteoarthrotic changes in the TMJs are much less prevalent than the study's data might suggest for all body sites. Specifically, as reported for a random sample of elderly Finnish subjects (between 76 and 86 years of age).[49] Aging, in and of itself, is not thought to cause osteoarthritis, but if a combination of several age-related changes occurs in the same individual, then OA will result. Specifically, forceful repetitive function (e.g., bruxism) and/or disk displacement along with synovial fluid alterations of the TMJ will predispose the elderly individual to OA. Arthritic disorders and their management are presented in Chapter 18.

1.3.E Disease 7: polyjoint osteoarthritis and the temporomandibular joint

Polyjoint osteoarthritis may also involve the TMJ; the difference between polyjoint and localized osteoarthritis lies mostly in etiology and prognosis. Polyjoint OA of the TMJ is less likely to be due to a local traumatic event and the odds of improvement are lower. There are several polyjoint arthritic conditions that affect the TMJ but OA is the most common.

Clinical criteria

The clinical findings in polyjoint OA of the TMJ do not differ from the findings described in Section 1.3.D, except that the patient must have other body joints involved. For example, one easily recognizable clinical marker of polyjoint OA is the formation of Heberden's nodes on the distal interphalangeal joint of the hand. The proximal interphalangeal joint, first carpometacarpal joint, spine, and knee and hip joints are also common OA sites.

Etiology

Primary polyjoint osteoarthritis is more or less considered idiopathic, although genetic defects are suspected strongly in this disease especially when a familial pattern of OA is present.[50] Secondary polyjoint osteoarthritis is defined as joint damage or cartilage changes characteristic of osteoarthritis caused by other identified congenital or developmental disorders.[51] Prior trauma, surgery, inflammatory disease, bone disease, blood dyscrasias, neuropathic joint diseases, excessive frequent intra-articular steroid injections, endocrinopathies, and metabolic disorders may damage joint surfaces and cartilage.[52] Finally, with severe and very aggressive polyjoint OA, it is necessary to also have a negative serologic test for rheumatoid factors before the diagnosis of polyjoint or generalized OA can be confirmed. It is likely that molecular–genetic defects in type 2 cartilage collagen binding proteins are involved since they are critical to joint health. A recent review on the genetic risk factors for OA discussed the findings from twin studies, segregation analyses, linkage analyses, and candidate gene association studies and summarized inheritance patterns and the location in the genome of potentially causative mutations.[53] However, the various studies do not always provide a consensus on the genetic factors that are etiologic for this condition.

1.4 Autoimmune arthritic, connective tissue, and vascular disorders causing facial pain

The third subgroup of orofacial pain conditions is facial pain due to chronic autoimmune-related disorders of joints (including the TMJ), connective tissues, or vascular tissues. In this subgroup and by far the most common is rheumatoid arthritis (RA). Second most prevalent is the vascular disease temporal arteritis, characterized by inflammation of large and middle-sized blood vessels with giant cell–type inflammatory cells inside the arteries.[54] Third, an uncommon inflammation of the trigeminal nerve causes a combination of pain and numbness in the trigeminal nerve. This sensory neuropathy has been associated with a variety of connective tissue autoimmunities, such as Sjögrens syndrome, lupus erythematosis, scleroderma, and mixed and undifferentiated connective tissue disease.

1.4.A Disease 8: rheumatic arthritis and the temporomandibular joint

Rheumatoid arthritis is a polyjoint disease that affects the TMJ. RA is the most common chronic, systemic, autoimmune, inflammatory disease that affects the TMJ; other polyjoint diseases include lupus erythematosis and psoriatic arthritis, but they are not included in this group of 30 most common disorders.

Clinical criteria

Rheumatoid arthritis is characterized by joint inflammation, erosive properties, and symmetric multiple joint involve-

ment. RA can involve other body organs and in some patients can be an aggressive disease causing progressive joint damage, decreased function, and increased impairment. The main serologic marker, rheumatoid factor (RF), an immunoglobulin M (IgM) autoantibody against the Fc portion of an IgG molecule, is found in 75–80% of patients. Edema, hyperplasia of synovial lining, and inflammatory infiltrate are early components of the clinical presentation. Chronic RA is characterized by hyperplasia of Type A synovial cells and subintimal mononuclear cell infiltration resulting in the massive damage of cartilage, bone, and tendons by the pannus, an infiltrating inflammatory synovial tissue mass.[55–58] Rheumatoid arthritis is found in the temporomandibular joint in more than 50% of adults and children with RA,[59] but the TMJ appears to be one of the last joints attacked by RA. Clinical findings include dull aching pain associated with function, joint edema, and limited mandibular range of motion. When severe, an anterior open bite can result but typically the patient has morning stiffness and has stiffness and pain at rest. Radiographic findings range from flattening of the condylar head to severe, irregular condyle deformity.

Etiology

While the etiology is unknown, certain genetic markers, *HLA-DR4* and *HLA-DR1*, are found in approximately 30% of patients with RA.

1.4.B Disease 9: temporal arteritis

This giant-cell-based inflammatory disease of the vasculature occurs when the cranial and scalp vessels become inflamed.

Clinical criteria

Patients with temporal arteritis have palpable vessels of the scalp that are sore, tender, thickened, and sometimes pulseless because of the inflammation.[60] The mean age of onset for temporal arteritis is 70 years and it is rare in people less than 50 years of age.[61] A study examining the influence of age on the clinical expression of biopsy-proven giant cell arteritis reported this disorder as more common in women (female-to-male ratio 1.58 : 1.00) and as occurring in patients with an age greater than or equal to 50 years.[62] Systemic symptoms (e.g., fever) occur in about half of patients, and in about 15% of patients it may be the presenting clinical manifestation. In approximately two-thirds of all patients, headache is the most frequent seminal symptom. The onset is more often gradual, but it can also be abrupt with new headache pain such as scalp tenderness as a primary complaint. The pain symptoms are usually confined to the temporal and sometimes the occipital arteries, but the occipital arteries are less often involved. Occasionally, intermittent claudication (fatigue or pain on function) may occur in the muscles of the jaw or even tongue. In rare cases, more marked vascular narrowing may lead to infarction of the scalp or the tongue. One serious complication of temporal arteritis is permanent partial or complete loss of vision in one or both eyes. Affected patients typically report partially obscured vision in one eye, which may progress to total blindness. If untreated, the other eye is likely to become affected within 1–2 weeks. Warning signals for temporal arteritis include onset of a new headache after the age of 50, the progressive course and systemic symptoms of malaise, and jaw claudication on function. The screening investigations usually ordered for clinically suspected temporal arteritis are (1) complete blood count, (2) erythrocyte sedimentation rate (ESR), (3) C-reactive protein, (4) urea electrolytes, (5) liver function, (6) bone biochemistry, (7) glucose, (8) thyroid function, (9) rheumatoid factor, (10) electrophoresis, and (11) a chest X-ray. If the ESR is elevated, a biopsy of a clinically affected scalp vessel is confirmatory.[63]

Etiology

The cause of temporal arteritis is thought to be related to multiple environmental and genetic factors that trigger this autoimmune-type inflammatory reaction.

1.4.C Disease 10: idiopathic trigeminal sensory neuropathy

Trigeminal sensory neuropathy (TSN) is a multifactorial inflammatory disorder of the trigeminal nerve causing sensory dysfunction (numbness, pain).

Clinical criteria

The TSN patient usually presents with unilateral or bilateral sensory loss of one or more divisions of the trigeminal nerve. The numbness can be either painful or nonpainful. Because of the association with mixed and undifferentiated connective tissue disease there may also be complaints of Raynaud's phenomenon, polyjoint arthritis, and sometimes muscle weakness.

Etiology

This condition is associated with Sjögren's syndrome, undifferentiated and mixed connective tissue disease, and scleroderma, which are all considered to be connective tissue

disorders.[64–70] The source of the underlying neural dysfunction is thought to be autoimmune because of this association.[71] The sensory deficits of facial pain and numbness can occur several years before a clear serologic confirmed clinical diagnosis of one of these connective tissue diseases, requiring vigilance for cancer-induced neural dysfunction.

1.5 Headache pains that cause orofacial pain

The fourth subgroup of 30 orofacial pain conditions is facial pain due to headaches. Approximately 90% of headache pain in the adult population is caused by migraines or tension-type headaches.[72] However, of the new headaches that develop in people over 50 years old, approximately one-third are due to intracranial lesions or some other systemic disease. The overall prevalence of headaches declines with age and it has been reported that the prevalence of headaches declines from 83% of individuals between ages 21 and 34 to 59% between ages 55 and 74.[73] One exception to this generalization is migraines, which sometimes occur for the first time after age 50; in fact, about 2% of all migraines start at this late age.[74] The following subsections discuss episodic headaches as well as those that have converted to the chronic form.

1.5.A Disease 11: migraine

This common disorder is considered to be a neurovascular dysfunction of the trigeminal nerve.

Clinical criteria

The main criteria for migraine with or without aura are (1) unilateral headache location, (2) a pulsetile headache, (3) nausea associated with the pain, and (4) photophobia and phonophobia. If an aura is present, it occurs before the headache pain develops and is described as a "flashing light or dizziness." Migraines occur slightly more often in women than men, and mostly in people under 40 years old. When the headache develops, it usually lasts 2–6 hours, but never more than several days. There are several migraine variants, such as: (a) hemiplegic migraine (head pain, transient motor–sensory changes); (b) ophthalmoplegic migraine (eye pain, transient optic nerve palsy with diplopia–ptosis); (c) complicated migraine (cerebral vascular ischemia with resulting infarction and cerebral tissue damage); (d) midface migraine (orodental pain, duration 4–72 hours, with nausea, vomiting, phonophobia, photophobia). When diagnosing systemic and intracranial diseases and other disorders that are often a cause of headaches in old age, it is prudent to obtain a CT scan or MRI of the head. A good general rule is that an unusual initial presentation or a change in symptomatology (other than frequency or intensity) of migraine is a "red flag" that calls for consideration of imaging studies.

Etiology

The fact that most migraine patients have a strong familial history of migraine indicates it has a genetic basis. A detailed discussion of migraine is provided in Chapter 15.

1.5.B Disease 12: cluster headaches and autonomic cephalalgias

Cluster headache (CH) is the most common of the trigeminal autonomic cephalalgias, but this headache group also includes paroxysmal hemicrania as well as short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT).

Clinical criteria

Cluster headaches are one-sided retro-orbital, supraorbital, and temporal pain lasting from 15 minutes up to 3 hours when untreated. The headaches often occur at night, waking the patient from a sound sleep with severe pain. With CH, the patients are very agitated during the attack (pacing and head pounding), have no preheadache aura, and, usually, have no associated nausea or vomiting. Among CH patients, the afflicted are mostly men (5–6 times greater prevalence than women), are mostly smokers, and have an age of onset between 20 and 40 years. Cluster headache patients must exhibit, on the affected side, one of the following autonomic signs: conjunctival injection; ptosis; miosis; eyelid edema; flushing or blanching of the face; forehead or nasal sweating; lacrimation; nasal congestion and rhinorrhea. The headaches occur in clusters and will often repeat several times in a 24-hour period (one attack every other day to as many as eight per day). The cluster period frequently lasts for weeks to months and is usually present in specific seasons of the year (greater in winter and spring) and can go into remission for months.[75,76]

Etiology

The etiology is unknown but a genetic defect is suspected as the basis of this disorder. A detailed discussion of CH and autonomic cephalalgia is provided in Chapter 15.

1.5.C Disease 13: tension-type headaches

Tension-type headaches (TTHAs) are the most common headache in society, with a lifetime prevalence in the general population of 30–78%. Even though this is the most

frequent type of headache, the symptoms are somewhat nonspecific.

Clinical criteria

A TTHA is generally a dull aching bilateral pain that is long lasting and increases slowly during the day to reach peak intensity near late afternoon. It may last for 1–2 days, but it must not occur more often than three times per week or it is not considered episodic. In most cases it is episodic and the pain is located in the suboccipital, temporal, and frontal regions. It is described as a "tight head band" and may be associated with pericranial tenderness. The headache may vary from a short duration to lasting hours, and it may increase slowly during the day to reach peak intensity near late afternoon.[77] Episodic tension-type headache (ETTH) does not present with migraine signs (e.g., throbbing, photophobia, nausea).

Etiology

Many theories have been put forth to explain the causation and pathogenesis of ETTH. An important and moderately controversial one is the role that pericranial muscle and fascial tenderness plays in the causation or triggering of ETTHs. The questions that need addressing are (1) "Does jaw or facial muscle tension cause an ETTH?" and (2) "If muscle tension is not causative, does muscle nociception from the jaw, face, and neck potentially assist in the triggering process for ETTHs and migraines?" These issues are important to the role that myofascial pain and local myalgia play in the overall headache management program.

1.5.D Disease 14: chronic daily headaches

The group of conditions called chronic daily headache (CDH) includes chronic migraine, chronic cluster headache, hemicrania continua, chronic tension-type headache (CTTH), and new daily persistent headache (NDPH). Migraine, cluster, and tension-type headaches initially present as episodic headaches but they all have the potential to convert or transform into a continuous headache.

Clinical criteria

The criteria for each chronic form are the same as for the episodic form, but to be considered a "transformed acute-to-chronic" headache requires that these disorders exist first in the episodic form and then over time transform to a more frequent or continuous headache. Once they convert, they are called CDH if present 4 or more days per week. Most of the time in CDH, the pain symptoms are present all of the time with only fluctuations up and down in intensity. One subcategory of the CDH headaches is medication overuse headache, also known as an analgesic rebound headache. The criteria are a steady head or midface pain with frequent–intermittent or continuous multiple pain foci; the headaches improve when analgesics are withdrawn. The most commonly overused medications are over-the-counter (OTC) analgesics, ergotamines, barbiturates, benzodiazepines, and opioids.

Etiology

In addition to using too many analgesics, there are genetic and behavioral factors that likely facilitate the neuropathic conversion from an episodic to a chronic headache. This process is discussed in more detail in Chapter 15.

1.6 Orofacial neurogenous pain: neuralgia, neuropathy, burning mouth

The common mechanism for this subgroup of orofacial pain conditions is trigeminal nerve damage. The trigeminal nerve, if injured or stimulated strongly and long enough, will undergo sensitization. There are also idiopathic neuropathic pain conditions since it is not uncommon that the triggering injury cannot be identified. Regardless of the cause, when neuropathic changes develop, pain can take many forms, such as sharp brief lancinating pains or more continuous sustained pains. The multiple neurogenic diseases that affect the trigeminal nerve are presented in the following subsections.

1.6.A Disease 15: facial pain related to trigeminal neuritis

This multifactorial disorder presents as a continuous burning pain, numbness, tingling, and hypersensitivity along the distribution of the involved trigeminal nerve. When an individual nerve or nerve trunk is inflamed, this is described as a mononeuritis.

Clinical criteria

Mononeuritis pains have an acute onset and the cause is usually obvious based on the examination and history. Those caused by neural compression are also easy to figure out if the source is exogenous (i.e., dental implant) or due to neural abrasion from a compressive osseous growth. The three most common infections to affect the trigeminal nerves are dental abscess, sinus infection, and herpes zoster (shingles). Herpes zoster infection causes small skin vesicles along the distribution of the affected nerve, although vesicles and ulcers can be seen intraorally. Often these vesicles follow

the pain and may present 1–5 days after its onset. If the inflammation occurs in two or more nerve trunks in separate body areas, this is called polyneuritis disorder. The causes of a polyneuritis are diabetes, adverse medication reactions, infection, and immune-mediated neuritis. The symptoms of neuritis, regardless of cause, are a combination of numbness, tingling, weakness, and burning sensation in the affected nerve.

Etiology

Inflammation can be due to neural trauma, bacteria, viruses, or toxins that are damaging the nerve. For mononeuritis, it is most commonly caused by trauma (e.g., fracture, intraneural injection, third-molar extraction, orthognathic surgical manipulations) or infection (bacterial or viral). Diabetic neuropathy is the most common known cause of polyneuritis and it can produce both an acute (usually reversible) nerve inflammation and chronic (irreversible) neuropathic changes in the trigeminal nerve. The diabetic neuritis patient will complain of numbness, tingling, and weakness in the fingers and toes. Immune-mediated neuritis occurs when the immune system turns against the body and causes an autoimmune reaction (e.g., Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy, neuropathies associated with vasculitis, neuropathies associated with monoclonal gammopathies). Viral-induced polyneuritis is caused by human immunodeficiency virus (HIV), *Cytomegalovirus*, *Poliovirus*, and hepatitis B or C infections causing vasculitic neuropathy. Bacterial-induced polyneuritis includes leprosy, diphtheria, Lyme disease, and trypanosomiasis. Nutritional-imbalance polyneuropathies are caused by deficiency of vitamins B_{12}, B_1 (thiamine), B_6 (pyridoxine), and E. Renal failure polyneuropathy can cause degeneration of peripheral nerve axons as a result of accumulated toxins. Toxin-induced polyneuropathy is caused by alcohol and other toxins (megadoses of vitamin B_6, lead, arsenic, mercury, thalium, organic solvents, and insecticides). Medication-induced neuritis and neuropathies include those caused by vincristine and cisplatinum in treating cancer; nitrofurantoin, in pyelonephritis; amiodarone, in cardiac arrhythmias; dideoxycytidine (ddC) and dideoxyinosine (ddI), in acquired immunodeficiency syndrome (AIDS); and dapsone, in leprosy.

1.6.B Disease 16: facial pain related to trigeminal neuroma

Peripheral neural injury will result in trigeminal neuroma formation if the neural injury transects the nerve. The initial injury may only be briefly painful but, as a result of the injury, the nerve forms a chronically painful neuroma.

Clinical criteria

Peripheral neuroma occurs when a nerve is transected, causing sprouting of the proximal nerve trunk to form a bundle of nerves (neuroma) that can be spontaneously active. In the area supplied by the severed nerve there is numbness. The resulting neuroma causes symptoms such as hypersensitivity to light touch and spontaneous pain.[78]

Etiology

The most common locations in the jaw where the nerve is transected are the lingual nerve, inferior alveolar nerve, and auriculotemporal nerve; it is most commonly due to a surgical intervention.

1.6.C Disease 17: facial pain related to trigeminal neuralgia

Trigeminal neuralgia (TN) often presents as severe lancinating pain located in the jaw. Patients present to the dental office with a sharp tooth-region pain and will inappropriately seek dental therapy (endodontics or extraction) as a first line of treatment.

Clinical criteria

Trigeminal neuralgia presents as a sudden, usually unilateral, severe, brief, stabbing, recurrent pain in the distribution of one or more branches of the fifth cranial nerve.[79] In 1988 the International Headache Society suggested the criteria for the diagnosis of TN, and a complete discussion of this disorder is presented in Chapter 6.[80]

Etiology

While recent evidence points to vascular injury (abrasion) of the trigeminal nerve root inside the cranial vault, this alteration is not usually visable using current imaging modalities. However, in up to 15% of patients there may be an underlying cause such as a benign or malignant tumor of the posterior fossa or multiple sclerosis.[81]

1.6.D Disease 18: facial pain related to a chronic trigeminal neuropathy

Local sustained pain in a tooth or gingival site without evidence of local dental or periodontal pathology is labeled as a trigeminal neuropathy. This diagnosis assumes you are now dealing with a neuropathic pain not a pulpal or periodontal disease. Over the years, many different terms have been used to describe dental pain of unknown origin. The most common is "atypical odontalgia".[82–87] Once the tooth

is extracted and the pain continues, then the term "phantom tooth pain" is used.[88–91]

Clinical criteria

The diagnosis of chronic trigeminal neuropathy is essentially a clinical process. The most prominent and sometimes the only symptom that is evident is pain. It is more commonly described as a continuous and spontaneous dull ache localized in a tooth or tooth region. The location may change to an edentulous area or entire parts of the maxilla or mandible. The pain also can be described as burning, sharp, or throbbing. It usually persists for months or years being continuous and persistent, but oscillating in intensity with episodes when the pain is more acute and severe. For a diagnosis of trigeminal neuropathy to be made, other pathologies characterized by tooth pain need to be ruled out. Several have been listed: pulpal toothache, trigeminal neuralgia, myofascial pain, sinusitis, cracked tooth syndrome, and migrainous neuralgia. Probably the most difficult task is to distinguish between trigeminal neuropathy and toothache from pulpal origin. Characteristics that are common to trigeminal neuropathy, but not common to pulpal toothache, are addressed in Chapter 17. A detailed discussion of the persistent orodental pain due to neuropathy and the appropriate management is presented in Chapter 17.

Etiology

The most accepted theory regarding what causes these pain phenomena is that trauma to the orofacial structures (traumatic injury, periodontal surgery, pulp extirpation, endodontic therapy, apicoectomy, tooth extraction, implant insertion), or even minor trauma (crown preparation, inferior alveolar nerve block) might alter the neural continuity of the tissues, creating sensitization of the peripheral nociceptive nerves. Multiple mechanisms are involved in the pathogenesis of neuropathic pain but the common process is that, following a nerve injury or regional inflammation, the afferent nociceptive fibers become sensitized showing a lower activation threshold and sometimes developing spontaneous ectopic activity as a result of increased expression or redistribution of sodium channels on the axon. This sensitization could easily explain some of the clinical manifestations of oral neuropathic pain such as the clear-cut mechanical or thermal allodynia and persistent spontaneous pain.

1.6.E Disease 19: facial pain related to postherpetic neuralgia

Infection with herpes zoster can lead to the development of continuous pain in the skin or sometimes mucosal tissues of the mouth during and following the viral infection. Herpes zoster infection strikes millions of older adults annually worldwide and disables a substantial number of them as postherpetic neuralgia. This event is more likely to occur in elderly people, partly because of age-related decline in specific cell-mediated immune responses to varicella-zoster virus.

Clinical criteria

The disease begins with localized abnormal skin sensations, ranging from itching or tingling to severe pain, which precede the skin lesions by 1–5 days. Healing of the skin lesions occurs over a period of 2–4 weeks, and often results in scarring and permanent changes in pigmentation. The cutaneous eruption is unilateral and does not cross the midline. Along with the rash, most patients experience a dermatomal pain syndrome caused by acute neuritis. The neuritis is described as burning, deep aching, tingling, itching, or stabbing pain, and ranges from mild to severe. This pain continues after the rash has healed in as many as 60–70% of patients over the age of 60 and is then considered postherpetic neuralgia, the more frequent and debilitating complication of herpes zoster in the elderly.[92]

Etiology

The most well established risk factors for postherpetic neuralgia are older age, immunocompromised status, greater severity of acute pain during zoster, and a more severe rash. The patient with postherpetic neuralgia may experience constant pain (described as burning, aching, or throbbing), intermittent pain (described as stabbing or shooting), and stimulus-evoked pain such as allodynia (described as tender). Furthermore, postherpetic neuralgia can impair the elderly patient's functional status by interfering with basic activities of daily life, such as dressing, bathing, and mobility, and instrumental activities of daily life, such as traveling, shopping, cooking, and housework. The appearance of herpes zoster is sufficiently distinctive that a clinical diagnosis is usually accurate. A direct immunofluorescence assay if needed would the best and only way (other than culture) to distinguish herpes simplex virus infections from varicella-zoster virus infections. Polymerase-chain-reaction techniques are useful for detecting varicella-zoster virus DNA in fluid and tissues.[93,94]

1.6.F Disease 20: burning mouth symptoms (not related to hyposalivation)

Continuous pain on the surface of the tongue, mucosa of the lips, and sometimes anterior gingival tissues is commonly

called burning mouth syndrome (BMS; stomatopyrosis) and its variant, burning tongue (glossopyrosis).

Clinical criteria

The sufferers are typically within an age range from 38 to 78 years.[95,96] Occurrence below the age of 30 is rare, and the female-to-male ratio is about 7:1. Presence of burning sensations is the main complaint, usually described as constant, gradually increasing throughout the day, or intermittent, without any reliable alleviating agents. Diagnosis of BMS is one of exclusion since, like other neurosensory disorders, there are measurable physical signs other than pain. Over two-thirds of BMS patients report a bitter, metallic taste sensation as well as the burning.[97–99] The BMS patient typically reports pain onset ranging from 3 years before to 12 years after menopause and approximately 50% of BMS patients complain of dry mouth (xerostomia) but do not exhibit measureable hyposalivation. The pain symptoms of BMS are invariably bilateral, and usually in multiple areas of the mouth. These symptoms often increase in intensity at the end of each day but seldom interfere with sleep. To be considered BMS, the patient should have had the pain continuously for at least 4–6 months. Pain levels may vary from mild to severe, but moderate pain is the most frequent presentation. The pain should be described as daily bilateral oral burning (or painlike) sensations deep within the oral mucosa, unremitting for at least 4–6 months. The symptoms should generally be continuous throughout all or almost all the day and should not interfere with sleep. Like many of the idiopathic diseases, it is a diagnosis made by taking a detailed history and then carefully going through the process to exclude other causes or diseases. The abnormalities that must be excluded are local pathology of the mucosal tissues, nutritional deficiencies (vitamin B_1, B_2, B_6, B_{12}, or B_c [folic acid]), salivary hypofunction, and diabetic neuropathy. If any of these problems are discovered or if oral lesions are present, the diagnosis is not stomatopyrosis. The frequent observation of taste changes and/or sensory–chemosensory dysfunctions in BMS patients suggests that this syndrome could reflect a neuropathic disorder.[100]

Etiology

The hypothesized underlying etiology of BMS is an idiopathic small afferent fiber atrophy disorder. The concept that BMS is due to psychogenic or psychosomatic factors has generally not been supported by scientific evidence, and the reverse is the case.[101,102] A detailed discussion of the burning mouth syndrome and its appropriate management is presented in Chapter 14.

1.7 Facial pain related to chronic oral inflammatory disease

Orofacial pain can arise from a persistent oral inflammatory disease, including blistering diseases, some of which can be extremely debilitating and even fatal. Many of these diseases are autoimmune in nature and may also be associated with certain human leukocyte antigen types. Some bullous diseases have serious sequelae, necessitating early treatment and intervention to prevent further morbidity or mortality. Autoimmune blistering diseases include pemphigus vulgaris, paraneoplastic pemphigus, bullous pemphigoid, cicatricial pemphigoid, dermatitis herpetiformis, linear IgA dermatosis, and graft-versus-host disease (GVHD). Here we focus on pemphigus, pemphigoid, and erosive lichen planus.

1.7.A Disease 21: pemphigus vulgaris

Pemphigus describes a disorder that causes pain because it produces blistering and sloughing of the oral mucosal tissues; it is one of a group of autoimmune blistering diseases that affects the skin and mucous membranes. Pemphigus vulgaris is a serious and deadly diagnosis in that it may be fatal if not treated with appropriate immunosuppressive agents.

Clinical criteria

Characteristically, lesions start in the oral mucosa, followed by the appearance of skin lesions months later. The bullae on the skin may remain localized for 6–12 months, then subsequently become widespread. Rarely, the lesions may arise as a generalized acute eruption. The lesions can be pruritic but are usually painful and accompanied by a burning sensation. Mouth lesions may be tender, preventing adequate food intake, which leads to weight loss. Its onset is slow to develop and the first lesions occur in the oral cavity. As the disease progresses, skin lesions will occur too. On the skin, the bullae last longer before rupture, a feature that makes diagnosis easier. Given the nonspecific nature of the intraoral ulcers, it is not uncommon for progression to skin lesions to occur before the true nature of the disease is appreciated. The microscopic features of intact bullae are usually specific enough to render a diagnosis of pemphigus vulgaris. The most significant of these is the finding of a cleft within the stratum spinosum (intraepithelial clefting) a finding that corresponds to the desmosome destruction. The cells of the stratum basale are unaffected and remain attached by the basement membrane to the underlying connective tissue. This finding creates an unusual appearance that pathologists call tombstoning, in reference to tombstonelike

basal cells. The lesions may be accompanied by weakness and malaise, and a history of epistaxis, dysphagia, and hoarseness. Pemphigus vulgaris is a serious autoimmune systemic dermatologic disease that may affect the oral mucous membrane and skin, manifesting as large fluid-filled rupture-prone bullae; it has a distinctive histologic appearance; anti-inflammatory agents are the only effective therapy and, unfortunately, pemphigus vulgaris has a high mortality rate.

Etiology

The presence of circulating antibodies against keratinocyte cell surfaces suggests that pemphigus is an autoimmune disease. Pemphigus vulgaris is equally prevalent in men and women, and the mean age of onset is between 40 and 60 years. Pemphigus vulgaris is also more common in persons of Jewish and Mediterranean descent.

1.7.B Disease 22: benign mucous membrane pemphigoid

Another painful blistering disorder, but far less morbid than pemphigus, is benign mucous membrane pemphigoid (BMMP); it is also an uncommon autoimmune condition that affects the oral mucosa (gingiva), manifesting as bullae and ulcers. BMMP has a distinctive histology and runs a benign course; improvement usually occurs with anti-inflammatory therapy; pemphigoid, unlike pemphigus, is not fatal.

Clinical criteria

Benign mucous membrane pemphigoid, "pemphigoid" for brevity, was also known as desquamative gingivitis, a designation that recognized its location (gingiva) and its basic lesion (surface sloughing). Recently the name "benign mucous membrane pemphigoid" has been adopted to recognize that it is not fatal (benign), that it occurs only on mucous membranes (mucous membrane), and that it superficially resembles pemphigus vulgaris (pemphigoid). In pemphigoid, autoantibodies attack basement membranes of the gingiva. The destruction of basement membrane proteins damages the attachment of the gingival epithelium to the underlying connective tissue, allowing the epithelium to become detached and form bullae and ulcers.

Etiology

Like other diseases of autoimmune origin, pemphigoid affects females more than males. It does not appear in people under 40 years of age and, unlike pemphigus, there is little potential for pemphigoid to cause death. However, it is important for patients with this disease to be treated by an ophthalmologist for potential eye involvement.

1.7.C Disease 23: lichen planus

This disorder will cause oral pain if it ulcerates. It is not nearly as dangerous as pemphigus and pemphigoid; it does not form blisters, but it is also an autoimmune disorder affecting the skin and mucosal surfaces of the mouth.

Clinical criteria

Lichen planus (LP) appears as a series of filamentous, white, lacy lines on the inside of the cheeks or other oral tissue and it can cause ulcerative changes in these tissues. LP lesions can occur on other parts of the body, most notably on the skin of the antecubital space (inside of the elbows). Most of these lesions are painless. If the patient has the erosive form of lichen planus, these lesions can be quite painful when eating spicy or sharp-edged foods.

Etiology

Lichen planus is a dermatological autoimmune disease but is often first diagnosed by a dentist due to its characteristic appearance in the mouth. The diagnosis of LP is confused in some patients who develop a lichenoid mucositis due to exposure to a local chemical in the mouth to which the patient may be sensitive (e.g., cinnamon). It is especially associated with certain antihypertensive drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), tetracycline, and several sulfonamides, as well as a number of illegal drugs. The condition often improves with the cessation of the offending drug. The condition is more of a severe nuisance than a disability.

1.7.D Disease 24: mucositis

Mucositis is a very painful mucosal disease most commonly seen after radiotherapy and chemotherapy.

Clinical criteria

When a patient exhibits a painful inflammation and ulceration of the oral mucous membranes, it is called oral mucositis (OM). When severe it can lead to significant complications, including dysphagia, malnutrition, electrolyte imbalance, systemic infection, and death. OM manifests initially as painful, erythematous mucosa that transforms

into more painful ulcerations.[103] The nonkeratinized mucosa of the oral cavity is typically affected with chemotherapy and radiotherapy. Lesions typically occur 1–2 weeks following chemotherapy or after radiotherapy (measured in grays [Gy]) greater than 30 Gy. The healing period is usually 2–4 weeks after cessation of either therapy. The extent and severity depend on the dosage and regimen of the therapy.[104,105] One major problem with severe mucositis is that it can cause patients to terminate their radiotherapy or chemoradiotherapy.

Etiology

The most common reason for a severe oral mucositis is as a side effect of chemotherapy and radiotherapy treatment for cancer.[106,107] The likelihood of oral mucositis depends on the chemotherapy regime being used.[108]

1.7.E Disease 25: other chronic (nonmalignant) ulcerative conditions of the mouth

Members of this group of oral inflammatory and ulcerative problems are chronic and painful. The pain seen with an oral ulcer is because it is an open sore inside the mouth caused by a break in the mucous membrane or the epithelium on the lips or surrounding the mouth.

Clinical criteria

These nonmalignant ulcerative disorders present as ulcers or inflammation of the mucous membranes inside the mouth. Distinction of a Behçet's ulcer from a chronic aphthous ulcer is difficult. Chapter 14 provides more detail on these problems.

Etiology

There are many reasons the tissue ulcerates, including trauma (physical or chemical) and infection from microorganisms and viruses. Various medical conditions and medications cause mucositis. After excluding the previously discussed vesiculobullous conditions of pemphigus vulgaris, benign mucous membrane pemphigoid, and ulcerative lichen planus, some of the medical conditions associated with chronic oral ulcers include Behçet's disease, celiac disease (also known as gluten sensitivity), graft-versus-host disease, Crohn's disease, ulcerative colitis, lupus erythematosus, and neutropenia.

1.7.F Disease 26: cancer pain in the jaw

The painful symptoms that are associated with a neoplastic invasion of the trigeminal nerve and/or a metastatic bone lesion of the jaw will present as pain that produces symptoms that mimic neuritis, neuralgia, and neuropathy or simply induce sensory loss if a cancer invades a nerve sheath or root. There will also be bone pain when patients have metastatic jaw bone lesions (e.g., multiple myeloma).

Clinical criteria

Orofacial pain not only has been the initial complaint of primary oral cancer patients but also has been reported to be one of the earliest indicators of recurrent cancer. A recent study described 12 patients who experienced recurrence of primary head and neck cancers that were preceded by severe orofacial pain.[109] When the pain was reported, the authors described their patients as not demonstrating other evidence of malignant disease despite clinical examination, plain radiography, CT scans, and even MRIs of the area.

Etiology

The most common cancers associated with the trigeminal nerve are posterior tongue–lateral pharyngeal cancer, causing pain in the lingual nerve, and cancer of the nasopharynx invading the infratemporal region and affecting the trigeminal nerve as it exits the foramen ovale.

1.8 Facial pain related to oral motor disorders

Orofacial "movement disorders" can be broadly classified as either "hypokinetic" or "hyperkinetic" conditions. The hypokinetic disorders (e.g., Parkinsonian rigidity) are not usually associated with pain. In contrast, the hyperkinesias spasm and trismus can produce pain. They can be further subclassified into the stereotypic dyskinesias, tremors, dystonias, tics, myoclonus, and choreas. Some might even add the parasomnias (e.g., habitual tooth clenching, sleep bruxism) and secondary spasms to this group. With the exceptions of tooth clenching and sleep bruxism, involuntary oral movement disorders are more common in older age. For example, Bourgeois and colleagues examined 270 elderly subjects in a residential nursing facility for dyskinesias, both spontaneous and drug induced.[110] They reported that females exhibited twice the likelihood of having a dyskinesia (27%) as males (12%). Within those who had dyskinesia, they were two-thirds of the time related to neuroleptic medications and one-third of the time of spontaneous onset. While some oral motor disorders do induce pain, in general, the link between pain and abnormal motor function is not strong. The hyperkinetic disorders that produce pain are discussed in the following subsections.

1.8.A Disease 27: dyskinesia

Orofacial dyskinesia, which usually presents more as a dysfunction than as a pain disorder, can be drug related or can occur spontaneously. The prevalence rate of drug-induced dyskinesia (tardive form) is approximately 15–30% in patients who receive long-term treatment with neuroleptic medications.[111] For spontaneous dyskinesias, the prevalence rate is 1.5–38% of elderly individuals, depending on age and definition.

Clinical criteria

The word "dyskinesia" means abnormal movement and is used to describe a continuous repetitive movement disorder of the jaw, lips, or tongue that can be drug induced (tardive) or can occur without clear cause (spontaneous). By definition, orofacial dyskinesias are involuntary, repetitive, stereotypical movement of the lips, tongue, and sometimes jaw during the day.[112,113] Sometimes the dyskinesia is medication induced (called tardive) or it can occur spontaneously. The spontaneous form of dyskinesia often affects the elderly. The tardive form of dyskinesia typically occurs in mentally ill patients who have had long-term exposure to medications used to treat the mental illness.[114] By definition, tardive dyskinesia requires at least 3 months of total cumulative drug exposure, which can be continuous or discontinuous. Moreover the dyskinesia must persist more than 3 months after cessation of the medications in question. Most dopamine receptor antagonists cause oral tardive dyskinesia to one degree or another. The typical antipsychotics and in recent years even the atypical antipsychotics, including clozapine (Clozaril™), olanzapine (Zyprexa™), and risperidone (Risperadal™), have been reported to cause both tardive dystonia and tardive dyskinesia. No adequate epidemiologic data exist regarding whether any particular psychiatric diagnosis constitutes a risk factor for the development of tardive reactions to medications, but the duration of exposure to antipsychotics required to cause tardive reaction is from months to years. Unfortunately, there is no more specific diagnostic test for dyskinesia other than clinical observation and history.

Etiology

Risk factors for the development of tardive dyskinesia are older age, female gender, and the presence of affective disorders.[115] Elderly women are twice as likely to develop the disorder.[116] When this disorder is associated with a drug use, the medications most commonly implicated are the neuroleptic medications now in widespread use as a component of behavioral therapy. There are isolated reports in the literature that implicate dental treatment as an etiologic factor for the onset of spontaneous orofacial dyskinesia. Exposure to antipsychotics need not be long, and a minimum safe period is not apparent. This duration of neuroleptic exposure seems to be shorter for women. A longer duration of exposure to neuroleptics does not correlate with the severity of the reaction. Treatment of orofacial dyskinesia is largely with medications, which unfortunately are not highly successful.

1.8.B Disease 28: dystonia

Dystonia usually presents more as a dysfunction than as a painful disorder; however, if the dystonic contraction is strong and frequent enough, pain can result.

Clinical criteria

Dystonia presents as an involuntary briefly sustained contraction of muscles. When the dystonia involves only one or two areas of the body it is labeled a focal dystonia. For example, some patients exhibit an involuntary repetitive contraction of the orbicularis oculi muscles, which produces eye closure. This disorder has been called blepharospasm. If the cervical muscles (usually sternocleidomastoid and trapezius) contract, this is called a torticollis. There are several focal dystonic patterns involving some combination of jaw, neck, tongue, and perioral muscles and they are described as focal orofacial, orolingual, oromandibular, and cervical dystonia.[117] Frequently the patient with a significant oromandibular dystonia will have compromised mastication and be unable to function with a removable dental prosthesis (especially mandibular full dentures). Some of the severe orofacial dystonias may actually create such difficulty that patients will be unable to eat and may lose weight. If the dystonia strongly affects the tongue musculature, this may compromise the patient's ability to speak clearly. If the patient exhibits a combination of blepharospasm and jaw opening dystonia, this has been labeled Meige's syndrome.[118,119]

Etiology

Most dystonia cases are spontaneous in origin.

1.8.C Disease 29: bruxism

Bruxism is a sleep-related motor disorder that if severe can induce pain and dysfunction in the jaw structures. These changes include broken or worn teeth, TMJ derangement, TMJ arthritis, and jaw muscle pain. Between 6% and 20% of the population has been reported to exhibit bruxism. This disorder is more common in children (14%), and then generally decreases after the age of 50 years.[120] The distinction between tooth grinding and tooth clenching is not clear-cut

but the latter is thought to occur more frequently, and more in women than in men.

Clinical criteria

It is somewhat difficult to confirm or refute the presence of bruxism or clenching since patients often do not know they are grinding and certainly may not know they are clenching. Moreover, there has been no population-based study involving a large number of patients where polysomnography has been performed, and unfortunately dental wear or attrition is not always a good indicator of current bruxism or clenching.

Etiology

The etiology of bruxism is unknown.

1.8.D Disease 30: habitual parafunction and spontaneous and secondary hypertonicity

Oral parafunction includes tooth clenching, habitual cheek chewing, and gum chewing as well as generalized jaw and neck muscle tension. Sometimes patients can be seen repeatedly clenching their masseter muscles during the clinical interview.

Clinical criteria

From a scientific perspective, little definitive information exists on the problem of tooth clenching because most habitual behaviors are not deliberate acts, but are performed at the edge of consciousness. What is known is that habitual tooth clenching for nonfunctional purposes is a common behavior, it appears to be of short duration and low amplitude, and it is exhibited several times per hour in healthy control subjects of both genders. The daytime habitual jaw muscle activity reported by nonpain, healthy controls suggest the peak amplitude of these activities probably ranges between 5% and 20% of maximum voluntary contraction and the duration of tooth contact periods is probably low (less than 5 seconds per event). However, in myogenous pain subjects, this behavior increases substantially in frequency, duration, and amplitude; at present we do not have adequate data to understand or describe the range of values (frequency, duration, and amplitude) exhibited by these subjects.[121,122] Based on self-reported tooth contact data, patients with muscle pain may exhibit approximately 4 times more tooth-contact-related activities than controls without pain. While experimental studies of clenching at high or low level force can produce pain during and for a short while after the clenching task, they do not support the idea that clenching alone produces any long-term pain, and the process of myogenous pain must be more complex than simple clenching-induced muscle injury. Some patients report chronic muscle stiffness (often unilateral) that has not been classified as a specific entity. This sensation would involve small changes in stiffness and muscle tone and not be easily distinguished from background normal activity, but any clinician who examines the jaw and neck muscles in patients with chronic pain will not infrequently discover that some patients have elevated firmness and reduced mobility of their muscles.

Etiology

Like bruxism there is no specific etiology for this problem. In the orofacial region, an example of this would be what is described as elevated masticatory and cervical muscle stiffness.[123,124] The obvious neurologic conditions (e.g., stiff-man syndrome) that include muscular rigidity are usually thought to be due to an elevated level of extrapyramidal activity.[125] Moreover, normal aging has also been associated with some development of spontaneous muscle activity,[126] as have primary psychiatric disorders such as major depression and schizophrenia. There are times that this elevated jaw muscle stiffness is centrally generated and involves medication-induced alteration in extrapyramidal motor neuron activity. The drug class most often reported is chronic exposure to neuroleptic drugs.[127] Another class of medication more recently associated with motor side effects is the serotonin selective reuptake inhibitors (e.g., paroxetine, fluoxitine), which are discussed in both Chapters 8 and 19.

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Chapter 2

Top 60 most important medications used in an orofacial pain treatment center

Glenn T. Clark, DDS, MS

2.1 What is chronic orofacial pain? What is pharmacologic treatment success?

As described in Chapter 1, there are many orofacial pain (OFP) diseases, disorders, and dysfunctions and several review articles have described them.[1–8] The purpose of this chapter is to introduce and briefly review the 60 top pharmacologic treatments provided for patients with chronic OFP. While there certainly are many more than 60 medications used to help manage painful orofacial conditions, we have elected to focus on the top 60. Before reviewing the relative efficacy and evidentiary basis of these 60 medications it is appropriate to explain that the majority of patients with chronic OFP will not find a "cure" to their pain with medications but might, with medications added to physical and behavioral treatment methods, find a way to manage their pain. Some patients will ask the question, "How long will I have to take these medications?" If they were being treated for diabetes or hypertension, this question would be not be logical because these two diseases, like chronic pain, are not usually cured, but instead are managed with medications. A 2005 study examined what defines treatment success from the patient's perspective.[9] Specifically this study asked chronic-pain patients (n = 110) what they would consider a success on four dimensions (pain, fatigue, emotional distress, interference with daily activities). They described that the mean level of pain, fatigue, emotional distress, and interference with daily activities was moderately high at their first visit to the clinic, and these patients reported they would consider their treatment "successful" if their pain scores were reduced between one-half and two-thirds. The problem is that, although patients and doctors expect and hope for this level of change, the actual long-term results from treatment of chronic OFP are more modest in a large percentage of patients. The general rule with chronic pain is that the longer a patient has the pain, the lower the reduction in pain achieved with treatment.

This point is illustrated by two studies on the long-term outcomes of patients in an OFP treatment center. The first study reported on 109 consecutive patients seen in a chronic-OFP clinic.[10] This group of patients had between 4 and 9 years from their first visit to the follow-up; of the 109, 85% responded to the questionnaire. The bad news was that only 27% of patients experienced total disappearance of pain and the remaining 73% still had ongoing pain. A second study examined the outcome of a cohort of 74 patients suffering chronic idiopathic facial pain who were first seen at a chronic pain center a minimum of 9–19 years prior.[11] Of the 74 cases eligible for follow-up, 13 patients had died and 16 did not wish to participate; of the 45 remaining patients, 10 out of 45 (22%) reported that they were free of orofacial pain at follow-up and, similar to the prior study, the remaining 78% reporting ongoing pain. Based on these two studies the best that can be said is that a full cessation or cure of chronic OFP with treatment is between 22% and 25%. It almost goes without saying that the relative mix of diseases in the OFP-clinic population, the methods of treatment and the medications used, and, most important, the ability of the clinicians to explain and render care would greatly influence the long-term results. The message taken from these two studies is that most patients with chronic orofacial pain are managed not cured.

2.2 What are the top 60 medications used to manage chronic orofacial pain?

The 60 medications included in this chapter were selected because they are commonly utilized "pain" medications, but

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it is also clear that the evidentiary basis for using these medications to treat orofacial pain is limited. To illustrate this point, we searched Medline, cross-referencing the name of the drug with the words (1) pain, (2) facial pain, and (3) orofacial pain. The results (Table 2.1) show that there are many studies linking these drugs to the pain literature, but there are relatively few literature citations where these medications have been linked with OFP disorders. Another example of this point is a study published in 1995 that examined the literature available for treatment of temporomandibular disorders (TMDs).[12] This meta-analysis examined the literature from 1980 to 1992 and found more than 4000 references; however, among these only 15% were clinical studies, and only approximately 1% ($N = 55$) were randomized controlled trials that provided the type of evidence usually considered essential for evaluating the efficacy of a therapeutic modality. Based on this, the authors concluded that it was not clear whether any of the therapies currently in use for TMDs provided any benefit over placebo alone.

2.3 What has the recent literature said about pharmacologic treatment of chronic orofacial pain?

The issue of what medications are useful for TMD–OFP and various other orofacial pain disorders has been addressed in two review articles. First, a 1997 paper focused on pharmacologic therapy for TMDs and reviewed nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, antidepressants, muscle relaxants, hypnotics, and anxiolytics.[13] The review found little data on the long-term use of NSAIDs and quite a few reports on the potential side effects of these medications used in this fashion. It suggested that a short trial of an NSAID may be considered in patients with an apparent inflammatory component to their pain complaint but that after 2 weeks, if great benefit is not achieved, they should be discontinued. Regarding the use of opioids for pain, this review suggested that further studies are needed but this class of drugs has potential for those patients with chronic severe OFP. Of course, careful patient selection is necessary to rule out drug-seeking behavior or other personality disorders; careful monitoring is needed to individualize dose, thereby minimizing side effects and dose escalation; and careful attention must be paid to regulatory procedures. Regarding the use of antidepressants for chronic nonmalignant OFP, the review concluded that tricyclic antidepressants (e.g., amitriptyline or doxepin) were potentially effective used in the lower dose range. The dose of antidepressants will usually be limited by anticholinergic side effects (dry mouth, constipation, blurred vision, and urinary retention) and should be adjusted in response to individual variation in analgesic response and side effects. Regarding the use of benzodiazepines, the review was neither supportive of nor opposed to their value in treating chronic OFP, and it suggested they should not be prescribed in large amounts and that careful monitoring for dose escalation and undue dependence on these medications was warranted. This review suggested they not be used in patients with depression. However, for cases of muscle pain and trismus, they can be used but only for a 2- to 4-week course. Regarding more traditional skeletal muscle relaxants for OFP-based myogenous pain and trismus, the review concluded that these medications, like the benzodiazepines, are best used only for a brief time (e.g., 2 weeks) and in conjunction with physical therapy regimens.

In 2003, another systematic review of the literature was published that assessed the pain-relieving effect and safety of pharmacologic interventions in the treatment of chronic TMDs, including rheumatoid arthritis (RA), atypical facial pain (AFP), and burning mouth syndrome (BMS).[14] The study reported on randomized clinical trials (RCTs) on adult patients with these diseases. They found a total of 11 studies—with a total of 368 patients who met the inclusion criteria—and concluded that amitriptyline was effective in 1 study and benzodiazepine in 2 studies. They described one study that showed intra-articular injection with glucocorticoid relieved the pain of RA of the temporomandibular joint (TMJ) and another that showed the combination of paracetamol, codeine, and doxylamine was effective in reducing chronic TMD pain. Finally, this review found no effective pharmacologic treatment for BMS and interestingly only minor adverse effects were reported in these studies. The conclusion, drawn from these two review articles, is that most chronic pain medications, other than opioids, do not provide a strong therapeutic benefit and it is also critical to assess the balance between therapeutic benefit and safety for each drug for each patient.

2.4 Why should we be cautious about the current literature?

As can be seen in Table 2.1, there is a great paucity of studies on medications used specifically for orofacial pain management. Among those that exist, many are methodologically flawed and the population of patients with OFP studied was very heterogeneous. Patients with myogenous pain, for example, are often not distinguished in clinical trials from those who have TMJ disorders such as degenerative arthritis or displacement of the meniscus.[15,16] Observations by clinicians and case series often fail to use standardized methods for measurement of pain and dysfunction. The main

Table 2.1 Time-delimited Medline search (10 years, January 1, 1997–December 31, 2007)

Drug name	Classification	Orofacial pain	Facial pain	Pain
1 Morphine	Strong opioid	31	31	6228
2 Oxycodone	Strong opioid	1	1	430
3 Methadone	Strong opioid	2	2	466
4 Codeine	Medium opioid	16	17	712
5 Hydrocodone	Medium opioid	6	7	116
6 Tramadol	Analgesic	9	11	757
7 Acetaminophen	Analgesic	40	40	1466
8 Aspirin	Analgesic	17	20	1556
9 Ibuprofen	NSAID	40	40	720
10 Naproxen	NSAID	9	8	338
11 Nabumetone	NSAID	1	1	27
12 Piroxicam	NSAID	2	2	215
13 Sodium diclofenac	NSAID	4	5	1003
14 Celecoxib	NSAID	14	12	458
15 Meloxicam	NSAID	1	3	153
16 Methylprednisolone	Steroid	14	19	1024
17 Triamcinolone	Steroid	4	4	222
18 Fluocinonide	Steroid	0	0	5
19 Lidocaine	Sodium channel blocker	41	41	2595
20 Benzocaine	Sodium channel blocker	9	9	64
21 Carbamazepine	Strong anticonvulsant	22	31	345
22 Oxcarbazepine	Strong anticonvulsant	0	1	55
23 Lamotrigine	Strong anticonvulsant	4	6	172
24 Levetiracetam	Strong anticonvulsant	0	0	33
25 Zonisamide	Strong anticonvulsant	0	0	31
26 Gabapentin	Mild anticonvulsant	9	10	802
27 Pregabalin	Mild anticonvulsant	0	0	141
28 Valproate	Migraine preventative (anticonvulsant)	1	1	130
29 Topiramate	Migraine preventative (anticonvulsant)	2	3	115
30 Tizanidine	Alpha-adrenergic blocker	2	4	54
31 Sumatriptan	Migraine abortive (triptan)	4	6	429
32 Eletriptan	Migraine abortive (triptan)	0	0	74
33 Frovatriptan	Migraine abortive (triptan)	0	0	19
34 Rizatriptan	Migraine abortive (triptan)	0	0	128
35 Butalbital	Barbiturate	0	0	19
36 Dihydroergotamine	Ergotamine	1	2	61
37 Timolol	Beta-adrenergic agonist	0	0	15
38 Propranolol	Beta-adrenergic agonist	2	2	74
39 Verapamil	Calcium channel blocker	2	2	208
40 Amitriptyline	Tricyclic antidepressant	18	20	411
41 Nortriptyline	Tricyclic antidepressant	3	3	64
42 Venlafaxine	SNRI	2	2	130
43 Duloxetine	SNRI	1	1	134
44 Escitalopram	SSRI	0	0	47
45 Citalopram	SSRI	0	0	57
46 Fluoxetine	SSRI	1	1	139
47 Metaxalone	Antispasmodic	0	0	4
48 Methocarbamol	Antispasmodic	0	0	5
49 Carisoprodol	Antispasmodic (other)	0	0	11
50 Cyclobenzaprine	Antispamodic (tricyclic)	0	0	26
51 Botulinum toxin	Antispasmodic, neurolytic	23	24	685
52 Baclofen	GABA agonist	5	7	278
53 Tiagabine	GABA reuptake inhibitor	1	1	26
54 Diazepam	Benzodiazepine	3	3	224
55 Clonazepam	Antispasmodic, benzodiazepine	4	4	54
56 Alprazolam	Benzodiazepine	0	0	24
57 Indomethacin	NSAID	25	26	1012
58 Ketamine	NMDA blocker	4	6	882
59 Antivirals	Antiviral, other	5	6	266
60 Antibiotics	Macrolide antibiotic	0	1	62

GABA, gamma-aminobutyric acid; NMDA, *N*-methyl-D-aspartate; NSAID, nonsteroidal anti-inflammatory drug; SNRI, serotonin–noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

evidence of a positive treatment outcome is too often the clinician's impression of improvement or the patients' failure to seek further treatment.[17,18] Another major weakness in previous studies has been the lack of an adequate control group receiving either a placebo, a drug with known efficacy as a positive control, or no treatment. These deficiencies in study design are particularly significant given the high rate of success reported for manipulations such as placebo splints, placebo drug, sham occlusal equilibration, a positive doctor–patient relationship, and enthusiastically presented treatment.[19–21] Another factor that may affect the evaluation of treatment outcome in response to drug therapy is the fluctuating nature of orofacial pain, which may undergo remissions and exacerbations independent of treatment. The high incidence of concurrent psychological problems described in this population may also influence the onset of symptoms, reporting of pain levels, and treatment response.[22–24] For some disorders, especially those that are not neuropathic in character, many patients eventually improve even if an initial course of therapy is not successful or if they receive no treatment at all.[25] The pharmacologic management of OFP rests on the same principles that apply to all other drugs: demonstrated efficacy for the indication (chronic OFP), an acceptable side-effect liability, and safety when given for prolonged periods.

Now, if you stopped reading at this point you might conclude that few medications are proven and even fewer should be used for chronic OFP. However, this is not the case and a quick visit to a chronic pain or headache center shows that they use multiple medications to help their patients. These medications are usually given in a series of titration trials to see if the patient achieves substantial benefit without remarkable side effects. When this happens, patients' lives are changed for the better. Therefore, this chapter provides a partial description of the characteristics and possible use of the top 60 pain-related medications and reviews some of the current evidence supporting their use for the chronic OFP disorders. Detailed information about each of the 60 drugs reviewed here is provided in subsequent chapters.

2.5 Drugs 1–5: opioids (morphine, oxycodone, methadone, codeine, hydrocodone)

The first and most important category of medications for chronic pain relief is the natural and synthetic derivatives of the opium plant, labeled opioids. These medications provide pain relief because they bind to opiate receptors in the central nervous system (CNS), thus altering pain perception. Unfortunately, the opiate receptors produce other effects leading to physical and emotional dependence on these drugs with prolonged use. Among the five opioids listed here, the most commonly used in an outpatient OFP clinic are hydrocodone and codeine drugs. In the United States, hydrocodone and codeine manditorily come in combination with nonopioid analgesics when prescribed. The most common combination is with acetaminophen, aspirin, or ibuprofen. The stronger opioids (morphine, oxycodone, and methadone) are prescribed as stand-alone analgesic agents, although oxycodone also can be prescribed combined with nonopioid analgesics. There are certainly some patients attending an OFP center who are candidates for morphine, oxycodone, or methadone, especially those patients with neuropathic pain that cannot be controlled with nonopioid analgesics, anticonvulsants, and other adjunctive pain analgesics. While opioids are powerful and have a proven efficacy at reducing pain, the long-term consequence of using opioids for nonmalignant pain is controversial. One recent study examined the long-term effects of opioids on pain relief, quality of life, and functional capacity in long-term or chronic noncancer pain and reported that, while pain is certainly managed with these agents, these patients are not cured and still have substantial problems plus the additional problem caused by using a drug that produces a powerful physical dependence.[26] For these reasons, the chronic use of opioids for patients with persistent orofacial pain requires careful patient selection to rule out those patients who might be exhibiting drug-seeking behavior or other personality disorders that would make opioid contraindicated. Logically any patient who is a candidate for opioid use must fully understand the drug-dependence issues that long-term use entails. When opioids are used, the cautious clinician will perform careful periodic monitoring of the patient while individualizing the patient's dose. Steps that a pain-knowledgeable dentist or physician should follow when prescribing opioid medications are given in Chapter 4. Only by this process can side effects be minimized, and abuse and dose escalation prevented.

2.6 Drug 6: analgesic (tramadol)

Tramadol is a centrally acting synthetic codeine analog that was approved by the US Food and Drug Administration (FDA) in 1995 for moderate to moderately severe pain. It is not categorized as a Schedule II or III drug and is currently categorized as a nonopioid analgesic, so it does not have a narcotic schedule classification. For all of these reasons, tramadol is being discussed seperately from the other opioids. Tramadol comes either alone or in combination with nonopioid analgesics such as aspirin, acetaminophen, and ibuprofen. Even though it is classified by the FDA as a nonopioid analgesic, this drug does bind to the μ-opioid

receptor in the CNS. It also acts like a tricyclic antidepressant agent causing inhibition of serotonin and norepinephrine at the synaptic cleft.[27,28] The effects of these actions (μ-opioid binding and serotonin–norepinephrine reuptake inhibition) both produce inhibition of the ascending pain signals and can activate the descending pain inhibitory pathway. Tramadol's opioid affinity and activity are also substantially less than those of morphine. Due to tramadol's (albeit weak) opioid activity, there have been questions about potential abuse. A proactive surveillance program revealed that the vast preponderance of patients who abuse tramadol have a previous record of substance abuse.[29]

2.7 Drugs 7 and 8: analgesics (acetaminophen, aspirin)

The World Health Organization (WHO) recommends nonopioid analgesics for the initial treatment of pain. The three most common analgesics that do not have opioid receptor binding action are aspirin, acetaminophen, and the nonsteroidal anti-inflammatory drugs (NSAIDs). Generally the WHO analgesic ladder is designed for acute pain management and unfortunately this organization does not modify its recommendations for chronic pain. This is a problem since, although aspirin (acetylsalicylic acid) is an important analgesic for acute pain, it does not appear appropriate for chronic pain use because of the known gastropathic-inducing side effects (gastric irritation and nausea). The same concern (induced gastropathic disease) also exists for NSAIDs. Nevertheless, aspirin is widely available and used for pain since it is an over-the-counter product. The primary mechanism of action of aspirin is that it inhibits prostaglandin synthesis and acts on the hypothalamus to reduce fever. When nociceptive fibers are being stimulated by an endogenous inflammatory reaction in the peripheral injury site, prostaglandin is a critical component of the inflammatory cascade of events. For this reason inflammatory pain is effectively blocked by aspirin. A review article on aspirin as a postoperative analgesic suggests it is effective but has substantial side effects, even in short-term use.[30] This meta-analysis examined 72 studies where aspirin was compared with other analgesic agents or placebo agents. These studies included in total over 6550 subjects divided between those receiving placebo and those getting the active agents. These studies were all short term because the primary use of aspirin is for postoperative pain. Aspirin was found to be significantly superior to placebo with single oral doses of 600 or 650 mg, 1000 mg, and 1200 mg.

Of course aspirin is used by patients with chronic pain and especially by patients with episodic pain due to headache, sometimes resulting in benefit and sometimes harm. One study examined the efficacy and tolerability of aspirin versus placebo for the acute treatment of a single acute attack of migraine.[31] This prospective, randomized, double-blind, parallel-group, placebo-controlled study evaluated the efficacy of a single, 1000-mg dose of aspirin for the treatment of acute moderate-to-severe migraine, with or without aura. Again this study examined only the short-term efficacy of aspirin, looking at headache pain response at 2 hours. Of 485 enrolled subjects with migraine attacks, 201 used aspirin and 200 used placebo. The 2-hour headache response rate was 52% with aspirin versus 34% with placebo ($P < 0.001$). Aspirin was significantly more effective than placebo for pain reduction beginning 1 hour after dosing ($P < 0.001$) and continuing throughout the 6-hour evaluation period. This study demonstrated that aspirin used in this fashion was safe and effective for treatment of acute migraine in appropriately selected patients.

Acetaminophen is another over-the-counter nonopioid analgesic used by pain patients. Like aspirin, this drug is an important analgesic for acute pain and if used at levels that are nontoxic, it can be used for chronic pain. Although acetaminophen does not cause gastropathy as a side effect, the major concern is that it is not uncommon for patients to inadvertently take more than the maximum daily dose (4000 mg/day) and produce a liver toxicity that causes rapid irreversible liver damage, which can be fatal.[32] Acetaminophen's primary mechanism of action is that it inhibits prostaglandin in the CNS and peripherally blocks pain-impulse generation, and it acts on the hypothalamus to reduce fever.[33] A recent meta-analysis examined this drug, assessing 46 clinical studies that compared acetaminophen and placebo.[34] These studies in total included 2530 subjects who received acetaminophen and 1594 who received placebo, and its value above and beyond placebo is well established. Both aspirin and, to a much greater extent, acetaminophen and its European equivalent, paracetamol, are used as headache abortive agents; depending on the frequency of the headaches, this can mean daily use of these drugs. A recent study examined the effectiveness of a nonprescription combination of acetaminophen, aspirin, and caffeine at alleviating migraine headache pain.[35] The study was a triple double-blind, randomized, parallel-group, single-dose, placebo-controlled experiment that included migraineurs with moderate or severe headache pain. The study enrolled 1357 patients; 1250 took study medication and 1220 were included in the efficacy-evaluable data set. The results showed that significantly greater reductions in migraine headache pain intensity occurred 1–6 hours after dose in patients taking the acetaminophen–aspirin–caffeine combination than in those taking placebo. Pain intensity was reduced to mild or none 2 hours after dose in 59.3% of the 602 drug-treated patients compared with 32.8% of the 618 placebo-treated patients

($P < 0.001$). In addition to the obvious efficacy, this drug combination also has an excellent safety profile and is well tolerated. Unfortunately, because it has a good effect for episodic headaches, over-the-counter analgesic medication sometimes is overused and this can lead to a disorder called medication overuse headache. The basic concept behind this is that analgesic use can cause central sensitization of the trigeminal and somatic nociceptive systems, and these changes are thought to occur in the cerebral supraspinal structures.[36]

2.8 Drugs 9–15: NSAIDs (ibuprofen, naproxen, nabumetone, piroxicam, sodium diclofenac, celecoxib, meloxicam)

In this category, we have selected for inclusion five commonly used nonspecific cyclooxygenase (COX) inhibiting nonsteroidal anti-inflammatory drugs for arthritis pain (ibuprofen, naproxen, nabumetone, piroxicam, and sodium diclofenac) and two cyclooxygenase-2 (COX-2) specific inhibiting medications (celecoxib, meloxicam). Like aspirin, these drugs are used for acute pain and for phasic arthritic pain. The primary mechanism of action of all of the NSAIDs reviewed here is that they inhibit prostaglandin synthesis by decreasing the activity of the cyclooxygenase enzyme. The main drawback of the five nonspecific COX-inhibiting NSAIDs when used continuously is that they cause gastropathy (gastric irritation and nausea).[37] Retrospective studies have established an association between increased risk of upper gastrointestinal bleeding and ingestion of aspirin or NSAIDs.[38–40] This side effect is less likely with the two COX-2 inhibitors, but they have the added side effect of an increased risk of cardiac damage.[41] Nevertheless, NSAIDs are used widely for both headache and arthritic pain since two of them (ibuprofen and naproxen) are available as an over-the-counter product. Considering the adverse effects of long-term use of NSAIDs, and the lack of clinical evidence demonstrating a therapeutic effect for these nonopioid analgesics in the symptomatic treatment of myalgia or fibromyalgia, this must be weighed against the potential for serious toxicity with chronic use for myogenous-based disease.

A short trial of an NSAID may be considered in patients with an apparent TMJ inflammatory component to their pain complaint, but a lack of therapeutic effect after a 7- to 10-day trial or the development of any gastrointestinal symptoms should prompt discontinuation of the NSAID. Patients with risk factors for gastrointestinal or kidney disease should be managed cautiously with NSAIDs or acetaminophen and should not take these drugs for prolonged periods of time. For those patients with gastritis the possibility exists for them to use a topical NSAID, and a recent study examined the efficacy and tolerability of a topical ketoprofen patch in the treatment of uncomplicated ankle sprain.[42] Of course it would be more relevant if such data were available for TMJ strain, but such data is not available. Nevertheless, for ankle strain, a randomized, double-blind, placebo-controlled, multicenter, 2-week trial was performed on 163 subjects. Pain levels were the primary outcome measure and it was found that the ketoprofen patch was better than placebo. Specifically ketoprofen demonstrated a greater reduction in pain after 7 days than those assigned to placebo. Adverse events (mostly local skin reactions) occurred in 30.9% of the ketoprofen group and in 24.4% of the placebo group.

The safety of COX-2 selective NSAIDs such as celecoxib and meloxicam has received great attention in recent years. A 2008 review examined the clinical effectiveness of several COX-2 selective NSAIDs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib, and lumiracoxib) for osteoarthritis (OA) and rheumatoid arthritis (RA).[43] This review included only randomized controlled trials and the authors concluded that, although the COX-2 selective NSAIDs as a class of medications offered protection against serious gastrointestinal events, the amount of evidence for this protective effect varied considerably across individual drugs. The relative cardiovascular safety also varied substantially between COX-2 selective NSAIDs. An increased risk of myocardial infarction (MI) compared with nonselective NSAIDs was observed among those drugs with greater volume of evidence in terms of exposure in patient-years. There is no study that has examined meloxicam for TMJ-related arthritis or pain, but a 2004 study on TMDs did examine the relative efficacy of celecoxib versus naproxen and placebo in a randomized controlled clinical trial.[44] This study included 68 subjects with painful TMJs secondary to disk displacement with reduction (DDWR). The results showed that naproxen significantly reduced the symptoms of painful TMJ–DDWR as determined by most efficacy measures and also showed a significant improvement in pain intensity during the study. Celecoxib and naproxen were equally well tolerated, with similar numbers of reported adverse effects. In conclusion, the final choice to use a COX-2 selective NSAID or a nonselective NSAID is left up to the practitioner, who will weigh the risk versus benefit of the medication.

2.9 Drugs 16–18: corticosteroids (methylprednisolone, triamcinolone, fluocinonide)

Three commonly used corticosteroids are methylprednisolone, triamcinolone, and fluocinonide. The first agent is often given systemically or via injection for acute pain and

inflammation.[45] The second agent is also available for systemic use, but it is more commonly used as an intracapsular injection for joint pain or as a topical application for skin reactions where inflammation is present. These agents are powerful anti-inflammatory agents and, like aspirin, are used for acute pain and even sometimes for chronic pain, but they are not specifically FDA approved for pain. They are approved for a wide variety of inflammatory diseases, including autoimmune disease (e.g., erosive lichen planus, pemphigus, graft-versus-host disease, rheumatoid arthritis). Like aspirin and NSAIDs these agents when used continuously will cause gastropathy (gastric irritation and nausea) as well as many other major side effects. Both methylprednisolone and triamcinolone are generally used short term either as a systemic dose for inflammatory disease or as an injectable agent for arthritic pain. Only occasionally will these agents be used chronically and then in generally lower doses. The primary mechanism of action of these two agents is to decrease inflammation by suppression of migration of leukocytes and reversal of increased capillary permeability. By producing a general suppression of the immune system, inflammatory-related pain is effectively blocked.

The third corticosteroid in this category is fluocinonide, and a recent double-blind clinical trial examined the efficacy of topical steroids for treatment of chronic oral vesiculoerosive disease.[46] This study compared two potent topical corticosteroids (clobetasol propionate and fluocinonide ointment in orabase) as treatments for controlling oral vesiculoerosive diseases. Sixty patients were included (43 women and 17 men) and final data were available for 55. The study duration was 28 days and outcomes included pain, erythema, atrophy, and size of lesion. The results showed that both medications had a beneficial effect in the control of symptoms and signs of oral vesiculoerosive diseases with minimal side effects, although candidiasis was observed in 13 patients at the end of treatment in this population. The authors suggested concurrent antifungal therapy is indicated in some cases.

2.10 Drugs 19 and 20: local anesthetics and sodium channel blockers (lidocaine, benzocaine)

The anesthetics lidocaine and benzocaine are both membrane stabilizing agents that work by blocking voltage-gated sodium channels. Local anesthetic agents have been shown to effectively treat neuropathic pain in animal models.[47] Clinically, neuropathic pain states respond transiently to intravenous infusion of lidocaine, but unfortunately the effect is only present during the infusion. There are two clinically available cutaneous local anesthetic preparations: (1) EMLA cream (AstraZeneca, Wayne, PA), which is a eutectic mixture of the local anesthetics lidocaine and prilocaine, and (2) Lidoderm (Endo Labs, Chadds Ford, PA), which is a 5% lidocaine patch.[48,49] Although EMLA is useful for venipuncture and cutaneous biopsy, it has not found a role in chronic pain management.[50] In contrast, the topical 5% lidocaine patch may be useful in management of peripheral neuropathic pain conditions. An open-label trial showed that the patch gave moderate or better pain relief in 81% of a small group of patients with cutaneous refractory neuropathic pain states.[51,52] Controlled studies are continuing, but the Lidoderm patch has been approved by the FDA for treatment of postherpetic neuralgia. The dose is one patch to the affected area every 12 hours, and serum levels are insignificant. In general lidocaine and even benzocaine are safe to use topically, but there is a risk of methemoglobinemia.[53]

2.11 Drugs 21–25: anticonvulsants (carbamazepine, oxcarbazepine, lamotrigine, levetiracetam, zonisamide)

In this category are five antiepileptic drugs (AEDs), which are also called anticonvulsants, that are known to depress abnormal neuronal discharges and raise the threshold for propagation of neural impulses. AEDs have been found to have therapeutic efficacy in all neuropathic pain, including orofacial neuropathic pain states. The most frequently used is carbamazepine, which has been the drug of choice, for many years, for treating trigeminal neuralgia.[54] These agents do not have an FDA narcotic schedule classification but have significant clinical toxicity nonetheless. These five agents reviewed here (carbamazepine, oxcarbazepine, lamotrigine, levetiracetam, zonisamide) are approved for control of epileptic seizures, and carbamazepine is approved for trigeminal neuralgia as well. Carbamazepine and oxcarbazepine are the mainstay of trigeminal neuralgia therapy. Oxcarbazepine is a ketocarbamazepine and its metabolite is the active agent and has many of the therapeutic properties of carbamazepine, while avoiding its toxicities, but it is off-label when used for trigeminal neuralgia. The primary mechanism of action of carbamazepine and oxcarbazepine is based on their ability to block voltage-gated Na^+ channels and modulating voltage-activated Ca^{++} currents as well. Since this disease is stimulation triggered, pain is suppressed when neuronal excitability is attenuated. Unfortunately, carbamazepine is a self-inducing drug, which means it acts to stimulate the liver enzymes that metabolize it. The end result is that after several weeks of continuous use the drug level in the blood drops as it is metabolized much faster, so the dose must be increased. The substantial advantage of oxcarbazepine is that it is not a self-inducer so once a dose is established it is more stable. Since there are known adverse effects on liver function the starting dose is 200 mg twice a day (b.i.d.) and the patient's dose is titrated upward to the effective dose

range from 400 to 1000 mg/day. The most common side effects are drowsiness, diplopia, and unsteadiness. Aplastic anemia occurs in 1:200,000; reversible leukopenia and thrombocytopenia are more common. Published reports have shown efficacy in trigeminal neuralgia.[55] For oxcarbazepine, the starting dose is 300 mg at bedtime, with weekly increases of 300–600 mg/day up to a maximum of 1200–2400 mg/day.

2.12 Drugs 26 and 27: anticonvulsants (gabapentin, pregabalin)

The two anticonvulsants discussed here, gabapentin and pregabalin, are distinct from the previously discussed anticonvulsants since they have much less risk of adverse events when used in pain patients. Gabapentin has been in use since 1994 and pregabalin was approved in 2005. Both have been used frequently for suppression of neuropathic pain. These agents do not have an FDA narcotic schedule classification and are approved for control of epileptic seizures. Pregabalin is also approved for diabetic peripheral neuropathy. These drugs have a low toxicity and exhibit few interactions since neither is metabolized and both are excreted in urine unchanged. Caution must be used in any patient with compromised renal function. Moreover, because gabapentin is not approved for neuropathic pain it is used off-label. The mechanism of action of gabapentin is uncertain, but most likely gabapentin acts similarly to pregabalin, which is known to affect a central voltage-dependent L-type Ca^{++} channel. Unfortunately neither of these drugs can stop neuronal activity, only suppress it, so efficacy of these agents for pain is limited. The most common side effects of gabapentin and pregabalin are drowsiness, somnolence, nausea, and fatigue. The common adverse side effects are usually self-limiting and subside after a couple of weeks, allowing gradual dose escalation. The usual starting dose for gabapentin is 100–300 mg/day taken at bedtime. The dose is gradually increased to 1200 mg/day and is taken over 10–15 days in a divided dose schedule. Some patients may require 3600 mg/day for a clinical effect. The starting dose for pregabalin is 150 mg/day and maximum dose is 300 mg/day. After the initial titration and adjustment period, these drugs can be switched from before sleep to dosing on a three-times-a-day schedule.

2.13 Drugs 28–30: chronic daily headache preventatives (valproic acid, topiramate, tizanidine)

This category includes three medications that are used as headache preventative agents. The first two are anticonvulsants and the third is an alpha-adrenergic agonist. Valproic acid is an anticonvulsant that has been shown to be effective in prophylaxis of migraine headache.[56] It blocks voltage-gated Na^{+} channels as carbamazepine and phenytoin do, but it also increases levels of aminobutyric acid (gamma-aminobutyric acid [GABA]) by decreasing its degradation. Side effects include nausea, vomiting, sedation, ataxia, rash, alopecia, and appetite stimulation. Forty percent of patients experience elevated transaminase levels, and 1 patient in 50,000 develops hepatic failure.

Topiramate was approved for use in 1997 and it has shown promise for cluster headache and diabetic neuropathy.[57] Topiramate is a unique monosaccharide compound structurally unlike other AEDs. It potentiates GABA responses, significantly increasing central nervous system GABA levels, and also blocks the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) kainate excitatory receptor. Topiramate is also a weak carbonic anhydrase inhibitor. The effective dose range is 200–400 mg/day b.i.d. The dose is 25 mg b.i.d. and is increased 50 mg per week up to the dose range. Side effects include unusual CNS effects such as abnormal delusional and psychotic thinking. Occasionally, patients develop renal stones. These side effects are rare, occuring in less than 2–3% of patients, but are troubling to those patients.

Tizanidine is an alpha-adrenergic agonist that has both a peripheral and a central mechanism of action in migraine headache. A recent literature review examined the relative value of various medications, including tizanidine, as preventative treatment for chronic migraine or tension-type headaches.[58] The author concluded that the literature demonstrated that use of tizanidine as a preventative treatment of chronic daily headache was better than placebo therapy. The author noted that it is often used in combination with a long-acting NSAID to aid in the treatment of medication rebound headache.

2.14 Drugs 31–34: migraine abortives (sumatriptan, eletriptan, frovatriptan, rizatriptan)

The triptan medications have been described as miracle drugs for episodic migraine sufferers. Although they are moderately expensive, do not always work, and the patient may not be able to tolerate the medications' side effects, the introduction of triptans has essentially changed how new migraine patients are now managed. For example, one study compared pharmacoepidemiology of headache treatment in two different groups. In one group were patients ($n = 612$) who were attending a headache center for their first visit; in another group were chronic headache patients ($n = 620$)

attending a headache specialty center for a follow-up treatment.[59] Most of these headache patients suffered from migraine. The vast majority of patients in the first-visit headache group were either taking drugs prescribed by a doctor (49.4%) or taking over-the-counter analgesics (41.5%), but only 9.1% were not taking any drug. Of the recall headache patients 81.3% were taking prescription drugs; 15.8%, over-the-counter analgesics; and 2.9%, not taking any drugs. Triptans were being used by only 9.1% of the first-visit group, whereas 31.8% of the recall chronic headache patients were using triptans. Amitriptyline was the drug most commonly used for prophylaxis among these patients.

2.15 Drugs 35 and 36: miscellaneous migraine medications (butalbital, dihydroergotamine)

Two older medications are still commonly used for recurrent episodic and chronic headaches. Butalbital is the main agent in a combination drug that also contains acetaminophen and caffeine. It is categorized as an analgesic but chemically is a barbiturate and as such has many of the adverse events and dependence complications associated with this class of drug. A 2002 study examined the amount of health resources utilized by patients who repeatedly use emergency department (ED) services for headache care.[60] The study included data on 54 subjects who were classified as "repeaters," representing over 10% of the 518 patients who visited the ED for primary headache complaints. This group of repeating patients produced over 502 visits (50% of total visits) during the study period. Pharmacy rosters showed use of opioids in 41 of these patients and butalbital products in 27 patients. The authors concluded that opioids and butalbital did not seem to provide a successful approach to the recurrent migraine or tension-type headache problems.

In agreement with the ED-utilization study are two reports that discuss the problems of using opioids and barbiturates for headache management. The first study examined the national trends of prescription medication use for headache[61] using secondary analysis of data obtained during the 2000 Medical Expenditure Panel Survey, a representative survey of the noninstitutionalized population in the United States. These authors reported that 46% of patients reported using at least one medication for the treatment of headache and migraine-specific abortive medication (i.e., selective serotonin receptor agonists and ergotamine derivatives) were the most frequently (36%) used medications. Opiate analgesics and butalbital-containing products were reportedly prescribed for 22% and 17% of survey respondents, respectively. The second report is a review of the literature on butalbital-containing drugs for migraine.[62] This study describes a qualitative systematic literature search that reported 14–36% of diagnosed migraineurs are prescribed butalbital-containing products, often as initial therapy, in spite of the fact that the only identified controlled trial of these drugs for migraine treatment showed that butalbital-containing products were inferior to butorphanol (an opioid). The article discusses guidelines published by a consortium of US headache specialists; they discourage administration of butalbital-containing products for migraine due to serious dependence issues with this medication.

Finally, a single-center open-label pilot study evaluated the efficacy of dihydroergotamine for migraine headaches with allodynia.[63] This drug is occasionally used for severe migraines when a patient is nonresponsive to a triptan medication, rather than giving the patient an opioid to control the pain. The study involved nine patients who were treated on two occasions for episodic migraine with allodynia using dihydroergotamine 1.0 mg administered via an intramuscular injection. The authors concluded that, whether they took the dihydroergotamine early or late in the attack, most patients (>55%) had headache relief within 2 hours, and at least 44% of patients achieved headache-free status by 8 hours postdose. The authors suggested a large, placebo-controlled trial of dihydroergotamine in allodynic patients was warranted.

2.16 Drugs 37–39: miscellaneous headache preventatives (timolol, propranolol, verapamil)

Beta-adrenergic receptor blockers and calcium channel blockers have been used for many years to help prevent chronic and frequent migraines. A recent open-label study examined the efficacy of combining a beta-blocker plus topiramate in migraine patients previously resistant to the two medications in monotherapy.[64] Those patients who had not responded to a beta-blocker or topiramate received combined treatment and 58 patients completed the study. Of these, 33 (57%) met criteria for chronic migraine or medication overuse headache, 18 (31%) for migraine without aura, and 7 (12%) for migraine with aura. The results showed that 10 patients (17%) discontinued due to adverse events but 36 of the other 48 patients who tolerated the combination showed a greater than 50% reduction in frequency of headache. The authors concluded that the combination of beta-blocker plus topiramate showed a benefit in around 60% of patients who had not previously responded to monotherapy but that adverse events led to discontinuation in one out of six patients.

Calcium channel blockers such as verapamil have been used for migraine and cluster headache prophylaxis. A

review of the literature by a European Federation of Neurologic Societies task force on treatment of the trigeminal autonomic cephalalgias included cluster headache, paroxysmal hemicrania, and SUNCT syndrome (short-lasting unilateral neuralgiform headaches).[65] They concluded that the literature supported the use of oxygen (100%) with a flow of at least 7 L/min over 15 minutes and 6 mg subcutaneous sumatriptan for the acute treatment of cluster headache. Prophylaxis of cluster headache was best performed with verapamil at a daily dose of at least 240 mg (maximum dose depends on efficacy or tolerability). Finally, they noted that, although the quality of the studies was lower, the use of corticosteroids (100 mg methylprednisone or an equivalent corticosteroid given orally or intravenously at up to 500 mg/day over 5 days then tapering down) was another method of managing cluster headache.

2.17 Drugs 40 and 41: tricyclic antidepressants (amitriptyline, nortriptyline)

Often described as adjunctive pain medications, the tricyclic antidepressant (TCA) drugs have been used for more than 30 years for the management of pain from a wide variety of conditions, including chronic orofacial pain.[66] The biomedical literature supports the clinical use of antidepressants for chronic nonmalignant pain when other treatments have failed or if depression accompanies the pain. Tricyclic antidepressants with both serotinergic and noradrenergic effects (e.g., amitriptyline, nortriptyline) appear to be most effective. There are multiple tricyclic medications that are useful alternatives to amitriptyline and have some differences in side-effect profiles and half-lives. For example, desipramine, the least anticholinergic and sedative of the TCAs, showed pain relief after 3 weeks, independent of mood alterations in a placebo-controlled RCT of 26 patients with postherpetic neuralgia.[67] Nortriptyline seems to be better tolerated than amitriptyline, using a starting dose of 10 mg at bedtime, increased after 3–5 days to 20 mg at bedtime, and then carefully titrated. A 2006 study compared whether selective serotonin reuptake inhibitor (SSRI) antidepressants were associated with an increased or decreased risk of cardiovascular adverse events (AEs).[68] The study examined the published literature and defined serious AEs as death due to a cardiovascular cause, heart failure, stroke, transient ischemic attack, and myocardial infarction. Nonserious adverse events were defined as palpitations, chest pain, angina, arrhythmia, hypertension, hypotension–syncope, and unspecified cardiovascular or neurologic events. Adverse event rates were calculated for four medication groups: (1) SSRIs, (2) TCAs, (3) other active therapies but not an SSRI or TCA, and (4) placebo. The authors reported that they were unable to detect differences in AE rates between SSRI and placebo for both serious and nonserious AEs. There were more nonserious AEs for TCAs versus SSRIs.

2.18 Drugs 42 and 43: serotonin–norepinephrine reuptake inhibitors (venlafaxine, duloxetine)

Duloxetine and the similar but older drug venlafaxine have been used both for chronic muscle pain and for neuropathic pain. There are two studies that examine duloxetine efficacy for fibromyalgia.[69,70] Using American College of Rheumatology (ACR) criteria, both studies enrolled patients with fibromyalgia and with at least moderate pain, and both had sensible exclusions. One dealt exclusively, and the other predominantly, with women. In the 532 randomized women, 38% had at least 50% improvement in pain over 12 weeks with 60 mg duloxetine (once or twice a day), compared with 21% for placebo. There were improvements in quality of life, but with more adverse events for duloxetine, especially nausea and dry mouth.

2.19 Drugs 44–46: selective serotonin reuptake inhibitors (escitalopram, citalopram, fluoxetine)

Clinically, it is well known that chronic pain induces depression, anxiety, and a reduced quality of life. Several animal studies of experimental neuropathic pain have demonstrated development of anxiety-like behavior with changes in opioidergic function in the CNS.[71] In a follow-up study, the anxiolytic-like effects of several types of antidepressants were examined on a chronic neuropathic painlike state.[72] The study used a sciatic nerve–ligated mouse model that demonstrated thermal hyperalgesia and tactile allodynia. Administration of the TCA imipramine, the serotonin–noradrenaline reuptake inhibitor (SNRI) milnacipran, and the selective serotonin reuptake inhibitor (SSRI) paroxetine showed a reduction in anxiety behavior in the mice after medication. These antidepressants also produced a significant reduction in thermal hyperalgesia and tactile allodynia. The authors concluded that serotonergic antidepressants were effective for treating anxiety associated with chronic neuropathic pain. Another study compared the use pattern of an SSRI (paroxetine or citalopram) versus an anticonvulsant medication (gabapentin) on 101 painful diabetic neuropathy patients.[73] The authors reported that, over a 6-month study period, the patients receiving SSRIs reported greater

satisfaction and fewer concerns with the side effects of their treatment ($P < 0.05$) compared with the patients taking gabapentin. There was statistically significant better mood in the SSRI group, but overall, 43.5% and 40.5% of those taking SSRIs and gabapentin, respectively, noticed no effect of the medication on their pain. The authors concluded that the lack of negative effects on quality of life, better compliance, and comparable efficacy of SSRIs on patient mood suggest that these drugs may be considered as alternatives to gabapentin in painful diabetic neuropathy.

2.20 Drugs 47–49: muscle relaxants (metaxalone, methocarbamol, carisoprodol)

Muscle relaxants or antispasmodics are often used as adjuvants for patients with chronic musculoskeletal pain, but the clinical evidence for their long-term use in true chronic pain states is weak. Two agents that are commonly used for short-term masticatory muscle spasm and pain are clonazepam and carisoprodol. These two agents are thought to reduce skeletal muscle tone because of their anxiolytic effects. Clonazepam is a benzodiazepine-type medication and is used for the treatment of certain types of seizures. It is also used in painful conditions, including myoclonus and muscle spasms. Clonazepam acts by enhancing the GABA-induced increase in chloride conductance. Side effects include sedation, lethargy, ataxia, and dizziness. Carisoprodol, one of the oldest drugs of this class, most likely acts centrally to depress polysynaptic reflexes.[74] It was first evaluated for chronic OFP in a study published in 1960.[75] Because some of these drugs may have a potential for dependence, determining the daily dosage and duration of treatment requires a careful doctor–patient discussion and mutual agreement. The clinician should consider alternative nonpharmacological treatment options, such as physiotherapy (with myofascial release techniques), massage, relaxation–biofeedback techniques, or acupuncture. There is insufficient evidence to assist clinicians in a rational approach to the use of these muscle relaxants as antispastic treatments to provide analgesia.

Overall, the scientific literature does not provide unequivocal support for either the use of benzodiazepines or their condemnation on the basis of lack of efficacy or potential toxicity. Like all drugs, they should only be used in patients whose symptoms are suggestive of potential efficacy and should not be prescribed in large amounts that would permit dose escalation without professional supervision or the development of dependence with long-term therapy. Patients whose pain appears to be of musculoskeletal origin may benefit from a 2- to 4-week course of a benzodiazepine, possibly in combination with an NSAID. A lack of efficacy or the onset of sedative side effects or depressive symptoms should be an indication to reduce the dose or discontinue the benzodiazepine. If difficulties in sleep onset or duration are the primary complaint, consideration should be given to the use of a benzodiazepine indicated for hypnosis (triazolam) to minimize drug effects during the day. Patients who appear to have depressive symptoms before therapy should be referred to a psychiatrist for consultation and possible antidepressant therapy rather than being prescribed a benzodiazepine with putative antidepressant properties. In any event, therapy with a benzodiazepine should not be extended beyond a few weeks, because the natural course of myofascial pain combined with conservative therapy will likely result in a lowering of symptomology to acceptable levels, which would not justify the risks of pharmacologic intervention. Patients for whom such a therapeutic course fails should be reevaluated for additional physical medicine and behavioral therapy rather than being "managed" with long-term benzodiazepine treatment.

2.21 Drug 50: antispasmodic (cyclobenzaprine)

Cyclobenzaprine is an antispasmodic drug that has less abuse potential than clonazepam or carisoprodol and it is thought to be partially effective for some chronic musculoskeletal disorders.[76] For example, cyclobenzaprine has been found to be superior to placebo for pain in the cervical and lumbar regions associated with skeletal muscle spasms[77] and reduces electromyographic signs of muscle spasm.[78] Although it has not been directly assessed for TMDs, these findings are suggestive of efficacy for muscle relaxation in the orofacial region.[79,80] There appears to be a discrepancy between the common clinical use of skeletal muscle relaxants and the results of controlled clinical trials evaluating their efficacy in comparison with placebo. It is also not clear whether they are specific for muscle relaxation or produce nonspecific CNS depression, thereby reducing muscle tone. Little supporting evidence exists for their efficacy in chronic OFP of myogenous origin, nor is it clear if they provide an additive effect with exercises or splint therapy aimed at muscle relaxation. Given this modest scientific support, clinicians should probably limit the use of skeletal muscle relaxants to a brief trial in conjunction with physical therapy regimens. Further studies are needed to document efficacy for chronic OFP in comparison with an active placebo with sedative properties to help differentiate nonspecific sedative properties from muscle relaxation. Five randomized trials were included in a meta-analysis, but neither the trials nor the review provided conclusive evidence.[81]

2.22 Drug 51: antispasmodic (botulinum toxin type A)

Botulinum toxins are potent neurotoxins produced by *Clostridium botulinum* that block acetylcholine release at the neuromuscular junction. *Clostridium botulinum* was first identified as a causative agent in food poisoning in 1895 and, by the 1920s, isolation of a relatively crude form of toxin had occurred. A crystalized form of the A subtype, BTA, became available and stimulated scientific interest. The FDA approved botulinum toxin type A for the treatment of strabismus in 1989.[82] With appropriate dosing, the injected muscle's motor function is only partially blocked. These effects occur within a few days to 2 weeks after injection and they last from 6 weeks to 6 months, but the typical duration is 2–3 months.[83] During the peak effect, histologic studies show evidence of atrophy, but fiber size and function return to normal, even after multiple cycles of injection and recovery.[84] Botulinum toxin type A has been approved by the FDA for use in painful orofacial and craniocervical muscle hyperactivity syndromes, including cervical dystonia (torticollis) and hemifacial spasm.[85] The recommended treatment interval between injections is at least 3 months and numerous studies confirm that injecting multiple sites within a muscle improves spasticity relief and decreases side effects. Most recently it has been shown helpful for chronic migraine problems that do not respond to medications, but this is an off-label use of this medication. There is much ongoing research on the efficacy of and indications for these injections for other conditions, including nonspastic neuropathy and even trigeminal neuralgia.[86] Evidence suggests these injections are best used for conditions where a clear-cut muscle spasticity is present; the literature on botulinum toxin type A for nonspastic pain disorders is unconvincing. A 2003 review of the literature examining preventative treatments for patients with chronic migraine or tension-type headaches, including botulinum toxin injections, concluded that this agent has some efficacy for medication-resistant chronic migraine sufferers but not for chronic tension-type headache patients. Fortunately, there are relatively few significant adverse events seen with the use of botulinum toxin type A in headache treatment.

2.23 Drugs 52 and 53: GABA-ergic drugs (baclofen, tiagabine)

Drugs that target $GABA_A$ and $GABA_B$ receptors are proven to suppress motor activity and also play a role in pain suppression. Baclofen is a GABA agonist and tiagabine is a selective GABA reuptake inhibitor. While there has been very limited research on the use of baclofen for prevention of chronic daily headache, this agent acts centrally via $GABA_A$ receptors, in migraine and cluster headache. The two open trials conducted to date both support the use of baclofen for the preventative treatment of headache. Tiagabine is both an anxiolytic and an anticonvulsant GABA reuptake inhibitor commonly used as an add-on treatment for refractory partial seizures. This drug has also been reported to have some value in the suppression of bruxism in severe cases.[87] A case report described that in four of the five cases tiagabine was able to effectively suppress nocturnal bruxism, trismus, and consequent morning pain in the teeth, masticatory musculature, jaw, and temporomandibular joint areas. Tiagabine has a benign adverse-effect profile, is easily tolerated, and retains effectiveness over time. Bed partners of these patients report that grinding noises have stopped; therefore, the tiagabine effect is probably not simply antinociceptive, but motor suppressive. The doses used to suppress nocturnal bruxism at bedtime (4–8 mg) are lower than those used to treat seizures, but additional data is needed on this drug for this off-label indication. Tiagabine has also been suggested to be of value for anxiety and for patients with pain-induced anxiety. Overall, tiagabine is generally well tolerated and not associated with changes in sexual functioning or depressive status.[88]

2.24 Drugs 54–56: benzodiazepine drugs (diazepam, clonazepam, alprazolam)

A 2004 study reported on a randomized blinded controlled trial of the effect of topical clonazepam on burning mouth pain.[89] The study included 48 patients of whom 41 completed the study. The 14-day-long protocol had the patients suck a 1-mg tablet of either clonazepam or a placebo three times a day. They were told to hold the dissolved medication–saliva mix near the pain sites in the mouth, without swallowing, for 3 minutes and then to spit. The clonazepam treatment was reported to yield significantly reduced pain versus the placebo and with negligible blood level of the clonazepam. A 1997 study examined the clinical efficacy and side effects of ibuprofen and diazepam on chronic myogenous facial pain in a double-blind, randomized, controlled clinical trial.[90] The study included 39 subjects (35 women, 4 men) with daily or near-daily orofacial pain of at least 3 months' duration and tenderness to palpation of masticatory muscles. The treatment groups included placebo, diazepam, ibuprofen, and the combination of diazepam and ibuprofen. Pain, mood, muscle tenderness, and maximal interincisal opening were measured following 2-week baseline and 4-week treatment periods. The authors reported that pain was significantly decreased in the diazepam and

diazepam-plus-ibuprofen groups but not in the ibuprofen or placebo groups. Analysis of variance showed a significant drug effect for diazepam but not for ibuprofen, indicating that pain relief was mainly attributable to diazepam. This study supports the efficacy of diazepam in the short-term management of chronic orofacial muscle pain.

2.25 Drug 57: episodic headache abortive (indomethacin)

There is a group of headaches (e.g., hemicrania continua, paroxysmal hemicrania, and short-lasting unilateral neuralgiform headaches) that have been shown to be very responsive to a specific NSAID medication (indomethacin).[91] One study examined the use of indomethacin on three cases of hemicrania continua and found that intramuscular injection of 50 mg relieved pain and thus served as a diagnostic test for these headaches.[92] Another study reported on two cases of hemicrania continua masquerading as a TMD.[93] The report described that indomethacin could help differentiate this headache from a TMJ problem.

2.26 Drug 58: *N*-methyl-D-aspartate–blocking drug (ketamine)

A 2005 study reported on the use of ketamine infusion for the treatment of complex regional pain syndrome (CRPS)[94] based on ketamine's mechanism of action as an *N*-methyl-D-aspartate (NMDA) receptor blocking agent. The study specifically looked at pain reduction in CRPS patients using an open-label, prospective, pain journal evaluation of a 10-day infusion of intravenous ketamine. The reported data showed that there was a significant reduction in pain intensity from initiation of infusion (Day 1) to the 10th day, with a significant reduction in the percentage of patients experiencing pain by Day 10 as well as a reduction in the level of their "worst" pain. More recently, the adverse effects of ketamine when used for chronic pain were reported by a study[95] that evaluated 32 patients with diabetic polyneuropathy and with postherpetic neuralgia. Substantial sedation and dizziness were observed in 15.6% and 44% of patients after the initial infusion and in 19% and 22% of patients in the course of the subsequent oral therapy, respectively. Interestingly during the observed 3-month treatment period, five patients (15.6%) withdrew from the treatment due to a failure of therapy and four patients (12.5%) due to untolerated side effects (dizziness, sedation, loss of appetite, nausea, and vomiting). One study examined the efficacy of ketamine when used in the management of atypical odontalgia (AO; 10 AO patients and 10 matched healthy controls).[96] Treatment involved intravenous infusion of ketamine or a μ-opioid agonist, fentanyl, on spontaneous AO pain. Outcomes included the effect of the medications on their chronic pain and, for both the AO and the control patients, intraoral pain was evoked by topical application of capsaicin. The study was performed in a randomized, placebo-controlled, crossover manner. The results showed that both drugs failed to produce an analgesic effect on spontaneous AO pain, but fentanyl effectively reduced capsaicin-evoked pain. Finally, a 1995 and a follow-up 2001 study examined the effect of a ketamine intramuscular injection test dose followed by oral ketamine for 3 nights on the neuropathic OFP patients.[97,98] The study reported that there was reduction in pain after the intramuscular injection. The authors noted a positive correlation between a long pain-history and lack of analgesic effect in these cases.

2.27 Drug 59: antivirals (acyclovir and others)

Antiviral drugs (e.g., acyclovir) are used mostly for acute viral disease with clear-cut clinical manifestations. However, sometimes patients are placed on a viral prevention protocol especially for idiopathic pain in the face and mouth. The efficacy of antiviral agents used in this fashion is not established by the literature, and the use of antiviral medications for a condition such as Bell's palsy has been questioned[99]: A 2007 double-blind placebo-controlled study on 551 patients with Bell's palsy concluded that early treatment with prednisolone significantly improves the chances of complete recovery at 3 and 9 months, but there is no evidence of a benefit of acyclovir given alone or an additional benefit of acyclovir in combination with prednisolone. These findings are remarkable since another paper with a smaller data set of Bell's palsy cases ($n = 221$) reported that valacyclovir was helpful.[100] Specifically the study involved a prospective randomized placebo-controlled design and the authors concluded that the combination of valacyclovir and prednisolone therapy was more effective in treating Bell's palsy than the conventional prednisolone-only therapy. Overall there is no evidentiary basis for using antiviral agents (acyclovir or valacyclovir) for the suppression of chronic pain.

2.28 Drug 60: antibacterial drugs (azithromycin and others)

Many physicians and dentists use antibiotics as a standard aspect of their postoperative protocol after a tonsillectomy or oral surgery. One study actually examined whether

antibiotics were of value for reducing pain postoperatively after tonsillectomy.[101] Specifically this study reviewed all randomized controlled trials to see if any consistent effect existed for antibiotics versus placebo. Based on their review of nine trials that met the eligibility criteria the authors concluded that there was no consistent or significant reduction in pain as a result of antibiotic usage postoperatively. The authors also concluded that antibiotics used postoperatively were also not associated with a reduction in significant secondary hemorrhage rates, although they did appear to reduce fever. These findings confirm the problematic nature of antibiotic use after surgery as a preventative for infection, suggesting that fewer if any antibiotics be used under these conditions.

Antibiotics are also used for chronic pain of unknown origin based on reports that certain antibiotics do suppress pain. There is growing evidence that a specific class of antibiotics (macrolides [e.g., azithromycin]) exert a beneficial effect not only by inhibiting or killing bacterial pathogens but also by downregulating pro-inflammatory mechanisms. Three recent articles describe the immunomodulatory properties of macrolide antibiotics in chronic rhinosinusitis by inhibition of pro-inflammatory cytokines such as interleukin-8.[102–104] This effect is probably secondary to inhibition of the activation of transcription factor NF-κB. As a result an attenuation of neutrophilic inflammation and pain takes place. The authors have cautioned that macrolide-resistant bacterial strains have to be monitored, but to date they have not been clinically important. Not all antibiotics are immunomodulatory, and others that provide pain relief might work because of a strong placebo effect. It does not seem logical or appropriate to recommend antibiotic therapy for chronic OFP, at least until more information about the pain-suppression effect is known and the possible risk of bacterial resistance is elucidated.

2.29 Conclusions: pharmacotherapeutic management of orofacial pain disorders

There are many very painful diseases, disorders, and dysfunctions that cause chronic OFP. Some involve acute inflammation, chronic inflammation, neurovascular, neurogenous, and neuropathic pain, and myogenous pain. These conditions are treated with many physical, behavioral, and even surgical methods. However, medications are also a critical aspect of the clinician's treatment approach. This chapter demonstrates that a knowledgeable OFP practitioner should understand the indication and safety of at least 60 drugs used in monotherapy and in combination. Some of the drugs in this chapter are being used on-label and some are clearly off-label. Dentists who treat their patients with off-label medications must fully understand the literature and evidence supporting any drug they use. This chapter illustrates that there are few well-controlled studies of our 60 selected medications being used specifically for chronic orofacial pain in the relevant patient population and being administered for periods that approximate their use clinically. This paucity does not mean that these medications cannot be used, only that they must be used with caution, with reasonable concern, and with full knowledge of the existing literature.

For example, assuming there is a reliable differential diagnosis, pain with a neuropathic or an atypical neurogenic component would logically be managed using a trial with tricyclic antidepressants, sodium channel blockers, and possibly even anticonvulsants. Pain of musculoskeletal origin is probably best managed by physical medicine procedures using TCAs and SNRIs as supplements. Patients with manifestations of psychosocial dysfunction may not benefit from drug therapy aimed at pain and should be considered as candidates for physical medicine modalities, behavioral methods, and SSRI medications. For patients on whom other therapeutic modalities have failed or for whom a specific treatment is not readily apparent, such as patients for whom the non-narcotic analgesic medications and physical and behavioral medicine procedures have not worked adequately, might be eligible for a trial with opioids. What is evident is that a wide variety of adjuvant analgesic and anticonvulsant drugs show efficacy in the treatment of chronic painful conditions. In 2006 a European Pain Task Force evaluated the existing published evidence about the pharmacological treatment of neuropathic pain.[105] Only pharmacologic treatments feasible in an outpatient setting were evaluated, and they used the effect of these agents on pain symptoms and signs, on quality of life, and on other disease co-morbidities as outcomes. They report that most of the randomized controlled trials included patients with postherpetic neuralgia (PHN) and painful polyneuropathies (PPN) mainly caused by diabetes. Using these diseases, the task force concluded that data provides a high level of evidence for the efficacy of TCAs, gabapentin, pregabalin, and opioids, with a large number of class I trials, followed by topical lidocaine (in PHN) and the newer antidepressants venlafaxine and duloxetine (in PPN). The biggest problem is that these recommendations apply only to PHN and diabetic neuropathy, and if they are used on other similar but untested conditions, such as atypical odontalgia and burning mouth syndrome, it is not clear if the stated efficacy will carry over to these disorders. For this reason, using medications such as these requires caution. Given the complex nature of chronic orofacial pain, a multidimensional treatment approach including nonpharmacological methods is advocated, avoiding use

of several adjuvant medications prone to frequent or severe adverse effects. Furthermore, periodic trials of decreasing dosages and eliminating chronic medications should be considered. However, targeted and limited use of adjuvant analgesic treatments for defined pain syndromes provides a valuable therapeutic strategy for the relief of pain.

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Chapter 3

Nonopioid analgesics, salicylates, NSAIDs, and corticosteroids for chronic pain

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3.1 Introduction

While pain during dental restorative, endodontic, and surgical therapy is usually adequately controlled by local anesthesia, postoperative pain control usually requires anti-inflammatory and/or analgesic medications. These same medications are also used for pain and inflammation control with various chronic orofacial pain (OFP) disorders (e.g., osteoarthritis involving the temporomandibular joint [TMJ], trigeminal neuropathic pain disorders, and oral ulcerative disease or mucositis). The rationale for selection of analgesic and anti-inflammatory medications and the protocol for their use postoperatively will be quite different than when used to manage chronic-OFP patients. Using too much medication in either situation will lead to side effects such as gastritis, drowsiness, nausea, and vomiting (from opioids) and using too little medication causes suffering. If acute pain is not adequately suppressed during the immediate postoperative period, in some susceptible patients this may contribute to the conversion of nociceptive pain into neuropathic pain.[1] Moreover, if a short-acting analgesic is used to suppress episodically occurring headache pain, this may lead to transformation of the headache into a chronic pain condition.[2] The mechanisms underlying these conversions are discussed in detail in Chapters 15 and 17. While systemic corticosteriod use is covered here, the use of corticosteroids as an injectable agent for TMJ pain or for severe oral ulcerative lesions and inflammation is covered in Chapter 18. Topical use of corticosteriods for local mucosal tissue inflammation and ulcerations is covered in Chapter 12. Disease-modifying arthritic drugs (DMARDs), which also alter inflammation, are also discussed in Chapter 18. The primary focus of this chapter is twofold. First we review the use of 14 different medications (summarized in Table 3.1): nonopioid analgesics (acetaminophen, tramadol), salicylates (aspirin, diflunisal), nonselective nonsteroidal anti-inflammatory medications (ibuprofen, naproxen, ketoprofen, meclofenamate sodium, piroxicam, diclofenac, and nabumetone), and cyclooxygenase 2 (COX-2) selective nonsteroidal anti-inflammatory medications (celecoxib, meloxicam, and etodolac). At the end of the chapter we review two commonly used systemic corticosteroids (prednisone and methylprednisolone) as they are used for various chronic pain situations.

3.2 Nonopioid analgesics

Not unexpectedly, the World Health Organization recommends that, for most conditions where pain is the primary problem, nonopioid analgesics (NOAs) are the first-choice medications.[3] In addition, and slightly less expected, is that the American College of Rheumatology (ACR) guidelines emphasize acetaminophen should be the first-line treatment for osteoarthritis of the hip and knee.[4–6] Two drugs that are classified as nonopioid analgesics are acetaminophen and tramadol. Some authors would include nonsteroidal anti-inflammatory drugs (NSAIDs) in this grouping since they are nonopioid also, but in this chapter, we limit discussion of the NOAs to acetaminophen and tramadol.

3.2.A Acetaminophen

Indications

Acetaminophen is used for headaches, musculoskeletal pain, and almost all acute disease pains (e.g., pulpitis) and as a postoperative analgesic. This drug has a fast onset and short half-life and therefore also has value in a patient with episodic headaches, acute temporomandibular osteoarthritis

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Table 3.1 Dosing information for common oral NOAs, salicylates, NSAIDs, and corticosteriods in the United States

Medication (class)	Oral formulations	Recommended dosing protocol			Comments
		Starting dose	Usual dose	Maximum dose	
Nonopioid analgesics					
Acetaminophen	*Tablets:* 325, 500, 650 mg; 650 mg CR *Suspensions and solutions:* 160 mg/5 mL; 500 mg/15 mL	*Dose:* 1–2 tabs p.o. q6h p.r.n.	*Adults:* 325–650 mg q4–6h or 1000 mg 3–4 times per day	Do **not** exceed 4000 mg/day.	No anti-inflammatory effect; rapid hepatotoxic effect if overdosed.
Tramadol	*Tablets:* 50 mg *Extended-release:* 100, 200, 300 mg SR	Start dose at 25 mg/day, titrating dose by 25 mg every 3 days, until reaching 25 mg q.i.d. The total daily dose may then be increased by 50 mg every 3 days as tolerated, to reach target dose of 50 mg q.i.d.	50–100 mg p.o. q4–6h p.r.n.; 100–300 mg q.d. for SR *Immediate-release formulation:* 50–100 mg q4–6h (not to exceed 400 mg/day)	400 mg/day	Maximum dose for SR form is 300 mg/day.
Salicylates					
Aspirin	*Tablets:* 81, 162, 325, 500, 650, 975 mg	500 mg/day	325–650 mg p.o. q4h p.r.n.	4000 mg/day	Bleeding risk is the most significant concern.
Diflunisal	*Tablet:* 500 mg	500 mg/day	500–1000 mg followed by 250–500 mg q8–12h	*Maximum daily dose:* 1.5 g	Approved for acute or long-term use for symptomatic treatment of (1) mild to moderate pain, (2) osteoarthritis, and (3) rheumatoid arthritis.
Nonselective NSAIDs					
Ibuprofen	*Tablets:* 100, 200, 400, 600, 800 mg *Suspension:* 40 mg/mL; 100 mg/5 mL	600 mg/day	400–600 mg p.o. q4–6h p.r.n.	3200 mg/day	Use with caution in patients with history of peptic ulcer.
Naproxen	*Tablets*: 250, 375, 500 mg *SR:* 375, 500 mg *Suspension:* 125 mg/5 mL	500 mg/day	250–500 mg p.o. b.i.d.	1500 mg/day for 3–5 days	Maintenance dose is maximum 1000 mg/day for 6 months.
Ketoprofen	*Tablets:* 12.5 mg *Capsules:* 25, 50, 75 mg *Extended-release:* 100, 150, 200 mg SR	50 mg/day	25–50 mg p.o. q6–8h	300 mg/day	Maximum dose for SR form is 200 mg/day.

Meclofenamate sodium	*Tablets:* 50, 100 mg	50 mg/day	50–100 mg p.o. q4–6h	400 mg/day	Use lowest effective dose, shortest treatment duration; give with food and use with caution in patients with history of peptic ulcer.
Piroxicam	*Capsules:* 10, 20 mg	10 mg/day	20 mg p.o. once daily	20 mg/day	May divide daily dose b.i.d.
Diclofenac	*Tablets:* 50 mg *Delayed-release:* 25, 50, 75, 100 mg SR	50 mg/day	50 mg p.o. b.i.d.–t.i.d.	150 mg/day	Alternative dose for SR form is 100 mg p.o daily.
Nabumetone	*Tablets:* 500, 750 mg	500 mg/day	500–2000 mg once daily	2000 mg/day	May divide daily dose to b.i.d.
COX-2 selective NSAIDs					
Celecoxib	*Capsules:* 100, 200, 400 mg	100 mg/day	200 mg p.o. b.i.d.	400 mg/day	COX-2 inhibitor
Meloxicam	*Tablets:* 7.5, 15 mg *Suspension:* 7.5 mg/5 mL	7.5 mg/day	7.5–15 mg p.o. once daily	15 mg/day	COX-2 preferential NSAID
Etodolac	*Tablets:* 400, 500 mg *Extended-release:* 400, 500, 600 mg SR *Capsules:* 200, 300 mg	200 mg/day	200–400 mg p.o. q6–8h	1200 mg/day	COX-2 preferential NSAID; the dose for SR is 400–1000 mg once daily.
Corticosteroids					
Prednisone	*Tablets:* 1, 2.5, 5, 10, 20, 50 mg	2.5 mg/day	5–60 mg p.o. q.d.; dose–frequency varies by condition; taper dose gradually after long-term use	Maximum daily dosage is 1 mg/kg per day p.o.	Improvement is usually noted after 7–10 days. The dose is then tapered over the next 2–3 months and discontinued.
Methylprednisolone	*Tablets:* 2, 4, 8, 16, 32 mg	24 mg/day	4–48 mg/day p.o. divided q.d.–q.i.d. *Alternative dosing:* start 24 mg/day, taper by 4 mg/day over 6 days per package instructions	Not available	Dose–frequency varies by condition; to avoid adrenal crisis, taper dose gradually after long-term treatment.

Dosing abbreviations: b.i.d., *bis in die* (a Latin phrase meaning "twice daily"); p.o., *per os* (a Latin phrase meaning "by mouth"); p.r.n., *pro re nata* (a Latin phrase commonly used in medicine to mean "as needed" or "as the situation arises"); q.i.d., *quater in die* (a Latin phrase meaning "four times daily"); q.d., *quaque die* (a Latin phrase meaning "every day"); q*x*h, every *x* hours (from *quaque hora*, a Latin phrase meaning "every hour"); t.i.d., *ter in die* (a Latin phrase meaning "three times daily").
COX-2, cyclooxygenase-2; CR, controlled release; NOA, nonopioid analgesic; NSAIDs, nonsteroidal anti-inflammatory drugs; SR, sustained release.

pain, pain due to acute internal derangement, and any chronic pain that is undergoing an acute flare-up. Acetaminophen is also commonly prescribed for cancer pain management, and pain specialists often undertake combination therapy with multiple analgesics, including adjuvant pain analgesics (e.g., amitriptyline), during the treatment of severe, refractory pain.

Dosage

Acetaminophen has a rapid onset of action and a relatively short half-life. Acetaminophen comes in 325-, 500-, and 650-mg tablets and it is common to take one tablet every 4–6 hours; however, patients should be very careful not to exceed 4000 mg/day.

Adverse effects

The biggest concern with the use of acetaminophen is liver toxicity. It is contraindicated in any patient with a preexisting liver disease. Doses higher than 4 g daily may cause serious, irreversible hepatic toxicity, which can be fatal in some patients. Damage to the liver is not due to the drug itself but to a toxic metabolite (*N*-acetyl-*p*-benzoquinone imine) that is produced by cytochrome P450 enzymes in the liver. Under normal circumstances this metabolite is detoxified by conjugating with glutathione in a phase 2 reaction; however, when a patient takes too much acetaminophen, a large amount of toxic metabolite is generated that overwhelms the detoxification process and leads to rapid and devastating hepatotoxicity.

Efficacy for chronic pain

There are three chronic pain conditions (osteoarthritis, chronic musculoskeletal pain, and episodic headaches) for which acetaminophen might be recommended as a first-line therapy. The recent evidence is reviewed next for each condition. There is little or no evidence that acetaminophen is efficacious as a primary treatment for neuropathic chronic pain states, but it is often used combined with an opioid analgesic in neuropathic pain. Information on the efficacy of combined acetaminophen and opioids for chronic pain is provided in Chapter 4.

Osteoarthritis

As mentioned earlier, the ACR recommends that acetaminophen should be a primary treatment for pain associated with osteoarthritis. A 2006 study examined the safety of acetaminophen in adult patients with mild to moderate osteoarthritis in a large multicenter randomized controlled 6-month-long study.[7] The dose used in the study was high (4 g/day) and it was administered for up to 12 months to 290 adult patients with osteoarthritis pain. This acetaminophen group was compared with 291 adult patients with osteoarthritis pain who were randomized to receive naproxen 750 mg/day. All subjects had liver and renal function assessments performed, as well as periodic physical examination. Both groups had a substantial dropout problem but no patient in either treatment group experienced hepatic failure, hepatic dysfunction, renal failure, or elevated serum creatinine levels. Two adverse events considered to be drug related and reported by more than 1% of patients were seen more frequently in the naproxen group than in the acetaminophen group: constipation (9.9% vs. 3.1%) and peripheral edema (3.9% vs. 1.0%). No adverse event reported in the acetaminophen group was considered both serious and related to study medication, but one subject in the naproxen group did develop gastrointestinal (GI) bleeding. The authors concluded that, with treatment under physician supervision, acetaminophen was found to be generally well tolerated for the treatment of osteoarthritis pain of the hip or knee for periods of up to 12 months. In contrast, a 2006 Cochrane database meta-analysis[8] on the efficacy of acetaminophen for osteoarthritis reviewed 15 randomized controlled studies (5986 subjects) that compared acetaminophen with either placebo or an NSAID. In the placebo-controlled studies, the authors acknowledged that acetaminophen was superior to placebo but the magnitude of the effect was considered of questionable clinical significance since the relative percentage improvement from baseline was 5% or 4 points on a 0-to-100 scale and the calculated number needed to treat (NNT) ranged from 4 to 16, which is quite poor. For the studies that compared acetaminophen and NSAIDs, the authors reported that acetaminophen was less effective overall than NSAIDs in terms of reducing pain and improving functional status. Moreover, the authors noted that no significant difference was found overall between the safety of acetaminophen and NSAIDs, although patients taking traditional NSAIDs were more likely to experience an adverse GI event. This analysis concluded that the data suggests that NSAIDs are superior to acetaminophen for improving knee and hip pain in people with osteoarthritis.

Chronic musculoskeletal pain

Although acetaminophen is not considered a highly successful therapy for osteoarthritis, myofascial pain, or fibromyalgia and most experts consider it inadequate for this purpose, it has substantial merit in the elderly with chronic musculoskeletal pain. In the elderly, frequently NSAIDs and even opioids are contraindicated and the side effects of anticonvulsant medications are intolerable; therefore acetamino-

phen is elevated to a primary pain control medication. A 2009 study examined the efficacy of acetaminophen for pain control in elderly chronic musculoskeletal pain patients with dementia.[9] The study enrolled community-dwelling elderly patients diagnosed with dementia, and it used a within-subjects repeated-measures A-B-A-B prospective design. The the patients were provided with a 1.3-g controlled-release (CR) formulation of acetaminophen three times a day (t.i.d.; every-8-hour dosing). The study used behavioral measures of pain and the authors concluded that, during both treatment phases, pain behaviors decreased in both frequency and duration relative to the control and baseline phases.

Episodic headaches

Third, acetaminophen is used frequently for control of pain related to episodic headaches such as migraine and tension-type headache (see Chapter 15).[10] However, the NSAIDs and nonopioid analgesics have an inherent risk when used frequently for headache control. A 2004 study examined the concept that chronic use of analgesics to manage a frequent episodic headache can cause medication overuse headache disorder.[11] The study collected data from 114 consecutive patients (96 women and 18 men, with a mean age of 54.2 years) diagnosed with a chronic daily headache due to overuse of medications. All patients in this group had been referred for inpatient detoxification of their analgesic medications. The authors determined that, of these patients, 71% had an initial headache diagnosis of migraine without aura and, of these, 38.6% were overusing simple analgesics, which included both NSAIDs and acetaminophen.

3.2.B Tramadol

Indications

The other NOA we discuss is tramadol, which has value as a chronic pain medication but is rarely considered effective as a rapid-acting analgesic for acute pain. The enigma of tramadol is that it is categorized as a nonopioid analgesic yet it binds (weakly) to an opioid receptor. It is marketed as an analgesic without scheduling under the US Controlled Substances Act, even though recent literature has suggested classic opioid withdrawal occurs with discontinuation or dose reduction and there are increasing reports of abuse and dependence.[12] Tramadol exhibits a combination of serotonin and norepinephrine reuptake inhibition (similar to what is seen in the tricyclic antidepressant drugs [TCAs]) and it is a weak μ-opioid agonist.[13] The manufacturer thus claims that tramadol can reduce chronic pain by affecting both the ascending and descending pain pathways.

Dosage

The common titration method for prescribing tramadol is usually 1 tablet every 4 days to full therapeutic levels (or minimum of 50% pain relief). A typical maintenance dosage for fibromyalgia patients is 300–400 mg/day in three to four divided doses, concomitant with acetaminophen at 2–3 g/day in divided doses. Commonly for chronic pain, therapy begins with just one tablet at bedtime for 1–2 weeks since this usually reduces the side effects and allows progressive increase of the dosage after this.

Adverse effects

Tramadol has the same set of side effects seen in TCAs (e.g., nausea and dizziness) and these side effects can be limiting at first in approximately 20% of patients. In addition, a review of idiopathic seizures in 11,383 patients showed that tramadol is not associated with a higher risk of seizure activity when compared with other analgesics.[14]

Efficacy for chronic pain

Like acetaminophen, tramadol is used for several types of chronic pain, including osteoarthritis and chronic musculoskeletal pain. It is not typically recommended for episodic headaches since it is usually too slow to achieve reasonable pain suppression. It does have a place in the control of neuropathic pain and other non-neoplastic chronic pain disorders.

Osteoarthritis

Painful degenerative joint disease of the knee responded to tramadol therapy in a two-phase trial of 129 patients with significantly improved pain intensity and pain relief scores compared with the placebo group.[15] Another osteoarthritis two-phase trial showed that patients given tramadol can significantly reduce their intake of naproxen without compromising pain relief.[16]

Chronic musculoskeletal pain

Three controlled studies have evaluated the efficacy of tramadol in fibromyalgia. The first small study used a double-blind crossover design to compare single-dose intravenous tramadol 100 mg with placebo in 12 patients with fibromyalgia.[17] The authors reported that fibromyalgia patients receiving tramadol experienced a 20.6% reduction in pain compared with an increase of 19.8% of pain in the placebo group. In a two-phase study in 2000, tramadol was again shown to reduce the impact of pain in fibromyalgia patients.[18] There was an initial 3-week, open-label phase of tramadol

50–400 mg/day followed by a 6-week double-blind phase in which only patients who tolerated tramadol and perceived benefit were enrolled. The results showed that more patients on tramadol than placebo tolerated the drug and achieved adequate pain relief in the double-blind phase. In 2003 a third study found that tramadol, in combination with acetaminophen, provided a substantial additive effect for pain reduction in fibromyalgia.[19] The randomized, controlled, double-blind trial (RCBT) examined the efficacy of tramadol (37.5 mg) combined with acetaminophen (325 mg) in 315 patients with fibromyalgia and found that patients taking tramadol and acetaminophen (4±1.8 tablets per day) were significantly more likely than placebo-treated subjects to continue treatment and experience an improvement in pain and physical function. Treatment-related adverse events were reported by significantly more patients in the tramadol/acetaminophen group (75.6%) than the placebo group (55.8%).

Neuropathic and other nonmalignant chronic pain disorders

Two studies examined tramadol in painful diabetic polyneuropathy[20] and painful polyneuropathy of different etiologies.[21] Both studies found tramadol was superior to placebo and exhibited an NNT of 3.1 and 4.3, respectively. In addition to its relief of ongoing pain, it reduced touch-evoked pain and experimentally induced mechanical hyperalgesia. Finally, a comparison of tramadol and morphine in 25 patients with severe chronic pancreatitis pain showed that tramadol interferes significantly less with GI function.[22]

3.3 Nonsteroidal anti-inflammatory medications

In this category are the salicylates and the various nonsteroidal anti-inflammatory drugs (NSAIDs). The NSAIDs are usually subcategorized into those that nonselectively inhibit and those that selectively inhibit cyclooxygenase (COX) enzyme 2. Nonselective or nonspecific COX inhibition means the NSAID exhibits inhibitory effects on both COX-1 and COX-2 enzymes, while the selective COX inhibition action usually means that the NSAID inhibits COX-2 enzyme only. We discuss salicylates first and then describe the various NSAIDs. The latter are the mainstay of therapy for the management of acute dental disease (e.g., pulpal abscess) and postoperative-related dental pain that occurs following surgical and endodontic procedures. When used as directed, nonprescription (i.e., over-the-counter) dosing regimens for ibuprofen (200 mg four times per day [q.i.d.]), ketoprofen (75 mg t.i.d), or naproxen sodium (220 mg two times per day [b.i.d.]) are both safe and effective for most patients across a wide variety of dental pain conditions.[23]

3.3.A Salicylates

We review two medications in the salicylate category: aspirin and diflunisal. Salicylates have been used in medicine (as willow bark) as an analgesic since 1763. The active agent in willow bark, salicin, was eventually used to produce salicyclic acid in 1838 and this led to the production of a substance with known chemical purity and properties. Aspirin itself was introduced in 1899 and since then has been widely used for pain control and reduction of fever and swelling. The mechanism of action of salicylates has since been identified—the inhibition of prostaglandin synthesis, which is critical to blocking the initial oxygenation of arachidonic acid by cyclooxygenase enzyme.

Aspirin

Indications

Aspirin is a weak acid that is well absorbed from the GI tract when taken orally. Its ability to dissociate favors absorption from the stomach, but it is principally absorbed from the small intestine because of the greater surface area. Acetylsalicylic acid, or aspirin, is rapidly metabolized to salicylic acid by plasma and gastric esterases. Salicylate, an active form of aspirin, is widely distributed in the body, is metabolized mainly in the liver by conjugation, and is excreted in the urine mostly as salicyluric acid. Although the efficacy of aspirin has been accepted for several generations based on over 100 years of clinical use, it is only in the past 20 years that controlled studies have documented its efficacy for dental pain. Through its inhibition of prostaglandin synthesis, aspirin has also been shown to affect platelet function. This may result in prolonged bleeding time when aspirin is used postsurgically. Aspirin should not be given to patients with liver disease, hypothrombinemia, hemophilia, or vitamin K deficiency. It should also be avoided in patients who are taking anticoagulant drugs. Allergic reactions to aspirin are uncommon but are more frequently seen in persons with asthma, nasal polyps, or a history of an allergic reaction to other aspirin-like drugs (including the NSAIDs). Aspirin interactions with insulin or oral hypoglycemic agents may result in a greater hypoglycemic effect; an alternative nonopioid analgesic should be considered in patients taking one of these agents. The relationship between plasma levels and therapeutic effect is not direct and no fixed dose,

schedule, or dosage form will provide the desired result in all patients.

Dosage

The maximum recommended dose is 650 mg every 4 hours (3900 mg/day) or 500–1000 mg every 4 hours, up to a maximum of 4000 mg/day.

Adverse effects

Aspirin has several side effects that are frequently the reasons for using other nonopioids in its place, and it is not suggested for prolonged use in a chronic pain population. The most commonly reported side effects are epigastric distress, nausea, ulceration, and, less frequently, vomiting. Aspirin-induced GI injury results from two known mechanisms. Local irritation of the mucosal lining allows diffusion of acid into the mucosa, with subsequent tissue damage. In addition, gastric prostaglandins that inhibit secretion of acid and promote secretion of cytoprotective mucus are inhibited by aspirin. For this reason, aspirin is contraindicated for patients with GI ulcers.

Efficacy for chronic pain

Aspirin is not logically used as a primary treatment in any of the chronic pain disorders (osteoarthritis, chronic musculoskeletal pain, or neuropathic pain) since gastric damage is so common with prolonged use. Unfortunately, frequent-headache patients do consume aspirin almost daily. A 2009 study reported on the patterns of medication use among those with chronic daily headache ($n = 206$) versus episodic headache ($n = 507$) in the general population.[24] Questions about analgesic use revealed that chronic-daily-headache (CDH) sufferers were more likely to use over-the-counter and caffeine-containing products, triptans, opioid compounds, and prescription pain medications. However, based on the data the authors reported that aspirin and ibuprofen were negatively associated with CDH (OR = 0.5 and 0.7) but opioids were positively associated with CDH (OR = 2.3). These data suggest that, with CDH, aspirin was not an effective medication for severe frequent headaches and the salicylates do not contribute greatly to the transformation of episodic to chronic daily headache.

Diflunisal

Indications

Diflunisal is a salicylic acid derivative [5-(2,4-difluorophenyl) salicylic acid] that is more effective than aspirin as an analgesic.

Dosage

The recommended diflunisal dosage for most people with mild to moderate pain is 1000 mg, followed by a dose of 500 mg every 12 hours. Some people may need to take diflunisal (Dolobid) every 8 hours in order to achieve adequate pain relief.

Adverse effects

Diflunisal has fewer GI and hematologic adverse effects than aspirin but, nevertheless, gastritis is the main complication of prolonged use.

Efficacy for chronic pain

There is very little information about the efficacy of diflunisal as a pain control agent in chronic pain conditions. No studies were available on its use in neuropathic pain or CDH, but an open trial with diflunisal (500 mg b.i.d.) in 766 outpatients with chronic back pain was published.[25] These patients (mean age 41 years) had a variety of back pain disorders; outcomes were pain at rest and during exercise, the patient's evaluation of the efficacy of the treatment, and the need for any supportive treatment. All side effects were recorded and those of the drug therapy were registered. In all diagnostic groups the relief of pain both at rest and during exercise was greater in patients receiving diflunisal than in the controls who received no drug therapy. The authors reported that taking the medication diminished the need for supportive physical therapy and the frequency of side effects was 8.6%, with 3% of the patients stopping the medication as a result.

3.4 Nonsteroidal anti-inflammatory drugs

The wealth of data from clinical trials using NSAIDs makes them one of the most well-studied drug classes for acute inflammatory pain in ambulatory patients. The acute postoperative sequelae of dental procedures include other signs of inflammation due to tissue injury, most prominently edema. While synthetic analogs of endogenous corticosteroids are used extensively to control the sequelae of both acute and chronic inflammation, their use postoperatively is tempered by their ability to suppress the immune system thereby increasing the risk of infection. NSAIDs have a more selective mechanism of action than glucocorticoids and a more favorable side-effect profile, suggesting that drugs of this class may inhibit inflammation without the

risks of corticosteroid administration. When considering the use of NSAIDs for prolonged use in chronic nonmalignant pain and cancer pain, there are several issues to consider.[26] For example, in patients with a history of peptic ulcer disease, advanced age (>60 years of age), and female gender, concurrent corticosteroid therapy should be considered before NSAID administration to prevent upper GI tract bleeding and perforation. When NSAIDs are administered in a peptic ulcer risk group, proton pump inhibitors are usually added to the therapeutic mix to try to prevent GI side effects induced by NSAIDs. NSAIDs should be prescribed with caution in patients having compromised fluid status, interstitial nephritis, concomitant administration of other nephrotoxic drugs, and renally excreted chemotherapy in order to prevent renal toxicities. A meta-analysis of 16 controlled studies suggests that users of NSAIDs have a threefold greater risk of developing serious adverse GI events than nonusers and that this risk is greater for those over 60 years of age.[27] NSAIDs alter kidney blood flow by interfering with the synthesis of prostaglandins in the kidney that are involved in the autoregulation of blood flow and glomerular filtration.[28] The inhibitory effects of NSAIDs on kidney prostaglandin production lead to acute, reversible kidney failure in 0.5–1% of patients who take NSAIDs chronically.[29] The most significant kidney-related side effect of NSAIDs is hemodynamically mediated acute kidney failure, which occurs in persons with pre-existing reduced kidney blood perfusion. A retrospective analysis of patients with end-stage kidney disease requiring hemodialysis demonstrated an association between chronic NSAID use (more than 5000 pills over a lifetime) and a ninefold increased risk of end-stage kidney disease.[30] Finally, the efficacy of systemic NSAIDs has been examined in several Cochrane reviews of various mixed but chronic musculoskeletal pain conditions.[31] These reviews have generally concluded that systemic NSAIDs are not effective as monotherapy for chronic pain. However, the toxicity associated with chronic high-dose NSAID administration is well documented, suggesting the need to carefully weigh the benefit-to-risk relationship for each therapeutic indication. The clinical pharmacology of NSAIDs is based in large part on studies performed in the oral surgery model.[32] With regard to NSAIDs for chronic orofacial pain, the data is mixed. A review article that examined the primary literature suggests that daily use of nonopioid analgesics offers benefit for chronic orofacial pain.[33] In contrast, the results of a placebo-controlled study suggest that NSAIDs are ineffective for chronic myogenous orofacial pain.[34] This study examined the analgesic effects of ibuprofen, 2400 mg/day for 4 weeks, and found it could not be separated from placebo in a group of patients with chronic orofacial pain characterized as myogenic in origin.

3.4.A Nonselective cyclooxygenase inhibitory medications

Research into the pathophysiology of inflammatory pain led to recognition that there are at least several forms of the cyclooxygenase enzyme responsible for the formation of products of the arachidonic acid cascade. One form, characterized as COX-1, is responsible for the normal homeostatic functions of prostaglandins in the GI tract that maintain GI mucosa integrity, initiate platelet aggregation, and regulate renal blood flow. The other form, COX-2, was initially thought to be induced only during inflammation and to contribute to the pain, edema, and tissue destruction associated with acute inflammation, rheumatoid arthritis, and osteoarthritis. Most of the NSAIDs are nonselective inhibitors of the COX enzymes (see, e.g., Table 3.1). This inhibition makes them slightly less likely to cause gastric disease than the salicylates, but gastric disease is still the main contraindication and the most frequent adverse event to occur with long-term use of NSAIDs. Next we review nine of the common nonspecific COX inhibitory NSAIDs used for pain and inflammatory suppression.

Ibuprofen

Indications

Ibuprofen, a propionic acid derivative, is the prototype of the NSAID class of analgesics and was first introduced into clinical practice in the United States in 1974. It is particularly useful for conditions in which aspirin or acetaminophen does not result in adequate pain relief or where the use of opioid-containing combinations would likely result in central nervous system or gastrointestinal side effects.

Dosage

Ibuprofen is widely used for acute and chronic orofacial pain by prescription in doses of 600–800 mg, and as a nonprescription analgesic in doses of 200–400 mg up to 1200 mg/day. It has a demonstrated analgesic activity over a dose range from 200 to 800 mg with a duration of activity from 4 to 6 hours.[35,36]

Adverse effects

Ibuprofen 400 mg produces analgesia similar to 100 mg of meclofenamate sodium but with a lower incidence of stomach pain and diarrhea.[37] The following adverse events are associated with this drug (and most of the other NSAIDs listed here): edema; headache; vertigo; drowsiness; dizziness; tinnitus; rash; urticaria; fasciitis; diarrhea; vomiting; nausea; abdominal pain; dyspepsia; peptic ulcer; GI bleed-

ing; constipation; flatulence; anorexia; stomatitis; heartburn; acute renal failure; nephrotic syndrome; reduced hemoglobin; bruising; prolonged bleeding time; thrombocytopenia purpura; anemia; abnormal liver function tests; porphyria; hyponatremia and breathing difficulties in aspirin-sensitive individuals.

Efficacy for chronic pain

Very little data exists on the use of ibuprofen as a standalone therapy for any chronic pain condition except rheumatoid arthritis or similar autoimmune inflammatory joint diseases. In the arena of neuropathic pain, a 2005 study conducted a systematic review of analgesic therapy for patients with postherpetic neuralgia (PHN).[38] The review included 25 studies that had adult patients with PHN of duration greater than 3 months, that used a blinded, randomized design, and that had at least one measure of pain outcome. The authors report that there was evidence to support the use of tricyclic antidepressants, strong opioids, gabapentin, tramadol, and pregabalin. However, ibuprofen was among several medications that were not found efficacious. Supporting the idea that ibuprofen is not a good medication for chronic pain, there is a study that used rats to investigate the effect of analgesics on experimental pain.[39] The pain was induced by either injecting capsaicin just under the skin or performing a spinal nerve ligation procedure. The study tested pain sensitivity before and after injection of multiple analgesic agents, including morphine, gabapentin, lamotrigine, duloxetine, celecoxib, and ibuprofen. While the other agents had substantial effects on pain, celecoxib and ibuprofen showed only weak effects if any.

Naproxen and naproxen sodium

Indications

Naproxen is also a propionic acid derivative but longer acting than ibuprofen. It is the only NSAID administered as a pure enantiomer, the S(+) isomer. It is available in two formulations, with the sodium salt being more rapidly absorbed than naproxen. The different formulations should not be used concomitantly, because they both circulate in the plasma as the naproxen anion and the resultant additive plasma concentration increases the possibility of dose-related adverse effects.

Dosage

An initial loading dose of 500–550 mg is used to reach therapeutic levels more rapidly, with subsequent doses of 250–275 mg given at 6- to 8-hour intervals. Over-the-counter (OTC) naproxen sodium is available in a formulation containing 220 mg, with a recommended dose of 1–2 tablets twice daily.

Adverse effects

See the adverse events provided for ibuprofen. Naproxen's long half-life is an advantage if effective pain relief is achieved, but in patients with inadequate relief, the long half-life prevents administration of a second dose for 8–12 hours. A review of 48 randomized double-blind clinical studies (25 in the dental pain model) indicated no overall difference in the rate of adverse events seen for naproxen sodium compared with placebo, ibuprofen, or acetaminophen.[40] The data suggests that OTC naproxen is well tolerated even when administered in the absence of professional supervision.

Efficacy for chronic pain

A 2008 article examined the literature and made recommendations for medications that can be used in chronic musculoskeletal pain in the elderly.[41] The authors suggested that elderly patients require careful selection of drugs to control pain. One medication that has been shown to have a lower profile regarding potential adverse cardio–renal effects is naproxen. Of course being "less likely to cause an adverse reaction" is not a strong endorsement of a medication's efficacy as a treatment for chronic pain and, like the other NSAIDs, there is no data on naproxen's efficacy as a treatment of neuropathic pain. There is data on its role as a primary treatment for chronic osteoarthritis pain. A 2004 study examined the analgesic efficacy and safety of nonprescription doses of naproxen sodium compared with acetaminophen in the treatment of osteoarthritis of the knee.[42] The authors described two identical multicenter, randomized, double-blind, placebo-controlled, multidose, parallel-design studies that included patients with diagnosed osteoarthritis of the knee. The patients had an average age of 60.6 and they were given daily doses of either 660 mg naproxen sodium or 4000 mg acetaminophen, or placebo for 7 days. The results demonstrated that both naproxen sodium and acetaminophen provided significantly greater improvement in pain on most measures than did placebo. When compared with acetaminophen, naproxen sodium was found to significantly reduce difficulty and pain on function, but overall both were found clinically effective treatments.

Ketoprofen

Indications

Ketoprofen is chemically related to other propionic acid derivatives with analgesic and antipyretic properties. It acts

peripherally via inhibition of prostaglandin and leukotriene synthesis like other NSAIDs, but it is also thought to act centrally as well.[43]

Dosage

Ketoprofen is effective as an analgesic for the relief of mild to moderate pain in doses ranging from 25 to 150 mg with greater efficacy than 650 mg aspirin[44] or codeine 90 mg.[45]

Adverse effect

See the adverse events provided for ibuprofen.

Efficacy for chronic pain

Again, very little data exists on the use of ketoprofen as a stand-alone therapy for any chronic pain conditions including neuropathic pain, chronic daily headaches, or chronic musculoskeletal pain. Ketoprofen has been used for the treatment of chronic osteoarthritis in a double-blind study.[46] This study compared ketoprofen versus a placebo in the treatment of osteoarthritis of the hip and found ketoprofen to be significantly more effective.

Meclofenamate sodium

Indications

Meclofenamate sodium is an NSAID with analgesic, anti-inflammatory, and antipyretic activity. It acts simultaneously to inhibit both the cyclooxygenase and lipoxygenase pathways, resulting in reduced formation of prostaglandins and leukocytes.[47]

Dosage

When used for the treatment of osteoarthritis or rheumatoid arthritis on adults without contraindications to the drug, it is prescribed as follows: 200–400 mg/day in three to four equally divided doses.

Adverse effects

See the adverse events provided for ibuprofen.

Efficacy for chronic pain

Very little data exists on the use of meclofenamic acid as a stand-alone therapy for any chronic pain condition including neuropathic pain, chronic daily headaches, and chronic musculoskeletal pain.

Piroxicam

Indications

Piroxicam is an oxicam NSAID; its plasma half-life has been estimated at 45 hours, allowing once-daily dosing, with peak plasma concentration occurring 2–4 hours after oral administration.[48]

Dosage

Piroxicam in single doses of 20–40 mg has been shown to produce analgesia approximately equivalent to aspirin 648 mg with a longer duration.[49]

Adverse effects

See the adverse events provided for ibuprofen.

Efficacy for chronic pain

Very little data exists on the use of piroxicam as a stand-alone therapy for any chronic pain condition including neuropathic pain, chronic daily headaches, and chronic musculoskeletal pain.

Diclofenac

Indications

Diclofenac is used to treat pain and inflammation symptoms seen in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Diclofenac has shown anti-inflammatory, analgesic, and antipyretic activity. As with other NSAIDs, its mode of action is not known; its ability to inhibit prostaglandin synthesis, however, may be involved in its anti-inflammatory activity.

Dosage

Diclofenac should be taken with food to reduce stomach upset; the most common recommended dose is between 100 and 200 mg daily.

Adverse effects

See the adverse events provided for ibuprofen.

Efficacy for chronic pain

In 2008, a study examined the relative efficacy of tramadol (200–400 mg controlled-release [CR] formulation) versus diclofenac (75–100 mg sustained-release [SR] formulation) for chronic pain due to osteoarthritis.[50] The study was a

randomized controlled trial and involved 45 patients on CR tramadol and 52 patients on SR diclofenac. Both groups demonstrated significant improvement and there were no significant differences between the two treatments. Interestingly, the incidence of adverse events was similar in both groups. In another double-blind study, diclofenac sodium (Voltaren®), 50 mg two or three times a day, was compared with placebo in 32 patients with pain localized to the temporomandibular joint (TMJ).[51] TMJ pain and tenderness to palpation showed a significantly greater reduction in the diclofenac group versus the placebo group. The authors suggested that diclofenac should not be used as a primary treatment of TMJ pain, but it could be used as a complement to other treatments of acute TMJ pain.

Nabumetone

Indications

Nabumetone, a prodrug, is a dual COX-1/COX-2 inhibiting member of the NSAID class and does not inhibit locally the gastroprotective prostaglandin E2 as do other NSAIDs. Its primary metabolite after first-pass through the liver is 6-methoxy-2-naphthylacetic acid (6-MNA), and this metabolite provides the analgesic and anti-inflammatory activity.[52,53] This metabolite is an inhibitor, preferentially, of COX-2 enzyme; the clinical efficacy of nabumetone is similar to other nonselective NSAIDs.

Dosage

The optimum oral dosage of nabumetone for osteoarthritis patients is 1 g once daily (500 mg b.i.d.). The recommended maximum dose is 1500 mg.

Adverse effects

See the adverse events provided for ibuprofen. Clinical trials and a decade of worldwide safety data and long-term postmarketing surveillance studies show that nabumetone is generally well tolerated. This is thought to be related to nabumetone being a nonselective NSAID that is nonacidic, is a prodrug formulation, and does not have biliary secretion of its active metabolite, 6-MNA. The most frequent adverse effects are those commonly seen with COX inhibitors, which include diarrhea, dyspepsia, headache, abdominal pain, and nausea. In common with other COX inhibitors, nabumetone may increase the risk of GI perforations, ulcerations, and bleeding (PUBs). However, several studies show a low incidence of PUBs, on a par with the numbers reported from studies with COX-2 selective inhibitors and considerably lower than for nonselective COX inhibitors. A 2007 study examined the tolerability to nabumetone and meloxicam in patients with NSAID intolerance.[54] This study was undertaken because both of these drugs preferentially inhibit COX-2 enzyme and both are reputed to be well tolerated by patients who report nonspecific NSAID-induced gastritis. The study involved 70 patients who were self-reported to be intolerant to NSAIDs. Of these, 30 were patients with asthma and a respiratory (rhinitis–asthma) intolerance to NSAIDs (group A); the other 40 (group B) were patients who had a cutaneous–mucous (urticaria–angioedema) NSAID intolerance. This intolerance was confirmed by a positive single-blind placebo-controlled oral challenge test in 36 patients. The study was a single-blind placebo-controlled oral challenge test with nabumetone in all patients and meloxicam in 51 patients. The results of this challenge test showed that 94.3% tolerated 1 g nabumetone and 96.1% tolerated 15 mg meloxicam. The authors concluded that there was no significant difference in nabumetone and meloxicam tolerability between groups, and they suggested both nabumetone and meloxicam are safe alternatives in NSAID-intolerant patients.

Efficacy for chronic pain

There is no data on the use of nabumetone for chronic neuropathic pain. In 2004, a study compared the pain management efficacy of four NSAIDs (rofecoxib, celecoxib, acetaminophen, and nabumetone) using a 6-week randomized study design in a population of osteoarthritis patients.[55] The authors reported that the discontinuation rate was higher for nabumetone than for rofecoxib and that this rate was correlated with a slower onset of activity for nabumetone, which is consistent with the longer half-life of this drug. Of course being faster does not mean being safer: rofecoxib has been withdrawn from the market by the US Food and Drug Administration (FDA) because of cardiotoxicity. In 2008, a study examined the safety of nabumetone with a specific focus on its GI tolerability.[56] This study examined pooled data from eight postmarketing, randomized, controlled trials and reported a lower cumulative frequency of GI problems (perforation, ulceration, and bleeding) with nabumetone versus nonspecific NSAIDs (0.03% vs. 1.4%, respectively). Limited comparative data also suggests that, compared with the selective COX-2 NSAIDs (coxibs), nabumetone is similar in GI tolerability without the increased cardiovascular risk or a high nephrotoxic and hepatotoxic potential.

3.4.B Preferential and selective cyclooxygenase-2 inhibitory medications

The spectrum of activity of NSAIDs reflects their generally accepted mechanism of suppressing the activity of both the

COX-1 and COX-2 isoforms of cyclooxygenase, with resultant decreased formation of products of the arachidonic acid cascade. Observations that COX-1 is constitutively distributed throughout the body whereas COX-2 expression is limited to a few specialized tissues and is induced during inflammation lead to the hypothesis that COX-1 is primarily responsible for the adverse GI effects of existing dual COX-1/COX-2 inhibitors whereas COX-2 mediates the synthesis of prostanoids during pathological processes. This hypothesis suggests that dual COX-1/COX-2 inhibitors such as ibuprofen produce both therapeutic and toxic effects at therapeutic doses, whereas selective COX-2 inhibitors should have therapeutic effects largely devoid of NSAID toxicity. The recent history of specific COX-2 inhibitors suggests that this subset of NSAIDs, namely, celecoxib, meloxicam, etodolac, nabumetone, rofecoxib, and valdecoxib, may indeed reduce the gastric side effects but at the same time increase the risk of myocardial infarctions. Exactly how much myocardial risk elevation exists for nonselective COX inhibiting agents is not clear, and this risk may vary substantially among the drugs in this group. The well-documented elevated risk of rofecoxib and valdecoxib caused them to be withdrawn from the market. The other NSAIDs just mentioned are all still on the market but now have a "black box" warning that has been added describing them as potentially having increased risk of serious and potentially fatal cardiovascular thrombotic events. Initially this warning was applied to the COX-2 selective NSAIDs but it was later extended to all of the NSAIDs.

Celecoxib

Indications

Celecoxib is indicated for the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis.

Dosage

For osteoarthritis and rheumatoid arthritis, the best approach is to use the lowest possible dose of celecoxib; usually the dose is 100 mg given twice a day. For more severe inflammation and pain as would occur in rheumatoid arthritis, the recommended oral dose is 100–200 mg twice per day.

Adverse effects

Celecoxib when used clinically appears to have reduced risk for producing GI perforations, ulcers, and bleeding compared with traditional NSAIDs such as ibuprofen, diclofenac, and indomethacin. Note that the standard NSAID warnings regarding gastrointestinal and renal toxicity also extend to the COX-2 selective inhibitors, as well as the previously mentioned cardiovascular thrombotic complications associated with COX-2 selective medications and now with all COX inhibiting NSAIDs.

Efficacy for chronic pain

Celecoxib is suggested for chronic pain associated with osteoarthritis and rheumatoid arthritis. There is no research suggesting this medication would be useful for neuropathic pain, chronic musculoskeletal pain, or chronic daily headache pain.

Osteoarthritis

Celecoxib has been shown to be more effective than placebo for the treatment of osteoarthritis and was approved and marketed for this indication. Regarding chronic orofacial pain, one study compared the efficacy and adverse effects of celecoxib (a COX-2 inhibitor) with naproxen (an NSAID) and placebo in the treatment of painful TMJs.[57] In this randomized, double-blind, placebo-controlled trial, 68 subjects with painful TMJs secondary to disk displacement with reduction (DDWR) received celecoxib 100 mg twice a day, naproxen 500 mg twice a day, or placebo for 6 weeks. Subjects were evaluated with standard measures of efficacy: pain intensity measured by visual analog scale, maximal comfortable mandibular opening, and quality of life questionnaire, at baseline (1 week after discontinuing previous analgesic therapy) and again after 6 weeks of drug treatment. Naproxen significantly reduced the symptoms of painful TMJ DDWR as determined by most efficacy measures. Significant improvement in pain intensity occurred within 3 weeks of treatment, and this was sustained throughout the 6-week study. Clinically significant improvement in mandibular range of motion was observed for naproxen compared with celecoxib and placebo. Overall, celecoxib showed slightly better pain reduction than placebo but was not significantly effective for temporomandibular-disorder pain.

Meloxicam

Indications

Meloxicam is a COX-2 specific inhibitor NSAID used mainly in treating pain associated with arthritis. It reduces pain, swelling, and stiffness of the joints.

Dosage

The usual oral dose for osteoarthritis is 15 mg daily, taken by mouth, usually once daily, but lower doses of 7.5 mg are advised in older patients.

Adverse effects

Doses higher than 15 mg increase the chance of gastric distress. Meloxicam has a slow onset and it may take up to two weeks before the full benefits take effect. The most common side effects are gastritis, nausea, drowsiness, and diarrhea. Serious side effects include bruising or bleeding, fainting, fast or pounding heartbeats, persistent or severe headache, mental or mood changes, ringing in the ears (tinnitis), sudden or unexplained weight gain, swelling of the hands or feet, and vision changes.

Efficacy for chronic pain

Meloxicam has had very little examination of its value in chronic facial pain. The only hint that it might have real value comes from a 2009 animal study that examined the antiallodynic effects of meloxicam on diabetic neuropathic pain.[58] The authors found that injection of meloxicam elevated the disease lowered threshold in the von Frey test and they concluded that it exerts antiallodynic effects on established neuropathic pain in diabetic mice. In summary, this drug is not suggested for chronic pain control.

Etodolac

Indications

Etodolac is indicated as an analgesic based on activity in the oral surgery model and a more favorable profile of GI safety. Etodolac is reported to be 10-fold more selective for COX-2 compared with its effect on COX-1. This sparing of COX-1 activity gives rise to greater gastric tolerance, which has been demonstrated in many studies.[59] The limited data in the oral surgery model suggests that etodolac is useful as an analgesic for dental indications, with a prolonged duration of action and favorable GI safety with repeated administration.

Dosage

The recommended total daily dose of etodolac for acute pain is up to 1000 mg. This medication is usually given as 200 or 400 mg every 6–8 hours. Doses of etodolac greater than 1000 mg/day have not been adequately evaluated in well-controlled clinical trials. For osteoarthritis or rheumatoid arthritis, the typical dose is 300 mg two or three times a day. For patient who needs to be on this medication for a sustained time, a maximum dose of 600 mg/day is suggested.

Adverse effects

The most frequently reported adverse experience, occurring in approximately 1–10% of patients taking etodolac, is GI pain related to gastritis, constipation, diarrhea, dyspepsia, gross bleeding, or perforation. Other less common side effects include abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritis, rashes, and tinnitus.

Efficacy for chronic pain

Like the other NSAIDs, etodolac has not been used for chronic pain control other than in patients with osteoarthritis or rheumatoid arthritis. However, in 2004 a study examined the effect of etodolac on experimental neuropathic pain in a rat model.[60] This study examined heat-evoked hyperalgesia changes before and after medication in a chronic nerve constriction injury (CCI) in the sciatic nerve of rats. The authors reported that etodolac alleviated heat-evoked hyperalgesia in the CCI rats and suggested that etodolac is useful for treatment of neuropathic pain.

Cardiotoxicity and NSAIDs

NSAIDs have been the mainstay in the treatment of pain of osteoarthritis and they are generally moderately effective for this purpose. However, the addition of an FDA black box warning on all of the NSAIDs regarding cardiovascular toxicity caused moderate concern for many patients. As mentioned previously, the COX-2 selective agent rofecoxib was withdrawn from the market in 2004 due to these concerns. What is not yet clear is whether and to what degree all of the NSAIDs (whether COX-2 selective or nonselective) have a similar risk profile to rofecoxib. Painting all of these agents with a broad brush is not logical but, conversely, ignoring the problem is not logical either. The NSAID medications presented in this chapter are useful in many patients, but concerns over side effects have begun to limit their use, with patients and clinicians reaching for alternate agents. However, in the absence of strong evidence the decision to use these medications is a calculation of risk versus benefit, made jointly by the prescribing doctor and the patient.

3.5 Systemic Corticosteriods

As mentioned in the introduction, corticosteroid injection into the TMJ and topical corticosteroid use for ulcerative and inflammatory reactions of the oral mucosa are covered in Chapters 18 and 12, respectively. Here we discuss the use of prescription corticosteroids taken systemically for acute and chronic oral pain.

3.5.A Methylprednisolone and Prednisone

Indications

Both methylprednisolone and prednisone are used to suppress inflammation. Methylprednisolone is available as an oral tablet but can also be given intravenously. Prednisone is given orally and the approximate equivalence between methylprednisolone and prednisone is 4 mg equivalent to 5 mg, respectively. This means that the difference is quite small with regard to the effects and side effects of these two medications. The initial dosage of methylprednisolone tablets may vary from 4 to 48 mg/day depending on the specific disease being treated. In situations of less severe inflammation, lower doses will generally suffice, whereas in selected patients higher initial doses may be required. The general rule is that the initial dosage should be maintained or adjusted, based on side effects, until a satisfactory response is noted. After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage that will maintain an adequate clinical response is reached. Because corticosteroids have substantial adverse effects associated with their use, constant monitoring of drug dosage is needed. Because these medications cause adrenal suppression, a patient who is going to be exposed to a known stressful situation (e.g., surgery) may need to have the dosage of methylprednisolone increased for a period of time consistent with the situation. Using this drug for more than 1 week necessitates that it be withdrawn gradually rather than abruptly. Because cancer can and does trigger inflammatory pain, corticosteroids possess analgesic properties for a variety of cancer pains, especially bone pain, neuropathic pain from neural infiltration or compression of neural structures, headache due to increased intracranial pressure, or arthralgia. Corticosteroids are used when NSAIDs are insufficient and as an interim therapy when awaiting more definitive answers about the cancer.

Dosage

For the reason just noted and because of the extended duration of action, corticosteroid therapy should be limited to episodic interventions. Pain crisis may respond to an aggressive 6-day course of oral methylprednisolone with rapid tapering. The choice of agent is the option of the clinician in the individual situation.

Adverse effects

Despite the potent anti-inflammatory and analgesic effects of glucocorticoids, prolonged administration is fraught with numerous well-known, potentially serious side effects that can affect many systems. Weekly assessments are required to ensure that benefits are sustained since, as mentioned, long-term corticosteroid therapy has substantial adverse effects.[61,62] The main indication for this drug is to suppress inflammation, but if a patient has an infection, the corticosteroid may suppress local inflammatory signs of the infection, thus allowing dangerous progression of the infection. Because it changes the natural immunosuppresion systems it is not uncommon for a patient taking methylprednisolone to develop a new infection (e.g., oral candidiasis) during the period of steriod use. Obviously with increasing doses of corticosteroids, the rate of these secondary infections increases.[63] There are many other complications associated with long-term corticosteroid use such as posterior subcapsular cataracts, and glaucoma with possible damage to the optic nerves. These drugs are not indicated during pregnancy, in nursing mothers, or in women of child-bearing age. Administration of live vaccines or live, attenuated vaccines is contraindicated in patients receiving corticosteroids, and the use of methylprednisolone tablets in a patient with active tuberculosis or any other infectious disease should be avoided.

Efficacy for chronic pain

Corticosteriods are used alone and in combination with other immunosuppressive medications to manage rheumatoid arthritis but have not proven helpful in chronic osteoarthritis, chronic musculoskeletal disease, or neuropathic pain.

Rheumatoid arthritis

A 2001 study reviewed the current status of these medications.[64] The principle behind using these corticosteroids is that early suppression of rheumatoid arthritis disease will prevent or minimize the amount of progressive joint destruction and functional impairment the patient suffers. Experts will advocate using combinations of methotrexate, sulfasalazine, hydroxychloroquine, and prednisolone. The combination of these drugs has been suggested to be more beneficial than monotherapy in patients with early rheumatoid arthritis. While methylprednisolone does not make sense for acute postoperative pain control, it does have potential additive value as a medication for the treatment of chronic mucosal-disease-induced inflammatory pain, such as benign mucous membrane pemphigoid (BMMP). The data on adding a systemic methylprednisolone medication to topical corticosteroid agents for oral mucosal disease is reviewed in Chapter 12.

Chronic musculoskeletal pain

In 1985, a double-blind crossover study compared prednisone with a placebo medication in the treatment of fibrositis

(an alternate term for fibromyalgia).[65] The study involved 20 patients who were diagnosed with fibrositis and compared the effects of prednisone versus placebo; each patient received either prednisone (15 mg/day) or placebo for 14 days of therapy. The authors concluded that this treatment did not help this group of patients and suggested that most of the outcomes worsened.

Neuropathic pain

Experimental peripheral mononeuropathic pain is mitigated by methylprednisolone, which presumably suppresses ectopic neural discharges from injured nerve fibers.[66] Corticosteroid suppression of neuroma discharge and evidence that steroids act directly on the membrane to block C-fiber transmission are further support for the antinociceptive effect of these medications.[67,68] Corticosteroids promote the synthesis of phospholipase A2 inhibitor, thus inhibiting the arachidonic acid–prostaglandin pathway of inflammatory sequelae. That chronic corticosteroid treatment prevents the development of substance-P-mediated autotomy and neuropathic edema, and blocks neurogenic extravasation, is further evidence of the anti-inflammatory aspect of steroid action.[69] The analgesic and anti-inflammatory effects of ingested or injected corticosteroids are useful in a variety of painful conditions. Chronic inflammatory joint pain is mitigated by intra-articular injection of corticosteroids, which may be a helpful adjunct for acute pain after arthroscopic surgery as well.[70] A short course of oral prednisone may benefit patients with migraines transformed to chronic daily headaches by medication overuse.[71]

Chronic daily headaches

Corticosteroids are used as a primary acute treatment for cluster headache[72] and occasionally to assist during the medication withdrawal period in patients suffering from presumptive medication overuse headache (MOH). In 2008 a report described the use of prednisone as an analgesic supplement during medication withdrawal.[73] A small and moderately controversial study compard the efficacy of prednisone for the treatment of withdrawal symptoms in 20 patients with MOH, using a randomized, placebo-controlled, double-blind design. Using the total number of hours the patient reported moderate to severe pain during the few days of analgesic medication withdrawal, they showed that the prednisone group was significantly lower than the placebo medication group. The authors suggested that prednisone might be effective in the treatment of medication withdrawal headache.

3.6 Special uses of salicylates, nonopioid analgesics, and NSAIDs

3.6.A Special case: cardioprotective effect of salicylates

Many patients have been advised by their physicians to use low-dose aspirin (81 mg) daily for its cardioprotective effect. A dilemma arises when a patient is also prescribed an NSAID to manage either acute or chronic pain. Should the patient stop the aspirin, take the aspirin and NSAID simultaneously, or take the aspirin first then wait an hour and take the NSAID (or vice versa)? The FDA notified consumers and healthcare professionals that taking ibuprofen for pain relief and low-dose aspirin at the same time may interfere with the benefits of aspirin taken for the heart. The notification stated that it is all right to use ibuprofen and aspirin together, because aspirin has a long-term ability to suppress platelet aggragation since it suppresses the production of prostaglandins and thromboxanes due to its irreversible inactivation of the COX enzyme. Cyclooxygenase is required for prostaglandin and thromboxane synthesis. Conversely, NSAIDs have only a short-term inactivation of COX; therefore logic dictates that the aspirin should be taken on waking and, after 30–60 minutes, the NSAID should be taken. The FDA recommends that consumers contact their healthcare professional for more information on the timing of when to take these two medicines, so that both medicines can be effective.[74]

3.6.B Special case: preventative analgesia

Most studies in which an NSAID is administered orally after onset of pain demonstrate an onset of activity within 30 minutes and peak analgesic activity at 2–3 hours after drug administration. An early attempt to optimize ibuprofen analgesia in the immediate postoperative period following local anesthesia offset involved administration of the drug prior to oral surgery. This allows sufficient time for drug absorption during the surgical procedure and the 1- to 2-hour duration of standard local anesthetics postoperatively. Preoperative administration of 400 mg ibuprofen was demonstrated to increase by approximately 2 hours the time to the first postoperative dose of analgesic compared with placebo pretreatment.[75] A subsequent study demonstrated that preoperative administration of 800 mg ibuprofen significantly lowered pain intensity over the first 3 hours postoperatively as the residual effects of the local anesthetic dissipated.[76] Administration of a second dose of ibuprofen 4 hours after the initial dose extended this preventive analgesic effect to result in less pain than placebo, acetaminophen

(given both pre- and postoperatively), or acetaminophen plus 60 mg codeine (administered postoperatively). The ability to suppress the onset and lower the intensity of postoperative pain up to 8 hours is replicable[77,78] and extends to the use of other NSAIDs.[79] Comparison of ibuprofen administration prior to periodontal surgery versus administration immediately following surgery demonstrated that both groups experienced a significant delay in pain onset compared with placebo.[80] A similar study in the oral surgery model using naproxen also could not differentiate between preoperative or postoperative administration, suggesting that preoperative administration is not critical for suppressing pain onset.[81] Recognition of the induction of COX-2 in the postoperative period[82] suggests that blockade of the formation of prostanoids released during surgery by constitutive COX-1 is less important than suppression of COX-2 and prostanoid release during the postoperative period. Consistent with this observation is the demonstration that both preoperative and postoperative administration of 800 mg ibuprofen are equally effective at suppressing pain and prostaglandin E_2 levels at the extraction site.[83] These observations support the administration of ibuprofen and other NSAIDs prior to the induction of COX-2 and subsequent release of prostanoids as a preventive analgesic strategy for suppressing pain in the immediate postoperative period as well as to inhibit peripheral and central hyperalgesia leading to pain at later times.

3.7 Final recommendations

Nonopioid analgesics for chronic orofacial pain

1. The American College of Rheumatology's recommendation to use acetaminophen as the first medication to manage osteoarthritis is both logical and controversial. It is logical because so many patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) get gastritis that acetaminophen is less likely to induce gastritis; it is controversial in that the medication unless taken in high doses (4000 mg daily) is not adequate for pain control.
2. The choice of a nonopioid analgesic versus an NSAID must be up to the clinician based on the individual patient's situation and response to treatment.
3. Tramadol is not logically used as a rapid-acting analgesic for acute pain, but it has been proven both logical and mildly efficacious for osteoarthritis, chronic musculoskeletal pains, and even in some neuropathic pain problems.
4. Tramadol has advantages over NSAIDs and stronger opioids in that it causes only a low level of gastrointestinal dysfunction. However, it does have opioid receptor binding so it has an abuse potential even though the US Food and Drug Administration (FDA) does not list it as a scheduled narcotic.

Salicylates for chronic orofacial pain

5. Although salicylates (aspirin and diflunisal) are beneficial for acute pain and for cardioprotection in a low-dose formulation, they have little or no role to play in chronic pain because of the high likelihood of aspirin-induced gastrointestinal injury.

NSAIDs for chronic orofacial pain

6. Both the nonselective and selective NSAIDs have a role to play in chronic arthritic disease management. However, they should be prescribed with caution because, like the salicylates, NSAIDs can induce gastrointestinal injury and they now have an FDA "black box" warning for cardiovascular thrombotic events.
7. Not all NSAIDs are equal in their potential to cause gastrointestinal (GI) injury and thrombotic events. The selective cyclooxygenase-2 (COX-2) NSAIDs (celecoxib [celebrex], meloxicam, etodolac) and to a lesser degree at least one of the nonselective COX inhibiting NSAIDs (e.g., nabumetone) have a lower prevalence of induced adverse GI events; comparative data on NSAID thrombotic events is lacking.

Systemic corticosteroids for chronic orofacial pain

8. Corticosteroids (e.g., prednisone and methylprednisolone) are used systemically for both acute and chronic oral pain due to inflammation and also have a substantial adverse side-effect profile that requires constant monitoring during treatment.

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Chapter 4

Opioids for chronic orofacial pain with a focus on nonmalignant chronic pain

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4.1 Opioids for pain control

Opioids are highly important and effective analgesics when dealing with pain, whether it be acute or chronic. Because these drugs have many side effects and a high abuse potential, all healthcare providers who consider prescribing an opioid analgesic for a patient must first undertake a risk-versus-benefit analysis that takes into account the patient's other medications, medical and psychological status, and pain level at a minimum. For example, when you perform a minor surgical treatment on a patient (e.g., tooth extraction) the choices for a postsurgical pain control medication include nonopioid analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioid medications. The two most commonly used opioid drugs in this situation are codeine and hydrocodone, which are usually dispensed in combination with ibuprofen or acetaminophen. These opioids are categorized as moderate-strength analgesics and they are categorized by the US Food and Drug Administration (FDA) as Schedule III drugs, which means they are less dangerous than the more potent, Schedule II opioids (e.g., morphine, oxycodone, fentanyl, hydromorphone, oxymorphone, methadone). Many consider codeine or hydrocodone to be the first-line treatment for management of acute pain due to postsurgical and post-traumatic injury. The vast majority of acute traumatic or procedural pain is mild to moderate pain; selecting an opioid medication as the first choice for analgesia is not an evidence-based clinical practice. Most experts recommend that a Schedule II or III opioid is appropriate postsurgically only when a patient has severe postsurgical pain that a nonopioid or an NSAID does not relieve.

The two main concerns regarding the appropriate use of any medication are its efficacy and its adverse-effect profile. For example, NSAIDs produce gastritis, and acetaminophen can induce liver toxicity; for some patients, this shifts the balance of risk-to-benefit in the favor of opioids and in particular the noncombination-drug opioids.[1] Added to these two concerns is a third issue, namely, the inappropriate use of a prescription medication. In the last decade, prescription drug abuse, mainly of opioid prescriptions, has become a growing problem for law enforcement and regulatory officials, based on a pattern of "overprescribing" opioids.[2] Annual surveys about drug use in household and school populations clearly show that there is a rapidly rising rate of prescription drug misuse and abuse.[3] These considerations and other factors that influence analgesic choice are described in this chapter.

4.1.A Schedule III opioids

The drugs that are categorized as Schedule III by US law are considered to have the following characteristics: (1) a potential for abuse that is less than the drugs or other substances in Schedules I and II; (2) a currently accepted medical use in treatment in the United States; and (3) the potential that abuse may lead to moderate or low physical dependence or high psychological dependence.[4] In this group of drugs are two of the most commonly prescribed opioids: codeine and hydrocodone. Both are commonly used by physicians and dentists after a surgical procedure and for other spontaneous pain disorders and will be reviewed next. One opioid that is actually listed by the FDA as a Schedule IV analgesic for mild pain that is not be reviewed here is propoxyphene. The reason for its exclusion is that in 2009 the FDA added a "black box" warning to the labeling that comes with this drug to reflect the risk of overdose[5]: "Pro-

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poxyphene should be used with extreme caution, if at all, in patients who have a history of substance/drug/alcohol abuse, depression with suicidal tendency, or who already take medications that cause drowsiness (e.g., antidepressants, muscle relaxants, pain relievers, sedatives, tranquilizers). Fatalities have occurred in such patients when propoxyphene was misused." Finally, the analgesic agent tramadol, which does binds to opioid receptors but is not listed by the FDA as an opioid nor has it been given a schedule rating, is covered in Chapter 3.

Hydrocodone

Indications

Hydrocodone is an opioid with moderate potency indicated for moderate to severe pain. It is always combined with either a nonopioid analgesic or a nonsteroidal anti-inflammatory medication. Combination therapy is widely used for the clinical management of acute pain based on the principle that combining two drugs with different mechanisms of action provides additive analgesic effects while reducing the risk for adverse effects.

Dosage

Hydrocodone comes as a tablet, a capsule, a syrup, a solution (clear liquid), an extended-release (long-acting) capsule, and an extended-release (long-acting) suspension (liquid) to take by mouth. The tablet, capsule, syrup, and solution are usually taken every 4–6 hours as needed. The extended-release capsule and the extended-release suspension are usually taken every 12 hours as needed. There is no maximum (ceiling) dose for any of the pure opioid agonists since tolerance makes an individual progressively immune to the effects of these medications; however, maximum doses are determined by the inclusion of acetaminophen or ibuprofen with the hydrocodone. The usually prescribed dose of hydrocodone combined with either acetaminophen or ibuprofen is 5 or 7.5 mg and the typical dosing is four times a day.

Adverse effects

The side effects of the various opioids are qualitatively similar and are discussed under "Opioid side effects" (Sec. 4.1.C). If a unique side effect is associated with a specific formulation, this is discussed in the section dedicated to that particular opioid. Hydrocodone is not used as a stand-alone medication but is combined with either acetaminophen or ibuprofen; the unique side effects of each combination are typically related to the nonopioid analgesic in the combination and these side effects are discussed in detail in Chapter 3.

Efficacy for acute pain

A 2005 study compared the efficacy and tolerability of various combinations of opioids and nonopioid or NSAID analgesics (oxycodone 5 mg/ibuprofen 400 mg vs. oxycodone 5 mg/acetaminophen 325 mg and vs. hydrocodone 7.5 mg/acetaminophen 500 mg) versus a placebo in a dental pain model on 249 patients.[6] This was a multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group, single-dose study in patients experiencing moderate to severe pain after surgical removal of at least two ipsilateral impacted third molars. The authors reported that oxycodone 5 mg combined with ibuprofen 400 mg provided significantly greater analgesia when compared with oxycodone 5 mg combined with acetaminophen 325 mg. Oxycodone also had greater efficacy than hydrocodone 7.5 mg combined with acetaminophen 500 mg or the placebo medication. The lowest frequency of nausea and vomiting occurred in the groups that received oxycodone 5 mg/ibuprofen 400 mg (6.5% and 3.2%, respectively) and placebo (3.2% and 1.6%). They concluded that in patients with moderate to severe pain after surgery to remove impacted third molars, oxycodone 5 mg/ibuprofen 400 mg provided significantly better analgesia throughout the 6-hour study compared with the other opioid/nonopioid combinations tested, and it was associated with fewer adverse events. However, the results of this study must be weighed against the previously mentioned national epidemic of prescription drug abuse occurring in the United States. In addition, while adding an opioid to ibuprofen will make the combination more effective and in some cases is justified, for most dental procedures this is not justified. A clinical study evaluating the therapeutic benefits of this drug combination suggested that adding the opioid would result in a marginal additive analgesic effect in combination with 400 mg of ibuprofen alone, but with a greater incidence of side effects than use of the NSAID alone.[7]

Efficacy for chronic pain

Short-acting (also called immediate-release) opioids are not suggested for management of chronic pain, based on the conventional wisdom that prescription drug abuse is less likely in longer acting (also called extended-release) opioids because the peak serum levels are lower and therefore less likely to induce euphoric effects. A recent study compared patient responses to a longer acting opioid (extended-release morphine) with responses to a shorter acting opioid (hydrocodone plus acetaminophen) and placebo in a randomized, double-blind crossover study using markers of abuse liability.[8] Patients indicated their craving for drugs on visual analog scales (VASs) and completed the Addiction Research Inventory (ARI) scale questionnaire. The results in this

study suggested that differences in the ARI scores were statistically significant between groups but were judged by the authors of the study to be clinically unimportant. They concluded, in contrast to conventional wisdom, that long-acting opioids do not have a substantially lower abuse potential than do short-acting opioids or placebo.

A study that compared the effectiveness of two combination-drug formulations showed that hydrocodone 7.5 mg combined with ibuprofen 200 mg was more effective than codeine 30 mg combined with acetaminophen 300 mg.[9] Another study with mixed chronic pain patients compared oxycodone 5 mg and acetaminophen 325 mg taken four times per day for at least 6 weeks.[10] The neuropathic pain subjects also were taking gabapentin up to a daily dose of 2400 mg. The osteoarthritic patient group reported 64.3% of patients showed improvements in pain symptoms after 15 days of treatment. The neuropathic group reported that 83.3% of patients showed improvement; however, these patients did not have as great a reduction in hyperalgesia and more of the neuropathic pain subjects dropped out of the study than did those in the osteoarthritis group (37.1% vs. 58.3% respectively). The authors concluded that low-dose oxycodone/acetaminophen improved pain symptoms in the majority of the drug-compliant patients.

Codeine

Indications

Codeine is another Schedule III opioid with lower potency used mostly for moderate to severe postoperative pain or acute pain disorders. Codeine is a prodrug, which means it is not an active drug until it has been metabolized by the liver. The primary active compounds of this metabolism are morphine and codeine-6-glucuronide.[11,12] Roughly 5–10% of codeine will be converted to morphine, with the remainder either free or conjugated to form codeine-6-glucuronide (approximately 70%). This metabolism is performed by the P450 cytochrome (CYP) enzymes that are in the liver, especially the CYP-2d6 isoenzyme.

Dosage

Acetaminophen with codeine is commonly used for acute pain and can be taken as frequently as every four hours (q4h) as needed for pain (up to a maximum dose of 360 mg) in opioid-naïve patients. Those patients who are using opioids daily will most likely need and can have a larger dose. The biggest problem with giving a patient more acetaminophen and codeine is the maximum daily dose for acetaminophen is 4000 mg of acetaminophen per day. The common combinations of codeine and acetaminophen are 300 mg of acetaminophen combined with a variable dose of codeine phosphate usually designated by a number (No. 2 has 15 mg of codeine phosphate; No. 3, 30 mg; No. 4, 60 mg).

Adverse effects

Like all opioids, codeine, even though it is a lower potency opioid, can produce physical and psychological dependence. Conventional wisdom holds that the withdrawal symptoms for codeine are relatively mild compared with the other opioids. Codeine is like many opioids that can cause a drug–drug interaction with other prescription drugs. The most concerning are those that interfere with CYP-2d6 metabolism such as the serotonin selective reuptake inhibitors (SSRIs), with the exception of (sertraline) Zoloft. The most potent inhibitor is paroxetine (Paxil), followed by fluoxetine (Prozac). In fact, taking a concurrent SSRI and a codeine-containing analgesic will produce an increase in serotonin, risking a dangerous serotonin syndrome adverse reaction.[13] Sometimes the result of this inhibition is that patients taking codeine postoperatively will take several tablets to relive their pain and the problem this causes is they are at risk of consuming a toxic, liver-damaging dose of acetaminophen.[14] If the drug-to-drug interaction can be predicted and codeine is still the analgesic choice, a reasonable work-around strategy is to suggest that the patient take a holiday from using the SSRI medication well before a planned procedure, based on the length of the half-life of the SSRI or other CYP-2d6 inhibitor being used. Finally, as mentioned, the conversion of codeine into an active analgesic requires the CYP-2d6 liver enzyme. This enzyme may be missing in some individuals due to a genetic polymorphism (about 7% of the Caucasian population). Individuals who inherited a CYP-2d6 deficiency will get many of the adverse effects associated with codeine but little analgesia or euphoria because it is not metabolized.

Efficacy for acute pain

A Cochrane review examined whether combining analgesic drugs from different classes with different modes of action improves the efficacy and tolerability or allows a lower dose of each drug than is achieved using the same drugs independently.[15] Specifically the review examined the efficacy of a single-dose oral acetaminophen plus codeine in treating acute postoperative pain and any associated adverse events based on 26 studies with 2295 participants. The review's results suggested that adverse events were mainly mild to moderate in severity and that incidence did not differ between groups. Moreover, combining acetaminophen with codeine provided clinically useful levels of pain relief in about 50% of patients with moderate to severe postoperative pain, compared with less than 20% seen with the placebo.

A clinical trial evaluating the combination of a single dose of 400 mg ibuprofen plus 60 mg codeine compared with each drug alone and placebo demonstrated that the ibuprofen-plus-codeine combination resulted in slightly higher mean hourly analgesic scores and produced substantially greater analgesia than codeine 60 mg, but the combination did not produce significantly greater analgesia than ibuprofen 400 mg alone.[16] Comparison of ibuprofen 400 mg plus codeine 60 mg versus ibuprofen 400 mg in another study demonstrated significant differences on several, but not all, derived measures of analgesic activity.[17] Side effects were more frequent following the opioid-containing combination but consisted of minor adverse events such as drowsiness and "faintness." McQuay demonstrated a 30% increase in analgesic effect with the addition of 20 mg codeine to 400 mg ibuprofen in a crossover study with two doses of the drugs being evaluated.[18] With this lower dose of codeine, no tendency for greater incidence of adverse effects was detected and greater than 70% of subjects expressed a preference for the combination. These and other similar studies provide a basis for adding codeine to a 400-mg dose of ibuprofen as needed to produce additive analgesia but with a dose-related increase in side effects. A minimum dose of 20–30 mg of codeine is needed in combination with 400 mg ibuprofen to produce detectable additive analgesia with minimal side effects. Administration of a traditional dose of 60 mg codeine will usually produce additive analgesia, but for relatively short duration (1–2 hours), compared with the usual duration of ibuprofen (4–6 hours) while producing a significant increase in the incidence of side effects. In the absence of a marketed fixed-dose combination, it may be more practical to initiate analgesic treatment with 400–600 mg ibuprofen on a fixed schedule and dispense 30-mg tablets of codeine to be taken as needed for pain not adequately controlled by the NSAID. This strategy will result in exposure to the opioid for only those patients in need of additional pain relief, thus resulting in a more favorable therapeutic ratio than exposing all patients to opioid side effects. Prescribing codeine as a single entity, that is, not in a fixed combination with another drug, requires careful adherence to regulations associated with Schedule II opioids.

Efficacy for chronic pain

Codeine combinations are not recommended for chronic pain for various reasons. First, the population has a high prevalence of polymorphisms that interfere with codeine metabolism. Second, the medication has a higher prevalence of nausea than many other opioids[19] and many patients claim to have had a prior adverse reaction to it. Third, while there is some research[8] that disputes the convention of using extended-release preferentially over immediate-release opioids, this conclusion is not widely held by experts in the field and needs additional verification.

4.1.B Schedule II opioids

When pain is severe and Schedule II opioids (e.g., morphine, oxycodone, fentanyl, hydromorphone, oxymorphone, and methadone) are indicated, the liabilities of these medications become a concern. Schedule II drugs have the following characteristics: (1) a potential for abuse that is less than the drugs or other substances in Schedule I; (2) a currently accepted medical use in treatment in the United States; and (3) the potential that abuse may lead to moderate or low physical dependence or high psychological dependence. Opioid adverse effects include nausea, constipation, dizziness, sedation, respiratory depression, dependency, and abuse. These adverse reactions often cause dentists to shy away from Schedule II opioids for analgesic control of orofacial pain, and without specific training and knowledge this caution is probably appropriate. In addition, Schedule II opioids are often not prescribed for fear of regulatory investigation and patients developing dependence on these medications. Fortunately, the current literature suggests that drug dependence is not a problem with opioid use in acute pain.[20] The use of Schedule II and III opioids on a longer term basis (for chronic nonmalignant pain) is discussed in Section 4.2.

Morphine

Indications

Morphine is considered the standard opioid and is often the drug of first choice in the treatment of moderate-to-severe cancer and noncancer pain.[21,22] Normally, morphine is titrated to maximum tolerability before moving on to another opioid such as oxycodone, fentanyl, hydromorphone, oxymorphone, or methadone. Morphine is available in a variety of formulations (parenteral, oral, rectal) and the oral form is available in a range of preparations, from immediate release to sustained release, allowing it to be better titrated to the patient's response.

Dosage

The immediate-release oral formulation of morphine is recommended initially due to its ease of administration and convenience of use. The generic form comes in 15- and 30-mg immediate-release (IR) tablets as well as 15-, 30-, 60-, 100, and 200-mg extended-release (ER) tablets. Most experts recommend switching from an immediate-release morphine sulfate formulation once an acceptable dose is established, to a controlled-release form so that the blood levels of the medication are more stable. A typical regimen

consists of a extended-release preparation given every 8–12 hours with breakthrough doses of immediate-release form given every 3–4 hours in between if needed. As a guide, the cumulative as-needed doses should not exceed the total dose given as a sustained preparation for that interval. For example, a patient requiring morphine 120 mg ER every 12 hours should receive morphine 30 mg IR every 3 hours, as needed for breakthrough pain. Regimens will require frequent adjustments, allowing 3–7 days for the patient to respond before initiating a change unless toxicity is apparent. Should a patient fail morphine therapy, another opioid should be instituted and dosed according to its morphine equivalency. Initial dosing of the new opioid should be 25–50% less than the expected equivalent dose of morphine since the patient may not be fully cross-tolerant to the new agent. Cross-tolerance can be seen particularly when changing from a more potent to a less potent agent and is a result of variable effects of each opioid on the opioid receptors.

Adverse effects

See "Opioid side effects" (Sec. 4.1.C) for information on the adverse effects of morphine.

Efficacy for acute pain

Morphine is FDA approved and an effective pain reliever, but it is not generally indicated as a first-line option for pain in the postoperative period for outpatients or for nonextensive acute traumatic pain. The logical approach—and the approach recommended by the World Health Organization (WHO)—for acute pain management is to use nonopioid analgesics first, medium-potency opioids second, and then and only then consider highly potent opioids such as morphine or any of the other Schedule II opioids (see Table 4.1).[23] The ultimate choice of the analgesic is the treating clinician's decision and should be based on the nature of the traumatic injury and the extent of the surgical procedure performed.

Efficacy for chronic pain

There have been several recent studies that have examined and demonstrated excellent efficacy of extended-release morphine sulfate tablets as a treatment for chronic pain.[24,25] An international expert panel reviewing evidence regarding the role of highly potent opioids in the management of chronic severe pain in the elderly concluded that "World Health Organization step III opioids are the mainstay of pain treatment for cancer patients and morphine has been the most commonly used for decades. In general, high level evidence data (Ib or IIb) exist, although many studies have included only a few patients."[26] Additional information on the efficacy of opioids for non-cancer pain and cancer pain is presented in Sections 4.2 and 4.3.

Oxycodone

Indications

Oxycodone is a strong opioid that acts at μ- and κ-opioid receptors. It has pharmacological actions similar to other opioids, but with a specific pharmacologic profile and greater analgesic potency than morphine.

Dosage

Oxycodone comes in an immediate-release form (5 mg IR capsules, or in combination products with aspirin [Percodan®] or acetaminophen [Percocet®]) for the relief of pain. It also comes in an extended-release or controlled-release form (Oxycontin®). The controlled-release tablets come in doses of 10, 15, 20, 30, 40, 60, 80, and 160 mg CR formulation. The typical prescription is one tablet every 12 hours. The three latter doses (60, 80, and 160 mg) are for use only in opioid-tolerate patients. Oxycontin® is effective for moderate-to-severe cancer pain and allows the convenience of every-12-hours administration. In most markets, oxycodone is significantly more expensive than morphine and is thus less attractive as a first-line analgesic for this and other reasons.

Table 4.1 Choosing a medication for pain management

Pain rating (scale of 0–10)	Primary medications	Adjunct medications
Mild pain or a rating of 0–3	Nonopioid, such as an NSAID or acetaminophen	Antidepressant or anticonvulsant
Moderate pain or a rating of 4–6	Weak opioid, such as codeine or hydrocodone	NSAID, acetaminophen, COX-2 inhibitors, antidepressant, or anticonvulsant
Severe pain or a rating of 7–10	Strong opioid, such as morphine, oxycodone, or fentanyl	NSAID, acetaminophen, antidepressant, or anticonvulsant

COX-2, cyclooxygenase-2; NSAID, nonsteroidal anti-inflammatory drug.

Adverse effects

See "Opioid side effects" (Sec. 4.1.C) for information on the adverse effects of oxycodone.

Efficacy for acute pain

Oxycodone is a strong opioid agonist used to treat moderate to severe pain and, like morphine, it is not a first-line agent for management of postoperative pain in outpatients or for nonextensive acute trauma. One advantage of oxycodone and morphine is that they are not mandatorily formulated as a combined drug as are hydrocodone and codeine. This is an advantage for a patient who cannot take NSAIDs or acetaminophen for various reasons. A 2009 meta-analysis of the analgesic efficacy of oxycodone alone and in combination with acetaminophen in adults with moderate-to-severe acute postoperative pain concluded that oxycodone 15 mg alone compared with placebo yielded a number-needed-to-treat (NNT) score of 4.6 (defined as 50% pain relief); for oxycodone 10 mg plus acetaminophen 650 mg, the NNT was 2.7.[27]

Efficacy for chronic pain

A number of randomized double-blind studies, comparing oxycodone versus morphine or comparing different release forms of oxycodone have demonstrated that the drug is equally as effective as morphine and in general is well tolerated in the treatment of cancer pain.[28–31]

Fentanyl

Indications

Fentanyl is used for cancer-pain management and as a palliative medicine in the form of a transdermal patch (e.g., Duragesic®), which is especially useful in those patients who do not have enteral (e.g., by mouth) access or for whom nausea and vomiting limit the ingestion of the required dose of opioid. However, fentanyl in a transdermal patch contains a high concentration of this potent Schedule II opioid agonist, resulting in a high potential for abuse and associated risk of fatal overdose due to respiratory depression.

Dosage

As this chapter does not cover the use of intravenous or injected opioids, the dosing for fentanyl citrate injections (50 µg/mL) is not discussed. Fentanyl in the transdermal patch has substantial limitations and risks and it is strongly recommended that it should only be used in patients who are already receiving opioid therapy and have demonstrated opioid tolerance and who require a total daily dose equivalent to or greater than 25 µg/h. Patients who are considered opioid-tolerant are those who have been taking at least 60 mg of morphine daily for a week or longer (or an equipotent dose of other Schedule II opioids).

Adverse effects

The results of eight studies in cancer and noncancer pain were pooled and demonstrated that pain scores were significantly reduced with fentanyl but adverse events were high in active and placebo groups.[32] See "Opioid side effects" (Sec. 4.1.C) for more details on opioid adverse effects.

Efficacy for acute pain

Fentanyl is not indicated for pain in the postoperative period.

Efficacy for chronic pain

The efficacy and tolerability of transdermal fentanyl for long-term treatment of cancer pain have been extensively studied and very well documented.[33–36]

Hydromorphone

Indications

Hydromorphone is a water-soluble opioid that is several times more potent than morphine, allowing for smaller doses to be used. It is available in parenteral, rectal, subcutaneous, and oral formulations. It can also be administered via epidural and intrathecal routes. Hydromorphone should be considered particularly for patients on morphine who are having side effects of increased confusion or myoclonus.[37]

Dosage

Hydromorphone comes in an immediate-release form and a continuous- or extended-release form. In non-opioid-tolerant patients, when used for acute pain, this medication is typically initiated at an oral dose of 2–4 mg every 4 hours. In elderly patients, the starting dose is usually lower. For chronic pain patients the dose and formulation of the analgesia (immediate or extended release) will vary substantially depending on the patient's opioid tolerance. In chronic pain, doses should be administered around-the-clock and if needed a "rescue" or supplemental dose of 5–15% of the total daily dose may be administered every 2 hours. Periodic reassessment after the initial dosing is always required.

Adverse effects

See "Opioid side effects" (Sec. 4.1.C) for information on the adverse effects of hydromorphone.

Efficacy for acute pain

Like morphine and oxycodone, hydromorphone is not indicated as a first-line medication for acute pain in the postoperative period following minor procedures, although it clearly has efficacy for acute pain.[38]

Efficacy for chronic pain

A number of randomized double-blind studies, comparing hydromorphone vs. morphine or comparing different release forms of hydromorphone, have demonstrated that the drug is equal to or better than morphine and in general is well tolerated in the treatment of cancer pain.[39–41] One report uniquely suggested this medication is better at relieving continuous dull pain versus sharp intermittent cancer pains.[42]

Oxymorphone

Indications

An oral immediate-release tablet formulation of oxymorphone is approved for the treatment of acute moderate-to-severe pain. This medication is also available as an extended-release formulation. Single doses of oxymorphone IR have been reported to provide significant pain relief after orthopedic surgery and dental surgery.

Dosage

Oxymorphone IR should be administered every 6 hours as 5- or 10-mg tablets. The extended-release form of oxymorphone hydrochloride (Opana-ER®) comes in tablet strengths of 5, 10, 20, and 40 mg for oral administration every 12 hours.

Adverse effects

See "Opioid side effects" (Sec. 4.1.C) for information on the adverse effects of oxymorphone.

Efficacy for acute pain

The extended-release, oral form of this medication (Opana-ER) is not indicated for pain in the immediate postoperative period due to the risk of oversedation and respiratory depression that outweighs the analgesic efficacy of the medication. A double-blind, placebo-controlled study evaluated three different doses of oxymorphone IR for efficacy and safety (compared with oxycodone IR) in patients with acute moderate-to-severe postsurgical pain.[43] Results showed that all oxymorphone IR doses were superior to placebo in pain-relief efficacy. Opioid-related adverse events for oxymorphone were equivalent to those seen with oxycodone and generally were of a mild or moderate level. This medication, however, would not be a first-line choice for minor procedures.

Efficacy for chronic pain

Two independent randomized and controlled studies examined the efficacy of oral oxymorphone (extended-release form) for the treatment of chronic low back pain.[44,45] One study concluded that oxymorphone ER is generally well tolerated without unexpected adverse events over the 12-week treatment period in opioid-naïve chronic back pain patients. The other study concluded that, in those patients who successfully titrated to an effective dose of oxymorphone ER, it was found to be effective and generally well tolerated, independent of patients' age, sex, or previous opioid use.

Methadone

Indications

Methadone is a useful alternative to morphine, but it requires greater clinical management due to its many potential drug–drug interactions. Because it is an effective opioid analgesic for severe pain and has a relatively low cost, it is increasingly used as a first-line opioid in chronic-pain centers.

Dosage

For chronic pain, the most conservative approach for dosing is to begin with a fixed dose of methadone, 5 or 10 mg orally two or three times per day for 4–7 days. Then if incomplete pain relief is still present, the dose is increased by 50% on a 4- to 7-day schedule until stable pain relief is achieved. For breakthrough pain while on chronic methadone, it is common to use an alternative short-acting oral opioid with short half-life (e.g., morphine 10 mg) every 1 hour as needed to provide adequate pain relief during the titration phase.

Adverse effects

The adverse effects of methadone, like all of the opioids, are sedation, confusion, and even death. The FDA issued a notice in 2006 to healthcare providers based on reports of death and life-threatening adverse events such as respiratory depression and cardiac arrhythmias in patients receiving methadone. These adverse events are the possible result of unintentional methadone overdoses, drug interactions, and

methadone's cardiac toxicities (QT prolongation and torsades de pointes).

Efficacy for acute pain

Methadone is not recommended for management of acute postoperative pain.

Efficacy for chronic pain

Methadone is efficacious in rotation with other opioids and may be an effective alternative for cancer patients, although its equianalgesic dosing to morphine has not been firmly established and can vary widely depending on the cumulative dose of morphine and the patients underlying level of opioid tolerance.[46–48] A 2009 article summarized the recommendations of the American Pain Society and the American Academy of Pain Medicine on the use of chronic opioid therapy in chronic noncancer pain patients.[49] These guidelines strongly recommend that due to methadone's complicated and variable pharmacokinetics and pharmacodynamics its use should be initiated and the dose titrated cautiously and only by clinicians familiar with its use and risks (based on moderate-quality evidence).

4.1.C Opioid side effects

Two issues to be considered regarding opioid side effects are drug–drug interactions and genetic variations that contribute to adverse effects. With regard to serious adverse drug reactions, other central nervous system (CNS) depressants, including sedative–hypnotics, general anesthetics, phenothiazines, antidepressants, and alcohol, used along with an opioid will produce additive CNS depressant effects. Some antihistamines and medications for allergies, hay fever, or upper respiratory infections also cause additive sedation. All of the following are known to cause adverse reactions when combined with opioids: almost all other prescription pain relievers; seizure medications such as carbamazepine; muscle relaxants such as cyclobenzaprine; hypnotics such as triazolam; some anesthetics (including dental anesthetics); serotonin selective reuptake inhibitors;[50] and monoamine oxidase (MAO) inhibitors. Serotonin–norepinephrine reuptake inhibitors, such as duloxetine, and tricyclic antidepressants, such as amitriptyline, may also lead to serious side effects, including coma. Anticoagulants such as warfarin will also interact with opioids and alter metabolism rates. Finally, antibiotics such as rifampin and antivirals such as zidovudine can cause serious side effects when combined with opioids.

The most common predictable side effects associated with opioid therapy are nausea, somnolence, and constipation. Moreover, patients with renal impairment and the elderly are at especially high risk of neurotoxicity, which may manifest as cognitive impairment, hallucinations, delirium, generalized myoclonus, hyperalgesia, and allodynia.[51] Respiratory depression can also occur with opioids but this is usually more of an issue in hospital settings. Nausea may occur with the initiation of opioid medications, but tolerance develops rapidly. Patients can be provided with antiemetics for the first 3–4 days to cover the potential for nausea. Sedation and cognitive impairment may also occur with initial dosing or with a dosage increase; however, patients usually develop tolerance to this effect. If they do not, consider changing opioid agents or adding a stimulant medication. Opioids slow gastric motility and inhibit the propulsive contractions in the bowel. Opioid-induced constipation is an important cause of chronic nausea and both are commonly seen in opioid users.[52] Hence, it is an essential part of management to ensure that the patient is well hydrated to maintain a soft stool. All patients taking opioids should be placed on a constipation-prevention protocol.[53] This protocol has three elements:

- *Changing lifestyle* Patients must be counseled to increase their dietary fiber, fluid intake, exercise or physical activity, and time spent in toileting.
- *Prescribe laxatives and/or cathartics* A laxative eases defecation by softening the stool, whereas a cathartic accelerates defecation. There are multiple types of laxatives (e.g., Sennoside, docusate, GlycoLax), including those that increase the amount of water in the gut, those that soften and lubricate stools, and those that increase bulk and soften stools. The cathartics directly counteract the effect of the opioid medications by increasing intestinal motility, helping the gut to push the stools along; however, cathartics are less suitable for chronic use.
- *Rectal interventions* These are indicated if the first two methods are unsuccessful. There are multiple rectal interventions, including suppositories (usually glycerine based) and enemas (with normal saline). Unfortunately, unlike some of the other side effects, tolerance to constipation does not occur. Constipation management is the area where a pharmacist can have one of the greatest impacts on patient care, and all patients having prescriptions dispensed for pain medication should be counseled on constipation and the appropriate treatments.

4.2 Chronic use of opioids for noncancer pain

There are many chronic pain sufferers who have severe orofacial pain, where prolonged use of strong opioids needs to be considered. Examples include chronic severe pain due to an ongoing disease such as trigeminal neuropathic pain

(phantom tooth pain, severe myofascial pain, painful TMJ arthritis, atypical odontalgia, burning mouth syndrome, or postsurgical and idiopathic neuropathic pain). Using opioids for noncancer pain is commonplace in medicine and a study reported on their use in clinical practice via a survey of randomly selected physicians ($N = 1912$).[54] The results of this survey indicate that prescription of opioids for long-term administration is widespread for the treatment of nonmalignant chronic pain in medical practice. However, this point of view is not without controversy and caveats. As recently as 1991, it was suggested that there is no place for opioids in the treatment of chronic benign (non-cancer-related) pain.[55] Several reports published since then, however, support the long-term administration of opioids for chronic nonmalignant pain. Several reviews have suggested that quality of life is not improved as much as hoped for with chronic opioid use (see Sec. 4.2.B, on quality of life).

4.2.A What does the evidence suggest about opioids for noncancer pain?

The evidence suggests that patients with chronic noncancer pain whose pain cannot be controlled with nonopioid methods will benefit from sustained-release opioids when they are titrated to proper levels. For example, an open-label study in 100 patients with chronic pain, for whom all other possible treatments had failed, demonstrated good (51%) or partial (28%) pain relief from sustained-release opioids with no signs of respiratory depression.[56] A more controlled trial evaluated sustained-release oral codeine in 46 patients enrolled in a 7-day double-blind trial.[57] Patients receiving the codeine reported significant analgesia and improvement on a pain disability index but a higher incidence of nausea compared with placebo. Oral morphine (up to 60 mg twice a day) in a randomized, double-blind crossover study of 6 weeks' duration in patients nonresponsive to codeine, NSAIDs, and antidepressants produced significant pain relief with little effect on cognitive function or memory.[58] A case series examining the efficacy of methadone in the management of intractable neuropathic noncancer pain included 50 consecutive intractable neuropathic noncancer pain patients (average age 52.7 years) drawn from a tertiary care center.[59] All 50 patients were given oral methadone and the mean duration of follow-up in this study was 13.9 months. These patients had failed treatment with one or more conventional opioid analgesics (mean 2.8) at a mean maximal morphine dose of 384 mg (or equivalents) per day and 12 patients had failed spinal cord stimulation. The results showed that 19 patients (38%) did not tolerate initial methadone titration or thought their pain was worse on methadone; 5 patients (10%) declared initial benefit but required repeated dose escalation and eventually became nonresponders; and 26 patients (52%) reported mild (4), moderate (15), marked (6), or complete (1) pain relief. These 26 responding patients continued on methadone at a mean maintenance dose of 159.8 mg/day for a mean duration of 21.3 months. The authors suggested that methadone might have unique properties, including *N*-methyl-D-aspartate antagonist activity that makes it useful in the treatment of neuropathic pain.

Two review articles examined multiple studies in the literature on the efficacy and side effects of opioids for chronic noncancer pain[60] and opioids for neuropathic pain specifically.[61] The first study found 41 randomized trials, involving 6019 patients; of these, 80% of the patients had nociceptive pain (osteoarthritis, rheumatoid arthritis, or back pain), only 12% had neuropathic pain, and 7% had fibromyalgia. The average duration of treatment was 5 weeks (range 1–16 weeks); 33% of the patients in the opioid groups dropped out compared with 38% in the placebo groups. The conclusions were that all opioids were more effective than placebo for both pain and functional outcomes in all patients (nociceptive pain, neuropathic pain, or fibromyalgia). Strong opioids (morphine, oxycodone) but not weak opioids (propoxyphene, codeine) were significantly superior to naproxen and nortriptyline and only for pain relief. Among the side effects of opioids, only constipation and nausea were clinically and statistically significant. Interestingly, other drugs (naproxen and nortriptyline) produced better functional outcomes than opioids, whereas for pain relief they were outperformed only by strong opioids. The second study, which focused only on opioids for neuropathic pain, found 23 clinical trials that met the inclusion criteria. The authors reported that the 14 short-term trials had contradictory results but all 9 intermediate-term trials demonstrated opioid efficacy for spontaneous neuropathic pain. Additional analysis of seven of these nine trials where data could be combined and reinterpreted showed significantly lower mean post-treatment VAS scores of pain intensity after opioids (13 units lower on a scale from 0 to 100) than after placebo. The most common adverse events were nausea and constipation, followed by drowsiness, dizziness, and vomiting (number-needed-to-harm [NNH] scores ranged from 4.2 to 8.3).

Overall, these data suggest that both weak and strong opioids have a clear effect on noncancer pain even in cases were prior treatments have failed. The choice of which opioid to use is still not resolved. The American Society of Interventional Pain Physicians has published guidelines for the appropriate use of opioids in the management of chronic noncancer pain.[62] These guidelines were created by an expert panel, which concluded that the evidence for the effectiveness of long-term opioids in reducing pain and improving functional status for 6 months or longer is variable. The evidence for transdermal fentanyl and sustained-release morphine is higher (level II-2), whereas for oxycodone the

level of evidence is slightly lower (level II-3), and the evidence for hydrocodone and methadone is lower still (level III). Since there is also significant evidence of misuse and abuse of opioids by patients, this must also influence their use by practitioners. The guidelines-panel concluded that opioids commonly prescribed for chronic noncancer pain may be effective for short-term pain relief. However, long-term effectiveness of 6 months or longer is variable, with evidence ranging from moderate to limited.

4.2.B Do opioids improve patients' quality of life?

The outcomes achieved with long-term opioid therapy for noncancer pain[63] were examined in a multisite case series derived from chronic non-cancer-pain patients who were under the care of 27 different physicians located across the United States. All physicians in the study filled out a standardized questionnaire on chronic-pain patients who had received at least 3 months of opioid therapy based on a clinical interview, review of the medical chart, and direct clinical observation. The questionnaire results suggested that the majority of these chronic-pain patients achieved relatively positive outcomes as evaluated by their prescribing physicians in all four relevant domains with opioid therapy. The pain score change from therapy was modest but meaningful, functionality was generally achieved, and the side effects were tolerable. Finally, potentially aberrant behaviors that might be indicators of addiction or prescription diversion were seen in only 10% of cases. In general, patients who are in pain and are being medically managed with opioids are receiving treatment for a specific reason and do not become dependent.

This study contrasts to one that examined the long-term effects of opioids on pain relief, quality of life, and functional capacity in long-term or chronic noncancer pain.[64] The study was based on data from the 2000 Danish Health and Morbidity Survey, which included 16,684 individuals (>16 years of age). Of these, 10,066 took part in an interview and completed a self-administered questionnaire. Cancer patients were excluded and the interview and the self-administered questionnaire included questions on chronic or long-lasting pain (>6 months), health-related quality of life (SF-36 questionnaire), use of the healthcare system, functional capabilities, satisfaction with medical pain treatment, and regular or continuous use of medications. Participants reporting pain were divided into opioid and nonopioid users and the statistical analyses performed were adjusted for age, gender, concomitant use of anxiolytics and antidepressants, and pain intensity. The study examined if the reported pain relief, quality of life, and functional capacity being reported were different for the two groups. The results showed that the opioid-use group was significantly associated with (1) reporting of moderate-to-severe or very severe pain, (2) poor self-rated health, (3) not being engaged in employment, (4) higher use of the healthcare system, and (5) a negative influence on quality of life (SF-36 questionnaire). Although there may be selection bias with the more severe pain cases being in the opioid-use group, the authors of this study commented on the fact that opioid treatment of long-term or chronic noncancer pain does not seem to fulfil any of the key outcome opioid treatment goals (i.e., pain relief, improved quality of life, and improved functional capacity).

The issue of opioid risk is also raised by opioid analgesic mortality statistics from the Centers for Disease Control and Prevention (CDC).[65,66] The CDC data listed 5528 deaths from opioid analgesic poisoning in the United States in 2002, which exceeded those due to either illicit heroin or cocaine.[67] Not all opioid analgesics are equal in their risk of lethal toxicity. Methadone may be particularly hazardous because of its potential for drug interactions[68] and its unique pharmacological characteristic of a much briefer duration of analgesia than of toxic effects, which can lead to accumulation to lethal levels.[69] The proportion of US deaths from prescription opioid analgesics that are due to their use in a manner not as prescribed or use by those to whom the opioid was not prescribed is uncertain. No doubt there are many. However, it is likely that thousands of deaths in the United States have resulted from the increased availability of prescription opioid analgesics. Public health considerations, especially those related to mortality, are essential to any discussion of the efficacy and use of opioid analgesics for chronic noncancer pain.

In agreement with the CDC findings is a more recent study that examined the utility and validity of a brief, self-administered screening instrument used to assess suitability of long-term opioid therapy in 396 chronic nonmalignant-pain patients from two pain centers.[70] All included subjects completed the questionnaire before being placed on opioids for their pain, and urine-based toxicology screens were gathered from the patients. The patients were categorized as a "high opioid abuse risk or low opioid abuse risk" based on the questionnaire using a score of 8 and higher as the cut-point. The results showed that the high-risk group did have significantly more abnormal urine screens compared with the low-risk group. The analysis showed that five factors were found to be associated with high risk: (1) history of substance abuse, (2) legal problems, (3) craving medication, (4) heavy smoking, and (5) mood swings. Although the long-term administration of opioids for nonmalignant pain is controversial, recent guidelines support the chronic use of opioids for chronic nonmalignant pain.[71] Considering the possible serious adverse effects associated with NSAIDs and acetaminophen when they are given chronically and the

absence of effective therapies for some forms of orofacial pain, the use of opioids should be considered for select patients: those with intractable pain, such as patients for whom TMJ implants have failed; or those with nonresponsive neuropathic pain. However, while opioid therapy was promoted strongly two decades ago[72,73] more recent data suggests that we must be cautious when we select patients for long-term opioid therapy and know that the promise of full restoration of all aspects of life with opioid treatment is not likely to occur. There are patients whose lives are improved, even transformed, by opioid treatment, and no one wants to revert to withholding opioid treatment from those with chronic pain conditions. Opioid treatment for chronic pain does not benefit all patients, but a cautious, structured, and selective treatment approach is the best way to preserve opioid therapy for those it does benefit.

4.3 Opioid therapy for cancer pain

The general rule is that for severe pain opioids are widely utilized, but for less intense pain nonopioid analgesics and other adjunctive medications are preferable. In the subset of chronic-pain patients with severe cancer pain or cancer-treatment-induced pain, opioids are the standard. Several Cochrane-style reviews have concluded sufficient evidence exists to state that morphine,[74] hydromorphone,[75] and methadone[76] are effective for managing cancer pain. This is not surprising, but these reviews also state that the amount of high-quality evidence for this conclusion is limited. The reviewers were unable to conclude which opioid is the ideal starting agent. While some authors advise morphine, others recommend using methodone as the initial agent to control cancer pain and reduce tolerance to opioids. However, in one randomized comparison of morphine versus methadone as the initial strong opioid used on hospice patients with cancer pain, morphine was found to be superior to methadone.[77]

An excellent set of treatment guidelines with a step-by-step algorithm was developed for hospital and hospice cancer patients to guide cancer pain therapy.[78] Briefly, these guidelines suggest the following: (1) opioid-naïve cancer patients with severe pain should receive rapidly escalating doses of short-acting opioids; (2) a constipation-prevention intervention should be used to treat this problem that inevitably develops as a consequence of opioid therapy; (3) opioid-naïve patients should also be given a nonopioid analgesic to supplement their opioid medication. The most common initial opioid medications are morphine, oxycodone, fentanyl, hydromorphone, oxymorphone, and methadone. The guidelines next suggest that, after the initial response and treatment of acute pain in the hospital, the patient should (1) have a comprehensive reassessment of the symptoms and signs and (2) the frequency for the routine follow-up should be set for at least every 3 months, on an outpatient basis, depending on patient conditions and institutional standards.

4.4 Choosing an analgesic agent

The term "adjuvant analgesic" describes any drug with a primary indication other than pain, but with analgesic properties in some painful conditions. Although they can be used alone, they are usually co-administered with more traditional analgesics such as acetaminophen, NSAIDs, or opioids when treating cancer pain. This co-administration is to enhance pain relief provided by the analgesics, address pain that has not or has insufficiently responded, and allow the reduction of the opioid dose to reduce adverse effects. Adjuvant analgesics often are administered as first-line drugs in the treatment of chronic nonmalignant pain or in cancer-remission patients who are resistant to opioid therapy. Unfortunately, there have been very few comparative trials, and the selection of the most appropriate adjuvant analgesic is based largely on trial and error and various medical issues gathered during a comprehensive assessment of the patient. A method of conducting a crude comparison between analgesic drugs is by using NNT and NNH calculations, but often these data are not based on medication efficacy in cancer pain. The main adjuvant analgesics include tricyclic antidepressants (TCAs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and anticonvulsants, and they are discussed in this section. Sequential single-drug trials are recommended when trying to establish the patient's pain medication regimen before proceeding to the next agent. Better understanding of how best to sequence medications is an important area for clinical research.[79,80]

Appropriate prescribing and dispensing of pain medication does not eliminate pain completely and permanently. The objective of pain management is to achieve the goals and appropriate endpoints, which will vary from patient to patient. General goals include the prevention and reduction of pain, improvement in function, improvement in mood and sleep patterns, and anticipation and treatment of side effects. These goals do not include reducing the analgesic dose to as low a level as possible, but rather to the lowest dose that appropriately relieves patients' pain and allows them to meet their goals. The initial choice of agents for the management of pain is based on the characteristics of the pain, the pain intensity, and the individual patient. As mentioned earlier, WHO has published guidelines regarding analgesic choices, which they call the analgesic ladder. This ladder is still the basis for pain management today. The pain rating is divided into three steps: mild, moderate, and severe. You can use the

previously discussed verbal pain scale to place a patient on one of these steps. Using the 0–10 scale, a patient with a pain rating of 0–3 has mild pain; 4–6, moderate pain; and 7–10, severe pain. The medication choice should then be based on the pain being experienced.

Most patients will require adjunct medications in combination with an opioid agent to achieve pain relief. These agents include NSAIDs, cyclooxygenase-2 (COX-2) inhibitors, antidepressants, anticonvulsants, and stimulants. The NSAIDs and COX-2 inhibitors are very useful agents in treating patients with inflammatory pain. These medications must be taken on a scheduled basis. Several different chemical classes may have to be tried before success is achieved. All of these agents have a "ceiling effect" or a maximum dose. Increasing the dose beyond this ceiling does not add to pain relief; however, it will increase the risk of adverse effects. Prior to beginning these agents, a patient must be appropriately assessed for risk versus benefit. Patients at high risk of an NSAID-related gastrointestinal adverse effect may benefit from a COX-2 inhibitor. Antidepressants are a very useful class of adjunctive analgesics. McQuay and colleagues[81] conducted a meta-analysis of the published trials to date using antidepressants for the management of pain. These trials calculated the number of patients who needed to be treated (NNT) to achieve pain relief in one patient. Sindrup and Jensen[82] updated this meta-analysis in 1999.

Overall, the agents with the most significant effect on pain relief are the TCAs and the newer SNRI antidepressants (i.e., duloxetine). These agents were shown to be very effective in diabetic neuropathy (NNT = 2.4), postherpetic neuralgia (NNT = 2.3), peripheral nerve injury (NNT = 2.5), and central pain (NNT = 1.7). The most widely studied tricyclics were imipramine, amitriptyline, and clomipramine. The meta-analyses revealed that the selective serotonin reuptake inhibitors (SSRIs) were not effective in the management of pain. For diabetic neuropathy, the NNT was 6.7. The authors concluded that the serotonergic TCAs were more effective in the management of chronic pain. Noradrenergic mechanisms may be involved in the activity of these drugs. In general, it seems that antidepressants, which affect several neurotransmitters, may be more effective in the relief of pain than any other agents.

Anticonvulsants are a third category of useful adjunctive analgesic agents. Gabapentin (Neurontin) is currently the most used agent in this class for the management of pain. Other choices include pregabalin, carbamazepine, phenytoin, lamotrigine, tiagabine, and topiramate. The success of this class of agents can be ensured by appropriate titration to avoid side effects. Gabapentin doses should be increased every 3–7 days to minimize these adverse effects.

Selection of the agent should also include assessment of the exact type of pain a patient is experiencing and whether the pain has responded to medication in the past (Table 4.1). For inflammatory pain, such as that due to bone metastases or acute muscle injury, NSAIDs are excellent choices. For neuropathic pain, anticonvulsants and/or antidepressants are excellent choices. These agents may need to be combined with an opioid agent as well. Regular reassessment of a patient's pain is essential to allow modification of dosage regimens and agents. Patients should be rapidly titrated and moved up the ladder as needed to relieve pain. Patient titration can occur over 24–48 hours with appropriate follow-up.

4.5 Special considerations with opioids

4.5.A Endogenous-opioid-induced tolerance to exogenous opioids

It is well established that opioids are not very effective in managing neuropathic pain. One explanation for the suggested poor efficacy of opioids in neuropathic pain patients is that they already are tolerant to opioids before the opioids are prescribed. This explanation is both biologically logical and supported by the research evidence. For example, a 2004 study has shown that neuropathic pain activates endogenous opioids and they in turn induce tolerance even though the patient has not taken any exogenous opioids.[83] This study examined tolerance in mice after inducing an experimental neuropathic pain state, but the concept is certainly generalizable to humans with neuropathic pain. If tolerance already exists, this would explain why some patients do not respond at doses to which opioid-naïve patients typically respond. The answer is simply to raise the dose until an analgesic response is seen. In fact, data clearly suggests that if clinicians carefully follow the WHO guidelines escalating from nonopioid analgesics to moderate-strength opioids and then move to stronger opioids when pain control is not adequate, they will see improvement in all patients regardless of initial pain diagnosis.[84] On the other hand, there is controversy regarding the use of high-dose opioids for neuropathic pain.

4.5.B Strategies for prevention of opioid tolerance

Prolonged use of opioids may lead to development of tolerance (the need to increase opioid dose with time to maintain equipotent analgesic effects) and opioid-induced abnormal hypersensitivity to pain (so-called pro-nociceptive sensitization). Experimental studies suggest that both phenomena could be related to *N*-methyl-D-aspartate (NMDA)

receptor mediated changes in the CNS.[85–87] Opioid desensitization and hypersensitization of NMDA receptors from prolonged opioid therapy may both contribute to an apparent decrease in analgesic efficacy. Thus, in some instances, treating increasing pain with increasing doses of the same opioid may be futile. NMDA receptor antagonists and low-dose opioid antagonists (naloxone, naltrexone) might partially reverse opioid tolerance. Opioid rotation (switching from one opioid to another) can be also used to overcome the unwanted adverse effects of opioid receptor desensitization.[88,89]

When using opioids, the issue of tolerance is frequently of concern. Conventional wisdom is, as tolerance develops, to increase the opioid dose and/or switch to another opioid to see if the side effects are reduced. One study even examined which opioid treatment protocol was associated with the most serious complications. The study examined 174 cancer-pain patients, recording the severity of 11 individual side effects to see which pain treatment protocols developed more side effects.[90] This study separated pain treatment into four types: (1) no opioids used, (2) as-needed (PRN) opioids, (3) around-the-clock (ATC) opioids, and (4) a combination group that used opioids around the clock and added additional opioids for breakthrough pain (ATC+PRN). As would be expected side effects were significantly more prevalent and more severe in the ATC and ATC+PRN groups or the patients with higher doses of opioid analgesics.

When tolerance is a concern, methadone is commonly selected as the patient's opioid because many suggest that, among all the opioids, this one is less likely to develop rapid tolerance. This drug is complex and may work, in part, by binding to the NMDA receptor and, thereby, interrupt mechanisms associated with opioid tolerance. In a small series of 18 patients with either malignant or nonmalignant pain, significant decrease in pain severity was reported with a median dose of 15 mg methadone daily.[91] Finally, one more recent study provides evidence that tolerance might be partially be suppressed with a novel strategy.[92] The study examined brain-tissue samples from chronic morphine-treated rats and showed that opioid receptor desensitization in response to chronic morphine is attenuated when an ultra-low-dose opioid antagonist is also administered.

4.5.C Recognizing opioid-seeking behavior

An estimated 7 million Americans abuse prescription drugs and an even greater number abuse cocaine, heroin, hallucinogens, Ecstasy, and inhalants, combined.[93] The estimated number of prescription drug abusers was just 3.8 million in 2000, an 80% increase in just 6 years. Prescription pain relievers are new drug users' drug of choice, versus marijuana or cocaine. Opioid painkillers now cause more drug overdose deaths than cocaine and heroin combined. Nearly 1 in 10 high school seniors admits to abusing powerful prescription painkillers. A startling 40% of teens and an almost equal number of their parents think abusing prescription painkillers is safer than abusing "street" drugs. Misuse of painkillers represents three-fourths of the overall problem of prescription drug abuse; hydrocodone is the most commonly diverted and abused controlled pharmaceutical in the United States. Twenty-five percent of drug-related emergency department visits are associated with abuse of prescription drugs. Methods of acquiring prescription drugs for abuse include "doctor-shopping," traditional drug-dealing, theft from pharmacies or homes, illicitly acquiring prescription drugs via the Internet, and acquiring them from friends or relatives. The US Drug Enforcement Agency (DEA) works closely with the medical community to help them recognize drug abuse and signs of diversion and relies on their input and due diligence to combat diversion. Doctor involvement in illegal drug activity is rare; less than one tenth of one percent of more than 750,000 doctors are the subject of DEA investigations each year, but egregious drug violations by practitioners unfortunately do sometimes occur. DEA pursues criminal action against such practitioners. DEA Internet drug trafficking initiatives over the past 3 years have identified and dismantled organizations based both in the United States and overseas, and arrested dozens of conspirators. As a result of major investigations such as operations Web Tryp, PharmNet, Cyber Rx, Cyber Chase, Click 4 Drugs, Bay Watch, and Lightning Strike, tens of millions of dosage units of prescription drugs and tens of millions of dollars in assets have been seized.

4.5.D Alternate forms of opioid delivery

There are many patients who cannot swallow pills because of various medical problems (e.g., mucositis) or if they can swallow them, they may not remember to take their medication in an appropriate fashion because of cognitive problems. One popular alternate form of delivering opioids to patients is to prescribe a fentanyl patch.[94] Peripheral injection of opioids in the oral cavity has also been evaluated in two different research studies. One study reported on a series of double-blind, placebo-controlled clinical trials that evaluated low doses of morphine (0.4, 1.2, and 3.6 mg) administered into the intraligamentary space (by syringe) of a chronically inflamed hyperalgesic tooth.[95] The authors concluded that this use of morphine produced a dose-related analgesia and that the effect was clearly local (presumably on peripherally located opioid receptors) and not via the effect of morphine on opioid receptors in the CNS. This conclusion was because morphine's analgesic effect with

intraligamentary injection was not produced by a subcutaneous administration of a similar (1.2 mg) dose of morphine. These findings were in contrast to the observation that submucosal administration of 1.2 mg morphine or 50 µg fentanyl to the site of extraction of an impacted third molar after the onset of acute pain failed to elicit an analgesic response. Another study examined the relative efficacy of peripheral injections of fentanyl with lidocaine into inflamed dentoalveolar tissues.[96] The double-blind study included 71 patients reporting with pain and tenderness in a maxillary tooth. The subjects were randomly assigned into either the experimental or control (local anesthetic and saline only) group. The experimental group received submucosal injections of a mixture of 40 µg fentanyl (0.8 mL) and 2% lidocaine hydrochloride with 1:200,000 epinephrine (2 mL). Prior to injection, 5 minutes after injection, and immediately after surgery the pain scores were recorded with a VAS. The results showed that the mean pain scores were not significantly different at any time intervals and a similar number of both groups required additional injection of anesthetic to get pain control. Overall, these data indicate that peripheral opioid analgesia can be demonstrated in a model of chronic, but not acute, inflammatory pain, suggesting a temporal dependent mechanism needed for the upregulation of peripheral opioid receptors during inflammation in humans. The use of morphine as an injectable agent for TMJ pain and during an arthroscopic TMJ procedure has also been proposed but it is discussed in Chapter 13, which deals with injectable agents for orofacial pain.

4.5.E Intravenous, intrathecal, or epidural delivery of opioids

Most patients with cancer pain achieve good analgesia using traditional analgesics and adjuvant medications; however, an important minority of patients (2–5%) suffers from severe and refractory cancer pain.[97] For these individuals, spinal analgesics (intrathecal or epidural) provide significant hope for pain relief over months or years of treatment to help improve quality of life. Spinal analgesics have been suggested as the fourth step in the WHO guidelines in the management of cancer pain. By delivering opioids and other agents directly to the central nervous system, intrathecal drug administration can offer superior pain relief with less toxicity at a fraction of the systemic dose. With adjuncts such as local anesthetics, clonidine, and baclofen, intrathecal therapy also allows for broader therapeutic options in the most difficult of cases.[98] A more controlled method of delivering opioids is via the use of implantable pumps. This technique delivers the medication intrathecally and is used for selected patients with malignant as well as nonmalignant pain. A 2007 study examined whether this method caused comparable side effects and how often the pump itself failed.[99] This study reported on 165 cases where intrathecal opioid pumps were used with a follow-up exceeding 3 years. The authors reported that the reduction of noncancer pain, using a VAS method of measurement, was considered good or excellent (pain decrease >50%) in 71.3% of the patients. They reported that complications such as catheter-related problems occurred in 17 of 165 patients and pump malfunctions occurred in 8 of 165 cases. Drug-related side effects, which were manageable, occurred in 32 of the 165 patients. Finally there is some evidence that the combination of using oxycodone with a low dose of an opioid antagonist (naltrexone) is better than using oxycodone alone. One study using a double-blind placebo-controlled trial on patients with chronic, moderate-to-severe low back pain reported this combination analgesic medication to be efficacious and to produce less physical dependence than taking oxycodone taken four times daily.[100]

4.6 Conclusion, caveats, and recommendations regarding opioids for noncancer orofacial pain

Opioids for noncancer orofacial pain

1. There are no direct evaluation studies that assess the efficacy and safety of long-term administration of immediate-release or extended-release opioids for patients with a temporomandibular disorder (TMD), osteoarthritic disorder of the jaw, or a continuous trigeminal neuropathic pain disorder.
2. Extrapolation of data from studies that have evaluated the efficacy of opioids on chronic low back pain, osteoarthritis, or mixed neuropathic pain disorders (postherpetic neuralgia and diabetic neuropathy) must be used to establish treatment protocols for chronic nonmalignant trigeminal pains.
3. Considering the possible serious adverse effects associated with NSAIDs when they are given chronically and the absence of effective therapies for some forms of TMDs, the chronic use of opioids should be further evaluated.
4. In theory, extended- or controlled-release formulations of opioids are better in that they would minimize cyclic fluctuations in pain associated with standard formulations, but this must be proven with more research.
5. The chronic use of opioids for patients with TMDs, before scientific and professional consensus is reached, requires careful patient selection to rule out drug-seeking behavior or other personality disorders; it also requires careful monitoring to individualize dose.

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Chapter 5

Nocebo-responsive patients and topical pain control agents used for orofacial and mucosal pain

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5.1 Introduction

This chapter deals with two distinct topics: topical medications and the nocebo-responsive patient. They are combined here because in many ways they are related, since many patients who are reluctant to take oral medications will use topical medications. Moreover, no book that focuses on the use of medications as a part of the therapeutic process is complete without a discussion of the issues of medication fear (pharmacophobia) and anxiety-induced nocebo reactions. We briefly review the basis of the placebo- and nocebo-responsive patient and how these two psychophysiologic reactions affect treatment choices. This is followed by a detailed discussion of the topical medication options available to the orofacial pain practitioner.

5.2 Nocebo-responsive patients

Most people understand that a placebo reaction is when a patient feels and reports a benefit even though the patient is taking a medication that is an inert or inactive substance. The opposite of this is the expectation and experience of a negative result or side effect even when the medication being administered is an inert substance.[1] This negative effect is called a nocebo response, which is considered to be a phenomenon that is exactly opposite to the placebo effect.[2] This response is robust enough that it can be induced experimentally in healthy normal subjects by simply delivering verbal suggestions of negative outcomes so that the subject expects clinical worsening. The mechanism of the patient's negative expectations of pain worsening is thought to be an anticipatory anxiety reaction and is mediated in the brain with the neurotransmitter cholecystokinin (CCK). This neurotransmitter, in turn, facilitates pain transmission; further proof that this is the correct mechanism is that CCK-antagonists have been found to block this anxiety-induced hyperalgesia.[3] These findings underscore the important role of cognition and expectation in the therapeutic outcome. The two questions that arise once you understand the nocebo response are: "How do you provide informed consent about the drug you are prescribing without implanting an expectation of negative results?" and "Does this reaction occur in everyone or are some patients more susceptible than others?"

With regard to the first question, the ethical practice of medicine necessitates that we must let patients know about both the risks and benefits of a treatment so that they can elect to participate in the treatment or not. This is called informed consent and it is not optional. On the other hand, how you present this information is critical and it is well known that a positive attitude suggesting treatment success is much more likely to result in success than a neutral or negative attitude about success. For example, one method, called motivational interviewing (MI), is an attempt to systematically and positively influence the doctor–patient interaction. In the case of the pharmacophobic patient, motivational interviewing would be defined as a nonjudgmental, nonconfrontational, and nonadversarial interview with the goal of attempting to increase the patient's awareness of their high responsivity to medications: educating the patient about the potential benefits of medication that suppresses pain activity, the concept of titration of medications to allow for adaptation, and the potential problems caused by an anxiety-induced nocebo reaction. The influence of this method on treatment outcome of patients being prescribed type-2-diabetes medications was examined in a study that looked at how training physicians in MI affected the attitude to behavior change in patients diagnosed with type 2 diabetes.[4] They performed a randomized controlled trial including two groups of physicians; half were trained in MI and half

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were not. The two groups of physicians treated 265 type 2 diabetic patients. Patients treated by the MI-trained physicians were found at 1-year follow-up to be significantly more autonomous and motivated in their inclination to change behavior (including using their medications properly) after 1 year compared with the patients treated by the control group of non-MI-trained physicians. Finally the authors of a 2009 review of the literature on the issue of medication adherence was published suggested that MI methods were potentially helpful in altering patient behavior.[5] They also recommended that prescribing doctors need to (1) devote time during the treatment visit to address medication adherence issues; (2) assess the patients' motivation to take prescribed medications; and (3) identify and address potential barriers to treatment adherence. Of course, this review focused on psychoactive medications, but it is logical to assume its findings also apply to pain-medication adherence.

With regard to whether there are patients who are more susceptible to a nocebo response, it is fairly easy to recognize nocebo-responsive patients: they will generally tell you who they are if you simply ask them how prone they are to have all of the side effects of a medication, often at a subtherapeutic dose. This reaction is generally considered a combination of attitudes and learning. One recent study examined the role of learning on the nocebo reaction.[6] In the study, healthy volunteer subjects were given verbal suggestions of pain increase before administration of either tactile or low-intensity painful electrical stimuli. The authors reported that verbal suggestions turned tactile stimuli into pain and low-intensity painful stimuli into high-intensity pain. Another study examined medication attitudes by categorizing 92 participants in an outpatient psychoeducational program as either pharmcophilic ($n = 59$) or pharmacophobic ($n = 33$) according to the Drug Attitude Inventory scale. They then examined these patients for associated factors that may have influenced these attitudes.[7] The patients in the study were suffering from schizophrenia or schizoaffective psychoses. The authors reported that the two groups did not differ significantly with regard to most sociodemographic variables, clinical symptoms, or classic personality traits such as locus of control, self-concept, and quality of life. The only differences that were significant were their prior experience of desired or undesired reactions to medications and their prior hospitalization history. In 2009, another study was published which reviewed the factors influencing the occurance of adverse drug events in analgesic clinical trials.[8] This study examined all adverse-event data from the placebo groups in studies on antimigraine drugs. The various active agents being studied in these trials were from the nonsteroidal anti-inflammatory drug (NSAID), triptan, and anticonvulsant drug classes. The adverse event profiles for patients in the placebo arms of the three drug classes were compared. They authors reported that the adverse events in the placebo arms corresponded to those of the antimigraine medication against which the placebo was compared. In other words, anorexia and memory difficulties, which are typical adverse events of anticonvulsants, were present only in the placebo arm of the anticonvulsant drug trials. The authors concluded that the negative side effects that occurred were not randomly distributed in the placebo-arm patients but were probably induced as a direct result of what these patients were told to expect as potential negative effect.

In summary, anxiety-prone, nocebo-responsive patients who have developed a pharmacophobic attitude toward some or all medications, if not handled properly, will not be able to tolerate or be willing to even try medications that could help them. As mentioned previously, these patients are usually identified as highly anxious patients who have had prior negative experiences with medications. Above and beyond their unwillingness to use medications that would potentially control their disease, these patients often fall prey to the medical predators. The definition of a medical predator is an individual who diagnoses diseases that are not recognized as ligitimate and provides treatments, often expensive, that have no reasonable evidentiary basis.[9,10]

For all patients, but in particular the nocebo-responsive patient, what is said to them about the medications being recommended is critical to the outcome. It is often to these patients that we recommend topical medications (covered in Sec. 5.3) since this is the only therapy that can be given without a substantial adverse reaction. It seems logical to recommend that all pain practitioners should read about and understand the principles underlying motivational interviewing because exactly what is said to a patient is probably far more important than is commonly understood by most healthcare practitioners.[11]

5.3 Topical pain medications: what are they and why use them?

In the field of pain medicine, the two most common types of topical pain relievers are those that contain local anesthetics (usually lidocaine or benzocaine) and those that contain analgesics (usually salicylates or NSAID-type medications). These two types of medications generally result in (1) a diminished propagation of nociceptive signals along the sensory neurons by blocking sodium channels and (2) local decreased production of inflammatory mediators in the tissue to which they are applied. Topical preparations of medication are usually applied to the skin as a cream, ointment, gel, aerosols, or patches but with orofacial pain conditions they can also be used intraorally as prepared as

lozenges, sticky pastes, and mouthwashes (covered later in this chapter).[12] Because of their rapid onset and low side-effect profile, topical medications offer a distinct advantage over systemic administration for those orofacial disorders that are regional, near the surface, and chronic and that demonstrate some response such as pain relief to topical or subcutaneous anesthetics. This chapter does not discuss transdermal patches for systemic drug delivery but instead focuses on topical local delivery of drugs, where the systemic levels of the drugs are miniscule or nondetectable. This chapter reviews the literature available on the efficacy of both custom-prepared and commercially prepared topical preparations. The specific use of topical and locally injected corticosteroid agents for mucosal pain and ulceration is covered in Chapter 12, not in this chapter.

As mentionend, topical medications have several distinct advantages over orally delivered mediations. First they are more likely to be accepted as a viable form of treatment in the highly anxious nocebo-responsive patient and in the polypharmacy and elderly drug-intolerant patient. One reason for their popularity is the widely held assumption that they produce a higher concentration of the drug at the site of application and have low or even negligible systemic blood levels. If this is true, then topical medications will produce fewer or no adverse drug effects other than local skin-based side effects. In 1998, a study examined local skin concentration versus plasma levels of acetylsalicylic acid after either a topical application of an aspirin in a diethyl ether mixture or oral aspirin.[13] Nineteen neuralgia patients were given either a single 500-mg oral dose of acetylsalicylic acid (ASA) or a topical dose (750 mg) of aspirin with diethyl ether (ADE) daubed onto the painful skin. Pain relief was scored before and after treatment and the data showed that topical application of ADE produced a significant decrease in pain (by 82.6%) compared with only a 15.4% decrease after oral ASA administration. Skin concentrations were highly elevated with topical application but not oral and there were no active drugs in plasma after topical administration. Of course this study cannot be generalized to all topically applied medications and especially those that are used inside the mouth, where patients are more likely to swallow a portion of the medication. With different medications, vehicles, and sites of application, there will be variable degrees of systemic absorption.[14]

Another potential advantage of localized applications is that due to the general lack of drug interactions a higher dose can be given initially because there is a diminished need to titrate doses to tolerability, which is often necessary in the elderly. It is quite clear that, with the elderly, topical medications are very popular. A 2006 study looked at the use of self-prescribed nonprescription medications and dietary supplements among residents of assisted living facilities.[15] A descriptive cross-sectional study was performed at two assisted living facilities in Oregon and Washington state that included a convenience sample of 45 assisted living facility residents. The main outcome measure was the prevalence and types of use of self-prescribed over-the-counter (OTC) medications and dietary supplements, misuse of these products, and participants' opinions concerning use of these products. The 29 women and 16 men with a mean age of 84.8 were using self-prescribed OTC medications and dietary supplements at the time of this study. The results showed that a mean of 3.4 products was used per participant. Nutritional supplements were most frequently used (32% of products), followed by gastrointestinal products (17%), pain relievers (16.3%), herbals (14.4%), topical products (12%), and cold or cough products (8.5%). Potential misuse of these topical medications was identified in 23 (51%) of the participants. These misuses were duplication (70%), potential drug–disease–food interactions (20.8%), and inappropriate use (9.1%). The majority (76%) of the participants believed the products were helpful in maintaining health, 56% of them wanted more product information, 49% sought product information from family and friends, while only 40% turned to their physicians and nurses for information, and 11% asked pharmacists for advice. The authors concluded that the use of nonprescription medications and dietary supplements among assisted living facility residents was high, and simultaneous use of multiple products with the same active ingredient was the most prevalent problem.

The contraindications for most topical agents include broken or inflamed skin, burns, open wounds, atopic dermatitis or eczema (skin disorders), a severe liver or kidney disease, and a history of methemoglobinemia (defective iron in the red blood cells, which inhibits oxygen delivery to tissues). Finally, topicals cannot be used on individuals who have an intolerance to any of the ingrediants or in severe asthmatic patients. Safe and effective use of a topical pain-relieving agent involves many of the same considerations as if taking an oral medication.

5.3.A Commonly used topical medications for orofacial neuropathic pain

The medications often used for oral and perioral neuropathies are the topical anesthetics benzocaine and lidocane and the neuropeptide capsaicin; however, other compounds such as NSAIDs (diclofenac, ibuprofen, and ketoprofen), the sympathetic agent clonidine, and the *N*-methyl-D-aspartate (NMDA)–blocking agent ketamine hydrochloride are also used. Because the evidence supporting the use of topically applied anticonvulsants, tricyclic antidepressants, and

antispasmodics is nonexistent, these medications are not covered here.

Topical anesthetics

Indications

Local anesthetics delivered topically are used widely for minor pain-inducing surgical procedures and injections,[16] but they also have been used for some types of chronic pain. Basically, if a neuropathic pain can be shown to be responsive to topical anesthetic in the office, then patients are taught how to apply the anesthetic agent several times each day. The goal is to maintain local numbness, reduce ectopic neuronal firing, and thereby reduce the peripheral neural sensitization. Complete cessation of pain on application of topical anesthetic may not be possible, as some of the neuronal changes may be central or due to neuropathic changes in neural tissues not easily reached by most topical anesthetics. The European Federation of Neurological Sciences established some recent guidelines regarding the pharmacologic treatment of neuropathic pain.[17] The guidelines evaluated the existing published evidence in the Cochrane Database and in Medline and concluded that high-level evidence was available on the efficacy of topical lidocaine for the treatment of postherpetic neuralgia.[18–20]

Formulations and dosing of topical anesthetics

One commonly used over-the-counter oral product that contains a local anesthetic (benzocaine 20%) is Orobase®, which is a sticky ointment that can be easily applied to the oral mucous and gingival tissue. It is used mostly intraorally, but it can also be applied extraorally. This is usually done by applying the agent to the painful facial site and then covering it with a clear plastic adhesive sheet, which keeps the anesthetic in the desired area.[21] Intraoral application usually requires a custom-made oral tissue-covering plastic stent that keeps the medications in the desired mucosal or gingival location. Topical lidocaine also comes as as a 5% transdermal patch and it is approved by the US Food and Drug Administration (FDA) for postherpetic neuralgia pain.[22,23] It requires a prescription and the patch is applied to the skin over the painful area. In theory, this medication decreases the neuronal firing in this area and thus relieves the pain.[24] Topical lidocaine is also available as a 5% viscous liquid for severe oral mucositis. Maximum recommended doses are 4.5 mg/kg, up to a total dose of 300 mg, to avoid lidocaine toxicity, which is characterized by central nervous system changes.[25] Lidocaine (2.5%) combined with prilocaine (2.5%) also comes in a paste and is called a eutectic mixture of local anesthetic (EMLA). This combination medication rapidly numbs the skin or oral mucosa for a period of 2–3 hours. When used in the oral mucosa, this mixture is a superior topical anesthetic agent for pain reduction, although it requires an extended contact time of several minutes for the area to be anesthetized.[26,27] The plasma concentrations of lidocaine and prilocaine show peak concentrations well below known toxic levels 45 minutes after skin application of 8 g of 5% occluded EMLA.[28]

Adverse reactions

With the exception of allergic sensitization and methemoglobinemia, an emergency medical condition characterized by cyanosis and dyspnea, systemically induced toxic reactions to topical anesthetics are very rare.[29–32] The most frequently reported adverse event is mild to moderate skin redness, rash, or irritation at the patch application site. However, it should be noted that, in late 2006, the FDA's safety information and adverse event reporting program notified healthcare professionals and consumers about the serious public health risks related to compounded topical anesthetic creams.[33] The FDA issued warning letters to five firms to stop compounding and distributing standardized versions of topical anesthetic creams, marketed for general distribution. Exposure to high concentrations of local anesthetics, like those in the compounded topical anesthetic creams, can cause grave reactions, including seizures, irregular heartbeats, and death. Compounded topical anesthetic creams are often used to lessen pain in procedures such as laser hair removal, tattoos, and skin treatments. They may be dispensed by clinics and spas that provide these procedures, or by pharmacies and doctors' offices. These creams contain high doses of local anesthetics, including lidocaine, tetracaine, benzocaine, and prilocaine. When different anesthetics are combined into one product, each anesthetic's potential for harm is increased. This potential harm may also increase if the product is left on the body for long periods of time or applied to broad areas of the body, particularly if an area is then covered by a bandage, plastic, or other dressing.

Efficacy of topical anesthetics for chronic orofacial pain

There is one randomized blinded study that provides data demonstrating the efficacy of lidocaine for chronic oral neuropathic pain.[34] Unfortunately this study examined the immediate effect of injected lidocaine, rather than topically applied lidocaine, on 35 consecutive patients with atypical odontalgia (AO). The study compared 1.5 mL local

anesthesia (20 mg/mL lidocaine and 12.5 µg/mL adrenaline) versus a similar volume of saline (9 mg/mL NaCl solution) as the control injection. These injections were performed in the painful area and a visual analog scale (VAS) pain score was kept for up to 2 hours after the injection. The authors reported that substantial pain relief was observed at 15 minutes and lasted for 120 minutes following the lidocaine injections compared with the placebo injections.

The nearest disease for which chronic use of topical lidocaine has been studied is postherpetic neuralgia (PHN). A recent Cochrane Database report on topical lidocaine for PHN examined only randomized or quasi-randomized trials comparing all topical applications of lidocaine, including gels and patches in patients of all ages with PHN.[35] They found and included results from 3 trials involving 182 participants treated with topical lidocaine and 132 control participants. They concluded that topical lidocaine relieved pain better than placebo, but overall these authors felt that there was still insufficient evidence to recommend topical lidocaine as a first-line agent in the treatment of PHN with allodynia. These results were confirmed in a large multisite, double-blind, placebo-controlled study of the effect of lidocaine patch applied in patients who had PHN.[36] This last study added evidence for the idea that a 5% lidocaine medicated patch can be considered a valuable treatment option for patients with PHN, providing beneficial effects on pain, allodynia, quality of life, and sleep, with minimal adverse effects.

Topical analgesics (NSAIDs and salicylates)

Indications

Discussion of topical analgesics usually describes topical creams, ointments, or gels that contain either a salicylate or an NSAID. These analgesics are used to reduce swelling and ease inflammation that can cause pain resulting from trauma or disorders such as osteoarthritis and rheumatoid arthritis.

Formulations and dosing of topical analgesics

Commercial products that contain an NSAID or a salicylate include Aspercreme®, Voltaren®, and Emugel.

Adverse reactions

Usually these medications do not induce a systemic dose that is large enough to induce gastrointestinal distress, but there is always the potential of a local or even a systemic allergic reaction. Adverse effects with topical NSAIDs can generally be divided into cutaneous and systemic reactions. Adverse drug reactions occur in up to 10–15% of patients, and cutaneous reactions (rash, pruritis at site of application) account for most of these. Adverse systemic effects, such as gastrointestinal effects, occur less frequently but are more likely in patients who have previously demonstrated such responses to oral preparations.

Efficacy of topical analgesics for chronic orofacial pain

In general, more studies of ketoprofen have been published than of the other NSAIDs and there have been three substantial reviews of the efficacy of topical NSAIDs. One of these addressed applications in musculoskeletal and soft-tissue injuries (e.g., sprains, strains, tendonitis) and rheumatic diseases,[37] another accessed a wider database including company trials (86 trials, >10,000 patients),[38] and the third focused on efficacy and safety, primarily in chronic rheumatic diseases.[39] Each overview concluded that there was clear evidence to support efficacy of topical NSAIDs given by gel, spray, or patch for such conditions. A multicenter trial of an NSAID patch for sports-related soft-tissue injury found similar benefit.[40] When NSAIDs are administered topically, relatively high concentrations occur in the dermis, whereas levels in the muscle are at least equivalent to those following systemic administration. Topically applied NSAIDs do reach the synovial fluid, but it is not clear whether this reflects local penetration or results from systemic circulation. In osteoarthritis and rheumatoid arthritis, the effects of topical NSAIDs may be modest at best. A 2004 meta-analysis examined the literature for evidence of efficacy of topical NSAIDs used in the treatment of osteoarthritis.[41] This review analyzed 13 studies involving over 2224 subjects. The authors concluded that topical NSAIDs were superior to placebo in relieving pain due to osteoarthritis only in the first 2 weeks of treatment and by weeks 3 and 4, no benefit was observed over placebo. They also reported that topical NSAIDs by comparison were inferior to oral NSAIDs in the first week of treatment and were associated with more local side effects such as rash, itch, or burning than seen with oral NSAIDs. This review concluded topical NSAIDS are less effective than oral NSAIDs during the first week but do not differ from oral NSAIDs for weeks 2–4. These treatments have been recommended by the American College of Rheumatology[42] and treatment guidelines have been developed in Europe and the United Kingdom that also suggest topical agents are helpful.[43,44]

Topical rubefacients

Indications

Rubefacients cause irritation of the skin, are most often combined with salicylate medications, and are believed to

relieve various musculoskeletal pains. They are available by prescription and are common components in over-the-counter remedies.

Formulations and dosing of topical rubefacients

Multiple commercially available products (too many to list) contain rubefacients alone or with aspirin.

Adverse reactions

In general, topical rubefacient agents are relatively safe and can be used with low risk for 2 weeks to see if they are beneficial.

Efficacy of topical rubefacients for chronic orofacial pain

There is a 2004 review available in the Cochrane Library database that examined topical rubefacient combined with salicyclate for the treatment of a mixed group of acute and chronic musculoskeletal pain.[45] This review concluded that topically applied rubefacients containing salicylates may be efficacious in the treatment of acute pain but for chronic musculoskeletal and arthritic pain the results varied from moderate to poor efficacy. In 2009 another Cochrane Library–style review was published on efficacy of topical rubefacients combined with salicylates for acute and chronic pain in adults.[46] This review examined all randomized, double-blind, placebo- or active-controlled clinical trials of topical rubefacients for musculoskeletal pain in adults, with at least 10 participants in each treatment group. The authors found 7 studies with 697 participants with acute pain and 9 studies involving 579 participants with chronic pain. The results from these studies were summarized as being "not robust" and, if they excluded the lesser quality studes, the results showed that topical rubefacients with salicylates provided no difference from the control condition. The calculated number needed to treat (NNT) for clinical success compared with placebo was 3.2 for acute pain and 6.2 for the chronic pain conditions.

Topical vanilloid compounds (capsaicin)

Indications

Capsaicin, the active pungent ingredient in hot peppers, is used commonly as a topical medication for neuropathic pain conditions of the skin or oral mucosa.[47] Topical preparations that contain capsaicin work by reducing the levels of the chemical substance P, which is involved in transmitting pain impulses to the brain. Capsaicin, an alkaloid derived from chilies, depletes the neurotransmitter substance P from sensory nerves. A further possible mechanism of action of capsaicin in peripheral neuropathic pain is degeneration of epidermal nerve fibers.[48] Of particular interest is its effect on the C-fiber type of primary afferent neurons and on a specific membrane recognition site identified as an ionotropic vanilloid receptor, or VR1.[49,50] The action of capsaicin on this receptor is to open the associated Ca^{++} ion channel. The inward ion flow causes neuronal depolarization and this receptor is primarily located on C-fibers. Capsaicin stimulates these nociceptors to release substance P and other peptide neurotransmitters, not only at the peripheral site of application, but also centrally.

Formulations and dosing of topical capsaicin

Topical capsaicin preparations of 0.025% and 0.075% are available in an over-the-counter form for human use. Repeated use of these creams produce skin analgesia in randomized double-blind placebo-controlled studies, open-label trials, and clinical reports.[51] These agents can also be mixed with a gelatin, pectin, methylcellulose, and benzocaine cream for intraoral use to improve their consistency and to incorporate the local anesthetic effect of benzocaine. While the onset of action of this therapy is immediate, it may take up to 4 weeks before long-term neuropathic pain desensitization (e.g., a lessening of the burning feeling) occurs. In cases in which capsaicin's side effects are objectionable, or in which a small amount has not proven helpful, it is recommended that the clinician use local anesthetic before the application to minimize pain perception.[52]

Adverse reactions

The most frequently encountered adverse effect with capsaicin is burning pain at the site of application, particularly in the first week of application. This can make it impossible to blind trials and can lead to dropout rates ranging from 33% to 67%.[53,54]

Efficacy of topical capsaicin for chronic orofacial pain

Topical capsaicin produces benefit in PHN,[55] diabetic neuropathy,[56] postmastectomy pain syndrome,[57,58] oral neuropathic pain, trigeminal neuralgia, temperomandibular joint disorders,[59,60] cluster headache (following intranasal application),[61] osteoarthritis,[62] and dermatological and cutaneous conditions.[63] Whereas pain relief is widely observed in these studies, the degree of relief is usually modest, although some patients have a very good result. Topical capsaicin is generally not considered a satisfactory sole therapy for chronic pain conditions and is often considered an adjuvant to other

approaches.[64] Topically applied capsaicin cream showed a significant effect in three out of five studies in diabetic neuropathy,[65–68] with NNT in the positive studies from 2.5 to 4.9 and a combined NNT for all studies of 5.9 (95% CI, 3.8–13). One caveat of all but one of these studies is an inadequate blinding owing to the burning skin sensation induced by capsaicin. One study used burning nicotinamide cream as a control and did not find any effect.[69] NNT calculation on this study alone is not meaningful, because a higher fraction of patients responded to placebo than to capsaicin. It should also be noted that, when the capsaicin application is discontinued, the pain typically returns. Unfortunately, no controlled quantitative long-term studies of the effect of capsaicin on oral neuropathic sensations have been performed. Capsaicin has been used successfully to control pain in dental traumatic neuropathy, trigeminal neuralgia, postherpetic neuralgia, diabetic neuropathy, postsurgical sensory disturbance involving the trigeminal nerve, and other conditions of neuropathic pain, such as pain from oral mucositis after chemotherapy or radiation.[70] The same group that conducted these two reviews also performed a review on topical capsaicin for chronic musculoskeletal and/or neuropathic pain and concluded that it was not shown to be an effective stand-alone topical treatment.[71]

Topical sympathomimetic agents

Indications

Sympathomimetic agents may be useful in some forms of chronic neuropathic pain where nociceptor activity is being stimulated by sympathetic fiber release of norepinephrine in the periphery. It has been shown that injured C-fibers express alpha-1-adrenergic receptors on their peripheral membranes. Sympathetic activity then would excite the C-fibers, signaling pain. Clonidine, an alpha-2-adrenergic agonist, has been used as a topical agent for neuropathic pain because it is able to interrupt the peripheral release of norepinephrine, thereby decreasing the C-fiber stimulation.[72,73]

Formulations and dosing of topical clonidine

Clonidine for local extraoral therapy is available as a transdermal patch. For intraoral use, it is better to have clonidine compounded into a transdermal penetrating cream and dispensed in a calibrated syringe so that the dose can be better controlled.

Adverse reactions

This drug may cause lightheadedness, dry mouth, dizziness, or constipation and hypotension.

Efficacy of topical clonidine for chronic orofacial pain

There is evidence from both clinical and preclinical studies that the sympathetic nervous system contributes to pain following nerve injury.[74–76] Transdermal clonidine has been shown to relieve symptoms of neuropathic pain in a subset of patients with diabetic neuropathy through a systemic action.[77] Clonidine patches also relieved hyperalgesia in some patients with sympathetically maintained pain due to a localized action, but had no effect on hyperalgesia in cases of sympathetically independent pain.[78] The efficacy of local clonidine in sympathetically maintained pain may result from presynaptic inhibition of noradrenaline released from sympathetic nerves as well as actions directly on primary afferent nerve terminals. There is one open-label study that has examined the effect of clonidine for orofacial pain.[79] This study included 17 patients with a clinical diagnosis of oral neuropathic pain or neuralgia involving the oral cavity. Patient were administered clonidine (0.2 mg/g) prepared in a cream base and applied four times daily to the site of pain. The authors reported that, in the patients with neuropathic pain, an overall mean reduction in severity of burning of 36% was observed and none of these patients stated they had complete resolution of symptoms. Of the patients with characteristics of neuralgia, brief electric-like pain, 57% improved; in those who reported improvement, a mean reduction of approximately 54% was reported. This open-label clinical trial suggests that topical clonidine may be effective in the management of some patients with oral neuralgia-like pain, but it may have a more limited effect in those patients with oral neuropathic pain.

Topical NMDA-blocking agents

Indications

Since there are NMDA receptors in the periphery, topical ketamine may be useful, but specific studies are needed to evaluate this therapeutic alternative. Ketamine also produces local anesthetic actions, blocks voltage-sensitive Ca^{2+} channels, alters cholinergic and monoaminergic actions, and interacts with opioid mechanisms; these actions also may contribute to its analgesic profile.[80–82]

Formulations and dosing of topical NMDA antagonists

As with clonidine, this medication would be best compounded into a transdermal penetrating cream and dispensed in a calibrated syringe.

Adverse reactions

Although this medication has promise for the treatment of neuropathies, it can cause adverse effects such as hallucinations and dysphoria, which necessitate a low dose.[83,84]

Efficacy of topical NMDA antagonists for chronic orofacial pain

Recent studies have shown that NMDA-receptor antagonists may be useful in the treatment of neurogenic pain.[85,86] One moderately good NMDA receptor antagonist is ketamine, which is considered a noncompetitive NMDA receptor antagonist in reducing pain responses. In a study of acute postoperative pain, ketamine enhanced local anesthetic and analgesic effects of bupivacaine by a peripheral mechanism.[87] In a thermal-injury model in healthy volunteers, subcutaneous injection of ketamine produced a long-lasting reduction in hyperalgesia in one study[88] but only produced a brief analgesia with no effect on hyperalgesia in another such study.[89] It appears that analgesic effects following peripheral administration of ketamine are variable and may be condition-dependent. There was a case report of intractable mucositis that described the use of topical ketamine delivered to the oral mucosa via an oral rinse.[90] This patient, a 32-year-old woman with squamous carcinoma of the tongue undergoing radiation therapy, was reported to have received substantial benefit from this rinse without side effects. Finally a randomized double-blind study evaluating topical use of 2% amitriptyline and 1% ketamine in neuropathic pain syndromes was reported in 2005.[91] The study included 92 patients with diabetic neuropathy, postherpetic neuralgia, or postsurgical or post-traumatic neuropathic pain with allodynia, hyperalgesia, or pinprick hypesthesia. Study subjects were randomly assigned to receive one of four creams (placebo, 2% amitriptyline, 1% ketamine, or 2% amitriptyline plus 1% ketamine combined). The authors reported that a significant reduction in pain scores was observed in all groups and there was no difference between groups, suggesting these concentrations were not better than a placebo agent.

5.4 Delivery systems for topical agents in the orofacial region

The purpose of a local delivery system is to apply a medication for a therapeutic action in a site-specific manner. The drug's molecular structure and its pharmacological behavior dictate the delivery site and system. Use of topical medications in the orofacial region is accompanied by some inconveniences. For example, when applied intraorally (such as in a dissolving lozenge), these agents will dissolve in saliva and consequently spread throughout the mouth and down the throat. If the topical agent does have some mucoadhesive properties (in other words, if it is a gel or a cream), it can be painted on the appropriate site, but, again, it will wash away from the area quickly. Several forms have been developed to counter this problem: toothpaste; chewing gum; candy; adhesive patches and powders; dissolving tablets, lozenges, and lollipops; tissue-covering stents; dissolving polymeric devices; mouthwashes; and medicated lipsticks. Recently, dentists have been using topical agents with increasing frequency as part of the therapeutic protocol for orofacial painful neuropathy.

Combining pluronic lecithin with an organogel produces a very good medication delivery vehicle. This vehicle provides rapid dermal and mucosal penetration and lends itself to being compounded with other medications. The organogel provides a hydrophilic component for binding and carrying the admixed medication, while the lecithin increases the vehicle's ability to penetrate the lipophilic epidermal barrier.[92] Changing the ratio of lecithin to organogel moderates the cream's solubility through the lipophilic membrane.

Custom-made intraoral tissue stents appear to be the best method for holding a medication in place inside the mouth. These devices can be fabricated in a dental laboratory, using either acrylic materials or vacuum-formed polyvinyl materials on a stone cast of the patient's mouth. These tissue stents help maintain the medication in one position, increasing mucosa–medication contact for a longer period and protecting the treatment area from further irritation.

5.5 Six final recommendations on topical medications for chronic orofacial pain

Efficacy of topical anesthetics for chronic orofacial pain

1 There is a moderate amount of data suggesting that 5% lidocaine is a good treatment, providing beneficial effects on pain and allodynia with minimal adverse effects.

Efficacy of topical analgesics for chronic orofacial pain

2 There is no data on orofacial pain; however, for other musculoskeletal pains it appears that topical nonsteroidal anti-inflammatory drugs (NSAIDs) are less effective than oral NSAIDs during the first week but do not differ from oral NSAIDs after this.

Efficacy of topical vanilloid compounds (capsaicin) for chronic orofacial pain

3 Topical capsaicin for chronic musculoskeletal and/or neuropathic pain has not been shown to be an effective stand-alone topical treatment.

Efficacy of topical sympathomimetic agents (clonidine) for chronic orofacial pain

4 Topical clonidine may have some limited value in the management of some patients with oral neuralgia-like pain who cannot take systemic anticonvulsant medications, but the data is too sparse to make any recommendations.

Efficacy of topical NMDA antagonists for chronic orofacial pain

5 The data is not clear whether NMDA-receptor antagonists may be useful in the treatment of intractable orofacial neurogenic pain.

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Chapter 6

Anticonvulsant agents used for neuropathic pain including trigeminal neuralgia

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6.1 Four common orofacial neuropathic pains

When you begin to consider using anticonvulsant medications in pain management, the presumptive pain diagnosis should be neuropathic in origin. In general anticonvulsants are not good analgesics but they will decrease hyperactive neuronal activity.[1] This means that if you are treating nociceptive pain secondary to inflammation, infection, or recent physical injury, analgesic medications are logical. However, when a nerve has undergone neuropathic conversion and is firing spontaneously or firing with minimal input because it is sensitized, this would logically indicate the need for anticonvulsants. The specific mechanism underlying the various neuronal changes that occur with neuropathic pain conversion is discussed in Chapter 17. To make sure the distinction between nociceptive pain and neuropathic pain is understood, this chapter starts with a review of the four common neuropathic pain disorders that affect the trigeminal system. These disorders can largely can be divided into one of the following four categories: (1) neuralgias (e.g., trigeminal and other cranial neuralgias), (2) neuritis (e.g., localized nerve trauma, nerve inflammation, immune-mediated neuritis, or cancer-related perineural invasion[2–6]), (3) neuroma (post-nerve-branch transection), or (4) neuropathy (e.g., traumatic neuropathy, postherpetic neuralgia,[7–11] diabetic neuropathy,[12,13] neuropathy induced by acquired immunodeficiency syndrome [AIDS],[14] and idiopathic chronic trigeminal neuropathy[15–19]). These neuropathic disorders are listed in Table 6.1. The second part of this chapter discusses the various anticonvulsant drugs available for use in the management of neuropathic trigeminal pain. This chapter does not cover the nonpharmacologic treatment methods used in management of neuropathic pain.

6.1.A Trigeminal neuralgia and other cranial neuralgias

When literally translated, the word neuralgia simply means "nerve pain," but is also has a narrower medical meaning. The word neuralgia implies you are dealing with a pain that is sharp, brief, and electric-like or stabbing in character, usually unilateral and severe, and it stays within the distribution of the involved nerve branch or branches. When the pain is continuous, or burning, multidivisional, or just does not fit the preceding description, we would describe the pain (if neuropathic in nature) as a neuropathy, not as neuralgia.

Trigeminal neuralgia

The most common neuralgia in the orofacial region is trigeminal neuralgia (also known as *tic douloureux*).

Clinical criteria

The International Headache Society defines trigeminal neuralgia as a painful unilateral affliction of the face, characterized by brief electric-shock-like pain limited to the distribution of one or more divisions of the trigeminal nerve. Pain is commonly evoked by trivial stimuli, including washing, shaving, smoking, talking, and brushing the teeth, but may also occur spontaneously.[20] The pain is abrupt in onset and termination and it usually last 15–20 seconds. It commonly afflicts a single division of the trigeminal nerve. In the vast majority of trigeminal neuralgia cases, it affects either the maxillary division or the mandibular division, with the ophthalmic division affected in less than 20% of cases. The unique feature of trigeminal neuralgia is that the pain can be triggered by a light innocuous touch of a perioral

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Table 6.1 Summary of key features of common neuropathic pain conditions

Condition	Pain features	Causes or mechanisms
Neuralgias —Trigeminal —Glossopharyngeal —Nervus intermedius	Along distribution of affected nerve Electric-like, stabbing, sharp Lasting a few seconds to minutes	Vascular compression and abrasion of the nerve root that results in demyelination of nerve fibers leading to ectopic nerve activity
Neuritis (peripheral nerve)	Continuous, unremitting, and burning	Localized nerve trauma Nerve inflammation Immune-mediated neuritis Cancer-related perineural invasion Release of inflammatory mediators and cytokines
Neuroma	Electric-like, stabbing, sharp; triggered by physical contact or movement	Nerve transection
Neuropathies		
Postherpetic neuralgia	Burning, recurrent, and persistent	Nerve damage induced by herpes zoster infection
Diabetic neuropathy	Continuous burning, tingling pain, paresthesia	Metabolic and vascular abnormalities resulting in nerve damage
Neuropathy induced by AIDS	Variable	HIV-induced nerve damage
Idiopathic chronic trigeminal neuropathy	Continuous burning, aching, or both	Most likely peripheral and/or central sensitization
Chronic trigeminal neuropathy sympathetically maintained	Continuous burning, aching, or both	Nociceptor sensitization to catecholamines (e.g., norepinephrine)

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

or intraoral site. After the pain attack subsides there is usually a pain-free period between attacks where the same innocuous stimulation does not trigger pain.

Etiology

This condition is seen far more often in individuals in their fifth or higher decade. The likely link between aging and trigeminal neuralgia is that the intracranial artery closest to the trigeminal nerve root becomes stiff and elongated in the elderly and these arteries can produce an intracranial vascular compression or abrasion of the fifth nerve root as it exits from the brain stem. The other known causes of are neural damage due to multiple sclerosis.[21,22] Multiple sclerosis associated trigeminal neuralgia is reported in 2–4% of patients.[23–25] Because multiple sclerosis develops in much younger patients and their neuralgia is more frequently bilateral, any young trigeminal neuralgia patient (less than 50 years old) or any with bilateral pain should be tested for this disease. Finally, neural compression due to an intracranial tumor is also a possibility (e.g., cerebello–pontine angle tumors such as acoustic tumors, meningiomas, cholesteatomas, schwannomas, and neurofibromas) and is found in 2% of patients who present with typical trigeminal neuralgia.[26] Occasionally oral and pharyngeal cancer can invade into the trigeminal nerve. Often this type of pain gives rise to sensory changes and constant pain, in other words, trigeminal neuropathy.[27]

Diagnostic procedures

The major limitation in diagnosing trigeminal neuralgia is that imaging of the nerve via magnetic resonance imaging (MRI) or computed tomographic (CT) scans is not yet reliable since usually the vascular abrasion cannot be easily seen, given the resolution of current imaging methods. Nevertheless, in 2008, the American Academy of Neurology in conjunction with the European Federation of Neurological Societies (EFNS) published a guideline on the diagnosis and treatment of trigeminal neuralgia (TN).[28] The guideline recommends that physicians consider sending all patients with trigeminal neuralgia for MRI or trigeminal reflex testing, since up to 15% of patients have an underlying structural cause such as a tumor.[29]

Treatment methods

The EFNS guideline recommends carbamazepine as first-line treatment, with oxcarbazepine as a possible alternative, and it goes on to suggest that surgery be considered for any medication-refractory case. See Sections 6.2.A and 6.2.B for details about the proper use of these medications.

Other cranial neuralgias

There are other cranial nerve (CN) neuralgias, which produce similar pains to trigeminal neuralgia.

Clinical criteria

For example, geniculate neuralgia (also know as nervus intermedius of CN VII) is a brief severe ear and preauricular pain triggered by ear canal touch, swallowing, or talking.[30,31] Glossopharyngeal neuralgia (CN IX) is a brief severe pain in the tonsillar, tongue-base, oropharyngeal region.[32] Vagal neuralgia, which is usually associated with glossopharyngeal neuralgia, presents with similar symptomatology but it might also present with vocal cord dysfunction, such as hoarseness.[33,34] Superior laryngeal neuralgia (CN X) is a brief severe pain in the laryngeal, thyroid region and is triggered by swallowing, yawning, or talking.[35,36]

Etiology

The etiology for these other facial-region neuralgias are not firmly established, but the same causes of trigeminal neuralgia should be suspected, namely, vascular compression, central nervous system (CNS) tumor, and multiple sclerosis

Diagnostic procedures

As with trigeminal neuralgia, MRI imaging is the primary diagnostic procedure, followed by a trial of an anticonvulsant to see if the neuralgia is suppressed effectively or not.

Treatment methods

While these neuralgias are rare and can produce pain that is identical to that of trigeminal neuralgia, they only differ by the location of the pain.

6.1.B Trigeminal neuritis

As this term implies, there is inflammation of a nerve and here we discuss four aspects of this condition: mononeuritis, which usually implies local pathology; polyneuritis, which implies more generalized pathology; the transformation of an acute neuritis to a long-lasting neuropathy disorder; and the special case of cancer-induced neuritis.

Trigeminal mononeuritis

The term mononeuritis is used when an individual nerve or nerve trunk is inflamed.

Clinical criteria

The symptoms of neuritis are pain and dysesthesia (tingling) or numbness. Moreover, it is known that neuritis leads to hypersensitivity.[37] These symptoms are continuous.

Etiology

For the mononeuritis disorders, the first cause that should be suspected is trauma (e.g., fracture, intraneural injection, third-molar extraction, orthognathic surgical manipulations, implant-induced compression), then infection (bacterial or viral) or inflammation of the nerve. The three most common infections to affect the trigeminal nerves are dental abscess, sinus infection, and herpes zoster (shingles).

Diagnostic procedures

There are no specific imaging procedures that can detect inflammation of a peripheral nerve. Fortunately, mononeuritis pains have an acute onset and the cause is usually obvious based on the examination and history. Those caused by neural compression are also easy to figure out if the source is exogenous (i.e., dental implant). However, when neural abrasion comes from osseous growth or other slowly progressive external pressure (i.e., overlying tendons and blood vessels) the symptoms are slow to develop and more difficult to figure out.

Treatment methods

Suppression of the inflammatory reaction is logical and using methylprednisolone is commonplace if an acute neuritis is present. See Chapter 12 for detailed instructions on the proper use of systemic methylprednisolone.

Polyneuritis involving the trigeminal nerve

Clinical criteria

A neural inflammation that involves two or more nerve trunks in separate areas is called a polyneuritis. The most common polyneuropathy that affects the trigeminal nerve primarily is trigeminal sensory neuropathy (TSN), which is a multifactorial inflammatory disorder of the trigeminal nerve causing sensory dysfunction (numbness, pain). TNS patients usually present with symptoms such as unilateral or bilateral sensory loss of one or more divisions of the trigeminal nerve. The numbness can be either painful or nonpainful. Because of the association with mixed and undifferentiated connective tissue disease (see Etiology) there may also be complaints of Raynaud's phenomenon, polyjoint arthritis, and sometimes muscle weakness. Diabetic neuropathy is also a common known cause of neuropathy and can produce both an acute (usually reversible) nerve inflammation as well as chronic (irreversible) neuropathic changes in the trigeminal nerve. Often the symptoms of diabetic-induced neuritis first occur in the fingers and toes (numbness, tingling, weakness). There are multiple immune-related

neuritic conditions that induce these symptoms, although the location of the symptoms is varied.

Etiology

Trigeminal sensory neuropathy is a condition that has been associated with Sjögren's syndrome, undifferentiated and mixed connective tissue disease, and scleroderma, which are all considered to be connective tissue disorders.[38–44] The source of the underlying neural dysfunction is thought to be autoimmune because of this association.[45] Unfortunately, the symptoms of facial pain and numbness can and do occur before a clear serologically confirmed clinical diagnosis of one of these connective tissue diseases, by several years and with all sensory deficits; vigilance for cancer-induced neural dysfunction must be maintained. Other causes of polyneuritis include diabetes or a generalized autoimmune disease such as Guillain–Barré syndrome; chronic inflammatory demyelinating polyneuropathy and neuropathies associated with vasculitis; and monoclonal gammopathies. Viral-induced polyneuritis is caused by human immunodeficiency virus (HIV); *Cytomegalovirus*; *Poliovirus*; hepatitis B or C infections, causing vasculitic neuropathy. Bacteria-induced polyneuritis includes leprosy, diphtheria, Lyme disease, and trypanosomiasis. Nutritional-imbalance polyneuropathies are caused by deficiency of vitamins B_{12}, B_1 (thiamine), B_6 (pyridoxine), and E. Renal failure polyneuropathy can cause degeneration of peripheral nerve axons as a result of accumulated toxins. Toxin-induced polyneuropathy is caused by alcohol and other toxins (megadoses of vitamin B_6, lead, arsenic, mercury, thalium, organic solvents, and insecticides). Medication-induced neuritis and neuropathies include those caused by vincristine and cisplatinum in cancer; nitrofurantoin, which is used in pyelonephritis; amiodarone in cardiac arrhythmias; dideoxycytidine (ddC) and dideoxyinosine (ddI) in AIDS; and dapsone, used to treat leprosy.

Diagnostic procedures

Since polyneuropathies have multiple causes many diagnostic procedures are appropriate, depending on the suspected underlying disease; generally polyneuropathies are outside the diagnostic scope of an orofacial pain specialist and referral to a neurologist or infectious disease specialist is appropriate.

Treatment methods

Again, depending on the underlying disease that is causing the polyneuropathy, the treatment will vary and is beyond the scope of this chapter. Of course, the neuropathic pain symptoms can be suppressed using anticonvulsants, beginning with gabapentin and moving toward carbamazepine as needed.

Neuritis conversion to neuralgia

Clinical criteria

As mentioned, nerve inflammations cause neuritis (acute pain); although in most cases the neuritis pain will fade as the inflammation resolves, sometimes acute neuritis can convert to chronic neuralgia. One example is postherpetic neuralgia (PHN).

Etiology

Postherpetic neuralgia is a continuous cutaneous itching, burning pain in the involved nerve division. The conversion into neuropathy also occurs with HIV neuritis and diabetic neuritis.

Diagnostic procedures

Postherpetic neuralgia is largely diagnosed by history and clinical examination since there are no physical visible signs with neuralgia.

Treatment methods

The treatment of PHN involves topical anesthetics as the primary treatment. The anesthetic is usually applied using patches that allow for transdermal transfer of the anesthetic agents (usually lidocaine) into the painful skin. See Section 6.2.K for details about the proper use of lidocaine.

Cancer-induced trigeminal pain

Cancer-induced trigeminal pain is listed in the neuritis category because, when a cancer invades a nerve, this process causes either acute compression or injury to the nerve.

Clinical criteria

If a cancer invades a nerve sheath or root this will also induce pain that mimics the previously mentioned disorders (neuritis, neuralgia, neuropathy).

Etiology

The most common cancers associated with trigeminal nerve are posterior tongue–lateral pharyngeal cancer, causing pain in the lingual nerve, and cancer of the nasopharynx invading the infratemporal region and affecting the trigeminal nerve as it exits the foramen ovale.

Diagnostic procedures

The primary diagnostic procedure needed with cancer-induced neurogenous pain is to confirm that the neoplastic tissue is indeed invading the affected nerve, using MRI to identify the shape, extent, and location of the neoplastic mass and its proximity to the nerve.

Treatment methods

If the cancer is inoperable, then pain management with opioids is appropriate. See Chapters 4 and 13 for discussions about opioid medication use in cancer patients. If the cancer is operable, obviously, surgical removal is indicated.

6.1.C Trigeminal neuroma

While there are neuromas that are neoplastic in origin, in this section we are considering only those that occur in peripheral nerves secondary to injury.

Clinical criteria

As discussed earlier, neural injury can produce an acute neuritis, but sometimes neuritis can result from transection of the nerve, resulting in numbness in the area being supplied by the nerve. Often this results in a degeneration of the nerve and subsequent numbness. If a larger axonal branch of a nerve is transected, then nerve sprouts may form a true neuroma at the proximal nerve stump. A neuroma is a bundle or ball of nerve fibers that may develop after damage to the peripheral nerve such as lacerations, crushing, cuts, or even stretching the nerve. Clinically it can appear as a slowly growing, whitish nodule that sometimes can be palpable; it represents an attempt at nerve reparation. The symptoms include hypersensitivity to light touch and spontaneously active pain. Furthermore, there might be tenderness on percussion, or pressure of the surrounding tissues.[46] The most common locations in the jaw are the lingual nerve, inferior alveolar nerve, and auriculotemporal nerve.

Etiology

Peripheral nerve transections and neuroma growth at the severed trunk are sequelae of trauma, often surgical.

Diagnostic procedures

If an inadvertent surgical transection did occur, the probable site of the neuroma is probably known, in which case a small amount of local anesthetic delivered in and around the neuroma will stop the pain. This is more or less diagnostic of the neuroma.

Treatment methods

Some neuromas are not highly active and can be treated with mild anticonvulsants (gabapentin or pregabalin), while others are highly active with continuous spontaneous neuronal activity. These can be treated with cryoprobes (freezing injections) in an attempt to desensitize the neuroma.[47]

6.1.D Trigeminal neuropathy

As mentioned previously, when neurogenic pain is continuous or burning and does not have a clinically or radiograpically evident pathologic basis in the ganglion or CNS, this pain is potentially a neuropathy. According to the International Association for the Study of Pain, neuropathic pain is, by definition, "pain initiated or caused by a primary lesion or dysfunction in the nervous system."[48] The pain is often described as aching and burning, varying in intensity from moderate to severe. Additionally, it can present with associated symptoms such as sensory loss, weakness, and dysesthesia. We have dedicated an entire chapter to chronic trigeminal neuropathy (see Chapter 17) so our discussion here is limited.

Clinical criteria

Trigeminal neuropathy usually produces a continuous pain sensation in the dental, alveolar, gingival–mucosal, or cutaneous tissues. This pain is localized to the distribution of the involved trigeminal nerve branch. Such pains have been described as atypical odontalgia, if pain is focused in the tooth–alveolar area. When the pain persists after the tooth is extracted it is described as a phantom tooth pain.

Etiology

Often the injury or tissue insult that produces this neuropathic problem cannot be clearly identified. For example, the previously described neuritis disorders due to acute injury or inflammation can convert into neuropathic disease due to irreversible changes in the nerve (called peripheral and central sensitization). These sensitization changes are usually divided by the extent of the alteration into the following:

1. *Peripheral sensitization* Initially the pain is completely blockable with a local anesthetic and is more focal in character;
2. *Central sensitization* Long-term nociceptive neuron potentiation and sensitization, which does not respond fully to anesthetic blocks, is less localized, often crossing divisions and midline.

3 *Complex–sympathetic sensitization* The afferent nerves express receptors that respond to sympathetic nerve neurotransmitters (e.g., norepinephrine), causing pain, are stress driven.

Diagnostic procedures

This is largely a diagnosis of exclusion, so local dental and periodontal pathology must be ruled out. See Chapter 17 for a thorough discussion of orofacial neuropathic disease diagnosis.

Treatment methods

Most commonly we use topical anesthetics and mild anticonvulsant medications to suppress the spontaneous activity in the damaged nerve. See Chapter 17 for more details on treatment.

6.2 Anticonvulsant drug therapy

The majority of the 12 anticonvulsant agents reviewed next (carbamazepine, oxcarbazepine, lamotrigine, levetiracetam, zonisamide, phenytoin, gabapentin, pregabalin, baclofen, valproic acid, topiramate, and lidocaine) are approved for control of epileptic seizures. Among these, only carbamazepine is approved for trigeminal neuralgia, but the others are used off-label for suppression of neuropathic pain as well. Anticonvulsants are not categorized with an FDA narcotic schedule classification but are dangerous nonetheless. If the neuropathic pain symptoms are severe, suppression of neuronal activity is best achieved with an anticonvulsant medication. Unfortunately anticonvulsant-type medications do not suppress just the painful nerve but they suppress all nerves, which means the medications have some serious side effects. While no patient wants pain, some also cannot tolerate the side effects, so all prescribing doctors will have to titrate the medication upward to balance the side effects with the pain relief. There are only few randomized controlled trials that have been conducted and in this section these various anticonvulsant medications are discussed.

This discussion must begin with a January 2008 FDA advisory letter to healthcare professionals that, based on placebo-controlled studies, the use of anticonvulsant drugs had approximately twice the risk of suicidal behavior or ideation (0.43%) compared with patients receiving placebo (0.22%).[49] The increased risk of suicidal behavior and suicidal ideation was observed as early as 1 week after starting the antiepileptic drug and continued through 24 weeks. The results were generally consistent among the 11 drugs analyzed, which included carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide. The relative risk of suicidality was higher in patients with epilepsy compared with patients who were given one of the drugs in the class for psychiatric or other conditions. They suggested that healthcare professionals should closely monitor all patients currently taking or starting any antiepileptic drug for notable changes in behavior that could indicate the emergence or worsening of suicidal thoughts or behavior or depression. More details about the individual anticonvulsant agents used in neuropathic pain management are discussed in the following subsections.

6.2.A Carbamazepine

Description, mechanism of action, and primary indications

The chemical structure of carbamazepine is related to the tricyclic antidepressant medications and to phenytoin. Carbamazepine acts by altering or slowing the opening and closing cycles of voltage-gated sodium ions across cell membranes. It does this by stabilizing the inactivated state of a sodium channel, which means that it takes longer for a sodium channel to close or reactivate after being opened. Carbamazepine has been used for trigeminal neuralgia, glossopharyngeal neuralgia, and other lancinating pain syndromes since the early 1960s and is approved by the FDA for treatment of these diseases.[50]

Starting dose

The starting dose for carbamazepine is 200 mg twice a day and the patient is then titrated upward to the effective dose range, 600–1200 mg/day.

Side effects and adverse drug reactions

Carbamazepine is metabolized by the liver cytochrome P450 enzyme 3A4 and it also induces the several cytochrome P450 enzyme systems. As a result it is known as a self-inducing drug. This means that its ability to induce or stimulate the liver enzymes that metabolize it to work faster, and the initial therapeutic dose where pain relief is found will stop working after a few weeks of continuous use. This is because essentially the drug level in the blood drops as it is metabolized much faster so the dose must be increased. For these reasons, it is necessary to conduct serologic assessment of the patient's liver function and hematologic status and to see if the drug is in the suggested therapeutic range with regular blood tests. Carbamazepine does have a high risk of adverse reactions because its therapeutic dose is

close to its toxic dose, and it produces a toxic epoxide metabolite that can cause liver damage and anemia quickly.[51] In addition, this drug produces a 10% incidence of rashes and has a negative effect on bone density. The most common side effects are drowsiness, diplopia, and unsteadiness although aplastic anemia, reversible leukopenia and thrombocytopenia, are also a concern. In 2007, the FDA issued a warning newsletter to healthcare professionals specifically about carbamazepine and its increased risk for development of Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in Asian individuals who carry the HLA-B*1502 allele.[52] This risk is now listed on the product labeling. They described two rare but life-threatening cases of an adverse dermatological reaction associated with the use of the anticonvulsant drug carbamazepine. Traditionally, the likelihood of developing CBZ-associated SJS/TEN has been considered very low.[53,54] Recent reports, however, indicate that certain Asian populations may be at increased risk (10 times higher than Caucasians) for developing these conditions.[55–59] The specific Asian populations that carry the HLA-B*1502 allele are Han Chinese, Filipino (Ivatan), Indonesians, Malaysians, Taiwanese (Minnan), Thai, and certain Asian Indians (Khandesh Pawra). There appears to be a lower incidence in allele frequency in Japanese individuals. The at-risk group is over 1 million individuals since 4–5% of individuals residing in the United States have identified themselves as Asian and up to 10% of Asian Americans will be positive for the HLA-B*1502 allele.[60] Finally this drug has a D rating for pregnancy risk and does cross into breast milk.

Efficacy for trigeminal neuralgia

With regards to efficacy for trigeminal neuralgia, there are at least three well-designed double-blinded, placebo-controlled crossover studies that have examined carbamazepine. Combined they included a total of 151 patients[61–63] with a good initial effect in approximately 70%. Based on the data from these three studies, a meta-analysis calculated the NNT (number-needed-to-treat) for effective pain control was 2.6 (defined as a >50% pain relief compared with placebo).[64] This same article also calculated the NNH (defined as the number-needed-to-harm or where the adverse effects were in excess of those seen with placebo) to be about 3.4. In 2007 a review of the literature examine multiple randomized controlled trials (RCT) on pharmacologic management of trigeminal neuralgia.[65] The evidence presented in this review suggests that carbamazepine is still the first-line drug for medical management. The authors of this review suggested that carbamazepine should be changed to oxcarbazepine if there is poor efficacy or unacceptable side effects. Combination of carbamazepine with lamotrigine or baclofen is the second-line treatment when monotherapy fails, but the evidence for this polypharmacy is scant. The authors also suggested that a neurosurgical treatment should be considered when a patient has poor efficacy and tolerability of drug treatment and no remission periods. There have been several small studies which have looked at the efficacy of other drugs (tizanidine, baclofen, pimozide, tocainade, and oxcarbazepine) for the treatment of trigeminal neuralgia but none have been proven superior to carbamazepine.[66–69] Unfortunately, there are almost no data on the long-term efficacy of carbamazepine in managing trigeminal neuralgia. Only one case-series report even attempted to examine this issue and it reported that there was a loss of effect or problems with tolerability in one-half of patients over a 10-year period.[70] There is the possibility that in some cases this loss of effect can be compensated to a degree by adding a second anticonvulsant (e.g., lamotrigine).

Efficacy for other neuropathic pain disorders

When dealing with other neuropathic pain disorders (e.g., diabetic neuralgia and postherpetic neuralgia, chronic trigeminal neuropathy) carbamazepine is not considered a first-line choice because of the high potential for adverse reactions and the complications to therapy that frequent blood tests produce. Nevertheless, carbamazepine has been suggested as a second-line anticonvulsant for neuropathic pain when the patient has not responded to gabapentin.[71] The dosage of carbamazepine for neuropathic pain is usually lower than that used for trigeminal neuralgia (≤400 mg twice a day). In painful diabetic neuropathy, carbamazepine has an NNT of 2.3.[72] In 2008 there was a report that examined the effects of carbamazepine and amitriptyline on tetrodotoxin-resistant (TTX-R) Na+ channels in immature rat trigeminal ganglion neurons.[73] This study found that both carbamazepine and amitriptyline were able to inhibite TTX-R sodium channels in a dose-dependent manner. Interestingly they actually found that amitriptyline was a more potent inhibitor. The authors concluded that both drugs would be useful for the treatment of trigeminal nerve injury-induced continuous neuropathic pain disorders. In 2003 an experimental neuropathic pain study examined the comparative activity of the anticonvulsants oxcarbazepine, carbamazepine, lamotrigine, and gabapentin.[74] With their rat model of partial sciatic nerve ligation they were able to show that neither oxcarbazepine nor carbamazepine reduced mechanical hyperalgesia or tactile allodynia. Conversely, with the same model in the guinea pig, both of these drugs produced up to 90% reversal of mechanical hyperalgesia. Lamotrigine was found to be effective against mechanical hyperlagesia in both species although it showed greater efficacy and potency in the guinea pig. Lamotrigine also produced slight

inhibition of tactile allodynia in the rat only at the highest dose tested. Gabapentin also produced significant dose-related reversal of tactile allodynia in the rat. However, gabapentin was poorly active against mechanical hyperalgesia in either the rat or guinea pig following a single oral administration, but with repeated administration it produced up to 70% and 90% reversal in rat and guinea pig, respectively.

6.2.B Oxcarbazepine

Description, mechanism of action, and primary indications

Oxcarbazepine is structurally related to carbamazepine and has many of the therapeutic properties of carbamazepine, while potentially avoiding its many toxicities. Oxcarbazepine acts by blocking voltage-gated Na^+ channels and it modulates voltage-activated Ca^{++} currents. This drug is not FDA approved for trigeminal neuralgia and is used off-label for this disease, but there are published reports that have shown efficacy in trigeminal neuralgia (see the subsection "Efficacy for trigeminal neuralgia").

Starting dose

Oxcarbazepine is typically started at 300 mg twice a day with a escalation plan of an additional 300 mg/day every 3 days up to a maximum of 1800–2400 mg/day. The half-life of this drug is 9 hours (metabolite) so that twice-a-day dosing is optimal.

Side effects and adverse drug reactions

Unlike carbamazepine, which is the active drug in its ingested form, oxcarbazepine is a prodrug or nonactive drug and its metabolite is the active agent. The substantial advantage of oxcarbazepine over carbamazepine is that it is not a strong inducer of the cytochrome enzymes so once the effective dose is established it is more stable. One known side effect is hyponatremia, and measurement of serum sodium levels should be considered during maintenance treatment, but drinking milk daily can prevent this complication.[75] The incidence of rash is 4%, and drug–drug interactions are few.[76] While the choice to institute therapeutic drug monitoring is based on the frailty of the patient, it is not mandatory to use blood monitoring with this drug. In 2007 a case report appeared about a trigeminal neuralgia patient who had been successfully treated with oxcarbazepine for many months, but then developed a full return of her symptoms while continuing her medications.[77] It turned out she had recently started taking an unregulated health-food product (healing earth) daily that interfered with the absorption of the medication. Stopping this health-food product brought her pain back into full control.

Efficacy for trigeminal neuralgia

With regards to an assessment of the efficacy of oxcarbazepine for trigeminal neuralgia, there are no high quality, large, scientifically rigorous studies, only case reports.[78] In 2002, a small prospective case series involving 15 patients (11 females) compared oxcarbazepine management versus surgical management of intractable trigeminal neuralgia pain.[79] The patients described in this report were prospectively followed for 13 years and were first treated with oxcarbazepine (1200 ± 600 mg daily dosage) and subsequently with surgery of their choice. Pain control was initially achieved in all patients and oxcarbazepine was used continuously or intermittently for at least 4 years. Twelve of the 15 patients required surgery (5 had microvascular decompressions and 7 had a surgery at the level of the Gasserian ganglion) to control their pain and were followed up for an additional 4 years postsurgery. The authors concluded that while oxcarbazepine is a potent medication for trigeminal neuralgia, with very good acceptability and tolerability, many patients will go on to have surgical treatment. They also suggested that patients may therefore benefit from having surgery earlier rather than later in the disease process in order to improve quality of life and for freedom from medication and the need for regular follow up, but it will not provide complete pain relief for all patients. In 2008, another case series report appeared in the literature that described the successful treatment of 35 trigeminal neuralgia patients with oxcarbazepine.[80] This prospective open-label study reported that all 35 of the patients were found to be unresponsive to treatment with carbamazepine first and all had been on oxcarbazepine monotherapy for at least 12 weeks before inclusion. Interestingly the mean daily dose for these 35 patients was moderately low, 773.7 mg/day. The authors reported that oxcarbazepine was well tolerated by all patients but long-term data on its continued efficacy was not provided.

Efficacy for other neuropathic pain disorders

When dealing with other neuropathic pain disorders, oxcarbazepine data is equally limited. It consists of a few case series and open-label trials, but it does appear promising.[81] A review of the literature published in 2007 examined the pros and cons of oxcarbazepine used off-label for neuropathic pain.[82] This review concluded that several double-blind, placebo-controlled trials have evaluated oxcarbazepine in painful diabetic neuropathy and found it highly useful and

generally well tolerated at doses of ≤1800 mg/day.[83] For neuropathic pain, the recommended dosage is lower than for trigeminal neuralgia (≤600 mg twice a day).

6.2.C Phenytoin

Description, mechanism of action, and primary indications

Phenytoin and carbamazepine are structurally similar and, for many years, either carbamazepine or phenytoin was the anticonvulsant of choice for treating trigeminal neuralgia. As mentioned, these drugs exert their effect by altering voltage-gated Na^+ channels and slowing their reactivation. This produces a so-called membrane-stabilizing"effect and reduced neuronal excitability.

Starting dose

The suggested starting dose of phenytoin is 200 mg. The therapeutic dose is 300–500 mg twice a day.

Side effects and adverse drug reactions

Phenytoin is metabolized in the liver and it is a saturable process, which means that a small increment in the dosage might cause the blood drug levels to be substantially increased. The common adverse effects of phenytoin include nausea, vomiting, constipation, epigastric pain, dysphagia, loss of taste, anorexia, and weight loss. The CNS-related adverse effects that are commonly found include mental confusion, nystagmus, ataxia, blurred vision, diplopia, and headache. The dental considerations of this medication are related to the development of gingival hyperplasia.

Efficacy for trigeminal neuralgia

In the United States, phenytoin is not approved for use in trigeminal neuralgia although, in the United Kingdom, it is licensed as second-line therapy to carbamazepine in trigeminal neuralgia if the carbamazepine is ineffective or intolerable. With the advent of oxcarbazepine and lamotrigine, phenytoin has been surplanted since phenytoin is simply better known as an antiepileptic drug and, with the exception of carbamazepine, the newer anticonvulsants are generally safer and better tolerated.[84]

Efficacy for other neuropathic pain disorders

While based on data from a single study, phenytoin has an NNT of 2.1 in painful diabetic neuropathy.[85] However, a different placebo-controlled study failed to demonstrate a significant effect of phenytoin on diabetic neuropathy.[86]

6.2.D Lamotrigine

Description, mechanism of action, and primary indications

Lamotrigine is a new anticonvulsant that acts by stabilizing slow inactivated sodium channels. It is possible that this medication also suppresses the neuronal release of glutamate.[87]

Starting dose

The therapeutic dose is between 100 and 400 mg daily.

Side effects and adverse drug reactions

Lamotrigine has more serious adverse effects than gabapentin (e.g., somnolence, dizziness, ataxia) and requires a slower titration, which may be problematic for patients in severe pain. Other side effects of the drug include skin rashes, which are common, occurring in up to 10% of patients.[88] Rashes can be minimized if the drug is started at a low dosage that is increased only every 5–7 days. Insomnia is a common side effect of this drug. In 2006, the FDA issued a letter to healthcare professionals that the use of lamotrigine in the first 3 months of pregnancy (commonly used to treat seizures and bipolar disorder) may have a higher chance of the baby being born with a cleft lip or cleft palate.[89]

Efficacy for trigeminal neuralgia

Unfortunately, there is a general lack of quality published multicenter randomized double-blind trials for this drug when used either for trigeminal neuralgia or other neuropathic pain disorders. One double-blinded clinical trial of note reported that lamotrigine was found helpful in treating refractory trigeminal neuralgia.[90]

Efficacy for other neuropathic pain disorders

Lamotrigine used for other neuropathic pain problems has shown limited efficacy in randomized trials on pain due to diabetic polyneuropathy,[91] central post-stroke neuropathy,[92] spinal cord injury,[93] and HIV-related neuropathy.[94,95] Lamotrigine has been suggested as a second-line anticonvulsant for neuropathic pain when the patient has not responded to gabapentin. However, a more recent 2007 study found no efficacy for lamotrigine used alone and in combination with other medications (gabapentin, a tricyclic antidepressant, or a nonopioid analgesic) for the suppression

of neuropathic pain.[96] The study was a double-blind, placebo-controlled trial and involved patients with various types of neuropathic pain (diabetic peripheral neuropathy, postherpetic neuralgia, traumatic or surgical nerve injury, incomplete spinal cord injury, trigeminal neuralgia, multiple sclerosis, or HIV-associated peripheral neuropathy) who were all considered to be inadequately controlled with their current medication protocol on these other medications. The authors essentially added lamotrigine (up to 400 mg/day) or a placebo and evaluated their pain level over a 1-week treatment period. They reported no statistically significant difference in the mean change in pain-intensity score between lamotrigine and placebo although it was generally well tolerated.

6.2.E Levetiracetam (Keppra®)

Description, mechanism of action, and primary indications

Levetiracetam is minimally metabolized in the liver, is less than 10% protein-bound, and has linear pharmacokinetics.[97]

Starting dose

For neuropathic pain, a dose of ≤1500 mg twice a day is suggested.

Side effects and adverse drug reactions

One major advantage with this anticonvulsant is that it has few adverse effects and although all drugs in this class affect cognition this drug generally exhibits fewer CNS effects than other anticonvulsants (except gabapentin and pregabalin). Moreover this drug has few drug–drug interactions since it is eliminated renally and is mainly unchanged (levetiracetam). The pharmacokinetic variability of levetiracetam is also less pronounced and more predictable, which means it is not required to conduct therapeutic drug monitoring blood draws.

Efficacy for trigeminal neuralgia

There is no body of literature that suggests levetiracetam is useful for trigeminal neuralgia.

Efficacy for other neuropathic pain disorders

To date, no controlled studies have been published on levetiracetam and neuropathic pain. A small study describing several cases indicated that it may have a role in the treatment of neuropathic pain.[98]

6.2.F Zonisamide (Zongran®)

Description, mechanism of action, and primary indications

Zonisamide is metabolized by the liver and therefore has an inherent pharmacokinetic variability.

Starting dose

The starting dose is 100 mg orally every day, titrated up every 2 weeks at minimum, to a maximum of 600 mg/day.

Side effects and adverse drug reactions

In 2008 a study was published that reviewed the pharmacology, clinical efficacy, tolerability, and safety of zonisamide.[99] The review described zonisamide as a sulphonamide-derivative anticonvulsant with multiple potential mechanisms that contribute to its anticonvulsant activity. It is commonly used off-label for nonepileptic disorders such as headaches and neuropathic pain. The review stated that this drug is generally well tolerated in long-term use and it has favorable pharmacokinetic characteristics.

Efficacy for trigeminal neuralgia

There is no body of literature that suggests zonisamide is useful for trigeminal neuralgia.

Efficacy for other neuropathic pain disorders

In 2002, a review examined the emerging evidence from animal models of where and how anticonvulsant medications alter the neuropathic pain process.[100] The review concluded zonisamide's mechanisms of action suggest that it would be effective in controlling neuropathic pain symptoms. Moreover the review suggested similarities between the pathophysiologic phenomena observed in some epilepsy models and in neuropathic pain models justify the use of anticonvulsants in the symptomatic management of neuropathic pain.

6.2.G Gabapentin (Neurontin®)

Description, mechanism of action, and primary indications

Gabapentin is a novel anticonvulsant that does not, as its name suggests, interact with GABA receptors or GABA metabolism. The mechanism of action of gabapentin is uncertain but most likely it acts to affect voltage-dependent L-type Ca^{2+} channels. Unfortunately gabapentin does not target only painful nerves but acts on all nerves that contain

Ca^{2+} channels so at best this drug suppresses neuronal activity since if stopped the patient would have serious functional impairment. It has been suggested that gabapentin binds to a subunit of N-type calcium channels on neurons. In a good-quality study that compared gabapentin with placebo in 165 patients with painful diabetic neuropathy an NNT of 3.7 was reported.[101] Gabapentin has been in use since 1994 and was originally approved as an adjunctive medication in the treatment of epilepsy. In 2002, the FDA granted approval to expand the use of gabapentin for the management of postherpetic neuralgia based on the published evidence.[102,103]

Starting dose

For neuropathic pain, the usual starting dose for gabapentin is 300 mg/day taken 100 mg three times daily. The dose is gradually increased (adding 300 mg every 3–4 days) to 1800 mg/day or higher if needed. The usual maximum dose is 3600 mg daily.

Side effects and adverse drug reactions

Gapapentin does not have an FDA narcotic schedule classification in addition to its analgesic effect; the greatest benefit of gabapentin is that it has good tolerability and rare drug–drug interactions (DDI). The low DDI level is because this drug is not metabolized by the liver and is excreted in urine unchanged, although caution must be used in any patient with compromised renal function. Side effects include peripheral edema in up to 10% of patients, particularly in the elderly or with dosages above 1800 mg/day. The other reported side effects of gabapentin are somnolence, dizziness, drowsiness, nausea, fatigue, and unsteadiness; however, these are not usually reason for discontinuing the medication. These side effects are usually self-limiting and subside after a couple of weeks allowing gradual dose escalation. Absorption varies significantly in patients and generally decreases with increasing doses.[104]

Efficacy for trigeminal neuralgia

In 2008 a case report was published that described the successful use of gabapentin for refractory idiopathic trigeminal neuralgia that was resistant to conventional pharmacotherapeutic methods.[105] In general gabapentin has not been shown to be highly or consistently effective for trigeminal neuralgia.

Efficacy for other neuropathic pain disorders

Gabapentin has also been tested for various other neuropathic pain conditions in double-blinded trials[106–110] as well as for cancer-related neuropathic pain.[111–113] It has also shown treatment efficacy in a number of randomized controlled trials in other neuropathic pain disorders, including painful diabetic polyneuropathy,[114] PHN, phantom limb pain,[115] Guillain–Barré syndrome,[116] spinal cord injury,[117] and complex regional pain syndrome type 1.[118] Gabapentin is frequently used on patients with chronic neuropathic pain where central neuronal sensitization is suspected.[119] One comparative trial showed that amitryptiline and gabapentin were equally effective for painful diabetic neuropathy.[120] In 2007, a study was published that compared gabapentin (1200–2400 mg/day) with a placebo treatment on patients diagnosed with fibromyalgia.[121] The study was a randomized, double-blind, placebo-controlled, multicenter trial and it involved 150 patients divided into two equal groups studied across a 12-week period. The outcome of concern in this study was a numerical rating of average pain on a 0–10 scale. Response to treatment was defined as a reduction of ≥30% in this score; the authors reported that gabapentin-treated patients displayed a significantly greater improvement in the average pain-severity score than the placebo group. Moreover, a significantly greater proportion of gabapentin-treated patients achieved response at endpoint (51% vs. 31% in placebo).

6.2.H Pregabalin (Lyrica®)

Description, mechanism of action, and primary indications

A new drug, similar in effect to gabapentin, that binds to a subunit of calcium channel and reduces neuronal activity has been approved by the FDA for neuropathic pain is pregabalin.[122,123] Pregabalin is an analog of gabapentin that is more effective in animal models of pain than gabapentin. This drug has analgesic, anxiolytic, and anticonvulsant activity in animal models.[124,125] It reduces the release of several neurochemicals, including glutamate, norepinephrine, and substance P. It was found to be effective in reducing the severity of body pain, improving quality of sleep, and reducing fatigue in fibromyalgia.[126] Pregabalin was approved in 2005 for epilepsy and for diabetic peripheral neuropathy. Pregabalin is a 3-substituted analog of gamma-amino butyric acid (GABA) and it is thought that the two compounds share similar mechanisms of action, binding to the calcium channels, modulating calcium influx, and resulting in analgesic, anxiolytic, and anticonvulsant activity.[127] The major difference between gabapentin and pregabalin is that the latter produces an equivalent efficacy at lower doses. Pregabalin is an analog of the neurotransmitter GABA that exhibits analgesic, anticonvulsant, and anxiolytic properties. Owing to its pharmacologic properties, the drug has been used

worldwide in the management of diabetic peripheral neuropathy, postherpetic neuralgia, generalized anxiety disorder, and social anxiety disorder.

Starting dose

This drug is given (300–600 mg/day) in 2–3 divided doses and is generally well tolerated. The starting dose for pregabalin is 150 mg/day and maximum dose is 300 mg/day. After the initial titration and adjustment period, pregabalin can be switched from before sleep to dosing on a three-times-a-day schedule.

Side effects and adverse drug reactions

The adverse effects of gabapentin include dose-related dizziness and somnolence that do diminish in intensity after several days of continuous use. Weight gain and peripheral edema occur in 5–10% of patients without evidence for an effect of the drug on the heart or kidneys. Like gabapentin, it is not metabolized, so no drug–drug interactions occur, but the dosage must be adjusted for patients with renal dysfunction. In 2008 pregabalin was suggested as the cause of heart failure in three patient case reports who were given the drug for treatment of neuropathic pain.[128] The main side effect associated with pregabalin use is CNS disturbance although peripheral edema and weight gain have also been reported.

Efficacy for trigeminal neuralgia

There is no body of literature that suggests pregabalin is useful for trigeminal neuralgia.

Efficacy for other neuropathic pain disorders

Pregabalin has shown efficacy in PHN[129] and diabetic polyneuropathy.[130] In 2005 pregabalin was examined for its efficacy in the treatment of fibromyalgia.[131] The study examined three different dose levels and compared them with a placebo drug over 8 weeks in 529 patients (90% women) with fibromyalgia. The authors described that there was a strong dose–response, with only the top dose of 450 mg/day pregabalin being significantly different from placebo. They reported at least a 50% reduction in pain was achieved by 29% of patients on pregabalin 450 mg, compared with 13% on placebo. The NNT over eight weeks was 6.3 (3.9–16) and the major adverse events included dizziness, somnolence, and dry mouth. Also in 2008 a review of the literature on the efficacy of both pregabalin and gabapentin for neuropathic pain in spinal-cord injury was published.[132] The meta-analysis found five studies that were of sufficient quality to analyze. They concluded that overall, pregabalin was found to be more efficacious than gabapentin on several important outcomes although it did have more side effects as well. In 2007 a retrospective evaluation of gabapentin and pregabalin used for PHN was published.[133] The study called up records for all new prescriptions of pregabalin (n = 100) or gabapentin in (n = 151) patients with PHN and looked at the prevalence of co-morbidities, exposure to other neuropathic-pain-related medications and if therapeutic levels (gabapentin, ≥1800 mg/day; pregabalin, ≥150 mg/day) were achieved in these patients. They reported that in patients with PHN in the usual-care setting, opioid use increased after the initiation of gabapentin and decreased after the initiation of pregabalin. Few of those prescribed gabapentin ever got to a therapeutic dose level, which suggests that pregabalin is generally more effective than gabapentin.

6.2.1 Valproic acid (Depakene®)

Description, mechanism of action, and primary indications

Valproic acid has proved to be useful in migraine prophylaxis.[134,135]

Starting dose

For neuropathic pain, a dosage of ≤500 mg three times a day is suggested.

Side effects and adverse drug reactions

Adverse effects of valproate include nausea, vomiting, sedation, ataxia, rash, hair loss (usually reversible), appetite stimulation, inhibition of platelet aggregation, liver enzyme abnormalities, potentially fatal hepatotoxicity, and drug–drug interactions. Forty percent of patients experience elevated transaminase levels, and 1 in 50,000 develops hepatic failure. These adverse reactions and other hematologic and nonhematologic effects make pretreatment screening and close follow-up mandatory.

Efficacy for trigeminal neuralgia

There is no body of literature that suggests valproic acid is useful for trigeminal neuralgia.

Efficacy for other neuropathic pain disorders

One study of sodium valproate found it to have proven efficacy for painful diabetic polyneuropathy.[136] Valproic acid blocks voltage-gated Na^+ channels as carbamazepine and

phenytoin do, but also increases levels of aminobutyric acid (GABA) by decreasing its degradation.

6.2.J Topiramate (Topamax®)

Description, mechanism of action, and primary indications

Topiramate, which was first approved for use by the FDA in 1997, is a unique monosaccharide compound structurally unlike other anticonvulsants. It does potentiate GABA responses, significantly increasing CNS GABA levels, and also blocks the AMPA/kainate excitatory receptor. Topiramate is a weak carbonic anhydrase inhibitor. The primary use of this agent is for chronic or frequent headaches.

Starting dose

The effective dose range is 200–400 mg/day twice a day. The dose is 25 mg twice a day and is increased 50 mg/week up to the dose range.

Side effects and adverse drug reactions

Topiramate side effects include unusual CNS effects such as abnormal delusional and psychotic thinking. Impairment of word finding and of simple skills such as signing a check appears to be a common side effect. Another potential side effect of this drug is weight loss in 10–20% of patients.[137] This may be beneficial, especially in obese patients with type 2 diabetes. Other adverse effects include renal stones, with a reported incidence of 1.5%.[138] Fortunately, topiramate, like gabapentin and pregabalin is easier to tolerate and is a lower risk anticonvulsant because of its pharmacokinetic characteristics; it is excreted mainly unchanged in urine and not susceptible to significant drug–drug interactions. Finally, no idiosyncratic reactions or organ toxicities have been reported thus far.[139]

Efficacy for trigeminal neuralgia

Topiramate has not been suggested for use in trigeminal neuralgia

Efficacy for other neuropathic pain disorders

For neuropathic pain topiramate seems to have a low potential for pain relief. However it is FDA approved for use as a migraine preventative agent and has some positive results for cluster headache.[140] Topiramate used for painful diabetic neuropathy was found ineffective in three placebo-controlled studies and effective in another.[141,142]

6.2.K Lidocaine (generic)

Description, mechanism of action, and primary indications

Because lidocaine is a nonspecific sodium channel blocker. One important predictor of treatment efficacy for neuropathic pain is when the damage or change is thought to be limited to the peripheral nerve without substantial change more centrally. In peripheral neuropathic pain, predominantly, the applications of topical or local injected anaesthetic may fully suppress the pain, but this is not so true if central neuropathic changes have developed. Essentially, this is the reason we use topical anesthetic as a diagnostic test since it indicates if local sodium channel blocking agents would be a useful therapeutic approach.[143–145]

Starting dose

When used as topically, lidocaine should be applied in the affected area as needed.

Side effects and adverse drug reactions

Commons side effects include injection-site pain, lightheadedness, tremor, confusion, anxiety, dizziness, euphoria, drowsiness, agitation, and hallucinations. Serious side effects are seizures, respiratory arrest, arrhythmias, and even coma.

Efficacy for trigeminal neuralgia

In general, lidocaine is not used for trigeminal neuralgia.

Efficacy for other neuropathic pain disorders

Lidocaine is applied topically, given intravenously, or taken orally (mexiletine or tocainide) in managing neuropathic pain.[146] Infusions of lidocaine are reported to relieve painful diabetic neuropathy and one study reports it to have an NNT of 3.[147] Infusions of lidocaine are not a convenient treatment, however, for most patients, and pain clinicians usually switch patients who show pain relief with intravenous lidocaine to its oral analog (mexiletine or tocainide). Two of the studies found a better effect for mexiletine compared with placebo in the treatment of diabetic neuropathy.[148,149] In contrast, four other studies have reported little effect[150–153] They reported NNT for mexiletine at its effective dose level (675 mg/day) was determined to be 10, which is quite high and usually unacceptable as a therapy. In a more recent publication (2005), a meta-analysis examined the efficacy of local anesthetic agents at treating neuropathic pain.[154] This review examined clinical trials with random allocation that were double blinded, with a parallel or crossover design.

The authors included 32 controlled clinical trials on the following drugs: intravenous lidocaine (16 trials), mexiletine (12 trials), lidocaine plus mexiletine sequentially (one trial), and tocainide (one trial). The authors' analysis revealed that lidocaine and mexiletine were superior to placebo, but when compared with carbamazepine, amantadine, gabapentin, or morphine the data was not positive (no difference in efficacy or greater adverse effects). The authors conclude that intravenous lidocaine and its oral analogs (mexiletine or tocainide) were safe drugs in controlled clinical trials for neuropathic pain and were better than placebo and equivalent to other commonly used medications. Finally, in 2007 a study examined specifically if amitriptyline or lidocaine would be better at blocking tetrodotoxin (TTX)-resistant or TTX-sensitive Na^+ channels.[155] This study is important since both medications are used for neuropathic pain and in many this pain state is due in part to an upregulation of TTX-R Na(v)1.8 sodium channels. The authors concluded that lidocaine was more effective than amitriptyline at blocking Na(v)1.8-mediated action potential firing.

6.2.L Baclofen (generic)

Description, mechanism of action, and primary indications

Baclofen is reviewed with the antispasmodics, but it is sometimes used for trigeminal neuralgia.

Starting dose

For trigeminal neuralgia, the usual starting dose is 5–10 mg/day. It should be titrated up until reaching a satisfactory pain control. The effective dose ranges from 50 to 75 mg three times daily.

Side effects and adverse drug reactions

The most commonly reported side effects of this medication are constipation, diarrhea, dizziness, drowsiness, fatigue, headache, increased breathing, increased salivation, itching, muscle weakness, nausea, and problems urinating.

Efficacy for trigeminal neuralgia

Baclofen alone seems to have only a moderate effect on trigeminal neuralgia, and its long-term efficacy remains in doubt.[156]

Efficacy for other neuropathic pain disorders

Baclofen seems to have a low potential for the treatment of neuropathic pain conditions. However, small studies have suggested the use of intrathecal baclofen as adjuvant in patients with neuropathic pain who have failed to obtain a good pain relief with spinal-cord stimulation.[157,158]

6.2.M Therapeutic drug monitoring for the newer anticonvulsants

A 1993 review article examined the pharmacokinetics of 10 antiepileptic drugs.[159] The reviewers described gabapentin, topiramate, and vigabatrin as having good pharmacokinetic features, namely, they are well absorbed, excreted mainly unchanged in the urine, and not susceptible to enzyme induction or inhibition, which means they are unlikely to cause drug–drug interactions. The review noted that oxcarbazepine is a prodrug with a very active hydroxy metabolite after oral administration. Another review of the pharmacokinetic variability of anticonvulsants was published in 2006 which asked the specific question, "When is monitoring needed?"[160] The review commented that because of their interindividual variability in their pharmacokinetics and a narrow therapeutic range, the older anticonvulsants (phenytoin, carbamazepine, and valproic acid) need to have serum monitoring performed periodically to adjust the dosage to achieve a serum drug concentration without toxic side effects. The review stated that therapeutic drug monitoring of the main metabolite of prodrug oxcarbazepine is useful. It also suggested that therapeutic drug monitoring for lamotrigine, tiagabine, and zonisamide should be considered since they have the same pharmacokinetic variability problems that the older anticonvulsants did, although their therapeutic range is not as narrow. For the anticonvulsant drugs that are eliminated renally and are completely or mainly unchanged (gabapentin, pregabalin, levetiracetam, and topiramate) therapeutic drug monitoring is not required.

6.3 Ten final recommendations on anticonvulsants for chronic neurogenic pain

Anticonvulsant drugs (specifically carbamazepine and phenytoin) have been used in pain management since the 1960s, very soon after they were first used for epilepsy. These drugs provided the first effective nonsurgical therapy for trigeminal neuralgia. Given this success it is disappointing that neither of these two drugs was highly successful for other neuropathic pain problems. Anticonvulsant drugs are not without risk since serious effects have been reported, including deaths from hematological reactions. The commonest adverse effects are impaired mental and motor function, which may limit clinical use, particularly in the elderly. Evidence for anticonvulsants as effective therapy for other neuropathic pain conditions is quite variable and two few

multicenter randomized double-blind trials have been published. Nevertheless, the available evidence suggests the following:

Recommendations for anticonvulsant medications for neurogenous and neuropathic pain

1. Carbamazepine has excellent efficacy in trigeminal neuralgia treatment.
2. Oxcarbazepine has a similar spectrum of effects to that of carbamazepine, with much better tolerability. Although the current evidence for oxcarbazepine as a treatment of trigeminal neuralgia is limited to a few case series and open-label trials, it still appears promising.
3. Anticonvulsants should be considered early in treatment for spontaneous pain that has no inflammatory basis or for sharp lancinating pains especially when the features of the pain include burning, dysesthesias, or allodynia. For the nonparoxysmal continous neuropathic pain disorders (e.g., chronic trigeminal neuropathy) gabapentin, pregabalin, levetiracetam, and zonisamide appear helpful.
4. While topiramate and divalproex sodium have utility in the prophylaxis or acute treatment of migraine, neither appears highly effective for trigeminal neuralgia or neuropathic pain.
5. Tricyclic antidepressants appear to be efficacious for neuropathic pain beyond anticonvulsants, and sometimes a combined approach is needed.
6. Topical lidocaine (or other topical anesthetics) is known to reduce focal neuropathic pain.
7. Lamotrigine has good data on its efficacy for nonmalignant neuropathic pain, coming from several randomized trials; however, it has more serious adverse effects than gabapentin (e.g., somnolence, dizziness, ataxia) and requires a slower titration.
8. Zonisamide has some evidence of efficacy for neuropathic pain.
9. One comparative trial showed that amitryptiline and gabapentin were equally effective for painful diabetic neuropathy.
10. Until more progress is made toward a mechanism-based classification, treatment is likely to be a trial-and-error process where drug combinations may also be considered.

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Chapter 7

Skeletal muscle relaxants and antispasticity drugs for orofacial pain disorders

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7.1 Introduction

When the craniomandibular and craniocervical musculature becomes painful and it is possible to feel by palpation that the muscles are firm or tight, then the relaxation of these presumed "hyperactive" skeletal muscles is a common goal of therapy.[1] For this reason, skeletal muscle relaxants are often prescribed in the treatment of acute temporomandibular disorders (jaw locking, trismus, masticatory, and cervical myofascial pain). This is done in an attempt to reduce pain, improve any limitations in range of motion, reduce trismus and hyperactivity (e.g., taut bands), and help the patient perform the prescribed rehabilitation exercises. Palpating muscles for taut bands is not easy, and two separate investigations have shown that clinician differences are quite large when conducting this examination.[2,3] Moreover, while needle electromyography can identify hyperactive endplates in myofascially involved muscles, this is a nonspecific electrophysiological finding, and therefore[4] surface electromyography is not sufficiently discriminatory for diagnosing these intramuscular phenomena.[5] Fortunately, new methods have been developed that provide a more quantitative measure of muscle stiffness and taut bands. These methods hold great promise for more quantification of focal muscle hyperactivity and careful assessment of treatments designed to reduce muscle hyperactivity. For example, one 2003 study reported on the correlation between muscle activity recorded with electromyography (EMG) and muscle stiffness recorded using magnetic resonance elastography (MRE).[6] These authors claimed that MRE, which generates a wave of activity in muscles, can then be used to noninvasively determine muscle activity. The authors used six healthy volunteers and imaged their muscles while they held varying degrees of isometric muscle activity in the muscle. They compared the elastographic wavelengths with the EMG-based activity in the muscle and found that the elastography wavelengths were linearly correlated to the muscular activity as defined by electromyography. A more recent study used this method to determine the mechanical properties of myofascial taut bands.[7] This study involved eight human subjects (four who had myofascial pain). The data showed that there was a statistically significant increase of shear stiffness in the taut band regions of the involved subjects relative to that of the controls or in nearby uninvolved muscles. This method has not yet been used in clinical trials looking at various therapies for these taut bands, such as muscle relaxants.

While the use of analgesics in the treatment of acute and chronic orofacial pain disorders is well documented by randomized, double-blind, placebo-controlled trials, there is scant data on the efficacy of muscle relaxants in this population.[8,9] Theoretically, there is some evidence that generalized hyperexcitability of the central nervous system pathways, either causal or as a consequence of chronic orofacial conditions, may be seen and therefore it may be argued that there is a role of centrally acting muscle relaxants in treatment.[10]

Within a chronic pain population, there are always some cases of true spasticity or involuntary movement disorder, although these are far less common. Regardless of the diagnosis, there is a need for caution when using skeletal muscle relaxants, mainly because many of the drugs discussed in this chapter have side effects such as sedation and weakness and when used, especially in the elderly, there is real risk of serious adverse events. Moreover, some of the medications have strong drug–drug interaction potential, and some produce a physical dependency and can induce addiction behavior.[11] Risk is always balanced against benefit so this chapter presents the available data on the efficacy and adverse events associated with skeletal muscle relaxants. First, we must point out that there are several drugs not covered in this chapter that are used primarily for

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involuntary movement disorders such as dyskinesia and dystonia and for sleep-related motor behaviors such as bruxism and myoclonus. These drugs include the anticholinergics, dopaminergics, botulinum toxin, and several others that are instead discussed in Chapters 19 and 11. There are also a variety of smooth muscle relaxants, also called antispasmodics, which are primarily used for gastrointestinal and bronchial tube spasm, but they are not discussed here.

7.1.A Skeletal muscle relaxants versus antispasticity drugs

In this chapter we review 10 drugs and 1 drug class (benzodiazepines), which reduce skeletal muscle contraction or tension levels. These drugs are broadly called spasmolytics, and all except one (dantrolene) are centrally acting and can be subdivided into two main subcategories: skeletal muscle relaxants and antispasticity medications.[12] The antispasicity drugs are usually reserved for those patients with spasticity secondary to neurological conditions (e.g., multiple sclerosis) or spinal cord injury. Spasticity is defined as an upper motor neuron disorder characterized by muscle hypertonicity and involuntary movements or clonic jerks.[13] Upper motor neurons are those that originate in motor region of the cerebral cortex or the brain stem and carry motor information toward the next neuron in the pathway. By definition, upper motor neurons are not directly responsible for stimulating the target muscle.[14] Lower motor neurons are those that actually connect the brain stem and spinal cord directly to muscle fibers; their axons travel through a foramen and terminate on an effector (muscle). The antispasticity drugs include baclofen, tizanidine, dantrolene, and tiagabine, as well as the benzodiazepines (diazepam, lorazepam, alprazolam, and clonazepam). Botulinum toxin is being used for spasticity and dystonia, but this drug is discussed in another chapter (see Chapter 11).

In contrast there are six so-called muscle relaxants (cyclobenzaprine, methocarbamol, metaxalone, ophendrine, chlorzoxazone, and carisoprodol). These drugs are primarily used to treat painful musculoskeletal conditions, which exhibit muscle spasms, secondary muscle guarding, bracing, tightening, or trismus.[15] Muscle spasm is a painful and involuntary muscular contraction that cannot be released voluntarily and is caused by pain stimuli to the lower motor neuron. These agents are also sometimes used to treat habitual (presumed to be volitional) behaviors such as anxiety-associated clenching and other muscle-specific habits, which are thought to contribute to the pain. Most clinicians endorse the idea that muscle pain induces some degree of muscle hyperactivity, which can in turn cause more pain. Although pain in a focal area does mandatorily induce tightening of the surrounding muscles, sometimes the opposite is true. Pain may inhibit rather than facilitate reflex contractile activity, so the decision to treat a patient with a muscle relaxant should not be based solely on pain but also on physical signs that include muscle tightness and/or taut bands. For acute pain of musculoskeletal origin, nonsteroidal anti-inflammatory drugs (NSAIDs) are used with much greater frequency than oral skeletal muscle relaxants or opioids. Unfortunately, there is very little evidence-based medicine available to guide the choice of a medication for an acute, uncomplicated musculoskeletal disorder since only a limited number of high-quality, randomized, controlled trials (RCTs) provide evidence of the effectiveness of muscle relaxants. As mentioned previously, the distinction between antispasticity drugs and muscle relaxants is based not on their site of action (e.g., central vs. peripheral) since most of these drugs act centrally, but on their relative ability to suppress upper and lower motor neuron activity. Because spasticity is quite disabling, the more potent antispasticity drugs, which also have more side effects and more associated adverse-event risk, are used in these cases. With minor skeletal muscle spasms such as a tight, sore, and stiff muscle, muscle relaxants are typically used since they are better tolerated, with relatively fewer adverse events. Finally, these agents have also been shown in some studies to demonstrate analgesia equivalent to either acetaminophen or aspirin. It remains uncertain if muscle spasm is a prerequisite to their efficacy as analgesics.[16]

7.2 Muscle relaxants

Six drugs are discussed in this section (carisoprodol, cyclobenzaprine, methocarbamol, metaxalone, ophendrine, and chlorzoxazone). These drugs are used mostly for muscle spasm and muscle hyperactivity, which occurs as a secondary phenomenon in association with musculoskeletal pain. The Cochrane Library database contains other reviews that have looked at muscle relaxants for treatment of acute and nonspecific low back pain.[17] These reviews focused on cyclobenzaprine, benzodiazepines, carisoprodol, or metaxalone and generally have concluded that there was enough evidence to support their short-term use for acute musculoskeletal pain. For a more chronic disease state, such as fibromyalgia, there is also some evidence that cyclobenzaprine is better than placebo (see Sec. 7.2.B). Finally, a non–Cochrane Library review of muscle relaxants for myofascial face pain was published.[18] This systematic review concluded that the use of muscle relaxants in patients with myofascial pain involving the masticatory muscles seems to be justified but that current research can only be judged as weak and that the risk–benefit ratio of these medications must be considered.

7.2.A Carisoprodol

Description, mechanism of action, and primary indications

Carisoprodol is FDA approved for relief of discomfort associated with acute musculoskeletal conditions for patients over the age of 16. Carisoprodol is a centrally acting skeletal muscle relaxant and it is thought to block interneuronal activity by activating GABA-A receptors in the descending reticular formation and spinal cord.[19] This drug is actually a prodrug that is metabolized the active drug, meprobamate which is an older antianxiety agent previously used to treat muscle spasms.[20]

Starting dose

The typical dosing for carisoprodol is 350 mg four times a day.

Metabolism, side effects, and adverse drug reactions

The common side effects of carisoprodol are drowsiness, and it can cause psychological and physical dependence. This means that withdrawal symptoms can occur with discontinuation. Moreover, use of this drug in combination with benzodiazepines, barbiturates, codeine, or other muscle relaxants is known to induce respiratory depression. Meprobamate is a Schedule III controlled substance with a potential for drug dependence and carisoprodol is not a controlled substance, although it has been reported to exhibit similar dependence tendency.[21] A case report that described four cases of carisoprodol intoxication was published in 2005.[22] All four cases fulfilled three different sets of criteria for the diagnosis of serotonin syndrome. These findings indicate that an increased serotonin level in the central nervous system could explain some of the symptoms and signs of carisoprodol intoxication. This may have implications for the clinical evaluation and treatment of such intoxications. Since few laboratories routinely screen for carisoprodol it is important to keep this drug in mind when encountering intoxications displaying serotonergic symptoms.

Efficacy for musculoskeletal pain associated spasm

A 2004 review article concluded that there is fair evidence that cyclobenzaprine, carisoprodol, orphenadrine, and tizanidine are effective compared with placebo in patients with musculoskeletal conditions (primarily acute back or neck pain). In contrast there is very limited or inconsistent data regarding the effectiveness of metaxalone, methocarbamol, chlorzoxazone, baclofen, or dantrolene compared with placebo in patients with musculoskeletal conditions.[23]

7.2.B Cyclobenzaprine

Description, mechanism of action, and primary indications

Cyclobenzaprine is FDA approved for relief of muscle spasm associated with acute, painful musculoskeletal conditions. Cyclobenzaprine's chemical structure, dosing, and side-effect profile are very similar to other tricyclic antidepressants (TCAs), even though it is not classified as such.[24] Like the TCAs it has a strong anticholinergic effects and long elimination half-life (12–24 hours). Its site of action is thought to be in the brainstem level of the central nervous system rather than the spinal cord level. Cyclobenzaprine is an antagonist at one or more of the serotonin 5-HT2 receptor subtypes and thus it reduces muscle tone via its antagonism of 5-HT2C receptors.

Starting dose

Typical dosing is to start with 5 or 10 mg at bedtime and increase dose by 10 mg every 3–7 days and switch to a three-times-a-day dosing schedule.

Metabolism, side effects, and adverse drug reactions

The major side effects of cyclobenzaprine are its anticholinergic effects (drowsiness, urinary retention, dry mouth). It is advisable to avoid using this drug in the elderly or in patients with arrhythmias, a heart block, heart failure, or recent myocardial infarction. This drug has been known to raise intraocular pressure, so avoid it in glaucoma patients also.

Efficacy for musculoskeletal pain associated spasm

A small randomized trial on jaw-pain patients found that cyclobenzaprine was superior to clonazepam or placebo.[25] A 2003 study described two short (8-day duration) randomized placebo-controlled clinical trials that involved 1400 patients with acute musculoskeletal pain.[26] The results of this study suggested that the 5- and 10-mg doses of cyclobenzaprine were superior to the 2.5-mg dose and that this drug has at best a mild-to-moderate effect on symptoms, and both somnolence and dry mouth were reported. A much earlier study[27] examined the relative efficacy of cyclobenzaprine compared with and combined with diflunisal (an NSAID) for acute low back pain. This 10-day study reported that the combined-drug protocol was better than a single-drug protocol for acute pain. The same result, namely, that combined therapy was better than single therapy, was seen in another study, which combined and compared cyclobenzaprine and naproxen. A recent prospective, randomized, open-label,

multicenter, community-based study compared cyclobenzaprine used alone or in combination with 1200 mg/day or 2400 mg/day of ibuprofen in adults with acute neck or back pain with muscle spasm.[28] The exact dosing was cyclobenzaprine (5 mg three times a day [t.i.d.]; given for 7 days) or ibuprofen (400 mg t.i.d. or 800 mg t.i.d.; given for 7 days). There were 867 subjects who gave post-treatment data; they were between the ages of 18 and 65 years and all had cervical or thoracolumbar pain and spasm for at least 14 days. The subjects were randomly assigned to one of three treatment groups and effect of treatment was measured at 3 and 7 days of therapy. Outcomes were primarily patient-rated scales assessing spasm, pain, global change, medication helpfulness, and disability. The authors reported that all three treatment groups demonstrated significant improvements from baseline for these outcomes, all three groups found the treatments tolerable, and adverse events (fatigue, somnolence, dizziness, sedation, and nausea) were equally distributed among the groups. Finally, a 2004 systematic review that examined efficacy and safety of cyclobenzaprine for fibromyalgia found five randomized controlled clinical trials that were of sufficient quality to include in the review on cyclobenzaprine.[29] The authors concluded that patients on cyclobenzaprine were more likely to report themselves to be improved versus the placebo group, but no remarkable improvement in fatigue or tender points were noted for these patients.

7.2.C Metaxalone

Description, mechanism of action, and primary indications

Metaxalone was approved by the FDA for treating acute musculoskeletal conditions in adults and in children over the age of 12 years. The advantage of this drug over other skeletal muscle relaxants include reduced sedation, diminished abuse potential, and limited accumulation of the drug because of its short elimination half-life. The mechanism of action for metaxalone is unknown in humans, but its effect is presumed to be due to general depression of the central nervous system.

Starting dose

Dosing for this drug is 800 mg three times a day or four times a day.

Metabolism, side effects, and adverse drug reactions

Common side effects of metaxalone include drowsiness, dizziness, headache, and irritability. It should not be used in patients with renal or hepatic failure or with a history of anemia, hemolytic, or other blood dyscrasias. The authors of this study examined Intercontinental Marketing Services data from January 2003 through January 2004 to determine which skeletal muscle relaxants were being utilized. They reported that carisoprodol, cyclobenzaprine, and metaxalone were the most commonly prescribed drugs for musculoskeletal pain. Based on this, they searched the literature on these drugs to find randomized controlled trials on metaxalone. This study concluded this drug was helpful for musculoskeletal pain but has some noticeable side effects (drowsiness, dizziness, headache, and nervousness) and some rare adverse events (leukopenia or hemolytic anemia and a potential for an elevation in liver function tests). Finally, paradoxical muscle cramps may also occur.

Efficacy for musculoskeletal pain associated spasm

Data for metaxalone is limited; its efficacy has been evaluated on low back pain patients.[30]

7.2.D Chlorzoxazone

Description, mechanism of action, and primary indications

Chlorzoxazone works primarily in the spinal cord and in the subcortical areas of the brain.[31] Its main action is to inhibit multisynaptic reflex arcs. It has no direct action on the contractile mechanism of striated muscle, motor endplate, or nerve.

Starting dose

This drug is indicated for relaxing stiff, sore muscles and its typical adult dose is 250 mg to up to 750 mg three times a day.

Metabolism, side effects, and adverse drug reactions

The main side effects of chlorzoxazone are dizziness, drowsiness, rare cases of hepatotoxicity, gastrointestinal irritation, and rare cases of gastrointestinal bleeding. There is a risk of respiratory depression if used with benzodiazepines, barbiturates, codeine or its derivatives, or other muscle relaxants.

Efficacy for musculoskeletal pain associated spasm

The quality studies on the use of this medication for musculoskeletal pain are few. See the comments in Section 7.2.A about the efficacy of carisoprodol for musculoskeletal pain, as chlorzoxazone is also discussed.

7.2.E Methocarbamol

Description, mechanism of action, and primary indications

Methocarbamol acts centrally and does not directly relax tense skeletal muscles in humans. Although the exact mechanism of action is not fully understood, it is thought to be due to methocarbamol's sedative properties. Methocarbamol is a carbamate derivative of guaifenesin.[32]

Starting dose

The typical dosing for this drug is 1500 mg four times a day for the first 2–3 days, then 750 mg four times a day.

Metabolism, side effects, and adverse drug reactions

Side effects include discoloration of the patient's urine (brown-to-black or green) and impaired mental status. Most of the precautions for methocarbamol are associated with its parenteral form, which is generally used to treat tetanus.

Efficacy for musculoskeletal pain associated spasm

In a small but well-designed study (double blind, placebo controlled, crossover) the effects of methocarbamol versus placebo were described using 14 subjects.[33] Psychomotor and cognitive performance was described before and at 5.5 hours after drug administration. The results showed that methocarbamol produced significant increases in sedation but only minor impairment of psychomotor and cognitive performance.

7.2.F Orphenadrine

Description, mechanism of action, and primary indications

Orphenadrine citrate is indicated as an adjunct to physical therapy treatment and for the relief of acute pain seen with musculoskeletal conditions. Orphenadrine is thought to be a noncompetitive antagonist at *N*-methyl-D-aspartate (NMDA) receptor complexes and it is an antagonist at histamine H1 receptors. Orphenadrine may also act as an antagonist at M1, M2, M3, and M4 muscarinic acetylcholine receptors. This drug has a mechanism of action that is similar to antihistamines,[34,35] The structure of orphenadrine is similar to that of diphenhydramine, but orphenadrine possesses greater anticholinergic effects. The effects of orphenadrine are presumed to be due to its analgesic and anticholinergic properties.

Starting dose

The typical dosing for this drug is 100 mg two or three times a day.

Metabolism, side effects, and adverse drug reactions

As mentioned orphenadrine has anticholinergic activity (which is responsible for some side effects such as dry mouth). The main side effects are also anticholinergic in nature (drowsiness, urinary retention, dry mouth). Like cyclobenzaprine, avoid using this drug in the elderly and avoid using it for any patient with glaucoma or gastrointestinal disturbances.

Efficacy for musculoskeletal pain associated spasm

A clinical trial evaluated intravenous administration of 60 mg of orphenadrine citrate compared with a placebo for the treatment of spastic hypertonia in 11 patients with spinal cord injuries.[36] The Ashworth Spasticity Scale was used to compare the effects, and the authors report that orphenadrine was found to be statistically superior to placebo.

7.2.G Miscellaneous other drugs used for spasticity

Multiple other drugs have been used for management of spasticity, including gabapentin[37,38] and clonidine. Both are being used off-label and neither has a systematic random-assignment controlled trial to document its efficacy for spasticity against a placebo medication. Nevertheless, case reports do suggest they may have value in the management of spasticity. Gabapentin is an anticonvulsant drug that is FDA approved for epilepsy and for neuropathic pain. Patients may require higher doses of gabapentin (2700–3200 mg/day), and its safety at this level over long periods in spasticity is unknown; thus, caution is advised. The second drug in this miscellaneous category is clonidine, which is an alpha-2-adrenergic agonist; its mechanism of action is similar to tizanidine and, like gabapentin, there are no double-blind, placebo-controlled studies to show its efficacy in spasticity. It is suggested for use as an alternative when other medications are ineffective.[39]

7.3 Antispasticity drugs

There are four drugs and one drug class discussed in this section (baclofen, tiagabine, dantrolene, and tizanidine and the benzodiazepines); while some can be used for muscle spasm due to musculoskeletal conditions, these drugs are really used mostly to treat spasticity due to neurological disorders such as spinal cord injury, brain trauma, and multiple sclerosis. There has been one very well done systematic Cochrane-style review of the literature that examined both the efficacy and likelihood of adverse events occurring with baclofen, dantrolene, and tizanidine when

used for long-term spasticity due to spinal cord injury.[40] The authors examined multiple published studies that met their quality standards and concluded that the depth and quality of the available data was such that there is insufficient evidence to guide clinicians in a rational approach to antispastic treatment for spinal cord injury. Nevertheless, the review concluded that there was a significant effect for intrathecal baclofen in reducing spasticity when compared with placebo, without any adverse effects. The authors also commented on another study comparing oral tizanidine with placebo and found it to be significantly better but with more adverse effects (drowsiness, xerostomia) than the placebo group. Finally, the review stated that several drugs were not effective for spinal cord injury spasticity, such as gabapentin, clonidine, diazepam, and oral baclofen. Of course there are more diseases than spinal cord injury that produce spasticity, and additional information about the more common antispasticity drugs is provided here.

7.3.A Measurement of treatment efficacy

When prescribing a strong antispasticity medication it is important to measure the benefit of this medication to assure that the risk of an adverse event is justified. The Ashworth scale and the modified Ashworth scale are the primary tools for assessing visually evident spasticity. The Ashworth scale is scored from 0 (no increase in tone) to 4 (limb rigid in flexion–extension).[41] Like most subjective assessment tools, the validity of the Ashworth scale is questionable and it generally has a lack of precision, poor inter-rater reliability, and low sensitivity.[42] One problem with this rating system is that the degree of resistance to passive movement, which is assumed to be involuntary muscle rigidity, may just as likely be voluntary guarding due to pain on motion. However, despite these shortcomings, the Ashworth scale is the most commonly utilized assessment tool in spasticity studies.[43] Another method of assessing muscle force throughout its range of motion is to use a force measurement device called a Cybex Isokinetic Dynamometer, which produces scores that are objective measures of muscle flexion.[44] The use of this and similar devices allows for an evaluation of baseline muscle tension and spasticity in those cases where the spasticity is not visually evident.

7.3.B Baclofen (generic)

Description, mechanism of action, and primary indications

Baclofen is a gamma-aminobutyric acid (GABA) derivative that serves as an agonist to GABA-B receptors and is FDA approved for treatment of spasticity, in patients with spinal cord injury, spinal cord diseases, and multiple sclerosis.[45] GABA receptors can be of the A or B type and baclofen acts as a GABA-B receptor agonist in the spinal cord inhibiting calcium influx into presynaptic terminal and suppressing the release of excitatory neurotransmitters. When an agonist binds to this receptor it functions generally to inhibit neuronal activity at the spinal level and also depresses the central nervous system. When GABA receptors are stimulated, this disrupts or suppresses polysynaptic and monosynaptic reflexes at the level of the spinal cord. Unfortunately, GABA receptors undergo desensitization and tolerance to a direct agonist over time. This means that the initial effective dose may need to be increased after a few days.

Starting dose

The starting dose is typically 10 mg at bedtime and it is increased by 5 mg each week to a maximum of 80 mg daily, which is the FDA's recommended maximum dose. Baclofen should be used on a three-times-a day schedule since it has a half-life of 5.5 hours.

Metabolism, side effects, and adverse drug reactions

The main side effects include drowsiness, confusion, dizziness, and weakness. There is a risk of seizures and hallucinations if this medication is withdrawn abruptly, so it should always be tapered off slowly.

Efficacy for musculoskeletal pain associated spasm

In multiple sclerosis, spasticity may affect 40–60% of patients.[46] It should be noted that baclofen is not indicated in the treatment of secondary skeletal muscle spasm resulting from rheumatic disorders. Baclofen is quite effective as an adjuvant analgesic in treating neuralgias that affect the orofacial region (e.g., trigeminal, glossopharyngeal, and postherpetic neuralgias).[47] In a systematic review, researchers identified two fair-quality studies of baclofen versus placebo as well as two fair-quality studies of tizanidine versus placebo.[23] Each trial of baclofen was a 10-week, double-blind, crossover study involving approximately 35 patients with multiple sclerosis. One demonstrated that low-dose baclofen (maximum 20 mg/day) improved participants' quadriceps spasticity in a statistically significant manner compared with placebo, as measured by Cybex flexion scores, when it was given alone or in combination with stretching exercises.[48] This study was considered to be of only fair quality because it had a crossover design and because the doses of baclofen were lower than those recommended for the treatment of spasticity. Another investigation on multiple-sclerosis-induced spasticity revealed that

baclofen 80 mg/day was superior in changing patients' general functional status, including improving spasm frequency ($p < 0.05$), knee clonus ($p < 0.01$), and resistance to passive movement ($p < 0.05$), compared with placebo.[49] This trial was also deemed only fair for various research design reasons. Another study showed that baclofen and diazepam were equally beneficial for flexor spasms.[50] Despite similar efficacy, patients favored baclofen, presumably because the increased sedation associated with diazepam had more bothersome side effects. The best data for baclofen is not for oral medications but for intrathecal injections delivered with an implantable pump, especially in the setting of multiple sclerosis.[51–54] The absolute and comparative efficacy and tolerability of antispasticity agents in multiple sclerosis are poorly documented, and no recommendations can be made to guide their use. Treatment with baclofen was compared with placebo in a double-blind, randomized study of 200 patients with acute low back pain. Patients with initially severe discomfort were found to benefit from baclofen, 30–80 mg daily, on days 4 and 10 at follow-up. Forty-nine percent of treatment patients complained of sleepiness, 38% of nausea, and 17% discontinued treatment.

7.3.C Tiagabine

Description, mechanism of action, and primary indications

Tiagabine is also GABA-ergic drug; it works not as an agonist but as a selective inhibitor of the GABA transporter, GAT-1. In general this drug is not used for spasticity treatment since the data suggesting efficacy is weak and it is an off-label use. Nevertheless, when the transport of a drug is impeded, it stays in the synaptic cleft longer and it is also migrates to surrounding neurons, producing what has been described as a inhibitory field effect.

Starting dose

Tiagabine like all of the anticonvulsant medications is started low and titrated upward to effect or intolerance. Typical dosing is to take 4 mg once daily for week 1, then escalate by 1 additional tablet a day on a weekly basis until the desired effect is achieved. It usually is taken with food two to four times a day.

Metabolism, side effects, and adverse drug reactions

The most commonly seen side effects with this medication are dizziness, weakness, and shakiness. If side effects occur, they are generally minor although some individuals may experience hostility or confusion.

Efficacy for musculoskeletal pain associated spasm

Tiagabine is FDA approved as an adjunctive anticonvulsant treatment of partial seizures.[55] It has recently been reported to be effective for "stiff man syndrome"[56] and neuropathic pain,[57] conditions in which its GABA-ergic mechanism is important. More recently tiagabine has been suggested for treating painful tonic spasms in multiple sclerosis.[58] This study was an open-label study on seven multiple sclerosis patients and 5–30 mg/day of tiagabine was administered. These patients all had painful tonic spasms and were considered nonresponsive or intolerant to other medications (e.g., gabapentin, baclofen, diazepam, or clonazepam). The authors reported that relief of painful tonic spasms occurred in four out of seven patients. Finally, tiagabine has been reported (in an open-label series of cases) to be helpful in bruxism reduction and symptoms of temporomandibular disorders.[59] The doses for tiagabine suggested by this author to suppress nocturnal bruxism at bedtime (4–8 mg) are lower than those used to treat seizures. Unfortunately, these studies are all open-label studies so they areless scientifically convincing; in February 2005, the FDA issued a letter that notified healthcare professionals and the public that tiagabine may trigger seizures in patients without epilepsy.[60] The letter described more than 30 patients prescribed tiagabine for conditions other than epilepsy (e.g., psychiatric illness patients).

7.3.D Tizanidine

Description, mechanism of action, and primary indications

Tizanidine is a central alpha-(2)-adrenoceptor agonist that exerts its effect presynaptically on the motor neuron and is chemically similar to clonidine.[61] This drug has been approved by the FDA for the management of spasticity. It is widely used to manage spasticity secondary to conditions such as multiple sclerosis, stroke, and spinal cord or brain injury.[62]

Starting dose

The dosing schedule for this drug is 4 mg taken in three or four divided doses each day with an increasing dose up to 12 mg three times a day; the maximum dose is 36 mg/day.

Metabolism, side effects, and adverse drug reactions

It has a relatively quick onset (1–2 hours) and a short duration (3–6 hours) of action. Main side effects are drowsiness, hypotension, dry mouth, bradycardia, and dizziness. Because this drug has a strong effect on the liver a standard protocol

is to conduct liver function tests periodically to check for elevated liver enzymes.

Efficacy for musculoskeletal pain associated spasm

Only limited data exists for tizanidine in secondary spasm related to primary musculoskeletal pain, although it has been used for migraine prevention. A study using a double-blind placebo-controlled crossover design with two 8-week treatment arms separated by a 1-week washout period at baseline evaluated the effect of tizanidine on spastic hypertonia due to acquired brain injury.[63] The 17 patients in this study were all residents in a tertiary care outpatient and inpatient rehabilitation center attached to a university hospital. The authors used the Ashworth rigidity scores, spasm scores, deep tendon reflex scores, and motor strength scores. They reported that after the subjects reached their maximal tolerated dosage, tizanidine was found to be effective in decreasing the spastic hypertonia associated with acquired brain injury.On the negative side, the authors clearly warned about side effects related to drowsiness. They recommended that it is best to start with a low dose of 2 mg at night and gradually add a 2-mg dose every second day until the patient is receiving 3 doses daily. The dose may then be increased gradually as needed to achieve the desired control of spasticity. Tizanidine was also featured in the systematic review by Taricco et al. (2000) referenced earlier in the section on baclofen (Sec. 7.3.A). The two tizanidine studies described in this review article involved 187 and 220 multiple sclerosis patients, respectively. In the first study, tizanidine did not improve Ashworth scores compared with placebo, but patients self-reported a substantial improvement (reduction) in the number of daily spasms and clonus events they experienced.[64] In the second tizanidine trial, the Ashworth scores improved 21% among patients given the drug; however, no effect on muscle strength, spasm frequency, or pain was observed.[65] Lastly, the review stated that patients taking tizanidine reported more adverse effects than those taking placebo, and the main reasons for drug discontinuation were dry mouth and somnolence. In spite of this, the review article noted that the physical therapists, physicians, and patients all viewed the treatment as effective and tolerable. An earlier double-blind crossover trial showed that tizanidine was as effective as diazepam and baclofen in reducing major spasticity in multiple sclerosis patients.[66] Tizanidine was also better tolerated than either of the other two drugs; however, the study was not strong enough methodologically to draw reliable conclusions about the superiority of one agent over another. A 1988 comparison study evaluated tizanidine with baclofen, also in patients with multiple sclerosis, and reported that patients in the baclofen groups had more muscle weakness than those in tizanidine groups, but the latter had more somnolence and dry mouth.[67] Two studies (1975 and 1976) compared dantrolene, baclofen, or tizanidine with either diazepam or each other and reported that all of the drugs improved major spasticity but none were shown to be more effective than the others.[68]

Because jaw muscle trismus is moderately common after oral surgery (third-molar removal), tizanidine has been tested as a muscle relaxant in a recent (2007) study.[69] The study involved 50 healthy patients who were given tizanidine (4 mg in the evenings for the first 2 postoperative days) in addition to antibiotic and anti-inflammatory medications. The authors repored that there was no statistically significant difference in facial pain and swelling between the two groups but the group receiving tizanidine did show an increased unassisted mouth opening ability at days 1 and 3. The authors went on to conclude that the addition of tizanidine was not justified by this modest improvement. Lastly, a 2008 review article examined the literature on tizanidine as a medication to treat spasticity associated with stroke and multiple sclerosis.[70] The review examined 53 studies in detail, all of which included tizanidine. These studies compared tizanidine with other oral antispasticity agents, including baclofen, diazepam, and dantrolene. The authors concluded that tizanidine provided a major spasticity treatment effect that was comparable to that of baclofen or diazepam with global tolerability data favoring tizanidine.

7.3.E Dantrolene

Description, mechanism of action, and primary indications

Dantrolene sodium is of particular interest, as its mechanism of action is purely at the peripheral level as opposed to the previously discussed centrally acting antispasticity medications. This drug induces inhibition of the ryanodine receptor, the major calcium release channel of the skeletal muscle sarcoplasmic reticulum, inhibiting the release of calcium, and therefore decreasing intracellular calcium concentration.[71]

Starting dose

Starting dose is 25 mg/day up to 400 mg/day (100–200 mg/day is usually adequate for a clinical effect).

Metabolism, side effects, and adverse drug reactions

Common side effects are drowsiness and sedation (mild to moderate), weakness, fatigue, paresthesias, diarrhea, nausea, vomiting. Because dantrolene can be hepatotoxic and 1 in 100 patients has serious liver toxicity, liver function tests should be periodically checked for elevated liver enzymes.

Symptomatic hepatitis has been attributed to high doses of dantrolene (>800 mg/day), but this complication has also been reported with lower doses.

Efficacy for musculoskeletal pain associated spasm

This drug is primarily used for spasticity of cerebral origin (e.g., stroke, cerebral palsy, and head injury). In one study, both dantrolene and diazepam improved clonus, spasticity, and hyper-reflexia, but dantrolene provided slightly more benefit in terms of hyper-reflexia than diazepam.[72] The use of dantrolene in musculoskeletal conditions has diminished because of limited evidence demonstrating its efficacy compared with other muscle relaxants and rare but serious hepatotoxicity.[23]

7.3.F Diazepam

Description, mechanism of action, and primary indications

Diazepam is a member of the benzodiazepine class of medications and it is an antispasticity drug that is commonly used to treat spasticity due to spinal cord injuries and multiple sclerosis. Diazepam's mechanism of action in spasticity is via binding to benzodiazepine receptors located on a GABA receptor, thereby increasing GABA affinity for its receptor.[73] They bind to a specific benzodiazepine receptor on GABA receptor complex.

Starting dose

If diazepam is used for relief of spasm due to non-neurological musculoskeletal disorders, it should be used only for a short period (1–2 weeks). For major-injury-related spasms, the typical dose is to start the patient at 2 mg twice daily up to 60 mg/day.

Metabolism, side effects, and adverse drug reactions

One complication of this drug is its long half-life, which is 27–37 hours. The most common side effects produced by benzodiazepines include drowsiness, confusion, trouble concentrating, and dizziness.

Efficacy for musculoskeletal pain associated spasm

Since diazepam is only one of several other benzodiazepine-based drugs (e.g., lorazepam, alprazolem, and clonazepam), the issue of which one is better is a frequently raised question and at present there is no evidence that any one benzodiazepine is more effective than another if adequate dosage is given. Critical to choosing which medication is most appropriate are the different half-life durations of the various benzodiazepines. As mentioned the benzodiazepine class of medications also includes lorazepam, clonazepam, and alprazolam, which are frequently administered to patients with chronic pain. Note that many pain specialists avoid using either diazepam or any of the other benzodiazepines because they are thought to induce more drug–drug interactions and to have a high potential for dependency and depression with long-term use. In opposition to this belief is a 1994 review[74] that examined whether benzodiazepines actually induce depression or just produce sedation that is mistaken as depression in chronic pain patients. Based on their review the authors concluded that there is evidence that chronic use of benzodiazepines is effective for some musculoskeletal pains. These authors also concluded that benzodiazepines used in high doses produce reversible sedation side effects that are mistakenly interpreted as depression. One study described physician prescribing patterns for benzodiazepines within a large health maintenance organization.[75] The prevalence of benzodiazepine use over a 6-month period was 2.8% of the patients and prevalence of continued use was 0.7%. More women were given these medications and this trend increased steadily with age of the patients; the most common reason for use was anxiety and depression (27%), insomnia (20%), and pain symptoms (38%). In another survey of 114 consecutive new patients at an academic pain center, the authors reported that 38% were taking one or more benzodiazepines and that the majority had been using the medication for 1–2 years' duration.[76] While the most common indication (86%) for the use of the benzodiazepine was to improve sleep, the authors concluded that these patients reported as many sleep problems as new patients who were not taking benzodiazepines and that this is suggestive of medication tolerance.

One 1991 study compared alprazolam, ibuprofen, or a combination of the two versus a placebo.[77] The study included 78 patients with fibromyalgia; the authors found significant clinical improvement in subjective pain severity scores and tenderness on palpation in the alprazolam-plus-ibuprofen group after 6 weeks. Unfortunately, the authors could not conclude whether alprazolam or ibuprofen was responsible for the improvement. A similar 4-week-long double-blind study on chronic masticatory myogenic patients ($N = 39$) compared ibuprofen (2400 mg/day), diazepam (17 mg/day), the two combined, and a placebo.[78] Visual analog scale (VAS) pain levels were found to be significantly decreased in the diazepam and diazepam-plus-ibuprofen groups but not for the ibuprofen or placebo groups. Certainly the small size of the study limits the findings, but these data are supportive of benzodiazepine-mediated relief of symptoms in chronic orofacial pain of myogenic origin over a 4-week period.

A 2005 study examined the short-term efficacy of 1 mg of clonazepam for the treatment of sleep bruxism using a polysomnographic analysis.[79] This study was a placebo-controlled study of 10 sleep-bruxism patients and it reported that, compared with the placebo, 1 mg clonazepam significantly improved the mean bruxism index from 9.3 to 6.3 per hour of sleep. It was also found to significantly improve several pararmeters of sleep (e.g., total sleep time, sleep efficiency, and sleep latency). The effect of clonazepam also was seen on periodic leg movements as these decreased significantly also. Unfortunately it is unclear if the positive acute effects will not continue with ongoing use of this medication, and a good long-term study on benzodiazepine for bruxism is lacking. The European Federation of Neurologic Science published a review of the literature on treatment studies for both restless leg syndrome and periodic leg movements (PLM) during sleep.[80] PLM is remarkably similar to bruxism so it is possible to extrapolate from these guidelines to what treatments might affect bruxism. They concluded that when clonazepam (0.5–2 mg/day) is used for PLM disorder, it is probably effective in ameliorating the sleep-related effects of periodic leg movements (poor sleep quality and excessive daytime sleepiness) and may actually reduce the total number of PLMs during sleep. As with bruxism, the long-term efficacy of this drug on PLM disorder is not fully known. In contrast this same group also reported that triazolam (0.125–0.50 mg/day) was not effective in ameliorating sleep efficiency and probably ineffective in reducing PLMs during sleep. Interestingly, this group stated that the adverse events with benzodiazepines (morning sedation, memory dysfunction, daytime somnolence, and muscle weakness) were usually mild, dose dependent, and reversible.

A double-blind, placebo-controlled, randomized controlled clinical trial involving 180 children with spastic cerebral palsy examined the clinical efficacy of a low dose of diazepam.[81] Of those enrolled, only 7 dropped out and the results showed that there was a significant reduction of measures of spasticity for those children taking the diazepam.

7.4 Reported adverse drug reactions for muscle relaxants (P450 issues)

The goal of this section is to increase awareness of prescribers of skeletal muscle relaxants about potential dangerous drug–drug interactions (DDIs). The specific DDIs that we enumerate here can be prevented by taking two simple precautions. First, begin at a low dose and titrate the dose upward, balancing efficacy with side effects. Second, perform a multidrug interaction check using one of several available software programs and strictly avoid prescribing drugs that produce any D- or X-level interaction.[82] D-level interactions are considered to be present when the "data demonstrate that the two medications may interact with each other in a clinically significant manner. A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken in order to realize the benefits and/or minimize the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes, choosing alternative agents." A D-level interaction means the clinician should consider therapy modification." An X-level interaction is considered to be present when the data demonstrate that the specified agents may interact with each other in a clinically significant manner. The risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered contraindicated and the clinician should avoid this drug combination. There are also C-level interactions that need to be considered and monitored, but as a group they are less dangerous (Table 7.1).

In addition to the obvious drug interactions listed in Table 7.1, there are several reports in the literature describing DDIs with some of the agents. For example, when two drugs that are serotonin modulators are given, there is always the potential for inducing a serotonin syndrome. A report 2005 described two cases of severe serotonin syndrome induced by the administration of cyclobenzaprine in patients who were already taking another serotonin modulator.[83] One case involved a phenelzine–cyclobenzaprine interaction; the other, a duloxetine–cyclobenzaprine interaction. The induced serotonin syndrome was characterized by symptoms of autonomic instability and severe agitation, which started 1–2 hours after taking the cyclobenzaprine prescription. Fortunately, both of these cases had a full recovery by 3 days after discontinuing these medications. In 2002 there was a case report on a deep venous thrombosis that occurred as a result of hypotonia secondary to intrathecal baclofen therapy in a 17-year-old cerebral palsy patient.[84] Some patients have a genetic polymorphism that affects their cytochrome P450 liver enzymes. A known polymorphism involving CYP2C19 isoenzyme was examined to see if such an anomaly would produce adverse drug events when patients used various skeletal muscles relaxants.[85]

7.5 Six final recommendations for skeletal muscle relaxants and chronic orofacial pain

Recommendations for antispasticity drugs and muscle relaxants

1 The antispasiticity drugs (e.g., intrathecal baclofen, tizanidine) have substantial value in treating spasticity due to neurological disorders such as spinal cord injury or multiple sclerosis.

Table 7.1 Drug–drug interaction table for D- and X-level interactions (www.online.lexi.com)

Muscle relaxant	D-level interactions with	X-level interactions with
Baclofen	None	None
Tiagabine	None	None
Tizanidine	Beta-blockers Tricyclic antidepressants Rituximab *Alpha-2 agonists antidepressants (e.g., clonidine) *CYP1A2 substrates	Ciprofloxacin Fluvoxamine
Dantrolene	CYP3A4 substrates/CYP3A4 inhibitors (strong)	None
Diazepam (or other benzodiazepines)	Azole derivative antifungal agents Calcium channel blockers Clozapine CYP2C19 substrates/ CYP2C19 inhibitors (strong) CYP3A4 substrates/ CYP3A4 inhibitors (strong) Fluconazole Grapefruit juice Macrolide antibiotics Nefazodone Protease inhibitors Rifamycin derivatives Theophylline derivatives	None
Carisoprodol	CYP2C19 substrates/ CYP2C19 inhibitors (strong)	None
Cyclobenzaprine	CYP1A2 substrates/ CYP1A2 inhibitors (strong) Pramlintide Tramadol	MAO inhibitors
Metaxalone	None	None
Chlorzoxazone	None	None
Methocarbamol	None	None
Orphenadrine	Potassium chloride Pramlintide Secretin	None

CYP, cytochrome P450; MAO, monoamine oxidase.

2 The term "spasticity" is not interchangeable with "spasm." Spasticity is only one of several components of the upper motor neuron (UMN) syndrome, known collectively as the "positive" phenomena, which are characterized by muscle overactivity.

3 The muscle relaxants (e.g., cyclobenzaprine, carisoprodol) should be used on a short-term basis primarily for acute musculoskeletal problems and should not be used long term in patients where muscle spasm is not evident on physical examination.

4 No single skeletal muscle relaxant has been proven to be superior to another; the most widely studied agent is cyclobenzaprine, with demonstrated efficacy for various musculoskeletal conditions but with significant sedation.

5 For acute musculoskeletal pain without clear-cut spasm, none of the skeletal muscle relaxants are superior to acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs).

6 All skeletal muscle relaxants are associated with adverse effects, including dizziness and drowsiness, and the potential for these adverse effects should be clearly explained to the patient.

7 There have been very few randomized clinical trials done on the efficacy of muscle relaxants specifically in orofacial pain disorders; therefore information must be extrapolated from studies on other, similar acute musculoskeletal disorders such as back pain.

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Chapter 8

Psychopharmacologic agents (antidepressants, antipsychotics, anxiolytics, and psychostimulants) used in chronic pain

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8.1 Introduction to psychoactive agents and pain

Psychoactive drugs are also described as psychopharmacological agents and they are primarily used in the treatment of mental disorders. This class of agents is used with the intent of behavior modification and alleviation of symptoms, and selection of a specific agent is based on current knowledge of the neurotransmitters, receptors, and neuronal circuits affected.[1] The drugs in this classification include antidepressants, antipsychotics, anxiolytics, and psychostimulants, among others. This chapter focuses on these agents as they have been used in the comanagement of chronic pain and orofacial pain, in particular. The linkage between these drugs and their use in pain is beyond the fact that, frequently, pain patients have co-morbid depression as well as other psychosocial disorders that impact pain.[2] Specifically some of the drugs discussed in this chapter are analgesic agents, which is a distinct pharmacologic property that is probably independent of their psychopharmacologic action.[3,4] Moreover, these analgesic effects can be differentiated from placebo, may be seen at doses lower than those usually effective in depression, and will be seen in patients who are not depressed. Of course some of the drugs discussed in this chapter are used primarily for their psychopharmacologic effects and not for their pain effect. On the other hand, in modern clinical care, pain is considered a "vital sign" that requires routine evaluation and symptomatic treatment, and as such, the detection, quantification, and treatment of pain are also becoming part of the comprehensive psychiatric evaluation and management.[5] A table listing the various medications that are considered psychopharmacologic agents and their relative importance to pain control is provided (Table 8.1).

8.1.A Serotonin versus norepinephrine as a pain inhibitor

Several psychoactive drugs have in common the ability to inhibit the reuptake of serotonin and norepinephrine. These drugs generally do not serve as agonists to the opioid receptors, yet they are known to have analgesic properties. This suggests that blocking uptake of one or both of these neurotransmitters is important to antinociception. Codd et al.[6] examined whether centrally acting analgesics (opioids) also inhibit uptake of serotonin and norepinephrine. The authors reported that certain opioids, such as morphine and naloxone, did not block norepinephrine or serotonin uptake, whereas levorphanol, levomethorphan, d-propoxyphene, and methadone did inhibit uptake. The opioids proven to block uptake also were examined to see how strong the correlation was between their antinociceptive activity and their affinity at the μ-opioid receptor ($r = 0.85$). The authors stated that when they considered serotonin uptake inhibiting activity (but not norepinephrine uptake inhibiting activity) this significantly improved the correlation between antinociceptive potency and the *in vitro* activity of these compounds ($r = 0.915$). The critical role of central nervous system serotonin in antinociception was confirmed by a recent series of articles which examined opioid medications in mice that were genetically engineered to lack neurons that produce serotonin.[7–9] The authors found that opioids do not

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Table 8.1 Various psychopharmacologic medications used in pain control

Medication	FDA approval	Common off-label pain use	Dose
TCA, tertiary amines			
Amitriptyline	Depression	Neuropathic pain; fibromyalgia	Start at 10–25 mg q.d.; increase by 10–25 mg q.d. up to 75–150 mg q.d.
Imipramine	Depression	Neuropathic pain; fibromyalgia	
Doxepin	Depression; anxiety	Neuropathic pain; fibromyalgia	
Clomipramine	Obsessive–compulsive disorder	Neuropathic pain; fibromyalgia	
TCA, secondary amines			
Nortriptyline	Depression	Neuropathic pain; fibromyalgia	10 mg h.s.—carefully titrated up to 75 mg
Protriptyline	Depression	Neuropathic pain; fibromyalgia	15–40 mg/day; can be taken in one daily dose
Desipramine	Depression	Neuropathic pain; fibromyalgia	Starts at 100–200 mg, either taken as a single dose or split into two doses per day
Serotonin–norepinephrine reuptake inhibitors			
Venlafaxine	Major depression, anxiety	Neuropathic pain	75 mg/day
Milnacipran	Fibromyalgia	Major depression, neuropathic pain	100–200 mg/day
Duloxetine	Major depression; diabetic neuropathy; anxiety disorder; fibromyalgia	Nondiabetic neuropathic pain	60 mg q.d.–b.i.d.
Selective serotonin receptor inhibitors			
Fluoxetine	Major depression; obsessive–compulsive disorder; panic disorder anxiety disorder; bipolar disorder	Fibromyalgia (weak)	20 mg/day
Citalopram	Major depression	Neuropathic pain, fibromyalgia (weak)	20–40 mg/day
Escitalopram	Major depression; anxiety disorder	Neuropathic pain, fibromyalgia (weak)	20–40 mg/day
Paroxetine	Major depression obsessive–compulsive disorder; panic disorder; anxiety disorder; PTSD	Diabetic neuropathy (weak)	Starting dose 10–20 mg daily
Sertraline	Major depression; obsessive–compulsive disorder; panic disorder; PTSD	Neuropathic pain; fibromyalgia	Starting dose 50 mg once a day
Fluvoxamine	Obsessive–compulsive disorder	Neuropathic pain; fibromyalgia	Starting dose 50 mg once a day
Norepinephrine reuptake inhibitors			
Bupropion	Major depression, adjunctive in smoking cessation	Neuropathic pain (questionable)	100 mg titrated up to 400 mg/day in divided doses
Maprotiline	Depression	Chronic pain, neuropathic pain, and fibromyalgia	Initial dose 75 mg daily in 2 or 3 divided doses
Serotonin receptor modulators			
Nefazodone	Major depression	Chronic pain, neuropathic pain, and fibromyalgia	Recommended starting dose 200 mg/day, administered in two divided doses
Trazodone	Major depression	Chronic pain, neuropathic pain, and fibromyalgia	Usual initial starting dose 150 mg/day
Antipsychotic medications			
Olanzapine	Schizophrenia, bipolar disorder, major depression	Possible adjuvant therapy in fibromyalgia, chronic headache, and diabetic neuropathy	20 mg/day
Haloperidol	Psychosis; Tourette's syndrome	Used as antiemetic in opioid-induced nausea and to control opioid-induced cognitive changes	0.5–2 mg b.i.d.–q.i.d.
Prochlorperazine	Nausea, vomiting; anxiety; schizophrenia	Used as antiemetic in opioid-induced nausea	5–10 mg IV q6–8h (IV) or 25 mg
Quetiapine	Schizophrenia, bipolar disorder	Used for chronic recalcitrant pain	Starting dose 25 mg/day; for bipolar disorder, 50 mg/day
Risperidone	Schizophrenia, bipolar disorder	Used for chronic recalcitrant pain	Starting dose 2 mg/day
Fluphenazine	Psychosis	Used for chronic recalcitrant pain	Injectable

Table 8.1 (*Continued*)

Medication	FDA approval	Common off-label pain use	Dose
Anxiolytic medications			
Diazepam	Anxiety, preoperative sedation; alcohol withdrawal; muscle spasm; seizures	Treatment of anxiety-induced pain	Usual starting dose 2–10 mg/day
Lorazepam	Anxiety; insomnia; status epilepticus	Treatment of anxiety-induced pain	Initial total daily dose should not exceed 2 mg/day; can be less
Oxazepam	Anxiety; alcohol withdrawal	Treatment of anxiety-induced pain	Usual starting dose 10 mg, t.i.d.
Temazepam	Insomnia	Treatment of anxiety-induced pain	Typical starting dose for adults 7.5–15 mg taken just before bedtime
Stimulant medications			
Dextroamphetamine	Narcolepsy	Treatment of opioid-induced sedation	2.5–5 mg b.i.d.
Modafinil	Narcolepsy; obstructive sleep apnea	Treatment of opioid-induced sedation	Usual dose 200 mg/day
Methylphenidate	ADHD; narcolepsy	Treatment of opioid-induced sedation	5–15 mg b.i.d.
Donepezil	Alzheimer's dementia	Used for chronic recalcitrant pain	Starting dose 5 mg daily

Dosing abbreviations: b.i.d., *bis in die* (a Latin phrase meaning "twice daily"); h.s., *hora somnia* (a Latin prase meaning "at bedtime"); q.d., *quaque die* (a Latin phrase meaning "every day"); q.i.d., *quater in die* (a Latin phrase meaning "four times daily"); q*x*h, every *x* hours (from *quaque hora*, a Latin phrase meaning "every hour"); t.i.d., *ter in die* (a Latin phrase meaning "three times daily").
ADHD, attention deficit hyperactivity disorder; FDA, US Food and Drug Administration; IV, intravenous; PTSD, post-traumatic stress disorder; TCA, tricyclic antidepressant.

relieve pain as well in these genetically altered mice. Some opioids completely lost their pain-relieving effects and yet the mice still developed tolerance to the drugs and even actively sought them out. This research demonstrates that serotonin is heavily involved in antinociception. A 2004 review of pain occurring in depressive disease noted that a dysfunction of the serotonergic and noradrenergic pathways is commonly accepted as playing a major role in depression.[10] These same monoamines and their neurons serve to inhibit painful stimuli coming from the intestines, the skeletal muscles, and other sensory input. Normally, these inhibitory effects are modest, but when needed, this inhibitory system may strongly suppress painful stimuli. Moreover, when a dysfunction at the level of the serotonergic and noradrenergic neurons occurs, this results in symptoms of both depression and pain.

It is important to mention that the descending spinal serotonergic pathway has an inhibitory mechanism on the primary afferent terminal via postsynaptic 5-HT1B/D receptor, but it also has a facilitatory activity on the dorsal horn excitatory 5-HT3 receptors. It has been presumed that this combination of both inhibitory and facilitatory actions of serotonin might explain why medications that increase only serotonin levels (the selective serotonin reuptake inhibitors [SSRIs]) are not as successful in the treatment of pain as drugs with actions on both serotonin and norepinephrine, which have been proven to be effective in various neuropathic pain states, such as diabetic peripheral neuropathic pain and fibromyalgia.

8.2 Antidepressants and pain suppression

Within the category of drugs listed as antidepressants are multiple medications and this section considers the analgesic properties of several types: the older antidepressants; the tricyclic antidepressants (TCAs); the SSRIs; and the newer serotonin and norepinephrine reuptake inhibitiors (SNRIs).[11,12] Among these, the TCAs are the medication class with the strongest evidence of an analgesic effect as shown in various studies on a variety of neuropathic pain syndromes (painful diabetic neuropathy, postherpetic neuralgia, and atypical facial pain).[13] In a meta-analysis, it has been shown that both TCAs and the newer SNRIs are more effective than placebo for neuropathic pain.[14] This article concluded that TCAs and SNRIs have a "number needed to treat" (NNT) of approximately 3.0, which is considered fair. This means that, for every three individuals with neuropathic pain who received an optimal dose of a TCA or SNRI, at least one patient will show a moderate improvement.

Another article that examined the treatment efficacy of various antidepressant medications used to manage neuropathic pain concluded that the NNT for various TCAs ranges from 1.4 to 2.5, which is considered good. For SSRIs this article put the NNT for neuropathic pain in the 6–7 range, which is considered poor.[15] Moreover, assuming these drugs are titrated to the optimal dose slowly, about 30% of the patients will have minor adverse reactions and about 1 out of 20 (5%) will have major side effects. Finally, a 2007

Cochrane Database updated report on the efficacy of antidepressants for neuropathic pain examined 61 clinical trials that tested the effect of over 20 different antidepressants.[16] The review concluded that TCAs are somewhat effective for neuropathic pain and have an NNT of 3.6 for the achievement of at least moderate pain relief and that for one SNRI (venlafaxine) there were 3 studies that produced an NNT of 3.1. Of course, pain relief qualities of a medication cannot be separated from its side-effect profile, and this is rated using an NNH score (number needed to harm). For NNT the lower the number, the more effective the drug; however, for NNH the higher the number, the more people that can take the drug without side effects. NNH can be rated in two ways: the NNH for withdrawal from a study (usually due to major adverse effects) and the NNH for reporting a minor side effect but not withdrawal from the study. The NNH for major adverse effects for a commonly used TCA (amiptriptyline) was 28 and for a common SNRI (venlafaxine), 16.2. However, for an NNH defined as a minor adverse event, the NNH for amitriptyline was 6 while for venlafaxine it was 9.6.

Caution

In 2007 the FDA sent out a notice to health professionals that all antidepressant medications may increase the risks of suicidal thinking and behavior in children, adolescents, and young adults (age <25 years) during the first 1–2 months of treatment.[17] This effect was not seen in adults older than 24 years of age, and adults 65 years of age and older taking antidepressants have a decreased risk of suicidality. The proposed updates apply to the entire category of antidepressants. Individuals currently taking prescribed antidepressant medications should not stop taking them and should notify their healthcare professional if they have concerns.

8.2.A Tricyclic antidepressants

As mentioned above, there is reasonable evidence that TCAs have analgesic properties when used on a variety of chronic nonmalignant pain conditions.[18–20] The mechanism of action for these drugs is that they increase the level of neurotransmitters in the central nervous system by inhibiting the reuptake of both serotonin and norepinephrine from the synaptic cleft. This class of drugs is usually separated into the tertiary amines (amitriptyline, imipramine, doxepin, clomipramine) and the secondary amines (nortriptyline, desipramine), and both are known to have antinociceptive properties. These drugs are frequently used for neuropathic pain and sometimes even for cancer pain.[21–24] The main drawback for these medications is their substantial side effects, which are many—limiting their use in patients with co-morbid disease or in older adults, who are generally much less tolerant than a younger cohort.[25] One of the more serious adverse effects is the potential cardiotoxicity of this class of medications.[26] The general rule is that patients who have significant heart disease (conduction disorders, arrhythmias, heart failure) should not be treated with a tricyclic medication. Regarding other side effects, the secondary amine tricyclic antidepressants, desipramine and nortriptyline, are slightly less anticholinergic and, therefore, better tolerated than the tertiary amines.

These drugs have been a favorite therapy for chronic musculoskeletal pain (e.g., fibromyalgia) although they are not FDA approved for this purpose. The evidence is considered fair to good that they are better than placebo medications in randomized controlled trials on fibromyalgia.[27] The advantage of these medications is that they also improve sleep and may even enhance the antinociceptive effects of NSAIDs and opioid analgesics. Most clinicians agree that when drugs in this class of antidepressants are used for pain management their analgesic effects are not due to their antidepressant effect.

Amitriptyline

Description, mechanism of action, and primary indications

The oldest and therefore the most tested drug in the TCA class, regarding its effect on pain, is amitriptyline. Laboratory studies on development and treatment of chronic pain have shown evidence that there is an interaction between tumor necrosis factor alpha (TNF-α) production and alpha(2)-adrenergic receptor response in the regulatory mechanism of neuropathic pain, which has been demonstrated to be altered by the administration of amitriptyline, inhibiting pain-induced increases in brain-associated TNF-α and transforming peripheral alpha(2)-adrenergic receptors, further regulating the production of TNF-α.[28]

Starting dose

Amitriptyline should be titrated up from a typical starting dose of 10–25 mg at bedtime, and increased by 10–25 mg per week up to 75–150 mg/day.

Metabolism, side effects, and adverse drug reactions

The main side effects are anticholinergic and can occur rapidly, although tolerance develops. Typical side effects are postural hypotension, sedation, constipation, urinary retention or frequency, weight gain, and dry mouth. Electrocardiograms should be checked in all patients over age 40.

Caution is appropriate for use of amitriptyline in patients with cardiac conduction defects or arrhythmias, and in patients with narrow-angle glaucoma and benign prostate hypertrophy. It is metabolized by the liver to produce the active metabolite of nortriptyline.

Efficacy for fibromyalgia

This drug has been evaluated in a meta-analysis[29] that reviewed studies where it was used in multiple placebo-controlled trials.[30–35] The largest reported result for this medication was that it clearly improved sleep quality and it had only a modest effect on palpation tenderness or muscle stiffness. One randomized blinded controlled trial examined a combination of fluoxetine (an SSRI) and amitriptyline in fibromyalgia and found them to be more effective than either agent used alone.[33]

Efficacy for other neuropathic pain disorders

Sharav et al.[36] demonstrated that a low dose of amitriptyline (mean dose, 23.6 mg) was as effective for chronic orofacial pain as a higher dose (mean dose, 129 mg); the usual daily antidepressant dose is 150–300 mg. Another study showed that 25 mg amitriptyline daily for 3 weeks was superior to placebo in patients with chronic nonmalignant pain.[37] Increasing the dose of amitriptyline to 75 mg or higher produces an improved sleep but it also causes significantly higher incidence of adverse effects.[38] Amitriptyline is also known to relieve pain in nondepressed patients independent of its effect on mood alteration.[39–41] Lastly, there are very few placebo-controlled studies in the literature that have examined the use of TCAs on patients with orofacial pain.[42,43]

Other tricyclics—imipramine, doxepin, clomipramine, nortriptyline, protriptyline, desipramine

Description, mechanism of action, and primary indications

See the discussion of amitriptyline (Sec. 6.2.A).

Starting dose

The starting dose for nortriptyline is 10 mg at bedtime, and increased after 3–5 days to 20 mg at bedtime, and then carefully titrated.

Metabolism, side effects, and adverse drug reactions

The other TCAs are useful alternatives to amitriptyline and have some small differences in their side-effect profiles and half-lives. They include imipramine, doxepin, clomipramine, nortriptyline, protriptyline, and desipramine. Most of the other TCAs have been studied for their analgesic effect compared with amitriptyline. For example, desipramine is the least anticholinergic and sedative of the TCAs. Nortriptyline is popular, maybe because it seems to be better tolerated than amitriptyline and, since it is the active metabolite of amitriptyline, it has a faster time to maximum dose.

Efficacy for fibromyalgia

Tricyclic antidepressants such as nortriptyline and desipramine have also been demonstrated to be efficient, with some limitations, in the treatment of fibromyalgia and are still considered the most cost-effective agents for this disease. As mentioned, their analgesic effect seems to be independent of the antidepressant effect.[44]

Efficacy for other neuropathic pain disorders

Desipramine has also been reported to exhibit pain relief after 3 weeks, independent of mood alterations, in a placebo-controlled randomized controlled trial of 26 patients with postherpetic neuralgia.[45] From 10 studies, including approximately 300 patients on active treatment, the NNT for TCAs was calculated to be 2.6. In two studies on imipramine in diabetic neuropathy, the dose was adjusted to obtain the optimal plasma concentration of imipramine plus its active metabolite desipramine, around 400 nM.[46,47] The target concentration was obtained in 16 of 19 patients in the first study with a median dose of 200 mg/day (range 25–350 mg/day). From the original data of that study, an NNT of 1.4 was calculated. The literature suggests that there is no difference in NNT between TCAs with balanced reuptake of serotonin and noradrenaline (imipramine, amitriptyline, clomipramine), with NNT 2.7, and TCAs with relatively selective noradrenaline reuptake (desipramine, nortriptyline, maprotiline) with NNT 2.5, which is in accordance with one study with a face-to-face comparison,[48] but in contrast to others.[49,50] However, the dosage policy may be particularly important in this comparison, as relatively selective drugs are better tolerated than the balanced drugs, and the potential effect may therefore be more fully achieved for these drugs than for the balanced compounds. The data from at least two controlled studies indicate that tricyclics are effective for both steady and lancinating or brief pains,[51,52] whereas it is more difficult to judge if these drugs also relieve touch-evoked pain. It is an inherited problem with these studies that none of them addressed the issue of an effect on different pain types, but only showed that patients with the different types of pain were relieved of pain in general.

8.2.B Serotonin and norepinephrine reuptake inhibitors

Description, mechanism of action, and primary indications

A more recent class of antidepressants is the so-called serotonin and norepinephrine reuptake inhibitors (SNRIs). These drugs (venlafaxine, milnacipran, and duloxetine) are claimed to have lower side-effects profiles than the TCAs. A 2005 review of the SNRI medications (venlafaxine, milnacipran, and duloxetine) described that these three agents block the reuptake of both serotonin (5-HT) and norepinephrine with differing selectivity.[53] The review noted that milnacipran blocks 5-HT and norepinephrine reuptake with equal affinity, duloxetine has a 10-fold selectivity for 5-HT, and venlafaxine a 30-fold selectivity for 5-HT. The review noted that these three agents are similarly efficacious for both anxiety disorders and are also helpful in relieving chronic pain (with or without depression). Unfortunately, tolerability of these three SNRIs is quite different, noting that venlafaxine seems to be the least well tolerated, while duloxetine and milnacipran appear better tolerated and essentially devoid of cardiovascular toxicity.

Starting dose

Duloxetine is typically given in doses of 60 mg 1–2 times per day. This drug is generally well tolerated by patients.

Metabolism, side effects, and adverse drug reactions

In a study that examined duloxetine, escitalopram, and sertraline for liver enzyme effects, duloxetine was found to have a strong metabolism-inhibitory effect on the cytochrome P450 2D6.[54] This raises concerns regarding drug interactions, such as the combination of duloxetine and methadone. Side effects of nausea, dry mouth, constipation, diarrhea, and anorexia were reported more frequently with active drug than with placebo. The FDA issued a drug safety notice in 2008 stating that there have been reports of overdose with venlafaxine, occurring predominantly in combination with alcohol and/or other drugs.[55] It urged healthcare professionals to prescribe this drug in the smallest quantity of capsules consistent with good patient management to reduce the risk of overdose.

Efficacy for fibromyalgia

Duloxetine is approved by the FDA for the treatment of fibromyalgia. In one study duloxetine was given in 60 mg twice a day (b.i.d.) to 207 patients with fibromyalgia with or without current major depressive disorder.[56] The duloxetine-treated patients were found to have improved significantly more on a total overall fibromyalgia questionnaire than the placebo-treated group. As a pain medication, the rationale for using these drugs in fibromyalgia is that increasing the activity of serotonin and norepinephrine may correct a functional deficit of serotonin and norepinephrine neurotransmission in the descending inhibitory pain pathways and, therefore, help reduce pain.

Efficacy for other neuropathic pain disorders

A randomized controlled trial evaluating venlafaxine showed good pain relief for painful polyneuropathy[57] and for neuropathic pain following treatment of breast cancer.[58]

8.2.C Selective serotonin reuptake inhibitors

Description, mechanism of action, and primary indications

Selective serotonin reuptake inhibitors (SSRIs) are approved for use as antidepressant drugs, but other studies have examined their use in the treatment of neuropathic pain. These drugs include fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram; they differ from classic TCAs in their specific inhibition of presynaptic reuptake of serotonin, but not of noradrenaline, and their lack of postsynaptic–receptor-blocking effects or quinidine-like membrane stabilization. SSRIs increase the extracellular level of serotonin in the synaptic cleft by inhibiting its uptake back into the presynaptic neuron. These drugs have a high selectivity for the serotonin transporters but a low binding affinity for the noradrenaline or dopamine transporters.

Starting dose

Variation in dose titration of fluoxetine from 10–20 mg to 60–80 mg daily has been studied but no satisfactory long-term pain relief has been reported. The combination of fluoxetine with amitriptyline was studied in a previously referenced study by Goldenberg.[33] Fluoxetine combined with cyclobenzaprine[59] was also studied for efficacy in the treatment of fibromyalgia and both studies suggested that this combination approach showed better efficacy than fluoxetine alone.

Metabolism, side effects, and adverse drug reactions

This selectivity significantly reduces the side-effects profile of SSRIs compared with the other antidepressants and reduces their risk of an interaction with other drugs, especially sedatives, antiarrhythmics, and sympathomimetics.[60,61]

SSRIs (except for citalopram and escitalopram) are potent enzyme inhibitors of various CYP450 enzymes with high potential for drug–drug interactions. Moreover they can increase the concentration and side effects of many drugs metabolized by the CYP450 enzymes. One major issue with SSRIs medication is that they produce the side effect of increased clenching and bruxism when used in the higher dose range.[62–65] The term "SSRI-induced bruxism" has been used incorrectly to describe this condition; instead, the induced motor behavior is most likely an increased, sustained, nonspecific activation of the jaw and tongue musculature. Patients report an elevated headache and tightness in their jaw, tongue, and facial structures. This topic is discussed in more detail in Chapter 19. Only case-based literature exists at this time and further research is needed in order to define prevalence and risk factors and to establish a causal relationship between SSRI use and jaw motor hyperactivity.

Efficacy for fibromyalgia

Overall, the various clinical trials where an SSRI has been used on fibromyalgia patients have shown mixed to poor results, suggesting that these medications are less antinociceptive than drugs with dual effects on norepinephrine and serotonin in the relief of pain. Citalopram, which has the highest selectivity for the serotonin reuptake transporters among the SSRIs, was not effective for the treatment of fibromyalgia in two small controlled studies,[66,67] or was effective but only for a short time. Fluoxetine was examined in a double-blind study on fibromyalgia and was shown to be better than placebo.[68] Finally, fluoxetine has been shown to have better analgesic effect than other SSRIs, but it requires higher doses[33] and has better results if combined with another drug. On the other hand, the SSRIs fluoxetine and paroxetine may have additional effects on norepinephrine at adequate doses,[69,70] and have been shown to improve overall symptomatology in patients with fibromyalgia in recent studies.[71,72] Paroxetine alone shows weak significant effect on pain measures.[73]

Efficacy for other neuropathic pain disorders

A review of 13 trials (636 patients) also revealed that SSRIs did not significantly prevent migraine headaches compared with placebo and were clearly not as effective as TCAs for treatment of tension-type headache (TTH).[74] Interestingly, the use of fluoxetine (an SSRI) combined with morphine in healthy volunteers in a double-blind study resulted in 3–8% increase in analgesia to electrical tooth stimulation, and reduced some of the morphine-associated symptoms such as nausea, mood reduction, and drowsiness, without affecting plasma morphine concentrations.[75] A laboratory study showed that the antinociceptive effect of fluoxetine in animals was blocked with administration of naloxone, thus making the authors suggest that the mechanism of antinociception induced by fluoxetine was related to central opioid and serotoninergic pathways.[76] However, the antinociceptive property of SSRIs seen in animal studies has never been achieved with substantial clinical human evidence, although it has been reported that fluoxetine at higher doses has a substantial antinociceptive activity. A recent report on fluoxetine noted that it has an antagonist action on 5HT2C receptors, which has an inhibitory effect on NE and DA release. As a result of the blockade of this receptor, there is a disinhibition of NE and DA, and it also shows weak NE reuptake blocking, which could be beneficial for clinical use, however, probably in very high doses.[77] Unfortunately they do not have satisfactory analgesic behavior. No studies have been done on the SSRIs for cancer pain. However, it is safe to say that the SSRIs have not been found helpful for the painful symptoms associated with chronic muscle pain.

In two studies on SSRIs in painful diabetic neuropathy, there was a significantly better effect of the SSRI than of placebo.[78,79] There is no obvious explanation for the difference in effect between the different SSRIs. Hitherto unknown differences in basic pharmacology may be responsible for some of the discrepancies. With respect to fluoxetine, the failure to find an effect may relate to the pharmacokinetics of fluoxetine hampering the crossover design of the study (see the previously referenced study by Max et al.). Fluoxetine has an active metabolite with a very long half-life. The individual NNT from the studies showing a significant effect is 2.9 (paroxetine) and 7.7 (citalopram), and the combined NNT for all three studies is 6.7 (95% CI, 3.4–435). Paroxetine seems to relieve both steady and lancinating pain.

From the results of these and other studies in diabetic neuropathy, it may be suggested that drugs with a balanced inhibition of serotonin and noradrenaline but without the postsynaptic and quinidine-like effects of the TCA could have similar effect as the tricyclics and, at the same time, be better tolerated. Venlafaxine has been marketed for the treatment of depression, but there are studies with NNT of 3.1 for neuropathic pain.[80]

8.2.D Norepinephrine reuptake inhibitors

Description, mechanism of action, and primary indications

Norepinephrine reuptake inhibitors (NRIs) are a type of antidepressant medication that may reduce neuropathic pain, although the data cited earlier on the link between serotonin and opioid receptors would suggest this is not the case. One

such drug is bupropion and it is known to block the reuptake of dopamine and norepinephrine with no direct action on the serotonin system.[81] It is primarily indicated for major depressive disorder and as an adjunct in smoking cessation.

Starting dose

Starting dose of 100 mg per day, increased by 100 mg per week up to 200 mg twice daily for the Bupropion SR formulation.

Metabolism, side effects, and adverse drug reactions

Bupropion has a lower risk of sexual dysfunction and weight gain compared with the TCAs and is an effective alternative or adjunctive treatment for depression in patients whose symptoms do not respond to SSRIs.[82] Compared with SSRIs, treatment with bupropion has the disadvantage of an increased adverse effect profile that includes headaches, tremors, and seizures. The risk of seizures decreases at doses less than 450 mg/day and with divided dosing.[83] Examples of norepinephrine reuptake inhibitors are bupropion and maprotiline, but limited data exists today that supports this drug as a strong antinociceptive agent.

Efficacy for fibromyalgia

No direct effect on pain of fibromyalgia has been reported with this class of medication. It seems that relief of symptoms in fibromyalgia would be primarily related to the symptoms of associated depression.[84]

Efficacy for other neuropathic pain disorders

A 2001 randomized placebo-controlled crossover design study evaluated sustained-release (SR) bupropion for the treatment of 41 neuropathic pain patients. The authors reported that there was a significant decrease in interference of pain on quality of life in the bupropion SR group compared with that seen in the placebo group.[85] In contrast a 2005 study evaluated bupropion SR for an analgesic effect compared with placebo in chronic low back pain subjects.[86] This study found that bupropion SR was not significantly better than placebo in the treatment of patients with non-neuropathic chronic low back pain.

8.2.E Serotonin receptor modulators

Description, mechanism of action, and primary indications

Serotonin receptor modulators (SRMs), which include nefazodone and trazodone, block the 5-HT2A serotonin receptor and serotonin reuptake and have efficacy similar to that of SSRIs for the treatment of depression and due to its sedative effect it has also been commonly used for depression-related insomnia. Nefazodone is less commonly used to treat depression because of the risk of hepatoxicity and sedation side effects. Serotonin reuptake inhibition occurs only at higher therapeutic doses (see prior reference to Stahl 2008). It has been considered that low to moderate doses of an SRM could be added to a full dose of a serotonin transporter inhibitor (SSRI, SNRI) as a synergistic agent and result in significant increase of serotonin levels. A laboratory study with rats chronically treated with nefazodone has demonstrated an increase in μ-opioid receptor expression in brain areas related to pain, such as periaqueductal gray, besides an increase in pain resistance or tolerance behavior; the authors suggested that this antidepressant might be effective on pain possibly through the opioid system.[87] Another laboratory study demonstrated that trazodone's antinociception effect was affected by a 5-HT3 receptor antagonist and suggested that the descending serotonergic pathway on 5-HT3 receptor is related to its antinociceptive action.[88] However, the antinociceptive property of this class of antidepressants has not been significantly achieved or proved clinically, and little evidence is available that could determine the ideal regimen for its use.

Starting dose

The current literature does not present a regimen specific for pain management.

Metabolism, side effects, and adverse drug reactions

This class of drugs has less prominent anticholinergic and adrenolytic side effects than other antidepressants such as TCAs, but it still can result in adverse reactions like dizziness, drowsiness, lethargy, nausea, vomiting, and headache.

Efficacy for fibromyalgia

Neither nefazodone or trazodone has a monotherapy randomized blinded controlled clinical trial on efficacy for chronic pain or fibromyalgia.

Efficacy for other neuropathic pain disorders

Serotonin receptor modulators are antidepressant medications that may relieve neuropathic pain.[89] These drugs work to achieve chemical balance within the brain by increasing the levels of serotonin available to transmit messages to other nerves.

8.2.F Serotonin-related adverse drug events

In 2006, the FDA sent a notice to healthcare professionals that the use of medications to treat migraine headaches (e.g., triptans) together with SSRIs and SNRIs could produce a life-threatening condition called serotonin syndrome.[90]

8.3 Antipsychotics and pain

Description, mechanism of action, and primary indications

One commonly used drug for schizophrenia and bipolar disorder is olanzapine. This drug has isolated case reports of its benefit in chronic recalcitrant orofacial pain such as burning mouth.[91,92] Unfortunately, this drug also has been proven to cause weight gain and possible hyperglycemia in its chronic users, which becomes important since many of the tricyclic medications used for pain also increase weight gain. A Cochrane Database review article analyzed the literature regarding the analgesic efficacy and adverse effects of antipsychotics in acute or chronic pain, such as fibromyalgia, chronic headache, and diabetic neuropathy, and the authors concluded that this class of medication seems to be an option for adjuvant therapy in the treatment of painful conditions; however, more RCT studies with larger samples must be developed.[93] Importantly, the use in combination with an opioid analgesic for the management of acute pain has presented increased risk of negatively influencing disease course and total mortality in unstable angina patients.[94] The use of antipsychotics has also been reported as counteracting agents to minimize adverse effects of opioid analgesics, such as nausea and other central nervous system side effects.[95] Various mechanisms have been related to opioid-induced nausea, including direct stimulation of the chemoreceptor trigger zone (CTZ), and antipsychotics' antiemetic function is related to the blockage of dopamine receptors within the CTZ. Haloperidol and prochlorperazine have been considered first-line options. Of course adverse effects must be closely monitored (e.g., akathisia, dystonias, sedation, and orthostatic hypotension). Cognitive changes (e.g., confusion, delirium) may also require the use of antipsychotics. Typically, low doses of haloperidol have been used based on clinical experience and the low incidence of cardiovascular and anticholinergic effects.[96]

Starting dose

The current literature does not present a specific regimen for pain management. For treatment of opioid-induced nausea, it has been recommended to use haloperidol 0.5–2 mg orally two to four times per day, or prochlorperazine maleate 5–10 mg orally every 6–8 hours. For opioid-induced central nervous system symptoms (reduced cognition or delirium), haloperidol 0.5–2 mg orally twice per day or quetiapine 25–50 mg orally twice daily, or risperidone 0.25–1 mg orally twice per day might be considered.[95]

Metabolism, side effects, and adverse drug reactions

Many of the older antipsychotic agents such as chlorpromazine, thioridazine, and fluphenazine have several major adverse side effects, so generally these are not used except in patients with co-morbid schizophrenia and neuropathic pain. Antipsychotics are known to cause adverse effects such as tardive dyskinesia, extrapyramidal reactions (movement disorders), and sedation. The new class of atypical antipsychotics show fewer side effects, but undesired reactions still can happen.

Efficacy for fibromyalgia

In 2006 an open-label study reported that olanzapine was helpful for the treatment of 51 patients with fibromyalgia and various co-morbid psychiatric disorders.[97] The patients reported general improvement with this medication on visual analog scales (VAS) of pain. In 2007, a study was done to evaluate the effect of ziprasidone (an antipsychotic medication approved for use in schizophrenia) on patients with fibromyalgia.[98] This study was an open-label, case-series report and it included 32 fibromyalgia patients who received a dose of 20 mg/day, which was adjusted according to clinical response and tolerability. Of the 32 patients, 10 withdrew from the study and a clinical global impression scale was used to evaluate the effect of the medication. The authors concluded that ziprasidone did not seem an especially useful adjunct drug in fibromyalgia.

Efficacy for other neuropathic pain disorders

In 2008, another study examined the effect of the antipsychotic drug, fluphenazine on mechanical allodynia in neuropathic rats.[99] They concluded that fluphenazine had an inhibitory action on ectopic afferent discharges, probably because it blocked voltage-gated sodium channels, and this in turn reduced mechanical allodynia in these animals. Finally there was a report in 2002 on the use of olanzapine for the management of eight cancer pain patients with substantial anxiety and mild cognitive impairment.[100] The authors concluded, based on these eight cases, that olanzapine may be useful in the treatment of patients with uncontrolled cancer pain associated with cognitive impairment or anxiety.

8.4 Anxiolytics

Description, mechanism of action, and primary indications

It has been observed that patients with chronic pain have elevated levels of anxiety. The scientific basis for this observation comes from an animal experiment that examined the anxiogenic effect of induced chronic pain in mice using injections of complete Freund's adjuvant (CFA) or by sciatic nerve ligation.[101] The study reported both methods (injection and surgery) produced a significant anxiogenic effect at 4 weeks after pain was induced, and it was found that this phenomenon was associated with significant changes in opioidergic function in the amygdala. The authors speculated that these brain changes produced the anxious behavior seen in the rats. Unfortunately data on the chronic use of anxiolytics in humans for chronic pain is generally lacking. Of interest is that GABA is one of the key neurotransmitters involved in anxiety and in the mechanism of action of many anxiolytic drugs, and it also is an important component in pain management. However, there are several GABA receptor subtypes, each with particular properties. The major types are GABA-A, GABA-B, and GABA-C. GABA-A and GABA-C receptors are ligand-gated ion channels. Only some subtypes of the GABA-A receptors are related to benzodiazepines, barbiturates, and alcohol. GABA-C receptors' activity has not been clearly defined, but they seem to be possibly related to some aspects of neuroendocrine regulation, and not responsive to benzodiazepines. GABA-B receptors are G-protein-linked receptors, which can be coupled to calcium and/or potassium channels, and may be involved in pain, among other central nervous system (CNS) functions.[102] However, benzodiazepines also show no binding to GABA-B receptors. On the other hand, it has been shown that intrathecal midazolam binds to GABA-A receptors in the spinal cord and it results in improvement in perioperative analgesia.[103] A laboratory study in rats also suggested that GABA/benzodiazepine receptor and the nitric oxide–cyclic GMP (NO-cGMP) pathway are involved in the "antinociceptive-like" effects of diazepam.[104] These results were explained by the findings that diazepam reversed the dysfunctional behavior of the rat in the pain-induced model, and this activity was abolished by a GABA/benzodiazepine receptor antagonist (flumazenil); also, this antinociceptive-like effect of diazepam was antagonized by nitric oxide synthase (NOS) inhibitors.

Starting dose

The current literature and clinical evidence do not support regimen-specific information for pain management.

Metabolism, side effects, and adverse drug reactions

Most benzodiazepines, other than lorazepam, oxazepam, and temazepam, are metabolized by the cytochrome P450 enzymes. Side effects include drowsiness, cognitive impairment, and ataxia.

Efficacy for myofascial pain

One exception to this lack of clinical studies in humans is a 1997 study that compared ibuprofen with diazepam for chronic orofacial muscle pain.[105] This study was a double-blind, randomized, controlled clinical trial that included 39 subjects with masticatory muscle pain of at least 3 months' duration and tenderness to palpation. The patients were randomly allocated to one of four treatments (placebo, diazepam, ibuprofen, or the combination of diazepam and ibuprofen). The authors showed a significant drug effect for diazepam but not for ibuprofen, indicating that pain relief was attributable to diazepam. They concluded that the lack of clinical effect for the NSAID indicated that inflammation is not the basis for chronic muscle pain in the orofacial region.

Efficacy for other neuropathic pain disorders

There is no clinical evidence supporting the safe and effective use of anxiolytics in the treatment of neuropathic pain. An interesting laboratory study using an animal model for neuropathic pain has demonstrated that diazepam has effective antinociceptive action; however, the required doses led to unacceptable CNS-related side effects. The authors report these results to be likely related to the fact that diazepam acts fully at all GABA-A subtypes α-1, α-2, α-3, and α-5, and GABA-A receptors containing α-1 subunit seem to be mostly involved with the sedative effect. So they tested the efficacy and side-effects profile of a novel subtype-selective GABA-A receptor-positive modulator (NS11394), which presents a higher affinity to the subunits α-2 and α-3 than α-1 receptors. GABA-A α-2 and probably α-3 predominantly receive nociceptive input from primary afferents. This could explain why this GABA modulator showed antinociceptive actions with minimal motor-impairing side effects in this animal model.[106] Although this action occurs at the spinal cord level, other studies have shown that activation of GABA-A receptors in the amygdala or the anterior cingulated cortex reverses both sensory and affective pain-like behaviors in neuropathic rats.[107,108] These findings might contribute to the development of new therapeutics that would approach both affective and neuropathic pain symptoms. Up to now, medications that seem to have demonstrated utility for this purpose (affective and nociceptive modulation) are gabapentin and pregabalin.

8.5 Stimulants and pain

Description, mechanism of action, and primary indications

A 1999 article discussed the pros and cons of stimulants to counteract opioid-induced sedation and concluded that the general use of this class of drugs for the treatment of opioid-induced sedation is not recommended.[109] Stimulants include methylphenidate, phentermine, dextroamphetamine, amphetamines, diethylpropion, modafinil, armodafinil, and donepezil. The authors did suggest that in very select circumstances these agents might be effective for patients who experience dose-limiting sedation with opioids and have exhausted all other options available to manage this adverse effect.

Starting dose

Recommended regimens for treatment of opioid-induced sedation include dextroamphetamine 2.5–5 mg orally twice per day, or methylphenidate 5–10 mg orally twice per day (see previous reference by Swegle and Logemann 2006).

Metabolism, side effects, and adverse drug reactions

In 2007 the FDA sent anotice to healthcare providers that modafinil can induce a serious skin reaction including erythema multiforme (EM), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) in rare cases.[110–112] Tremor, delirium, decreased appetite, and hallucinations are possible adverse effects and judicious use with close monitoring is required. One significant side effect noted with this stimulant class of medications is that they mostly have been reported to induce bruxism and dystonic extrapyramidal reactions.[113–117] This issue is discussed in more detail in Chapter 19, but as these drugs are being used with greater frequency to treat obesity or as stimulants for children with attention deficit hyperactivity disorder (ADHD) or narcolepsy, and even severe depression,[118] this side effect (jaw pain and headache) is more frequently seen.

Efficacy for fibromyalgia

There is no specific information about the use of psychostimulants for comanagement of fibromyalgia. This may be because high-dose opioids are not commonly used for fibromyalgia.

Efficacy for other neuropathic pain disorder

In 2005 a study reviewed the literature on the issue of opioid-induced sedation in chronic pain.[119] The study found literature on several drugs used for this purpose, including methylphenidate, donepezil, and modafinil, and the authors concluded that pharmacologic treatment of opioid-induced sedation should be utilized selectively and may be considered in appropriate patients.

8.6 Psychopharmacologic agents: special concern for older adult patients

Finally, when considering the use of psychoactive agents in the chronic pain patient, the issue of how age effects your decision is critical. For example, in a patient with chronic pain and co-morbid depression a TCA or SNRI medication is commonly used; however, if the patient is an older adult, the potential for side effects and complications would direct the clinician away from TCAs and toward SNRIs, SSRIs, or alternative nonpharmacologic therapies. In general depression and the co-morbid pain would be treated from the outset; however, when prescribing an antidepressant to an older adult patient, the initial dose of the agent must be determined by individual symptom response, known adverse effect profile, drug–drug interactions, and any co-morbid medical and psychiatric conditions. The initial doses in the older adult are usually much smaller than you would prescribe for younger patients due to impaired hepatic and renal elimination.[120] For example, while venlafaxine may be effective and be associated with fewer drug–drug interactions than a TCA, it does have some undesirable cardiovascular effects, such as hypertension, orthostatic hypotension, and new-onset tachycardia or palpitations.[121] Most of the studies on the use of TCAs for chronic pain were not based on subjects over the age of 65, so the rate of adverse events in these studies is generally lower than will be seen in a typical pain practice. All psychoactive agents used in the older adult need to be carefully monitored and the lowest possible dose utilized.

8.7 Final considerations

This chapter discussed the use of antidepressants, antipsychotics, anxiolytics, and psychostimulants in the management of painful symptoms or as counteracting agents for the adverse effects of other chronic pain management drugs. We selected 10 specific findings to restate in our summary:

Recommendations on psychoactive medications for chronic pain

1 The tricyclic antidepressants (TCAs) and the serotonin-norepinephrine reuptake inhibitors (SNRIs) both have better-than-placebo effect on various neuropathic pain states, such as diabetic peripheral neuropathic pain, and

on fibromyalgia. In general the TCAs are more efficacious than the SNRIs but also are associated with more side effects than the latter.

2 The TCAs have a higher "number needed to harm" score (NNH) for major adverse events causing withdrawal (NNH = 28) than do the SNRIs (NNH = 16.2). However, when the NNH is defined as a measure of minor side effects the TCAs have a lower NNH (NNH = 6) than do the SNRIs (NNH = 9.6).

3 Among the SNRI-class drugs, duloxetine and milnacipran are better tolerated and are approved by the FDA for the treatment of fibromyalgia. Duloxetine is also approved and provides fair to good pain relief for painful polyneuropathy.

4 The selective serotonin reuptake inhibitors (SSRIs) have fewer side effects but have a much higher "number-needed-to-treat" score (NNT) for neuropathic pain (NNT = 6–7 range) than do either the TCAs (NNT = 1.4–3.6) or the SNRIs (NNT = 3.1), so generally they are not used in chronic pain conditions unless there is a co-morbid depressive disorder.

5 The SSRIs and the stimulant drugs can cause an extrapyramidal system activation that causes tooth clenching, with resulting jaw pain and headaches, at medium to high doses; therefore they should be used sparingly in patients with orofacial pain or headaches.

6 The norepinephrine reuptake inhibitors (bupropion) may also reduce neuropathic pain, but this effect is minimal at best.

7 Serotonin receptor modulators (nefazodone and trazodone) have some antinociceptive properties, but this effect is minimal at best.

8 Antipsychotics (olanzapine) have no proven effectiveness beyond their psychoactive effect for chronic pain such as fibromyalgia.

9 Because patients with chronic pain often develop elevated levels of anxiety, anxiolytic- class medications (diazepam, lorazepam, temazepam) have some antinociceptive effects in high-anxiety patients, but they are not considered primary medications for pain control.

10 Stimulant-class medications are used to counteract opioid-induced sedation, but such medications, with few exceptions, should be used sparingly if at all in chronic-pain patients.

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Chapter 9

Antibacterial agents as analgesics in chronic pain

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9.1 Introduction

It is common in an orofacial pain center for a new patient to report how she or he has received substantial pain relief as a result of using one or multiple antibiotic medications. This story is not surprising if the patient was treated for a dental or sinus infection, but when you examine the patient, there is frequently no physical evidence of an infection. It is not uncommon for these patients to report that they have had unsuccessful root canal treatments on several teeth or even had several extractions in addition to multiple courses of various antibiotics. Moreover, when you inquire if the antibiotics provided relief for an extended period of time, the patient typically reports that as soon as they stop taking the antibiotics their pain returned to its original intensity. This clinical course has several possible explanations: (1) antibiotics reduce pain by suppressing local infection and associated swelling, which will indirectly reduce pain; (2) antibiotics might reduce pain directly via analgesic properties; or (3) antibiotics reduce pain via a placebo effect like all medications. However, there are adverse consequences in the chronic use of antibiotics to control pain.

9.2 Indirect effect of antibiotics on tooth pain due to reduction of swelling and inflammation

Pain reduction with antibiotics in the presence of infection is presumably due to decreased inflammation as the bacteria are killed. However, four prospective well-controlled trials in patients with painful pulpitis or periapical infections have failed to provide evidence of antibiotic efficacy for decreasing pain or decreasing analgesic consumption when compared with a placebo medication.[1–4] The results did not differ if the antibiotic (penicillin or amoxicillin) was given prophylactically (before) or immediately after the endodontic treatment was performed. Overall these studies suggest that prescribing antibiotics (penicillin or amoxicillin) for pain control is not effective for dental pulpal infections and the most important pain control method is removal of the infection itself. These findings do not explain the clinical observations that patients with chronic orodental pain report pain relief when they take antibiotics.

9.3 Known antinociceptive action of various antibiotics

One possible explanation for the analgesic effect of antibiotics is that these medications are not suppressing pain by reducing or killing bacteria, but they have direct analgesic properties. This issue has been examined by a series of experiments, mostly *in vitro* studies, described in the subsections focusing on the following antibiotic types: beta-lactams, aminoglycosides, tetracyclines, chemically modified tetracyclines (CMTs), and nucleoside antibiotics.

9.3.A Beta-lactam antibiotics

The initial demonstration of an innovative study examining the antinociceptive effects of antibiotics used an experimental rat model of pain created by sectioning dorsal roots C5 to T1 unilaterally.[5] The rats demonstrated self-mutilation of the denervated limb that was quantified before and after the injection of four substances: a morphinomimetic drug and three antibiotics (chloramphenicol, amoxicillin, and doxycycline). The animals of the group treated with the

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morphinelike drug (pethidine) performed significantly less autotomy than did the animals in the control group. This same self-mutilation of the denervated limb was found when the animals were injected with chloramphenicol and amoxicillin, but doxycycline was found less efficacious. Another study in an acute pain model (hot plate) examining the effects of nine randomly selected antibiotics in rats[6] also demonstrated that several antibiotics have antinociceptive properties. This antinociceptive effect was comparable to the effect produced with salicylate and ketoprofen. They reported that pain reduction was long lasting with chloramphenicol (10 hours or more) and the authors concluded that these antinociceptive properties cannot be attributed to sedation but are most likely due to analgesia.

9.3.B Aminoglycoside antibiotics

Another series of studies in a variety of animal models have demonstrated antinociceptive effects of aminoglycoside antibiotics, including gentamicin, neomycin, kanamycin, and streptomycin.[7–18] The effects were dose-related and their relative antinociceptive potency was similar to the efficacy for blocking N-type calcium channels with anticonvulsant medications or neural blockade with local anesthetic. These studies provide ample preclinical evidence that aminoglycosides have real antinociceptive effects. Unfortunately, no published report has evaluated whether these antibiotics are analgesic in humans. There has been one report in the literature of inadvertent epidural infusion of gentamicin instead of fentanyl in a patient with back pain postpartum.[19] The pain in this case was not controlled with this infusion, and in fact there was a return of pain that prompted the nurse to discover the inadvertent use of gentamicin.

9.3.C Tetracycline-class antibiotics (minocycline and doxycycline)

The effects of minocycline on activation of glial cells (microglia and astroglia) in the spinal cord of rats were examined after experimental nerve injury.[20] This study reported that intrathecal administration of minocycline, a selective inhibitor of microglial cell activation, inhibits low-threshold mechanical allodynia, as measured by the von Frey test, in two models of pain facilitation. In a rat model of neuropathic pain induced by sciatic nerve inflammation (sciatic inflammatory neuropathy), minocycline delayed the induction of allodynia in both acute and persistent paradigms. In addition, minocycline was able to stop the established inflammatory-induced allodynia at day 1, but not at 1 week later, suggesting a limited role of microglial activation in more-persistent pain states. This data is consistent with a critical role for microglial cells in initiating, rather than maintaining, enhanced pain responses. In addition to the above study, a 2006 study supports the concept that minocycline suppresses microglial-driven neuronal activity for at least 1 day after nerve injury.[21] Additional studies demonstrate that minocycline suppresses serum levels of interleukin-6 (IL-6) in a chronic constriction injury (CCI) model of neuropathic pain in rats,[22] suppresses microglial cells when given preemptively before an experimental nerve injury,[23] and prevents or delays the development of neuropathy.[24]

In humans, there are three studies of importance to note. The first was a 1996 study that examined the anti-inflammatory effect of minocycline in rheumatoid arthritis (RA) subjects.[25] Serum samples of 65 RA patients who completed a 26-week randomized double-blind trial of minocycline (100 mg twice a day) versus placebo were studied. The authors reported that several clinical parameters and in particular the acute phase response markers of inflammation decreased significantly in the minocycline-treated group. Serum levels of IL-6, a proinflammatory cytokine decreased in the minocycline-treated group only and this decrease was positively correlated with the decrease in C-reactive protein (CRP) levels. Minocycline significantly decreased serum immunoglobulin-M rheumatoid factor (IgM-RF), IgA-RF, total IgM, and total IgA levels. No such changes were observed in the placebo-treated group. The anti-inflammatory effect of minocycline in RA patients may be due to the reduction in the synthesis of IL-6 and rheumatoid factor. Although this study did not measure pain outcome, minocycline could indeed play a role in pain relief by decreasing inflammation. Further studies with pain outcome will be useful to understand clinical impact of minocycline in pain relief in rheumatoid arthritis patients.

A second study in patients with osteoarthritis indicates that doxycycline slows the progression of osteoarthritis.[26] As determined by less joint space narrowing (JSN) in the drug group compared with the placebo group, pain scores in both treatment groups were low at baseline and remained low throughout the trial, thereby preventing determination of an analgesic effect in osteoarthritis patients. Finally, minocycline oral rinses were compared with a placebo aqueous solution mouthwash for assessing pain relief in patients suffering from frequent episodes of recurrent aphthous stomatitis (RAS).[27] Minocycline mouthwashes were reported to result in significant reduction in the severity and duration of pain (recorded by visual analog scale) due to RAS. Seven patients also participated in a crossover study and the findings were comparable with that of the randomized study. The authors concluded that minocycline oral rinses reduced pain in patients with RAS and may have implications for treatment in other noninfectious inflammatory ulcerative oral mucosal diseases. In summary, the minocycline and

doxycycline studies just described show anti-inflammatory effects, which may reduce the pain levels. However, whether the pain reduction is actually due to the effects of these drugs needs to determined with further research.

9.3.D Chemically modified tetracyclines

Chemically modified tetracyclines (CMTs) do not have antimicrobial properties but maintain their function as matrix metalloprotein inhibitors (MMPs)[28,29] and are now being studied as anti-inflammatory agents[30] and antineoplastic agents.[31] However, no analgesic efficacy testing of CMTs has been conducted in animals or humans. For example, Periostat® is doxycycline hyclate modified to remove its antibacterial properties. Studies have shown that Periostat® inhibits or reduces collagenase activity in gingival crevicular fluids and periodontitis.[32–35] Periostat is given orally as a 20-mg tablet as an adjunct to scaling and root planing procedures to aid in periodontal tissue healing. However, no studies have been done to show analgesic activity of Periostat.

9.3.E Nucleoside antibiotics

An incidental finding of the successful inhibition of neuropathic pain in a patient with long-standing Raynaud's disease who received the trial chemotherapeutic agent KRN5500, a derivative of the nucleoside antibiotic spicamycin, led to further research which concluded that KRN5500 is effective against neuropathic pain but interestingly not against nociceptive pain.[36–38] Further research should shed more light on the mechanisms of antineuropathic pain effects of this class of antibiotics. In summary, the above data seems to suggest that there is some evidence to support analgesic effect of certain antibiotic classes such as tetracyclines, but further research especially in humans is necessary to address this issue.

9.4 Placebo effect of antibiotics

The antibiotics most commonly used for dental infection are penicillin, amoxicillin, amoxicillin with clavulanate potassium, and cephalosporin. Patients taking these antibiotics do sometimes report pain relief during the time they are taking these drugs. This raises the issues of the placebo effect of antibiotics in chronic pain sufferers. This issue needs to be examined by looking at RCT-style studies where patients with bacterial infections were put on a placebo drug. Such studies would allow us to understand the magnitude of pain relief associated with antibiotics and whether they are actually acting as placebo drug when pain relief is reported.

9.4.A Expectation fulfillment and antibiotics

In the late 1950s it was proposed that chest pain due to angina could be relieved with a surgical procedure involving ligation of the internal mammary artery. In theory, this surgery diverted blood flow to the heart and reduced angina pain. This theory was tested by surgeons in a random-assignment, single-blind study where some patients scheduled for this surgery had only skin incisions with sutures placed instead of actually having the internal mammary artery ligated.[39] The authors reported that all 18 nontreated patients had less angina 6 weeks afterward, some had improved exercise electrocardiographs, and the effect lasted for years in some. Years later, after the discovery of endogenous opioids, there have been multiple studies that have looked at how these pain-reducing endogenous chemicals could be naturally activated. One study provided patients with hidden infusions of naloxone prior to being given an infusion that they thought might be an analgesic agent.[40] Interestingly, the pain-reducing effect of the placebo infusion was not blocked by the hidden naloxone infusion. The authors concluded that placebo-induced analgesia was not necessarily induced by endogenous opioids. These findings were substantiated by a more recent 1999 study.[41] The authors induced ischemic pain with a blood pressure cuff. Subjects then were given several active and placebo agents and some expectations cues, and then they were given naloxone to see if the induced hyperalgesia would be reversed. The results showed that expectations had a strong influence on the placebo effect, that placebo-induced analgesia can be evoked in separate ways, and that while some are mediated via endogenous opioids others are not. Unfortunately, no systematic random-assignment antibiotic versus placebo controlled study with naloxone reversal has been done on chronic tooth pain or one of the other neuropathic pains in the facial region.

Recently, advanced imaging studies such as functional magnetic resonance imaging (fMRI) have been used to understand the mechanisms of placebo analgesia.[42,43] In one study, the authors showed that placebo analgesia involves a complementary mechanism of sustained and transient activity in different areas of the brain using fMRI. Sustained activity activated the emotional regulation circuitry needed for memory formation of the event, as seen by involvement of the temporal and parahippocampal cortices. The mechanisms with transient activity processing cognitive and evaluative information of the stimuli in the context of the placebo suggestion to confirm the expectations set by it included linguistic centers in the left hemisphere and frontal regions of the right hemisphere generally associated with executive functioning. The authors conclude that these mechanisms were likely to be engaged in analgesic processes.

In summary, we suspect placebo analgesia is the predominate mechanism underlying the antihyperalgesic effects of antibiotics, but this must be tested with research. It is entirely possible that in the case of tooth pain, where both the dentist and the patient think there might be an infected pulp, a prescription of antibiotics is potentially a powerful placebo analgesic agent.

9.5 Downside effects of frequent use of antibiotics for persistent pain

In addition to the inconclusive evidence, there are many reasons not to use antibiotics for pain. In 2005, a review article described and summarized the pros and cons of frequent antibiotic use and antibiotic resistance. It is well documented that increasing antimicrobial resistance has resulted in increasing difficulties in the treatment of bacterial infections. Resistance leads to inappropriate empirical therapy, delay in starting effective treatment, and the use of less-effective, more-toxic, and more-expensive drugs.[44] Although studies are not always consistent, antimicrobial resistance in the infecting organisms is associated with treatment failure, prolonged or additional hospitalization, increased costs of care, and increased mortality. Additional costs and lost bed days are incurred by the need to control the spread of antimicrobial-resistant organisms within hospitals. All this has significant direct impact on patients and secondary effects on the cost effectiveness of healthcare delivery. This recognition has prompted concern to control antimicrobial resistance by improving antibiotic use and reduction of hospital cross-infection.

The Centers for Disease Control (CDC) has estimated that invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections caused more than 94,000 life-threatening infections and nearly 19,000 deaths in the United States in 2005. Most MRSA infections were associated with health care, and incidence rates were highest among persons 65 years and older. This is a major public health problem primarily related to health care and is no longer confined to intensive care units, acute care hospitals, or any healthcare institution. Indiscriminate use of antibiotics has led to this problem.[45] The American Society for Microbiology (ASM) Task Force has put forth a recommendation to reduce such antibiotic resistance: *to reduce the indiscriminate prescribing of antibiotics should be the immediate response by practicing physicians, dentists, and veterinarians*. Since dentists prescribe approximately 10% of all common antibiotics, the American Dental Association (ADA) has set guidelines[46] for prescribing antibiotics (see Table 9.1).

Establishing guidelines alone may not help in reduction of antibiotic prescriptions. To this end, a randomized controlled study done in Wales in 2006 can be cited which assessed whether educating dentists on appropriate prescription of antibiotics for acute dental pain reduced the antibiotic prescriptions.[47] General dental practitioners were included in this study and were randomized to three study groups (control group; guideline group, who received educational material by mail; and intervention group, who received educational material by mail and an academic detailing visit by a trained pharmacist). Antibiotic prescriptions were deemed to be inappropriate if the patient did not have obvious signs of spreading infection. Patients who were treated by dentists who received educational material by mail and an academic detailing visit by a trained pharmacist received significantly fewer antibiotic prescriptions than patients in the control group and significantly fewer inappropriate antibiotic prescriptions. However, the authors found that antibiotic and inappropriate antibiotic prescribing were not significantly different in the guideline group compared with the control group.

Table 9.1 American Dental Association guidelines for appropriate prescription of antibiotics

1. Make an accurate diagnosis.
2. Use appropriate antibiotics and dosing schedules.
3. Consider using narrow-spectrum antibacterial drugs in simple infections to minimize disturbance of the normal microflora, and preserve the use of broad-spectrum drugs for more complex infections.
4. Avoid unnecessary use of antibacterial drugs in treating viral infections.
5. If treating empirically, revise treatment regimen based on patient progress or test results.
6. Obtain thorough knowledge of the side effects and drug interactions of an antibacterial drug before prescribing it.
7. Educate the patient regarding proper use of the drug and stress the importance of completing the full course of therapy (i.e., taking all doses for the prescribed treatment time). The most important decision for the dental practitioner is not *which* antibiotic to use but *whether* to use one at all.

9.6 Four final recommendations on the use of antibiotics as a pain suppression medication

Recommendations on the use of antibiotics as a pain suppression medication

1. Antibiotics do reduce pain by reducing local infection and associated swelling, and this will indirectly reduce pain; however, it is illogical to use them long term unless definitive proof of an ongoing infection exists.

2 Some antibiotics do reduce pain directly via their analgesic properties, but this is not a logical way to suppress pain since there are serious consequences to ongoing antibiotic use.
3 Unfortunately, all antibiotics do reduce pain via their powerful placebo effect.
4 The downside consequences to the chronic use of antibiotics in pain control would be increased odds of developing antibiotic resistance of microbes plus adverse drug reactions and frequent gastrointestinal side effects, among others.

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Chapter 10

Using oral medications, infusions, and injections for differential diagnosis of orofacial pain

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10.1 Diagnostic dilemmas in orofacial pain

There are many different reasons for pain in the orofacial region; some of these problems are very difficult to differentiate and pose a challenge for the clinician. For example, when a patient has jaw pain and limited opening, it could be due to an intracapsular disorder (disk derangement) or an extracapsular disorder (trismus). Determining the exact cause of a restricted jaw opening is not always easy and trying to identify the causation with advanced imaging such as computerized tomography (CT) and magnetic resonance imaging (MRI) can be expensive for the patient and may not be covered by health insurance policies. An alternate and faster diagnostic procedure is to inject an anesthetic solution into the painful joint to see if the patient can then open his or her mouth. Using injectable or even oral medications to assist in the diagnosis of jaw locking is one example, but there are other examples of diagnostic dilemmas that can be evaluated with medications. This chapter focuses on how various medications can be used as tests to diagnose orofacial pain problems.

10.1.A Source of pain is not always visible on imaging studies

According to the National Institute of Neurologic Disorders and Stroke (NINDS) website, there is no test or device available that can measure the amount of pain or image the area of pain or locate the pain precisely. Currently, the best aid to diagnosis in chronic pain is the patient's own description of the type, duration, or location of pain.[1] These sentences capture one of the major frustrations that is inherent in being a diagnostician specializing in pain disorders, namely, that pain without an obvious organic pathology is not visible on a radiograph or standard MRI image. Of course functional MRI (fMRI) images can show you what areas of the brain are activated by experimental pain, but these images are not specific to the diagnosis and will not work in chronic pain since there is no prepain baseline to compare against. Because most pain disorders are without an incontrovertible physical examination finding or image-based "gold standard," gathering a careful history is critical to the process. However, once a diagnosis has been formulated, it is logical to have a test of the correctness of this theory. Most of the time, proof-of-concept testing is done with treatment and, for neuropathic pain in particular, with medications.

10.1.B Accuracy of diagnostic tests

An experienced diagnostician knows that diagnostic tests are rarely infallible and this is just as true in the field of orofacial pain as it is for any other area of medicine. The diagnostician, like a good investigative journalist, should insist upon having at least two sources (positive tests) to arrive at a diagnosis. For instance, a positive radiograph showing arthritic change in the temporomandibular joint (TMJ), palpation findings demonstrating capsular pain, plus reduction in pain with an anti-inflammatory drug all lead to the conclusion that arthritis associated inflammation is the pain source. The same process needs to be put forth with medications as diagnostic tests, in that they should be only one piece of information and must be used in combination with available examination, history, and imaging data. For example, it is common to give antibiotics to patients with a toothache (even when the tooth has no obvious signs of infection clinically or radiographically). One conclusion that could be made if the pain decreased as a result of the antibiotic is that the patient has an infection. This conclusion is not always true, however, since it is known that some

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antibiotics may be analgesics.[2,3] See Chapter 9 for more information on antibiotics as analgesics.

10.1.C Effect of inactive substances in differential diagnosis of orofacial pain

Certainly, all clinicians will tell you that certain patients are more responsive to medications than others. In fact, some patients are labeled as placebo-responders,[4] which implies that they respond positively with clinical improvement to an inactive agent. Negative placebo responders are called nocebo-responders,[5] which means they experience adverse effects following the administration of an inactive substance. Such responders pose a problem in using medications for diagnosing pain disorders.

10.1.D Withdrawal of medications as a diagnostic test

There are many situations where taking a patient off a medication might be a valuable diagnostic test. Let us assume a patient presents with a chronic daily headache and is using analgesics multiple times a day to try to suppress the pain. One possibility in their diagnosis is that they have a medication overuse headache (MOH).[6] Withdrawal of the analgesics to improve the pain seems paradoxical, but if the MOH diagnosis is correct, this is proof of the diagnosis.[7] Another scenario where medication withdrawal will confirm the diagnosis is face-and-jaw pain in a patient, caused by a selective serotonin reuptake inhibitor (SSRI) that is causing a dystonic extrapyramidal reaction affecting the jaw muscles.[8]

10.2 Local anesthetic use in orofacial pain

Local anesthetics act to selectively block sodium channels in the nerve fibers and increase the threshold for spontaneous firing of the nerves. Occasionally, nerve blocks are used diagnostically for facial pain. An example is the use of a nerve block to assess chronic orodental pain of possible neuropathic origin. In this situation, if the pain does not diminish as expected after local infiltration of 2% lidocaine in the area, the neuropathic changes are considered to be more central (affecting the second- and third-order neurons). The conclusions made as a result of a failed dental anesthesia is that patients will require systemic (usually anticonvulsant) medications in addition to the topical anesthetics to manage the chronic pain. Whether they are used diagnostically or therapeutically, nerve blocks have an associated risk in that sometimes the nerve can be aggravated by the injection. This was described in a case series of 83 patients (55 women and 28 men) who were referred to a tertiary care center with permanent alterations of the trigeminal nerve (sometimes painful and sometimes paraesthesia) after an inferior alveolar nerve block.[9] Most of these cases involved the lingual nerve (79%) and fewer in the inferior alveolar nerve (21%). They concluded that, while rare, occasionally an inferior alveolar nerve block can result in increased activity of the nerve. It is possible that some of these patients developed neuropathic changes secondary to direct nerve injury during the inferior alveolar block.

10.2.A Auriculotemporal nerve block (temporomandibular joint injection)

The auriculotemporal (AT) nerve is a branch of the mandibular division of the trigeminal nerve that supplies the TMJ and preauricular skin. Sensitization of the AT nerve may result in chronic dull aching or burning pain that is unresolved with routine anti-inflammatory medications. This condition is referred to as AT neuropathy and is often difficult to diagnose. AT nerve blocks are diagnostic blocks that are performed to differentiate between inflammation-mediated pain emanating from the TMJ and neuropathic pain originating from the nerve itself.

This nerve block is simple and easy to learn and perform. The injection setup is shown in Figure 10.1 and includes a 3-mL disposable Luer lock syringe, a 23-gauge needle to withdraw the solutions, a 27-gauge needle to inject the joint, 2% lidocaine without epinephrine, triamcinolone acetonide (40 mg/mL), and alcohol or iodine pads. The triamcinolone acetonide (a corticosteroid) is mixed with lidocaine and used for cases where the pain is suspected to have an inflammatory cause, for example, TMJ arthritis (see Sec. 19.3.B). The injection is performed in the superior joint space of the TMJ

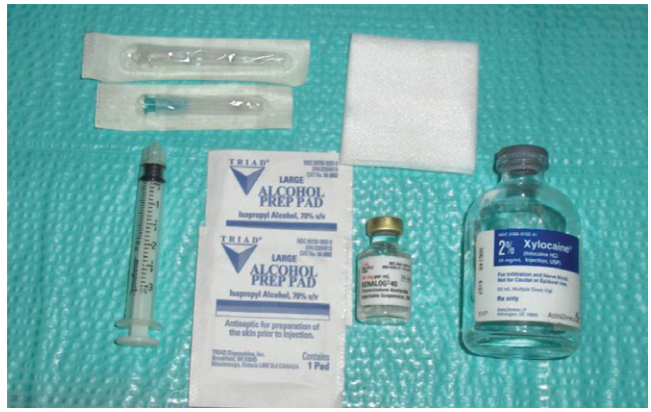

Figure 10.1 Setup for auriculotemporal (AT) nerve block or temporomandibular joint (TMJ) injection.

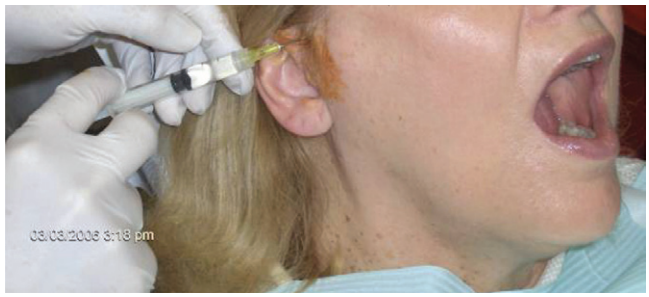

Figure 10.2 Right-sided AT nerve block or TMJ injection using 1.5 cc of 2% lidocaine without epinephrine after preparing preauricular skin with povidone–iodine swab.

after wiping the preauricular skin with iodine or alcohol (Fig. 10.2). An equivocal result following a block is indicative of sensitization and neuropathic changes in the AT nerve. The next step will be to control the pain using 5% topical lidocaine patches, topical lidocaine in pluronic lecithin organogel (PLO), or centrally acting medications such as neurontin or pregabalin.

A recent study evaluated the efficacy of AT nerve blocks on somatosensory function in the TMJ by injecting bupivacaine in 14 healthy volunteers with no history of TMJ disorders.[10] The results of this study showed that AT nerve blocks with local anesthetic caused a significant decrease over time in the pinprick sensitivity—which, however, did not differ significantly from saline (placebo injection in the opposite joint). There was a significant increase in the pressure pain thresholds at 30 minutes and pressure pain tolerance at 30 minutes, 1 hour, and 2 hours after bupivacaine injections compared with saline.

10.2.B Sphenopalatine ganglion block

The blockade of the sphenopalatine ganglion has been used to manage intractable headaches such as cluster headaches and facial pain presenting with autonomic signs such as rhinorrhea, lacrimation and, nasal congestion. The block is more often used as a last resort for managing intractable facial pain than for diagnostic purposes. The sphenopalatine ganglion is the largest peripheral parasympathetic ganglion having multiple connections to general sensory fibers, and the internal carotid plexus without synapses. There are generally three approaches to block this ganglion: (1) transnasal application of topical anesthetic with a cotton-tipped applicator to the nasopharyngeal mucosa posterior to the middle turbinate; (2) transoral approach with a curved dental needle up to the sphenopalatine foramen through the posterior palatine canal; and (3) the lateral approach with a straight needle to the pterygopalatine fossa through the infratemporal fossa.[11] The transnasal application of topical anesthetic is the simplest and the most tolerable technique among the three approaches. However, the diffusion of topical anesthetic to the ganglion is unpredictable and the blockade is not durable with this approach. A new approach of transnasally injecting the sphenopalatine ganglion was described by Yang and Oraee in 2006.[12] The injection was done with triamcinolone 20 mg in 1.5 mL of 0.2% ropivacaine. The technique was reported to be safe and effective for short-term management of intractable cluster headache pain in one patient. Four-percent lidocaine has been used in studies to block the sphenopalatine ganglion for management of myofascial pain of the head and neck or fibromyalgia pain. The blocks were found to be no better than placebo in these cases.[13,14] As a general rule, this block must always be performed by an experienced anesthesiologist or pain specialist.

10.2.C Stellate ganglion block

The cervical sympathetic chain is composed of superior, middle, intermediate, and inferior cervical ganglia. However, in approximately 80% of the population, the inferior cervical ganglion is fused with the first thoracic ganglion, forming the stellate ganglion also known as the cervicothoracic ganglion.[15] Peripheral sympathetic blocks, though popular among pain specialists, are not supported by evidence in the scientific literature. First, the actual success rate of blocking the sympathetic activity with these blocks is not known. Second, no placebo-controlled trials have been published. Third, the mechanism of pain relief when achieved may be local anesthetic activity on peripheral somatic nerve fibers and not sympathetic fibers via local anesthetic systemic concentration or local spillage.[16–18] In fact, patients who have reported transient pain relief with sympathetic block may also report similar degrees of pain relief with intravenous lidocaine infusion and then obtain chronic relief with oral mexiletine (see Sec. 10.5.A). Nevertheless, sympathetically mediated pain (SMP/CRPS type I) of the head, neck, and upper arm can be distinguished from other overlapping pain disorders by performing a stellate ganglion block. Successful block of sympathetic fibers to the head is indicated by the appearance of Horner's syndrome (ptosis, miosis, enophthalmos, anhidrosis of the neck and face) and relief of pain. Therefore, this block must always be performed by an experienced anesthesiologist or pain specialist.[19]

10.2.D Occipital nerve block

The greater and lesser occipital nerves supply most of the posterior scalp and are the source of pain in occipital headaches, occipital neuralgia, and other painful conditions affecting the back of the head.[20] Occipital nerve block is a very safe block that can be performed to distinguish between

occipital neuralgia, occipital headaches, and musculoskeletal pain.

10.2.E Cervical plexus block

Pain originating from the cervical plexus may refer to other sites of the orofacial complex especially to the posterior aspect of the head, and is implicated in the pathogenesis of cervicogenic headaches or C2 neuralgia. A thorough clinical examination of the neck and associated structures along with appropriate imaging to visualize the cervical joints is a must to rule out obvious pathological sources of pain such as lesions and arthritis. The block has been reported to be effective in relieving orofacial pain originating from the cervical region. Significant pain relief was obtained with the cervical plexus block compared with regional anesthesia or trigger-point injections. It has been suggested that the block may be effective in the differential diagnosis of pain originating from deep cervical muscles and nerves.[21]

10.2.F Local anesthetic blocks for trigeminal neuralgia pain

Trigeminal neuralgia pain is often diagnosed clinically by the presence of trigger zones and unique characteristic features of unilateral, episodic, paroxysmal, lancinating pains that typically last from a few seconds to minutes with multiple attacks during the day. In general, the diagnosis can be established with a thorough history. Occasionally, patients may present with pain attacks, preventing the practitioner from obtaining a thorough history or performing an examination. In such cases, diagnostic local anesthetic blocks of the infraorbital nerve (performed intraorally or extraorally) or the inferior alveolar nerve (performed intraorally) provide quick and effective relief.

10.2.G Trigger-point injections using local anesthetics

Myofascial trigger points are well-known sources of referred pain in the orofacial and cervical region. The diagnostic value of trigger-point injections is when they are used to assess whether the trigger point in the muscle is responsible for the patient's more distant pain complaint (referred pain). This assessment can be done in three ways. First, pain can be elicited by manual compression of the trigger point, which will often elicit not only focal pain at the trigger point site, but also distant pain in another area. Second, pain of the trigger point and sometimes at the referred sites can be suppressed briefly following stretching of the involved muscle.[22] Third, trigger-point pain and usually the referred pain can be suppressed with a trigger-point injection. This is done by identifying a trigger point by palpation and then injecting it with 0.5 mL of 0.5% lidocaine without epinephrine. This provides prompt, symptomatic pain relief and helps to stretch the involved muscle.[23]

Trigger-point injections have both a therapeutic and a diagnostic value. This technique uses a small needle (usually 27 gauge), the syringes are Luer-lock disposable plastic syringes (either 1- or 3-mL size). The commonly used anesthetic solutions injected are 0.5% procaine and 0.5% lidocaine. Because procaine has reports of higher allergic reactions, the latter is usually preferred to reduce this risk.[24] In addition to anesthetics, sometimes botulinum toxin A is used to treat resistant trigger points associated with taut bands. Most physicians and dentists use the anesthetic to provide some transient pain relief associated with immediate postinjection soreness and, more important, to ensure that any referred pain coming from a trigger point is suppressed as a result of the injection. It is unlikely that solutions stronger than 0.5% are more effective when injecting trigger points, and higher concentrations of these local anesthetic solutions increase the risk of myotoxicity.[25] Of the anesthetic solutions, lidocaine is clearly more myotoxic than procaine. Epinephrine is never used with these injections as it is far more myotoxic than the anesthetic itself.[26]

Trigger-point injections have been described in the literature for more than 50 years.[27] Limited data beyond open-label studies exists on the efficacy of this method of treatment. One study examined the relative efficacy of trigger-point injections within the context of a randomized double-blind protocol.[28] The subjects were 63 low back pain patients and all had normal lumbosacral radiographs. They were assigned to one of four treatment procedures: (1) lidocaine, (2) lidocaine combined with a steroid, (3) acupuncture, and (4) vapocoolant spray with acupressure. The results indicated that an injection (with or without medication) was effective and that the injected substance was not critical to the effect. A systematic review of the myofascial trigger point literature concluded that direct needling of the trigger point was an effective treatment, but whether the effect is related to changes induced by needling the trigger point or nonspecific suppression of pain is not clear.[29]

10.2.H Topical anesthetic challenge test in neuropathic pain diagnosis

It is not uncommon to have a situation where a root canal is completed on a tooth and the patient still has pain. The typical diagnostic dilemma is to distinguish between a residual dental pulpal–periapical infection causing tooth pain and a sensitized alveolar nerve causing tooth pain. The latter is called a chronic trigeminal neuropathy or atypical odontalgia (AO). This condition is different from trigeminal neuralgia, which presents typically as episodic, sharp, shooting pain that lasts for a few seconds and occurs several times a

day with pain-free intervals between attacks. Sometimes a peripheral nerve neuropathy will induce secondary central sensitization as well. This means that neural alterations extend into the trigeminal nucleus at the level of the pons, as well as in the third-order neuron and above.[30–35] In these cases topical anesthetics may help establish that the pain is a neuropathic disorder. The best approach is to perform a local anesthetic challenge test (Table 10.1). This involves isolating the area, rating the pain, and then applying either a topical anesthetic or a nonanesthetic placebo to the painful site.

The patient rates the pain change using the visual analog scale (VAS) (Figs. 10.3, 10.4, and 10.5A–C). Complete resolution of the pain with topical anesthetic (e.g., benzocaine 20%) indicates neuropathic pain with peripheral sensitization. If such is the case, a custom-fabricated vacuum-formed tissue stent that covers the painful area can be made to hold the topical benzocaine in orabase (Orabase® or Orabase-B®).[36,37] The purpose of the stent is to hold the medication at the painful site.[38–41]

If the pain does not resolve with topical anesthetic, this lowers the chances of sustained application being therapeutic and even reversing the neuropathic changes. In these cases the next step is to try blocking the pain by performing a local infiltration of 2% lidocaine in the area (Fig. 10.5D).

Table 10.1 Anesthetic test protocol of USC Orofacial Pain and Oral Medicine Clinic

1	Use cheek retractor and cotton rolls to isolate the painful area.
2	Dab the painful area dry with a 2 × 2 gauze.
3	Record the patient's level of pain on a VAS scale of 0–10.
4	Apply topical benzocaine 20% to the painful area.
5	Every 3 minutes record the patient's pain level on the VAS scale.
6	If there is incomplete pain relief, infiltrate the painful site with 2% lidocaine.
7	Again, record the pain level on the VAS scale after 3 minutes.

VAS, visual analog scale.

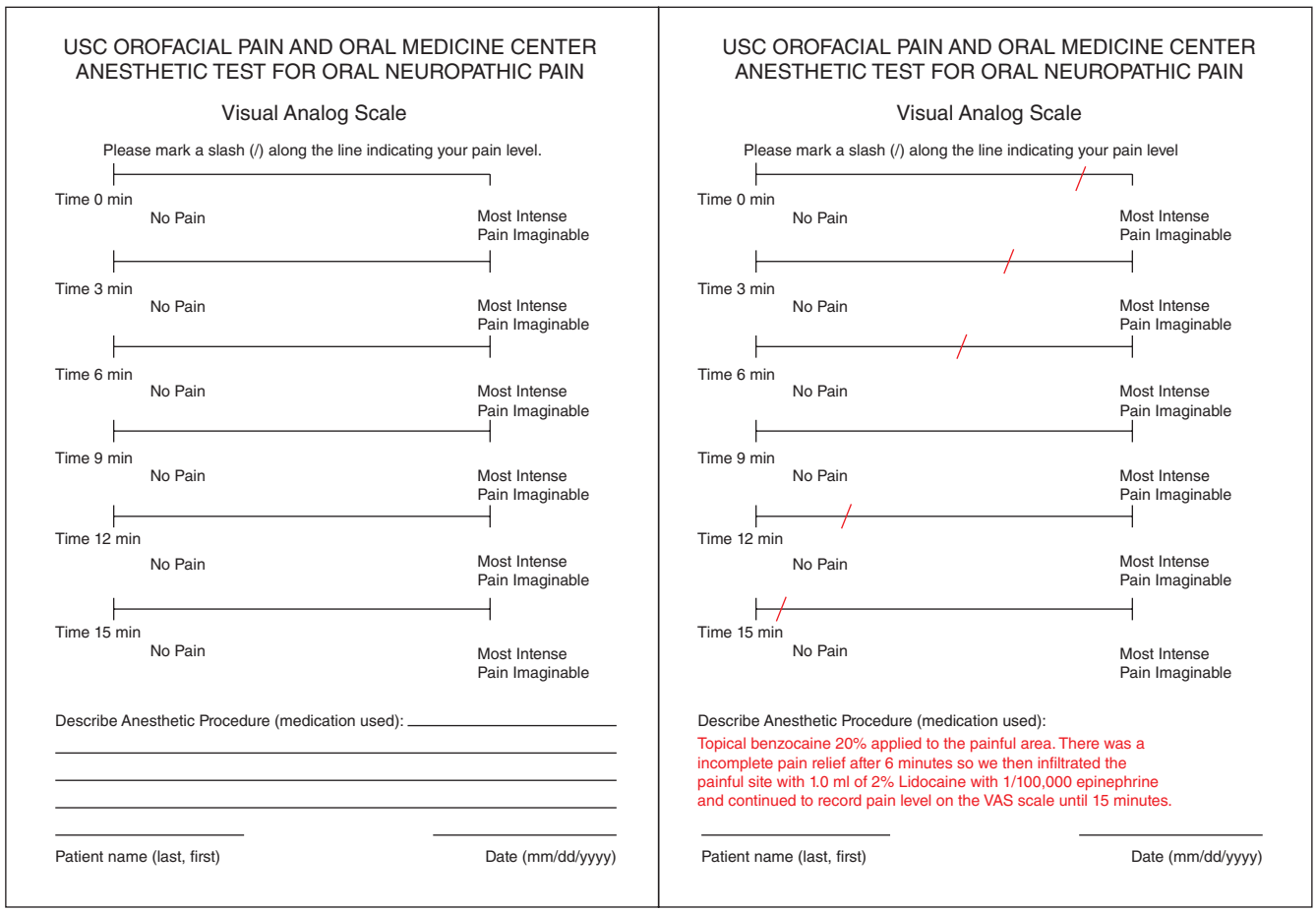

Figure 10.3 Visual analog scale for anesthetic test. The left side of the figure shows a blank form and the right side shows one filled out.

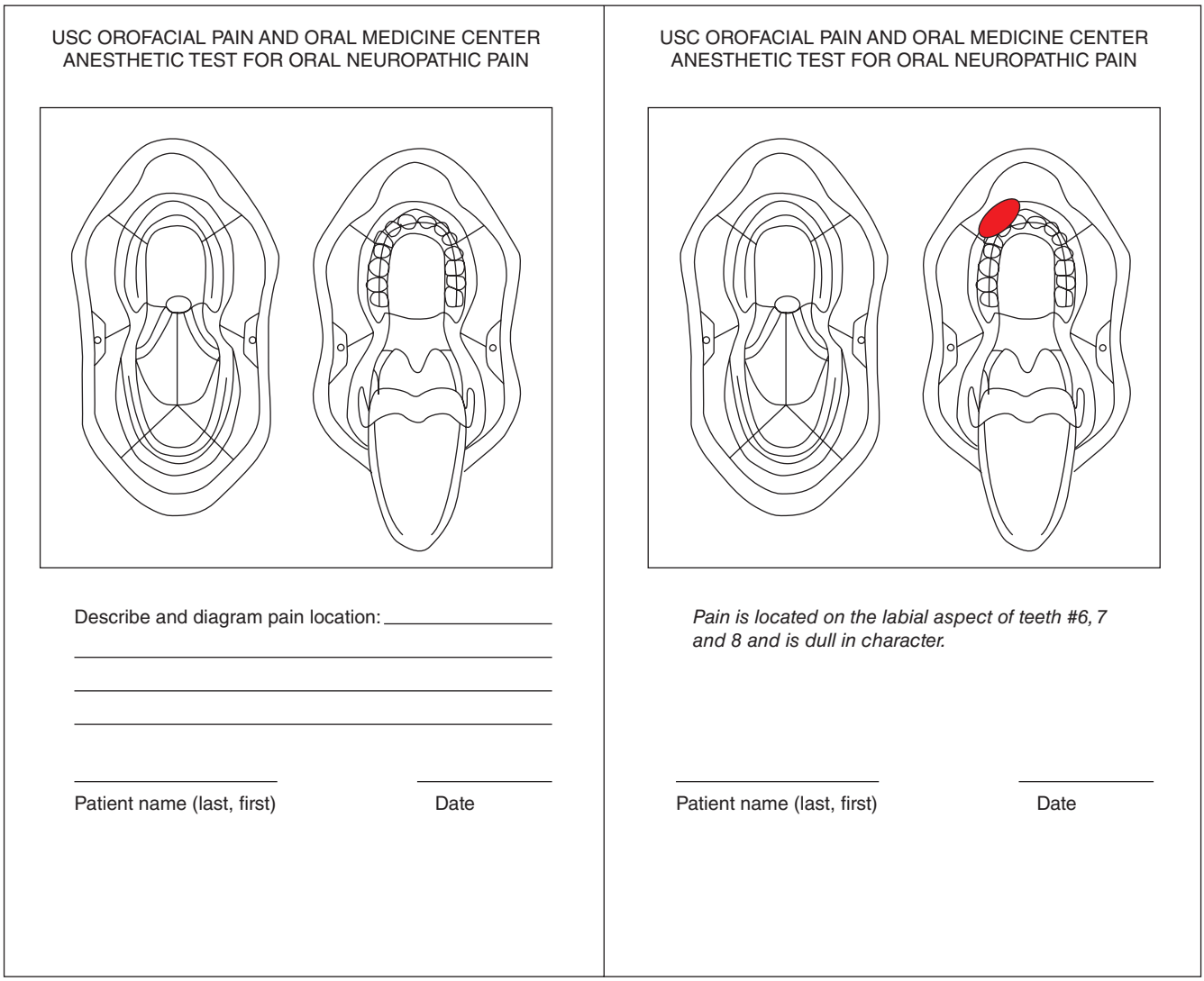

Figure 10.4 Diagram for anesthetic test. The left side of the figure shows a blank form and the right side shows one filled out.

As mentioned earlier, the neural changes are considered more central when anesthetics fail and systemic medications are considered for management. A double-blind controlled study assessed the effect of injecting lidocaine versus saline intraorally at AO sites (trigeminal neuropathy). The VAS pain relief was significantly greater at 15–120 minutes following the lidocaine injections compared with the placebo injections. In conclusion, trigeminal neuropathy patients experienced significant, but not complete, pain relief from administration of local anesthetics compared with placebo. The findings indicate that the spontaneous pain in trigeminal neuropathy patients only to some extent is dependent on peripheral afferent inputs and that sensitization of higher order neurons may be involved in the pathophysiology of neuropathic pain.

Another alternative medication that has been tried as a diagnostic test for patients with AO is intraoral 5% capsaicin as a topical application. Increased VAS pain scores were reported in patients with AO compared with controls.[42] This test is relatively new and needs further validation in terms of sensitivity and specificity.

10.3 Corticosteroids and anti-inflammatory medications in orofacial pain

Nonsteroidal anti-inflammatory drugs (NSAIDs) exert their anti-inflammatory and analgesic actions by inhibiting cyclooxygenase enzymes (COX-1 and COX-2) and thereby

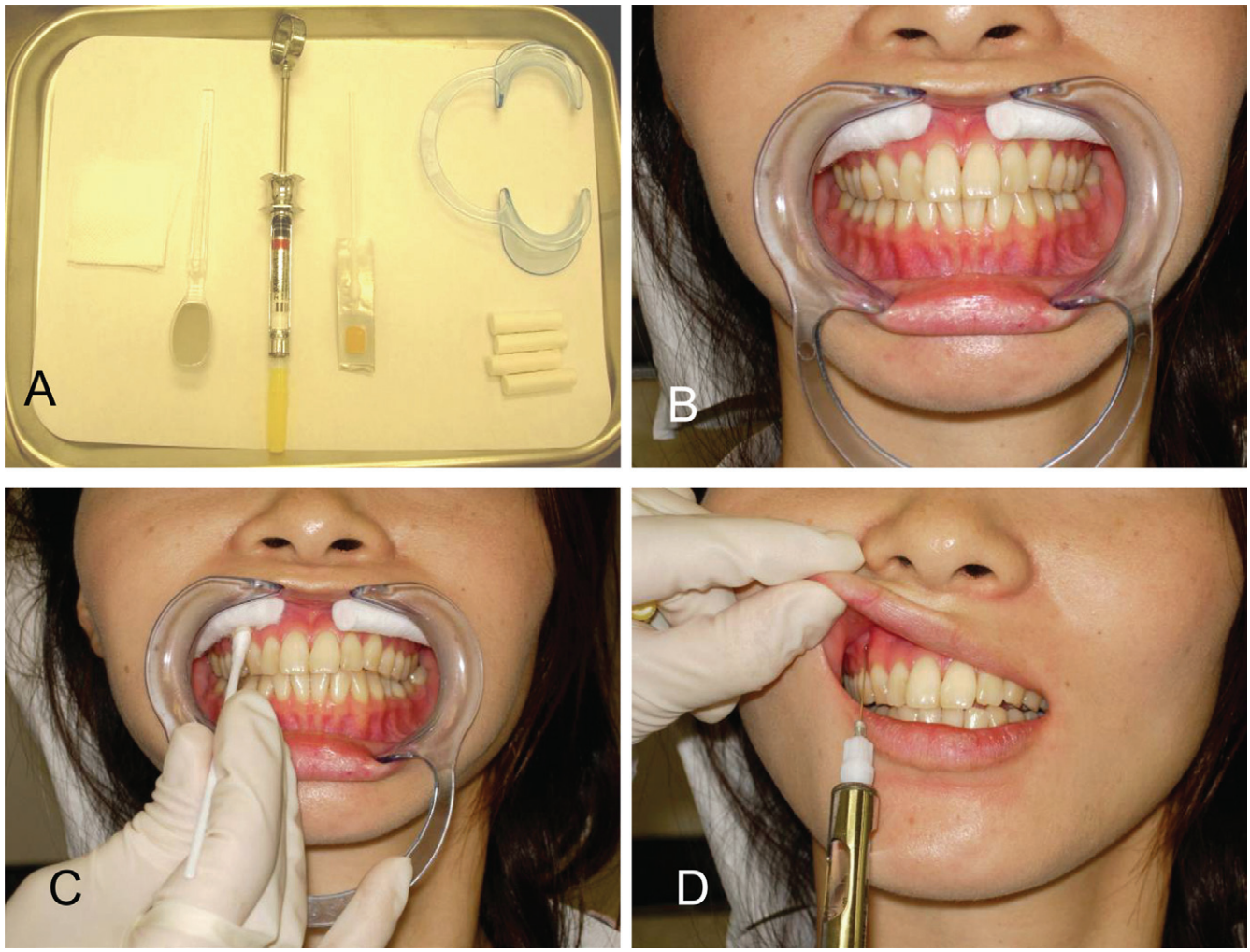

Figure 10.5 Anesthetic test. (A) Armamentarium containing 2 × 2 gauze, mouth mirror, 2% lidocaine syringe, 20% topical benzocaine swab, cheek retractor, and cotton rolls. (B) Isolation using cotton rolls and cheek retractor. (C) Application of 20% topical benzocaine. (D) Infiltration anesthesia using 2% lidocaine without epinephrine.

reducing prostaglandin synthesis.[43] The orofacial pain conditions for which NSAIDs are often prescribed initially are arthralgia, capsulitis, arthritis, myofascial pain, and a locked TMJ. The commonly used NSAIDs are ibuprofen (Motrin®, Advil®) and nabumetone (Relafen®). The recommended dosage for ibuprofen is 600 mg four times a day or 800 mg three times a day, orally, not to exceed 3200 mg/day. The recommended dosage for Relafen is 500 or 750 mg orally two or three times a day, and may increase up to 1500–2000 mg/day. In suspected cases of tension-type headaches NSAIDs such as ibuprofen (600–2400 mg) or naproxen sodium (220 mg to a maximum of 660 mg/day) may be used as the first-line treatment of choice. In addition, triamcinolone acetonide (Kenalog-40®) is a commonly used corticosteroid medication for intra-articular injection.[44] The primary indication for this procedure is substantial tenderness of the joint capsule.

10.3.A Topical NSAIDs as a diagnostic test for inflammation

NSAIDs are effective for both acute and chronic pain conditions and are associated with a number-needed-to-treat (NNT) of between 3 and 5 for musculoskeletal and joint pain problems.[45] Topical NSAIDs offer the advantage of reduced gastrointestinal side effects compared with their systemic counterparts, and a decreased plasma concentration of the drug with high concentrations at the site of application.[46,47] Among the available NSAIDs, the 10–20% ketoprofen mixed into a carrier vehicle like pluronic lecithin organogel

(PLO) has been extensively used as an effective topical NSAID owing to favorable chemical properties such as lipophilicity, rapid absorption, and therapeutic response of the PLO vehicle.[48] Topical ketoprofen 20% in PLO gel is indicated for patients with long-standing capsulitis or arthritis of the TMJ where systemic NSAIDs are contraindicated due to adverse gastrointestinal side effects. NSAIDs are used to treat mild to moderate pain of acute or chronic nature caused by trauma, surgery, or inflammatory conditions. Recently, a topical ketoprofen patch has been developed and it may prove more convenient to apply on the skin than the gel in terms of better control of dosage and ease of use.[49,50]

Like other joints the TMJ nerves (i.e., the auriculotemporal nerve) are susceptible to neuropathic changes. If this is determined to be so, a typical method of treating a sensitized nerve is to use topical sodium channel blocking agent such as lidocaine. In these situations, a 5% lidocaine patch can be applied to the skin over the painful joint or lidocaine can be applied topically in a skin-penetrating cream such as PLO. The lidocaine patch 5% (Lidoderm®) has been approved by the FDA for use in patients with postherpetic neuralgia (PHN). The systemic absorption of lidocaine from the patch was found to be minimal in healthy adults when four patches were applied for up to 24 hours/day, and lidocaine absorption was even lower among PHN patients than healthy adults at the currently recommended dose. Most adverse events have been reported at patch application sites and no clinically significant systemic adverse effects have been reported, including when used long term or in an elderly population. In patients with PHN, the lidocaine patch 5% has demonstrated relief of pain and tactile allodynia with a minimal risk of systemic adverse effects or drug–drug interactions.[51] Because of its proven efficacy and safety profile, the lidocaine patch 5% has been recommended as a first-line therapy for the treatment of the neuropathic pain of PHN.

10.3.B Injectable steroids as a diagnostic test for inflammation

Intra-articular corticosteroids are occasionally used as a diagnostic test to assess whether the joint palpation pain is inflammatory in character (Fig. 10.2). Partial or incomplete pain relief may indicate a central neuropathy of the AT nerve. While a long-lasting suppression of joint pain after an intra-articular injection of a corticosteroid is thought to indicate inflammatory pain, this may not be a fully valid assumption. One study recently examined the effect of corticosteroids on neuropathic pain.[52] Specifically the corticosteroids act by suppression of ectopic neural discharges from the injured nerve fibers. When the joint pain is chronic in nature and is not associated with arthritis and is not relieved with the NSAIDs, then one should suspect an underlying neuropathic pain process. In this clinical situation, one can also try a local anesthetic injection into the joint space and pericapsular region. If the joint pain is not relieved with the anesthetic and the corticosteroid did not provide long-lasting relief, then it signifies that the patient potentially has a complex peripheral and central neuropathic pain condition affecting the region. Usually a corticosteroid injection in a small joint such as the TMJ is not performed more than 10 times total and no more often than once in 3 months (maximum of 4 injections a year). It would not be the initial choice of therapy either since it would be more prudent to try oral or topical NSAIDs as first-line medications.

10.4 Limited opening testing

Certainly when a patient presents with acute-onset limited opening, one consideration is whether the limitation is due to involuntary active contraction (e.g., trismus) or disk displacement without reduction in the TMJ. Vapocoolant sprays and muscle relaxants are potential diagnostic assessment tools for this differentiation.

10.4.A Skeletal muscle relaxant use in orofacial pain

There are numerous drugs that are used for relief of chronic regional musculoskeletal pain, including carisoprodol, chlorzoxazone, cyclobenzaprine hydrochloride, metaxalone, methocarbamol, and orphenadrine citrate.[53] These medications are now generally used only for acute clinically proven muscle spasm and not for long-term use. This is because the evidence shows that these muscle relaxants are not beneficial for individuals with chronic muscle pain affecting the neck and lower back.[54,55] For example, when acute muscle spasm is suspected, cyclobenzaprine hydrochloride (5–10 mg twice a day) is often administered for short periods of time to see if the jaw pain and mobility increase. Cyclobenzaprine is structurally similar to tricyclic antidepressants and therefore demonstrates similar anticholinergic effects.[56] One study compared the efficacy of cyclobenzaprine hydrochloride at 2.5, 5, and 10 mg three times a day over a 1-week period in patients with acute muscle spasm of the lumbar and cervical region.[57] In terms of onset of relief, patients who received cyclobenzaprine 5 mg reported experiencing discernable relief more rapidly than those receiving placebo, but not as rapidly as those receiving cyclobenzaprine 10 mg. Somnolence was the most common adverse effect, followed by dry mouth. The incidence of somnolence increased at

higher cyclobenzaprine doses. In those cases where the diagnostician is unsure if a muscle spasm is present, a prescription of a muscle relaxant is given to see its effect.

10.4.B Using vapocoolant sprays for diagnostic purposes

Vapocoolant spray followed by stretch is a widely used and effective noninvasive modality for the management of myofascial trigger points. It involves passively stretching the target muscle and simultaneously applying a vapocoolant spray to the skin over the taut muscle band. The sudden drop in skin temperature is thought to produce temporary blocking of the spinal stretch reflex and the sensation of pain at a higher center. The decreased pain sensation allows the muscle to be passively stretched toward the normal length, which then helps to inactivate trigger points, relieve muscle spasm, and reduce referred pain. Currently, a new spray has been introduced to replace the fluorimethane spray used in the past.[58] This spray contains pentafluoropropane and tetrafluoroethane (Gebauer's Spray and Stretch®). which are nonflammable and environmentally friendly. In patients exhibiting short-duration limited mouth opening, acute muscle spasm may be the underlying cause. When muscle spasm is suspected, the Spray and Stretch is used diagnostically to confirm that the muscles can be stretched to full length and a disk derangement or other extracapsular restriction is not present.

10.4.C Temporomandibular joint injection

As mentioned earlier in Sections 10.2.A and 10.3.B, the AT nerve block or TMJ injection is a very safe and effective means to anesthetize the TMJ. This is done for the patient with limited mouth opening with a hard end feel wherein the disk serves as a source of mechanical obstruction to joint translation. In this scenario, skeletal muscle relaxants and vapocoolant sprays provide little or no benefit. Upon anesthetizing the TMJ, manual mobilization of the jaw is done by standing behind the patient and supporting the patient's head against the operator's chest and gently pulling the jaw downward and opposite to the side of locking.

10.5 Comparative intravenous infusions for diagnostic–predictive purposes

Over the years several authors have looked at the concept of using medications to predict which treatment would be best and/or whether such pharmacologic tests could help distinguish better the diagnosis. Intravenous (IV) infusion tests have been used to predict subsequent response to oral analgesics.[59] This is an increasingly popular method used to enhance medical care and conserve resources. Because no infusion test is completely accurate, the potential benefits of these tests must be weighed against the frustration and waste in resources encountered with false positives, and the failure to use a potentially beneficial treatment with false negatives.

10.5.A Lidocaine challenge test

One of the earliest pharmacologically based "diagnostic tests" used in decision making for pain treatment was the IV lidocaine infusion challenge test. The main purpose of this test was to assess whether an oral sodium channel blocking agent called mexilitine would be a good treatment or not for a particular patient. A recent meta-analysis of nine controlled clinical trials on the effect of oral mexiletine for neuropathic pain reported that mexiletine (median dose, 600 mg daily) was superior to placebo and equal to morphine, gabapentin, amitriptyline, and amantadine.[60] The common adverse effects were drowsiness, fatigue, nausea, and dizziness, making mexiletine a difficult drug to tolerate. It is also proarrhythmic and known to cause hepatic injury; therefore it is common for pain specialists to perform a lidocaine infusion to see if it produces a substantial reduction in pain before using oral mexiletine. One study examined if the lidocaine challenge infusion would predict response to oral mexiletine in nine subjects with chronic neuropathic pain.[61] They used a lidocaine infusion and followed this with a 4-week protocol using oral mexiletine. The results of the study showed that response to oral mexiletine was significantly correlated with the average response to the lidocaine infusion challenge. Mexiletine dose and blood levels were not correlated with pain relief.

Another study examined the efficacy of lidocaine infusion as a predictor of the response to oral drug therapy (antidepressants, channel blockers, and anticonvulsants) in 183 inpatients diagnosed with central and peripheral neuropathic pain.[62] They administered intravenous lidocaine at a dose of 4 mg/kg and, based on a VAS rating taken before and at every 5 minutes during the infusion, patients were categorized as lidocaine responders ($n = 85$) or nonresponders ($n = 71$). All patients were then put on pain medications as their symptoms dictated (irrespective of lidocaine drip test results). A VAS pain rating was taken one month after the drug therapy and it was reported that 90% of the lidocaine responders reported substantial pain reduction with the oral drug therapy. In contrast, only 15% of the lidocaine nonresponders had similar pain relief. They concluded that

intravenous lidocaine was a very good predictor of response to adjuvant analgesics in neuropathic pain patients. Therapeutically, lidocaine infusions should generally be restricted to patients with neuropathic pain who are unable to take oral medication.[63] Interestingly, advanced age and increased pain have been shown to be predictors for positive response to a lidocaine infusion test.[64] A systematic review showed that lidocaine and oral analogs were safe drugs in controlled clinical trials for neuropathic pain, were better than placebo, and were as effective as other analgesics.[65]

10.5.B Intravenous N-methyl-D-aspartate–blocking agents for diagnosis

Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist that is available for clinical use as a general anesthetic. It also exhibits multiple pharmacological actions including NMDA receptor block, Na^{2+} and Ca^{2+} channel block, block of cholinergic receptors, inhibition of biogenic amine reuptake, and interactions with opioid receptors. The chronic use of intravenous ketamine is usually limited by its psychomimetic side effects. One recent study examined if the effect of an oral NMDA receptor antagonist (dextromethorphan) as a pain relief agent in cases of chronic pain could be predicted by an intravenous infusion of another NMDA antagonist (ketamine).[66] They gave 25 patients a small dose (0.1 mg/kg) of IV ketamine before putting them on oral dextromethorphan treatment regimen. Using a criterion of two-thirds reduction in pain, they found that the ketamine test response had a 90% positive predictive value and an 80% negative predictive value with the overall observed agreement being 84%. These data suggest that the IV ketamine test was useful as a diagnostic test for response to oral dextromethorphan. Unfortunately, this medication is known to produce substantial side effects and is poorly tolerated in many patients. Moreover, it was found to be ineffective in attenuating pain in 10 patients with atypical odontalgia.[67]

10.5.C Morphine infusion challenge test

Intravenous opioids have also been used as a diagnostic predictor of treatment response. One recent study examined the analgesic responses to intravenous administration of morphine, lidocaine, and ketamine in chronic neck pain patients.[68] The study used 33 patients with diagnosed whiplash-associated neck pain who were given (in a randomized, double-blind, crossover design) intravenous administration of morphine (0.3 mg/kg), lidocaine (5 mg/kg), ketamine (0.3 mg/kg), or placebo (isotonic saline). Pain ratings were made before, during, and after the infusions and patients were classified as nonresponders, placebo-responders, or responders to the drugs. The authors noted that the groups did not show any clear relationships between pretest pain duration and the test results, but nevertheless they speculated that these subgroups might be useful for deciding on the therapeutic approach.

10.6 Special-case medications

There are three special-case medications that have a specific diagnostic value in the differential diagnosis of orofacial pain.

10.6.A Triptans as a diagnostic test

Triptans that are selective for 5-HT1B and 5-HT1D receptor subtypes reduce both sensory activation in the periphery and nociceptive transmission in the brainstem trigeminal nucleus, where they diminish central sensitization. Triptans also induce cerebrovascular vasoconstriction, which counteracts vasodilation believed to be involved in the pathophysiology of migraine. Sumatriptan is the most commonly used drug of this class to treat migraine; other drugs are zolmitriptan, naratriptan, and rizatriptan. When a patient responds with full pain relief to the use of a sumatriptan nasal spray (5–20 mg per nostril) or sumatriptan tablet (25 mg) this is considered confirmatory evidence of a migrainous pain disorder. The nasal spray has a more rapid onset of action than the tablet. Of course, there are dangers in relying too much on a medication response to make the diagnosis. In particular with sumatriptan, there have been few reported cases of patients with headaches secondary to subarachnoid hemorrhage (SAH) that responded well to intranasal or subcutaneous sumatriptan.[69,70] An antinociceptive effect of sumatriptan can be observed in SAH patients in good clinical condition, which suggests a specific craniovascular antinociceptive action. This may lead to misdiagnosis as migraine and delayed appropriate diagnosis and treatment and in worst cases death.[71] Therefore, it is highly recommended that patients with sudden-onset headache pains have brain MRIs to rule out intracranial pathology as the source of pain.

10.6.B Carabamazepine as a diagnostic test

Carbamazepine is an anticonvulsant that probably acts by a combination of GABA inhibition, neuronal cell membrane stabilization, sodium channel blocking, and NMDA receptor antagonism.[72] Trigeminal or glossopharyngeal neuralgias typically present with an acute episodic lancinating pain that lasts for a few seconds to minutes. Carbamazepine (Tegretol®) is the drug of choice for treatment of trigeminal neuralgia; when a patient has the correct mix of clinical

symptoms and also responds completely to carbamazepine, this response is confirmatory proof of the diagnosis. Most of the time, the clinical symptoms are most important in making the diagnosis but when a patient has an atypical form of trigeminal neuralgia or several co-morbid symptoms that are confusing the diagnosis, carbamazepine (200–400 mg twice a day to a maximum of 600 mg twice a day) could be used to confirm the diagnosis.[73]

10.6.C Indomethacin as a diagnostic test

A group of headache disorders that are uniquely responsive to the nonsterioidal anti-inflammatory medication indomethacin are classified by the International Headache Society as indomethacin-responsive headaches.[74] These unique headaches are primary (no identifiable organic pathologic cause) and are characterized by a prompt and often complete response to indomethacin. These indomethacin-responsive headaches fall into categories: (1) a select group of trigeminal–autonomic cephalalgias such as hemicrania continua (HC) and chronic paroxysmal hemicrania (CPH), (2) Valsalva-induced headaches, and (3) primary stabbing headache ("ice-pick" headache or "jabs-and-jolts" syndrome). These heachaches can present as orofacial pain and the practitioner must be careful not to overlook this diagnosis, especially since it can be diagnosed easily by simply prescribing a short trial of indomethacin or by performing the "indotest".[75] The indotest is a simple test that involves intramuscular administration of 50 mg indomethacin; a positive response helps establish a diagnosis of an indomethacin-responsive headache. In patients with HC, the time between indotest and complete pain relief was 73 ± 66 minutes. The pain-free period after indotest was around 13 hours (i.e., 13 ± 8 hours after 50 mg).[76] Unfortunately, the intramuscular form of indomethacin is not available in the United States. The other alternative test is to administer indomethacin 25 mg three times a day and should be increased to 50 mg three times a day if there is no response or only partial benefit.

10.7 Recommendations on the use of medications as diagnostic tests

Recommendations on the use of medications as diagnostic tests

1. Medications and therapeutic modalities can be used as diagnostic tests for the differential diagnosis of various orofacial pain disorders.
2. The prudent practitioner should use these tests only after obtaining a thorough history and performing a physical exam.
3. A clear understanding of the various indications and outcomes for these diagnostic tests is important in achieving an accurate diagnosis.

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Chapter 11

Interventional therapy and injected agents for orofacial pain and spasm (including botulinum toxin)

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11.1 Needle- and injection-based interventional treatments

A variety of needle-based and injection-based interventional therapies exist for chronic pain and this chapter examines the evidence for these therapies. The chapter is divided into two main parts. The first part discusses various needle- and injection-based therapies (e.g., acupuncture, local anesthetic, cryotherapy, phenol, glycerol, and dextrose solutions) that are used for orofacial pain. Corticosteroid injections are discussed in the chapter on arthritis pain (Chapter 18). The second part of this chapter discusses botulinum toxin (BoNT [i.e., botulinum neurotoxin]) injections, including some background on BoNT as a medicinal therapy, and how it is used in both spasm control and pain control.

11.1.A Acupuncture

Acupuncture encompasses a range of procedures, including manual needling, electrical acupuncture, moxibustion, acupressure, heat, and laser stimulation of acupuncture points. Using a Chinese medical philosophy that disease occurs when there is a disruption of normal energy flow called *Qi,* over 2000 acupuncture points arranged on "meridians" have been mapped representing channels of energy flow. The stimulation of these points corrects the imbalances of *Qi.* While the history of acupuncture is quite ancient, modern science has only evaluated its efficacy within the past two decades. In 1990 a meta-analysis evaluated the efficacy of acupuncture as a treatment of chronic pain. The authors concluded that acupuncture as a therapy for chronic pain is, at best, doubtful.[1] In 1997 a National Institutes of Health (NIH) consensus conference examined the literature and offered a statement on the current evidence for using acupuncture.[2] This prestigious body concluded that "Although there have been many studies of its potential usefulness, many of these studies provide equivocal results because of design, sample size, and other factors." It also concluded that acupuncture analgesia has been demonstrated in controlled laboratory studies to produce greater analgesia than appropriate placebos.[3] The mechanism of acupuncture has been hypothesized as counterirritation analgesia and is essentially a brainstem mechanism in which a brief, intense stimulation of afferent nerve fibers induces a brainstem inhibitory control structure to modulate pain response. This response activates both opioid and nonopioid systems. Unfortunately, the NIH conference did not comment on the efficacy of acupuncture for treating chronic pain disorders.[4]

In 1999 and 2000, there were three systematic reviews of the literature published that assessed the efficacy of acupuncture (primarily manual needling) on chronic pain. Each review dealt with a different disease group (fibromyalgia, chronic pain of all types, and low back pain) and each reached a different conclusion. The first review focused on fibromyalgia but it was not a Cochrane Library–based review.[5] It concluded that acupuncture was better than sham-acupuncture. The second review focused on acupuncture for chronic pain (of all types) and was also not Cochrane Library based.[6] It concluded that the available studies were not of sufficient methodological quality to offer an endorsement. The third review focused on acupuncture for management of acute and chronic low back pain and it was a Cochrane Library review.[7] It examined 11 clinical trials but stated that only two were of sufficiently high quality. It also concluded that current evidence was not of sufficient methodological quality to offer an endorsement.

With regard to orofacial pain, in 2007 an article described the short-term effect of acupuncture on myofascial pain patients after clenching.[8] Visual analog scales (VAS) were

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used to rate the pain in 15 chronic myofascial pain patients using a single-blind, randomized, controlled, clinical trial with an independent observer. Subjects were randomly assigned into two groups (acupuncture [$n = 9$] and sham-acupuncture [$n = 6$]). Acupuncture or sham-acupuncture was administered at the Hegu Large Intestine 4 acupoint and facial–jaw pain was then induced or exacerbated by having subjects clench their teeth continuously for 2 minutes. An algometer invoked a mechanical pain stimulus to the jaw muscles, and the subject rated his or her pain level using a VAS. Pain tolerance in the masticatory muscles increased significantly more with acupuncture than sham-acupuncture. An additional study in 2007 examined the effect of acupuncture-like electrical stimulation on chronic tension-type headache using a randomized, double-blinded, placebo-controlled trial in 38 chronic tension-type headache patients.[9] These patients were randomized into a treatment group and a placebo group. Pain duration and pain intensity were recorded on a 0–10 cm VAS, and the number of headache attacks and use of medication were recorded in a 2-week diary. The treatment was a surface electrode attached to an electrical stimulator or a sham stimulator and they were instructed to use the device at home. Six acupoints were used in the treatment (bilateral EX-HN5, GB 20, LI 4) and treatment was to be applied for 3 minutes twice a day. Data was collected 2 weeks before treatment, at 2- and 4-week points during treatment, and at 2, 4, and 6 weeks after treatment. Although both pain duration and pain intensity decreased during treatment there were no significant group differences. The only group difference was for a decrease in analgesic use in the acupuncture group, but not in the sham-acupuncture group.

To summarize, no definitive conclusions about acupuncture for chronic orofacial pain can be made. The lack of quality data combined with recent studies of better quality has only suggested short-term and minimal effects from acupuncture overall. Until additional scientifically valid studies are published, acupuncture as a treatment for chronic orofacial pain may provide, at best, transient pain relief. However, this may be an acceptable clinical strategy for some chronic pain sufferers and the treatment is generally a low-risk procedure.

11.1.B Trigger-point injections

Injection of a local anesthetic is a common treatment for myofascial trigger points; more recently BoNT has been used, which is discussed later in this chapter. The local anesthetic may allow better stretching of the taut band in which the trigger point resides, and it may desensitize the trigger point.[10] Trigger-point pathogenesis is covered in the chapter on myogenous disease (see Chapter 16). Unfortunately, not a great deal of high quality evidence exists on the efficacy of trigger-point injections versus a control (sham injections) or comparison therapy (e.g., acupuncture) for myofascial pain.

In 1981 a controlled randomized double-blind crossover clinical trial examined the injection of bupivacaine 0.5%, etidocaine 1%, or saline into trigger points in 15 patients with myofascial pain.[11] Outcome measures were based on the patient's subjective pain response to these injections 15 minutes, 24 hours, and 7 days after treatment. The authors concluded that trigger-point injections with bupivacaine and etidocaine were generally preferred over saline. In 1989 a prospective randomized, double-blind study evaluated 63 subjects with low back pain treated with one of four treatments (0.5% lidocaine, 0.5% lidocaine combined with a steroid, acupuncture, and vapocoolant spray with acupressure).[12] No significant difference was found between the different methods of treatment, and the authors concluded that injection of lidocaine is not the critical factor, since direct mechanical stimulus to the trigger point seems to give an equal effect.

In 2001 a review article examining the previous studies and others concluded that trigger-point injections using anesthetic solutions were no better than injecting sterile saline or dry needling alone.[13] However, this finding does not mean that trigger points are placebo therapy and it might be better to conceptualize them as acupuncture-like therapy, namely, a treatment that induces a temporary pain suppression effect at best. This point of view is supported by a 1988 study that investigated the use of intravenous naloxone (an opioid receptor antagonist) given after trigger-point injection therapy.[14] The double-blind, crossover study included 10 patients with myofascial trigger point pain; each patient received an injection of 0.25% bupivacaine, which generally decreased their pain and increased range of motion. Following these injections, patients received either an intravenous infusion of naloxone (10 mg) or saline in a crossover design. All improvements afforded by the trigger-point injection therapy were significantly reversed with intravenous naloxone but not so with intravenous placebo. These results point to an endogenous opioid system as a mediator for the decreased pain and improved physical findings following the anesthetic injections.

More recently several additional experimental studies on trigger points and one new meta-analysis have been published. In 2005 a single-blind study compared 0.5% lidocaine injection, 10–20 units of botulinum toxin type A (BoNT/A [also BoNT-A]), and dry needling of trigger points in 29 patients (23 females; 6 males) with myofascial pain using 87 individual trigger points in the cervical and/or periscapular regions.[15] Subjects were randomly assigned to one of the three treatment methods and cervical range of

motion, trigger-point pain pressure threshold (PPT), pain scores (PS), and VAS for pain, fatigue, and work disability were evaluated at entry and after 4 weeks. All treatments were followed by daily self-stretching of the muscle groups involved. The authors reported that PPT and PS significantly improved in all three groups but in the lidocaine-treated group, PPT values were significantly higher than in the dry needle group. Pain scores were also significantly lower for the lidocaine-treated group than in both the BoNT/A and dry needle groups. Finally, VAS pain scores significantly decreased in the both the lidocaine-treated group and BoNT/A-treated groups but not in the dry needle group. The authors concluded that lidocaine injections were more practical and rapid, and less expensive than BoNT/A treatment and both were better than dry needling. In 2007 a study reported on the efficacy of intramuscular and nerve root stimulation versus 0.5% lidocaine injection to trapezius muscle trigger points in 43 myofascial pain patients.[16] The subjects were divided into two groups and treatment was rendered on days 0, 7, and 14. The results shows that intramuscular stimulation was more effective than trigger points, using pain scale scores at all visits. Another 2007 study compared acupuncture needling versus 0.5% lidocaine injection in upper trapezius muscle trigger points in 39 elderly myofascial pain patients.[17] The subjects were divided into two groups and all received treatment at 0, 7, and 14 days and outcomes were assessed at 28 days. Both groups improved, but there was no significant difference in reduction of pain between the two groups. In 2008, the effectiveness of injection therapy (e.g., corticosteroids or anesthetics) for low back pain was examined in a recent meta-analysis. The patients on which these injections were used all had subacute or chronic low back pain.[18] The study examined papers between 1999 and 2007 in multiple languages. They included only RCTs on the effects of injection therapy involving epidural, facet, or local sites for subacute or chronic low-back pain. The authors concluded that there was no strong evidence for or against the use of any type of injection therapy.

In summary, the preponderance of data suggests that trigger-point injections using low amounts of anesthetic solutions were no better than injecting sterile saline or dry needling of the trigger point. This would suggest that this form of therapy is best conceptualized as an acupuncture-like therapy, namely, a treatment that induces a short-lived pain-suppression effect.

11.1.C Prolotherapy

The injection of various solutions aimed at producing a sclerosing effect has been used to treat soft-tissue injuries (e.g., inguinal hernia) for more than 100 years. In the 1930s, this treatment approach was applied to injured joints in an attempt to stimulate connective tissue repair. Although several studies have been published about this method of treatment for various orthopedic and spinal indications (termed prolotherapy), its use remains controversial. In both 2004[19] and 2005[20] critical reviews of the literature examined intraligamentous injection of sclerosing solutions (i.e., prolotherapy) for spinal pain. The 2004 report found four randomized or quasi-randomized clinical trails and the 2005 report found five trials that were randomized clinical trials (RCTs). Neither review was able to make definite conclusions about the efficacy of prolotherapy versus control injections. It was pointed out in the 2005 review that in general these studies did not use a consistent sclerosing agent and in fact 20 different sclerosing solutions were used. The most common sclerosing agent used was a mixture of dextrose 12.5%, glycerin 12.5%, phenol 1.25%, and lidocaine 0.25%. Looking at the individual studies, two showed significant differences between the treatment and control groups but in one co-interventions confounded interpretation of results and in the other the data analysis revealed no significant difference in mean pain and disability scores between the groups. A third and fourth study found little or no difference between groups in pain and disability. The most updated review (in 2008) described two randomized controlled trials in which prolotherapy was administered using 6 weekly injections of 20–30 mL of a combination solution containing dextrose, glycerin, phenol, and lidocaine.[21] Injections were given in conjunction with spinal manipulation therapy and exercise and both demonstrated positive results. No evidence for efficacy of prolotherapy injections alone was concluded.

Most of the available studies focus on back pain and other regions of the body and no convincing data shows prolotherapy to be effective in the absence of co-interventions such as spinal manipulation therapy. The use of a sclerosing solution for pain in the head and neck has never been evaluated with a randomized blinded controlled clinical trial; therefore, currently no acceptable evidence of efficacy for prolotherapy injections for the treatment of trigeminal-nerve-related pain exists.

11.1.D Occipital nerve block for headache

Occipital nerve blockade (ONB) is a diagnostic and treatment procedure where anesthetics (typically lidocaine or bupivacaine, sometimes with a corticosteroid agent added) are injected near the occipital nerve on the back of the head near the base of the skull. In 2006 a retrospective chart review study assessed the outcome of patients who had frequent primary (migraine and cluster) headaches who had received occipital nerve blockade containing local anesthetic and corticosteroid agents.[22] The authors reported that 26 of 57 (46%) ONB injections in 54 migraineurs yielded a complete or partial pain reduction response that lasted a

median of 30 days. For cluster headache 13 of 22 ONB injections yielded a complete or partial pain reduction response lasting a median of 21 days. The authors speculated that tenderness over the greater occipital nerve was strongly predictive of outcome but, of course, scientific evidence is not based on retrospective chart reviews.

A 2006 double-blind randomized controlled study examined the effect of occipital nerve blockade on cervicogenic headache.[23] Analgesic consumption was the primary outcome of the study. Fifty adult patients diagnosed with cervicogenic headache were randomly divided into either receiving preservative-free normal saline or local anesthetic. The authors reported that analgesic consumption, duration and frequency of headache, nausea, vomiting, photophobia, phonophobia, decreased appetite, and limitations in functional activities were significantly less in the block group compared with the control group at the 2-week follow-up point. Finally, in 2007 a single patient case described the beneficial effect that massaging over the greater occipital nerve has on migraine headaches.[24] The authors speculated that this was evidence of trigemino-cervical convergence and massage produced a diffuse nociceptive inhibitory control (DNIC) that was inhibitory to the migraine mechanisms.

In summary, a randomized controlled study reported that occipital nerve blockade with lidocaine was more effective in pain reduction in cervicogenic headache sufferers than a placebo injection at the 2-week follow-up point.

11.1.E Sphenopalatal nerve block

The sphenopalatine ganglion is located in the sphenopalatine (pterygopalatine) fossa, posterior to the middle turbinate and inferior to the maxillary nerve. Anesthetic blockade of this ganglion has been reported to be effective in the relief of a wide variety of facial pains and headaches. It can be anesthetized either via the transnasal approach, using cotton applicators soaked with 4% lidocaine inserted into the nose passing along the upper border of the inferior turbinate and directed backward until the upper posterior wall of the nasopharynx, or via the intraoral approach with injection of local anesthetic through the greater palatine foramen. Unfortunately there is little or no randomized controlled clinical trial data on this method in spite of the fact that sphenopalatine ganglion blocks have been used to treat headache and facial pain for many years.

In 1998, a study examined the use of sphenopalatine ganglion blockade (SPGB) for the treatment of chronic myofascial pain of the head, neck, and shoulders.[25] This study was a double-blind, placebo-controlled, triple crossover study involving 23 myofascial pain patients that compared SPGB with either 4% lidocaine or saline. In a washout period between these two treatment conditions, all patients received trigger-point injections (TPIs) using 1% lidocaine. Treatment order was randomly assigned and they consisted of either (1) SPGB with 4% lidocaine, then TPI with 1% lidocaine, and SPGB with saline or (2) SPGB with saline, then TPI with 1% lidocaine, and SPGB with 4% lidocaine. Treatments were given sequentially at 1-week intervals for both groups. Pain scores using VAS were gathered before, 30 minutes, 6 hours, 24 hours, and 1 week after each treatment. The authors reported that the analgesic effect of SPGB with 4% lidocaine was no better than placebo and actually less efficacious than administration of standard TPIs for the treatment of myofascial pain of the head, neck, and shoulders.

Sphenopalatine ganglion blockade is used for atypical facial pain and cluster headache more commonly than myofascial pain, so the above study did not dissuade practioners from using this treatment in these conditions. In fact in 2006 a report appeared in the literature which described a transnasal sphenopalatine ganglion injection.[26] The transnasal application of topical anesthetic is the simplest and most common technique but also more variable in its effect. Another described the effect of blocking the sphenopalatine ganglion.[27]

In summary, at this point there have been no controlled studies that have examined the effect of sphenopalatine ganglion block for chronic neurovascular or neurogenic pain in the trigeminal nerve region, including atypical facial pain or cluster headache. For myogenous pain in the head and neck region, sphenopalatine ganglion block with lidocaine was examined in a randomized controlled trial and was found no better than the effect induced with a saline injection.

11.1.F Stellate block

A sympathetic nerve block is one that is performed to determine if the pain can be related to spontaneous activity of the sympathetic nerves. The supply of sympathetic fibers to the head is through the stellate ganglion. Normally the injection involves infusion of lidocaine but the injection of opioid drugs close to the sympathetic ganglia has been reported to provide good pain relief without side effects in patients with postherpetic neuralgia, sympathetically maintained pain, and reflex sympathetic dystrophy.[28–30] In 2006 an article described three patients with medication-resistant chronic headache or idiopathic facial pain who were treated with an injectable opioid (buprenorphine) applied to the region at the stellate ganglion.[31] The authors reported a decrease in pain intensity, reduction of pain medications, and improvement in quality of life as a result of these injections. In contrast to this report Spacek et al. showed no benefit of buprenorphine, compared with placebo.[32] These authors conducted a randomized, controlled, double-blind, crossover study on stellate ganglion opioid injections in refractory trigeminal neuralgia. In the two groups, either buprenorphine or 0.9% sodium chloride

(saline) was applied to the superior cervical ganglion; significant pain relief occured in both groups. Another study describes a series of opioid injections applied in the area of the superior cervical sympathetic ganglion on patients with atypical orofacial pain, burning mouth syndrome, and glossodynia.[33] The authors of this paper suggested that a very large placebo effect explains the temporary improvement of symptoms. In 2008 another randomized comparison study examined the role of stellate ganglion block (SGB) for facial pain.[34] It enrolled 50 patients with chronic facial pain of various origins (traumas, iatrogenic issues, herpes zoster, or neurological pathologies). The study provided (1) SGBs using 10 administrations of 10 mg of levobupivacaine given every other day, followed by one administration per month for 6 months thereafter or (2) tramadol 100 mg/day and gabapentin 1800 mg/day orally for 6 months. The results reported were that the mean VAS pain level reported by patients was greatly reduced (8.89 down to 0.2) and it remained at that reduced level for the 6th and 12th months. For the tramadol group the VAS pain score was also reduced (from 8.83 to 4.9 after 12 months). Of course an injection therapy versus a prescription drug does not remove the therapeutic bias and strong placebo response induced by the injection of an anesthetic into the neck multiple times. Furthermore, this population was a quite mixed diagnostic group, so the chronicity of diseases being treated is also suspect.

In summary, it appears that the predominate pain reduction effect in a group of refractory trigeminal neuralgia pain patients produced by an injection of opioid agent or a local anesthetic agent into the area of the superior cervical sympathic ganglia is probably a powerful placebo response. Until additional studies are done examining this effect in more detail, stellate ganglion blocks are proven effective through double-blind random controlled trials.

11.1.G Intra-articular morphine and other substances

In 2001 a randomized double-blind parallel group multicenter study evaluated the use of a single dose of intra-articular morphine on 53 patients with unilateral temporomandibular arthralgia or osteoarthritis.[35] VAS pain scores at maximum mouth opening and at jaw rest were collected in a diary 3 days before and 5 days after intra-articular injection of either 1.0 mg morphine HCl, 0.1 mg morphine HCl, or saline (placebo) into the temporomandibular (TMJ). The authors reported that the VAS pain score at maximum mouth opening was considerably reduced for up to 10 hours after injection but without significant differences between groups. Interestingly at the follow-up, the median VAS pain score at maximal mouth opening was significantly lower in the 0.1-mg morphine group than in the 1.0-mg morphine or in the saline group. There was no difference in the incidence of adverse events between the groups and overall they were few in number. The authors concluded that the evidence for the analgesic property of the locally applied opioid was inconclusive.

Confirming this study a randomized double-blind controlled clinical trial which examined pain relief from intra-articular saline with or without morphine 2 mg in patients with moderate-to-severe pain after knee arthroscopy.[36] In this study the pain intensity decreased from about 50 to about 10–15/100 in both groups and the sum of pain intensity differences at 2 and 22 hours was not significantly different between the two groups. Considering the data from both of the above studies it would suggest that opioid receptors inside joints are few in number and even arthritic pain does not readily induce upregulation of these receptors. One interesting more recent animal experiment has actually shown that if more opioid receptors were present inside arthritic joints, this might be a way of reducing arthritic pain and destruction.[37] This experiment induced human μ-opioid receptor (HuMOR) expression in arthritic joints of mice using a DNA-containing viral vector into the temporomandibular joints of transgenic mice. The results of this paper showed that MOR overexpression in joints successfully prevented pain and dysfunction in these animals.

In summary, quality research shows that the analgesic property of the locally applied opioid to the temporomandibular joint for arthralgia and osteoarthritis pain relief for the knee is not better than a placebo injection.

11.1.H Phenol nerve block for trigeminal neuralgia

Over the last 50 years, peripheral neuroablation of trigeminal nerve branches using a variety of substances has been described. In 1999, a retrospective chart review on 18 patients (9 females and 9 males) with diagnosed trigeminal neuralgia treated with trigeminal nerve peripheral branch phenol/glycerol injections for trigeminal neuralgia was published.[38] Sixty injections of 10% phenol in glycerol were administered to 18 patients, 46 were administered into the infraorbital nerve canal, 11 were into the mandibular nerve just proximal to the mandibular canal, and 3 were into the supraorbital nerves canal. The reported results were that 87% of the injections produced marked or total relief initially and 37% of these still provided relief after 1 year and 30% after 2 years. There were no serious complications or dysesthetic pain reported in these 18 patients; although most had full facial sensory loss postinjection, this generally recovered within 6 months and was well tolerated.

In 1998 a prospective case study on nine patients described the effect of peripheral absolute glycerol neurolysis inducing injections on trigeminal neuropathic pain after nerve injury.[39] Although this is an uncontrolled study, the interesting aspect of the report is that the authors performed a quantitative sensory testing before and after the injections to document changes in abnormal pain and sensory perception in these nine patients. The injections of glycerol were performed proximal to the site of nerve injury. The authors reported little or no effect on pain levels in eight patients at 6 weeks after injection, although in one patient complete and sustained pain relief was observed. The authors speculated that pain relief in the one patient was probably related glycerol's ability to inhibit ongoing ectopic activity in the damaged nerve.

To summarize this section, uncontrolled studies and case reports are not proof of efficacy and these descriptive reports need to be followed with reasonable quality scientific studies. Finally, a 2002 review of the literature examined how ganglion-based neuroablation compared with peripheral neuroablation in trigeminal neuralgia patients.[40] The authors reviewed available literature and concluded that expertly performed ganglion-level procedures (radiofrequency thermocoagulation, balloon compression, and glycerolysis) were more effective than peripheral procedures but neither approach was likely to produce long-term pain relief.

11.1.I Cryoneuroablation

Several case reports in the literature report efficacy of cryoneuroablation of peripheral nerve branchs as an effective method of treating atypical facial pain and even trigeminal neuralgia.[41–43] In 1988 a retrospective review of 145 patients with paroxysmal trigeminal neuralgia claimed pain relief lasted from 13 to 20 months in different branches of the trigeminal nerve.[44] This report stated that patients regained normal sensation long before the return of pain and did not claim any major adverse events. In a 2002 case series 19 patients with trigeminal neuralgia had either the infraorbital nerve or the inferior alveolar nerve frozen using a cryoprobe.[45] This report claimed that the pain was absent for at least 6 months but did recur in 13 out of 19 patients within 6–12 months.

In summary, there are several claims in the literature that cryoneuroablation can relieve peripheral nerve branch pain, and that it might be effective for treating atypical facial pain and even trigeminal neuralgia; however, to date there have been no controlled randomized blinded studies using cryoneuroablation applied to peripheral branches of the trigeminal nerve for the management of chronic facial pain of any type.

11.1.J Recommendations on interventional therapy for chronic orofacial pain

At present no Cochrane study is available that examined needle- and/or injection-based therapies for the treatment of chronic orofacial pain. However, a Cochrane-style review cited earlier (Staal et al., 2009) examined the role of injection therapy for subacute and chronic low back pain. This study systematically reviewed randomized controlled trials (RCTs) that sought to determine if injection therapy is more effective than placebo or other treatments for patients with subacute or chronic low back pain. The authors discovered 18 eligible clinical trials (1179 participants) in their review. The injection sites varied from epidural sites and facet joints (i.e., intra-articular injections, periarticular injections, and nerve blocks) to local sites (i.e., tender and trigger points). Overall, the results indicated that there is no strong evidence for or against the use of any type of injection therapy for back pain. The general conclusions that can be derived regarding various forms of chronic orofacial pain from the specific therapy studies cited in Sections 11.1.A–11.1.I are listed at the end of the chapter (Sec. 11.3).

11.2 Botulinum toxin in orofacial pain disorders

The second part of this chapter reviews how BoNT evolved for medical purposes. The evidence is based on a critical review of the literature regarding the use of BoNT for both spasm and pain in the orofacial region.

11.2.A Botulinum toxin as a medicine

The concept that a toxin produced by the bacteria *Clostridium botulinum* might have medical uses came to mind in the 1920s after the botulinum neurotoxin (BoNT) was purified.[46] This toxin was discovered to have several subtypes, which were serologically distinct (BoNT/A, B, C, D, E, F, and G).[47]

Botulinum toxin used "on-label"

The US Food and Drug Administration (FDA) approved boulinum toxin type A (BoNT/A [Botox®, manufactured by Allergan, Irvine, CA]) in 1989 for focal muscle hyperactivity disorders (e.g., focal dystonias).[48] Specifically, the FDA approved BoNT/A for the temporary treatment of blepharospasm and strabismus and then for cervical dystonia in 1990.[49] In 2000, the FDA also approved Myobloc® (BoNT/B manufactured by Solstice Neurosciences, Inc., San Diego, CA) for the treatment of cervical dystonia in patients who

developed BoNT/A resistance. Since then BoNT/A has been approved for the treatment of primary axillary hyperhidrosis (excessive sweating) and for reduction of deep glabellar lines in the face. BoNT/A is supplied in vials in a lyophillized form, at a dose of 100 units (U) per vial. Dysport® is marketed outside of the United States by Ipsen Ltd in Europe. All these preparations, Botox, Myobloc, and Dysport, differ in formulation and potency; hence, their units are not interchangeable.

"Off-label" botulinum toxin use

In addition to these on-label uses, BoNT/A is used off-label in the orofacial region to help treat primary and secondary masticatory and facial muscle spasm, severe bruxism, facial tics, orofacial dyskinesias, dystonias, and even idiopathic hypertrophy of the masticatory muscles. With the exception of hypertrophy, the common link for these conditions is that they are all involuntary motor hyperactivity disorders and, although they are off-label uses, they are similar in pathophysiology to the condition for which BoNT is FDA approved. Even more off-label is the suggested use of BoNT for pain disorders without clear-cut motor hyperactivity being present. These pain disorders include conditions such as chronic migraine headache, chronic daily headache, chronic myofascial pain, focal sustained neuropathic pain, and more recently episodic trigeminal neuralgia. Using a drug off-label sometimes generates interest from the medical, legal, and federal regulatory communities but off-label drug use is legal, and the FDA recognizes this. The practitioner's professional judgment determines the best treatment possible for their patients, which may include off-label use of a medication. The practitioner who elects to use a drug off-label bears some inherent risk, and legal rulings have suggested that off-label drug use may be evidence of negligence. The practitioner should weigh potential benefit against the risk for the patient, and full disclosure of risk should be explained to the patient, including a consent form signed by both parties. The practitioner should have reasonable knowledge of the body of scientific evidence supporting the off-label application of a drug.

Mechanism of action

Exocytosis of acetylcholine (ACh) on cholinergic-containing nerve endings of motor nerves is inhibited by BoNT/A.[50] Autonomic nerves are also affected by the inhibition of ACh release at the neural junction in glands and smooth muscle.[51] BoNT achieves this effect by its endopeptidase activity against SNARE proteins, which are a 25-kDa synaptosomal-associated protein required for the docking of the ACh vesicle to the presynaptic membrane. It has been suggested that when BoNT is used for the treatment of neuromuscular disorders, particularly focal dystonias and spastic conditions, patients have reported a marked analgesic benefit.[52] This benefit was initially believed to be due to the direct muscle relaxation effect of BoNT. However, various observations have suggested that BoNT may exert an independent action on peripheral nociceptors by blocking exocytosis of such neurotransmitters as substance P (SP), glutamate, and calcitonin gene related peptide (CGRP). In addition, because BoNT does not cross the blood–brain barrier, and since it is inactivated during its retrograde axonal transport, the effect is believed to be in the first-order sensory nerve and not more centrally.[53]

Injection preparation, dosing, and effect duration

The BoNT/A is kept frozen (2–4°C) in a vial until it is ready to use. The drug is put into solution, following manufacturer's guidelines, by adding normal saline (preservative-free 0.9% saline solution). Once prepared it should be used within 4 hours. The preferred syringe is a calibrated 1.0-mL tuberculin syringe, and the needle selected for injection is usually between 26 and 30 gauge. Skin preparation involves alcohol wipes and dry sterile gauze sponges. Aspiration before injection is recommended. Dosing is usually established by the diagnosis and reason for use of the toxin, size of the muscle, and medical conditions or medications. Until studies narrow down all specifics, the final dilution and dosage used is left to the clinical experience and discretion of the practitioner. The number of injection sites is usually determined by the size of the muscle. Theoretically, it may be appropriate to inject more sites with smaller doses, and using more injection sites should facilitate a wider distribution of BoNT/A to nerve terminals. However, too many injection sites may cause local injection site pain. The proper targeting of muscles is a crucial factor in achieving efficacy and reducing adverse effects from BoNT/A injections. The therapeutic effects of BoNT/A first appear in 1–3 days, peak in 1–4 weeks and decline after 3–4 months. Motor nerve block induced by BoNT/A has a duration ranging from 8 to 16 weeks.

Adverse events and side effects

Side effects can be divided into (1) site-of-injection side effects and (2) medication-related side effects. With regard to site-of-injection side effects, the needles being used for most injections are small (between 27 and 30 gauge) and if the skin is cleaned properly, then the chances of local hematoma, infection, or persistent pain in the injection site are extremely low. Medication-related side effects are generally few, transitory, and well tolerated by patients if they

occur. The most common medication-related side effect is adjacent muscle weakness (e.g., an inadvertent weakening of the muscles of facial expression or swallowing when this is not desired). For patients who have had injections into the lateral pterygoid or palatal muscles, slurred speech with palatal weakness is a distinct possibility as well. In general, these "inadvertent weakness" complications due to local diffusion of the drug can and do occur and, moreover, are dependent on technique and dose.[54–56] A second side effect seen with BoNT injections of the masticatory muscle is an alteration in the character of the saliva of patients who have not had direct salivary gland injections. While this is an uncommon problem, some patients report that their saliva is diminished and thicker (i.e., ropy saliva), and this is more likely for higher doses and for injections around the parotid or submandibular gland. In most cases, these complications are usually less problematic than the untreated original motor disorder and will not generally stop the patient from seeking additional injections. However, if the injections are being used primarily to treat pain secondary to contraction, then these complications might be more bothersome. Fortunately, persistent, more-significant complications are rare. For example, systemic complications are uncommon and although several studies have reported a flulike syndrome, particularly after the first injection, such symptoms have also been reported following placebo injection.

Finally, some patients develop antibodies to the toxin. It is unclear exactly what factors predispose to development of antibodies, but some studies suggest that risk is increased by higher and more frequent injections; for this reason injections are not done more often than once every 12 weeks. In February of 2008 the FDA did issue an advisory letter describing that BoNT injection has been linked to respiratory failure and death.[57] The advisory letter suggested that these reactions may be related to overdosing and there was no evidence that these reactions were related to any defect in the products. Moreover, approximately 1% of patients receiving BoNT/A injections may experience severe, debilitating headaches that may persist at high intensity for 2–4 weeks before fading.[58]

11.2.B Botulinum toxin for oromandibular motor disorders and facial spasms

There are various muscle hyperactivity disorders in the orofacial region for which BoNT has been used. In 2003 a thorough review of BoNT for oral motor disorders was published which described the potential uses and current evidentiary basis for using this medication in the orofacial region.[59] In general, this treatment is only palliative, except maybe in some headache disorders where a chronic headache pain may diminish substantially and for a much longer time than the 8- to 16-week effect seen in muscle spasm. With regard to the masticatory muscle spastic disorders described here, it would be fair to say that the majority of the data reviewed was mostly open-label clinical trails or case-report based.

Bruxism and botulinum toxin

In cases where the disorder is very severe and the damaging consequences are well beyond the teeth, one option is to inject the masseter and/or temporalis muscle about every 3–6 months to minimize the power of the bruxism activity. A brief report in 1990 described a brain-injured patient who was treated for severe bruxism with BoNT/A injections (100 units total into the masseter and temporalis).[60] Several years later two additional reports were published which described the successful BoNT/A treatment of brain-injury patients with severe bruxism.[61,62] One subject did experience dysphagia as a side effect of the injections. Additionally, a case report of a young child (age 7) with severe brain-injury-induced bruxism described successful management with BoNT.[63]

Masseteric and/or temporalis muscle hypertrophy

Masseteric hypertrophy has been described by several authors and, prior to BoNT, its treatment involved surgical muscle stripping, with substantial contracture and scarring as a consequence of this approach. Successful treatment of masticatory hypertrophy with BoNT/A was reported in two separate papers.[64,65] In 1998 a case report describing two patients provided additional information about how much and for how long the hypertrophy was actually reduced.[66] They utilized repeat injections with BoNT/A (40–60 units per muscle). They described that about a 20% decrease in volume of the muscle resulted from this treatment after several injection cycles. Since then there have been several additional case reports on BoNT/A for the treatment of masseteric hypertrophy.[67–71]

Secondary masticatory muscle spasm (sometimes with contracture)

The clinical use of BoNT/A for severe sustained jaw-closing spasm was addressed in a series of case reports published in 1989, 1994, and 1995.[72–74] The BoNT injections were found to be quite helpful. Controversially, the use of BoNT/A in a patient with a motor-paralysis-inducing disease such as amyotrophic lateral sclerosis appeared in a report describing the successful treatment of jaw trismus using BoNT in such a patient.[75]

Hemimasticatory spasm

The first use of BoNT for the rare disorder called hemimasticatory spasm was published a report on a single case in 1992.[76] This was followed by another report on the successful treatment of two additional cases in 1995 and another case in 2000.[77,78]

Oromandibular dystonia (with recurrent jaw opening motion)

Treatment with BoNT has been found helpful in many variations of oromandibular dystonia. In involuntary jaw-opening dystonia there have been two publications (in 1997 and in 2000) describing the treatment of recurrent, involuntary TMJ dislocation using BoNT/A.[79–81] The primary target was the lateral pterygoid muscle because this is the muscle most responsible for opening, and these injections produced an effect that lasted from 4 to 10 months. In 1999 a paper described the use of a customized electromyographic (EMG) needle-insertion guide which attached to the maxillary teeth of the patient and had a guide tube in the buccal posterior vestibule of the maxillary arch to assist with accurate injections of the inferior portion of the lateral pterygoid.[82] This tube allowed a reproducible needle insertion angle to be used for injecting into the lateral pterygoid muscle using an intraoral approach. Unfortunately, no independent assessment has verified that this device helped with actual placement of the solution. In 1999 two reports described the injection of submandibular muscles (e.g., anterior digastric and platysma) as a therapy for suppressing jaw-opening activity.[83,84] It is not clear how much these muscles contribute to jaw opening versus the lateral pterygoid itself and no systematic research has been done to elucidate this.

Hyperactivity of the tongue

No matter the origin of tongue hyperactivity, it can be suppressed with BoNT injections into the intrinsic tongue muscles and even the genioglossus. Injection into the tongue itself runs a higher risk of dysphagia and would not be logical for simple dyskinesia, which does not affect speech or swallowing activities. In severe tongue hyperactivity such as in cerebral palsy where dysarthria and dysphagia may also be present, reducing tongue activity becomes advantageous. Unfortunately, this particular application has not been studied systematically.

In 1991, a case series report described the use of BoNT in patients with lingual dystonia but cautioned clinicians that dysphagia was a problem in some of their cases.[85] In 1997, a case series of nine patients with repetitive tongue protrusion resulting from oromandibular dystonia or Meige's syndrome were treated with BoNT injections into the genioglossus muscle at four sites via a submandibular approach.[86] Six of these patients were helped and the average dose injected was 34 units, producing a 3- to 4-month effect. Clearly, there is a need to explore when, where, and to what degree BoNT may become useful in management of tongue hyperactivity.

Hemifacial spasm

In 1987 a case series of 93 patients with various manifestations of focal dystonia (4 were hemifacial spasm) showed benefit with the use of BoNTs.[87] In 1988, 21 patients with hemifacial spasm were treated successfully with BoNT injections.[88] The authors reported that in 93.1% of cases there was total relief of periocular and perioral spasms, with a mean interval of treatment effect of 17.4 weeks. In 1990 another 13 patients with hemifacial spasm were treated with BoNT injections, which were successful in 92% of these patients.[89] The authors also described the average duration of maximum improvement as lasting about 3 weeks longer than had been reported for other muscle groups (15 weeks).

By 1997 one of the first randomized trials on BoNT treatment for 42 subjects with hemifacial spasm analyzed the method in the treatment.[90] These patients were assigned randomly to one of several treatment groups, which differed based on the site of injection. The authors concluded that the position of the injection sites around the orbicularis influenced the effectiveness and side effects of BoNT treatment for patients with hemifacial spasm. They suggested that a brow injection has an equally long duration of effect as that of the standard treatment with fewer side effects. Since then there have been several additional case reports on BoNT for hemifacial spasm, all with profound and long-lasting results and no report of any major adverse events.[91–94]

11.2.C Botulinum toxin and pain

How efficacious BoNT is in controlling pain was first reviewed in a systematic review of the literature in 2004.[95] The reviewers examined published data on various head and neck pain conditions by performing a thorough search of the medical literature, striving to find randomized, blinded, controlled trials (RBCT s) that evaluated the effect of BoNT on specific conditions. In general they found that the data they could find did not demonstrate conclusive evidence regarding the effectiveness of BoNT on head and neck pain conditions.

Botulinum toxin and experimental pain in humans

Two recent placebo-controlled, double-blinded, randomized clinical trials examined experimental pain and BoNT in humans. These studies show conflicting results. A 2002 double-blind placebo-controlled study specifically measured cutaneous nociception in 50 healthy volunteer adults who

received bilateral subcutaneous forearm injections of 100 units of BoNT/A (Dysport) or placebo.[96] Pain thresholds for heat and cold in the treated skin areas were measured quantitatively. Quantitative sensory testing was performed before and 4 and 8 weeks after BoNT injection. The results showed that heat and cold pain thresholds increased from baseline to week 4 by 1.4°C and this increased to 2.7°C by week 8. In comparison, the placebo site showed a 1.1°C and a 1.2°C change at weeks 4 and 8, respectively. A similar trend was seen for electrical-induced pain thresholds, but none of these differences was found to be statistically significant. The authors concluded that no strong direct cutaneous antinociceptive effect for BoNT/A was demonstrated by their study. In contrast, Barwood et al., in 2000, studied the analgesic effect of BoNT versus placebo on 16 young children (mean age 4.7 years) for management of their spastic cerebral palsy.[97] These authors reported that, compared with the placebo, BoNT/A injections reduced pain scores 74% ($P<0.003$). They did not measure pain threshold using quantitative sensory testing, and pain measurement in children this young might be problematic.

In 2006, an article examined the effects of BoNT/A on a capsaicin-evoked pain, flare, and secondary hyperalgesia in the forehead of 32 healthy male volunteers.[98] The experiment sought to find out if BoNT/A inhibits peripheral sensitization of nociceptive fibers and indirectly reduces central sensitization. The study involved the injection of either BoNT/A or saline into the precranial, neck, and shoulder muscles in a double-blind randomized manner. Before and 1, 4, and 8 weeks after these injections, capsaicin was injected intradermally to cause local pain, inflammatory flare, and a secondary hyperalgesia reaction. The authors reported a significant suppressive effect of BoNT/A on pain, flare, and hyperalgesia area compared with the saline condition. However in 2007 a similar study was performed which did not confirm the above results.[99] This study used 50 healthy volunteer subjects and again injected 100 mouse units of BoNT/A (Dysport) or placebo in a double-blind paradigm. Before and after 4 and 8 weeks following these injections localized allodynia was induced in the skin areas with capsaicin ointment. Moreover, heat and cold pain threshold temperatures were measured with quantitative sensory testing, and threshold intensities using electrical stimulation. In this study no BoNT/A-related differences in pain perception were found. These authors concluded that there is neither a direct peripheral antinociceptive effect nor a significant effect against neurogenic inflammation of BoNT/A in humans.

Myofascial trigger points

Myofascial trigger points (MTrPs) are thought to be the result of abnormal motor end-plate activity which produces an excessive continuous release of the neurotransmitter acetylcholine (ACh).[100] In theory, using neuromuscular blocking agents such as BoNT for myofascial trigger-point pain would eliminate the end-plate dysfunction by blocking the release of ACh and thereby reduce pain. An open-label case series on 77 patients published in 2003 reported reduced VAS pain levels after using BoNT/A for persistent trigger points.[101] In contrast, in 2006 a double-blind, randomized, placebo-controlled, parallel clinical study examined the effect of BoNT on pain from muscle trigger points.[102] They reported that, although BoNT does reduce motor end-plate activity, it had no better effect on either pain or pain thresholds compared with isotonic saline. They concluded that BoNT does not have a specific antinociceptive or analgesic effect. In 2006, another double-blind, randomized, and controlled crossover BoNT trial was reported on 31 subjects with neck and shoulder myofascial pain.[103] These authors concluded that there was no difference between the effect of small doses of BoNT/A and those of physiological saline in the treatment of myofascial pain syndrome. Finally, there are three other randomly assigned, double- or single-blind studies which have compared BoNT/A with a control or comparison treatment. The first of these RBCTs compared trigger-point pain treated with BoNT/A versus saline.[104] The study included 132 patients with cervical and/or shoulder myofascial pain with active trigger points and used VAS pain reports, pressure algometry, and pain medication use as the outcome measure. The authors reported no significant differences between the saline-injected and the BoNT/A-injected groups. Another randomized, double-blind, crossover study compared BoNT/A with bupivacaine and included 18 patients.[105] The authors compared the effectiveness of trigger-point injections using the two agents done in combination with a home-based rehabilitation program. After being injected, the subjects were followed until their pain returned to at least 75% of their preinjection pain for two consecutive weeks. After an additional 2-week washout period, the subjects received the other treatment injection. Both treatments were effective in reducing pain compared with baseline, but without any significant difference between the injected agents in the duration or magnitude of pain relief, function, or satisfaction. A third randomized, single-blind treatment comparison study evaluating BoNT/A with dry needling and lidocaine injections into cervical myofascial trigger points was reported in 2005.[106] This study involved 29 patients. The results showed that pain pressure thresholds and pain scores significantly improved in all three groups with a slightly greater response in the lidocaine and BoNT/A groups.

The first good double-blind examination (published by Wheeler et al. in 1998) described the effect of BoNT injections on refractory, unilateral, cervicothoracic, paraspinal, myofascial pain syndrome.[107] The study used normal saline

injected into symptomatic trigger points as the control condition and examined 33 subjects divided into 3 subgroups (50 units injected, 100 units injected, or normal saline) and then re-evaluated them after a 4-month period. They described that all three groups showed significant treatment effects with no treatment being found superior to the control condition. In 2000, Porta also performed a comparative trial testing BoNT/A versus methylprednisolone injections into trigger points in myofascial pain syndrome cases and pain from chronic muscle spasm.[108] The subjects were randomized and evaluated 30 days after the injections. They reported that pain decreased significantly from baseline in both treatment groups, with no significant difference between the two treatment groups. However, at 60 days postinjection, these authors found that pain severity score for the BoNT-treated patients was significantly lower than for those treated with steroid injections. The only complication is that some of these patients did have "muscle spasm" and many also received physiotherapy, and the authors described that compliance with the stretching program was lower in the steroid group, which weakens the importance of the treatment differences reported as being due to the injection only.

While the above papers do not address the masticatory system, in 1995 Clark et al. reported that there are a number of oral motor disorders that occur in the orofacial region and may be causal of or at least co-morbid with altered function of the temporomandibular system.[109] In 1999 Freund et al. did suggest that BoNT can be useful for myofascial pain in the trigeminal motor system.[110] They used BoNT for the treatment of temporomandibular disorders in 15 subjects in an open-label, uncontrolled clinical trial. These individuals had BoNT/A injected into the masseter muscles (50 units each) and the temporalis muscles (25 units each) bilaterally under EMG guidance. Subjects were examined four times every 2 weeks (with outcome measures VAS pain, bite force, interincisal opening, tenderness to palpation, and function); with the exception of bite force, they reported a significant improvement in their pain. Obviously, additional controlled, blinded, randomized research into this issue is needed with more specific acceptable diagnostic groups being studied. Noted that the evidence that myofascial pain and even chronic tension-type headache disorders involve chronic muscle contraction is weak. For example, Clark et al. evaluated the daily patterns of chronic tension-type headache pain and temporalis muscle EMG activity during a 3-day period in 36 patients and 36 controls. They found that, although stress and pain were correlated, there was no correlation between headache pain and temporalis muscle EMG activity.[111] In a follow-up paper these authors looked at functional (e.g., chewing and talking) versus nonfunctional daily activity patterns in the above chronic tension headache patients. They reported that clearly the patients had more muscle activity with function than the control subjects, which suggests and interaction between pain and muscle activity, even if it is not a causal relationship.[112] For this reason alone, the work on BoNT and chronic tension-type headache is worth pursuing, but the need is for randomized, controlled, blinded clinical trials with both subjective and objective outcomes, not more open-label preliminary studies.

In summary, the RBCT studies discussed here suggest that BoNT is no better or longer lasting than the other standard trigger-point-based therapies and the studies to date for resistant myofascial trigger points demonstrate no difference than already accepted lidocaine injections or even placebo injections.

Temporomandibular pain and dysfunction

An open-label study on 15 adult patients who had a nonspecific heterogeneous diagnosis of TMJ pain and dysfunction occurred in 1999 (previously cited study by Freund et al.). All subjects were given 150 units of BoNT/A, divided among the right and left masseter and temporalis muscles. Jaw pain (VAS) and muscle tenderness decreased, with no reported side effects. In 2000, these authors expanded their data set to 60 patients with mixed temporomandibular disorders, many of whom qualified as having chronic tension-type headaches ($n = 46$). BoNT/A was used under open-label uncontrolled conditions.[113,114] The authors reported significant results for all measured outcomes except for maximum bite force.

In 2001, another open-label study evaluated BoNT/A used for chronic facial pain in 41 patients with the diagnosis of temporomandibular dysfunction.[115] The authors injected an average of 200 U of BoNT/A (Dysport) on each side into the jaw-closing muscles and followed the patients for an average of 6.7 months. They reported that 80% of patients improved by a mean pain reduction of 45% VAS. One patient had reversible speech and swallowing difficulties. A recent open-label case series looked specifically at temporomandibular disk function in a group of 26 patients using BoNT/A (12.5 U) injected into the lateral pterygoid muscle, and some patients received injections of the temporalis, medial pterygoid, and masseter muscles when severe tenderness was noted.[116] They report that, except for clicking of the right joint, all outcome measures (pain, opening, left TMJ clicking, and headache) improved.

Of course, open-label case reports do not constitute strong evidence, and all such preliminary reports need to have RBCTs conducted in order to fully assess the true effect of the therapy being examined. There are two randomized, blinded, placebo-controlled studies in the literature. The first involved 90 patients with a heterogeneous diagnosis of

chronic facial pain including temporomandibular dysfunction. Sixty subjects received masticatory muscle injections with BoNT/A (Botox) and 30 subjects received a placebo injection.[117] This study was only single blinded, meaning that the injectors knew what substance was being injected, which increases the risk of inducing bias in the study outcome. The methodology of the injections was not clearly stated. Whether the authors injected bilaterally is unknown, and assuming they did inject 70 units per muscle bilaterally (medial pterygoid, masseter, and temporalis), then close to 400 units of BoNT/A (Botox) was used in each patient. The results of this study were that 91% percent of the patients who received BoNT/A showed an improved VAS pain score. The mean change was 3.2 points on a 10-point scale. This change was significantly different from the change seen with placebo injections, where only a 0.4 VAS change was seen.

In contrast to this study the second RBCT study had a smaller sample size of 15 women with chronic moderate-to-severe jaw muscle pain.[118] This double-blind study evaluated a total of 150 units of BoNT/A (Botox) divided between the right and left temporalis and masseter muscles. Data was collected at baseline and at 8, 16, and 24 weeks postinjection. A major difference between this and the previous study was that the subjects were crossed over to the comparison treatment after 16 weeks. Five subjects did not complete the study. For the 10 who finished, no statistically significant difference was found in pain variables. These authors concluded that the results do not support the use of BoNT/A for moderate-to-severe jaw closing muscle pain. Based on these two studies, it is not clear if the effect of BoNT/A injections for jaw muscle pain using doses in the 100–150 units range will be sustained.

In summary, for temporomandibular pain and dysfunction the published data is flawed, with a heterogeneous population being used as well as unclear methodology and low number of patients being tested. That being stated, insufficient evidence is available to make specific treatment recommendations.

Botulinum toxin and chronic migraine

Patients reporting relief of migraine symptoms after having BoNT injections for hyperfunctional facial lines was noted by Binder et al. in 2000.[119] Two additional studies have concluded that BoNT/A is an effective and safe prophylactic treatment for headache across a range of patient types,[120,121] including migraine of cervical origin.[122] A 2004 review of the literature summarized the data on BoNT/A for migraine prophylaxis.[123] Based on a combination of open-label data and three double-blind, random-assignment, placebo-controlled studies on episodic migraine, it was concluded that BoNT/A is effective in migraine prophylaxis. The main effect was to reduce the frequency, severity, and disability associated with migraine headaches. The first of these studies, in 2002, examined 123 subjects using a random-assignment, double-blind, vehicle-controlled approach. All subjects had a history of 2–8 moderate-to-severe migraine attacks per month, with or without aura.[124] Diaries were kept during a 1-month baseline and for 3 months following the injection period. The BoNT/A group that received 25 units showed significantly fewer migraine attacks per month, a reduced maximum severity of migraines, a reduced number of days of acute migraine medication use, and a reduced incidence of migraine-associated vomiting.[125] The second study was less convincing and examined 60 migraine patients using an RBCT method. Subjects received either BoNT/A or placebo injections. The overall results showed that there were no significant differences between the BoNT groups and the placebo study groups with respect to reduction of migraine frequency, number of days with migraine, and the number of total single doses to treat a migraine attack. Overall, this study did not report any added efficacy of BoNT/A for the prophylactic treatment of migraine above and beyond placebo, but subsequently the question has arisen about whether the dose of 16 units was too low. Finally, a third RBCT study looked at a subset of 228 patients on the use of BoNT/A or placebo for the prophylaxis of chronic daily headache (CDH), presumed to be of migrainous origin, without the confounding factor of concurrent prophylactic medications.[126] The subjects were all adults with 16 or more headache days per 30-day period, and all had a history of migraine or probable migraine and were not receiving concomitant prophylactic headache medications. One hundred seventeen subjects received BoNT/A and 111 received placebo injections. The maximum change in the mean frequency of headaches per 30 days was −7.8 in the BoNT/A group compared with only −4.5 in the placebo group. This difference was statistically significant, and the authors concluded that BoNT/A is an effective and well-tolerated prophylactic treatment in migraine patients with CDH who are not using other prophylactic medications.

In summary, for migraine prophylaxis, there is a general consensus among clinicians who treat migraine that BoNTs may have an effective role in the migraine population who have failed other modalities. It is the opinion of the authors that the use of botulinum toxin injections for migraine prophylaxis has the most evidence and that in the more refractory cases it is a viable treatment modality.

Botulinum toxin and chronic tension-type headache

In contrast to the open-label studies, where some benefit was shown,[127,128] the randomized blinded controlled clinical trials

which examined the use of BoNT/A for chronic tension-type headache (CTTH) patients and CDH patients suggest little to no benefit. In 2001, a RBCT involving 60 subjects concluded "in the important outcome variables, such as pain intensity, number of pain free day and consumption of analgesics, there were no statistical differences between the [BoNT/A] and control group."[129] In 2004, another double-blind, randomized, placebo-controlled clinical trial on BoNT/A was performed involving 40 subjects with CTTH.[130] From their data, the authors concluded that there was no significant difference between the two treatment groups (BoNT/A or saline) on the patient's assessment of improvement after 12 weeks. Finally, a large, multiple-center RBCT was performed.[131] This study examined 112 patients with CTTH using BoNT/A versus placebo injections; no significant differences between the BoNT/A group and the placebo group were reported in any of these variables. Again, these authors concluded that there is no evidence of improvement with the use of BoNT/A on CTTH. In 2006 two additional RBCTs reported that "for the primary endpoint, the mean change from baseline in the number of TTH-free days per month, there was no statistically significant difference between placebo and four BoNTA groups"[132] and "the between-group difference of 1.5 headache-free days favored BoNT-A treatment, although the difference between the groups was not statistically significant."[133] Based on these 5 RBCTs which examined the use of BoNT/A in CTTH, the authors conclude that the evidence for efficacy of BoNT in CTTH and CDH is nonexistent or weak at best.

The concept that a "nonspastic" disorder such as chronic daily tension-type headache and myofascial pain could be stopped by a therapy specifically designed for true muscle spasm disorders is controversial. Current speculation is that the BoNT may alter neurotransmitter secretion in afferent nerves as it does in efferent motor nerves, but this has yet to be proven. When considering using BoNT in this manner, the prudent clinician will first conduct a trial local anesthetic block (no epinephrine) into the target painful muscle site. The most logical local anesthetic to use is procaine since it is least myotoxic of all of the local anesthetics. If the procaine offers substantial short-term help, then the chances of the BoNT injection helping are higher. Note that conclusive data for BoNT in CTTH is still missing. In summary, for chronic tension-type headaches the evidence does not support the use of BoNT injections.

Botulinum toxin and focal chronic orodental neuropathic pain

Based on animal studies and the pharmacology of the drug, BoNT/A may well be effective as a treatment for focal trigeminal neuropathic pain. While there is no substantive proof that oral neuropathic pain will respond, there are several preliminary reports that support this idea although the data do not specifically address trigeminal pain. For example, one study examined localized postamputation pain in patients before and after BoNT injections.[134] This open-label case report described four successfully treated cases of chronic phantom pain of more than 3 years. The authors used BoNT/A injected into four muscle trigger points in the amputation stump of each patient. All trigger points were painful to compression before injection and all patients reported referred sensations in the phantom foot from at least one of the trigger sites. In all cases, the phantom pain was reduced about 60–80%. A 2008 study examined the analgesic effect of BoNT/A in chronic neuropathic pain patients.[135] Specifically this study included 29 patients with focal painful neuropathies and mechanical allodynia and employeed a randomized, double-blind, placebo-controlled design. Patients received a single intradermal administration of BoNT/A into the painful area and mean pain and sensory threshold levels were assessed at 4, 12, and 24 weeks. The authors reported that BoNT/A treatment produced a persistent effect on spontaneous pain intensity that was evident up to 14 weeks postinjection. Moreover, BoNT/A injections decreased allodynia to brush and decreased pain thresholds to cold, without affecting perception thresholds. Another study examined BoNT/A for the treatment of diabetic neuropathic pain using a randomized double-blind crossover study.[136] The study examined 18 patients with diabetic neuropathic pain and compared subcutaneous injections of BoNT/A with placebo injections. The authors reported significant BoNT/A-treatment-related reduced pain levels at 12 weeks after injection (2.5) versus only 0.5 point in the placebo group at the same time point. The authors concluded that a significant reduction in diabetic neuropathic pain was produced by BoNT/A injections subcutaneous in the painful area. Lastly, in 2009, a rat study was done comparing BoNT/A in experimental neuropathic pain which also reports an antinociceptive effect independent of the effects on muscular relaxation on this model.[137] In summary, the above data are encouranging and even suggestive that BoNT may also be useful to treat atypical odontalgia, phantom tooth pain, burning mouth syndrome, or even trigeminal neuroma pain; however, in the absence of specific studies, it is currently impossible to formulate an opinion on whether BoNT/A will be helpful in treating these problems.

Botulinum toxin for trigeminal neuralgia

Several authors have described the effects of BoNT injections on trigeminal neuralgia. Unfortunately these studies have all been open-label uncontrolled reports. The first was a report on 11 patients with chronic facial pain due to trigeminal neuralgia. The authors reported that 75% (8 of 11)

patients responded favorably, and they claimed the duration of the beneficial effect lasted between 2 and 4 months. In this open-label study BoNT was used with a dose range from 25 to 75 units of BoNT/A per patient.[138] Three additional case reports followed this initial report. The sample sizes for these three studies ranged from a single patient to as many as 13 cases. All of these reports described substantial pain reduction as a result of BoNT injections in patients; the dose used ranged between 10 and 100 units and the improvement lasted between 2 and 6 months.[139–141] While these case reports are interesting they do not provide enough quality data and the methodology is not adequately described to make any recommendation about the efficacy of BoNT injections for trigeminal neuralgia.

Botulinum toxin for trigeminal autonomic cephalalgia

Trigeminal autonomic cephalalgias (TACs) include cluster headache, SUNCT, and chronic paroxysmal hemicrania. These painful highly disruptive pain disorders are not prevalent enough in most clinics for a randomized blinded clinical trial to be conducted assessing the effect of BoNT. For this reason there are no randomized controlled studies that can be used to guide us about the efficacy of BoNT for suppressing TAC pain events.

In summary, for the trigeminal neuropathic conditions (e.g., atypical facial and odontogenic pain and phantom tooth pain, and neuromas) acceptable evidence is lacking. For the use of BoNT in trigeminal neuralgia the literature is limited to case reports with few individuals and unclear methodologies. BoNT has not been tested in a placebo-controlled, double-blind fashion in trigeminal neuralgia; therefore, it is the opinion of the authors that insufficient evidence exists to be able to come to a definitive recommendation for the use of BoNT for trigeminal neuralgia. For the autonomic cephalalgias (e.g., cluster headache, chronic paroxysmal hemicrania, and SUNCT) the literature is not sufficient; therefore, the authors again are unable to come to a definitive recommendation.

11.3 Final recommendations on botulinum toxin type A

Recommendations on using therapeutic injections, including botulinum toxin type A (BoNT/A) for pain and spasm

1. No Cochrane study is currently available that examined needle- and/or injection-based therapies for the treatment of chronic orofacial pain.
2. A Cochrane-style review (Staal et al., *Cochrane Database Syst Rev* 2008 Jul 16;(3):CD001824) examined the role of injection therapy for subacute and chronic low back pain, and the results indicated that there is no strong evidence for or against the use of any type of injection therapy for back pain.
3. At best, transient pain relief is delivered using acupuncture and trigger-point injections using low-dose anesthetics (e.g., 0.5% lidocaine).
4. Neither acupuncture nor trigger-point injections are prone to adverse side effects and there is some evidence that both have a better-than-placebo effect, although more studies with better "more credible" placebo therapies are needed to fully justify this conclusion.
5. Prolotherapy using sclerosing solutions for pain suppression has very low quality experimental data and it has an increased risk of adverse side effects over both acupuncture and trigger-point injections.
6. Regardless of method, transient clinical pain suppression using injections or needle-based therapy may occasionally be an acceptable clinical strategy for some chronic pain sufferers.
7. For cervicogenic headache sufferers, a randomized controlled study reported that occipital nerve blockade with lidocaine was more effective in pain reduction at the 2-week follow-up than a placebo injection.
8. With regard to cluster headaches, chronic migraine, and idiopathic atypical facial pain, there have been no controlled studies that demonstrate a long-term pain-suppression effect for sphenopalatine ganglion block.
9. For myogenous pain in the head and neck region, sphenopalatine ganglion block with lidocaine was found to be no better than the effect induced with a saline injection.
10. Stellate ganglia blocks are clearly the most dangerous of all the head and neck pain based injection therapies, and stellate blocks using anesthetics have not been proven effective through double-blind random controlled trials.
11. The use of opioid injections as a pain-suppressing method for chronic temporomandibular joint arthralgia and osteoarthritis is also not found to be more efficacious than a placebo injection.
12. Needle- or injection-based therapies that induce a neuroablation of peripheral nerves in refractory trigeminal neuralgia patients have been found to have some benefit, but the evidence is very limited and these methods are reserved only for unusual cases where other, less-destructive methods of treatment have failed.
13. There are no controlled randomized blinded studies using cryoneuroablation applied to peripheral branches of the trigeminal nerve for the management of chronic facial pain of any type.

Recommendations regarding musculoskeletal spasm and BoNT/A injections

1. With proper technique local site-of-injection side effects from BoNT injections are rare.
2. The two most common medication-related side effects from BoNT orofacial injections are alterations in salivary consistency and inadvertent weakness of the swallowing, speech, and facial muscles. These complications are injection-site specific (e.g., more common with lateral pterygoid injections and palatal and tongue muscle injections) and dose-dependent problems.
3. BoNT/A side effects are bothersome but limited and are not contraindications for the therapy if it is needed.
4. The information summarized here represents mostly promising case series or open-trial reports, but randomized, blinded, controlled trials (RBCTs) must be done to establish the true efficacy of this modality of therapy for the orofacial motor disorders.
5. The general latency for BoNT/A is 1 week, its duration is 2–3 months, and it is recommended that injections be done no more frequently than every 12 weeks to avoid development of antibodies against the toxin.
6. Depending on the target muscle the dosage range is between 10 and 50 mouse units (of BoNT/A) per site, with a total dose of 200 units in the masticatory system. More than this can be used (up to 400 units maximum) if other sites in the head and neck are included in the injection protocol.
7. For hemifacial spasm, BoNT/A injections have the largest number of open-label, clinical trials, some of which have a 10-year follow-up; the conclusions reached by all of these reports are that treatment of hemifacial spasm with repeated injections of BoNT has been highly successful and that the dose and relative effect of the injections is quite stable over time.
8. For BoNT/A injection methodology, while electromyographic (EMG)–guided injection placement may be useful, it is neither practical nor needed in most situations for orofacial injections since most of the orofacial muscles are easily palpable or have definitive bony landmarks to help with the localization process.

Recommendations for myofascial and trigeminal neuropathic pain and BoNT/A injections

1. When injecting painful muscles without palpable muscle hardness, EMG-determined spasticity, or observable involuntary movements such as in chronic myofascial trigger points or as the site of chronic daily headache pain, BoNT injections might be helpful, but conclusive data for this application is still lacking.
2. Evidence suggests that BoNT/A might decrease neural input to the trigeminal nuclei and thus potentially reverse chronic neuropathic pains manifested in the head, neck, and orofacial regions, although this evidence is not strong.
3. The suggestion that if local anesthesia aids in blocking chronic pain phenomena, then BoNT/A might also be therapeutic is not fully supported by the evidence reviewed and certainly should be better studied.
4. The recent use of BoNT/A subcutaneously for neuropathic pain is both encouraging and even suggestive that BoNT may also be useful to treat atypical odontalgia, phantom tooth pain, burning mouth syndrome, or even trigeminal neuroma pain, but in the absence of specific studies, it is currently impossible to formulate an opinion on whether BoNT/A will be helpful in treating these problems.

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Chapter 12

Treatment for oral mucositis and noninfectious, non-neoplastic oral ulcerations

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12.1 Introduction

This chapter focuses on two mucosal disease problems that cause significant pain and discomfort. First we review oral mucositis (OM) induced by radiotherapy and/or chemotherapy. Second, we review multiple non-neoplastic, noninfectious oral ulcerative (OU) conditions. As mentioned, both conditions cause substantial pain, and patients with either condition need help with pain management. Fortunately, for OM there are recent evidence-based guidelines for treatment that have been endorsed by the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society for Oral Oncology (ISOO).[1,2] Where we could find them, Cochrane-based reviews on these treatment methods have been included.[3,4] With regard to the subgroup of non-neoplastic and noninfectious oral ulcerative (OU) conditions, we discuss the palliative and immunosuppressive management methods that are common for almost all of these conditions. Where a specific oral ulcerative condition has a unique and evidence-based treatment method, this is also reviewed.

12.1.A Oral mucositis

Oral mucositis is a condition that is essentially a side effect of cancer therapy, namely, radiotherapy and chemotherapy. These treatments cause a painful, erythematous mucosa that transforms into even more painful ulcerations.[5] The specific features of OM are provided next.

Clinical presentation

This condition is a painful and often dose-limiting complication of radiotherapy (RT) and combined chemoradiotherapy (CRT) to the head and neck. It also develops in association with standard chemotherapy (CT) protocols used for cancer therapy as well as the high-dose conditioning regimens used with hematopoietic stem cell transplantation (HSCT). The healing period is usually 2–4 weeks after cessation of either therapy. OM along with pharyngeal and other alimentary tract mucositic inflammation can lead to significant complications, including dysphagia, malnutrition, electrolyte imbalance, systemic infection, and even death. If the patient is not already hospitalized, it is not uncommon for a severe OM to force hospitalization and untoward treatment modifications and interruptions.

Location

For chemotherapy-induced mucositis, the nonkeratinized mucosa of the oral cavity is typically affected (Figs. 12.1 and 12.2). The keratinized mucosa is generally spared with chemotherapy-induced OM, but may be affected following radiotherapy.

Grading the severity of oral mucositis

Treatment of secondary OM is largely governed by the severity of the problem (e.g., more severe problem dictates a more aggressive treatment approach) so it is essential to rate OM. Several clinical measurement scales of OM have been used by clinicians and researchers. The World Health Organization (WHO) scale is preferred by many clinicians for its simplicity and ease of use (Table 12.1). This scale measures clinical signs and symptoms as well as functional ability, mainly to eat and drink. The other commonly used scales are the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0,[6] the Oral Mucositis Assessment Scale (OMAS),[7] and the Eastern Cooperative Oncology Group (ECOG) common toxicity criteria.[8]

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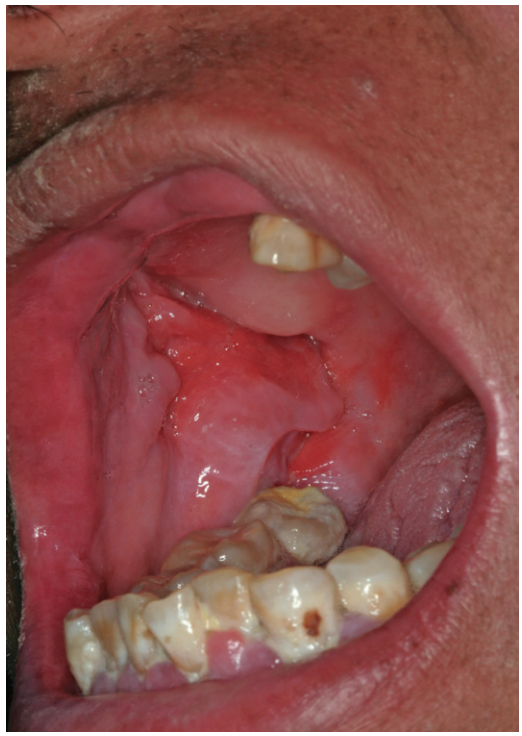

Figure 12.1 Clinical presentation of radiation-induced oral mucositis.

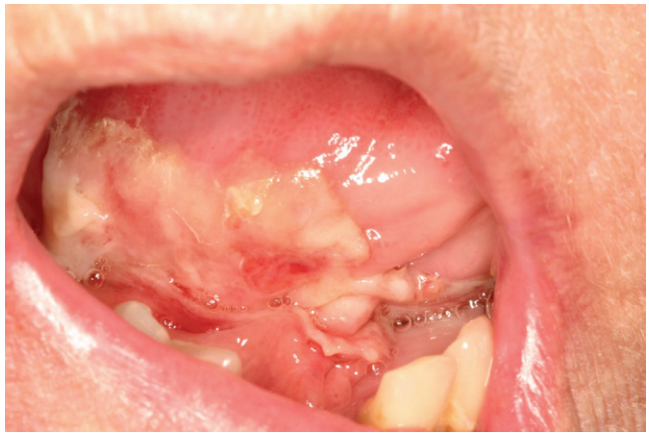

Figure 12.2 Clinical presentation of chemotherapy-induced oral mucositis. (Photograph courtesy of Nathaniel S. Treister, DMD, DMSc, Division of Oral Medicine and Dentistry, Brigham and Women's Hospital.)

Table 12.1 World Health Organization scale for oral mucositis

Grade 0	No oral mucositis
Grade 1	Erythema and soreness
Grade 2	Ulcers, able to eat solids
Grade 3	Ulcers, requires liquid diet
Grade 4	Ulcers, alimentation not possible

Etiology

The frequency and severity of OM varies with different modalities of oncologic treatment regimens.[9–11] As a general rule, OM lesions typically occur 1–2 weeks following chemotherapy or after radiotherapy doses greater than 30 Gy (gray, a unit of absorbed radiation).

12.1.B Oral mucositis epidemiology

The type of antineoplastic treatment logically dictates the number and severity of patients who have OM. In a comprehensive analysis of more than 400 studies, Sonis et al. noted that mild mucositis problems (Grades 1 and 2 according to the WHO scale) were not reported consistently in many studies; however, when grades 3 and 4 were combined, data on the incidence of mucositis was determined.[12] This study examined which treatment regimes were more likely to cause mucositis and they reported that when 5-fluorouracil (5-FU) was added to a chemotherapy regimen the rate of Grade 3–4 OM was greater than 15%. Use of new agents, such as imatinib and taxane- and platinum-based regimens, was associated with a lower incidence of oral and gastrointestinal mucositis.[5,12] In contrast, radiation therapy to the head and neck results in Grade 3–4 OM in at least 50% of patients; depending on the tumor site, it may induce OM in 100% of patients. If a patient is undergoing HSCT with a total body irradiation containing conditioning regimen, the rate of mucositis was around 60% whereas the incidence rate declined to 30–50% with chemotherapy alone.[12] Recently (2008), the European Blood and Marrow Transplantation Mucositis Advisory Group reported on OM.[13] This study assessed the incidence, duration, and determinants of severe OM (WHO oral toxicity scale grades 3–4) in patients with multiple myeloma (MM) or non-Hodgkin's lymphoma (NHL) receiving high-dose conditioning chemotherapy before autologous HSCT. They found that of the 109 patients with MM and 88 patients with NHL who were treated, severe OM occurred in 46% of MM patients and 42% of NHL patients respectively. OM incidence rates, however, are at best rough estimates due to the lack of well designed prospective studies.

12.1.C Oral mucositis consequences

The burden of OM not only compromises the quality of life (QOL) of the patients but also significantly increases the cost of treatment and hospitalization due to associated pain and secondary infection management, diet and nutritional supplements, and gastrostomy tube placement. In a prospective, multicenter, observational study to evaluate a new QOL instrument, the Oral Mucositis Weekly Questionnaire–Head and Neck Cancer (OMWQ-HN), increasing mouth and

throat soreness (MTS) corresponded with a steady decline in function, with the greatest impact on eating, swallowing, and drinking.[14] In a retrospective study assessing the in-hospital complications of autologous HSCT in multiple myeloma and lymphoma patients, incident infectious complications, stomatitis, and the use of total parenteral nutrition (i.e., providing nutrition via an intravenous line) increased the mean cost of hospitalization by more than threefold.[15] Similar findings were reported in a retrospective cohort of 204 head and neck (HN) cancer patients undergoing radiotherapy or chemoradiotherapy, analyzed for risk, cost, and clinical and economic outcomes of OM. In this study, a total of 91% of patients developed OM of whom 66% had severe mucositis (Grade 3–4). For both OM groups, a substantial increased cost of care was seen.[16]

12.1.D Oral mucositis pathogenesis

Oral mucositis is the clinical manifestation resulting from a complex sequence of events involving the activation of several intracellular signaling pathways with concomitant molecular changes. It is now known that OM is not a condition exclusively affecting the epithelium, but rather involving all the cellular components of the mucosa. With the cumulative knowledge gained by molecular research over the last decade or so, the proposed mechanisms of OM have evolved into a five-phase (or stage) model.[17] Understanding this model may help researchers develop more targeted molecular therapies in the future:

- *The initiation phase* At the cellular and molecular level, immediately after administration of chemotherapy (CT) or radiation therapy (RT), the direct DNA damage caused by these treatment modalities leads to the production of reactive oxygen species (ROS), which results in death of cells in the basal layer and submucosal cells; collectively these events are referred to as the initiation phase.
- *The primary damage response phase* This second phase, the primary damage response phase, is characterized by the production of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and IL-1β, and activation of signaling pathways, such as the ceramide pathway, mediated in large part by the transcription factor nuclear factor kappa B (NF-κB).
- *The signal amplification phase* The signal amplification phase is characterized by positive feedback via NFκB with further upregulation of TNF-α, IL-6, IL-1β, cyclooxygenase-2 (COX-2), and other pro-inflammatory mediators, amplifying the damage caused to the tissues by increased inflammation and apoptosis.
- *The ulceration phase* The ulceration phase follows when there is clinically evident breakdown of the mucosa.

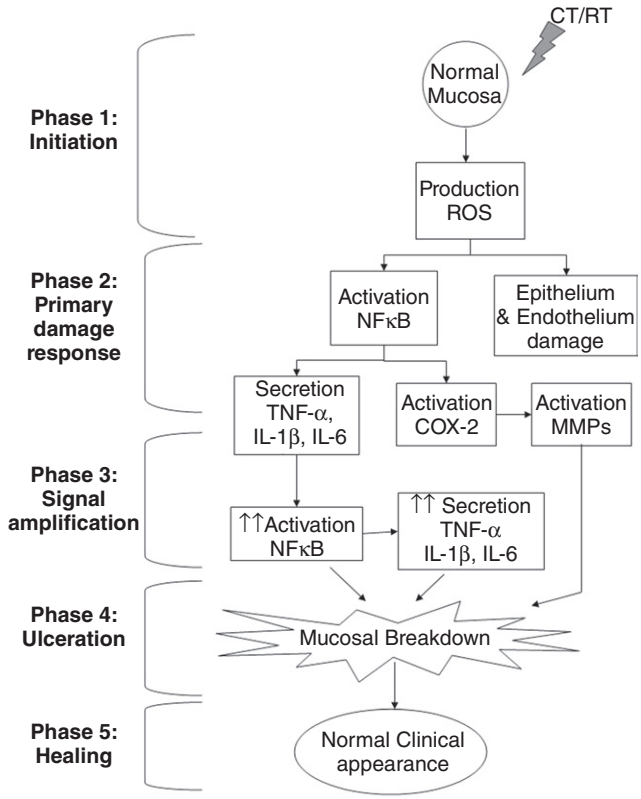

Figure 12.3 Summary of the main cellular and molecular events in the five-stage model of the pathogenesis of oral mucositis. (Adapted from Sonis ST, et al., *Cancer*, 2004;100(9 Suppl):1995–2025; Sonis ST, *Oncol*, 2007; 5(9 Suppl 4):3–11.)[12,19]

Pain is greatest during this phase, and secondary bacterial colonization of the ulcerated mucosa can further contribute by triggering more production of pro-inflammatory cytokines.

- *The healing phase* The healing phase is defined by restoration of the integrity of the mucosal tissues following termination of CT or RT treatment. The mechanisms involved here are yet to be completely elucidated (Fig. 12.3).[18,19]

Cytokines and nuclear factor

Due to the relevance of NF-κB and pro-inflammatory cytokines in the pathogenesis of OM, a more detailed review of its role on this condition is warranted.[20–22] It is important to highlight that NFκB is an important transcription factor responsible for the activation of several genes involved in inflammatory processes. NF-κB is activated in response to pathogens and pro-inflammatory cytokines and by radiotherapy and chemotherapeutic agents. In addition, an

increase in the expression of COX-2, which is regulated by NF-κB, is also observed, providing further evidence for the role of NF-κB and its target genes on the pathogenesis of OM.[23] In regards to the role of TNF-α and IL-1β in OM, the most convincing recent data has come from hamster studies. Hamsters that have received radiation and developed OM have an increased epithelial expression of TNF-α and IL-1β at day 15 postradiation. In this study the higher levels of these cytokines had a positive correlation with the severity of OM.[24] Similarly, in rats that had OM induced by treatment with either 5-FU or methotrexate (MTX) there was an increased expression of NFκB, TNF-α, IL-1β, and IL-6 in the involved oral mucosa.[25] Agents that block TNF-α, such as pentoxifylline (PTX) and thalidomide (TLD), have been shown to inhibit cytokine synthesis in hamsters, which in turn resulted in decreased OM.[26] However, pentoxifylline has been used in clinical trials with no remarkable success for prevention of OM. The MASCC/ISOO panel does not recommend the use of pentoxifylline to prevent OM in patients undergoing HSCT, with similar observation from Cochrane review.[27,28]

12.2 Oral mucositis management

The management of OM is largely palliative, consisting mainly of pain relief, nutritional support, and improved quality of life. With regard to prevention of OM, several pharmacologic interventions have been reported as promising; unfortunately, the majority of studies conducted have not been well designed and are not randomized, placebo-controlled trials. Wherever possible, our recommendations are based on those put forth and endorsed by MASCC and the ISOO and are supplemented with Cochrane reviews whenever applicable.

12.2.A Basic oral hygiene, diet, and nutrition

All patients who are scheduled to undergo radiotherapy or chemotherapy regimes that have a high likelihood of OM development need to have a careful and detailed review of their oral hygiene practice. In addition they need to understand how their diet must change and how proper nutrition might affect the course of their healing reaction.

Basic oral hygiene

Maintenance of oral hygiene is essential in patients with OM to prevent secondary infection and sepsis, to reduce pain, and to improve function. Preventative care may reduce the risk of OM in children.[29–31] It is generally agreed that good oral care is an important adjunct to the prevention, severity, and management of oral mucositis, but it is rarely stressed in clinical practice.[32] Patients, routinely, are not taught how to care for their mouths, and the nursing practice of assessing for oral complications and educating families on the importance of oral hygiene is often overlooked.[33,34] Additionally, oral hygiene greatly varies across and even within clinical institutions. One survey that looked at 92 transplant centers saw few similarities regarding the management of oral care and found that oral care procedures were based on tradition or subjective evaluation rather than evidence-based practice.[35,36]

Good oral hygiene is the only intervention that has demonstrated a clear benefit in the prevention or treatment of mucositis in children.[37] Tooth brushing, flossing, rinsing with a bland agent, such as sterile water, and using mouth moisturizers prevents infections of the oral soft tissue and helps alleviate pain and bleeding.[1,38] Oral hygiene should be performed regardless of hematologic status, myelosuppression, and/or thrombocytopenia.[39] It is reasonable to continue flossing without traumatizing tissues during immunosuppressive periods and throughout therapy, but dental floss should only be allowed if the patient is properly trained. Though the literature varies regarding the implementation of "basic oral hygiene," most agree that tooth brushing is the best way to keep the mouth clean, preferable to oral sponges.[40,41] Oral sponges or toothettes should only be used when the patient cannot tolerate a regular toothbrush. Tooth brushing should be encouraged two to three times a day, brushing should last at least 2 minutes, and the brushes should be air-dried between uses.[42] It is important to note that the toothbrush itself can become colonized with bacterial organisms, stressing the importance of replacing toothbrushes often, such as after each febrile illness and/or cycle of chemotherapy, to prevent excessive accumulation of oral bacteria.[43]

- The MASCC/ISOO panel recommends regular, systematic, oral care hygiene with brushing (with a soft-bristled toothbrush which should be replaced regularly), flossing, bland rinses, and moisturizers using a standardized oral care protocol for all OM patients.
- The panel notes that an interdisciplinary approach to oral care involving physician, dentist, nurse, dental hygienist, dietician, pharmacist, and others as relevant will be essential for providing comprehensive supportive care for OM patients.[1]

Diet and nutrition

Intake of regular diet and maintaining adequate nutrition become very difficult in OM patients. A liquid or soft diet that does not require chewing is recommended. General

guidelines include the following: using topical analgesics prior to eating; the intake of small pieces of food, avoiding highly acidic, salty, bitter, and spicy foods; using a straw with liquids; use of nutritional supplements; and nonalcohol mouthwash following meals.[44] A gastrotomy tube (enteral nutrition) or a Hickman line (parenteral nutrition) may be placed in some patients in anticipation of severe OM.[27]

12.2.B Prevention of secondary infections

Because incipient dental disease can rapidly progress in a mouth that is not cleaned daily, correction of pre-existing oral conditions prior to the initiation of chemotherapy and subsequent aggressive mouth care reduce the incidence and severity of mucositis.[45] Standard care should therefore include dental evaluation and correction of any periodontal disease before beginning chemotherapy. Patients should also receive instruction on mouth care and be encouraged to adhere to an aggressive oral hygiene regimen throughout the treatment period. Maintenance of oral hygiene becomes extremely difficult, thus creating an ideal situation for opportunistic oral and potentially systemic infections. Although routine or prophylactic use of antibacterial,[46] antiviral,[47] or antifungal[48] treatment is not effective in preventing OM, as these microorganisms are not believed to play a role in its pathogenesis, their use in the treatment of a secondary, concurrent infection is appropriate.[49]

Chlorhexidine

Chlorhexidine rinses at a 0.12% concentration have been widely used in dentistry as an antibacterial mouthrinse, especially in patients with periodontal disease who cannot clean their mouths effectively. Chlorhexidine mouthrinses are used as part of oral decontamination in OM patients in some centers but would typically be discontinued with severe OM onset since the alcohol in the mouthwash would be too irritating. As a preventative agent, chlorhexidine is ineffective in preventing or treating OM.[50,51] The Cochrane review concluded that there is insufficient evidence to support or refute that chlorhexidine is more or less effective than placebo or no treatment in prevention of OM.[3]

- The MASCC/ISOO panel has recommended not using chlorhexidine to prevent OM in patients undergoing radiotherapy for solid tumors of the head and neck or to treat established OM.[1]

On a practical clinical note, it should be remembered that if mucositis develops, chlorhexidine rinses should be discontinued if irritating, and alcohol-free formulations should be used instead.[52]

12.2.C Medications for pain control in oral mucositis

Pain is mostly based on severity and extent of lesions and unfortunately is the hallmark symptom of OM.[53] The physical and emotional distress due to the cancer and its treatment can lead to more subjective increase in pain in many patients and is explained by the biopsychosocial model of pain.[54,55] The subjective and objective assessment of pain and its impact on function is critical for appropriate management and interventions. The need for proper subjective and objective pain assessment in terms of function and need for medications has been reported.[56,57] Management includes systemic analgesics (mainly opioids) and local palliative measures such as topical anesthetics, analgesics, and mucosal protective agents.

Systemic analgesics

Morphine is the opioid that has been used primarily for management of OM pain either as patient-controlled analgesia (PCA) or hospital infusions.[58] PCA has been shown to require less total opioid use for the management of OM pain compared with continuous hospital infusion with equivalent levels of pain control.[59,60] Interestingly, another mode of drug delivery called pharmacokinetically based, patient-controlled analgesia (PKPCA), where patients adjust the rate of continuous morphine infusion to increase or decrease their plasma morphine concentration, was shown to provide more pain relief than conventional bolus dose PCA without a significant increase in side effects.[61]

- The MASCC/ISOO panel recommends PCA with morphine as the treatment of choice for OM pain in patients undergoing HSCT.

There may be a role for tricyclic antidepressants (TCAs) and fentanyl transdermal therapeutic system (FTTS) in the management of OM pain but further studies are needed.[62,63] Chapter 4 covers the proper use of opioids for malignant and nonmalignant pain.

Topical anesthetics and analgesics

Topical anesthetics such as 2% viscous lidocaine and "magic" mouthwash (a term that refers to different formulations used as mouthwash and consisting of a mixture of ingredients). While the formulations vary, often magic mouthwash is made of equal parts viscous lidocaine (2%), liquid diphenhydramine, and a mucosal coating agent (e.g., Maalox® or kaopectate). The typical approach is to have the pharmacist mix these agents together, dispense them with a 15-mL dosing cap and instruct the patient to keep this liquid

cool (stored in the refrigerator at home). The patient is instructed to rinse with 15 mL up to four times a day. Specifically, the patient should swish it in the mouth for 30 seconds and then spit out. Compared with saline rinses, topical lidocaine is much more effective at reducing pain secondary to OM. Sometimes anti-inflammatory agents are not adequate. For example, a randomized study with a small group of 26 OM patients being treated with concomitant chemoradiotherapy for head and neck cancer compared the efficacy of morphine mouthrinse versus a magic mouthwash (i.e., equal parts lidocaine, diphenhydramine, and magnesium aluminum hydroxide).[64] The authors reported that the duration of severe pain and intensity of oral pain were found to be significantly lower in the morphine group than the magic mouthwash group. A recently published randomized double-blinded crossover study showed significant pain relief with topical morphine compared with placebo and the pain relief lasted for almost 2 hours with topical morphine solution.[65] Additional information on topical anesthetics for oral pain can be found in Chapter 5.

12.2.D Mucosal protective agents

Several agents or formulations have been used and studied as a protective mucosal barrier to aid in patient comfort during OM.[66] Of these, sucralfate, Gelclair® (Helsinn Healthcare SA, Lugano, Switzerland), and Caphosol® (Cytogen Corporation, Princeton, NJ) are briefly discussed here.

Sucralfate

Sucralfate, a basic aluminum salt of sucrose sulphate has been used for both prevention and treatment for OM. However, studies have not shown much benefit.[67,68] The Cochrane review found no statistically significant differences, concluding that there is insufficient evidence to support or refute that sucralfate is more or less effective than placebo.

- The MASCC/ISOO panel does not recommend the use of oral sucralfate for reduction of side effects of radiotherapy.

Gelclair

This agent comes as an oral gel containing mainly polyvinylpyrrolidone and sodium hyaluronate that forms an adherent barrier over the oral mucosa. Its protective barrier forming abilities seem to provide transient comfort to OM patients.[69] A recently reported randomized clinical trial comparing Gelclair against a mixture of sucralfate and Mucaine® (which mainly contains oxethazaine in alumina gel of aluminum hydroxide and magnesium hydroxide; Wyeth-Ayerst Laboratories) in 20 patients with radiotherapy-induced OM found no significant difference between the two. Both agents provided good short-term pain control but relief did not last for the full 24-hour assessment period in this study. Further randomized, placebo-controlled trials will have to establish the efficacy of this agent.

Caphosol

This agent comes as a mouthrinse and it is a neutral, supersaturated, calcium phosphate (Ca^{2+}/PO_4^{3-}). Calcium and phosphate downregulate the inflammatory process, blood clotting cascade, and tissue repair and are believed to exert their beneficial effects by diffusing into intercellular spaces in the epithelium and permeating OM lesions. A double-blind, prospective, randomized clinical trial studied the efficacy of Caphosol with fluoride treatments against a standard regimen of fluoride rinsing and placebo tray treatments in 95 patients undergoing HSCT. The authors found a statistically significant decrease in days of OM and duration of pain, besides other parameters.[70] While these findings appear to be promising, no additional studies have been published and the result has not been replicated at other centers.

12.2.E Chemopreventative agents to prevent and/or reduce severity of oral mucositis

The idea that you can use a medication before the radiotherapy or chemotherapy to ward off or minimize the severity of OM has received much attention.

Cryotherapy

Cryotherapy has been shown to reduce OM in patients receiving stomatotoxic chemotherapy with a short half-life and doses over short periods of time.[71–73] Oral cryotherapy causes local vasoconstriction, reduces blood flow to the oral mucosa thereby decreasing the uptake of 5-FU, and eventually less OM. In cryotherapy, ice chips are typically placed in the mouth 5 minutes before administration of chemotherapy and are replenished over 30 minutes. It should be noted that cryotherapy is not useful in radiation-induced OM as it causes direct mucosal damage in the radiation field.

- The MASCC/ISOO panel recommends that patients receiving bolus 5-FU chemotherapy undergo 30 minutes of oral cryotherapy to prevent OM; it also suggests the use of 20–30 minutes of oral cryotherapy to decrease OM in patients treated with bolus doses of edatrexate and the use of cryotherapy in patients receiving high-dose melphalan as a conditioning agent in HSCT.

Keratinocyte Growth Factors

Keratinocyte growth factor (KGF) is a 28-kDa heparin-binding member of the fibroblast growth factor (FGF) family and specifically binds to the KGF receptor expressed only in epithelial tissues. KGF mediates proliferation and differentiation in a wide variety of epithelial cells, including keratinocytes in stratified squamous epithelia.[74] Systemic administration of recombinant human KGF (rHuKGF) has been shown to provide significant epithelial protection in animal models of epithelial–mucosal damage.[75] The successful animal studies led to studies in humans with recombinant human KGF (palifermin), which was shown to cause epithelial proliferation as well, especially in patients with OM.[76–79] Recombinant human KGF1 (fibroblast growth factor 7 [FGF-7] or palifermin) is a member of the FGF superclass. The cytoprotective effect of palifermin is attributed to several functions: mitogenic effect which results in increased thickness of mucosal epithelium; upregulation of Nrf2, a transcription factor in keratinocytes which upregulates genes encoding reactive oxygen species–scavenging enzymes;[80] generates IL-13, an anti-inflammatory cytokine which reduces TNF-α; exerts antiapoptotic effects; and reduces angiogenesis. The US Food and Drug Administration (FDA) approved palifermin (Kepivance®) for patients with hematologic malignancies receiving chemotherapy and radiation therapy and requiring HSCT.[81]

- The MASCC/ISOO panel recommends the use of keratinocyte growth factor-1 (palifermin) in a dose of 60 µg/kg per day for 3 days prior to conditioning treatment and for 3 days post-transplantation for the prevention of OM in patients with hematologic malignancies who are receiving high-dose chemotherapy and total body irradiation with autologous HSCT.

Another KGF, repifermin (KGF-2) was studied in a Phase I/II randomized, placebo-controlled trial evaluating the safety and clinical effects to reduce OM in 42 patients undergoing autologous HSCT.[82] This agent, however, did not demonstrate efficacy.

Granulocyte–macrophage colony stimulating factor

Granulocyte–macrophage colony stimulating factor (GM-CSF) stimulates cells of the innate immune system in mucosal tissues. Several studies evaluating the usefulness of GM-CSF mouthwash in OM patients found that it did not decrease the frequency and duration of severe OM in patients.[83–85] The Cochrane reviewers after evaluating nine trials until 2003 concluded that the comparisons between GM-CSF and placebo or no-treatment groups were not significant and therefore there is insufficient evidence to support or refute the efficacy of GM-CSF.

- The MASCC/ISOO panel suggests that GM-CSF mouthwashes not be used for the prevention of OM in patients undergoing HSCT.

Benzydamine hydrochloride

As pathogenesis of mucositis primarily involves production of inflammatory cytokines such as TNF-α, anti-inflammatory medications have been studied to reduce the severity of OM.[86] Benzydamine hydrochloride (HCl) is an indirect cytoprotectant with anti-inflammatory, analgesic and antimicrobial activity. Benzydamine HCl was studied in a multicenter, randomized, double-blind, placebo-controlled clinical trial for prophylaxis of radiation-induced OM. Benzydamine HCl was used as 15 mL oral rinse for 2 minutes, 4–8 times daily before and during RT, and for 2 weeks after completion of RT. The benzydamine HCl oral rinse significantly reduced erythema and ulceration by approximately 30% compared with the placebo and also delayed the use of systemic analgesics compared with placebo. However, it was found to be ineffective in subjects receiving accelerated RT doses (≥220 cGy/day). Based on this trial and other pervious trials,[87,88] the Cochrane review concluded that this agent may have some benefit in preventing or reducing the severity of OM associated with cancer treatment.

- The MASCC/ISOO panel recommends the use of benzydamine for prevention of radiation-induced OM in patients with head and neck cancer receiving moderate-dose radiation therapy (regimens with cumulative doses up to 5000 cGy).

Of note, a recent study sponsored by McNeil was conducted to study the efficacy of benzydamine and was discontinued after an interim analysis and the recommendations of the Data Monitoring Committee.

Amifostine

Amifostine is a thiol drug which is cytoprotective by several mechanisms, including scavenging oxygen-derived free radicals, DNA protection and repair acceleration, and induction of cellular hypoxia. While amifostine has FDA approval to reduce the incidence of moderate to severe xerostomia in patients undergoing postoperative radiation treatment for head and neck cancer,[89–91] studies on management of OM have shown conflicting results.[92,93] The Cochrane review concluded that amifostine appears to have small benefit in preventing and reducing the severity of mild OM.

- The MASCC/ISOO panel recommends the use of amifostine for the prevention of esophagitis in patients receiving chemoradiotherapy for non–small-cell lung cancer and suggests that intravenous amifostine at a dose of

340 mg/m^2 daily prior to radiotherapy may prevent radiation proctitis in patients who are receiving standard-dose radiotherapy for rectal cancer.

However, the panel found that most of the amifostine studies on the reduction of OM have been small, single-center studies with conflicting results.

Glutamine (Saforis® or AES 14)

Glutamine is a nonessential amino acid which is widely distributed throughout the body and becomes an essential amino acid during disease or trauma.[94] Glutamine has been shown to improve immunologic function by decreasing the inflammatory response and to improve OM after high-dose chemotherapy followed by autologous HSCT. Multiple trials studying its effect on OM prevention have shown some promise.[95–97] In 2007, a Cochrane review concluded that there is insufficient evidence to conclude that glutamine is effective for the prevention of OM formation at any level of severity. The MASCC/ISOO panel concurs and recommends against the use of systemic glutamine for the prevention of gastrointestinal mucositis because of lack of efficacy. Recently, Saforis (MGI Pharma, Minneapolis, MN), a proprietary oral suspension of L-glutamine powder, has shown beneficial effects in OM. It is believed to aid in uptake of glutamine into epithelial cells and may reduce mucosal injury by reducing the production of proinflammatory cytokines and cytokine-related apoptosis.[98,99] A Phase III randomized, placebo-controlled trial of Saforis for prevention and treatment of OM in breast cancer patients receiving anthracycline-based chemotherapy showed a significant reduction in incidence of OM.[100]

Low-level laser therapy

Finally, there is some literature support for the use of low-level laser therapy (LLLT) in reducing the symptoms and severity of OM.[101,102] The mechanism of action is not well elucidated, but it is believed that the absorption of laser energy by chromophores on mitochondria or other intracellular organelles results in the upregulation of wound-healing mechanisms. The various studies evaluating LLLT have been difficult to compare owing to different parameters utilized, such as different types of laser sources (HeNe, GaAlAs, and GaAs), wavelengths (632.3, 650, 660, 780, 810–820, and 901 nm), powers (15–70 mW), and energy densities.[103]

- The MASCC/ISOO panel suggests the use of LLLT to reduce the incidence of OM and its associated pain in patients receiving high-dose chemotherapy or chemoradiotherapy before HSCT.

The panel noted that LLLT requires expensive equipment and specialized training and hence suggests its use only if the treatment center is able to support the necessary technology and training.

12.3 Nonmalignant and noninfectious oral ulcerations

Before discussing the nonmalignant and noninfectious subgroup of oral ulcerative diseases, it must be said that clinical history, careful examination, and laboratory studies including culture and biopsy are critical to making sure you have correctly eliminated the infectious (viral, bacteria, fungal) and neoplastic causes for an oral ulcer. This chapter does not review these methods as there are several excellent articles and textbooks that will help the clinician distinguish between oral mucosal lesions.[104–107]

12.3.A Description and classification

Ulcers, by definition, are characterized by a loss of surface tissues and they affect both the epithelium and underlying connective tissue.[108] The term "erosion" must be differentiated from ulcers in that erosion involves only superficial epithelium and can be as painful as an ulcer. However, as this chapter focuses on treatment of pain mainly, the term "ulcer" is generally used to include erosions caused by vesiculobullous diseases and other causes. Oral ulcers are very common lesions of the oral mucosa and are generally painful.[109] Many authors classify oral ulcers into two main groups: (1) acute ulcers with abrupt onset and short duration, and (2) chronic ulcers (greater than 2 weeks in duration) with slow onset and progression. Unfortunately, the distinction between acute and chronic is not based on etiology and sometimes, when an ulcer is chronic, it may mean that the etiology is simply still present. For example, a patient who has a contact-allergy-induced ulceration will have a chronic presentation if the offending agent is not identified and removed. In this chapter we suggest that the noninfectious and non-neoplastic ulcerative disorders might be better grouped according to their suspected etiologies, not by duration (see Sec. 10.3.C). To assist in differentiating these ulcers, the typical clinical features are presented in tabular form (Table 12.2)

12.3.B Epidemiology

In 2004, using the data from the Third National Health and Nutrition Examination Survey, one study reported on the most common oral lesions in the United States. They found that many of the lesions seen were related to dental

Table 12.2 Nonmalignant and noninfectious ulcers: clinical features

Oral ulcerative disease	Clinical features
Drug-induced ulcers	Single, isolated ulcers, located on the side of the tongue, surrounded by an erythematous halo and resistant to usual treatments
Erosive lichen planus	Areas of atrophy, erosions, or painful ulcers, generally resistant to conventional treatments
Pemphigus vulgaris	Bullae appear in oral cavity (posterior region), forming painful ulcers with necrotic fundus and erythematous halo.
Mucous membrane pemphigoid	Spontaneous onset of bullae that readily rupture, giving rise to a highly painful ulcerated area (most commonly on palate and gingiva)
Lupus erythematosus	Erythema and oral ulcers, without induration and accompanied by whitish striae and a tendency to bleeding
Reiter's syndrome	Arthritis, urethritis, conjunctivitis, and oral ulcers similar to those of recurrent aphthous stomatitis
Eosinophilic ulcer	Large ulcer, generally in the tongue, with raised, indurated borders and white-yellowish fundus that may resemble a malignant lesion; persists for weeks or months
Traumatic ulcer	Ulcers appear in short and painful episodes; white or yellowish central clear area with erythematous halo
Recurrent aphthous stomatitis	One or multiple recurrent and painful ulcers; well-defined, round or oval ulcers covered by a white or greyish pseudomembrane and surrounded by an erythematous halo
Behçet's disease	Recurrent oral (aphthae) and genital ulcers, skin lesions, and ocular, musculoskeletal, cardiovascular, gastrointestinal, and neurological symptoms
Necrotizing sialometaplasia	Extensive deep ulcers with indurated borders located in hard or soft palate
Allergic reactions	Features ranging from erythema to ulceration in oral mucosa
Erythema multiforme	Erythema, vesicles, and ulcers in oral mucosa; involvement of the lips in almost all cases, leaving scabs; typical target skin lesions
Blood-disease related	Ulcers similar to those of recurrent aphthous stomatitis

prostheses and tobacco use.[110] A 2002 study examined the oral mucosa of 500 residents of Thailand who were 60 years of age or older.[111] They reported that 83.6% of those examined had some type of abnormality, and traumatic ulcer had an incidence rate of 15.6%. In 2005 a review of the literature described that children have oral lesions with incidence rate ranging from 4.1% to 52.6% of the population, of which the most common were recurrent aphthous stomatitis (0.9–10.8%), labial herpes (0.78–5.2%), and traumatic injury (0.09%–22.15%).[112]

12.3.C Etiology-based subgroups for noninfectious and non-neoplastic oral ulcers

We suggest six etiologic groups: (1) trauma, (2) allergic reactions, (3) nonspecific adverse drug reactions, (4) ulcers associated with autoimmune disease, (5) ulcers associated with blood disorders, and (6) idiopathic ulcers. The clinical presentation will vary depending on the allergen, the trauma, or the drug involved. In the following subsections, we present these six subgroups and 15 specific and different oral ulcerative conditions within these groups (see Table 12.3).

Trauma-induced oral ulcers (subgroup 1)

Direct trauma

Clinical presentation

Depending on the nature of the traumatic injury, the location, depth, and appearance of the ulcer will vary. As a general rule, however, traumatic ulcer is characterized by

Table 12.3 Noninfectious and non-neoplastic oral ulcerative diseases

Oral ulcerative disease	Etiology
Traumatic oral ulcers	External physical trauma, chemicals, electricity, and heat
Recurrent aphthous disease	Inflammatory disease of unknown origin
Behçet's disease	Genetic, environmental, infectious, immunological, and hematological factors have been implicated.
Necrotizing sialometaplasia	Ischemic injury secondary to trauma or to damage from a chemical or biological agent
Allergic contact stomatitis	Contact allergic reaction
Erythema multiforme	Late cell-mediated immune reactions to drug
Ulcers related to blood diseases	Associated with blood deficiencies (anemias, leukemias, lymphomas, multiple myeloma, and neutropenias)
Drug-induced oral ulcers	Allergic reaction to drugs
Lichen planus	Autoimmune disease (T-cell-mediated attack on basal keratinocytes)
Pemphigus vulgaris	Autoantibodies to desmosomal proteins
Mucous membrane pemphigoid	Autoimmune disease
Lupus erythematosus	Autoimmune disease of the connective tissue.
Reiter's syndrome	Autoimmune disease
Eosinophilic ulcer	Etiology uncertain, but associated with traumas

acute pain of moderate intensity and by a white or yellowish central clear area with an erythematous halo.

Causation

The most common causative agents are external physical trauma, chemicals, electricity, and heat. In addition, self-inflicted trauma, caused by sharp teeth and tooth edges or a chewing incoordination, can produce oral tissue damage and ulcers. Ill-fitting dental prothestic devices can cause chronic mucosal reactions due to localized pressure and simple friction to the tissues.[113] Some patients have a greater predisposition to oral mucosal trauma than others, namely, older patients and diabetes mellitus patients. Biting of the tongue or lower lip after dental anesthesia can be the source of self-induced mucosal trauma as well as incorrect or too aggressive tooth brushing.[114] Some medications can be caustic enough to induce ulcers via direct contact. While we will discuss separately the nonspecific adverse mucosal tissue reactions associated with systemic medications in section covering subgroup 3, there are also caustic chemical reactions of the mucosal tissues due to direct and prolonged contact of various medications on the tissues (e.g., aspirin tablets held in the mouth).[115–117] Oral ulcerations can also occur from illegal drugs that come into prolonged contact with oral tissues (e.g., cocaine).

Necrotizing sialometaplasia

Clinical presentation

Necrotizing sialometaplasia is an uncommon lesion which presents as a large deep ulcer with indurated borders that is located on the hard or soft palate, without obvious traumatic injury. It is commonly mistaken as a malignant neoplasm but actually is a self-limiting and benign necrotizing inflammatory disease of the minor salivary glands.[118]

Causation

The cause is believed to be an ischemia secondary to trauma or to damage from a chemical or biological agent. Local anesthesia, thermal trauma due to smoking, traumatic tissue injury, surgical trauma, upper respiratory infection, and allergies have been pointed out as etiological agents. These injuries are theorized to affect the vascular system, causing an ischemia in the salivary glands that may result in local tissue necrosis.[119]

Ulcers induced by allergic reactions (subgroup 2)

Allergic contact stomatitis

Clinical presentation

Allergic contact stomatitis usually presents with edema, erythema, ulcer, hyperkeratotic changes, or a burning sensation. These reactions can range from mild erythematous changes in the oral mucosa (with or without ulceration) to severe ulcerative blistering reactions. In most cases, the diagnosis of this problem is not actually based on the clinical characteristics of the tissue changes but on a careful detailed medical history that includes gathering information about all oral products, foods, or medications being used.

Causation

Contact stomatitis is very commonly due to cinnamon-flavored chewing gum or other cinnamon-flavored dental products. There are numerous other food substances and medicines that come into contact with the oral mucosa and, in susceptible patients, can induce a contact allergic reaction in the mouth.[120] Restorative materials that contain mercury are known to be able to induce an allergic reaction called a lichenoid lesion in the contacting tissue. While a local lichenoid lesion can be distinguished by its location it may not be histologically distinguished from oral lichen planus.[121–124] The most common location of oral lichenoid lesions are the buccal mucosa and lateral tongue borders adjacent to the suspected causative restoration. With oral lichen planus, the tissue changes are not limited to those sites that are in direct contact with restorations and many patients may have cutaneous or other mucosal sites with lesions (e.g., skin or vulvo-vaginal mucosa).[125] When a direct contact allergy is suspected it is possible to perform cutaneous patch testing using various dental restorative materials in the test. This test is normally on the skin of the arm or back but the validity of this testing process is questionable.[126–130] At present data suggests that mercury-containing restorations are more prone to allergic reactions, but some reports also exist regarding allergic reaction to gold, porcelain, composite, and glass ionomer cements as well.[131]

Erythema multiforme and its subtypes

Clinical presentation

This allergy-induced vesiculobullous mucocutaneous disease is potentially life-threatening and is diagnosed only after exclusion of other diseases. It can present in one of three forms.

Erythema multiforme minor

The minor form typically presents as an acute, self-limiting, and episodic problem and is not life-threatening. Patients will typically have target-shaped skin lesions (1–2 cm discoid urticarial and erythematous reactions with a centrally located blister with a blue-red base). To be considered minor, they must occur symmetrically over less than 10% of the body surface area. While the mucosa can be spared in many cases, when it is involved what is seen is erythematous vesicles and ulcers and involvement of the lip. These ulcers will eventually form a crust as they heal and this reaction will appear a few days after the onset of symmetrical target skin lesions develop.

Erythema multiforme major

The major form of this disease is also self-limiting but it can be episodic. It is defined by previously described symmetrical target lesions on the skin, but should involve at least two separate mucosal sites (mouth, anogenital, and ocular regions). Some experts consider Stevens–Johnson syndrome (SJS) to be a separate condition from erythema multiforme (EM) major while others consider it as the same disease. EM is a vesiculobullous disease and it has a positive Nikolsky sign.[132] Intraorally, there are usually multiple painful ulcerative erosions (tongue, lips) covered with a gray-white pseudomembrane in the mouth. Hemorrhagic cheilitis with bleeding crusts is characteristic of EM major/ SJS.

Toxic epidermal necrolysis

This disease is characterized by erythematous skin lesions that occur in a nonsymmetrical pattern with severe erosions and bullae and epidermal detachment of more than 30% of the body surface area. Toxic epidermal necrolysis (TEN) affects oral and other mucous membrane sites.[133] Patients will often have a fever and tachycardia and are at risk of pneumonia.

Causation

The most commonly offered explanation for these diseases is that they are delayed or late-onset cell-mediated immune reactions that remit when the medication or causative substance is stopped or withdrawn.[134] Several medications are reported to have triggered an EM reaction (e.g., sulfonamide, nonsteroidal anti-inflammatory drugs [NSAIDs], allopurinol, barbiturates, and anticonvulsants). There are reports of viral or bacterial infections and even vaccinations that might trigger this reaction.[135] Lastly, idiopathic EM has been reported in 15–25% of all cases.[136]

Oral ulcers associated with adverse drug reactions (subgroup 3)

Clinical presentation

Although adverse drug reactions can present as serious and life-threatening reactions such as erythema multiforme (or one of its subtypes), a more commonly seen drug-induced oral reaction is simple oral ulceration. Drug-induced oral ulcers are usually single, isolated, and located on the side of the tongue and may be surrounded by an erythematous halo. They are relatively resistant to the usual treatments and can become chronic if the causative agent is not identified and withdrawn. All newly prescribed medications would be suspected as a cause and the oral lesions usually disappear when the drug is withdrawn. Unfortunately, depending on the medication, a complete and abrupt cessation of the medication is not always feasible.

Causation

In drug-induced oral ulceration or in lichenoid-type oral tissue reactions, the offending agent is not always the drug itself as it could be one of the elements of the medication (e.g., flavor-enhancing and aroma-enhancing agents). Drugs that are commonly reported to induce oral lichenoid reactions and oral ulcers include some beta-blockers, immunosuppressants,[137] anticholinergic bronchodilators,[138] platelet aggregation inhibitors,[139] vasodilators,[140] bisphosphonates, protease inhibitors, antibiotics, NSAIDs, antiretrovirals, antirheumatics, and antihypertensives.[141,142]

Autoimmune-induced oral ulceration (subgroup 4)

Lichen planus

Clinical presentation

This disease is a common disease that affects both the skin and mucosa (oral and genital areas) of less than 1% of the population. Typical age of onset is between 30 and 60 years. The most common appearance of the oral mucosa is with whitish colored striae (called the reticular form of lichen planus). In more involved cases the affected tissues develop areas of either erosion or atrophy (called erosive or atrophic lichen planus, respectively). When a patient has an erosive form of lichen planus, one issue is deciding if the lesion is a more serious vesiculobullous disease, namely, either pemphigus vulgaris (PV) or benign mucous membrane pemphigoid (BMMP). This decision can be definitively made with a biopsy.[143] Because lichen planus is considered precancerous, there is a chance of the lesion converting into a neoplastic state so patients with this disease must have regular recall visits for re-examination. The skin form of this disease presents as shiny papules on the skin.

Causation

The etiology is considered to be cytotoxic T-cell-mediated autoimmune reaction involving the basal keratinocytes to an unknown antigen. Lichen planus is seen more often in patients with diabetes mellitus, hepatic disease (hepatitis C), and hypercholesterolemia, although these associations are not necessarily considered causative.

Benign mucous membrane pemphigoid

Clinical presentation

This disorder involves the skin, oral and ocular mucosa, esophagus, nasopharynx, and larynx mucosa. BMMP has an incidence of 0.7 per 100,000 annually and it affects women three times as often as men. It is most common in the sixth and seventh decades of life and it presents with persistent redness, blisters (called bullae) that rupture, and then erosions of the mucosa that slowly heal. The palate and gingival areas are commonly involved and these oral lesions usually heal without scarring. In contrast, the mucosa of the eye does undergo some scarring with whitish striations, atrophy, and fibrous strands being evident. Patients with BMMP produce antibodies that attack the mucosal basal membrane and this makes the oral tissues subject to sloughing with any friction. For this reason, removable prosthetic devices that are tissue borne exacerbate the damage. Finally BMMP as well as PV can occur as paraneoplastic disease or after the use of certain medications (e.g., furosemide, low-potassium diuretics, sulfonamides, ampicillin, d-penicillamine, and angiotensin-converting enzyme [ACE] inhibitors).

Causation

This is an autoimmune disease and the subepithelial bullae form because inflammation (deposits of immunoglobulin G [IgG], immunoglobulin A [IgA], or complement fraction C3) occurs throughout the basal membrane of the affected tissues. The antigens against which the immune reaction occurs are thought to be laminin-5, type IV collagen, laminin-6, subunit b4 of integrin, uncein, and bullous pemphigoid antigens 1 and 2.[144]

Pemphigus vulgaris

Clinical presentation

Pemphigus vulgaris is another chronic vesiculobullous disease; it is far more widespread than BMMP and affects

many different areas of the skin and mucosa. PV has an annual incidence of less than 1 per 100,000 individuals; up to 90% of patients have involvement of the oral mucosa. Like BMMP, this disease starts with a blistering, that is followed by ulcerations that are quite painful. The blisters or bullae often first appear in the oral cavity on the nonkeratinized buccal mucosa, which is under mechanical stress, and on the epithelium of the cheeks, soft palate, and lower lip long before skin lesions are seen. The definitive diagnosis of PV versus BMMP usually requires an immunofluorescence-type biopsy. The histopathology will typically show acantholytic intraepithelial vesicles and Tzanck cells, and the immunofluorescence will show the presence of IgG or IgM and complement fragments in intercellular spaces.[145] Because brushing often causes more tissue injury it is quite difficult to clean the mouth and secondary candidiasis is common. The skin lesions also manifest with blisters and crusts and are usually first seen on the scalp, forehead, nasal vestibule, lids, and about the ears, and later spread to apparently normal skin.

Causation

This is an autoimmune disease that affects the skin and mucosa and the antibodies are thought to be the desmoglein 3, especially in mucous membrane involvement, and desmoglein 1, as well as desmocollin.[146] Desmoglein 1 is expressed in keratinizing epidermis, while desmoglein 3 is mainly expressed in the mucosal epithelium.[147] Medications are sometimes thought to trigger or aggravate PV.[148]

Paraneoplastic pemphigus

Clinical presentation

This is a pemphigus variant and can occur with or be triggered by lymphoma, thymoma, and less often other tumors. This disease typically involves the mucosa, and lesions are often polymorphous and resemble erythema multiforme.[149]

Causation

Like PV, the disease is an autoimmune disorder caused by an antigen–antibody reaction, desmosomal proteins (e.g., desmoplakin I, II), and hemidesmosomal proteins.

Oral ulcers associated with lupus erythematosus

Clinical presentation

Lupus erythematosus appears in two forms: systemic lupus erythematosus and discoid lupus erythematosus. Both types of lupus can give rise to oral features similar to those of lichen planus. The oral lesions can both precede and follow the cutaneous features of the disease.[150,151] The percentage of patients reported to develop oral lesion varies from 5% to 50% for discoid lupus erythematosus, and approximately 50% for systemic lupus erythematosus.[152] The common appearance of chronic discoid lupus is an erythematous erosion on the buccal mucosa or palate with a radiating pattern around the margin. In systemic lupus the oral ulcers are more atypical, but usually affect the palate.[153] Lupus erythematosus of the oral mucosa seldom occurs without skin lesions.

Causation

Lupus erythematosus is an autoimmune disease of the connective tissue.

Behçet disease

Clinical presentation

This is a systemic vasculitis characterized by recurrent oral and genital ulcers, skin lesions, and ocular, musculoskeletal, cardiovascular, gastrointestinal, and neurological symptoms.[154] The oral lesions are often the first clinical symptoms of the disease, they occur at least three times a year, and they are aphthous like ulcers that occur on the mucosa, gingiva, lips, soft palate, and pharynx. Behçet disease begins within the second or third decade of life and is a relatively rare disorder with a prevalence of less than 1 per 100,000. The diagnosis is usually formed based on a combination of symptoms. There is an International Study Group for Behçet Disease that has proposed some criteria.[155] Other organ manifestations of this disease include ocular, neurological, thromboses, gastrointestinal, and pulmonary complications.

Causation

This is a genetic autoimmune disease that is triggered by several factors.

Reiter's syndrome

Clinical presentation

Reiter's syndrome is an uncommon disease and is characterized by arthritis, urethritis, conjunctivitis, and oral ulcers similar to those of recurrent aphthous stomatitis.

Causation

Reiter's syndrome is an autoimmune disease; the main diagnostic criterion is a positive reaction for human leukocyte antigen B27.[156]

Ulcers related to blood disorders (subgroup 5)

Neutropenia oral ulcers

Clinical presentation

Oral ulcers, similar to those of recurrent aphthous stomatitis, may appear in diseases associated with blood deficiencies, (e.g., anemias, leukemias, lymphomas, multiple myeloma, and neutropenias).

Causation

The commonest cause of a blood dyscrasia oral ulceration is cyclic neutropenia. Cyclic neutropenia is believed to be caused by mutation in the gene for neutrophil elastase (ELA2), located at 19p13.3. This enzyme, which is formed in the neutrophil precursors, causes early death of precursors when mutated.[157]

Idiopathic oral ulceration (subgroup 6)

Recurrent aphthous stomatitis

Clinical presentation

Recurrent aphthous stomatitis (RAS) is characterized by recurrent and painful ulcers (aphthae) in the oral mucosa. Recurrent aphthae are the most common inflammatory lesions affecting the oral mucosa, with a prevalence of 10–20%.[158] There are three well-differentiated clinical forms: (1) minor aphthae, (2) major aphthae, and (3) herpetiform aphthae. The disease is characterized by recurrent crops of solitary or multiple highly painful, fibrin-coated ulcers with a hyperemic and erythematous border. The lesions usually affect the oral mucosa, but sometimes involve genital or perigenital areas. The diagnosis of RAS is based on the clinical history of the patient and on clinical findings, but there is no specific diagnostic test. Assuming no other underlying causation, the prognosis is generally good, and spontaneous remission can occur after several years.

Minor oral aphthae

These are small ulcers that measure less than 1 cm in diameter and that heal within 4–14 days, rarely with scarring. Minor aphthae are the most common (85%) of the aphthous lesions. They are characterized by the formation of 1–5 well-defined superficial ulcers that are round or oval with a diameter <10 mm, covered by a white or greyish pseudomembrane and surrounded by an erythematous halo. They normally appear in the nonkeratinized mucosa and are rare in the keratinized gingiva, palate, or tongue dorsum.

Major oral aphthae

These are larger ulcerations measuring more than 1 cm in diameter which are often deeper. These take 10–30 days to heal and often result in scarring. Major aphthae (10%) are similar to minor aphthae but are larger (>10 mm) and very painful. They can occur as single or multiple ulcers. They may appear at any site but have a predilection for the lips, soft palate, and throat and commonly leave scars.

Herpetiform aphthae

These are rare, tiny oral aphthae measuring 1–2 mm in diameter each are extremely painful.[159] Herpetiform aphthae (5%) are characterized by the presence of multiple (50–100), small (2–3 mm), and painful ulcers throughout the oral cavity, which tend to coalesce and form ulcers of larger size. They usually heal within 7–10 days without leaving scars.

Causation

Recurrent aphthous stomatitis is an inflammatory disease of unknown or idiopathic origin. When an aphthous ulcer is suspected it is important to rule out an association with systemic disease that cause similar lesions (e.g., Behçet's disease, cyclic neutropenia, FAPA, coeliac disease) and to explore possible causative factors, including blood deficiencies.[160–162] Underlying diseases such as anemia, cyclic neutropenia, deficiency of folic acid, iron, vitamin B (pellagra), or familial selective vitamin B_{12} malabsorption can contribute to the recurrence of aphthous disease. Local traumas such as bite wounds, tooth brushing, and pressure from dental instruments or nuts are variable triggering factors. Various factors have been implicated in the etiology of RAS, including familial and genetic factors, autoimmune factors, hormonal changes, hypersensitivity to certain foods, drugs, blood deficiency, zinc deficit, stress, tobacco, local traumas, infectious agents, and various systemic diseases. Aphthae are less common in patients who smoke, suggesting that tobacco plays a protective role.[163] This disease has unknown origin, therefore there is no specific treatment.

Eosinophilic ulcer

Clinical presentation

Eosinophilic ulcer of the oral mucosa is an uncommon, benign, self-limiting, and generally asymptomatic lesion that heals spontaneously. It presents as a large ulcer, generally on the tongue, with wide indurated borders and a yellowish-white base that may resemble a malignant lesion. It develops rapidly and can remain for weeks or months.[164]

Causation

Its etiology is uncertain therefore idiopathic, but it is associated with traumas.

12.4 Treatment of noninfectious, non-neoplastic oral ulcers

A complete medical history and oral examination of the patient, in conjunction with complementary diagnostic methods, are essential in order to achieve a specific diagnosis which includes the presumptive etiology of the oral ulcer(s). The diagnosis, the severity of the oral disease, and the presence or absence of extraoral lesions are the key factors that determine the selection of a treatment. The primary treatment considerations are as follows: (1) self-treatment protocols, including oral hygiene, antiseptic mouth rinses, and avoidance of any potential causative agent or medication; (2) prevention and treatment of secondary infections; (3) corticosteroids, including topical gels, rinses, injections, and systemic medications; (4) immunosuppressive agents; (5) retinoids; (6) phototherapy; and (7) the special case of graft-versus-host disease oral ulceration treatment. Unfortunately, there are few randomized placebo-controlled trials that examine the efficacy of various drug treatments for oral ulcers. The published trials generally included small study populations and lacked proper documentation, which made it difficult to accurately measure the outcome. Only limited therapies were tested in randomized, placebo-controlled clinical trials and they are not confirmed. Therefore, at present, recommendations for the treatment are based mainly on clinical experience and the current scientific literature with all of its flaws.

12.4.A Self-treatment methods for oral ulcerations

Modified oral hygiene

When your mouth has a painful ulcer, it is virtually impossible to use a tooth brush in the area of the ulcer. In these cases the patient should be advised to switch to a very soft toothbrush until the ulcer heals.[165] If this is not possible, oral sponges or toothettes can be used to clean the teeth.

Topical antiseptic agents and antibacterial mouthrinses

When a patient is not able to brush their teeth adequately, topical antiseptic or antibacterial mouthrinses are recommended. Unfortunately these products usually contain alcohol and they burn when they come into contact with an open mucosal lesion. One relatively easy home remedy is to apply dilute hydrogen peroxide (1 part hydrogen peroxide [3%] to 1 part water) with a cotton swab on the ulcer and surrounding area. Another home remedy that should be added is to have the patient avoid spicy food and rinse frequently with water. Patients with a very localized ulcerative condition can apply a over-the-counter anesthetic agent (an example is Orobase® with 20% benzocaine). Finally, chlorhexidine has become available in a non-alcohol-containing formulation. A recent study conducted a randomized clinical trial in 21 patients comparing two mouthrinses containing chlorhexidine (with and without alcohol) on gingival inflammation, pain, and acceptability after third-molar surgery.[166] The authors reported no significant differences in the acceptability of the two mouthrinses and both were effective at reducing gingival inflammation at the surgical site.

Avoidance of all causative and contact allergy inducing agents

When a dental or food product is suspected as the cause of a contact stomatitis, the first approach is to stop its use, wait for the stomatitis to heal, and use it again to see if the reaction returns. In some cases, cutaneous patch testing can be used to identify the responsible agent. In about 50% of patients with suspected oral allergic reactions the result is positive.[167] If the product is not optional (e.g., toothpaste), then recommend the patient to use a nonflavored, nonalcohol, neutral pH toothpaste. When the ulcerative disorder is secondary to a medication, if it is an optional medication, discontinue it and observe the results. If the reaction is not life-threatening and the medication is essential, it is logical to request the prescribing doctor to switch the medication to another medication that does not cause an oral ulcerative reaction. There may be essential (nonoptional) medications that must be stopped also, when the reaction is severe and life-threatening (i.e., drug-induced erythema multiforme). Adding emergency medications to counteract the allergic reaction such as high-dose corticosteroid therapy in patients with severe erythema multiforme may be required; systemic corticosteroid use is discussed in Section 12.4.C. Once the causative agent is stopped, the symptoms usually resolve within days or weeks after the cause has been eliminated. It is not recommended to concurrently use topical intraoral steroid ointments or steroid rinses since this will confound the issue and make it difficult to be sure what the causative agent was. Some dental restorative products have been known to cause oral lichenoid lesions and in such cases the lesion should be seen in direct topographic relationship to the offending agent. This reaction is most often attributable to dental restorative materials, most commonly amalgam.[168,169] With the removal and replacement of the putative causative

material, the majority of such lichenoid lesions resolve within several weeks to months. Finally, oral lichenoid and ulcerative drug reactions do exist. The most common drugs implicated are the ACE inhibitors and NSAIDs. However, oral hypoglycemic drugs, penicillamine, and gold have also been implicated. Drug reactions may occur anytime, even years after the introduction of the drug, and withdrawal is the appropriate method to manage such reactions.[170]

12.4.B Prevention and treatment of secondary infections

Infectious diseases must be managed with the appropriate (antiviral, antibiotic, or antifungal) topical and/or systemic treatment available. This chapter does not cover treatment of primary infectious oral disease but the reader is provided with several comprehensive references that will help.[171–175] However, in the next section we do discuss and recommend using corticosteroids in multiple forms to treat oral ulcerations. One major and fairly predictable consequence of this treatment is "corticosteroid-induced candidiasis."[176–178] In such cases it is necessary to emphasize oral hygiene, especially tongue cleaning, and add an antifungal agent (e.g., Nystatin) to the prescriptions being used.

12.4.C Corticosteroid medications

Glucocorticoids (also known as corticosteroids) are the most important medications for treatment of noninfectious and non-neoplastic ulcers. They can be applied in a topical gel, ointment, or mouthrinse, injected locally into the tissues under the ulcer, or given systemically. They work by suppressing the various allergic, inflammatory, and autoimmune causes of the tissue damage. These drugs suppress both cell-mediated and humoral immunity.

Potency of various corticosteroids

All corticosteroids are not equipotent (Table 12.4). Most corticosteroids are rated as being multiples of the primary corticosteroid, hydrocortisone, which has its potency arbitrarily set at 1.0. For example, prednisone's potency is between 3.5 and 5.0 times stronger than hydrocortisone. Along these same lines, prednisolone is rated as 4 times more potent, triamcinolone is rated as 5 times more potent, methylprednisolone is rated at between 5.0 and 7.5 times more potent. Dexamethasone is rated at between 25 and 80 times more potent, and betamethasone is rated between 25 and 30 times more potent than hydrocortisone.

Table 12.4 Corticosteroid potency table

Name	Glucocorticoid potency	Duration of action ($t_{1/2}$, hours)
Hydrocortisone (cortisol)	1	8
Prednisone	3.5–5	16–36
Prednisolone	4	16–36
Triamcinolone	5	12–36
Methylprednisolone	5–7.5	18–40
Fludrocortisone acetate	15	—
Dexamethasone	25–80	36–54
Betamethasone	25–30	36–54

Adverse effects

The major concern with corticosteroid intake is the resulting adrenal suppression that using an exogenous corticosteroid will cause. Adrenal suppression makes it possible for the patient to get into an adrenal crisis if they have a stressful episode that would require them to produce their own endogenous cortisol. Corticosteroids suppress the immune system so patients are more susceptible to secondary infections and they often have psychological effects from the medications, such as mania, insomnia, andother psychiatric disturbances such as agitation. There are multiple diseases where the use of corticosteroids may be contraindicated, including status asthmaticus, acute bronchospasm, congestive heart failure, diabetes, gastrointestinal disease, hepatic or renal impairment, myasthenia gravis, acute myocardial infarction, ocular disease, osteoporosis, seizure disorders, thyroid disease, or in the elderly. Finally it should be understood that topical corticosteroids are more readily absorbed through ulcerated or inflamed tissues than they would be if applied to intact skin or mucosa.

Topical corticosteroid agents, gels, and ointments

Indications and dosing

For most of the noninfectious and non-neoplastic oral ulcers, topical corticosteroids are currently central to their treatment. In cases of oral ulcers confined to a single location, use of topical corticosteroids delivered in an adherent vehicle such as orabase (carmellose sodium) or in a gel or ointment is highly indicated. The tissue is typically dried and the gel or paste is painted onto the ulcer and allowed to sit for 5 mintues. Patients are instructed to apply a small amount to the target area after meals (3–4 times per day), and not to eat or drink for at least 30 minutes after application. While there are several choices of topical agents, a common and highly effective one is fluocinonide 0.05%, which is intended for topical administration (Rx: Fluocinonide [Lidex®] (0.05% Cream); Disp: 15 gr; Sig: apply to oral lesions t.i.d. [i.e., three times per day]). Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by

the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

Potency

Lower down on the potency ladder is (0.1%) triamcinolone in orabase (Rx: Triamcinolone [Kenalog®] in Orabase 0.1%; Disp: 15 gr; Sig: apply to oral lesions t.i.d.). The basic rule is that a topical corticosteroid of a potency appropriate to the severity of the clinical symptoms should be used, at the lowest possible concentration and frequency compatible with maintaining the effectiveness of the treatment, in a vehicle that minimizes the area exposed to the drug. Mild- and moderate-potency steroids such as 1% hydrocortisone hemisuccinate or 0.1–0.2% triamcinolone acetonide are generally considered appropriate for the treatment of clinically unimportant autoimmune diseases of the oral mucosa, and for maintenance treatment in more severe diseases that have responded to systemic corticosteroids and/or high-potency topical corticosteroids such a fluocinolone. High-potency steroids such as 0.025–0.05% clobetasol propionate, 0.05% fluocinonide acetonide, or 0.025–0.1% fluocinolone acetonide are considered appropriate for the treatment of clinically severe diseases. The evidence also suggests that higher potency corticosteroids, such as clobetasol (Rx: Clobetasol propionate [Temovate®] (0.05% Cream); Disp: 15 gr; Sig; apply to oral lesions b.i.d. [i.e., two times per day]) are probably more effective but are also more likely to induce adverse effects.

Adverse effects

Topical agents are unlikely to cause serious side effects. There is no study determining if adhesive vehicles are better than mouthrinses. However, empirical evidence seems to suggest that mouthrinses are of value in patients with widespread symptomatic oral lichen planus, where the lesions are not easily accessible to the placement of ointments or gels.

Steroid rinses

Indications and dosing

In cases of multiple oral ulcers affecting several locations, aqueous topical corticosteroids as solution mouthwashes are preferred. These are recommended to be used 3–4 times per day, after meals, and patients should not eat or drink for at least 30 minutes after use. The patient should hold the liquid in the mouth without swallowing for as long as possible, generally for 5–10 minutes. Patients must be clearly informed about the need to avoid ingesting the drug. If pain is present, 2% lidocaine can be added to the formulation.

Potency

Most commonly preferred rinse is dexamethasone [High Potency] for which a typical prescription is "Rx: Dexamethasone elixir (0.5 mg/5 mL) Disp: One tsp swish & expectorate t.i.d. or q.i.d." (i.e., three or four times per day).

Adverse effects

See the adverse effects for topical corticosteroid ointments described above.

Intralesional injection of corticosteroids

Indications and dosing

For major aphthous ulcers and other severe oral ulcerations, corticosteroid injections have been shown to be effective.[179,180] Typical dosing is for triamcinolone (10 mg/mL); 1 mL applied submucosally. These injections can be repeated in 2 weeks as needed, although this method should be used only in cases where topical ointments have proven unsuccessful.

Potency

Triamcinolone is considered a moderate-potency corticosteroid.

Adverse effects

See the adverse effects for topical corticosteroid ointments described above.

Systemic corticosteroids

Indications and dosing

In general, systemic corticosteroid medications are only to be used when the inflammatory reaction is severe and there is widespread ulceration and erythema and topical treatments are ineffective. In the acute disease, corticosteroids may be given (e.g., an initial dose of 1 mg/kg body weight per day or depending on organ manifestation). The most common treatment protocol for oral ulcerative conditions is to use short courses or bursts of high-dose corticosteroids, such as prednisone, at 0.5–1.0 mg per kilogram of

the patient's body weight, per day, until a therapeutic response has been achieved. This is then followed by rapid tapering of the corticosteroids. This approach has been shown to be effective in other symptomatic autoimmune diseases.

Potency

Methylprednisolone and prednisolone are the most common systemic corticosteroids and are considered moderate- to high-potency steroid agents.

Adverse effects

See the beginning of this section (Sec. 12.4.C) for acute adverse effects of corticosteroid use. For those patients needing long-term systemic corticosteroid therapy, the patient should be monitored for potential co-morbidities such as hypertension, diabetes mellitus, gastric or peptic ulceration, bone mineral density loss, and cataract formation.

12.4.D Systemic immunosuppressive agents

There are many immunosuppressive agents that can be used in patients with an autoimmune oral mucosal reaction, when corticosteroids do not work. In this section we cover only cyclosporine, tacrolimus, pimecrolimus, dapsone, and azathioprine.

Cyclosporine

Indications and dosing

Cyclosporine has been shown to result in a marked improvement in the oral symptoms but cyclosporine mouthrinse was not significantly better than 1% triamcinolone paste when compared.[181] The most common use of cyclosporine for oral ulceration is a 500-mg rinse used one or three times a day.[182] In one study a single dose of 500 mg/day was used.[183] One study used 128 mg in adhesive gel three times daily.[184]

Adverse reactions

In all of the studies, the side effects were minimal and mainly consisted of a transient burning sensation.

Tacrolimus and pimecrolimus

Indications and dosing

Tacrolimus and pimecrolimus are newer calcineurin inhibitors, with an improved safety profile in comparison with cyclosporine, for the prevention of rejection in organ transplant recipients and GVHD in allogeneic hematopoietic stem-cell transplant recipients. Only a limited number of studies have been published.[185–189]

Adverse reactions

However, there is an FDA "black box" warning attached to the use of these agents because of a theoretical increased risk of malignancy (squamous cell carcinoma and lymphoma) in patients using topical tacrolimus/pimecrolimus for cutaneous psoriasis. In a recent case report of a patient with oral lichen planus (OLP), the topical use of tacrolimus 0.1% was suggested to be the cause of the development of a squamous cell carcinoma of the tongue.[190] Therefore, the use of these agents should be restricted and patients should be made aware of these concerns.

DADPS or dapsone (diamino-diphenyl sulfone)

Indications and dosing

This is another immunosuppressive agent that has been used for recurrent severe aphthous ulceration.[191] It is the drug of choice in IgA pemphigus, is a sulfone which has uses for the primary treatment of dermatitis herpetiformis, and serves as an antibacterial drug for susceptible cases of leprosy. The drug is administered daily (e.g., 100–200 mg daily for 16 weeks). Immunoglobulin A (IgA) pemphigus is an intraepidermal blistering skin disease which is not usually seen on the mucosal tissues. IgA pemphigus is characterized by tissue-bound and circulating IgA autoantibodies that target epidermal desmosomal proteins.

Adverse reactions

Dapsone is a difficult drug to tolerate for many patients and its use must be carefully considered. It causes a dose-related hemolysis that can be quite severe. Patient will show drug-related loss of hemoglobin, an increase in the reticulocytes, a shortened red cell life span, and a rise in methemoglobin. Peripheral neuropathic symptoms are also quite commonplace in dapsone users. Sometimes motor weakness can be predominant and severe. Finally, some patients will complain of nausea, vomiting, abdominal pains, pancreatitis, vertigo, blurred vision, tinnitus, insomnia, fever, headache, psychosis, phototoxicity, pulmonary eosinophilia, tachycardia, albuminuria, nephrotic syndrome, hypoalbuminemia without proteinuria, renal papillary necrosis, male infertility, drug-induced lupus erythematosus, and an infectious mononucleosis-like syndrome.

Azathioprine

Indications and dosing

Systemic azathioprine (AZA) is used in the management of immune-mediated oral ulcerations, such as pempigus vulgaris, for its steroid-sparing benefit.[192,193] Topical forms as rinses (a rinse of 5 mL of 5 mg/mL AZA in methylcellulose used three to four times daily for over 1 minute and expectorated) and gels (5 mL of 5 mg/mL AZA in 3% methylcellulose topically applied) has been evaluated in the management of vesiculobullous oral ulcerations and has been found effective.[194]

Adverse reactions

The serious adverse effects of systemic AZA include leukopenia, thrombocytopenia, hepatitis, pancreatitis, and malignancy. No significant adverse effects have been reported with topical use of AZA.[194]

12.4.E Retinoids

Indications and dosing

Acitretin (0.5 mg/kg body weight, tapering over about 6 months) is sometimes used for OLP. Several studies were identified that dealt with the use of retinoids for the treatment of OLP.[195–201] A total of 183 individuals participated in the studies. Four of the studies examined the effect of different concentrations and frequency of application of topical retinoids (0.05%, 0.1%, 0.18%, used 2–4 times a day). Only one study examined systemic use of retinoids, 25 mg 3 times per day. The duration of the studies ranged between 4 and 12 weeks. They all reported improvement, but less than with corticosteroids when these were used for comparison. Based on a histopathologic follow-up study, reticular OLP responded better than less keratinized lesions, but only 1 in 6 lesions showed complete healing over an 8-week period. The overall outcome suggests that retinoids are potentially effective in the treatment of OLP, but probably inferior to topical corticosteroids.

Adverse reactions

The most commonly reported side effect was a transient burning sensation. Systemic retinoids are associated with a number of serious adverse effects that would prohibit their routine use for the management of OLP, and include elevated or deranged transaminase levels, hyperlipidemia, cheilitis, dermatoxerosis, alopecia, and dystrophic nail formation. Retinoids are teratogenic and therefore their use in women of childbearing age would be contraindicated.

12.4.F Phototherapy

Indication and dosing

There has been one study of the benefits of phototherapy using psoralen ultraviolet A (PUVA) light,[202] in which 18 individuals were randomized based on side; the contralateral side served as control. The total treatment was 16.5 J/cm^2 UV radiation, given in 12 sessions, 2–3 days apart with 0.6 mg/kg methoxypsoralen (Puvamet) per visit. Fourteen of the 16 patients had side effects, of which 2 had such severe adverse reactions they had to withdraw. Nine patients had a marked improvement. The authors suggested using topical psoralens to avoid side effects seen with systemic administration. This study was included in the Cochrane review. UV light has a known oncogenic potential. Therefore, its use for OLP should be seriously questioned.[203,204]

Adverse reactions

There is the potential of oncogenic induction with ultraviolet light.[205,206]

12.4.G Special case of treatment of graft-versus-host disease–induced oral ulcers

Graft-versus-host disease is a major complication that arises in recipients of allogeneic hematopoietic stem-cell or bone marrow transplantation. Although the etiopathogenesis of GVHD is not fully understood, it appears to be due to donor T-lymphocytes' reaction to minor histocompatibility tissue antigen expression by recipient cells. GVHD is divided into acute and chronic. Acute GVHD occurs within 100 days after transplantation, is often painful, being erythematous, ulcerated, and may have marked desquamation. Chronic GVHD, appearing more than 100 days after transplantation, usually has keratotic white striae or plaques, with areas of erythema, erosion, or ulceration.[207] Acute GVHD affects predominantly three specific organ systems: the skin, the liver, and the gastrointestinal tract, including the oral cavity. In chronic GVHD (cGVHD) a greater number of organs tend to be involved, and oral involvement, including salivary glands, is more prevalent. Previous studies suggest that GVHD and concomitant immunosuppressive therapy may increase the risk for solid cancers, particularly squamous-cell carcinomas (SCCs) of the oral cavity and skin.[208–211] GVHD is a common complication of allogeneic hematopoietic stem-cell transplantation, despite aggressive prophylaxis. The overall incidence, regardless of stem-cell source, is 85%.[212] GVHD with oral lichenoid lesions contributes to patient morbidity in its own right, but it may also serve as an indicator of active GVHD involvement of critical organs such as the gastrointestinal tract, liver, and lung. A recent

review on therapy for GVHD suggested that using high-dose systemic corticosteroids is the primary treatment for GVHD. Steroids are usually supplemented by cyclosporine or tacrolimus and topical oral steroids as needed.

12.5 Conclusions for oral mucositis and oral ulcers

Recommendations on the use of medications for oral mucositis

1. This chapter endorses the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society for Oral Oncology (ISOO) guidelines for treatment of oral mucositis (OM).
2. The management of OM is largely palliative, consisting mainly of pain relief, nutritional support, and oral hygiene.
3. All patients who are scheduled to undergo radiotherapy or chemotherapy regimes that have a high likelihood of OM need counselling and a careful evaluation of the current oral hygiene regime and diet.
4. The evaluation should consist of new dental radiographs and probing, deep scaling, and cleaning before beginning treatment.
5. The patient must purchase the necessary brushes, mouthrinses, and moisturizing agents as well as cleaning implements that may be needed.
6. The patient must have a counseling session on how to modify diet and fluid and food intake during the therapy. The patient should purchase the appropriate foods and supplies to go on a liquid or soft diet before beginning therapy.
7. Standing prescriptions for palliative anti-inflammatory and, if needed, antibacterial and non-alcohol-containing mouthrinses are needed at the pharmacy.
8. Although it will not prevent mucositis, the recent availability of nonalcohol chlorhexidine rinse (at 0.12% concentration) is recommended to prevent secondary infection in severe OM cases.
9. Prevention of OM has involved multiple medications.
10. Pain needs to be controlled and using opioids is both logical and appropriate. In patients who have severe OM and cannot swallow pills, the use of intravenous infusions is required.
11. Using topical anesthetics can provide short-term relief allowing the patient to eat and clean their mouth and both 2% viscous lidocaine, alone or in combination with diphenhydramine, and magnesium aluminum hydroxide provides effective short-term pain relief in OM patients.
12. The most often used mucosal coating agents for severe OM are sucralfate, Gelclair, and Caphosol; however; most studies show these agents as having minimal short-term benefit, if any.
13. The recommended and most often used preventative agents for OM are ice chips (given 30 minutes before chemotherapy) or keratinocyte growth factor-1 (palifermin), and amifostine (a thiol drug).

Recommendations on the use of medications for oral ulcerations

1. For oral ulcers, a classification system that is etiologically based is needed.
2. The treatment approach for oral ulceration (OU) needs to be palliative with careful attention paid to removal of any triggering agents or medications.
3. Topical corticosteroid therapy using highly potent topical gels and rinses is the mainstay of treatment for OUs that are noninfectious and non-neoplastic.
4. All patients with OUs need to have a self-treatment regime established via counseling and review of current oral hygeine procedures.
5. In those patients with moderate to severe autoimmune diseases (e.g., lupus or pemphigus vulgaris), systemic steroids or appropriate immunosuppressive agents need to be considered and management usually involves both the dentist and a rheumatologist or dermatologist.

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Chapter 13

Management of orofacial pain and other co-morbidities in oropharyngeal and nasopharyngeal cancer patients

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13.1 Oropharyngeal or nasopharyngeal cancer pain

It is estimated that over 50 million people are partially or totally disabled due to pain and it is a common symptom of patients with cancer.[1] Pain in cancer accounts for 30–40% of the main complaints of cancer patients and is of multifactorial etiology. Pain may be a presenting symptom of primary tumors, metastatic disease, systemic cancer, or distant non-metastasized cancer. When patients have cancer, pain is an extremely common co-morbidity afflicting 65–85% of this population. In approximately 20–40% of cancer patients, pain is described as an agonizing severe pain.[2] It is estimated that, worldwide, 3 million people require treatment for cancer pain every year. Although pain is only one of the innumerable symptoms of cancer, it affects physical functions, has emotional impact, and affects the quality of life.[3] In head and neck cancer, pain affects the oral functions and is the complaint in about 58% of the patients awaiting treatment, and in 30% of treated patients.[4]

13.2 Pain prevalence in cancer patients

The various factors that influence cancer pain prevalence include primary tumor type, stage of tumor, and proximity of tumor to neural tissue. Patients with cancer often have multiple causes of pain and multiple sites of pain.[5–9] Based on a variety of survey data, up to one-third of patients had more than one pain and 81% of patients reported two or more distinct pain complaints; 34% reported three pains. A 2002 National Institutes of Health (NIH) State-of-the-Science panel found that pain is one of the most common side effects of cancer and cancer treatments.[10]

A 2007 study examined the prevalence of pain in cancer patients by targeting hospitalized cancer patients in Norway.[11] They surveyed 453 individuals and found that 52% were having cancer-related pain with a mean pain level of 4 on a 10-point scale in spite of their medications. A similar study with similar results was performed by a group of physicians in Italy.[12] This group administered a questionnaire to 258 cancer patients hospitalized at the National Cancer Institute of Milan. They found 133 patients (51.5%) had pain. They further reported that 49.6% of these patients had pain because of their cancer surgery and 29.3% had pain because of the tumor mass itself. One study in 2008 conducted a national cross-sectional survey of cancer patients in oncologic wards in Italy and found 901 (34%) of 2655 patients had pain with higher pain levels observed in inpatients and those with bone metastases.[13]

A study to understand the prognoses and preferences for outcomes and risks of treatments in cancer showed that 50% of adults who die in the hospital experience moderate to severe pain in the last 3 days of life.[14] The 10-year experience of a German anesthesiology-based pain service associated with a palliative care program reported on the course of treatment of 2118 patients over a period of 140,478 treatment days.[15] In their survey, gastrointestinal and head and neck cancers were the most common types, with the majority of pain (85%) caused by tumor involvement. Pain intensity data were collected throughout the course of treatment. Eighty-two percent of patients had moderate to very severe pain at the beginning of treatment, but only 7% reported pain of such high intensity at the completion of treatment.

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Table 13.1 Types of pain reported as the initial symptom in oropharyngeal cancer patients

Pain type	Percentage of sample
Sore throat pain	37.6%
Tongue pain	14.0%
Mouth pain	12.9%
Pain when swallowing	11.1%
Dental pain	05.9%
Earache	05.9%
Pain in the palate	04.1%
Burning mouth	03.3%
Gingival pain	02.2%
Pain when chewing	01.1%
Neck pain	01.1%
Facial pain	00.7%

Table derived from Cuffari et al., *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, 2006;102(1):56–61 (ref. 16).

13.3 Orofacial pain as the first sign of oropharyngeal and nasopharyngeal cancer

Cuffari et al. (2006) examined how often pain was reported to be the first clinical sign of oral cancer by looking at the hospital charts of 1412 patients (1977–1998) with oral cancer (238 female and 1174 male).[16] Pain was reported as the initial complaint on average in 19.2% of their sample and even categorized the types of pain experienced by these patients (Table 13.1). Orofacial pain has not only been the initial complaint of primary oral cancer patients but has also been reported to be one of the earliest indicators of recurrent cancer. Wong et al.[17] described 12 patients who experienced recurrence of primary head and neck cancers that were preceded by severe orofacial pain. When the pain was reported, the authors described their patients as not demonstrating other evidence of malignant disease despite clinical examination, plain radiography, computed tomography (CT), and even magnetic resonance imaging (MRI) of the area.

13.4 Co-morbidities as a result of cancer and its therapy

Patients treated by surgical excision, radiotherapy, and chemotherapy for cancers frequently experience other problematic orofacial symptoms as well.[18,19] The most substantial chronic oral side effects include pain (neuropathic pain and mucositis), dysfunction (trismus or contractures of the jaw muscles), and oral sensory alterations (numbness and sensory distortions). In addition to these treatment complications, patients with a hematologic cancer who undergo bone marrow transplant therapy and immunosuppression will also demonstrate severe oral and pharyngeal mucositis secondary to graft-versus-host disease (GVHD). Mucositis and GVHD are covered in detail in Chapter 12.

13.4.A Cancer-related neuropathic pain

Cancer pain is often referred to as a mixed mechanism pain, as it rarely presents as a pure neuropathic, visceral, or somatic pain syndrome, but rather a complex syndrome with components of inflammatory, neuropathic, and/or ischemic mechanisms often in multiple sites.[20] Neuropathic pain is caused directly by cancer-related pathology (compression or infiltration of nerve tissue) or by diagnostic and therapeutic procedures (surgical procedures, chemotherapy, radiotherapy). Manfredi et al. (2003) examined painful neural lesions in 187 cancer patients with pain, referred to a cancer hospital. Based on medical history, pain descriptors, physical examination, and radiological and electrophysiological studies, the pain was categorized as "neuropathic" in 103 patients.[21] The most frequent sites of neurological injury were nerve roots, spinal cord and cauda equina, brachial and lumbosacral plexus, and peripheral nerves. There were no patients with pain due to brain injury. In 93 of these patients, the pain was caused by ongoing neural injury; in 10 patients, the neural injury was old and stable.

Work on cancer-related neuropathic pain (chemotherapy induced, or direct invasion) has identified distinct differences in the signature of neuroreceptor–transmitter alterations and unique damage and disruption to neuronal function, and it may yet reveal differences in initiation and maintenance. This evidence would suggest unique features of cancer-related neuropathy, giving a unique molecular signature, while acknowledging some similarity to non-cancer-related neuropathies.[22,23] Although the exact prevalence of neuropathic pain in cancer patients remains unknown, it is predicted that at least 15–20% of patients are likely to suffer from neuropathic pain during the course of the disease, and an even higher proportion at advanced stages of the disease.[24]

Chemotherapy-induced peripheral neuropathy is a common side effect observed following exposure of patients to the vinca alkaloids, the taxanes, the platinum-derived compounds, suramin, thalidomide, and most recently also associated with bortezomib therapy. Reports on the incidence range widely among various studies anywhere between 10% and 100%.[25,26] This neuropathy typically affects mostly the small myelinated and unmyelinated nerve fibers. In a phase I trial, patients receiving paclitaxel (Taxol) developed symptoms of neuropathy as early as 1–3 days following treatment.[27] Specific signs and symptoms of chemotherapy-induced peripheral neuropathy with cisplatin, oxaliplatin, and vincristine are listed in Table 13.2. Another

Table 13.2 Agent-specific signs and symptoms of chemotherapy-induced peripheral neuropathy

Agent	Neurotoxic dose	Signs and symptoms	Observations
Cisplatin	300 mg/m^2 cumulative dose	Frequent paresthesias, tingling of hands and feet, loss of vibration and position sense, loss of tendon reflexes, ataxia	Although frequently associated with doses >300 mg/m^2, it is also observed with lower doses and various administration schedules. Motor nerves are normally spared and muscle weakness is rare. Symptoms persist beyond treatment in up to 60% of patients and may be only partially reversible.
Oxaliplatin	No threshold doses for early signs; >300 mg/m^2 cumulative dose	Acute hyperexcitability; neuropathy occurs within 30–60 min of dosing, described as cold allodynia; dysesthesias and pain typical later signs	Cumulative dose appears to have a significant impact on severity. Early symptoms disappear within a few days; long-term symptoms are partially reversible in 80% of patients and completely resolve after 6–8 months in 40%.
Vincristine	>4 mg cumulative dose	Early manifestation of small-fiber neuropathy that includes paresthesias of hands and feet, loss of Achilles tendon reflexes; occasional extraocular and vocal cord palsy	Nervous system toxicity is well documented; accidental intrathecal administration almost always results in fatal nervous system destruction. Most symptoms are reversible after months or years.

Table derived from from Fine PG, Miaskowski C, Paice JA. Meeting the challenges in cancer pain management. J Support Oncol. 2004 Nov–Dec; 2(6 Suppl 4):5–22.

nonsurgical example of cancer-treatment-induced neuropathic pain is peripheral neuropathy secondary to chronic GVHD in BMT recipients.[28]

Neuropathic pain either due to or after cancer surgery has been reported to have a prevalence of 25%.[29] Surgical interventions which stretch or transect the nerve have a higher incidence of painful sequelae. Surgical interventions such as mastectomy or debulking tumors often results in deafferentation pain. Postmastectomy patients report a constellation of symptoms, including pain or discomfort in the chest wall, surgical scar, upper arm, and shoulder, which may be suggestive of intercostobrachial nerve damage, and phantom breast sensations.[30] Finally, radiation-induced fibrosis can injure peripheral nerves (e.g., fibrosis of brachial plexus) causing chronic neuropathic pain that begins months to years following treatment.[31]

13.4.B Limited mouth opening secondary to muscle spasm and contracture

Trismus, a tonic contraction of the jaw-closing muscles, has now received broader application in use, including all conditions characterized by the inability to open the mouth adequately. Normal maximal mouth opening ranges from 40 to 60 mm. A mouth opening of less than or equal to 35 mm is a functional cutoff point for trismus in head and neck oncology patients.[32] In head and neck carcinoma patients, it is very difficult to discriminate the true cause of trismus. It has been reported as the mechanical obstruction of the mandibular coronoid process and/or condylar process, secondary to local tumor extension into the pterygoid musculature, buccal mucosa, or retromolar area, as well as infratemporal fossa or pterygoid muscle fibrosis in the postirradiation period.[33–35] A number of studies have reported trismus in patients with malignant tumors in the head and neck.[36–38] Ng and Wei (2006) reported on the prevalence of trismus of the jaw (defined as an interincisal opening less than 25 mm) in 41 patients who had undergone maxillary swing surgery to treat nasopharyngeal carcinoma.[39] They found that eight patients (20%) developed postoperative fistulas, and 29 (71%) had severe trismus. Goldstein et al. (1999) suggested that the most decisive factor in whether trismus develops or not is probably the inclusion of the medial pterygoid muscles in the treatment portal during surgery or radiotherapy.[40] Inchimura and Tanaka (1993) reported that trismus developed in 21 of 212 patients, of whom 4 showed the symptom at the first presentation and the remaining cases showed the symptom during or after treatment.[41] Trismus after irradiation is found in between 27% and 30% of patients with nasopharyngeal carcinoma.[42,43]

Treatment of surgical or radiation induced persistent postoperative trismus or contracture generally has a low prognosis. The primary approach when a patient exhibits persistent limited mouth opening is (1) stretching under sedation to distinguish trismus from contracture and (2) weekly office and daily home use of a mechanical jaw-stretching device.[44] The Therabite® (Fig. 13.1) is one such device that is available on the market today (http://www.

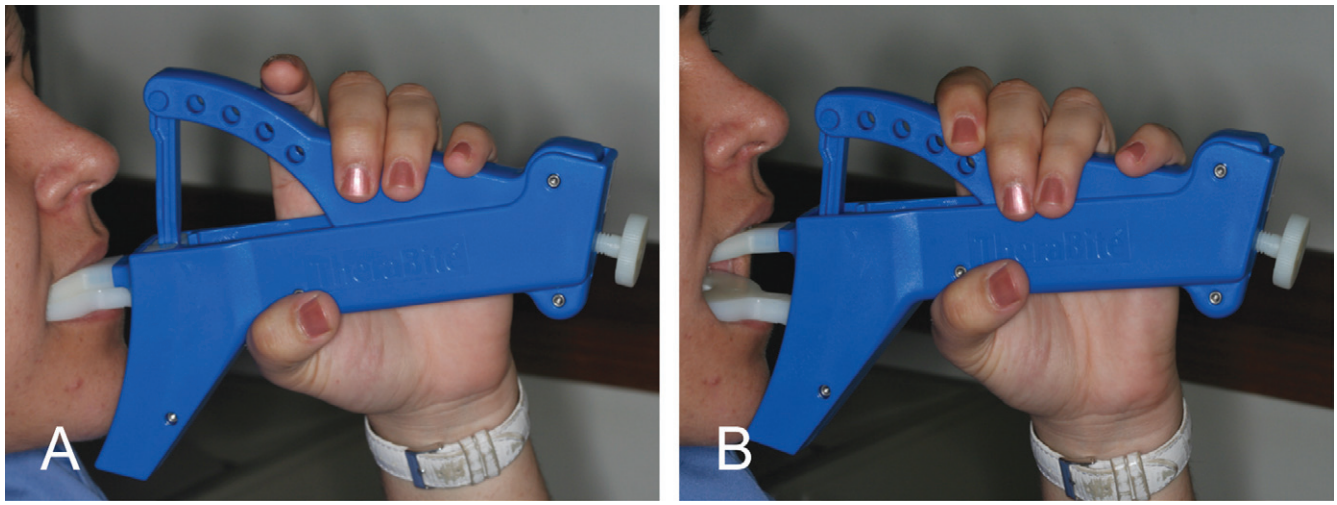

Figure 13.1 (A, B) Using Therabite® to improve limited mouth opening.

atosmedical.com/Products/Mouth_Jaw/The_TheraBite_System.aspx).

A low-cost alternative to the Therabite includes the use of a stack of tongue blades to increase the size of mandibular opening (Fig. 13.2). Buchbinder et al. (1993) compared Therabite with tongue-blade therapy and unassisted jaw opening exercises in postirradiated patients and found that a sustained increase in mouth opening was achievable only with the Therabite 10 weeks following initiation of therapy.[45] The gain in mouth opening for the Therabite group was 6.6 mm greater than the tongue-blade therapy group and 9.2 mm greater for the unassisted exercise group. Stretching exercises or devices need to be implemented early and aggressively in the treatment period to maintain maximum opening and jaw mobility.[46] In another study, the use of Therabite was shown to improve the maximal interincisal opening, in postsurgical trismus patients, by an average of 10 mm.[47] Patient compliance and perseverance are critical factors for successful treatment outcome despite the choice of therapy.

Surgical measures such as coronoidectomy have been reported to be efficient in improving trismus that is not responsive to physical therapy. Bhrany et al. (2007) reported on 18 patients with radiation- or surgery-induced trismus who underwent either unilateral ($n = 3$) or bilateral ($n = 15$) coronoidectomies to improve mouth opening.[48] These patients had tried and not benefitted from physical therapy in the form of tongue blades or Therabite. Overall, the mean increase in interincisal difference immediately postprocedure was 27 mm, decreasing to 22.2 mm at 6 months postprocedure. Patients followed for 1 year maintained the effect of coronoidectomy, having a mean improvement in interincisal distance of 22.7 and 21.8 mm at 6 months and 1 year, respectively. When the cancer disease or treatment is causing spastic reaction in the jaw-closing muscles, botulinum toxin (BoNT) injection into the involved muscles provides the needed spasticity control.[49] The use of BoNT for the orofacial musculature is covered in detail in Chapter 11.

Finally, a systematic review of the literature was conducted by Dijkstra et al. (2004) to identify criteria for trismus in head and neck cancer, risk factors, and the interventions to treat trismus.[50] Nine different criteria for trismus were found without justification for these criteria. Radiotherapy (follow-up, 6–12 months) involving the structures of the temporomandibular joint and or pterygoid muscles was found to reduce mouth opening by 18%. Exercises using a Therabite device or tongue blades increased mouth opening significantly. Microcurrent electrotherapy and pentoxifylline were also shown to increase mouth opening significantly.

13.4.C Oral neurosensory alterations

Somatosensory abnormalities that interfere with speech, mastication, swallowing, voice quality and resonance, and intraoral sensations are not uncommon in patients who have undergone treatment for oral and nasopharyngeal cancer. Due to these complications, many head and neck cancer teams include a speech and swallowing rehabilitation protocol as part of their postcancer treatment procedures.

Speech, masticatory, and swallowing deficits

It is very well established in the medical literature as to how common chewing, speech, and swallowing problems are after head and neck cancer therapy. Borggreven et al. (2005) analyzed speech outcome for patients with advanced oral or

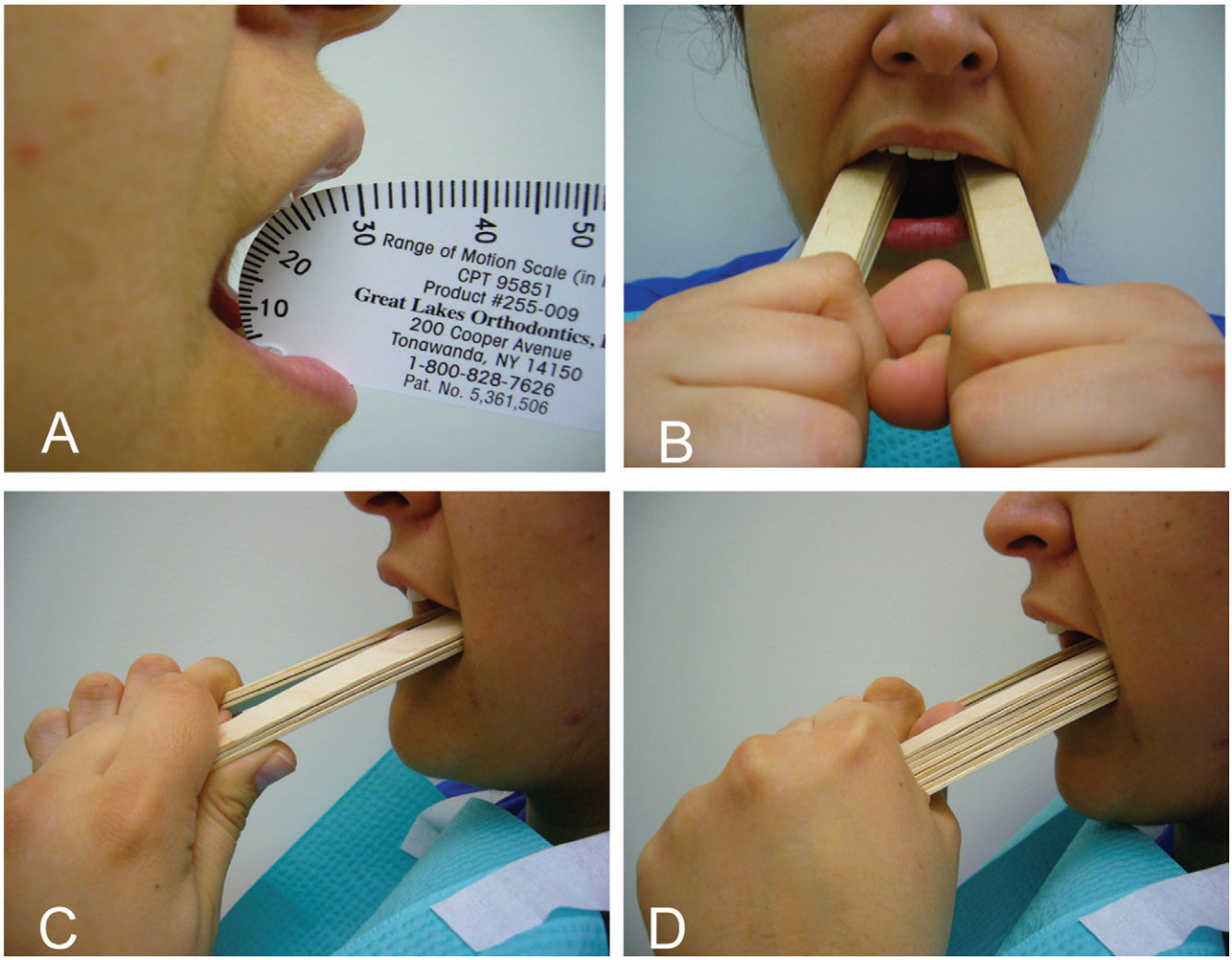

Figure 13.2 (A) Limited mouth opening of 25 mm. (B, C, D) Using stacks of three to eight tongue blades as a home-based exercise protocol to improve limited mouth opening.

oropharyngeal cancer treated with reconstructive surgery and adjuvant radiotherapy.[51] Speech tests (communicative suitability, intelligibility, articulation, nasality, and consonant errors) were performed in a control group and in patients before treatment ($n = 76$), and 6 months ($n = 51$) and 12 months ($n = 42$) after treatment. Speech tests were significantly worse for patients before and after treatment compared with the controls. Speech did not improve between 6 and 12 months. After treatment, patients with T3–4 tumors showed a significantly worse score for communicative suitability, intelligibility, and articulation than patients with T2 tumors. Markkanen-Leppänen et al. (2006) prospectively examined the articulatory proficiency of "r" and "s" sounds, voice quality and resonance, speech intelligibility, and intraoral sensation were before operation and at four time points during a 1-year follow-up after microvascular transfer.[52] Forty-one patients with a large oral or oropharyngeal carcinoma undergoing tumor resection and free-flap reconstruction usually combined with radiotherapy participated in the study. Articulation, voice, and resonance were investigated both live and from recorded speech samples by two trained linguistic examiners. The patients completed a self-rating of their speech intelligibility and were assessed for anterior intraoral surface sensation by means of two-point moving discrimination. Misarticulations of "r" and "s" increased significantly after the therapy. Voice quality and resonance remained essentially normal. Speech intelligibility deteriorated significantly. Intraoral sensation decreased postoperatively but was not related to speech outcome. Sensate flaps did not prove to be superior in relation to speech tasks. The authors advocated a multidisciplinary approach in assessment of speech outcome after cancer surgery. Speech therapy

was strongly recommended, even in the absence of a gross articulatory handicap.

McConnel et al. (1998) conducted a multi-institutional prospective study of speech and swallowing function before and after soft-tissue reconstruction of the oral cavity and oropharynx, and compared three methods of reconstruction with respect to speech and swallowing function: (1) primary closure, (2) distal myocutaneous flap, and (3) microvascular free flap[53]; 284 patients treated at the four leading head and neck cancer institutions were matched for the location of the oral cavity or oropharyngeal defect and the percentage of oral tongue and tongue base resection. The patients underwent speech and swallowing evaluation preoperatively and 3 months after healing. This evaluation included videofluoroscopic studies of swallowing and tests of speech intelligibility and sentence articulation. Videofluoroscopy provided measures of swallowing efficiency and bolus movement. Liquid and paste consistencies were used in evaluating swallowing function. They found that patients who had primary closure were more efficient at swallowing liquids, had less pharyngeal residue, a longer oral transit time with paste, and higher conversational intelligibility than patients who underwent reconstruction with a distal flap. Compared with patients who underwent reconstruction with a free flap, those who had primary closure had more efficient swallowing of liquids, less pharyngeal residue, and shorter pharyngeal delay times with paste. No difference in the speech and swallowing function existed between patients treated with distal myocutaneous flaps and those treated with microvascular free flaps. The authors found that the use of primary closure resulted in equal or better function than the use of flap reconstruction in patients with a comparable locus of resection and percentage of oral tongue and tongue base resection.

In 2007, Borggreven et al. conducted another study to assess the swallowing outcome in advanced oral or oropharyngeal cancer patients treated with microvascular reconstructive surgery and adjuvant radiotherapy.[54] Postoperative videofluoroscopic swallowing studies (VFSS) and scintigraphy tests were performed at 6 and 12 months in 80 patients. Swallowing parameters such as the oropharyngeal swallow efficiency and the Penetration/Aspiration Scale were analyzed and impaired swallowing status was found at 6 months, which remained stationary at 12 months. Larger tumors (T3–T4 vs. T2) and resections of the base of tongue and soft palate combined (vs. defects of other dynamic structures) were associated with most profound swallowing problems ($p < 0.05$). In a similar study, Zuydam et al. (2000) reported that oropharyngeal cancer patients who had undergone surgical resection had swallowing disorders. The disorders were related to the extent of the resection and the consistency of the bolus.[55] Those with involvement of a quarter of the tongue base or more generally had greater impairment, and radiotherapy tended to exacerbate these problems. Aspiration was a major problem in these patients. Interestingly, compensatory procedures and therapy techniques such as chin tuck and supraglottic swallow were effective in 50% of patients who aspirated, and tended to be more effective between the 1-month and 6-month follow-up in patients with smaller resections.

The previously cited paper by Markkanen-Leppänen et al. (2006) also prospectively assessed the swallowing and intraoral sensation outcomes after microvascular free-flap reconstruction in 41 patients with a large oral or oropharyngeal carcinoma who had undergone free-flap surgery, usually combined with radiotherapy. The patients completed modified barium swallow, self-rating of swallowing, and two-point moving discrimination preoperatively and at four time points during a 12-month follow-up period. A plain chest X-ray was done 1 year after operation. Intraoral sensation deteriorated and swallowing was impaired with respect to an objective and subjective measure after therapy. Rates for nonsilent and silent aspiration increased during the follow-up and the swallowing outcome was not related to sensation. One year after surgery, 86% of the patients ate regular masticated or soft food. The authors concluded that microvascular transfers offer a reasonable option for oral reconstruction. Swallowing problems should be routinely sought and patients rehabilitated during a sufficiently long follow-up with videofluorography regardless of the patient's perception of swallowing. In conclusion, head and neck cancer patients who had microvascular free flap reconstruction or primary closure seem to have better outcomes with respect to speech and swallowing defects in comparison to those who had a distal flap reconstruction only.

Masticatory, speech, and swallowing problems are not inherent to only head and neck cancer patients. Gurney et al. (2006) examined the long-term effects of hematopoietic stem-cell transplantation therapy on 235 childhood cancer survivors.[56] The study was unique in that it used 705 noncancer siblings as their control group. All participants completed a survey with questions on post-transplant impairments, and the median length of follow-up was 11 years. Interestingly, persistent pain was reported by 21% of survivors and they were also 7.7 times more likely to report chewing or swallowing problems.

Intraoral sensory alterations

Bodin et al. (1999) tested oral sensory discrimination using a hole size identification test in 31 patients with a diagnosed malignant tumor of the oral cavity or pharynx.[57] The testing was performed four times (before treatment, after radiotherapy, and 6 months and 1 year after surgical treatment).

The study included a control group of healthy individuals of the same age who were tested two times at a 2-month interval. The results showed the sensory discrimination ability in the oral cancer patients was not diminished after radiotherapy, but it was after cancer surgery and this change was still present after 1 year. In contrast, the pharyngeal cancer group did not have a change in their oral sensory discrimination after radiotherapy or surgery. The authors concluded that "cancer surgery of the oral structures causes a persistent loss of sensory discrimination." They speculated that this might contribute to the frequently seen mastication and swallowing difficulties exhibited by oral cancer surgery patients. Also, the patients' capabilities of shape recognition had deteriorated significantly with no difference between the oral cancer group and the pharyngeal cancer group and the nonoperated side did not compensate for the operated side.[58] Bodin et al. (2004) conducted a similar study on 27 patients and 20 controls with oral cancer who had undergone only radiation therapy.[59] A delayed deterioration of oral sensation was revealed on the nontumor side 6 months after radiotherapy and there was no recovery in this deterioration even 1 year post-treatment. Patients who had undergone mandibular resection for benign tumors such as ameloblastomas suffered some degree of neurosensory deficit, but some recovery was seen especially in patients younger than 16 years.[60]

Surgeons have been performing reconstructive surgery to repair surgical defects in the head and neck region using flaps for several decades. Interestingly, in recent years, microvascular reconstructive surgery with anastomosis of nerves from the flap to the severed nerves at the surgical site has been shown to decrease neurosensory deficits and improve sensation by at least 50%. Sensate flaps have been shown to be more superior to nonsensate flaps. Boyd et al. (1994) showed that patients who received sensate radial forearm flaps in which the lateral antebrachial cutaneous nerve was anastomosed to the (divided) lingual nerve had greater two-point discrimination and pressure sensitivity compared with the ones who received noninnervated radial forearm flaps.[61] One rather interesting finding in this study was that patients who received pectoralis flaps had lesser sensory re-innervation compared with those who received either innervated or noninnervated radial forearm flaps. This difference in sensory perception apparently is due to the fact that radial forearm flaps have greater density of free-nerve endings compared with pectoralis flaps. Another interesting finding in this study was that the sensory discrimination in the forearm flaps was greater even though that degree of discrimination is not normally present in the forearm. The explanation for this finding is that the flap which is anastomosed with the lingual nerve is now represented by a larger area (for the tongue) in the sensory cortex compared to the area for the forearm. Kimata et al. (1999) conducted a study comparing differences in sensation between innervated and noninnervated thigh flaps and rectus abdominus flaps.[62] As in the earlier study, the innervated flaps had a greater degree of sensation and the degree of sensory recovery of innervated thigh flaps was significantly greater than that of innervated rectus abdominus flaps. Similarly, greater sensory recovery has been reported in fasciocutaneous radial forearm flaps compared with jejunal flaps.[63]

Finally, mental neuropathy may be the first manifestation of systemic cancer, a symptom of spread of an established tumor, or a sign of infiltration in an intraoral lesion. It is characterized by the presence of a sensory defect in the form of paresthesias or dysesthesias in the territory innervated by the mental nerve and is indicative of a very poor patient prognosis. Sanchis et al. (2008) studied 22 cancer patients with chin paresthesia.[64] The patients were divided into two groups. Group 1 comprised patients ($n = 11$) with chin paresthesia who had a primary tumor in some other region at a distance from the oral cavity or maxillofacial zone. Group 2 ($n = 11$) in turn comprised patients with primary malignancies of the oral and/or maxillofacial territory and who likewise presented with chin paresthesia. Data were collected relating to patient age, gender, primary intraoral lesion (location, size, histologic diagnosis), primary systemic tumor, and mean patient survival. In group 1, the mean survival after the diagnosis of chin paresthesia was 14.8 ± 16.5 months and only 1 patient was still alive after 9 months. Group 2 consisted of 11 patients with oral squamous cell carcinoma, with the exception of 1 case of fibrosarcoma. In this group the mean survival of the 8 patients who died was 28.2–29.6 months. Three patients survived for a mean of 17 months. The authors concluded that chin paresthesia is a very important prognostic symptom determining the degree of infiltration of intraoral lesions, and in some cases it may be indicative of the existence of a primary tumor (identified or otherwise), with poor short-term survival given that 81.9% of the patients studied (18 cases) had died before a mean of 20 months. Although mean survival was shorter (14.8 months) among the patients in group 1 than in group 2 (28.2 months), the difference was not found to be statistically significant.

13.5 Challenges in cancer pain management

Barriers to pain management include issues related to clinicians, patients, and the health system. The traditional model of care is focused on disease-specific treatments. If these treatments fail, the focus shifts to palliation. The most general and common physician-related barriers to cancer pain management are concerns about side effects to opioids, prescription of inefficient doses of opioids, and very poor

prescription for the treatment of side effects from opioids.[65] With regard to the use of analgesics for cancer pain in the United States, a survey reported that 86% of physicians felt the majority of patients with cancer pain were undermedicated. Only 51% believed pain control in their own practice setting was good or very good; 31% would wait until the patient's prognosis was 6 months or less before they would start maximal analgesia. Adjuvants and prophylactic side-effect management were infrequently used in the treatment plan. Concerns about side-effect management and tolerance were reported as limiting analgesic prescribing. Poor pain assessment was rated by 76% of physicians as the single most important barrier to adequate pain management. Other barriers included patient reluctance to report pain and patient reluctance to take analgesics (both 62%) as well as physician reluctance to prescribe opioids (61%).[66] A study of 4000 elderly nursing home residents with cancer revealed that 24%, 29%, and 38% of those over age 85 years, 75–84 years, and 65–74 years, respectively, reported daily pain.[67] Twenty-six percent in daily pain did not receive any medication. Those older than 85 years who reported pain were most likely to receive no analgesic. There is a need for educational programs in cancer pain targeted toward healthcare practitioners to better understand these barriers and address them effectively.

13.6 Management of cancer pain

Regardless of whether the pain is neuropathic, nociceptive, cancer induced, or cancer-treatment induced, if it is severe, opioids are widely utilized for pain relief. For mild-to-moderate pain, nonopioid analgesics and other adjunctive medications are used per the World Health Organization (WHO) recommendations for cancer pain management.

13.6.A Pharmacologic management: NSAIDs and nonopioid analgesics

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) and nonopioid analgesics such as acetaminophen is common in cancer pain management. In fact, pain specialists often undertake combination therapy with multiple analgesics, including two or more analgesics, during the treatment of severe, refractory pain. The use of NSAIDs along with opioids in cancer patients reduces the need for an opioid dose escalation or allows the use of lower doses. Their use is associated with a more intense gastric discomfort, but results in less opioid-related constipation.[68] In cancer patients, the use of NSAIDs may delay the development of opioid tolerance although central toxicity may be observed with NSAIDs. These adverse effects may interfere with optimal patient function, and limit the quality of residual life. Diclofenac sodium and ketorolac are popular NSAIDs for cancer pain and are often used with opioids. Diclofenac does not modify morphine or methadone pharmacokinetics in cancer patients, which indicates that its analgesic effect is independent of any modification of the opioid. Ketorolac has been reported to be effective for malignant bone pain secondary to metastatic invasion.[69] The addition of NSAIDs is particularly useful for patients experiencing opioid toxicity upon escalating the opioid dose.[70]

History of peptic ulcer disease, advanced age (>60 years of age), female gender, and concurrent corticosteroid therapy should be considered before NSAID administration to prevent upper gastrointestinal tract bleeding and perforation. When NSAIDs are administered in a peptic ulcer risk group, proton pump inhibitors are usually added to the therapeutic mix to try to prevent gastrointestinal side effects induced by NSAIDs. NSAIDs should be prescribed with caution in patients having compromised fluid status, interstitial nephritis, concomitant administration of other nephrotoxic drugs, and renally excreted chemotherapy in order to prevent renal toxicities. Although widely used, evidence on the effectiveness of NSAIDs in cancer pain is limited because of the small number of randomized clinical trials and the wide range of medications, dosages, and schedules encountered in attempts to perform meta-analyses. More trials with NSAIDs are necessary as they may modulate inflammatory pathways that generate pain, and the treatment is cost-effective.

Acetaminophen is another drug that is often prescribed with opioids. Owing to its hepatotoxicty effect, the dose is usually limited to a maximum of 4000 mg/day in normal patients and 1000–2000 mg/day in patients with hepatic disease.[71] With long-term use, acetaminophen should be used with caution in patients with renal disease owing to its nephrotoxic potential.

13.6.B Pharmacologic management: adjuvant analgesics

The term "adjuvant analgesic" describes any drug with a primary indication other than pain, but with analgesic properties in some painful conditions. Although they can be used alone, they are usually co-administered with more traditional analgesics such as acetaminophen, NSAIDs, or opioids when treating cancer pain. This co-administration is to enhance pain relief provided by the analgesics, address pain that has not or has insufficiently responded, and allow the reduction of the opioid dose to reduce adverse effects. Adjuvant analgesics often are administered as first-line drugs in the treatment of chronic nonmalignant pain or in cancer remission patients who are resistant to opioid therapy. Unfortunately, there are very few comparative trials, and the

selection of the most appropriate adjuvant analgesic is based largely on trial and error and various medical issues gathered during a comprehensive assessment of the patient.[72] The commonly used adjuvant analgesics for cancer pain management are listed in Table 13.3.

Anticonvulsant drugs

Anticonvulsants should be considered early in treatment for spontaneous pain that has no inflammatory basis or for sharp lancinating pains especially when the features of the pain include burning, dysesthesias, or allodynia. In fact there is good evidence that the anticonvulsant drugs are useful in the management of neuropathic pain.[73–75] Gabapentin has been used for neuropathic pain in the last decade and its analgesic efficacy has been established in several types of nonmalignant neuropathic pains[76–81] as well as for cancer-related neuropathic pain.[82,83] Ross et al.[84] have shown a 33% reduction in the pain scores of more than 45.2% of neuropathic pain patients receiving gabapentin. In addition to its analgesic effect, the greatest benefit of gabapentin is that it has good tolerability and rare drug–drug interactions. The usual maximum dose is 3600 mg daily and the typical initial effective dose is 1800 mg/day. An adequate therapeutic trial should include 1–2 weeks at the maximum tolerated dose; the common adverse effects are somnolence, dizziness, and unsteadiness but these are not usually reason for discontinuing the medication. Pregabalin is a new anticonvulsant with a mechanism identical to that of gabapentin and equivalent evidence of analgesic efficacy.

Other anticonvulsants used for cancer pain include lamotrigine, which has good data on its efficacy for nonmalignant neuropathic pain coming from several randomized trials.[85–88] Lamotrigine has more serious adverse effects than gabapentin (e.g., somnolence, dizziness, ataxia) and requires a slower titration. Oxcarbazepine is a metabolite of carbamazepine and has a similar spectrum of effects, with much better tolerability. Although the current evidence for oxcarbazepine is limited to a few case series and open-label trials, it appears promising. Topiramate, tiagabine, levetiracetam, and zonisamide have some evidence of efficacy. Among the older drugs, evidence of efficacy is best for carbamazepine and phenytoin, and valproate has been widely used. Carbamazepine is the drug of choice for trigeminal neuralgia. In cancer patients, carbamazepine has been used specifically in managing the acute shocklike neuralgic pain in the face caused by tumor infiltration or surgical injury. However, due to their frequent side effects (sedation, dizziness, nausea, unsteadiness) and potential for drug–drug interactions, the use of these drugs has declined with the introduction of the newer anticonvulsants mentioned previously.

Tricyclics, SSRIs, and SNRI antidepressants

There is reasonable evidence that tricyclic antidepressants have analgesic properties when used in a variety of chronic nonmalignant pain condition, especially neuropathic pain.[89–91] Both the tertiary amines (amitriptyline, imipramine, doxepin, clomipramine) and the secondary amines (nortriptyline, desipramine) are analgesic. Although few clinical trials have specifically evaluated these drugs for cancer pain, partially controlled[92,93] and uncontrolled trials,[94] as well as clinical experience, generally support them as having a mild analgesic effect. The use of the tricyclic antidepressants as analgesics in medically ill or elderly patients may be limited by the frequent occurrence of side effects.[95] Although their most serious adverse effect, cardiotoxicity, is uncommon,[96] patients who have significant heart disease (conduction disorders, arrhythmias, heart failure) should not be treated with a tricyclic. The secondary amine tricyclic antidepressants, desipramine and nortriptyline, are less anticholinergic and, therefore, better tolerated than the tertiary amines.

Regarding other types of antidepressants, such as the selective serotonin reuptake inhibitors (SSRIs), the evidence is far less than that which supports the efficacy of the tricyclic drugs. No studies have been done on cancer pain for the SSRIs. The main advantage of the SSRIs is their favorable side-effect profile.[97] Venlafaxine and duloxetine are called serotonin–norepinephrine reuptake inhibitors (SNRIs) and both have been shown to be analgesic in several studies on neuropathic pain. Randomized controlled trials showed good pain relief for painful polyneuropathy[98] and for neuropathic pain following treatment of breast cancer.[99]

Ketamine and other N*-methyl-*D*-aspartate receptor blockers*

Another class of drugs used in neuropathic pain comprises those that act directly at the *N*-methyl-D-aspartate (NMDA) receptor. This receptor is known to be tonically activated in neuropathic pain, so modulating or blocking it can reduce pain activity. Antagonists at the NMDA receptor may offer another approach to the treatment of neuropathic pain in cancer patients. At the present time, there are four commercially available NMDA receptor antagonists in the United States. They are the antitussive, dextromethorphan; the dissociative anesthetic, ketamine; the antiviral drug, amantadine; and a drug approved for the treatment of Alzheimer's disease, memantine. Among these drugs, only ketamine has found some success in treating neuropathic pain, especially in a situation where large doses of opioids have contributed to the development of severe hyperalgesia.[100] Ketamine can be given by multiple routes: intravenous, intramuscular, subcutaneous, oral, rectal, nasal, transdermal, epidural, or even

Table 13.3 List of some commonly used adjuvant analgesics for cancer pain management

Drug class	Examples	Side effects	Precautions
Antidepressants			
Tricyclic antidepressants	Amitriptyline, nortriptyline, desipramine	Sedation, confusion, orthostatic hypotension, weight gain, tachycardia, arrhythmia, anticholinergic effects (dry mouth, blurred vision, urinary hesitancy)	Caution in elderly and medically ill, cardiovascular disorders, or seizure history; contraindicated with narrow-angle glaucoma
SSRIs	Paroxetine, citalopram	Nausea, headache, diarrhea, insomnia, dizziness, tremor, sexual dysfunction	Caution if seizure disorders
SNRI	Venlafaxine	Nausea, somnolence, hypertension, dry mouth, sexual dysfunction	Caution if hypertension or seizure disorders
Others	Bupropion	Tachycardia, insomnia, agitation, tremor, headache, dry mouth	Contraindicated with seizure history or MAOIs
Corticosteroids	Dexamethasone, prednisone	Hyperglycemia, increased appetite, weight gain, edema, cushingoid habitus, dyspepsia, delirium, insomnia, agitation	Caution if hypertension, heart failure, peptic ulcer, diabetes, infection, thromboembolic disorders
Alpha-2-adrenergic agonists	Tizanidine	Somnolence, dizziness, hypotension (usually orthostatic), dry mouth	Caution in cardiovascular disorders; discontinue clonidine slowly to avoid rebound hypertension.
Anticonvulsants	Gabapentin, topiramate, lamotrigine, carbamazepine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, zonisamide, phenytoin, valproic acid	Somnolence, dizziness, headache, nervousness, tremor, fatigue, mood changes, confusion, weight gain, edema, hyponatremia, increased liver enzymes; serious rash (black box warning)	Increase dose gradually to improve tolerance; decrease dose gradually to avoid seizure and discontinue at first sign of rash.
NMDA receptor blockers	Ketamine, dextromethorphan, memantine, amantadine		
Ketamine		Hypertension, tachycardia, tremor, nystagmus, diplopia, airway resistance, myocardial depression	Contraindicated with hypertension, heart failure, angina, aneurysms, cerebral trauma, recent myocardial infarction; caution with psychotic disorders, thyrotoxicosis, seizures
Amantadine		Orthostatic hypotension, peripheral insomnia, agitation, confusion	Caution in uncontrolled psychosis, or seizure history
GABA agonist	Baclofen	Dizziness, somnolence, headache, confusion	Caution in seizure history

Table derived from Lussier D, Huskey AG, Portenoy RK. Adjuvant analgesics in cancer pain management. Oncologist. 2004;9(5):571–591.
GABA, gamma-aminobutyric acid; MAOI, monoamine oxidase inhibitor; NMDA, *N*-methyl-D-aspartate; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

intrathecal, although the optimal route of administration remains unclear due to a lack of good clinical trials and limited experimental studies. Ketamine has been used in a variety of neuropathic pain syndromes that are refractory to high-dose opioids, such as central pain, ischemic pain, and pain associated with post-traumatic nerve or spinal cord injury, as well as in fibromyalgia, refractory facial pain, and postherpetic neuralgia. However, there is very limited data on ketamine trials in cancer pain management. In addition, apart from a few cases of complete resolution, ketamine generally did not provide a long-term solution in clinical trials for chronic pain.[101] Nevertheless, ketamine may be still used in refractory cancer pain management as an adjunctive modality for its opioid-sparing benefits, allowing smaller doses of morphine to be given.

The concept of administering subanaesthetic doses of ketamine to improve opioid-tolerant cancer pain is termed "burst" ketamine therapy. Two small RCTs, one using intravenous[102] and the other intrathecal administration, and numerous open-label studies and case reports suggest that ketamine improved opioid-based analgesia in refractory cancer pain but with considerable side effects.[103] Parenteral ketamine infusion decreased pain scores and opioid requirements in approximately two-thirds of patients with refractory cancer pain.[104,105] Side effects include feeling "spaced out," hallucinations, drowsiness, and respiratory depression. The psychotrophic effects of ketamine include "floating," "out-of-body experiences," near-death experiences, distorted perception such as time, space, and morphology, hallucinations, and schizophreniform psychosis.[106] For this reason, it is recommended to lower the opioid dose when starting ketamine. The opioids methadone, dextropropoxyphene, and ketobemidone are also antagonists at the NMDA receptor.[107] Consequently, NMDA receptor antagonists may represent a new class of analgesics and may have potential as co-analgesics when used in combination with opioids.

Corticosteroids

Corticosteroids, like NSAIDs, also possess analgesic properties for inflammatory cancer pains, especially bone pain, neuropathic pain from neural infiltration or compression of neural structures, and headache due to increased intracranial pressure or arthralgia. They are usually administered in either a high- or a low-dose protocol. The high-dose regimen (e.g., dexamethasone, 100 mg, followed initially by 96 mg/day in divided doses) has been used for patients who experience an acute episode of severe pain that cannot be promptly reduced with opioids.[108] The dose is tapered over the next 2–3 weeks after the initiation of other analgesic approaches (e.g., opioid therapy). Conversely, the low-dose protocol (e.g., dexamethasone at a dose of 2–4 mg once or twice daily) is used for patients with advanced cancer who continue to have pain despite optimal dosing of opioid drugs. In most cases, long-term therapy is then planned, and the dose should be tapered down to the lowest effective dose.

The efficacy of corticosteroids as adjuvant drugs to opioids for analgesia in cancer patients is controversial. A recent prospective randomized study showed that corticosteroids did not provide significant analgesia when used as adjuvant drugs to opioids. However, they were reported to decrease the opioid-related gastrointestinal symptoms and improve a sense of well being among cancer patients.[109] When the pain suppression is substantial, corticosteroid drugs can improve appetite, nausea, malaise, and overall quality of life, but a moderate number of pain patients cannot tolerate this drug.[110,111] Weekly assessments are required to ensure that benefits are sustained since, as mentioned, long-term corticosteroid therapy has substantial adverse effects.[112] Long-term administration of corticosteroids increase the risk of peptic ulcer disease.[113] The chances of developing this undesirable side effect are increased when corticosteroids are administered along with NSAIDs. Some clinicians avoid prescribing steroids with NSAIDs. As mentioned earlier, other clinicians prefer prescribing gastroprotective agents such as proton pump inhibitors in these cases.

Skeletal muscle relaxants

Pain that originates from injury to muscle or connective tissue is frequent in patients with cancer.[114] The efficacy of so-called muscle relaxants and other drugs commonly used for the treatment of musculoskeletal pain has not been evaluated in cancer patients. These agents include antihistamines (e.g., orphenadrine),[115,116] tricyclic compounds structurally similar to the tricyclic antidepressants (e.g., cyclobenzaprine), and others (e.g., carisoprodol, metaxalone, methocarbamol). Although these drugs can relieve musculoskeletal pain,[117–120] these effects may not be specific, and there is no evidence that they relax skeletal muscle in the clinical setting. The most common adverse effect is sedation, which can be additive to other centrally acting drugs, including opioids, and are therefore problematic. Most pain clinicians will select a diazepam or other benzodiazepine, an alpha-2-adrenergic agonist such as tizanidine, or the GABA-B agonist baclofen if true muscle spasm is present.

Recently injections of botulinum toxin (BoNT) also have been considered for refractory musculoskeletal pain related to muscle spasms.[121] Botulinum toxin type A (BoNT-A) has only been studied and proven to be effective in relieving neuropathic pain in rat models.[122,123] BoNT has been studied for management of chronic neck pain after neck dissection, radiation-induced pain, trismus, and masticator spasm in head and neck cancer. A pilot study of BoNT-A on 16 patients with chronic neck pain after neck dissection showed a significant reduction in chronic pain (4.5 before to 3.3 after

treatment, $p = 0.005$) and in shooting pain (6.1 before to 4.7 after treatment, $p = 0.005$).[124] A prospective nonrandomized study included patients ($n = 19$) in complete remission with radiation-induced pain and trismus with or without masticator spasms. BoNT did not improve trismus but significantly improved pain scores and masticator spasms.[125] Wittekindt et al. (2006) reported that BoNT-A in a low concentration seems to be a useful therapeutic option in chronic neuropathic pain of the neck and shoulder after neck dissection.[126] However, a recent review does not show strong evidence of efficacy for BoNT on chronic orofacial pain disorders.[127]

13.6.C Pharmacologic management: opioids

The opioid analgesics are drugs which act by binding with multiple central nervous system opiate receptors. The agonist drugs, with morphine as the prototype, are most commonly used in the management of cancer pain. Given its place on the WHO essential drug list, familiarity to physicians, and wide oral use in cancer pain management, a WHO expert consensus panel named morphine as the drug of choice for the management of patients with cancer pain. Opioid analgesics used for moderate to severe cancer pain include morphine, hydromorphone, methadone, fentanyl, meperidine, levorphanol, oxycodone, and oxymorphone. Drugs such as codeine and tramadol have a limited analgesic efficacy. These drugs are used for mild to moderate pain and have been included in step II of the analgesic ladder. Oxycodone is included in both step II and step III of the analgesic ladder.

Alternative opioid medications should be considered in patients who are unable to tolerate morphine or who have excessive side effects of nausea or sedation. In patients over 65 years of age, hydromorphone, oxycodone, and fentanyl may be better tolerated with fewer side effects than morphine.[128] In recent years, several systematic reviews have concluded sufficient evidence exists to state that morphine, hydromorphone, and methadone are effective for managing cancer pain.[129–131] This is not surprising, but these reviews also state that the amount of high-quality evidence for this conclusion is limited. The reviewers were unable to conclude which opioid is the ideal starting agent. Some authors advise morphine others advise using methadone as the initial agent to control cancer pain and reduce tolerance to opioids. However, in one randomized comparison of morphine to methadone as the initial strong opioid used on hospice patients with cancer pain, morphine was found to be superior to methadone.[132] Finally, chronic neuropathic pain has been historically referred to as opioid-nonresponsive pain but recent data suggests that opioid therapy does provide significant pain relief in patients with such neuropathic pain syndromes as postherpetic neuralgia and painful diabetic neuropathy, although pain reduction appears to be related to higher dosage levels.[133–135]

The six most commonly used opioids in the elderly based on the WHO step III ladder for cancer pain include morphine, oxycodone, buprenorphine, fentanyl, hydromorphone, and methadone.[136] Since this book contains a separate chapter on opioids, further discussion of these drugs is deferred to Chapter 4. In addition, the use of opioids in nonmalignant orofacial pain is discussed in detail in Chapter 4.

Modifications to the WHO analgesic ladder for cancer pain management

The three-step WHO analgesic ladder is the most widely followed and well-established protocol for management of cancer pain. However, in recent times this analgesic regimen has come under fire from a number of palliative care specialists who argue that the WHO program, even though updated in 1990, has not kept pace with the rapidly changing developments in oncology and pain research.[137] The current ladder method consistently failed to provide sufficient relief to 10–20% of advanced cancer patients with pain, particularly in cases of neuropathic pain and pain associated with bone involvement.[138] Therefore, it was suggested that a fourth, "interventional," step be added to the three-step WHO analgesic ladder once opioids and other drugs fail, which will incorporate nerve blocks, intrathecal drug delivery systems, and other surgical interventions.[139] Nersesyan and Slavin (2007) suggested a more sophisticated five-step algorithm that would separate potentially reversible neuromodulation (electrical or chemical) from virtually irreparable destructive procedures, such as cordotomy, rhizotomy, or thalamotomy, and would also include physical and psychological modalities at every step along the entire continuum of care.[140]

13.6.D Anesthetic management

An anesthetic approach to management of pain in the head and neck region is an option available to practitioners for managing cancer-related intractable pain. There are a few case reports of mandibular neurolytic blocks performed to obtain long-term pain relief in advanced cancer cases.[141,142] In one case, an indwelling catheter in the mandibular nerve was used to administer the block with lidocaine (1%) and bupivacaine (0.25%) for a week followed by a neurolytic block. If the pain is musculoskeletal in origin and is caused by taut muscle bands or trigger points, then injecting the trigger points with 0.5% lidocaine or 0.5% procaine is a viable option for achieving temporary pain relief. Anesthetic blocks for the head and neck region and trigger-point injections are covered in detail in Chapter 11.

The development of a lidocaine 5% patch has facilitated the topical application of local anesthetics.[143] The lidocaine patch, approved by the FDA for use in postherpetic neuralgia, is usually applied 12 hours per day, but a few studies indicate a high level of safety with up to three patches for periods up to 24 hours.[144] The most frequently reported adverse event is mild to moderate skin redness, rash, or irritation at the patch application site (see Chapter 5, Sec. 12.3.A). The use of a lidocaine infusion therapy via an intravenous approach is available for nonmalignant neuropathic pain.[145,146] Brief infusions can be administered at varying doses within the range of 1–5 mg/kg infused over 20–30 minutes. Although prolonged relief of pain following a brief local anesthetic infusion may occur, relief usually is transitory. If lidocaine appears to be effective but pain recurs, long-term systemic local anesthetic therapy can be accomplished using an oral local anesthetic, typically mexiletine (see Chapter 6, Sec. 6.2.K). Controlled studies of mexiletine have demonstrated a relatively high rate of adverse effects (nausea, vomiting, tremor, dizziness, unsteadiness, and paresthesias) and discontinuation due to toxicity in almost one-half of patients.[147] Finally, with lidocaine infusions negative results have generally been obtained in randomized controlled trials in neuropathic cancer pain so its use has declined in recent years.[148,149]

13.6.E Neurosurgical procedures in the orofacial region

Peripheral cranial neurotomies and other neuroablative procedures are available for managing intractable cancer pain. Procedures such as peripheral cranial neurotomies carry the risk of producing greater nerve damage and loss of sensation and therefore should be considered as a last resort in those patients with intractable cancer pain localized to the trigeminal or glossopharyngeal nerve region. Central ablative neurosurgical procedures are now very rarely performed for cancer pain because of better available pain management modalities such as long-term intraspinal or intraventricular administration of analgesics. Electrical neuromodulation, the electrical stimulation of neural structures (peripheral nerves, dorsal columns of spinal cord, and brain stimulation), although widely used for successful treatment of intractable neuropathic and central pain, has almost no role in the treatment of cancer-related pain.

13.6.F Cannabinoids

Cannabinoids have been shown to exhibit antinociceptive effects in animal models. Cannabinoid receptor 1 (CB1) agonists have been shown in rat models of neuropathic pain to effectively reduce thermal and mechanical hyperalgesia and mechanical allodynia.[150] In rat models with cancer, CB1 agonist administration has shown to reduce tumor-evoked hyperalgesia on a short- and long-term basis.[151] There are several potential mechanisms of analgesia for endocannabinoids. CB1 receptors are present in areas that modulate pain transmission, and cannabinoids appear to act at both spinal and supraspinal levels to produce analgesia.[152,153] Furthermore, endocannabinoids may have analgesic activities by modulation of pain signals in both ascending and descending pathways, by direct spinal action, or by actions on peripheral nerves.[154–156] Endocannabinoids are now emerging as suppressors of angiogenesis and tumor spreading since they have been reported to inhibit angiogenesis, cell migration, and metastasis in different types of cancer, pointing to a potential role of the endocannabinoid system as a target for a therapeutic approach of such malignant diseases.[157]

A review of human trials using cannabinoids has shown that these agents are not ready for widespread clinical use for analgesia. Findings also showed that oral tetrahydrocannabinol (THC) in doses of 5–20 mg and intramuscular levonantradol in doses of 0.5–3 mg were approximately equivalent to codeine 60–120 mg. Additionally, adverse effects of mild to moderate severity were noted in almost all patients who used cannabinoid agonists for analgesia, including feelings of euphoria or dysphoria, dry mouth, and drowsiness.[158]

Currently, only three cannabinoid agonists are available internationally: dronabinol (synthetic thetrahydrocannabinol/THC), nabilone (THC analog), and cannabis medical extract (CME). Of these three agents only nabilone is indicated for managing chemotherapy-induced nausea and vomiting. Currently, none of these agents are approved for managing cancer pain. CT3 or ajulemic acid is an analog of THC and has shown a more favorable side-effect profile than THC. Some of the cannabinoids in development, such as HU-211 and AM 1241, may prove to have more desirable adverse effect profiles as results of human studies become available.[159] The field of cannabinoid pharmacotherapy is still in its stages of infancy and holds a lot of promise for chronic pain management in the near future.

13.6.G Complementary and alternative medicine

There is wide variability in the nonpharmacologic approach to treatment of neuropathic pain and cancer pain.[160] This is because in general there is a serious lack of multi-institutional RCTs evaluating complementary and alternative medical interventions for cancer pain with adequate power, duration, and sham control. Despite this, there is an increase in the use of complementary and alternative medicine (CAM) for managing chronic diseases in the United States. The National Health Interview Survey in 2002 showed that arthritis (59.6%) was the most common condition for which CAM

was sought by patients, followed by cancer or lung disease alone or two or more chronic diseases (55%).

Twenty seven different types of CAM were categorized into four groups as defined by the National Center for Complementary and Alternative Medicine at the National Institutes of Health (http.//nccam.nih.gov) and based on previous analysis of the survey (advance data report).[161] The first group is biologically based practices that use substances found in nature and include the use of herbs, special diets, or vitamins. The second group is alternative medical systems that are built on complete systems of theory and practice such as acupuncture and ayurveda. The third group is mind–body medicine, which uses a variety of techniques designed to enhance the mind's ability to affect body function and systems and includes biofeedback, meditation, guided imagery, and prayer for health reasons. The fourth group is manipulative-based practices, which are based on manipulation or movement of one or more body parts, such as chiropractic care or massage. The most commonly used CAM modalities in 2002 were herbal therapy (18.6%, representing over 38 million US adults) followed by relaxation techniques (14.2%, representing 29 million US adults) and chiropractic (7.4%, representing 15 million US adults). Among CAM users, 41% used two or more CAM therapies during the prior year. Among the factors associated with highest rates of CAM use were ages 40–64, female gender, non-black/non-Hispanic race, and annual income of $65,000 or higher.[162] Of the cancer patients (55.3%) using CAM therapies, 43.4% reported using biologically based CAM, 37.9% manipulative CAM, 37.7% mind–body CAM, and 16.8% reported using alternative systems of CAM. The reasons for CAM use among cancer patients included the following: (1) conventional treatment not helpful (8.9%), (2) conventional treatment too expensive (4%), (3) combined with conventional treatment (16.3%), (4) suggested by conventional medical professional (7.7%), (5) thought it would be interesting (14.7%). Only 27.6% of cancer patients had spoken to a healthcare professional about the use of CAM.[163]

13.7 Eighteen final recommendations on treatment of cancer-related orofacial pain and dysfunction

Recommendations on the treatment of cancer-related pain and dysfunction

1. Pain in cancer accounts for 30–40% of the main complaints of cancer patients; it can be the presenting symptom of various types of cancer.
2. In head and neck cancer, pain affects the oral functions and is the complaint in about 58% of the patients awaiting treatment, and in 30% of treated patients.
3. Fifty percent of adults who die in the hospital experience moderate to severe pain in the last 3 days of life.
4. Pain has been reported as the initial complaint on average in only 19.2% of patients with oral pharyngeal cancer although this number is higher in recurrent cancer.
5. Head and neck cancer treatment (surgery, radiotherapy, and chemotherapy) patients often have other symptoms such as mucositis, jaw dysfunction (trismus or contractures), and oral sensory alterations (numbness and sensory distortions).
6. Neuropathic pain is present in 15–20% of cancers and is caused either directly by cancer-related pathology (compression or infiltration of nerve tissue) or secondarily by diagnostic and therapeutic procedures (surgical procedures, chemotherapy, radiotherapy).
7. Trismus, a tonic contraction of the jaw-closing muscles, is more common in surgical and radiation therapy patients than in chemotherapy patients and generally has a poor prognosis with current treatments once it develops.
8. The primary approach for trismus is (1) stretching under sedation and (2) weekly office and daily home use of a mechanical jaw-stretching device.
9. Stretching exercises and devices need to be implemented early and aggressively in the cancer treatment period to maintain maximum opening and jaw mobility.
10. When the cancer disease or treatment is causing spastic reaction in the jaw-closing muscles, botulinum toxin (BoNT) injection into the involved muscles provides the needed spasticity control.
11. Somatosensory abnormalities that interfere with speech, mastication, swallowing, voice quality and resonance, and intraoral sensations are not uncommon in patients who have undergone treatment for oral and nasopharyngeal cancer, and post-treatment speech and swallowing rehabilitation protocol should be standard therapy.
12. Sensory discrimination ability in oral cancer patients was not diminished after radiotherapy, but was after cancer surgery and this change was still present after 1 year.
13. Cancer pain management typically involves opioid therapy, and a large majority of physicians feel that patients with cancer pain are undermedicated.
14. Nonopioid analgesics and nonsteroidal anti-inflammatories are widely utilized for pain relief when the pain is of mild to moderate severity, although they have a risk of side effects such as gastrointestinal, renal, and hepatic disease.

15 Adjunctive pain medications, including tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitor (SNRI) medications and anticonvulsants, lidocaine, and *N*-methyl-D-aspartate (NMDA) antagonists, are frequently used when patients are resistant to opioid therapy.

16 Corticosteroids also possess analgesic properties for inflammatory cancer pains, especially bone pain, neuropathic pain from neural infiltration or compression of neural structures, and headache due to increased intracranial pressure or arthralgia.

17 Cannabinoids have been shown to exhibit antinociceptive effects in animal models and are quite popular adjunctive pain agents in cancer pain.

18 Many patients have a desire to use nonpharmacologic therapy for cancer pain management, and the research suggests that, while they may be largely placebo in mechanism, complementary and alternative therapies have efficacy compared with no treatment.

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Chapter 14

Burning mouth syndrome: an update on diagnosis and treatment methods

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14.1 Diagnosis of burning mouth syndrome

Imagine the frustration of having a continuous painful disorder that cannot be definitively diagnosed with any known test or X-ray, interferes with eating, becomes progressively worse, has no known cause, and lacks any highly effective treatment. This is what patients with burning mouth syndrome (BMS) deal with every day of their lives.

Clinical presentation

Burning mouth syndrome has various synonyms, such as stomatopyrosis, glossopyrosis, stomatodynia, glossodynia, sore mouth, sore tongue, and oral dysesthesia. These terms are used to emphasize the quality and or the location of pain in the oral cavity. The diagnostic criteria are as follows: (1) pain in the mouth is present daily and persists for most of the day; (2) oral mucosa is of normal appearance; and (3) local and systemic diseases have been excluded.[1] The International Classification of Disease (version 9 [ICD-9]) has assigned the term glossodynia, which included the subterms glossopyrosis and painful tongue, a specific identity code number (ICD-9 #529.6).[2]

Onset and pattern

Burning mouth syndrome typically has a spontaneous onset, although its intensity will increase gradually over time. The International Association for the Study of Pain has identified BMS as a distinctive named entity characterized by oral burning pain episodes lasting at least 4–6 months.[3] There is no published data on the natural life history of burning mouth syndrome. While many speculate that, over time, this disorder fades in intensity, data is lacking.

Character

It is characterized by sensory symptoms, both positive (burning pain, dysgeusia, dysesthesia) and negative (loss of taste, paraesthesia).

Location

The primary locations for these symptoms are the lips and tongue (mainly the tip and anterior two-thirds). BMS patients also complain of sensory discomfort in the hard palate and alveolar ridges. Conversely, the buccal mucosa and floor of the mouth are almost never involved.[4] At least for the tongue, the anatomic distribution of the burning pain in BMS patients corresponds, to a great degree, to where tastebud density is greatest in the mouth. With regard to the issue of location, one study examined tastebud density on the tongue and found that tastebud density was 4.6 times higher on the tip than the midtongue region.[5] In the anterior hard palate or alveolar ridges this association between tastebuds and BMS is not absolutely tied to tastebud density because tastebuds are not commonly located on the inner lip mucosa. Nevertheless, most BMS patients report a persistently diminished taste or altered (metallic) taste sensations. Acidic foods such as tomatoes and orange juice cause considerable distress with an increase in burning sensations. These descriptions vary but often include a stinging or burning sensation as if the patient's mucosa has been scalded.

Diagnostic tests

Most of the common laboratory tests suggested for BMS patients, which we present in table form (see Sec. 14.6, Table 14.2), will turn out to be negative.[6] In fact, the International Classification of Headache Disorders classifies

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burning mouth syndrome as an intraoral burning sensation for which no medical or dental cause can be found.

14.2 Are there subpopulations of burning mouth syndrome?

The population of patients that have burning mouth syndrome tend to be female patients over the age of 50 and there are more oral disease and dysfunction problems in this age population than in a younger group of patients (e.g., hyposalivation, lichen planus, autoimmune diseases). A recent paper suggested that a subpopulation of BMS cases presents with a common triad of symptoms including (1) idiopathic sensorial disturbance of burning mouth, (2) taste disturbance (dysgeusia), and (3) dry mouth.[7] Another paper suggested three subgroups with BMS type 1 being characterized by burning pain increasing throughout the day and reaching its peak in the evening; BMS type 2 was characterized by complaints of continuous sensory disturbances; and BMS type 3 had intermittent symptoms with pain-free periods during the day. [8] The most pragmatic method of grouping BMS is by dividing patients into the primary BMS sufferers (no other evident disease) and secondary BMS sufferers (oral burning from other clinical abnormalities). In fact, using this last classification scheme, one paper examined 69 BMS patients (83% female) and asked them to fill out both the Multidimensional Pain Inventory and Symptom Checklist 90–Revised.[9] The study found that the primary BMS patients and the secondary BMS patients showed no differences with respect to age, pain duration, pain intensity, or levels of psychologic distress. There was one substantial difference: If the associated clinical abnormality was treatable, then the burning sensations would improve in the secondary BMS group, but the primary BMS group did not demonstrate remarkable symptom cessation with treatment.

14.3 Epidemiology

Burning mouth symptoms are reported in up to 4% of adults; this percentage increases with age, becoming more prevalent in the fifth to seventh decades. One study surveyed 669 men and 758 women randomly selected from 48,500 individuals ages 20–69. Researchers reported that 53 individuals (3.7%) exhibited BMS (11 men, or 1.6%; 42 women, or 5.5%).[10] The presence of BMS was found to be very uncommon before the age of 30 years (40 years for men) and the onset in women usually occurs within 3–12 years after menopause and is higher in women who have more systemic disease.[11] Another epidemiologic study surveyed US adults and estimated the overall prevalence of burning mouth to be 0.7% of the adults up to age 65.[12] This study was repeated on a subset of over 5800 individuals 65 and older in South Florida.[13] Researchers report a prevalence of 1.7% for burning mouth pain in this elderly group. Clearly, the differences in these prevalence figures are related to sampling bias in surveyed populations and disease definition being used.

14.4 Quantitative sensory testing in burning mouth syndrome

The frequent occurrence of numbness, pain, dysgeusia, and dysesthesia in BMS has prompted researchers to perform a quantitative assessment of the sensory and chemosensory functions in these patients.

14.4.A Neurosensory threshold testing

Until recently, researchers have not consistently found a statistically significant alteration in the sensory perception (touch and temperature) of BMS patients. For example, one study carefully examined 20 BMS patients versus 20 controls for different abilities to perceive different shapes of objects with their tongues.[14] No systematic disparity was evident in the two groups regarding object size perception ability. Of course, detecting the shape of objects with your tongue is not the only test of sensory acuity; several years ago researchers used argon laser stimulation to examine 23 BMS subjects versus 23 age-matched controls for differences in their sensory and pain thresholds.[15] This study used brief laser stimulation to six test sites (tongue tip, lower lip mucosa and skin, buccal mucosa, anterior hard palate, and dorsum of the hand). The study reported the sensory thresholds were significantly higher and the ratios between pain and sensory thresholds significantly lower in patients with BMS at all tested sites. The resulting widespread sensory threshold differences seen in this study argues for a centrally mediated sensory amplification abnormality.

14.4.B Blink reflex testing

Another study used an objective electrophysiological examination of the trigeminal–facial nerve system using the blink reflex response in 11 BMS subjects and 10 controls.[16] Researchers reported BMS patients have clear-cut alterations in their blink response to applied stimulation. Finally, a study examined evoked brainwave potentials after lingual nerve stimulation in 22 BMS patients with pain, 10 BMS patients with reported numbness, and 6 controls. [17] The study found that pain thresholds were significantly lower and evoked potential response latencies were significantly

different (shorter) in the BMS with pain group. The latencies in the BMS with numbness were significantly longer. Overall these sensory data suggest that peripheral and/or central nervous system changes are clearly present in BMS but the data do not pinpoint where within the somatosensory system the responsible underlying changes are to be found.

14.4.C Taste threshold changes and burning mouth syndrome

Dysgeusia is a term used to describe a distorted gustatory perception or persistent gustatory sensation in the absence of gustatory stimulants.[18] As mentioned earlier, BMS patients frequently report a positive taste sensation which they describe as a persistently altered (metallic) taste. They also have a diminished ability to detect bitter flavors, and spicy and acidic foods increase their burning sensations. One recent study examined 50 patients with BMS (study group) and 50 healthy subjects (control group) and analyzed their ability to taste three flavors (bitter, acidic, and spicy substances).[19] This study found that taste sensations were normal in all controls but 30 of the BMS patients had a diminished response to bitter taste. The use of a spicy substance (pepper sauce) applied to the tongue produced a strong burning sensation on the tongue in 28 patients of the BMS group but the same response was seen in only 10 of the controls. Another study examined 180 subjects with complaints of BMS, xerostomia, and taste disturbances versus 90 age- and gender-matched healthy controls.[20] This study also reported that the BMS patient group had clear-cut taste acuity differences compared with the controls, with more of the BMS patients reporting sweet abnormality than with the other three taste substances (salt, bitter, and sour). Another study examined taste acuity in 73 BMS patients (57 women and 16 men) and 52 control subjects (38 women and 14 men) who were age and gender matched to the BMS group.[21] Researchers used various concentrations of sweet, salty, sour, and bitter solutions and asked subjects to rate the intensity and quality of each solution. The study found that the 57 women in the BMS group gave lower-intensity ratings for salty and sweet test solutions than the 38 women controls. For the women in this study, there were no group differences on sour or bitter test solutions, and for the men in this study, there were no group differences on any of the substances tested.

14.4.D Special case of metallic dysgeusia

Because metallic dysgeusia is a common early symptom of a BMS disorder, it would be appropriate to review a 2004 article that describes medication-induced dysgeusia.[22] This paper reports that the medications most commonly linked to metallic dysgeusia are those used to treat bacterial infections, psychosis, arthritis, and hypertension. The study found case reports for metallic dysgeusia linked with tetracycline,[23] lithium carbonate,[24,25] D-penicillamine,[26] and captopril. A 1985 paper described a link between metallic dysgeusia and Crohn's disease that is manifesting oral effects as well as the usual intestinal changes.[27] In summary, metallic dysgeusia is not well understood, but in the absence of medications or brain disease causing it, the possibility remains that it may be related to damaged peripheral nerves, especially considering the information already presented about small sensory fiber neuropathic changes in the tongue. The hypothesis that pain and taste pathways are both affected and interact is reasonable and certainly worthy of further testing, especially if an animal model could be developed.

14.4.E Chorda tympani, taste, and burning mouth syndrome

There are patients who complain of numbness of the tongue after an otologic procedure, probably related to surgical damage of the chorda tympani nerve during the procedure. Examining this issue, a 2006 study assessed tongue sensations in 15 patients before and twice after undergoing middle ear surgery and in 18 nonsurgical controls.[28] The authors reported that 47% of the surgery patients complained of numbness or tingling of the tongue shortly after surgery, with a significant reduction in sensitivities to light touch and two-point discrimination on the operated side. This sensory deficit returned to baseline levels on subsequent evaluations and no patient in this study developed burning mouth syndrome. The main difference between subjects in this study and those in the burning mouth patient population was age: the study subjects were substantially younger. Another 2007 study found similar results. They reported on changes of trigeminal sensitivity of the tongue after middle ear surgery.[29] The authors concluded that pain-related sensitivity of the ipsilateral tongue side decreases after the mentioned surgery, suggesting that the chorda tympani nerve function influences both gustatory sensibility and intraoral trigeminal sensitivity, but again no increased pain or burning sensation resulted in this population.

14.5 Other local oral factors and burning mouth syndrome

Many local and systemic precipitating factors have been suggested beyond the salivary changes and sensory dysfunction changes described previously. The local factors included other diseases that may be causing burning sensations such as oral candidal infections, autoimmune mucosal

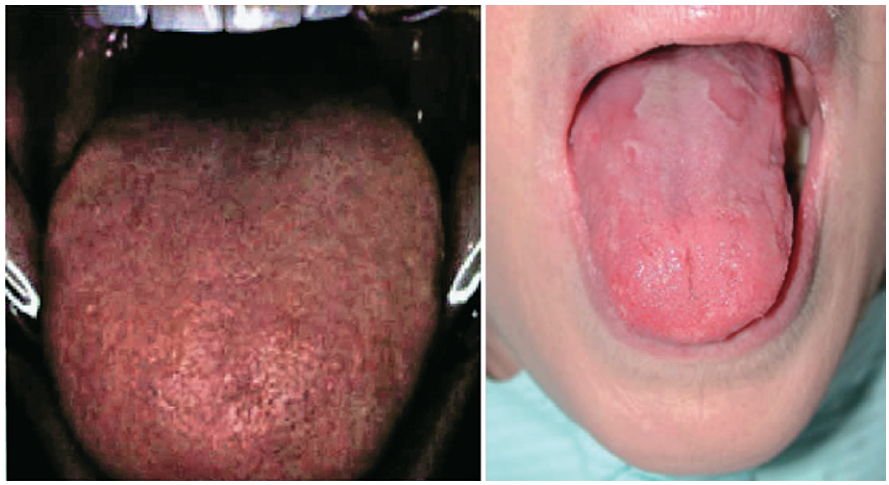

Figure 14.1 Bald or atrophic tongue (left) and geographic tongue (right).

reactions such as lichen planus, geographic tongue, atrophic tongue (Fig. 14.1), and tissue trauma from ill-fitting dentures.

Of course there are always case reports of burning type pains occurring from oral carcinomas that invade the trigeminal nerve and from a variety of local oral mucosal tissue irritants.[30] These local oral conditions have been seen often enough to suggest that some cases of BMS are secondary BMS cases.[31] More than one-third of all BMS patients presenting for diagnosis are estimated to have multiple causes; the most common causes of secondary BMS are listed in Table 14.1.

14.6 Other common co-morbid systemic diseases

Various systemic conditions have been associated with BMS, including diabetes, hormonal changes, and nutritional or mineral deficiencies. The condition of BMS is more prominent in female patients over 40.[32] The causal relationship between hormonal changes in women that occur with menopause and BMS is unclear. One study examined the effect of hormonal replacement therapy (HRT) on BMS. The researchers found that HRT helped in 15 of 27 of their postmenopausal women with BMS.[33] Unfortunately, this study was an open-label study and not a randomized blinded placebo-controlled study and thus the data are not convincing proof of a causal link between hormone alterations and BMS. Patients with BMS often have high blood glucose levels, but this does not occur on a consistent basis so no causal relationship has been demonstrated.[34] Next, nutritional deficiency (vitamins B_1, B_2, B_6, and B_{12}, iron, folic acid, zinc, etc.) is yet another reported systemic abnormality associated with BMS. Like hormonal status and diabetes, these suggested nutritional deficiencies are not consistently supported by the literature. Nevertheless, local and systemic factors must be ruled out before a final diagnosis of BMS is made. Femiano's group (2008) proposed that the study of thyroid function tests and echography be inserted in the diagnostic process for BMS patients. The study reveals that individuals with thyroid alterations are often considered to be BMS patients and that hypothyroidism could be responsible for oral burning and/or dysgeusia in some supertaster subjects. Their protocol allows researchers to easily distinguish patients with true BMS from those who present burning mouth as a result of hypothyroidism.[35] The common diagnostic tests used for BMS are listed in Table 14.2.

14.7 Psychological factors

Anxiety is prominent feature of BMS patients and many speculate that the pain disorder itself causes increase anxiety over time. Various other psychological disorders, including depression and somatization, are also commonplace features in a BMS patient population, but the presence of co-morbid psychological disease is not evidence of causality.[36] Because BMS patients are generally older, the question is, "Are psychological disorders in higher prevalence in BMS patients compared with an age-matched control group?" One study examined 25 patients with a diagnosis of primary BMS and 25 age- and gender-matched patients with organically based painful disorders of the mouth; the authors reported a positive psychiatric diagnosis in 44% (11/25) of the BMS patients but in only 16% (4/25) of the non-BMS patients.

Table 14.1 Primary and secondary burning mouth syndrome

Presumed etiology	Clinical presentation
Primary BMS treatment	
Nerve atrophy	Focal neuropathic pain involving small-fiber atrophy of the oral tissues.
Secondary BMS treatment	
Dry mouth (xerostomia)	Several medications cause decreased salivary flow (tricyclic antidepressants, central nervous system depressants, lithium, diuretics, and medications used to treat high blood pressure). It can also occur with aging or Sjögren's syndrome.
Oral infection	Yeast infections (thrush) have been seen in BMS patients and may be related to immune dysfunction (e.g., HIV infection), uncontrolled diabetes, poorly maintained or cleaned dentures, and certain immunosuppressive medications.
Autoimmune mucosal prescriptions	Lichen planus and geographic tongue are conditions that are usually painless, but sometimes cause a stomatitis and a sore, patchy tongue.
Nutritional deficiencies	Being deficient in nutrients, such as iron, zinc, folate (vitamin B_9), thiamin (vitamin B_1), riboflavin (vitamin B_2), pyridoxine (vitamin B_6), and cobalamin (vitamin B_{12}), may affect oral tissues and cause a burning mouth. These deficiencies can also lead to vitamin-deficiency anemia and oral stomatitis.
Allergies	The mouth burning may be due to allergies or reactions to foods, food flavorings (especially cinnamon), other food additives, fragrances, dyes, or other substances. Similarly, direct chemical irritation and allergic reactions to dental materials may be a factor in BMS.
Reflux of stomach acid	The sour- or bitter-tasting fluid that enters the mouth from the upper gastrointestinal tract may cause irritation and pain.
Certain medications	ACE inhibitors, used to treat high blood pressure, may cause side effects that include a burning mouth.
Endocrine disorders	Endocrine disorders such as diabetes and underactive or overactive thyroid are known to produce peripheral neuropathic pain and generalized hyperalgesia.

ACE, Angiotensin-converting enzyme; BMS, burning mouth syndrome; HIV, human immunodeficiency virus.

Table 14.2 Diagnostic tests used as part of the diagnostic process for burning mouth syndrome

Complete blood cell count (CBC)	This common blood test provides a count of each type of blood cell in a given volume of blood. The CBC measures the amount of hemoglobin, the percentage of blood that is composed of red blood cells (hematocrit), the number and kinds of white blood cells, and the number of platelets. This blood test may reveal a wide variety of conditions, including infections and anemia, which can indicate nutritional deficiencies.
Other blood tests	Because nutritional deficiencies are one cause of a burning mouth, running a test on the blood levels of iron, zinc, folate (vitamin B_9), thiamin (vitamin B_1), riboflavin (vitamin B_2), pyridoxine (vitamin B_6), and cobalamin (vitamin B_{12}) is important. Also, because diabetes causes neuropathic pain, a check may be done of the fasting blood sugar level.
Allergy tests	While it is not common, occasionally, testing to see if the patient may be allergic to certain foods, additives, or even substances in dentures can be ordered through an allergist.
Oral swab culture or cytologic smear	If a fungal infection is suspected, a small tissue sample (biopsy) or an oral swab of the mouth for culture and examination may be ordered.
Tongue tissue biopsy	With the recent suggestion that small nerve fibers are depleted in the affected area, some special tests may be ordered when a biopsy is taken.

This study involved an interview by a psychiatrist and a questionnaire that screened for psychiatric disorders. While 44% seems a high number, when compared with other chronic pain patients this rate is not unusual or even high. For example, the same 28-item psychiatric screening questionnaire (general health questionnaire [GHQ-28]) used in the prior study was given to 31 primary BMS subjects. These authors found that although 51.9% of the patients showed evidence of psychiatric illness using the GHQ-28 questionnaire, this rate was similar to or lower than what has been reported for other chronic pain subjects, except those attending a psychiatric clinic.[37] One study examined 74 BMS patients using a psychiatric interview plus the Hamilton's Depression and Anxiety Scales (HADS).[38] This study

reported that a positive psychiatric diagnosis (mostly depression) was established in 38 of the 74 cases (51.4%). The HADS questionnaire data suggested that, when anxiety was present, it strongly influenced the psychiatric condition of these patients. An elevated rate of positive findings when a systematic psychometric analysis of BMS patients is performed was confirmed again in a more recent study that examined 32 BMS patients and 32 matched control subjects using a comprehensive, reliable, and validated inventory.[39] Like the studies cited previously, their results showed highly significant differences between the BMS group and the non-BMS controls with regard to several personality factors. Unfortunately, high levels of anxiety, depression or even somatization tendencies are not unusual or unique to BMS patients. Chronic disease patients in general have elevated findings when compared with age- and gender-matched nonpain patients. The question remains whether the BMS pain is etiologically related to these personality characteristics or vice-versa. A report on 33 BMS patients suggested that psychological factors are not consistently elevated over control subjects in this population.[40] These authors used the revised Symptom Checklist (SCL-90R) and the Multidimensional Pain Inventory (MPI) on their BMS patients and compared the resulting data with data from population samples that included both non-BMS chronic pain patients and a normal nonclinical sample. The researchers concluded the BMS patient scores were not significantly elevated on the measures of depression, anxiety, and somatization. Researchers did note that 21% of the BMS cases (7/33) had substantially elevated psychologic distress. Anxiety is a symptom that is often associated with BMS and a rise in the cortisol level is one of the most important physiological effects during anxiety.[41] A 2008 study evaluated the anxiety and salivary cortisol levels in BMS patients.[42] They found that BMS patients had elevated cortisol levels (approximately 1.4 times higher) compared with the control group. The study concluded that even though recent work on BMS suggests it is primarily a neuropathic disorder, their results propose that there is also an association between high biological stress (high anxiety levels, salivary cortisol levels) and BMS. Clearly, more studies with larger samples are needed to understand the link between stress, aging, and neuropathic change in BMS.

14.8. Possible salivary and serologic biomarkers of burning mouth syndrome

In a 2007 study on serum interleukin-6 (IL-6) levels in patients with BMS, a relationship was found between this chemical, depression, and pain. They found that the serum IL-6 (which plays various roles in the nervous system, including glia proliferation, neuronal survival and differentiation, axonal regeneration, and proinflammatory activities) was decreased in patients with BMS and it was negatively correlated to chronic pain. This group considered that the neuroprotective and/or neuropreparative function of IL-6 could be modulated by lower serum levels, which also could aggravate hyperalgesia. They concluded that both psychological and neuropathic disorders might act as precipitating factor on the trigeminal nociceptive pathway, which subsequently contributes to the chronic pain.[43] Interleukin-1 (IL-1) is a proinflammatory cytokine that also plays a pivotal role in several chronic diseases.[44] IL-1 has also been implicated in the modulation of pain sensitivity. Exogenous administration of IL-1, particularly IL-1β, usually produces hyperalgesia.[45,46] They observed association of the polymorphism at IL-1β + 3954 (C/T) with BMS; they could not determine whether IL-1β high producer genotype is associated with pain sensitivity and/or depression symptoms associated with the syndrome. The research conducted by Daria Simcić[47] also proved the presence of IL-2 and IL-6 in all saliva specimens. In patients with BMS, concentration of these cytokines was increased and statistically significant. This supports the assumption that IL-2 and IL-6 are objective markers for diagnostics and detection of painful BMS. However, another study found no differences in the salivary levels of IL-1β, IL-6, IL-8, and TNF in patients with BMS compared with control group.[48]

14.9 Current etiologic theories

Searching for the causal link is one of the more difficult endeavors in science. It is a well-known scientific principle that association does not prove causality; unfortunately many authors have not made this point clear when reporting on clinical findings that are seen in association with BMS symptoms. For example, it is just as likely that the observed elevated depression and anxiety traits and the elevated somatic focus on their burning pains is an effect of the pain symptoms and not a causative factor. The same could be said about diabetes, menopause, candida infections and their relationship to BMS. For example, it is just as likely that the patients do not clean their mouths as thoroughly because of the burning and this causes candida overgrowth. Other local factors and systemic factors could also be coincidental findings that may have no specific relationship to the causation of the BMS. To establish a causal link between two factors, there must be good consistency of data. This means that the association is present in all cases no matter how many ways it is studied. The association should be strong and it should account for most of the variability seen in the data. There should be a positive dose–response relationship between the

two associated factors. This means that when there is a small amount of the predictor, there is only a small amount of outcome. As the predictor increases so does the outcome response. A biologically plausible explanation must be available regarding how the predictor variable causes the outcome and the suggested association must be independently verified. Given these caveats, there are at least three current hypotheses for BMS that we review here.

14.9.A Dysfunction of the chorda tympani nerve theory

The first deals with the interplay of sensory and taste systems which innervate the tongue. The anterior two-thirds of the tongue sends taste sensations centrally via the chorda tympani nerve, and nontaste sensations are supplied by the trigeminal nerve (lingual branch). The essential theory is that burning mouth pain symptoms occur when there is an abnormal interplay between lingual nerve function and chorda tympani function.[49] These authors have further speculated that there is a specific group of patients, at risk of developing burning mouth pain, who have a large number of fungiform papillae. They speculate that individuals with increased fungiform papillae innervations (labeled as supertasters) are more at risk of disturbance of the balance between these two nerves (trigeminal and chorda tympani). In other words, if there is damage to the chorda tympani nerve over time, there is greater potential to develop pain and taste alterations (dysgeusia). In support of this theory is a recent study on 22 patients with BMS, in which researchers report possible chorda tympani dysfunction in 18 of the 22 patients.[50] They found the mean electrical taste/tingling detection thresholds ratio and the taste detection thresholds (via electrogustatory testing) were considerably higher in patients presenting burning mouth than in patients having secondary BMS. The authors considered this evidence that chorda tympani nerve dysfunction may be related. The explanation the researchers give for the high involvement of the tip of the tongue is that in approximately 2 cm of the tongue tip, the chorda tympani nerve crosses over and innervates the opposite side. An earlier study (1992) showed that the tongue tip is the most sensitive region of the tongue, followed by the lateral dorsal and lateral ventral regions.[51] The researchers also conclude that the chorda tympani nerve has a role in conferring general sensation from the tongue.

14.9.B Small afferent fiber atrophy theory

The second theory is similar but does not require a disturbed interplay between taste nerves and sensory nerves. It is based on two new studies that suggest that BMS is due to small fiber neurologic damage in the oral cavity. Of course, the idea that a neuropathic change may underlie BMS is not new, but strong evidence supporting this idea has been lacking. The first study of significance is one that examined 52 BMS patients using quantitative sensory tests (QSTs) in addition to the blink reflex (BR) recordings.[52] Researchers suggested that while BMS patients have different types of neural change (some with diminished neural responses and some with elevated neural responses), the majority (90%) of those tested had some form of altered sensory thresholds or reflex reaction. The other critical study, supporting a neuropathic etiology for BMS, examined nerve fiber atrophy using biopsy sample evidence from burning mouth patients. This study collected epithelial samples of the tongue in 12 chronic BMS patients and 9 healthy controls using tongue tissue biopsies to assess whether damage of peripheral nerve fibers underlies the pathogenesis of the disease.[53] These researchers used immunohistochemical and microscope methods to examine for nerve damage in the tongue. The study reported a significantly lower density of epithelial nerve fibers for BMS patients than controls. The authors described epithelial and subpapillary nerve fiber changes suggestive of axonal degeneration. Researchers concluded that BMS is caused by a trigeminal small-fiber sensory neuropathy.

14.9.C Upregulated TRPV1 receptor theory

Consistent with the preceding theory of spontaneous loss of small afferent nerve fibers, a 2007 study reported an upregulation or increased number of heat and capsaicin receptor TRPV1 in nerve fibers.[54] They also reported that nerve fibers penetrating the epithelium were less abundant in BMS ($p < 0.0001$), indicating a small fiber neuropathy. TRPV1-positive fibers were overall significantly increased in BMS ($p = 0.0011$), as were nerve growth factor (NGF) fibers ($p < 0.0001$) and basal epithelial cell NGF staining ($p < 0.0147$). These authors suggested that TRPV1 and NGF blockers may someday provide a new therapy for BMS. With regard to the upregulation of TRPV1 receptors, multiple publications have shown that association between transient receptor potential vanilloid type-1 (TRPV1) and burning pain. For example, the TRPV1 receptor has been shown to play a role in animal models of inflammatory hyperalgesia. TRPV1 is expressed by sensory neurons and activated by capsaicin,[55] heat (>43°C), acid (pH < 5.9) and inflammatory mediators, with depolarization leading to burning pain. TRPV1 activation also leads to local release of sensory neuropeptides including calcitonin gene-related peptide (CGRP) and substance P (SP), which in turn activates their effector cell receptors and contributes to the process of neurogenic inflammation. The presence of TRPV1 in axons is consistent with previous animal and human

studies. For example, TRPV1 has been demonstrated in ferret lingual nerve fibers, rat sciatic nerve fibers, and nerve fibers in the human tooth pulp, and bowel; changes in the TRPV1 are seen after peripheral nerve injury.[56,57] TRPV1 is likely to be activated by the products of inflammation in irritable bowel syndrome (IBS), and its upregulation, may contribute to pain. There was evidence of nerve fiber sprouting, as PGP 9.5 nerve fibers were increased. Inflammation-mediated upregulation of TRPV1 is well established and has been shown to involve various mechanisms including NGF, along with sensitization of TRPV1 by bradykinin B2 via intercellular enzymatic pathway. NGF production in peripheral tissues is enhanced by inflammation and NGF is taken up and transported in a retrograde manner by nerve fibers to their cell bodies, leading to nerve sprouting and increased expression of TRPV1 and SP.[58] Not only does NGF sensitize TRPV1 receptors to protons, enhancing their effect, but also it increased expression of TRPV1. A 2008 study found increased total nerve fibers, and nerve fibers immunoreactive to TPRV1 and SP in patients with IBS may be mediated via the effects of NGF. This TRPV1 activation produces an influx of calcium and sodium ions, along with release of neuropeptides (SP, CGRP).[59] This in turn triggers and promotes the process of neurogenic inflammation; these findings provide a mechanism which may help in understanding the pathophysiology of pain in IBS and this concept possibly could be applied to BMS. However, in the previously referenced study by Biggs et al. (2007), they conclude that there is no significant difference in the expression of TRPV1 in injured nerves from patients with burning pain and those without pain. This suggests that TRPV1 receptors at the injury site do not have a primary role in the maintenance of neuropathic pain followed by nerve injury. These contradictory findings demonstrate the need to find a method to confirm the effect of the receptors and their ligands on the taste system and in BMS specifically.

14.9.D CNS pain pathway and dopamine receptor alteration theory

It should also be pointed out that neuropathic pain phenomena are not limited to peripheral neural changes altering transduction and transmission of impulses into the brain. Most neuropathic disorders also have ongoing altered central modulation of nociceptive information as an integral part of the disease process. In this regard, two additional studies have examined BMS patients for more central neural changes, specifically on dopamine receptors in the basal ganglia.[60] The study measured dopaminergic function of the putamen in 10 BMS patients and 14 healthy controls using positron emission tomography (PET). Researchers reported that the presynaptic dopaminergic function was significantly decreased (between 17% and 20%) in the putamen of the BMS patients compared WITH control subjects. This data was supported by a subsequent study using a more specific ligand which specifically bonded to dopamine D1 and D2 receptors in these patients. Again, they examined 10 BMS patients and 11 healthy controls. Researchers concluded from the ligand uptake data that a decline in endogenous dopamine levels in the putamen was present in burning mouth patients.[61] The number of available striatal D2 receptors is thought to dictate the extent of central pain suppression.[62] All in all, these studies suggest that brain function changes occur along with peripheral nerve changes and support the idea that central modulation of sensory signal occurs in BMS cases. In fact, altered central nociceptive signal processing is an expected consequence with all neuropathic disease processes, not just BMS.

14.9.E Burning mouth syndrome is an autoimmune disorder similar to lichen planus

Another theory is that burning mouth is somehow related to lichen planus since both conditions (oral lichen planus and BMS) have elevated expression of CD14 mRNA and decreased levels of TLR-2 mRNA in their saliva.[63] Additional proof for each theory will need to be added to differentiate the best one.

14.10 Management strategies for burning mouth syndrome

In general the research on burning mouth syndrome therapy is sparse and the common agreed-upon statement in many of the meta-analyses conducted on BMS finds that none of the trials examined were able to provide conclusive evidence of high effectiveness. Nevertheless, we have described what can be concluded from the literature.

14.10.A Cognitive behavioral therapy for burning mouth syndrome

An RCT study demonstrating benefits when compared with placebo suggests that psychotherapy or cognitive therapy sessions of one hour per week over 12–15 weeks have beneficial effects on reducing BMS pain intensity for up to 6 months.[64] An additional study showed some improvement resulting from psychotherapy over 2 months, with significant improvement when combined with alpha-lipoic acid therapy.[65] A Brazilian group headed by Miziara suggested group psychotherapy as an important tool for those dealing with BMS since group therapy has an advantage due to its lower cost when compared with cognitive psychotherapy,

and also works as a support group, where patients are able to share information about symptoms and fear. It also helps to avoid the isolation and loneliness of the patient.[66]

14.10.B Pharmacologic therapy for burning mouth syndrome

The most common medications used in BMS cases are presented in Table 14.3. These medications include but are not limited to tricyclic antidepressants,[67] clonazepam,[68] trazodone,[69] serotonin–norepinephrine reuptake inhibitor (duloxetine), sodium channel blocking agents, antipsychotic medications (olanzapine, amisulpride),[70] anticonvulsants (gabapentin, pregabalin), and alpha-lipoic acid, a nutritional supplement.

Clonazepam

Among these medications, the most widely accepted treatment for BMS is clonazepam. This drug has been evaluated in open-label studies on BMS with reported positive results.[71] More recently, a randomized, double-blind, placebo-controlled multicenter clinical trial was performed on the efficacy of topical clonazepam for BMS.[72] This study reported on 48 patients (4 men and 44 women) who were given either a placebo tablet or a 1-mg tablet of clonazepam to suck on and hold the saliva in the area of burning for 3 minutes then expectorate. This was done three times per day for 14 days. Researchers reported that pain intensity decreased significantly more in the clonazepam group and blood levels of clonazepam were extremely low. They hypothesized that clonazepam, which is classified both as an anticonvulsant and an anxiolytic agent, acts locally to disrupt the mechanism(s) underlying stomatodynia.

Gabapentin

Gabapentin was approved by the US Food and Drug Administration in May 2002, for treatment of postherpetic neuralgia. Even before this, gabapentin had been used off-label for many types of neuropathic pain disorders, including BMS. A meta-analysis of gabapentin shows it to be a promising medication in the treatment of sustained continuous pain, but no study has examined it specifically for BMS.[73] A recent case report did show that in at least one patient this medication was helpful at reducing burning pain.[74]

Alpha-lipoic acid

Another agent that has been suggested as potentially helpful in BMS is alpha-lipoic acid (ALA). This is a readily available nutritional supplement that is promoted as an antioxidant and for its pain suppressing effect on diabetic neuropathic pain.[75–77] Evidence is mixed for this agent, with studies on diabetic neuropathic pain showing mixed results for pain. On the negative side, one study examined the short-term effect (3 weeks) of 600 mg of ALA per day for diabetic polyneuropathy.[78] This study was a multicenter randomized double-blind placebo-controlled trial on 509 outpatients with neuropathic pain symptoms in the feet. The subjects were randomly assigned to receive 600 mg ALA once daily intravenously, 600 mg ALA three times a day orally for six months, or placebo in various sequences. Using the total symptom score as an outcome, the study found no significant difference between the ALA group and the placebo group. In contrast, in BMS patients, there was one double-blind randomized controlled study that involved 60 BMS patients who were given either ALA or an inert control substance. This study reported significant improvement in the ALA group compared with the placebo group, with the majority showing at least some improvement after 2 months.[79] Finally a more recent study on ALA and BMS suggests that this antioxidant may not be as successful as indicated by the prior BMS studies.[80] This study involved a double-blind, randomized, placebo-controlled 8-week study. The 66 BMS patients in the study were divided into three groups and given a placebo medication, ALA (400 mg) alone, or ALA (400 mg) with vitamins. Symptoms were evaluated by using a visual analog scale (VAS) and the McGill Pain Questionnaire (MPQ) at 0, 2, 4, 8, and 16 weeks. The authors reported that all three groups had significant reductions in the VAS score and on the mixed affective/evaluative subscale of the MPQ. The authors concluded that this population of patients is subject to a quite high placebo response and this study failed to support a role for ALA in the treatment of BMS.

Antidepressants and antipsychotics for burning mouth syndrome

A three-treatment, randomized, single-blind comparison study examined amisulpride (50 mg/day), paroxetine (20 mg/day), and sertraline (50 mg/day) over an 8-week period on 76 BMS patients. The study demonstrated beneficial effects on reducing BMS pain intensity for all three agents although amisulpride was the fastest acting of the three agents and no subject assigned to this agent stopped participation in the study.[81] No serious adverse events were reported, and the incidence of side effects did not differ among the three groups. It is interesting to note that amisulpride is an antipsychotic that is disinhibitory at low doses (<10 mg/kg), with specific dopamine D_2 and D_3 receptor blocking and little effect on other receptors.[82] Unfortunately this study had no placebo control condition

Table 14.3 Medications for BMS

Medications (class of drug)	Common dosage range	Prescription	Mechanims of action; FDA approval status	Evidence basis for use
Nortriptyline (TCA)	10–75 mg/day	10 mg h.s.; increase dosage by 10 mg q4–7d until oral burning is relieved or side effects occur.	TCAs inhibit the activity of such diverse agents as histamine, 5-hydroxytryptamine, and acetylcholine. It increases the pressor effect of norepinephrine. This drug is approved for use of the symptoms of depression, but is used off-label for neuropathic pain.	No published evidence for it in BMS, but it is used commonly for neuropathic pain.
Oral clonazepam (benzodiazepine)	0.25–2 mg/day	0.25 mg h.s.; increase dosage by 0.25 mg q4–7d until oral burning is relieved or side effects occur; as dosage increases, medication is taken as full dose or in three divided doses.	Mechanism is unknown, although it is believed to enhance the activity of GABA, the major inhibitory neurotransmitter in the CNS. This agent is approved by the FDA for seizures and for panic disorders. It is used off-label for neuropathic pain and BMS in particular.	Open clinical trials show some efficacy for BMS. No RBCT study (not exception below) is available.
Topical clonazepam (benzodiazepine)	1-mg tablet t.i.d., after meals	Let tablet dissolve and hold fluid in mouth in area of most intense burning for 3 minutes and then expectorate.	Same as for oral clonazepam	RBCT is available showing this approach is helpful in many BMS patients and is better than placebo.
Gabapentin (anticonvulsant)	300–2400 mg/day	100 mg h.s.; increase dosage by 100 mg q4–7d until oral burning is relieved or side effects occur; as dosage increases, taken in three divided doses	Anticonvulsant action is unknown; gabapentin is known to prevent seizures as do other marketed anticonvulsants. This drug is FDA approved for partial seizures and for PHN pain.	Case-report data suggests this agent may be helpful in some patients. No RBCT study performed.
Pregabalin (anticonvulsant)	100 mg p.o. t.i.d.	100 mg p.o. t.i.d.	This is a new drug that is being suggested for use in neuropathic pain patients. Its mechanism of action is thought to be similar to gabapentin. It is approved by the FDA as an adjunctive agent in adult patients with partial onset seizures and for PHN and diabetic neuropathy.	No data for BMS is yet available, but it should work similarly to gabapentin and is thought to have better pharmacokinetics. No RBCT study performed.
Topical lidocaine (anesthetic)	Viscous gel 2%	5 mL q.i.d.; rinse for 2 minutes then expectorate	This agent is a sodium channel blocking agent and provides analgesic effects when applied topically. It is FDA approved as a topical anesthetic agent but its use is specified as an aid for minor surgeries or skin abrasions.	No data for BMS is yet available. No RBCT study performed.

(*Continued*)

Table 14.3 (*Continued*)

Medications (class of drug)	Common dosage range	Prescription	Mechanims of action; FDA approval status	Evidence basis for use
Alpha-lipoic acid (antioxidant)	200 mg t.i.d.	200 mg t.i.d. for 2 months in association with gastroprotector	This agent is not a drug and it is described as an antioxidant. It is not regulated by the FDA and therefore requires no prescription because it is consider a nutritional supplement.	RBCT shows that this agent is helpful for BMS.
Duloxetine (serotonin, norepinephrine reuptake inhibitor)	60 mg p.o. qd	Start with 30 mg for 1 week then increase to 60 mg qd	Mechanism is unknown. The antidepressant and pain-inhibitory actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS. This agent is approved by the FDA for major depression and for treatment of diabetic neuropathic pain.	No RBCT study performed so no data specific to BMS is available.
Tramadol (analgesic, non-narcotic)	50 mg taken up to 4/day	50 mg in the evening is the starting dose, but if needed the dose can be increased up to 4 tablets per day or more (depending on side effects).	While it is classified as a nonopioid medication, most consider tramadol as an opoiod because it does bind to opioid receptors. It also inhibits reuptake of norepinephrine and serotonin similar to TCAs. It is FDA approved for moderate to severe pain relief.	One RBCT study showed that tramadol was ineffective for BMS.
Hydrocodone (narcotic analgesic)	5 mg/500 mg	One tablet q6h	Used primarily for chronic pain control. It is FDA approved for moderate to severe pain relief.	No RBCT study performed so no data specific to BMS is available. Obviously this is a powerful pain-relieving agent.
Olanzapine (atypical antipsychotic agent)	5 mg/day	5 mg once a day	Antipsychotics decrease unusually high levels of brain activity. This drug is FDA approved for schizophrenia.	Only a single case report has reported it is helpful for BMS. No RBCT study performed to date.
Amisulpride (atypical antipsychotic agent)	50 mg/day	50-mg tablets up to t.i.d.; maximum dose not to exceed 400mg/day	Same as for olanzapine, but not available in the United States.	One RBCT study showed that amisulpride was ineffective for BMS.

Dosing abbreviations: b.i.d., *bis in die* (a Latin phrase meaning "twice daily"); h.s., *hora somnia* (a Latin prase meaning "at bedtime") p.o., *per os* (a Latin phrase meaning "by mouth"); qd, *quaque die* (a Latin phrase meaning "every day"); q.i.d., *quater in die* (a Latin phrase meaning "four times daily"); q*x*h, every *x* hours (from *quaque hora*, a Latin phrase meaning "every hour"); t.i.d., *ter in die* (a Latin phrase meaning "three times daily").

BMS, burning mouth syndrome; CNS, central nervous system; FDA, US Food and Drug Administration; GABA, gamma aminobutyric acid; PHN, postherpetic neuropathy; RBCT, randomized blinded placebo-controlled trial; TCAs, tricyclic antidepressants.

and amisulpride is not available in the United States. In 2008 a randomized placebo-controlled double-blind study examined the effect of St. John's Wort (*Hypericum perforatum* extract) on BMS patients.[83] The study included 43 (35 women, 4 men, aged 65 years) and all subjects took 300-mg capsules containing either *H. perforatum* extract (hypericin 0.31% and hyperforin 3.0%) or placebo three times a day for 12 weeks. The pain was evaluated using VAS scales. The authors did not find statistically significant differences between the two groups. Next, a 2007 study examined levosulpiride, an antipsychotic and antidepressant medication, in a case series of 39 subjects with BMS.[84] Levosulpiride binds selectively and reversibly to the D2 dopaminergic receptors with sodium-dependent functions located on the presynaptic membrane.[85] The preliminary data from the case series report suggested that levosulpiride is more effective in patients with a shorter duration of BMS and could be of help for those patients suffering BMS, but not one patient experienced complete remission of symptoms during treatment with levosulpiride. As with amisulpride this product is not available in United States and more rigorous placebo-controlled studies are needed. Finally, for the extremely affected BMS patients, there are case reports suggesting that an atypical antipsychotic medication, olanzapine, can be helpful in such cases.[86]

14.10.C Meta-analysis of the literature on burning mouth syndrome

In 2003 and also twice in 2007, researchers conducted systematic reviews of the treatment literature for BMS.[87–89] The 2003 review authors identified several trials that tested antidepressants, cognitive behavioral therapy, analgesics, hormone replacement therapy, and vitamin complexes used to provide relief of the burning and discomfort in BMS. Researchers found that none of the trials examined were able to provide conclusive evidence of high effectiveness. Researchers did report that cognitive behavioral therapy may be beneficial in reducing the intensity of the symptoms and that the clinician needs to provide support and understanding when dealing with BMS sufferers and that psychological interventions help patients to cope with symptoms. In one of the 2007 reviews (Minguez Serra et al.), the authors concluded that neither capsaicin nor clonazepam, administered systemically via the oral route, is effective and has moderately bothersome adverse reactions. Gabapentin has not shown efficacy. They noted that alpha-lipoic acid was better than placebo, but it loses efficacy over time. They concluded that topical clonazepam presently seems to be the best treatment approach, with healing noted for almost half of all patients (40%). In the other 2007 review (Patton et al.), the authors also concluded that both topical clonazepam and cognitive behavioral therapy have proven efficacious in some patients. They also suggested that the antioxidant, alpha lipoic acid, has been found helpful.

14.11 Prognosis

In spite of the many behavioral and medication-based treatments, the management of BMS is still not satisfactory. There is no definitive cure, although help is provided with these methods. Untreated BMS represents a disorder with a very poor prognosis in terms of quality of life, and the patient's lifestyle may worsen when psychological dysfunctions occur. Spontaneous remission of pain in BMS subjects has not been definitely demonstrated. The current treatments are palliative only. While they may not be much better than a credible placebo treatment, few studies report relief without intervention.

14.12 Nine final recommendations on the diagnosis and treatment of burning mouth syndrome

Recommendations on the use of medications for burning mouth syndrome

1. Burning mouth syndrome (BMS) is a distinctive, probably neuropathic disease characterized by oral burning pain of the lips and tongue (mainly the tip and anterior two-thirds) without any clinically observable pathologic findings that has persisted at 4 months.
2. Burning mouth symptoms are reported in up to 4% of adults and this percentage increases with age after the fifth decade
3. Because metallic dysgeusia is a common early symptom of a BMS disorder, all medications that also cause this adverse effect should be eliminated if possible.
4. The most common co-morbid diseases seen with BMS are diabetes, hormonal changes, and nutritional or mineral deficiencies.
5. Anxiety is a prominent feature of BMS patients and BMS probably amplifies this behavior over time.
6. There are several theories that might explain BMS, including the following:
   - (a) Burning mouth pain symptoms occur when there is an abnormal interplay between lingual nerve function and chorda tympani function.
   - (b) BMS is due to small fiber neurologic damage in the oral cavity.
   - (c) BMS is due to an upregulation in the number of heat and capsaicin receptor TRPV1 in nerve fibers.

(d) BMS is associated with a decline in endogenous dopamine levels in the putamen, which results in altered central nociceptive signal processing.
(e) BMS is a variant of lichen planus, which is an autoimmune disorder.

7 Cognitive behavioral therapy has beneficial effects on reducing BMS pain intensity.
8 The four common medications used in BMS cases which have some efficacy are:
(a) tricyclic antidepressants
(b) topical and systemic clonazepam
(c) trazodone
(d) serotonin–norepinephrine reuptake inhibitor (duloxetine)
9 The management of BMS is still not satisfactory since no definitive cure is available and the prognosis for a cure is quite low.

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Chapter 15

Headaches with a focus on chronic daily headache medications

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15.1 Introduction to headaches

The International Headache Society (IHS) separates headaches into two forms: primary (no underlying etiology) and secondary (where an underlying cause is present).[1] Primary headaches can be further divided into those that are episodic and those that are continuous or quite frequent. This chapter discusses both, although our focus is clearly on primary continuous headaches, and it is divided into five sections. First we briefly discuss some of the acute but potentially very dangerous secondary headaches followed by a discussion of the features, etiology, and common methods of treatment of the two most frequently seen primary episodic headaches (tension-type and migraine) that plague patients. The last part of this section covers some of the other, rarer episodic headaches. In Sections 15.2 and 15.3 we discuss the various etiologies and mechanisms that are thought to contribute to headache causation as well as treatment methods for the episodic headaches. In Section 15.4, we then review the group of disorders described as chronic daily headaches. We will discuss how migraines and tension-type headaches can transform from an episodic form of the disease into a chronic form over time and we examine in detail the factors that make this happen. Finally, and most important, in Sections 15.4 and 15.5, we describe the common chronic daily headaches and how to manage them. Unfortunately, headache patients may present with more than one type of headache, confusing the picture for the clinician.

15.1.A Dangerous (secondary) headaches (diagnosis)

Secondary headaches are caused by a specific structural or medical condition and are often life-threatening. Fortunately, they are rare and account for about 1% of all headaches in primary-care settings.[2] In the revised classification put forth by the International Headache Society (IHS-2), they are subdivided into eight categories (Table 15.1). When attempting to diagnose a headache, there is no substitute for a thorough history and physical examination, but one should keep in mind certain "red flags" which may indicate a high suspicion for a secondary headache and the need for further workup and neuroimaging. The presences of these red flags has been shown in one study to correlate with abnormal neuroimaging.[3] This study showed that papilledema, drowsiness, confusion, memory impairment or loss of consciousness, and paralysis were important clinical markers of central nervous system (CNS) pathology. A broad mnemonic to help remember these red flags is "SNOOP": S—systemic signs or symptoms (e.g., fever); N—neurological signs or symptoms (e.g., partial paralysis); O—onset of a new or sudden headache; O—other associated conditions (e.g., headache is subsequent to head trauma, awakens patient from sleep, or is worsened by a Valsalva maneuver); and P—prior headache history (absence of prior headaches).[4] Headache patients who have any of these red flags usually need further testing, starting with neuroimaging. In the following subsections we discuss some of the commonest and more dangerous secondary headaches.

Subarachnoid hemorrhage headache

The typical patient with this problem is over 40 years of age. The subarachnoid hemorrhage headache (SAH) is often called "thunderclap headache" since it is a sudden, severe, generalized headache that reaches maximum intensity within 1 minute. The patient describes it as the "worst headache of my life." This pain is secondary to leaking aneurysmal vessel bleeding beneath into the subarachnoid space. If the

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Table 15.1 International Headache Society classification of secondary headaches

Headaches attributable to
1 Vascular disorder
2 Nonvascular intracranial disorder
3 Head and neck trauma
4 Infection
5 Disorders of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures
6 Disorders of homeostasis
7 Substance or its withdrawal
8 Psychiatric conditions

hemorrhage occurs within the cerebral or cerebellar tissues, it will be a rapid onset, severe, and deadly. Depending on the size of the ruptured vessel, the patient often presents with progressive loss of consciousness, vomiting, increasing pain symptoms, and clear neurologic deficits (i.e., hemiplegia or aphasia). Due to the pressure from the hemorrhage as well as pain-induced muscle spasm, the patient might experience nuchal rigidity and stiff neck. As the pressure increases, the patient my become semicomatose or fully comatose. Not all patients have full-blown aneurysmal rapidly progressive bleeds; some may have a sentinel bleed with less severe symptoms which can be followed with a more severe bleed in a few days.[5] Vomiting can occur and increasing pain symptoms are often reported even though there are few, if any, neurologic signs of abnormality. The hemorrage can be seen on a computed tomographic (CT) scan, and further the leaking vessel can be identified with an arteriogram. Immediate medical assessment and treatment is essential to life.

Temporal arteritis (giant cell arteritis)

This headache usually involves one or both temporal regions, is moderate to severe, and is often associated with polymyalgia rheumatica.[6] The headache may be generalized (polyarteritis nodosa) or localized (temporal arteritis). These headaches are localized in the area of the most severely affected arteries and are often described as a steady burning pain around the temples. Jaw claudication (fatigue) is pathognomic but uncommon. Age of onset is over 50 years in virtually all cases. Main criteria are (at least one of) the following: (1) swollen and tender scalp artery (usually superficial temporal artery); (2) elevated erythrocyte sedimentation rate (usually extremely high at around 100); (3) disappearance of headache within 48 hours of steroid therapy; (4) positive temporal biopsy showing giant cell arteritis.[7] Temporal arteritis is a common form of this condition, and the patients are usually in their 60s or 70s. Typically, the arteries are elevated and tender to palpation and if there is severe artery occlusion and infarction (especially the ophthalmic artery) blindness will result.

Headache in stroke syndromes

Ischemic stroke patients present with less severe headache than patients with SAH. In fact headache is not commonly seen in lacunar (arterial) stroke patients and is a presenting symptom in 17–34% strokes, mostly posterior circulation ones.[8] The typical stroke patient with headache is over 40 years old but some younger patients (especially female) have veno-occlusive disease.[9] In addition to the headache, the patient will have clear neurologic deficits as a result of the infarction. The patient may present with vague head pains which are not severe. Headache is a much more common symptom of cerebral venous thrombosis and should be considered in every peripartum woman with or without other neurological signs or symptoms. Cerebral venous thrombosis may be accompanied by seizures and papill-edema on neurological examination.

Brain tumor headache

Infratentorial brain tumors commonly present with headache in 80–85% cases.[10] With the advent of advanced neruoimaging, headache is less often seen as an initial presenting symptom in brain tumors of other locations. Brain tumor headache is hard to distinguish from other musculoskeletal headaches because it may not have a specific characteristic and is typically described as a deep, aching, steady, dull pain.[11] The headache may be severe but not usually as intense as migraines or cluster headaches. The "classic" brain tumor headache described as early morning headache is not common as an isolated symptom and is seen in less than 20% of cases. What distinguishes this headache from benign primary headaches is the associated neurological signs and symptoms: cognitive changes, focal neurological deficits, seizures, or signs of raised intracranial pressure that include worsening of headache with Valsalva.[12]

Meningitis headache

The headache pains from meningitis are of rapid onset, severe, and associated with fever and signs of bacterial or viral infection.[13] The patient often presents with an altered mental neurological deficit, vomiting, and increasing pain. Clinical findings of this disorder are a very stiff neck, limitation of straight leg rising, and a positive lumbar puncture with abnormal cerebral spinal fluid. The typical patient with meningitis is young, although anyone can get meningitis. Immediate medical management is essential to the patient's recovery.

Secondary brain abscess

This condition occurs when bacteria enter the brain from an infection in an adjacent site such as the nasal and aural structures. Brain abscess causes fever, leukocytosis, and vomiting.[14]

Post-traumatic headache

This is a common secondary headache type that can be induced by mild-to-moderate closed head injury. Women have a 1.9-fold increased risk of post-traumatic headache (PTH) compared with men.[15] Other risk factors include old age, position of head on impact (inclined or rotated), and previous history of headaches. Head trauma can trigger the onset of migraine headaches. In 85% of patient PTH resembles tension-type headache.[16] This is a mild-to-moderate, deep aching headache which is often generalized, and worsened by even minimal physical or mental activity. Besides PTH, patients may have a variety of symptoms that constitute the spectrum of post-traumatic syndrome and include light-headedness, memory impairment, reduced attention span, inability to concentrate, anxiety, depression, and quick frustration. PTH onset occurs within 48 hours after the trauma, although delayed onset by several weeks is not uncommon. IHS criteria require that the headache onset should be within 2 weeks of head trauma to be classified as a post-traumatic headache. PTH is classified as major if loss of consciousness was significant, or if there is post-traumatic amnesia or at least two clinically abnormal neurologic signs. Complaints may persist for several months or even years.

15.1.B Episodic headaches

There are many forms of episodic headaches, including episodic migraine (EM), probable migraine (PM) (a migraine subtype missing just one migraine feature), and episodic tension-type headache (ETTH).

Episodic tension-type headaches

This is the most frequent type of primary headache and lifetime prevalence in the general population ranges from 30% to 78%. Schwartz reported 1-year prevalence of 38% of ETTH in the United States population with preponderance in women.[17] The 1-year prevalence of TTH is much higher in Denmark at 84.7%.[18] In this study, tension-type headaches were divided into infrequent episodic, frequent episodic, and chronic tension-type headache, and the prevalence for each was also reported (48.2%, 33.8% and 2.3%, respectively). There was female preponderance and self-reported migraine was a risk factor for frequent episodic and chronic tension-type headache. These figures were confirmed by a study of tension-type headaches in twin pairs that was examining to see if genetic factors were important.[19] This study recruited twin pairs from the population-based Danish Twin Registry. A total of 3523 monozygotic 4150 dizygotic same-gender and 3526 dizygotic opposite-gender twin pairs were included. The authors reported that the prevalence of infrequent episodic headache was 68% in men and 66% in women. More important for this discussion, the prevalence of frequent episodic headache was 9% in men and 24% in women. ETTHs are usually described as "tight hat band headache" and maybe associated with pericranial tenderness involving the head and neck muscles.[20] Even though this is the most frequent type of headache, the symptoms may be nonspecific. The International Headache Society has specific criteria for making this diagnosis (Table 15.2). Headache duration may vary from short, to that lasting hours, and may increase slowly during the day to reach peak intensity near late afternoon.[21]

Episodic migraine with or without aura

Migraine headaches affect 2 million Americans annually and account for over $30 billion in lost productivity.[22] The prevalence of migraine in Western countries is 12–16% and is highest in persons aged 25–55 years. Migraines occur slightly in more women than men. The peak of onset of migraine without aura in men is 10–11 years and for women 14–17 years. Migraine with aura peaks at an earlier age. Approximately 66% of headache pain in the elderly is

Table 15.2 Episodic tension-type headache (ETTH)

Infrequent ETTH

- **A** At least 10 episodes occurring on less than 1 day per month (<12 days per year) and fulfilling criteria B–D
- **B** Headache lasting from 30 minutes to 7 days
- **C** Headache has more than two of the following characteristics:
  - **1** Bilateral location
  - **2** Pressing or tightening (nonpulsating) quality
  - **3** Mild or moderate intensity
  - **4** Not aggravated by physical activity
- **D** Headache has both of the following characteristics:
  - **1** No nausea or vomiting (anorexia may occur)
  - **2** No more than one of phonophobia or photophobia

Frequent ETTH

- **A** At least 10 episodes occurring on ≥1 but <15 days per month for at least 3 months (≥12 and <180 days per year) and fulfilling criteria B–D
- **B–D** Same as for infrequent ETTHs
- **E** Not attributed to another disorder*

*See ref. 1 (Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders, 2nd edition. *Cephalalgia*. 2004;24(Suppl 1):9–160).

caused by either migraines or tension-type headaches and this figure is well over 90% in a younger cohort.[23] The good news is that the overall prevalence of headaches declines with age and in fact it has been reported that the number of headaches declines from 83% of individuals between 21 and 34 years to 59% between ages 55 and 74.[24] One exception to this is that migraines sometimes occur for the first time after age 50; about 2% of all migraines start at this late age.[25] A large epidemiologic study was reported in 2000 which described headache prevalence in Norway.[26] These authors reported the 1-year prevalence for migraine was 12% (16% in women and 8% in men). They also reported the prevalence for chronic daily headache (>14 days per month) as 2%, and while this figure may include other forms of chronic headache, many were due to converted episodic migraine. Migraine is not simply a headache; it is a syndrome that comprises emotional, psychological, and neurological symptoms.[27] Migraines are typically episodic headaches with much greater severity than ETTH. The main difference is that patients with ETTH pain often continue to work while migraine pain will be aggravated by or cause avoidance of normal activities. The International Classification of Headache Disorders (2nd revision) divides migraine into six categories (Table 15.3).

Migraine headaches have a set of defining criteria set forth by the International Headache Society (Table 15.4). Migraine aura is present in only 20% of patients, is usually a visual phenomenon, and is typically described as a "flashing light or dizziness." A migraine headache typically occurs within 60 minutes of the onset of the aura. There are several migraine variants, such as hemiplegic migraine (head pain, transient motor–sensory changes), ophthalmoplegic migraine (eye pain, transient optic nerve palsy with diplopia–ptosis), migrainous infarction (cerebral vascular ischemia with infarction and cerebral tissue damage), and midface migraine (orodental pain, 4–72 hours, nausea, vomiting, phonophobia, and photophobia).

Cluster headaches and other trigeminal autonomic cephalalgias

While far less common than migraine or tension headache, the trigeminal autonomic cephalalgias (TACs; cluster headaches, paroxysmal hemicranias, and SUNCT) must be described also.[28] Cluster headaches (CHs) are a rapid-onset, intense paroxysmal one-sided orbital, supraorbital, and temporal pain lasting 15–180 minutes when untreated (Table 15.5). The incidence is 1 in 1000. In CH, the afflicted are mostly men (5–6 times greater than women), heavy smokers and drinkers, with age of onset, 20–40 years.[29] A typical leonine face with deep nasal furrows, scant eyebrows, and

Table 15.3 International Headache Society–based migraine categories

1 Migraine
- 1.1 Migraine without aura
- 1.2 Migraine with aura
  - 1.2.1 Typical aura with migraine headache
  - 1.2.2 Typical aura with nonmigraine headache
  - 1.2.3 Typical aura without headache
  - 1.2.4 Familial hemiplegic migraine (FHM)
  - 1.2.5 Sporadic hemiplegic migraine
  - 1.2.6 Basilar-type migraine
- 1.3 Childhood periodic syndromes that are commonly precursors of migraine
- 1.4 Retinal migraine
- 1.5 Complications of migraine
  - 1.5.1 Chronic migraine
  - 1.5.2 Status migrainosus
  - 1.5.3 Persistent aura without infarction
  - 1.5.4 Migrainous infarction
  - 1.5.5 Migraine-triggered seizure
- 1.6 Probable migraine

Table 15.4 International Headache Society criteria for migraine without aura

- A At least five episodes fulfilling criteria B–D
- B Headache lasting from 4 to 72 hours (untreated or unsuccessfully treated)
- C Headache has more than two of the following characteristics:
  - 1 Unilateral location
  - 2 Pulsating quality
  - 3 Moderate or severe intensity
  - 4 Aggravated by or causing avoidance of routine physical activity
- D During headache one or more of the following:
  - 1 Nausea and /or vomiting
  - 2 Phonophobia and photophobia
- E Not attributed to another disorder

Table 15.5 Cluster headache criteria

- A Severe, unilateral, supraorbital, and/or temporal pain lasting 15–180 minutes
- B Headache accompanied by at least one of the following ipsilaterally:
  - 1 Conjunctival injection and/or lacrimation
  - 2 Nasal congestion and/or rhinorrhea
  - 3 Miosis and/or ptosis
  - 4 Eyelid edema
  - 5 Forehead and facial sweating
  - 6 Sense of restlessness or agitation
- C Frequency of attacks: 1–8 per day

Table 15.6 A comparison of trigeminal autonomic cephalalgias

Features	Cluster headache	Paroxysmal hemicrania	SUNCT
Sex	3:1	1:3	8:1
Prevalence	0.9%	0.02%	Very rare
Duration of attack	15–180 minutes	1–30 minutes	5–240 seconds
Frequency	1–8 per day	1–40 per day	30 per hour
Autonomic	++	++	+
Circadian rhythm	+	–	–
Acute treatment	O_2, triptans, ergots	Aspirin	None
Preventative		Indomethacin	Lamotrigine

SUNCT, short-lasting unilateral neuralgiform headache with conjunctival injection and tearing.

skin changes that include peau d'orange and telangectasias has also been described with these patients. With a cluster headache, the patients are very agitated during the attack (pacing and head pounding) and have no preheadache aura and usually no associated nausea or vomiting. Attacks can be precipitated by alcohol, histamine, or vasodilators. The CHs will often repeat several times in a 24-hour period (1 attack every other day to as many as 8 per day). The headaches often occur at night, and attacks wake patients usually within 60–90 minutes after falling asleep. Recent studies report that up to 80% of CH patients have obstructive sleep apnea. The cluster period frequently lasts for weeks to months and is usually present in specific seasons of the year (more in winter and spring) with months of remission. CH is classified as episodic but there is a chronic subform based on the length of remitting period (episodic, remission period of 1 month or longer between cluster periods; chronic, attacks last over 1 year or remitting period shorter than 1 month in length). Women have shorter duration clusters, fewer autonomic symptoms, less miosis. Migrainous symptoms are commoner. There is a strong genetic predisposition to this disease; there is a 14-fold increased risk of CH in first-degree relatives. Family history is positive in 11% cases of CH. Recently polymorphism of the hypocretin receptor 2 gene (responsible for narcolepsy) was found to be associated with CH, and there is a fivefold increased risk of CH in homozygotes.[30] Interestingly hypocretin-secreting cells are highly concentrated in the hypothalamus, and new data suggests dysfunction of hypothalamus in cluster headaches.

Paroxysmal hemicrania

This even rarer TAC-type headache disorder affects mostly women (the female-to-male ratio is around 2:1).[31] Prevalence is unknown and is estimated to be around 1 in 50,000. The pain occurs as a sharp, intense pain and is often described as a breath-taking, "stop-what-you're-doing" immediate pain. The symptoms of paroxysmal hemicrania (PH) involve shorter and more frequent pain events each day than in cluster pain. There must be 20 or more headaches per day (Table 15.6). Unlike CH, PH patients do not have seasonal occurrence and each pain event is about 5–20 minutes. In a 24-hour period there will be 10–30 pain events. Nausea and vomiting are occasionally seen; the patient can be awakened from sleep, but this is not the typical presentation. In PH, the pain symptoms are usually localized to temple, forehead, ear, eye, or occipital regions and autonomic symptoms (flushing, rhinorrhea) are similar to cluster headache. A unique feature of PHs is that they are almost always responsive to indomethacin (150 mg/day). PH is also classified as episodic and chronic subform based on the length of remitting period (same as with cluster headache).

Short-lasting neuralgiform headache with conjunctival injection and tearing (SUNCT)

This syndrome was described by Sjaastad and is the rarest of all TACs. There are only 30 documented cases worldwide.[32] It is characterized by short-lasting attacks of unilateral orbital, supraorbital, or temporal pain that are much briefer than those seen in CH or PH. Pain must be accompanied by ipsilateral conjunctival injection and lacrimation. Attacks of stabbing or pulsating pain last 5–240 seconds and occur with a frequency from 3 to 200 per day. Treatments that have been used successfully in patients include intravenous lidocaine 4 mg/min, carbamazepine 1200 mg, lamotrigine 200 mg, topiramate 200 mg, and gabapentin 2400 mg.

15.1.C Other primary headaches

Some of the headaches in this category are induced by a specific activity (e.g., cough or exertion) and therefore these headaches have been named after their inducing activity. There is usually no specific treatment for this category and etiopathogenesis remains puzzling. A list of the conditions in this group are seen in Table 15.7.

Table 15.7 Other primary headaches

1. Primary cough headache
2. Primary exertional headaches
3. Primary headache associated with sexual activity
4. Hypnic headaches
5. Primary thunderclap headache
6. Primary stabbing headache ("jolts" and "jabs"): This disorder presents as sudden and sharp and lasts only for seconds to a few minutes; it affects more females than males. It is common in a migraine population, but it may occur as a primary manifestation in some, especially those above the age of 60. This condition is frequently responsive to indomethacin (150 mg or less daily).

15.2 Suggested etiologies and mechanisms for episodic headaches

15.2.A Etiology of tension-type headaches

Of course there are many theories that are put forth to explain the causation and pathogenesis of ETTH. An important issue we must discuss, and one that is moderately controversial, is the role that pericranial muscle and fascial tenderness play in the causation or triggering of ETTH. The questions that need addressing are twofold:

1. "Does jaw or facial muscle tension cause an ETTH?"
2. "If muscle tension is not causative, does muscle nociception from the jaw, face, and neck potentially assist in the triggering process for ETTHs and migraines?"

These issues are important because later, in the section on treatment, the role that myofascial pain and local myalgia play is critical to the overall headache management program.

Jaw muscle activity as an etiologic factor for episodic headaches

Regarding the first question in Section 15.2.A, some argue that pericranial tenderness is evidence that elevated substantial muscle tension levels are causative of ETTH. On this point, the data are actually quite clear that the presence of strong habitual or involuntary motor contraction as a precursor to headache is not correct. In 1995 a study documented the relationship between stress, pain, physical activity, and temporalis muscle electromyography (EMG) in 36 tension-type headache patients and 36 age- and sex-matched controls.[33] Every 30 minutes EMG level, pain intensity, stress, and physical activity levels were recorded in a daily diary for a 3-day period. A time-lagged cross-correlational analysis between pain, stress, physical activity, and EMG showed that the highest correlation coefficient values occurred between pain and stress at the same ($r = 0.33$) and at the two preceding 0.5-hour time points ($r = 0.21$ and $r = 0.26$) in the headache group, suggesting that stress precedes the headache in many cases. The study found virtually no correlation between pain, stress, or physical activity with temporalis muscle EMG for either group. Unfortunately, the subjects in this study were not self-acknowledged "tooth clenchers" and, moreover, wearing an EMG recording unit and stopping to record their levels every 30 minutes in a diary may have interfered with any oral habit, even if present. Some of the recent data on tooth clenching suggests that a stronger correlation does exists between tooth clenching and myofascial pain than ETTH, but this is an still unproven causal relationship (see Chapter 19 for a detailed discussion of oral motor disorders). Nevertheless, the data reported by Clark et al.[33] suggested that temporalis muscle activity levels were not related to the rise and fall of the subjects' headache pain or stress levels. Conversely, elevated stress did appear to be related to headache pain. A further analysis of these data in 1997 looked at the subjects' collected cumulative temporalis muscle activity.[34] The authors reported that neither the waking nor the sleeping overall muscle activity levels for these two groups were statistically different. However, when the waking EMG data were dichotomized into functional and nonfunctional activities, a significant difference was found between groups during jaw function (i.e., chewing and talking). These data suggest that headache subjects are using their temporalis muscles with less efficiency than nonheadache subjects during function and the authors concluded that this elevated EMG is more likely a consequence of pain (via protective splinting or guarding) rather than a cause in tension-type headache sufferers.

Myofascial pain as a trigger for episodic headache

Regarding the second question posed at the beginning of Sec 15.2.A, few suggest that clenching plays a prominent role in the genesis of migraine, but several studies have suggested clenching may increase the likelihood that patients will have more myofascial pain and this nociceptive process may then trigger both migraine and tension-type headache events.[35] For example, in 2006, the findings above were confirmed by a study that examined stress-induced pain and muscle activity in patients with migraine and tension-type headache.[36] This study recorded pain and surface electromyography (EMG) from the neck and jaw muscles in 22 migraineurs during headache-free periods, 18 patients with tension-type headache (TTH), and 44 healthy controls. Recordings were made during both a 60-minute experimental cognitive stress task and a 30-minute relaxation period in the laboratory. The authors reported that TTH patients had higher pain reports in the temporalis and frontalis regions

than neck region (trapezius and splenius) but EMG responses were not different from controls in headache patients, and EMG responses did not correlate with pain responses.

In 1999 a pathophysiological mechanism for tension-type headache was offered[37,38]: (1) tension-type headache was the most prevalent form of headache, with a lifetime prevalence of 78% in a general adult population; (2) 30% were affected more than 14 days per year and 3% were chronically affected (i.e., had headache at least every other day); (3) females were more frequently affected and were more tender on palpation than males, and young subjects more frequently affected and more tender on palpation than older subjects. Substantially more pericranial muscle tenderness was found in subjects with tension-type headache compared with migraineurs or control nonheadache patients. Tenderness increased significantly with increasing frequency of tension-type headache in both males and females. Subjects with chronic tension-type headache had slightly increased EMG levels during resting conditions. In a subsequent clinical, controlled study, the effect of 30 minutes of sustained tooth clenching was studied; within 24 hours, 69% of patients and 17% of controls developed a tension-type headache. Likewise, psychophysical and EMG parameters were studied in 28 patients with tension-type headache, both during and outside of a spontaneous episode of tension-type headache. It was concluded that a peripheral trigger for tension-type headache is possible but it is most likely in the episodic subform, whereas a secondary, segmental central sensitization and/or an impaired supraspinal modulation of incoming stimuli seems to be involved in subjects with chronic tension-type headache. Prolonged nociceptive stimuli from myofascial tissue may be of importance for the conversion of episodic into chronic tension-type headache. In summary, the authors emphasize that tension-type headache is a multifactorial disorder with several concurrent pathophysiological mechanisms, and that extracranial myofascial nociception may constitute only one of them. The pericranial muscle tenderness and abnormal EMG activity that are observed in these patients are independent of the headache; on the one hand, there is abnormal pain sensitivity due to supraspinal facilitation and, on the other, there is ineffective antinociception.

15.2.B Pathogenesis of migraine

The etiology of migraine is thought be related to central neurologic excitability and there clearly is a genetic basis to this disease.[39,40] Current research supports the trigeminovascular theory to explain the pathogenesis of migraine. According to this theory, there is baseline neuronal hyperexcitability, which in aura patients leads to cortical spreading depression that ultimately triggers a wave of sterile inflammatory neurochemical due to which there is the final pathway of vasoconstriction and vasodilatation and head pain.[41] Positron emission tomographic (PET) studies have clearly shown the brain stem as the generator for migraine, with activation of the contralateral pons during acute migraine.[42]

15.2.C Pathogenesis of trigeminal autonomic cephalalgias

Recent studies have shown that the hypothalamus is the generator of cluster headaches and is responsible for stimulation of the parasympathetic and sympathetic pathways and the trigeminal vascular system.[43] Matharu et al. have also shown that the hypothalamus may play an equally important role in HC and CPH and therefore the TACs as a group may end up having a common neuroanatomic basis.[44,45]

15.3 Episodic headache treatment

There are multiple modalities of treatments available for episodic headache, including over-the-counter medications, stress reduction, myofascial-based therapy, triggering factor avoidance, behavioral therapies, physical medicine modalities, trigger point and other injections, and of course stronger abortive medications such as the class of serotonin modulators called triptans and ergots. The efficacy evidence for these medications and procedures is discussed below.

15.3.A Over-the-counter medications

Normally a brief, nondisabling, ETTH is not enough of a problem for a patient to seek a medical or dental consultation, that is, unless it becomes quite frequent or is severe in intensity. In most cases patients with mild to moderate and infrequent episodic headaches, occurring only a few times a month, are managed with over-the-counter analgesics, or a bite guard appliance for those who suspect habitual clenching of the teeth as a cause. When the headache is not "frequent," over-the-counter (OTC) medications available include acetaminophen, aspirin, ibuprofen, and naproxen, and all can be an effective method of relieving the headache. While some data shows that nonsteroidal anti-inflammatory drugs (NSAIDs) may be more effective than acetaminophen and aspirin for headache management, there is no strong evidence to suggest that one is consistently better than the others.[46] Costwise, this is a very inexpensive therapy compared with many prescription medications.[47]

The problem arises with more severe or more frequent headaches. One such problem resulting from frequent use of analgesic medications is a medication overuse headache (MOH), which will become much more difficult to treat.[48]

Alternatively, patients with frequent or severe headaches do start consulting their physicians about the problem and then they are given a stronger medication such as opioid-class drugs (hydrocodone or codeine) or drugs with barbiturate properties (e.g., Fiorinol or Fioricet). In general, these latter drugs are not recommended as appropriate for frequent headaches since they have dependence, tolerance, and paradoxically sometimes even antianalgesic properties with ongoing use.

15.3.B Headache avoidance checklist

Episodic tension-type headaches (ETTH) are usually triggered by stress, but like migraines, they may have other triggers including behavioral and psychiatric.[49] For this reason, it is always prudent to give the patient a headache avoidance checklist to follow. The patient should also be given a headache calendar to record each episode of headache and the medications taken, along with any possible triggers such as food or activity prior to headache. Some well-known food triggers include old cheese, red wine, certain food additives (e.g., aspartame and MSG). This checklist has several elements (Table 15.8).

Table 15.8 Episodic headache avoidance checklist

1. Diet instructions (e.g., do not miss meals)—hypoglycemia triggers migraine and ETTH.
2. Wear sunglasses outside—bright light simulation triggers migraine.
3. Ice packs applied where the headache hurts—cooling decreases pain nerve activity.
4. Posture awareness—instruct the patient to watch neck posture so that the cervical spine is in a neutral position.
5. Ergonomic changes to workspace—it is important to have students and office workers raise the level of their desk so the neck is not as flexed; use a speakerphone, and avoid bending the neck when using the telephone.
6. Daily stretching of neck muscles—every 2 hours perform neck stretching exercises to reduce nociceptive activity and tension in neck.
7. Alcohol, tobacco, and caffeine avoidance or moderation—these drugs can trigger headache; however, if the patient is a daily user of these agents, abrupt cessation of these drugs can trigger a withdrawal headache, so in this case moderation of drug use is appropriate.

Note: Cluster headaches can be triggered by smoking, alcohol, and vasodilators such as nitroglycerine. Unfortunately, the other TACs are not usually triggered by easily avoidable environmental factors.

ETTH, episodic tension-type headache; TACs, trigeminal autonomic cephalalgias.

15.3.C Myofascial-based treatment for headache

As we described earlier, muscle pain is one of the triggers for neurovascular pain. For this reason, it is prudent to also enroll the patient who is being withdrawn from analgesics and put on a preventative agent to participate in a concurrent self-treatment protocol called myofascial pain therapy.[50] Briefly, it involves several elements: (1) identify and avoid activities that are potentially harmful to the jaw and neck system, (2) increase local blood flow in the tissues that are painful, (3) stretch stiff and painful muscles frequently to try to decrease postural tone in the sore muscle. It is the last element of this program that is critical to promote to the patient. In fact, teaching the patient how to stretch sore jaw and neck muscles multiple times a day is equally important as the preventative medications. Daily (every 2 hours) stretch therapy involves two specific exercises: (1) the jaw open stretch and (2) the chin-to-chest stretch. These therapies are described in greater detail in Chapter 19, which deals with myogenous pain in the jaw and neck.

15.3.D Trigger-point and other injections for migraine, ETTH, and TAC

Hand-in-hand with the self-treatment-based myofascial pain protocol in Section 15.3.C is the idea that sometimes myofascial pain trigger points (TrPs) are contributors to the genesis of an episodic headache. This was evaluated in a 2007 study that included 78 migraine patients with cervical active TrPs whose referred areas (RAs) coincided with migraine sites (frontal, temporal).[51] These subjects underwent electrical pain threshold measurement in skin, subcutis, and muscle in TrPs and RAs at baseline and after 3, 10, 30, and 60 days; migraine pain assessment (number and intensity of attacks) for 60 days before and 60 days after study start. Fifty-four patients (group 1) underwent TrP anesthetic infiltration on the 3rd, 10th, 30th, and 60th day (after threshold measurement); 24 subjects (group 2) received no treatment. Twenty normal subjects underwent threshold measurements in the same sites and time points as patients. At baseline, all patients showed a significantly lower than normal electrical pain thresholds in TrPs and RAs in all tissues. During treatment in group 1, all thresholds increased progressively in TrPs and RAs, with sensory normalization of skin and subcutis in RAs at the end of treatment. In addition to this, the level of migraine pain decreased and the threshold increase in RAs and migraine reduction correlated linearly. In group 2 and normal subjects, no changes occurred. Although the study did not have a credible pseudotherapy the authors suggested that cervical TrPs with referred areas in migraine sites thus contribute substantially to the migraine triggering mechanism. In this

chapter we do not discuss trigger-point injections in detail or present information on how to perform this therapy but they are discussed in Chapters 11 and 16. Sphenopalatine ganglion block has been used for over a century to treat various pain conditions, including acute cluster headaches and migraine.[52] Greater occipital nerve block is a relatively simple procedure which can be effective in treating migraines and cluster headaches.[53,54]

15.3.E Treatment for episodic migraines

Migraine can be triggered by both environmental and internal (e.g., anxiety) factors. Therefore, a multidisciplinary approach that treats the whole person, not just the headache, is more likely to be successful in the long term. Clinicians and patients should use a standardized, simple questionnaire on each visit to assess migraine disability, and one of the goals of treatment should be reducing disability. One example of a standardized measure is the Migraine Disability Assessment Questionnaire (MIDAS), which takes just a few minutes to complete. Disability assessment and stratifying the care of patient is important because it will help in the choice of acute abortive therapy.[55]

Acute abortive treatment

For the best chance of relieving migraine headache, medications should be taken within 15–30 minutes of the onset of headache and when the headache is mild.[56] There are many medications used to abort migraines and patients who have mild symptoms and disability can be adequately treated with acetaminophen, NSAIDs, propoxyphene, or a combination of these. The first over-the-counter medicine to be approved by the US Food and Drug Administration (FDA) for migraine treatment is the combination of acetaminophen 250 mg, aspirin 250 mg, and caffeine 65 mg per tablet in 1998. Patients with moderate disability need migraine-specific oral medications called triptans and ergots. Triptans and ergots are 5-hydroxytryptamine (5-HT) receptor (subclass 5-HT1d and 5HT1b) agonists and are usually very effective in relieving migraine. The antimigraine activity of the triptans likely lies in their agonist effects on the 5-HT receptors which reside on the intracranial blood vessels and nerves of the trigeminal system. Agonists' action will produce a cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release from nerves. For moderate-to-severe migraines the triptans are generally the preferred abortive method.[57] These drugs include sumatriptan (Imitrex), rizatriptan (Maxalt), naratriptan (Amerge), zolmitriptan (Zomig), eletriptan (Relpax), and frovatriptan (Frova) and each has a different speed of action and duration. If taken too late in the migraine cycle, they are not as effective. Usually, one dose is taken by mouth at the first signs of a migraine attack and if needed the patient will take a second dose within 2–4 hours. Side effects include flushing, dizziness, weakness, nausea, drowsiness, stiffness, or feelings of tingling, heat, fatigue. A recent study has shown that a combination of sumatriptan and naproxen is more effective than placebo as an abortive agent for migraine attacks.[58] This study has opened up new discussion regarding the use of combination treatment for migraine.

Ergot alkaloids are also 5-HT receptor agonists and are very effective (and an inexpensive alternative to triptans) as acute abortive treatment for migraine. However, ergotamine is not tolerated as well as triptans are because of the adverse effect of nausea; ergotamine needs to be administered with an antiemetic. Ergotamine is available as tablets, sublingual, or rectal formulation. Dihydroergotamine (DHE) is extremely useful in the inpatient setting for severe migraines, since it can be given parenterally (intravenous, intramuscular, subcutaneous, intranasal).[59] Rebound headaches are rare, and lower headache recurrence is reported with the use of DHE than with short-acting triptans. This may be because of the longer half-life of DHE. Ergots are contraindicated with concomitant use of potent CYP3A4 inhibitors (e.g., macrolides, protease inhibitors, azole antifungals) because of the risk of life-threatening peripheral ischemia.

Antiemetics can be used to treat migraine and accompanying symptoms in two ways. First, nausea and vomiting often accompany migraines and can be incapacitating. Second, some evidence indicates that antiemetics may also relieve the headache of migraine. Promethazine, prochlorperazine, chlorpromazine, and droperidol have been studied most often and are generally safe and effective. Adverse effects include asthenia, anxiety, akathisia, and somnolence.

Patients with severe headaches need subcutaneous, intravenous, or oral formulations of these drugs. Approximately 40% of all attacks do not respond to a given triptan or any other substance. If all else fails, an intractable migraine attack (status migrainosus), or an attack lasting longer than 72 hours, patients may need to be hospitalized for a short period. Patients with severe nausea and vomiting at the onset of an attack may respond best to intravenous prochlorperazine. These patients may be dehydrated, and adequate hydration is necessary. Parenteral DHE or valproate are some of the options for treatment in an inpatient setting. Some patients may need opioids in addition, although their role in the treatment of migraine is controversial.

15.3.F Chronic abortive treatments

Sometimes long-acting triptans can be used for "miniprophylaxis" for 3–5 days especially for women who have

perimenstrual migraines that are regular and very severe. This is helpful only if the patient is still having a good response to triptan medications but has been using them only as an abortive. In these cases, the typical prescription is to use a time-contingent twice-daily dosing of a long-acting triptan such as frovatriptan (2.5 mg) or eletriptan (20 mg) beginning 2–3 days prior to menstruation and continuing for a few days depending on migraine duration. Use this protocol for 4–9 days maximum. The real advantage of these medications is that they have a long half-life (frovatriptan, 26 hours; eletriptan and its active metabolites, 13 hours). This means that drug rebound with more pain is not likely if they are used one in the morning and one in the evening on a regular schedule. If a patient has more migraines during the rest of the month, it would be prudent to start a daily preventative treatment and choose one of the medications described above.

15.3.G Acute abortive treatment for cluster headache

There are many agents for aborting a cluster headache and oxygen therapy is safe and effective; thus, it is the treatment of choice (Table 15.9). Oxygen delivered through a face mask at a dose of 8 L/min for 10 minutes, early on during an attack, often terminates or diminishes the intensity of the attack. Oxygen is postulated to be a vasoconstrictor and increases synthesis of serotonin in the CNS, which may be the reason for its efficacy. Recently, certain triptans have been shown to be effective for cluster headache treatment. Subcutaneously administered sumatriptan (6–12 mg) is effective in treating an acute attack of cluster headache. In one study, 74% of patients responded to subcutaneous sumatriptan, compared with 26% who took placebo. Oral agents are less effective and less useful because cluster headache typically lasts for less than 30 minutes and oral agents may take up to 1 hour to be effective. Transitional prophylaxis with nightly administration of oral or suppository ergotamine (2 mg) can also be used. Relief is reported in more than 50% of patients when ergotamine is given early during the attack. The inhaled form of ergotamine is given in the dose of 0.5 mg, with a maximum total dose of 2.16 mg delivered in as many as six puffs. The sublingual dose is 2 mg every half-hour, with a maximum of 8 mg/day. Dihydroergotamine is as effective as ergotamine, but it has the disadvantage of self-administration during an attack. The dose is 0.5–1 mg given intravenously or intramuscularly. Cocainization of the sphenopalatine ganglion has been shown in the past to abort cluster headaches; thus, viscous lidocaine dropped into the ipsilateral nose may work. Intranasal administration of 2% lidocaine (1 mL) with the patient in the supine position is effective in some patients.

Table 15.9 Acute treatments for cluster headaches

1	Oxygen 7 L/min with non-rebreathing mask
2	Sumatriptan 6 mg subcutaneously
3	Sumatriptan nasal spray 20 mg
4	Zomig nasal spray 5 or 10 mg
5	DHE 1 mg subcutaneously or intravenously
6	Ergotamine *orally* 2 mg or as *suppository* every day at bedtime
7	Cocainization of sphenoplatine ganglion
8	Lidocaine 4–10% nasal spray,1 mL

DHE, dihydroergotamine.

15.4 Chronic daily headaches

Chronic daily headache (CDH) is a common disorder that is often not recognized or treated appropriately. Primary CDH is defined as headaches that occur for more than 15 days per month for at least 3 months, are not related to structural or systemic disease, and may occur with or without analgesic overuse. The overall worldwide prevalence is 4–5%, and the female-to-male ratio is 2 : 1.[60] A population-based survey from 1998 to 2000 showed that 4.1% of Americans, 4.35% of Greeks, 3.9% of elderly Chinese, and 4.7% of Spaniards had primary CDHs.[61] There are two peaks of age-related prevalence: 20–24 years of age and those above the age of 64 (8% for both).

There are certain risk factors that predispose a patient with episodic headaches to convert to chronic daily headaches: not readily modifiable ones include female gender, white race, lower educational level, being previously married (e.g., divorced, widowed, or separated), diabetes, head injury, and arthritis. Scher et al. also found that controls with higher headache frequency, obesity, snoring, or medication overuse were all more likely to have new-onset CDH at follow-up.[62] Moreover, the risk of new-onset CDH was significantly higher in control subjects with more than two headaches per month. It is therefore important for clinicians to promptly treat patients with frequent headaches to prevent progression to CDH. Patients with episodic migraine or tension-type headache ultimately develop the same daily headache and, when daily headaches become intermittent again, they seem to reassume the initial headaches. It is therefore difficult to determine whether people with certain headache types are more predisposed to chronicity. Two commonly speculated upon etiologies for CDH are medication overuse and trauma.[63]

Chronic daily headache includes chronic migraine (CM), chronic tension-type headache (CTTH), hemicrania continua (HC), and new daily-persistent headache (NDPH)

(Table 15.10) The commonest type of CDH is either CTTH or CM. These patients usually have a previous history of episodic tension-type or migraine headaches, respectively.[64] All headache disorders described the following subsections (except NDPH) may masquerade as dental and orofacial pain and be co-morbid with temporomandibular disorders and orofacial neurogenic pain disorders, so the differential diagnosis is more problematic. Figure 15.1 suggests a process by which these chronic headaches can be separated.

Table 15.10 Chronic daily headache classification

Primary
Headache duration longer than 4 hours
Chronic migraine
Chronic tension-type headache
New daily-persistent headache
Hemicrania continua
Headache duration less than 4 hours
Cluster headache
Chronic paroxysmal hemicranias
SUNCT
Hypnic headache
Idiopathic stabbing headache
Secondary variety
Post-traumatic headache

SUNCT, short-lasting unilateral neuralgiform headache with conjunctival injection and tearing.

15.4.A Hemicrania continua

This is a rare headache disorder that is now more frequently being recognized by headache clinics. The clinical characteristic of HC is a continuous and always unilateral headache that is described as moderate in intensity. It may have some jabbing episodes associated with pain and must have at least one of autonomic symptoms. Resolution of headache with indomethacin is a key characteristic which is in fact a diagnostic criterion as determined by IHS. HC should be considered in every patient with CDH, especially those who seem to be refractory to usual treatment, and a trial of indomethacin should be given. A single intramuscular dose of 50 mg (an "indo-test") can be used, or oral doses starting with 25 mg twice a day to a maximum of 300 mg/day can be used.[65] There is also a sustained-release indomethacin tablet for daily dosing.

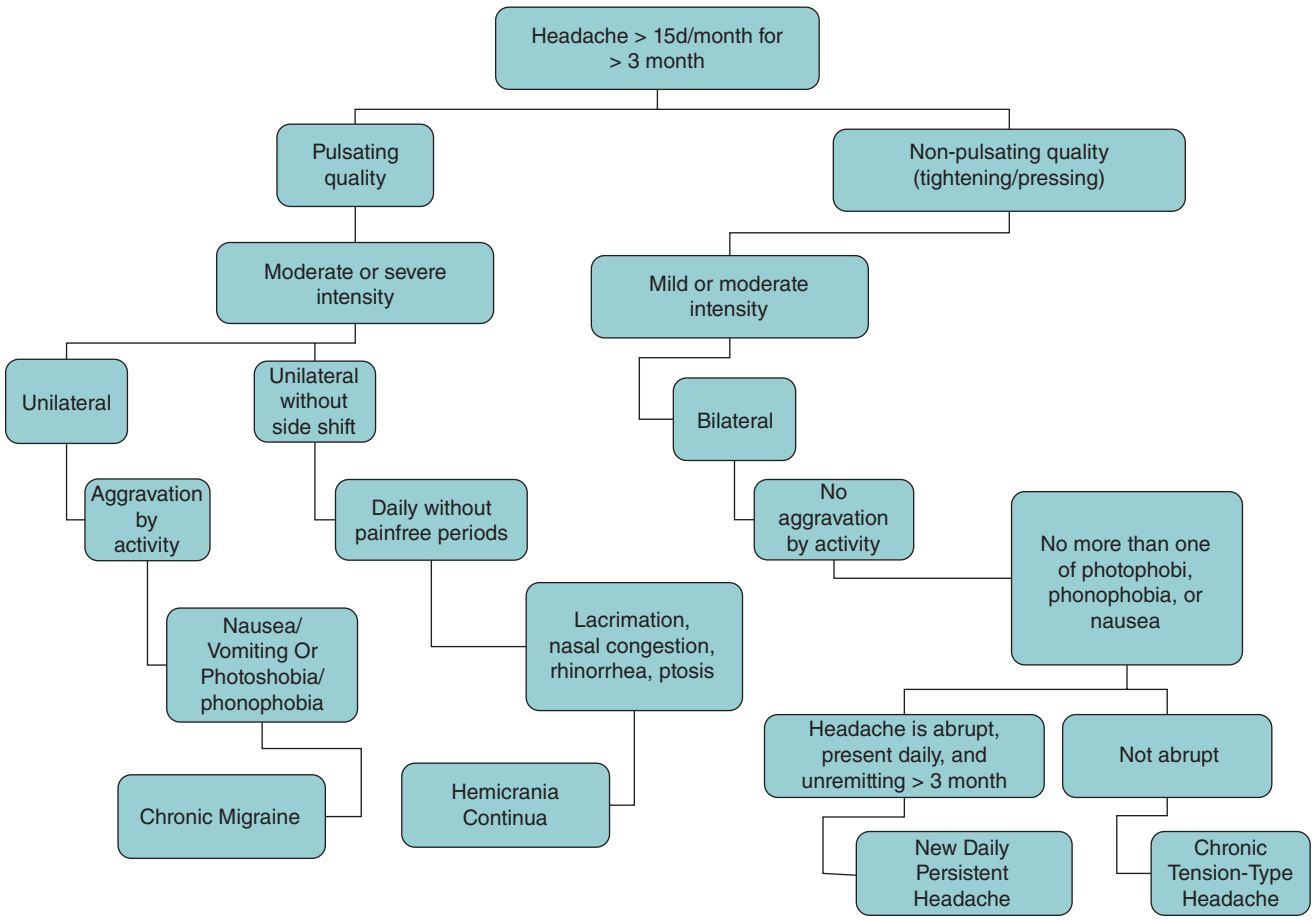

Figure 15.1 Chronic headache diagnosis algorithm.

Table 15.11 Medication-overuse headache

Headache present on more than 15 days per month with at least one of the following:
1. Bilateral
2. Pressing or tightening (nonpulsating) quality
3. Mild-to-moderate intensity
4. Intake of analgesics on more than10 days per month for more than 3 months
5. Headache has developed or markedly worsened during medication overuse.
6. Headache resolves or reverts to its previous pattern within 2 months after discontinuation of medication.

15.4.B New daily-persistent headache

New daily-persistent headache (NDPH) is a new subtype that has been created by the latest IHS classification and therefore not much is known regarding its epidemiology, pathogenesis, and treatment. What distinguishes it from other chronic headaches is that the patient can clearly recall the onset of the headaches. Also, in contrast to CM and CTTH, there is no previous history of headaches in patients with NDPH.

15.4.C Medication overuse headache

Also known as an analgesic rebound headache, medication overuse headache (MOH) is the most frequently seen type of secondary CDH. The criteria are (Table 15.11) a steady head or midface pain with frequent–intermittent or continuous multiple pain foci. To be called an MOH, the headaches must improve when analgesics are withdrawn. The most commonly overused medications are OTC analgesics, ergotamines, barbiturates, benzodiazepines, and opioids. There are two theories that explain how this paradoxical response occurs: (1) analgesics wear off in the presence of sustained pain input, which causes increased nociceptive stimulation and results in sensory nerve sensitization and the paradoxical pain we know as MOH; and (2) sustained analgesic use produces direct upregulation of pro-nociceptive systems similar to the paradoxical pain occurring with hyperalgesia induced by chronic morphine use.[66]

15.4.D Pathogenesis of chronic daily headache

Similar to other chronic pain states, the biochemical basis of CDH is postulated to be due to the imbalance between the excitatory and inhibitory pain pathways. The proposed mechanisms include NMDA receptor activation, increased maintained production of sensory neuropeptides and nitric oxide production and supersensitivity. Gallai et al. showed elevated levels of glutamate, nitrite, and cyclic GMP levels in CDH patients and interestingly showed a statistically significant correlation between the visual analog scale and these levels.[67] Perhaps the repeated activation of the glutamate/NO system is the basis for the headache becoming chronic. The result is increased sensitivity of peripheral nociceptors which discharge spontaneously, resulting in peripheral and ultimately central sensitization. Aurora et al. reported brainstem dysfunction in chronic migraine patients on PET scans and neurophysiological[68] examination and it remains to be seen whether there is a brainstem generator for chronic migraine, as is known for episodic migraine headaches.

15.5 Treatment protocols for chronic daily headaches

First, one must be sure of the diagnosis, that is, that the CDH with which the patient suffers is not due to a secondary etiology. Assuming the patient does not have secondary headaches, the most likely cause is central neuronal sensitization due to increasing pain frequency or due to a medication rebound phenomenon. Second, a clear medication history of daily analgesic use should be recorded and if history of analgesic overuse is present, then MOH should be treated (as described in the next section). This should include all analgesics, prescription or OTC and the amount. Third, if a CDH is strictly unilateral, then one should keep in mind that this could be an indomethacin-responsive headache (e.g., HC) and an indomethacin trial should be considered. Fourth, preventative treatment should be instituted. Fifth, co-morbid conditions (e.g., anxiety and depression) should be actively treated.

15.5.A Withdraw symptomatic medication

Medication withdrawal is necessary in patients where you have documentation that they are overusing analgesics and you suspect a MOH headache. Most patients have noticed that the headaches have increased in severity as their analgesic consumption has accelerated. If it is clear that analgesic overuse is the major cause, a detailed history of prior headaches and particularly the amount and type of medication that the patient is taking must be elicited. Often patients are receiving analgesic medication from a variety of physicians and every effort must be made to keep all healthcare providers in communication. If one assumes care of the patient, both patient and physician should agree that there should be only one prescribing physician involved and patients need to keep a daily chart of headache intensity and a detailed listing of all analgesic preparations being used, including all OTC medications, vitamins, alternative medical therapies, and acute emergency room visits. Based on this

information, several methods of treatment are available. Unfortunately it is problematic to use a cold-turkey approach to medication withdrawal in a patient taking caffeine. The same problem (e.g., withdrawal symptoms) will occur if a patient is taking a narcotic (Vicodin) or a barbiturate medication (fiorinal). For the medications tha are difficult to withdraw, the patients need to be firmly convinced that a slower reduction in medication is indicated. The general rule of thumb is to reduce the analgesic products by 50% every 2 days getting the patient off all analgesics in 6–8 days although in some cases you may elect to reduce by 25% every 2 days and thus take longer in the withdrawal process. Expected outcome is that withdrawal of the analgesics will result in a 50% reduction of headache frequency and an improvement in symptoms.

While they are being withdrawn from analgesics, patients can be started on a preventative regimen. The patient should be made to understand that no preventative regimen is likely to be effective until they are fully off the analgesic medications. In some situations, when outpatient "detoxification" is ineffective an inpatient stay in a facility or hospital service that understands analgesic abuse may be needed, where a higher degree of coordination and communication among all healthcare providers is provided.

15.5.B Indomethacin as an abortive headache agent

Although this medication is not an OTC medication, it is an NSAID and it has a special place in headache diagnosis and prevention because it is a drug that can uniquely suppress certain headaches when no other drug works. Essentially, there are several types of headaches that are unusually responsive to indomethacin, including (l) chronic paroxysmal hemicrania[69]; (2) hemicrania continua[70]; (3) sharp, short-lived head pain syndrome (SSHP), which is also called by various other names such as "ice-pick" headache, "jabs-and-jolts" headache, and "needle-in-the-eye" syndrome[71]; (4) exertional headache[72]; and (5) hypnic headaches.[73] Specific action of indomethacin in this syndrome is not clear but it suggests a possible role of prostaglandins and prostacyclins in the production of head pains. The recommended dose for adults is 50–200 mg/day split into 2–3 doses. Indomethacin should be taken with food in order to reduce stomach discomfort as it does produce substantial gastritis.[74]

15.5.C Starting a preventative medication for chronic daily headache

Preventative treatment is quite effective in controlling chronic headache and is given for 3–6 months. The primary goal is to reduce the frequency, severity, and duration of headaches. Regardless of the type of medication, as a general rule medication should start at minimum dose and be adjusted slowly until efficacy is achieved or side effects are reported. The FDA has approved five drugs for migraine prevention: topiramate, methysergide, propranolol, timolol, and divalproex sodium. However, there are other drugs (Table 15.12) and other methods of treatment that must be considered as well. To date, only amitriptyline, fluoxetine, gabapentin, tizanidine, topiramate, and botulinum toxin type A (BoNT/A) have been evaluated as "prophylactic treatment of CDH in randomized, double-blind, placebo-controlled or active comparator-controlled trials."[75] Muscle relaxants or antianxiety agents can also be used as a part of treatment regimen if muscle spasm or anxiety is co-morbid.

Table 15.12 Preventative therapy for chronic daily headache or chronic migraine

Drug	Class of agent	Daily oral dosage range
Amitriptyline	Tricyclic antidepressant	10–200 mg
Nortriptyline	Tricyclic antidepressant	10–150 mg
Divalproex sodium	Anticonvulsant	250–2000 mg
Topiramate	Anticonvulsant	25–200 mg; titrate, 25 mg/week
Gabapentin	Anticonvulsant	900–3600 mg
Propranolol	Beta-blocker	40–240 mg
Timolol	Beta-blocker	20–60 mg
Verapamil	Calcium channel blocker	120–480 mg
Lisinopril	ACE inhibitor	10 mg
Candesartan	Angiotensin receptor blocker	4–30 mg
Tizandine	Alpha-adrenergic agonist	8–20 mg
Botulinum toxin	Neurotoxin	25–200 U for 2–3 months

ACE, angiotensin-converting enzyme.

Tricyclic antidepressants as preventative agents for chronic daily headache

Description, mechanism of action, and primary indications

Currently many physicians consider antidepressants as the primary choice for the treatment of CDH since they have been studied most extensively. The tricyclic antidepressants (TCAs) are a front-line drug for managing the chronic daily headaches and in particular those that are accompanied by significant myofascial nociceptive afferent activity. Tricyclic antidepressants potentiate the action of 5-HT and

norepinephrine (NE) by inhibiting their reuptake into the CNS. Two such agents are amitriptyline and nortriptyline and both are known to provide a general reduction in headache pain levels and frequency of headaches.

Starting dose

The standard drug chosen for neuronal suppression is nortriptyline; it is prescribed with a starting dose of 10 mg taken at 1–2 hours before bedtime. The dose is titrated upward to a therapeutic dose of 50–100 mg.

Metabolism, side effects, and adverse drug reactions

The side effects of the TCAs are many, including sedation, difficulty urinating, dry mouth, constipation, and weight gain over time. One approach for nortriptyline-induced progressive weight gain is to lower the nortriptyline dose and then add a small amount of topiramate.

Efficacy for chronic daily headache

Several double-blind, placebo-controlled studies were summarized in the review by Redillas and Solomon.[76] Gobel et al. in 1994 studied 24 chronic tension-type headache patients and found a decrease in headache duration by 30% after a 6-week amitriptyline treatment regimen.[77] Bendsten et al. in 1996 compared amitriptyline and citalopram against placebo in 34 patients and reported that amitriptyline was effective in decreasing headache frequency and duration but that citalopram had no effect.[78] Of course all medications should be chosen based on the drug's side-effect profile and the patient's coexisting and co-morbid conditions.

Anticonvulsants as preventative agents for chronic daily headache

The two anticonvulsants that are FDA approved are topiramate and divalproex sodium and we discuss each here. The evidence for the efficacy of anticonvulsants for headache prevention was described in a 2004 meta-analysis.[79] This review found 15 studies (2024 patients) that were eligible for inclusion and of them 14 were placebo-controlled studies. The anticonvulsants examined by these various studies were divalproex sodium ($n = 4$), topiramate ($n = 3$), sodium valproate ($n = 2$), gabapentin ($n = 2$), carbamazepine ($n = 1$), clonazepam ($n = 1$), and lamotrigine ($n = 1$). The authors performed data pooling and reported that anticonvulsants reduce migraine attacks by an average of 1.4 attacks per month versus placebo medications. Looking at the data in a slightly different way the authors found that anticonvulsants doubled the number of patients who reported at least a 50% reduction in migraine frequency. The study calculated "number-needed-to-harm" (NNH; i.e., adverse drug reactions) for the different drugs and found that sodium valproate gave an NNH in the range of 6.6–16.3 but topiramate had an NNH which ranged from 2.4 to 32.9 depending on the dose used. The authors concluded that anticonvulsants appear to be effective in reducing migraine frequency and are reasonably well tolerated but no drug provided a robust result.

Divalproex sodium

Description, mechanism of action, and primary indications

Divalproex sodium (Depakote) is probably effective because of its dual mechanism of action; it blocks voltage-gated Na^+ channels but also increases levels of aminobutyric acid (GABA) by decreasing its degradation.

Starting dose

The medication plan is to increase the dose to 1000 mg/day over a 3-week period. Many patients improve on as little as 250 or 500 mg of Depakote, but the effect is not an immediate one and it will take at least 3 weeks to evaluate its efficacy.

Metabolism, side effects, and adverse drug reactions

Because Depakote is difficult for the liver to metabolize, it is necessary to gather blood work before and during the use of this medication. The common serologic tests performed include a complete blood count (CBC) and a serum metabolic assay that looks at electrolytes and at renal and liver function after 3 weeks. Side effects include nausea, vomiting, sedation, ataxia, rash, alopecia, pancreatitits, and appetite stimulation. Forty percent of patients experience elevated liver enzyme (transaminase) levels, and 1 in 50,000 develops hepatic failure, so liver-function testing is needed when this drug is prescribed. Of course, there should be a careful discussion with child-bearing females when starting this drug, since it is a D category for pregnancy risk. Besides the risks of teratogenicity, some patients on divalproex can get polycystic ovary disease, and therefore these risks must be clearly explained to female patients. All females of child-bearing age on anticonvulsants should be on at least 1 mg of folic acid as it provides some protection from teratogenicity in case of an unexpected pregnancy.

Efficacy for chronic daily headache

According to a consortium of headache experts, one of the best of the migraine preventative agents is divalproex sodium (Depakote).[80]

Topiramate

Description, mechanism of action, and primary indications

Approved by the FDA for migraine prophylaxis in 1997, topiramate potentiates GABA responses, significantly increasing central nervous system GABA levels, and also blocks the AMPA kainate excitatory receptor.[81]

Starting dose

The effective dose range is from 100 to as much as 400 mg/day. The typical dosing for topiramate is to start with 25 mg every day then gradually increase the dose by 25 mg every week to 100–150 mg/day. The total dose can be divided into twice-a-day dosing.

Metabolism, side effects, and adverse drug reactions

Side effects include weight loss, renal stones, and abnormal delusional and psychotic thinking; 5–15% of patients experience cognitive dysfunction in the form of mild confusion or word-finding difficulty. The effect can even be seen at the lowest starting dose, 25 mg at bedtime. Other side effects include dyesthesia (burning) of the fingers or toes, but this usually disappears after a few days. A rare side effect is sudden increase in intraocular pressure with blurred vision and eye pain. Patients should be warned to immediately discontinue upon developing ocular pain.

Efficacy for chronic daily headache

A 2009 study examined the efficacy of topiramate for treatment of chronic migraine pain.[82] The study was a randomized, double-blind, placebo-controlled, multicenter clinical trial involving 306 patients who were given either topiramate (100 mg/day) or a placebo drug. The analysis used an intent-to-treat methodology and the authors reported that the reduction in mean monthly migraine or migrainous days for the topiramate group was significantly more than seen in the placebo group. Overall the decrease in mean monthly total headache days and headache-free days for topiramate versus placebo treatment was 5.8 versus 4.7 days and there were no reported serious adverse events. In another 2009 study topiramate was compared with amitriptyline regarding their relative efficacy as preventative treatment for frequent episodic migraine in 331 patients.[83] This 26-week-long randomized double-blind noninferiority study compared both the efficacy and tolerability of 25 mg/day of topiramate versus 25 mg/day of amitriptyline in the prophylaxis of episodic migraine headache. Both drugs were titrated to higher doses (maximum of 100 mg/day) as tolerated. The mean monthly number of migraine episodes in an intent-to-treat analysis showed that there was not significant difference between the topiramate and amitriptyline groups. However, the subjects receiving topiramate had a mean weight loss of 2.4 kg, compared with a mean weight gain of 2.4 kg in subjects receiving amitriptyline. There were treatment-related adverse events with both medications. The topiramate group reported paresthesia (29.9%), fatigue (16.9%), somnolence (11.9%), hypoesthesia (10.7%), and nausea (10.2%). By comparison, the amitriptyline group reported dry mouth (35.5%), fatigue (24.3%), somnolence (17.8%), weight increase (13.6%), dizziness (10.7%), and sinusitis (10.7%).

Gabapentin

Description, mechanism of action, and primary indications

This is an antiepileptic which is also approved for diabetic neuropathic pain by the FDA. It is structurally analogous to GABA, an inhibitory neurotransmitter, and also binds voltage-gated calcium channels.

Starting dose

Gabapentin is usually started at low doses (100 mg/day up to 100 mg three times a day). After 3 days it can be increased by 100–300 mg and increased by this amount again every 3 days to a point where pain is diminished or side effects are noticed. A typical schedule might be as follows: day 1, 300 mg daily at bedtime; day 3, 300 mg twice a day; day 6, 600 mg twice a day; day 9, 600 mg three times a day. The usual effective total daily dose is between 900 and up to 3600 mg. The dosing schedule is usually three times a day and the titration rate should proceed more slowly in elderly patients.

Metabolism, side effects, and adverse drug reactions

Adverse events include dizziness, somnolence, ataxia, and nausea.

Efficacy for chronic daily headache

Spira et al. reported 9% overall improvement in headache-free days per month for CDH patients on 2400 mg of gabapentin compared with placebo.[84]

Antihypertensives as preventative treatment for migraine

A recent meta-analysis reviewed 94 clinical trials in which headache data was reported for four types of

antihypertensives: thiazides, beta-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs).[85] The authors concluded that any of these agents decreases headache by one-third. It is doubtful that the antihypertensive action is responsible for improvement in headache; yet-unproven, but likely, is that these drugs induce a membrane-stabilizing effect.

Calcium channel blockers

Description, mechanism of action, and primary indications

Calcium channel blockers are especially useful in patients with co-morbid migraine and hypertension, since this is the primary indication for these drugs and in patients with a contraindication to beta-blockers, such as asthma and Raynaud's disease. Calcium channel blockers impede the influx of calcium through calcium channels. They also inhibit calcium-dependent enzymes which form prostaglandins and may assist in downregulation of the serotonin system.

Starting dose

Therapy is initiated with 80 mg/day for 2 days, then 80 mg twice a day for 2 days, then 80 mg three times a day for 2 days, and then switch to the 240-mg sustained-release form.

Metabolism, side effects, and adverse drug reactions

The primary side effect of verapamil is constipation, which may be avoided by using stool softeners such as Fiber-Con. Other side effects vary and depend upon the individual drug but do include dizziness, headache (particularly with nifedipine), depression, vasomotor changes, tremor, orthostatic hypotension, and bradycardia.

Efficacy for chronic daily headache

Calcium channel blockers include the drugs verapamil, nifedipine, and nimodipine; however, data supporting the effectiveness of calcium channel blockers is relatively weak.[86] Verapamil can be useful with patients who have aura and hemiplegic migraine, due to the relationship between calcium channel activity and the cortical spreading depression that is associated with aura.[87] Calcium channel blockers may lose their effectiveness against migraines over time, but this can sometimes be remedied by taking a higher dose of the drug or switching to a similar drug.

Beta-blockers

Description, mechanism of action, and primary indications

There are two beta-blockers approved for migraine prevention by the FDA: propranolol and timolol. There are clearly some patients who are responsive to one and not to other drugs in this class, so if a patient does not respond to propranolol it is reasonable to proceed with nadolol (80–240 mg), atenolol (50–100 mg), or timolol (20–100 mg).

Starting dose

The typical starting dose for propranolol is 40 mg twice a day. This dose is increased by 20 mg every 3 days until headache frequency is reduced or blood pressure is lowered to produce orthostatic hypotension and, hence, dizziness on rapid standing. Since this drug does not always work, if no effect is seen by 200 mg/day, the proper protocol is to taper off and discontinue this medication.

Metabolism, side effects, and adverse drug reactions

The main side effects of a beta-blocker are drowsiness, fatigue, lethargy, sleep disorders, nightmares, depression, and (rarely) esophageal spasm. Less-common side effects include orthostatic hypotension, significant bradycardia, impotence, and aggravation of intrinsic muscle disease. The beta-blockers can cause depression and aggravate asthma, and therefore some have specific contraindications, including asthma, heart block, and congestive heart failure.

Efficacy for chronic daily headache

The prototypical beta-blocker is propranolol and it has been shown to reduce the frequency of migraine attacks in 60–80% of people.[88] Studies have been carried out with other beta-blocking agents but none have been superior to propranalol.

ACE inhibitors and angiotension receptor blockers

Description, mechanism of action, and primary indications

The ACE inhibitors and ARBs are very gently antihypertensive and are generally very well tolerated in the authors' experience.

Starting dose

Lisinopril is an ACE inhibitor which has effectiveness for migraine prevention at low dose of 10 mg per day.[89] Cande-

sartan starting dose is 4 mg and can be titrated up to 32 mg every day.

Metabolism, side effects, and adverse drug reactions

Side effects include dizziness, syncope, and cough (ACE inhibitors). The ARBs have an advantage over ACE inhibitors since they do not cause the side effect of coughing.

Efficacy for chronic daily headache

Several clinical trials have shown the efficacy of angiotensin II receptor blockers for migraine prevention.[90] A meta-analysis of 27 studies and 22,000 patients showed that the risk of headache was one-third lower in patients on an ARB.[91] The ARB olmesartan has been shown to be effective in hypertensive or prehypertensive patients for migraine prevention at doses of 10–40 mg.[92]

Serotonergic modulators for prevention

Description, mechanism of action, and primary indications

Selective serotonin reuptake inhibitors (SSRIs) inhibit 5-HT, NE, and platelet 5-HT uptake and therefore increase the levels of serotonin available in the synaptic cleft.

Starting dose

Not applicable.

Metabolism, side effects, and adverse drug reactions

Methysergide, a serotonin modulator and very effective for migraine prevention, has been withdrawn from the market and is no longer available in the United States due to its side effect of retroperitoneal fibrosis.

Efficacy for chronic daily headache

The SSRIs have been tested as migraine preventative agents in several studies. A meta-analysis on the efficacy of serotonin-specific reuptake inhibitors as preventative agents for migraine was published in 2005.[93] The authors found 13 randomized blinded clinical trials (including 636 subjects) that could be utilized in their analysis. A comparison with a placebo was done in many and some compared SSRIs versus TCAs for effect on headache frequency and they also documented the nature of adverse drug reactions occurring with this class of medications. The big problem with most of these studies was inherent methodological shortcomings and a short follow-up period. The authors found that SSRIs did not consistently reduce migraine headache index scores any more than placebo did. Moreover, when compared with TCAs the latter reduced CTTH duration by 1.26 hours per day, not SSRIs. There were major adverse drug reactions (ADRs) in all subjects, but no remarkable differences were seen in ADRs for those in the SSRI group versus those in the placebo group. The authors concluded that, within the 2-month period examined by most studies, SSRIs were no more efficacious than placebo in patients with migraine; in patients with TTHs, TCAs were better than SSRIs, but the burden of adverse events in patients receiving TCAs was greater. Saper et al. indicated an increase in headache-free days in 40% of CDH patients on fluoxetine, and there was at least a 50% improvement from baseline in overall headache status.[94] Foster and Bafaloukos reported headache improvement in an open-label study of 60 CDH patients treated with paroxetine. In this study, 44 patients reported a decrease in headache frequency by at least 50%.[95]

Botulinum toxin

Description, mechanism of action, and primary indications

One interesting, atypical preventive medication that has been studied for CDH is botulinum toxin (BoNT-A). It is especially useful for CDH patients already on multiple oral medications, since the toxin is given subcutaneously on the forehead, temples, and sometimes back of the neck, every 2–4 months.

Starting dose

Doses vary from 25 to 200 units and two injection approaches are used: follow the pain (inject where there is pain), and fixed injection (same site, wherever the pain may be).

Metabolism, side effects, and adverse drug reactions

This medication is relatively safe but will induce side effects (transient motor paralysis) in direct proportion to the amount injected. The specific amount of botulinum toxin that is used depends on the size of the muscle and the treatment protocol, namely, it can be used to achieve partial muscle paralysis (larger amounts) or as a headache or neuropathic pain preventative agent (smaller amounts). Chapters 11 and 19 both discuss the use of botulinum toxin for muscle spasm and pain.

Efficacy for chronic daily headache

Mathew et al. studied 571 patients for 11 months, in a double-blind randomized placebo-controlled study and reported that

a significantly higher percentage of patients on BoNT-A (BOTOX) had a decrease in headache frequency of over 50% compared with placebo (32% vs. 15%).[96] The study concluded that BoNT-A was safe, well tolerated, and effective in reducing the frequency of headaches. A similar study by Ondo at higher doses of BOTOX (200 units) showed a significant improvement in headache-free days from week 8 to week 12.[97]

Preventative treatments for cluster headache

For cluster headache, in particular, the preventative medications and therapies are listed next.

- *Corticosteroids* Cluster headache can be treated with a corticosteroid, prednisone; the typical starting dose is 5–10 mg taken every morning. This will normally suppress the headaches but long-term use of prednisone is not desirable.
- *Calcium channel blockers* Verapamil is the preventative treatment of first choice for frequent cluster headaches, based on anecdotal evidence In these cases, verapamil is prescribed at a starting dose of 40 mg orally three times a day, and it can be escalated to 80 mg orally three times a day.
- *Lithium* Lithium is very effective for treating both episodic and chronic cluster headaches and its mood-stabilizing effect is helpful for some of those patients who may be very agitated and aggressive during cluster periods. The dose for lithium is 600–900 mg/day in divided doses. Adverse effects include hypothyroidism, renal complications, and adverse neurological effects (e.g., tremor, slurred speech, blurred vision, confusion, nystagmus, ataxia, extrapyramidal effects, and seizures).
- *Antiepileptics* Anecdotally, topiramate and divalproex sodium have been effective in some patients with refractory cluster headaches. The doses used are similar to those used for migraine.
- *Somatostatin* This medication inhibits the release of calcitonin gene–related peptide and vasoactive intestinal peptide. The chief source is the hypothalamus. Octreotide is a somatostatin analog, and it has a peripheral mode of action. Matharu et al. reported on a study of 57 patients given octreotide (46 provided efficacy data) and 45 given placebo.[98] In this study, the headache response rate with 100 µg of octreotide subcutaneously was 52%, and the headache response rate was 36% for those given placebo. Gastrointestinal upset was the main adverse effect reported.
- *Psilocybin (a chemical derivative of mushrooms), LSD (a hallucinogenic), and melatonin* All three of these drugs have case-based evidence that they can be effective in some patients.
- *Occipital nerve anesthetic or corticosteroid injection* Injection near the occipital nerve is another therapy option for occipital headache. Methylprednisolone acetate at 120 mg in polyethylene glycol with lidocaine is injected into the ipsilateral greater occipital nerve, resulting in remission of the attack.
- *Ipsilateral hypothalamic stimulation* This deep brain stimulation method has now been used on more than 20 patients as a treatment for intractable chronic cluster headache. The hypothesis is that the hypothalamus is the clock-pulse generator. Constant depolarization discontinues the biological clock like an impulse from a distant trigeminal anatomic execution. Leone et al. reported the results over 4 years in 20 patients, the first procedure being in 2000. Thirteen of 16 patients did extremely well. Only transient diplopia was noted as an adverse effect.[99,100]

15.5.D Behavioral treatment supplement for chronic daily headache

The FDA has determined that biofeedback and other nonpharmacologic treatments for episodic migraine have grade A evidence (i.e., proven to be highly effective by double-blind controlled randomized trials). The knowledge gained from episodic headache patients is a good indication that a multimodal team approach to CDH—namely, by offering both pharmacologic and nonpharmacologic options—gives the patient the best likelihood of success. Alternative and complementary therapies such as acupuncture and biofeedback have been studied for CDH, but due to the lack of standardization of techniques and double-blind, placebo-controlled studies, no consensus has been reached regarding their effectiveness. Cognitive–behavioral therapy is another supplemental therapy for the patient who is having stress-related headache and for whom pharmacologic and physical medicine treatments are insufficient. The psychologist would assist the patient with learning self-treatment skills needed to reduce pain.

15.5.E Complementary and alternative medicine

Americans spend more than $13.7 billion a year on complementary medicine and more than 70% of patients do not tell their doctors about it. Interest in the use of complementary and alternative medicine (CAM) by headache patients has been increasing. A recent survey showed that greater than 85% of headache patients use CAM therapies and 60% felt they provided some relief. Recently, some good studies have demonstrated the effectiveness of the herb butterbur (*Petasites hybridus*) in preventing migraines.[101] The most commonly reported adverse events due to *P. hybridus* are gastrointestinal disorders (e.g., burping). In one study, 22–

25% of patients taking *P. hybridus* reported such symptoms versus 6.7% of patients taking placebo. Another herb, feverfew, is also widely used and some studies have shown it to be safe and possibly effective for migraine prevention. Riboflavin at doses of 200–400 mg /day effectively reduces the number of headache days per week after about 3 months of use.[102]

15.5.F Hospitalization for chronic daily headache

The most common reasons for hospitalization of a CDH patient include severe and refractory symptoms. The other reason that should be presented is that the extent of their drug overuse and potential of drug–drug interactions will not allow outpatient treatment. Hospitalization is appropriate for the patient with a substantial psychiatric or behavioral co-morbidity problem or a confounding medical illness. In a hospital environment, the staff will usually use intravenous pain-control medications, detoxification treatment, and opioids to break the headache pain cycle. Repetitive treatment with intravenous dihydroergotamine (DHE) and metoclopramide can be used to break the cycle of CDH.[103] A typical protocol is to use 5 mg compazine with 0.5–1 mg DHE every 8 hours (via subcutaneous, intravenous, or intramuscular route) till the headache resolves. An initial test dose of 0.25 mg for patients who have never received an ergot may be prudent. It is important to remember that ergots are very emetogenic and antiemetics must be administered prior to each dose. It is usually effective in 2–3 days. Intravenous valproate can also be used in the inpatient setting.

15.5.G Chronic daily headache disability and long-term prognosis

Unfortunately, CDH is not only common but also disabling for patients. Studies on quality of life with CDH showed that patients were greatly affected by this disease. Using the generic instrument Short Form–36 (SF-36), Guitera et al. conducted a case–control study analyzing the quality of life for CDH patients in Spain.[104] Individuals were scored in eight areas: physical functioning, physical role, bodily pain, general health, vitality, social functioning role, emotional, and mental health. The SF-36 scores were then adjusted for co-morbid conditions. The results indicated that CDH subjects had lower scores in each section of the SF-36 compared with healthy subjects. The lowest scores were in the role of physical, bodily pain, vitality, and social functioning. Chronic migraineurs also had lower scores in each section compared with patients with episodic migraine. There was no significant difference in SF-36 scores between subjects with chronic tension-type headache and those with chronic migraine. The Guitera et al. study observed that quality of life seemed to be "affected more by the chronicity than by the intensity of pain." A study on the same subject of disability in CDH patients by D'Amico et al. used the Migraine Disability Assessment Score (MIDAS) in its validated Italian version to study the quality of life and disability in Italian CDH patients.[105] The result showed chronic migraine patients were impaired in everyday tasks, including domestic, workplace, and social activities. Among the 150 chronic migraine patients studied, 39% of them reported work lost, 53% reported work reduced by 50% or more, 69% reported household work lost, 71% reported household work reduced by 50% or more, and 83% reported family, social, and leisure activities lost.

Studies show varying degrees of effectiveness in treating CDH patients. Scher et al. reported, in a longitudinal CDH study, a projected 1-year remission rate to less than 160 headaches per year at 57%; however, remission to a more episodic pattern of less than one headache per week was low at 14%.[106] Another study reported CDH remission in response to medication withdrawal and other treatments were similar.[107] In summary, CDH patients are a challenging headache population, and managing these patients usually requires ongoing multimodal treatment. A majority of these patients will have decrease in headache frequency with treatment, but will probably continue to struggle with headaches in the long term. Relapse can and does occur and there are some clear caveats that must be stated with CDH treatment. First it should be understood that preventative headache treatment for CDH does not eliminate all attacks. Patients must still monitor their headaches with a diary and compare effects of drugs on these headaches so that their doctor can adjust their medications. Second, when a breakthrough headache occurs it should be treated just like any acute episode with appropriate abortive medications. The only concern here is to be sure that patients with a proven history of MOH do not use short-term analgesics. Finally and most importantly the clinician must know when to consider hospitalization of a patient to help with the chronic headache problem. It is important to have a good referral source for this procedure if the orofacial pain specialist is to treat headache.

15.6 Seven final recommendations on the diagnosis and treatment of chronic daily headache

Recommendations on the use of medications for treatment of chronic daily headache

1 Chronic daily headaches (CDHs) are present in as much as 2% of the population.

2 Chronic daily headaches are among the most disabling of the primary headache disorders.
3 Chronic daily headaches, like all chronic pain, cause intensification of any psychiatric or behavioral disorders, and inappropriate medication use is a major confounder to treatment.
4 Chronic daily headache treatment requires complex medication regimens combined with physical medicine, behavioral medicine, drug withdrawal, and sometimes a hospital-based detoxification protocol.
5 Chronic daily headache studies are needed to identify key factors contributing to treatment responses and to look for effective medications-based protocols
6 It is unknown if there are separate risk factors for each subtype of CDH and if the medications have different effectiveness on different subtypes of CDH.
7 Prompt recognition and treatment of CDH is better than delayed treatment from both the clinicians' and the patients' perspective.

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Chapter 16

Differential diagnosis and management of masticatory myogenous pain and dysfunction

Glenn T. Clark, DDS, MS

16.1 Understanding muscle pain classification and causation

The first section of this chapter deals with the differential diagnostic process and the criteria for the various painful masticatory myogenous pain (MMP) subgroups that patients present with. The current system for classifying myogenous disorders is an anatomically based system; therefore, the differential diagnosis process is relatively easy since it mostly involves careful palpation of the muscles and joint tissues (Table 16.1). However, above and beyond the clinical examination, an expert clinician must also strive to determine the etiology and pathophysiologic changes that occur with the various types of muscle pain. This determination is based on a thorough history and an in-depth understanding of the muscle pain research. Unfortunately, no valid additional diagnostic testing methods (radiographic, serologic, or electromyographic [EMG]) are available that will help to further classify subgroups of myogenous pain. In Section 16.2, we focus on treatment which is largely a self-directed treatment physical medicine and behavioral intervention approach that the patient needs to perform daily. We also review the current medications that have been used for myogenous pain disorders.

16.1.A Diagnosis with muscle palpation

Logically, the first component of the differential diagnostic process is to conduct a thorough review of the patient's history, looking for the most likely etiology or etiologies that might be causing or maintaining the pain. The second component, which is covered in this section, is to fully verify and document the anatomic extent and character of the myogenous pain using palpation. The third or last component is to decide, based on the examination and history gathered, which pathophysiologic changes would best explain the patient's current muscle pain disorder. How to gather a medical history and various etiologies and pathophysiologic processes associated with them are discussed in the following subsections.

How do you palpate the craniomandibular muscles?

There are several articles that review how to properly conduct a muscle and trigger point palpation examination.[1] Unfortunately the literature suggests that reproducibility of this examination between examiners is low.[2–4] In spite of this limitation muscle palpation is the accepted clinical examination when diagnosing a myogenous disorder. The palpation pressure used in the masticatory system varies (in the range 1–2 kg) but is generally lower than is used when palpating large leg, arm, shoulder, or neck muscles, where 4 kg of pressure is commonly recommended.[5] This palpation is done with the index finger being moved over the muscle of concern when in the relaxed state. The pressure used should be steady firm pressure (2 kg of pressure) applied for at least 1–2 seconds. While doing this palpation, ask the patient to rate the tenderness (if any) that is produced with this pressure, using 0 for none, 1 for mild, 2 for moderate, and 3 for severe tenderness. The level of tenderness at each muscle site should be recorded. When you palpate the muscle you must not only check for tenderness but also examine the muscle to see if it has a taut band (they always run parallel to the direction of the muscle fibers). Once you find the band, make sure you examine it for a trigger point and determine if this point produces referred pain to a nearby site. To do this examination it is presumed the examiner knows the landmarks needed to identify the underlying muscle. The common sites of palpation for the jaw closers are are the superficial and deep masseter muscles and the

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Table 16.1 Categories and criteria for myogenous pain in the masticatory system

Myogenous pain	Criteria
Focal myalgia due to direct trauma	• History of recent muscle trauma preceding the onset • Subjective pain in the muscle on function • Pain that can be replicated by muscle palpation
Primary myalgia due to stress and/or parafunction	• No history of recent muscle trauma • Subjective pain in the muscle on function • Pain that can be replicated by muscle palpation • No discernable taut band or trigger point in this band
Secondary myalgia due to active local pathology or recent medications	• History of recent joint, oral soft tissue, or pulpal disease or a medication that coincides with onset of muscle pain • Subjective pain in the muscle on function • Pain that can be replicated by muscle palpation
Myofascial pain	• No history of recent muscle trauma • Subjective pain in the muscle on function • Pain that can be replicated by muscle palpation • Discernable taut band and a trigger point in this band that causes pain to radiate on sustained compression
Widespread chronic muscle pain and fibromyalgia	• Subjective pain in multiple sites aggravated by function • Widespread pain involving more than three body quadrants • Symptoms more than 3 months in duration • Strong pain on muscle palpation in at least 11 of 18 body sites

anterior, middle, and posterior temporalis muscles. The cervical muscles that should be palpated are the sternocleidomastoid muscle and the upper and oblique portion of the trapizius muscle (just under the occiput and at the top of the shoulder). Note that the medial pterygoid can be best palpated at the angle of the mandible just inside the inferior edge of the mandible, but the lateral pterygoid cannot effectively be palpated.

Confirming that the patient's primary pain complaint can be reproduced by palpation of the muscle(s) is essential to the diagnosis of myogenous pain. However, getting a patient to report that your palpation pressure replicates their primary pain complaint is not proof that another source for the pain is not present. In fact, the opposite is true: if you cannot replicate the pain complaint by palpation, you have a high chance some othere pain-inducing disease process is present and unaccounted for.

The International Association for the Study of Pain Subcommittee on Taxonomy has classified myofascial pain as pain in any muscle with trigger points that are very painful to compression during palpation and causes referred pain.[6] Essentially the term "myofascial pain" is used only when specific criteria are satisfied. These criteria are both subjective (history based) and objective (examination based). The three subjective criteria that patients should endorse include (1) spontaneous dull aching pain and localized tenderness in the involved muscle(s), (2) stiffness in the involved body area, and (3) easily induced fatigueability with sustained function. The four objective criteria are (1) a hyperirritable spot within a palpably taut band of skeletal muscle or muscle fascia, (2) upon sustained compression of this hyperirritable spot, the patient reports new or increased dull aching pain in a nearby site, (3) decreased range of unassisted movement of the involved body area, and (4) weakness without atrophy and no neurological deficit explaining this weakness. Many have included the presence of referred autonomic phenomena upon compression of the hyperirritable spot and/or a twitch response to snapping palpation of the taut bands as additional diagnostic criteria.[7–11] However, inclusion of the last criterion is not endorsed by all since it is not a reliably present physical finding.[12] The interesting aspect of this study was that taut muscle bands and muscle twitches were common and noted equally in all three diagnostic groups (fibromyalgia, regional myofascial pain, and healthy control subjects). This finding suggests that the clinical examination-based criteria for myofascial pain are not reliable and myofascial pain patients are best identified using a combination of historical and clinical criteria. This research report suggests that additional work is needed to establish a reliable set of diagnostic criteria for this disorder.

The American College of Rheumatology (ACR) has set forth criteria for the diagnosis of fibromyalgia.[13] These criteria include specific (1) duration, (2) location, and (3) examination findings that must be satisfied. The duration criterion specifies that a history of widespread pain has to be present for at least 3 months. For pain to be considered widespread, it must involve (a) both sides of the body and (b) be located above and below the waist. Moreover, the location criteria state that the pain must involve multiple areas of the axial skeleton, including the cervical spine, anterior chest, and thoracic spine or lower back regions. If the patient has low back pain, this will satisfy the criterion for below-the-waist pain. Finally, the examination-findings criteria specify that a "painful" response must be elicited in 11 of 18 tender-point sites on digital palpation. The ACR criteria specify the exact location of these tender-point sites; they also specify that a manual finger palpation force of

approximately 4 kg is to be used during the examination and that the allowable responses to palpation are no pain, tender, and painful.

Why are the same muscles always tender?

Nontraumatic primary myogenous pain occurs in roughly the same anatomic locations from patient to patient in the masticatory and craniocervical systems. It was recently described that the slow time to peak motor units, which are presumably the slow twitch type 1 fibers, are clearly more sensitive to ischemia than the "fast" time to peak group.[14] That would explain why postural muscles, which have a much higher proportion of slow twitch (type 1 fibers), are much more likely to exhibit diminished perfusion and show ischemic injury sites.[15–17] Studies have shown that pH values of 6 or lower can be reached during ischemia and sustained contractions or exhaustive exercise.[18,19]

16.1.B Subtypes of myogenous pain

Myalgia (of all types) requires the following additional criteria to be satisfied: (1) the patient has an awareness of pain in the muscle on function; (2) this pain must be replicated by palpation. Based simply on its extent, the myogenous masticatory pain (MMP) can be divided into several subcategories. There are those patients with (1) focal masticatory myalgia, those with (2) regional craniocervical and masticatory myalgia (involving several muscles of the jaw and neck on the same side), and (3) those with a widespread chronic musculoskeletal pain that also involves the masticatory system. This anatomically based categorization system is inadequate, however, and a more logical system would be to have additional categories based on a combination of anatomic features and etiology: (1) myalgia due to direct muscle injury; (2) secondary local and regional myalgia; (3) primary local and regional myalgia; (4) myofascial pain; and (5) widespread chronic muscle pain and fibromyalgia.

Myalgia due to direct muscle injury

Local myalgia can develop as a result of muscle damage resulting in histologically evident changes within the muscle called myositis.[20,21] Such injuries are not common in the masticatory system, but when they do occur they are quite dramatic. Patients typically report strong focal pain and severely limited opening due to secondary trismus.[22]

Secondary local and regional myalgia

Sometimes local and even regional myalgia and trismus will develop in response to a local painful pathologic process such as an acute arthritis affecting the temporomandibular joint (TMJ). In local pathology cases the muscle pain develops unilaterally (on the side of the pathology, assuming it is one-sided). The pain in the muscle tissue is secondary, probably due to local hypoxia from the trismus reaction in these muscles. Also, a secondary myalgia can develop as a direct result of certain medications that activate the extrapyramidal system, such as psychological stimulants and certain types of antidepressants (e.g., serotonin selective reuptake inhibitors [SSRIs]).

Primary local and regional myalgia

When a direct muscle injury explaining the muscle pain cannot be found and the patient does not have another adjacent pathology in the area that would cause secondary muscle guarding effects (e.g., arthritis of the TMJ or internal derangement of the TMJ), then one of the criteria for a primary myalgia is satisfied. Pain in these cases is most likely related to stress and parafunction inducing a localized hypoxia, but eventually sensitization of muscle nociceptors will result. Using the term "myalgia" means that taut bands and active trigger points are not identified in the muscle.

Myofascial pain

If palpation reveals taut bands, trigger points within the taut band, and referred pain sensations upon sustained compression of the trigger point, then the term "myofascial pain" should be used instead of "myalgia." Several authors have offered explanations for the referred-pain phenomena.[23–27] However the more interesting question is, "What are trigger points and how do they develop?" Needle-EMG-based studies have reported that a sustained spontaneous EMG activity can be found within 1–2 mm of hyperirritable or "trigger" points in a muscle but not from control nonpainful sites or from the surface above the muscle.[28] That this activity is influenced (increased) by the sympathetic nervous system was recently demonstrated by using a Valsalva maneuver to induce a transient sympathetic activation. This research suggests that that sympathetic neural outflow increases painful-area motor nerve activity and this may be contributing to a focal contraction (palpable taut band) at the painful trigger point site.

Widespread chronic muscle pain and fibromyalgia

For widespread chronic musculoskeletal pain, if the appropriate criteria are satisfied, then the term "fibromyalgia" is used.[29] A small percentage of the population develops widespread chronic musculoskeletal pain. Based on epidemiologic studies, syndromes of diffuse musculoskeletal pain are

reported to occur in 4–13% of the general population.[30–32] Fibromyalgia (FM) is a specific disorder with published diagnostic criteria and it is less common, with a prevalence of 2% in the community. Widespread diffuse musculoskeletal pain syndromes, in particular FM, often occur in concert with several additional diseases, most notably chronic fatigue syndrome, irritable bowel syndrome, temporomandibular disorders, and headaches. In general, fibromyalgia is treated using multimodal approaches that simultaneously target the biological, psychological, and environmental–social factors that maintain the pain. With regard to the underlying differences between focal–regional myalgia and myofascial pain versus fibromyalgia, there is substantial evidence that fibromyalgia sufferers have central neuronal changes in their pain system. For example, fibromyalgia patients show clear-cut altered sensory processing versus normal subjects. Normals show an increase in their pain threshold with repeated skin stimulation, but this does not occur in fibromyalgia, which suggests a reduced descending inhibitory pain suppression system. Moreover, functional CNS changes can be demonstrated in fibromyalgia by several different imaging techniques. For example, one study reported that fibromyalgia patients have a decreased thalamic and caudate blood flow compared with healthy controls on single-photon-emission computed tomography (SPECT) imaging.[33]

16.1.C Etiologic agents underlying myogenous pain

Of course, the anatomically based classification of masticatory muscle pain described previously does not account for the etiology, so this must be appended, if known, to the diagnostic subgroup. An example of this type of classification would be "local masticatory myalgia secondary to temporomandibular joint osteoarthritis." The most common etiologies for myogenous pain are (1) direct muscle trauma, (2) adverse effects from medications, (3) secondary pathology-induced trismus, (4) parafunctions (both waking and sleeping), and (5) stress-induced hypoperfusion. In addition, while they are not etiologies per se, it is necessary to determine to what extent any secondary neurogenic effects have occurred: (6) peripheral muscle motor nerve and nociceptor sensitization and (7) central pain pathway sensitization. These etiologies and neurogenic adverse effects are discussed in the following subsections.

Direct muscular trauma

The most common traumatic cause of myositis in the jaw system is an inadvertent intramuscular injection of local anesthetic during dental treatment. In these cases, the nature of the injury is influenced by the amount of injected material, the type of anesthetic used, and more important, whether a vasoconstrictor such as epinephrine was included in the anesthetic solution. Several authors have described and documented the effect of an inadvertent anesthetic injection into muscle tissue.[34–37] Other forms of local muscle injury can occur (e.g., neck musculature can be injured during a low-velocity rear-end collision) that produces a regional cervical muscle strain and secondary cervical and masticatory myalgia. Current data suggests that the jaw closing and opening muscles themselves are not stretched or torn during a low-velocity rear-end motor vehicle collision, but they may become involved as a secondary phenomenon after the craniocervical muscles are injured. It has been claimed that actual muscle tearing type damage and tissue inflammation can occur as a result of high levels of sustained clenching and eccentric bruxism-like contraction in some patients, but the evidence does not support this claim. Several researchers have tried to induce this type of muscle pain in volunteers who performed prolonged sustained centric and eccentric exercises of the jaw.[38–41] The data from these experiments do show that some acute pain is inducible during and shortly after the exercise task, and some mild increased tenderness can be demonstrated, but overall the masticatory motor system is actually quite resistant to this form of muscle injury. If a direct muscle trauma is suspected as the etiology, then the traumatic event is usually easily identified in the patient's history. The standard treatment for traumatic focal or regional myalgia is rest, ice, NSAIDs, and then frequent daily active mobilization of the jaw and neck muscles until normality of range movement is maintained.[42] The latter is important because traumatic myositis frequently induces a substantial trismus of the jaw in an attempt to prevent movement. This trimus is a logical and appropriate acute injury response but, if prolonged, it can lead to chronic loss of jaw motion due to contracture development.[43] Most healthy patients manage to overcome these injuries and achieve normal function with the minimal amount of disruption, but poorly treated patients often end up with significant long-term limitations of jaw opening.

Trismus-induced secondary myogenous pain

That the nociceptors inside a joint and even a tooth can induce a secondary motor reaction in the anatomically adjacent muscles has been clearly demonstrated in the literature.[44–46] When a patient presents with one-sided muscle pain in the absence of trauma or a strong stress or parafunction history, the clinician would be wise to carefully examine the TMJ, oral mucosal tissues, and teeth for local disease or dysfunction. In these cases it is logical and appropriate to manage or minimize the local pathology first and then re-

examine the myogenous pain for resolution or persistence. As with injection-induced trismus, in some cases, acute secondary trismus can convert to chronic contracture of the involved muscle.[47]

Medication-induced myalgia

First, if a patient is using psychological stimulant medication or is using an SSRI, then a medication-induced myalgia would be suspected. The various medications that can induce muscle pain are reviewed in Chapter 19 and are not discussed here.

Parafunction

Although most oral parafunctions do not induce myalgia, if the behavior is prolonged, occasionally they can. Parafunction-induced myalgia should be suspected when a patient admits to, or if the clinician observes, repetitive oral habits. Oral parafunctions may be present both during waking and sleeping hours and during specific activities such as chronic gum chewing.[48] Several studies have reported that there is a moderately strong positive association between self-reported clenching and chronic masticatory myofascial pain (MMP).[49–51] Unfortunately, these studies do not specify whether the clenching is occurring during waking or sleeping periods because to do so accurately would require an actual recording of the jaw motor behaviors in question over moderately long periods of time (minimum, 2 weeks). A 2003 study examined various potential contributing factors such as clenching, grinding, head–neck trauma, psychological factors using the Symptom Check List 90 Revised Questionnaire (SCL-90R), and various sociodemographic characteristics for their effect on chronic masticatory myofascial pain.[52] They used a case–control designed study with 83 patients with MMP, selected from the dental clinics of the Jewish General and Montreal General Hospitals, Montreal, Canada, and 100 concurrent controls. Using unconditional logistic regression analysis they found that self-reported clenching or grinding either in association with an elevated anxiety score (OR = 8.48) or an elevated depression score (OR = 8.13) was statistically associated with chronic MMP. They concluded that tooth clenching, trauma, and female gender strongly contribute to the presence of chronic MMP even when other psychological symptoms are similar between subjects. Interestingly, grinding-only behavior, age, household income, and education were not related with chronic MMP. This report of no association between tooth grinding and chronic muscle pain is in conflict with other studies. For example, one study performed a questionnaire-based epidemiologic cross-sectional study and another used a clinical-based case–control design.[53,54] These two studies found a positive relationship between self-reported nocturnal tooth grinding and self-reported jaw pain. This conflict will require additional data to resolve.

Stress-related muscle hypoperfusion

Stress-associated myalgia should be suspected if a patient reports a prolonged increase in their environmental (job or personal) stress levels. With regard to stress, psychological factors have been associated with chronic facial and jaw pain.[55] Unfortunately we cannot be sure if the chronic pain is influencing the psychologic factors or visa versa. Chronic muscle pain is known to be highly prevalent and induces daily-life disability in humans.[56,57] Although significant effort has been devoted to determining its pathophysiology, the exact mechanisms have not been firmly established. In recent years, localized intramuscular hemodynamic disturbance has been recognized as one of the possible mechanisms that cause or sustain this pain condition.[58] Several studies evaluated intramuscular hemodynamics using near infrared (NIR) spectroscopy to understand muscle pain mechanisms and discovered some interesting findings. For example, dynamic muscle blood flow in fibromyalgia has been studied by numerous researchers using different methods to monitor blood flow.[59–61] These studies have found there is a significantly reduced intramuscular perfusion in the focal myalgia subjects. These differences in vasodilative response in focal myalgia cases might be related to desensitization of beta-adrenergic receptors, which occurs with long-term exposure to the stress-associated neurotransmitter epinephrine. Overall, these studies suggest there are demonstrable changes in intramuscular perfusion of chronic regional myalgia involving the masseter and trapezius muscles. This hypoperfusion occurs in these subjects both during and after muscle activity. One study reported that intramuscular blood flow increases provoked by cold pressor stimulation, which increases systemic sympathetic nervous activity and produces a vasodilation reaction, was significantly diminished in painful muscles compared with healthy individuals.[62] This hemodynamic response to cold pressor stimulation in chronic localized muscle pain is very similar to the hemodynamic response observed in normal subjects who are intravenously administrated a nonselective beta-adrenergic antagonist.[63] In all subtypes of beta-adrenergic receptor (βAR), the beta-2-adrenergic receptor (β_2AR) is known to be abundantly localized on smooth muscle cells in skeletal muscles.[64] This receptor induces vasodilation when the sympathetic system is activated, and the preceding findings support the notion that β_2AR activity is diminished in chronic muscle pain patients. Additionally, research has provided the evidence that β_2AR is easily desensitized or

downregulated by chronic βAR agonist exposure.[65,66] For these reasons, we have speculated that β_2AR abnormality is associated with chronic muscle pain pathophysiology. In a prior study on β_2AR function on mononuclear cells it was demonstrated in fibromyalgia patients that a β_2AR abnormality is associated with the chronic fibromyalgia state. However, it is still unknown whether this association is also present in the localized myalgia state.

Peripheral muscle nociceptor sensitization

Considering what is now known about muscle pain mechanisms, specifically about jaw muscle activity, intramuscular blood flow, and the effect of prolonged stress on masticatory muscle blood flow, the following hypothesis has been put forth: (1) prolonged stress causes local intramuscular hypoperfusion, which seems to selectively target muscles with higher proportions of type 1 (slow twitch) fibers that are involved in postural maintenance; (2) this focal hypoperfusion induces a local partial ischemic condition and endogenous chemicals accumulate in the muscle, causing local muscle pain; (3) once the pain develops to a sufficient level in the muscle, this causes reactive neurogenic changes; (4) the neurogenic changes include focal hyperactivity of motor nerves, and sensitization of muscle nociceptors adjacent to the motor end plates. These neurogenic changes induce taut bands and painful foci in the muscle, called trigger points. If multiple areas of the muscle are affected, then whole muscle splinting or trismus can result. The central neurogenic effects of this process are described in the next subsection; there is some evidence to suggest that some patients may have a genetic susceptibility to this central sensitization process. Evidence for this theory comes from several sources. First, one study concluded that the electrical activity characteristics of trigger points are similar to those described from needle EMG recording in and around motor end plates.[67] The authors speculated that the spontaneous activity recorded from a trigger point is probably related to excessive release of acetylcholine (ACh) at the end plate, suggesting a hyperactive motor nerve. They also speculated that these end plates were the source of trigger-point pain because the sensory nerve fibers that surrounded these end plates were sensitized and were spontaneously active or active during stressful periods of the day and in turn caused local pain and more focal motor nerve activity in the end plate. Focal hypoxia is the most likely mechanism that causes pain and muscle nociceptor sensitization. The basis of this focal hypoxia is that the release of acetylcholine produces a muscle contraction, which among other things causes a compression of local vasculature in the area and produces reduction in the local supply of oxygen. This impaired circulation, combined with the increased metabolic demands generated by contracted muscles, results in a rapid depletion of local adenosine triphosphate (ATP). One study showed that ATP directly inhibits ACh release, so depletion of ATP increases ACh release.[68] In the muscle cell, ATP powers the calcium pump, which returns calcium to the sarcoplasmic reticulum. Hence, loss of ATP also impairs the reuptake of calcium, which increases contractile activity.[69] Finally, the ATP energy crisis causes a local release of a variety of chemicals, peptides, and cytokines (i.e., bradykinins, cytokines, serotonin, histamine, potassium, prostaglandins, leukotrienes, somatostatin, and substance P) that have the potential to activate and sensitize nociceptive nerves in the region and more centrally.[70]

Central sensitization

When a patient exhibits widespread chronic myalgia and or fibromyalgia, the patient's pain is usually so long-standing by the time fibromyalgia has developed that the original etiology that triggered the cascade of events leading to this disorder is not discoverable. The one scientific fact that everyone agrees upon is that central sensitization and aberrant central nervous system processing of pain is the predominant issue and a major perpetuating factor in fibromyalgia.[71–73] This means that patients have developed an increased response to painful stimuli (hyperalgesia) and experience pain from normally non-noxious stimuli (allodynia). Both hyperalgesia and allodynia reflect an enhanced CNS processing of painful stimuli that is characteristic of central sensitization.[74] In fact, fibromyalgia patients show substantially elevated levels of substance P in their cerebral spinal fluid, which would enhance the likelihood of sensitization of second-order spinal neurons.[75,76] Muscle nociceptor sensitization in fibromyalgia[77,78] is known to be an important contributor to pain pathogenesis.[79] How nociceptors become altered or "sensitized" has been presented in several recent reviews.[80–82] One theory suggests that dysfunction in serotonin and norepinephrine in these pain-inhibitory pathways may contribute to the central sensitization and hyperexcitability of the spinal and supraspinal pain transmitting pathways and is manifest as persistent pain associated with fibromyalgia and some other chronic pain conditions.[83–88] Another theory suggests that chronic muscle pain patients have an associated abnormal sympathetic system function.[89,90]

How do you determine etiology?

Etiologies often prove far more difficult to discover than "where the pain is located and what physical characteristics are revealed by palpation." To a large degree the information gathered during the medical interview is the process by

which an etiologic discovery is made. Of course, establishing the chief complaint is the starting point and, after identifying this, the history of the present illness must be established. These details include (1) location, (2) severity (use a 0–10 score here), (3) duration, and most important (4) causation (if known). Under duration, make sure you include the course of the symptom(s) over a 24-hour period and the course since the symptoms first developed. Under causation (whether or not an exact cause is known), it is important to detail any event or situation which now precipitates or aggravates the symptoms. Also include all alleviating factors. If trauma is a cause, establish the details of the injury or iatrogenic trauma. Next the patient's past medical history must be reviewed (current diagnosed diseases; general health; last physical examination; the exact types and daily dosage of any medications; all prior, recent, or ongoing treatments being rendered, including success, failure, compliance, and adverse reactions of these prior treatments; and all recent surgical interventions and hospitalizations). Added to this information, a thorough review-of-systems (ROS) questionnaire that includes at least nine systems should be filled out by the patient and reviewed during the interview. Next, probe for any family history of similar problems in the patient's sibling(s) or parents, and ask about any ongoing serious medical problems in the family. At the end of the medical questions, ask several questions about the patient's current job and home responsibilities, how many sick days, if any, are directly related to his or her problem, and how it interferes with desired social activities. Ask about recent change in stress, anxiety, or depression levels in the patient's life and about the presence of a counselor, therapist, or confidant, if any. Be sure to ask about the patient's awareness of any waking or sleeping clenching, night grinding (bruxism), facial tension, gum chewing, or abnormal jaw–tongue–face muscle posture habit. Observation of the patient for repetitive orofacial habits during the interview is an important feature of this aspect of the social history. Finally, as a part of the social history, ask about any disability claims that are pending or planned and establish if any litigation related to the patient's complaints is pending or planned. There is no guarantee that the information gathered during a medical interview will pinpoint probable etiologies, but it is certain that a poor or incomplete history will not help.

16.2 Treatment of masticatory myogenous pain

This section of the chapter covers self-applied treatment, office-based treatment, pharmacologic treatment, and behavioral treatment. Because it is a relatively new therapy, we report on botulinum toxin injections for myofascial pain. Finally, where no substantive scientific evidence is available, current best clinical practice as understood by the author is described and identified clearly as clinical opinion. The most respected form of scientific evidence available for assessing a specific treatment effect is a randomized, blinded clinical trial (RBCT). Even better is when there are several RBCTs assessing the same method; the conclusions that can be drawn across several RBCT studies are usually described in a systematic review of the literature. Typically the reviews considered most valuable are those which qualify for inclusion in the Cochrane Library database, an international collaboration that promotes evidence-based reviews of the literature (http://www.cochrane.org). Where they were available we report on Cochrane review results. Here we have endeavored to find those review articles that specifically deal with local or regional myogenous pain in the craniocervical or temporomandibular region. However, if such information was not available, we looked at low back pain treatment outcome reviews hoping to generalize the data on this regional musculoskeletal disorder to masticatory myogenous pain. Finally, we examined systematic reviews on the treatment of fibromyalgia or, in some cases, chronic pain disorders if no systematic myogenous pain review was available. The hope is that, although such collecting together of disparate information has its disadvantages, the advantages and overall conclusions will outweigh the limitations of the data.

16.2.A Self-directed treatment

Whether the masticatory musculoskeletal pain is localized, regional, or generalized, the first line of treatment is almost always self-treatment; this includes education about the specific masticatory muscle disorder the patient is experiencing and an individualized self-treatment program. This self-treatment program generally includes four elements: (1) identify and avoid activities that are potentially harmful to the jaw system; (2) increase local blood flow in the muscles which are painful; (3) stretch stiff and painful muscles to try to decrease postural tone in the sore muscle; and (4) when the patient is able, encourage the patient to start a daily nonimpact exercise program.[91] Each of these four elements will be discussed in this section. With regard to education about the disease process of chronic musculoskeletal pain, there are severeal patient-driven self-help groups which host helpful websites and meetings. For example, the National Fibromyalgia Association (NFA) is a patient-run nonprofit group and it recommends strongly that fibromyalgia sufferers make many lifestyle accommodations to manage their pain. The NFA endorses vitamin supplements, relaxation–meditation techniques (e.g., yoga, relaxation exercises, breathing techniques, aromatherapy),

daily exercise (e.g., gentle aerobic exercise and stretching), avoidance of stimulants (caffeine, sugar, and alcohol), participation in a local fibromyalgia support group, and thermal therapy for pain relief. Of course, the extent to which a patient incorporates these self-directed treatments into daily life will largely depend on the training received and the severity of the problem. Fortunately, patients with focal and even regional myalgia or myofascial pain will have far less disability and life interference.[92]

Avoidance therapy

This treatment approach also has four elements; it is one of the treatment methods that has little or no hard scientific evidence and is largely based on common sense. For musculoskeletal pain, common sense dictates that, if it hurts, avoid the behavior that causes the pain. In the case of jaw pain, the four elements of avoidance behaviors are as follows:

- *Clenching avoidance* Clenching avoidance is best done by instructing the patient to hourly find a relaxed position of the jaw, tongue, and lips. The most commonly used instructions to achieve this position are to say the letter N and then hold this position for as long as possible. Additionally patients are told that they should bring their teeth together only when swallowing, eating, or talking and they should practice recognizing when they are clenching their teeth and be more vigilant during these times (such as when they are undergoing emotional stress). Patients are also known to clench when concentrating on a specific task such as driving, watching television, working on the computer, or exercising.
- *Poor head and neck posture avoidance* The common sense rationale underlying this treatment is that reducing the abnormal strain that bad head and neck posture has on muscles and joints of the spine will reduce upper cervical muscle pain and possibly even jaw muscle pain. The best approach to avoiding bad posture is to teach the patient what is a good posture. This is done by showing the the patient how to keep their head up, with their ears aligned with their shoulders and also to keep their shoulders back so that the head is centered, upright, and relaxed. One commonly used self-treatment exercise to try to achieve good head and neck posture is to ask the patient to sit in a chair and pull their shoulders back at the same time as turning their hands outward. Both the "N"-position exercise and the head-and-neck postural position exercises are performed for a count of 10 (or four slow breaths) and then repeated 5–6 times every 2 hours or at least 6 times a day.
- *Jaw joint clicking avoidance* Once a temporomandibular disk is out of place it cannot be put back; avoidance of any motion or food that induces clicking is presumed to reduce wear and tear on the disk. Fortunately, the jaw joint can hinge open two fingers' width (25 mm) without sliding forward, so teaching a patient how to open without clicking is not that hard. First you instruct the patient to put their hands over their jaw joints to feel whether the joint is sliding forward or rotating. Next you insist that the patient only take small food bites and eat only soft foods. For those who have a one-sided click it is also often possible to eat even medium- hard food in one area of the mouth (often on the same side as the click) without inducing a jaw click. To monitor how successful these steps are, the patient should keep track of how many times a day the joint clicks.
- *Other habit avoidance* This involves having the patient consciously identify and avoid any repetitive habits that might strain or load the jaw muscles and joints, such as wide-open yawning, nail biting, cheek or lip chewing, pen or pencil chewing, gum chewing. ice cube chewing, or even repeatedly snapping the neck vertebrae or opening the mouth to "equalize middle ear pressure."

Increased intramuscular blood flow therapy

With regard to self-applied methods of stimulating blood flow in the jaw system, most patients report benefit from either heat or ice packs applied to the painful site. In addition, they will often say they feel better after a hot bath or shower. Many find that a hot bath or shower can be more effective than an analgesic medication for headache, body pain, and stiffness. The local application of heat or ice will both increase circulation and relax muscles in the region. Cold applications rather than heat are preferred by some patients. Although not specific to the masticatory system, a review of the scientific literature on thermal therapy for chronic rheumatic diseases involved 15 published papers which tested thermal and spa therapy on a mixed group of rheumatic diseases.[93] The results of this review suggested that this form of treatment produces a consistent positive result. Of course caution must be exercised in those patients who are hypotensive and heat intolerant. The following are specific methods useful to increase blood flow in a patient with jaw and neck muscle pain:

- *Thermal (hot bath or shower) therapy* Hot bath or shower therapy is a practical and inexpensive treatment method that increases intramuscular blood flow, reduces muscle tension, and generally relieves muscle pain for a period of time. Like avoidance therapy, no study has systematically examined the long-term benefits of 3 weeks of daily 20-minute hot bath soaking for masticatory muscle pain, but this treatment recommendation makes sense. Common sense dictates that bath therapy is a

better vasodilator induction method than showers, but for obese patients or patients on hypertension medication, a hot bath increases the risk of causing a lowered blood pressure and precipitating syncope. This therapy should not be initiated in the hypotensive, syncope-prone patient. In general, the hot bath water should be warm enough that the patient does not feel substantial burning when first getting in. This would be about 90°F, depending on the patient's preference. After entering the tub, add more warm water and let the temperature rise until it is between 103 and 104°F. Duration of the soak, once it reaches temperature, should be 15–20 minutes. Repeat this three times per week for 3 weeks, while conducting the stretching and strict avoidance therapy components of the self-treatment protocol. Alcohol consumption and any opioid medications or any drug that alters blood pressure substantially taken before or during hot bath use should be totally avoided. Individuals suffering cardiac medical conditions such as heart disease, blood pressure and circulatory system problems, or diabetes should check with a physician before using the hot bath; pregnant women can use the hot bath at temperatures below 100°F. In addition to syncope, hyperthermia (heat stroke) is a dangerous condition brought about by excessive heat. It especially affects the very young, the elderly, individuals under the influence of alcohol or drugs, and those who are on certain medications. The symptoms of hyperthermia are sweating, dizziness, nausea, faintness, convulsions, increased pulse rate, and shallow breathing—and, in the extreme, unconsciousness.

- *Local hot pack therapy* This involves applying a hot pack to the painful site for 20 minutes up to 3 times a day. The heat will increase circulation and remove pain-inducing metabolites from the muscle and fascia sites locally. The easiest method is to have the patient purchase an electric heating pad. Care must be taken not to leave it on the site for a long time since surface burns can result. If possible have the patient buy a "moist heat" electric heating pad because it is more effective than dry heat and less likely to produce a skin burn. Alternatively, patients can purchase a medical-grade "hydrocollator" (and a large coffee maker at a discount store to heat the water in). A hydrocollator bag is a canvas bag filled with very small heat-retaining rocks; it will hold heat for at least 15–20 minutes. The canvas bag is removed from the hot water, wrapped in cloth, and applied to the pain site. Hydrocollator bags can be purchased at a medical supply store or pharmacy (special order). A wet towel. as well as microwavable commercial products, can be heated in a microwave. Wet the towel, remove excess water, place it in a plastic bag, and heat on high for 5 minutes. The patient must be instructed how to carefully remove the hot towel from the plastic bag with tongs, cover it with an additional dry towel to prevent skin burns, and place around back of neck and sides of face. With all forms of heat, leave it on the painful muscle site for 20 minutes and do this 2–3 times per day.
- *Ice pack therapy* There are many gel packs that can be purchased at a pharmacy. These packs are kept in a freezer and then wrapped in a towel before applying to the pain area. Some patients do better with heat and some with ice. This is determined by trial and error and to some degree patient preference. It is somewhat paradoxical that ice and heat are used for the same purpose (i.e., to increase local blood flow in the painful muscle) but, like heat, ice packs applied to a local area of the body will also increase regional circulation. Although, obviously, the skin under the ice is cooled, the tissue beneath the cooled area has a reactive vasodilation to attempt to warm the site back to body temperature. In either case, increased circulation results. One distinct advantage of ice is that it will decrease nerve activity in the area being cooled so, if the pain is more of a nerve irritation and is on the surface, then ice packs are preferred. A 2004 study examined whether cold ("cryotherapy") improves outcome after a soft-tissue injury.[94] The authors examined the literature for controlled studies that compared cryotherapy with placebo or other therapies. They included 22 studies in the analysis and the types of injuries varied widely (e.g., acute or surgical). The data was gathered only for a short time (1 week after the injury), but the authors concluded that ice submersion with simultaneous exercises was significantly more effective than heat. Ice application was equal to combination therapies such as ice and low-frequency or high-frequency electric stimulation on swelling, pain, and range of motion. Ice and compression seemed to be significantly more effective than ice alone in terms of decreasing pain. The authors concluded that cryotherapy seems to be effective in decreasing pain after actue injury. No comparable data exists for treatment of chronic pain with ice.

Stretch therapy

The third and most important component of a self-applied treatment program for masticatory muscle pain is stretch therapy. It is important to note that stretch therapy should not be considered just one additional facet of exercise therapy, as it often is. The differences are that stretch therapy must be done multiple times a day to be effective, and its purpose is not to strengthen or condition muscles but to suppress muscle tension levels. Exercise programs are performed for 20–60 minutes once a day at most; however, if this is how often stretching is performed, it will be unsuccessful. Common sense and clinical experience suggest

stretch therapy is critical to treatment of spontaneous muscle pain disorders (myofascial and fibromyalgia) and especially those that exhibit taut band and stiffness. Stretch therapy is certainly worthy of review separate from traditional exercise therapy, such as nonimpact aerobics or water-exercise therapy. The two essential elements of a stretch program are as follows:

- *Jaw open stretch* This exercise is done by placing the tip of the tongue up against roof of mouth (in the "N" position). Stretch the jaw open in a straight line without dropping the tongue. If the jaw is tight, the patient will feel the muscles being stretched; they should hold this open position for about 5–6 seconds and repeat the stretch about 5–6 times every 2 hours. For some patients it is necessary to add a slight degree of pressure with their index finger to the lower teeth to assist them with the "N"-stretch exercises.
- *Chin-to-chest stretch* Standing or sitting in correct postural position, look straight forward and perform axial extension (chin tuck). Now slowly tilt your head to your chest. Alternative versions of this stretching exercise involve a slight turning of the head to the side during the chin-to-chest stretch. This allows slightly different and more lateral neck muscles to be stretched. As with the "N"-stretch it is usually helpful to add a slight pressure to the head during the stretch by placing a hand on top of the head during the stretch.

Exercise therapy

This is the one treatment which is endorsed by all three of the medical societies reviewed in this chapter: the International Association for the Study of Pain (IASP), the American College of Rheumatology (ACR), and the National Fibromyalgia Association (NFA). There have been two systematic reviews available which offer a consistent point of view on the data. On is a Cochrane Library review that examined 16 clinical trials, which included a total of 724 participants.[95] Of these 16 studies, 7 were judged to be of high scientific quality: 4 on aerobic training; 1 on a mixture of aerobic, strength, and flexibility training; 1 on strength training; and 2 on exercise training as part of a composite treatment. The other review was not a Cochrane Library review but did cover 17 clinical trials which examined the effect of exercise treatment in a fibromyalgia population.[96] Both of the reviews endorsed aerobic exercise as a beneficial evidence-based treatment for fibromyalgia. Both suggested that supervised low-intensity aerobics has sufficient, although weak, evidence to recommend it. One problem with all self-applied treatment methods is patient compliance, and long-term adherence to exercise programs after completion of a study has been consistently low in the studies of fibromyalgia. Overall the use of exercise as a therapy for fibromyalgia received support in the reviews, but the effects of aerobic training on pain, fatigue, and sleep were weak and inconsistent. Only three of the studies examined long-term effects of the exercise intervention. Improvements in self-reported physical function and self-efficacy for function were seen at 1-year follow-up in one study,[97] but another study found that, 4.5 years after the exercise intervention, improvements were not retained in the exercise group, although most were no longer exercising.[98] Lastly, an uncontrolled 3- and 6-month follow-up of participants in a program that included aerobic pool exercise and education found that participants reported significant improvements in the 6-minute walk test, fatigue, and self-efficacy.[99]

16.2.B Office-based physical medicine treatment

There are many physical medicine methods that are recommended for treatment of local and regional myalgia or myofascial pain as well as fibromyalgia. Most of the RBCT-type reviews of this form of therapy show that at best they are equivalent to placebo therapy. One view of this is to assume they are of no value, but another view is to assume that placebo therapies provided in the context of a clinical experiement are active behavioral therapies and both have value. A common treatment used for clinically identified myofascial trigger points is to inject them with a small amount of local anesthetic and even botulinum toxin. This therapeutic approach is not covered in this chapter, however, as it is discussed in detail in the chapter on needling and injection-based therapies (Chapter 11). All other forms of office-based therapies for myofascial pain, including manual physical therapy procedures such as therapeutic massage, acupressure, and osteopathic or chiropractic mobilization and manipulation are discussed. With self-directed therapies, the extent to which a patient pursues these treatments will depend on the severity of the problem. A meta-analysis examined both pharmacological (33 studies) and nonpharmacological (16 studies) treatment studies of fibromyalgia completed between 1966 and 1996.[100] The review of pharmacological treatments is discussed in Section 16.2.D, which deals with medications. The nonpharmacological therapies reviewed included various methods: exercise, education, cognitive–behavioral therapy, electroacupuncture, acupuncture, and hypnotherapy; the review did not individually analyzed these methods but rather considered them as a group. The authors concluded from their review that both pharmacological and nonpharmacological treatments were associated with improvement in physical status, fibromyalgia symptoms, and psychological status but only nonpharmacological treatment improved daily functioning. Nonpharmacological treatments were found to be superior to pharmacological treatments on fibromyalgia symptoms.

A different systematic review of randomized, controlled trials of several nonpharmacological treatments for fibromyalgia completed between 1980 and 2000 examined 25 studies that included exercise therapy, educational intervention, relaxation therapy, cognitive–behavioral therapy, acupuncture, and forms of hydrotherapy.[101] This review did not lump these methods together and reported individually on aerobic exercise (9 studies), education (4 studies), and relaxation (4 studies). The authors concluded that no strong evidence existed supporting any single intervention; however, moderately strong evidence existed for aerobic exercise but, since the sample sizes were small, they were compelled to say that data is still inconclusive due to the methodological limitations of most of the studies.

16.2.C Behavioral treatment for chronic muscle pain

Behavioral treatments include making sure the patient has a good understanding of the disorder and engages in daily physical exercise and relaxation. The self-management program is critical to make sure the patient is not having increasing feelings of anxiety and helplessness which aggravate the disease.[102] Many patients can be helped by encouragement, reassurance, and regular aerobic exercise. Patients with fibromyalgia tend to remain symptomatic at unchanged levels for many years. Most, if not all, should be encouraged to continue working and to maintain regular social activities despite their symptoms. The management of fibromyalgia patients involves a complex interplay between pharmacological management of pain and associated symptoms and the use of nonpharmacological modalities. Regular follow-up and modification of the initial management strategy is usually required, depending upon the response pattern. Fibromyalgia patients typically have a number of complaints beyond pain and fatigue, which is cited as a significant cause of morbidity for the vast majority of fibromyalgia patients. The potential causes of fatigue in these patients are manifold, but recent evidence suggests that sleep disturbances may play a particularly important role. Exercise interventions for these patients vary depending on the extent and severity of symptoms as well as factors that affect patient motivation and adherence. Secondary psychosocial effects are pervasive and include depression, reduced confidence in the ability to manage the disease, and disruption of relationships with friends and family. Unfortunately, depression and reduced self-confidence make it particularly difficult to adhere to an exercise program.

There are many behavioral therapies suggested for treatment of local and regional myalgia and myofascial pain as well as fibromyalgia. These treatments include various forms of therapy with a psychologist, the most common being cognitive behavioral therapy. Sometimes these methods are a component of a combined multidisciplinary program and sometimes they are stand-alone treatments. A systematic review has been published which focused only on mind–body therapies such as autogenic training, relaxation exercises, meditation, cognitive–behavioral training, hypnosis, guided imagery, biofeedback, or education for fibromyalgia.[103] The review included 13 randomized or quasi-randomized controlled trials conducted between 1966 and 1999 that were evaluated using a best-evidence synthesis method. The review concluded that there was strong evidence that mind–body therapies were more helpful at teaching the patient to cope effectively with their disease than a waiting list or a treatment-as-usual control condition. Specifically, improvements in coping training or "self-efficacy" did not correspond to improvements in other clinical measures such as pain reduction or improvement in function. Most important, the review determined that strong evidence existed that exercise was more effective than mind–body therapies for short-term improvement in pain intensity or tender-point pain threshold and physical function.[104] Also, patients with fibromyalgia who were also severely depressed were not responsive to mind–body therapies, and those that used cognitive restructuring and coping components were not significantly better than education or attention controls[105]; and neither method produced a substantial improvement in pain intensity.[106] More recent studies have generally agreed with these reviews. Specifically, in a 2002 study, 145 patients with fibromyalgia were randomized to either standard medical care (pharmacological treatment and advice to engage in aerobic fitness exercises) or standard medical treatment and a six-visit program of cognitive behavioral therapy (CBT).[107] Significantly more (25%) of the 62 patients who completed the CBT protocol scored higher on the physical component summary score of the SF-36 compared with the control group (12% of 60 completers). However, there were no significant differences between the control and CBT groups on pain scores using the McGill Pain Questionnaire. This study concluded that targeted, brief, group CBT, in conjunction with standard medical care, might improve physical function in some patients with fibromyalgia. In 2005, a coping skills training (CST) intervention for adolescents with fibromyalgia was developed to include developmentally appropriate explanation and training guidelines as well as a parent training component.[108] In an 8-week study 30 adolescents with fibromyalgia were randomly assigned to either CST or a self-monitoring condition in which patients monitored daily symptoms without instruction. After 8 weeks, patients were crossed over into the opposite treatment arm for an additional 8 weeks. At the end of 8 and 16 weeks, there were no significant differences in function disability or depressive

symptoms between the CST and self-monitoring groups. However, the CST group had a higher increase in pain-coping skills.

The question of whether a combination "multidisciplinary" treatment approach involving behavioral, physical medicine, and pharmacologic therapy is better than an individual but knowledgeable pain practitioner providing care has been studied. One randomized controlled study examined this issue and compared (1) the effect of outpatient multidisciplinary pain treatment (MPT group) versus (2) treatment by a knowledgeable general medical practitioner after initial consultation by a pain specialist (GP group) versus (3) a 6-month waiting list group (WL group).[109] The participants were 189 patients with chronic nonmalignant pain and assessments were performed at initial visit and at 3 and 6 months after treatment. At 6 months, the patients in the MPT group ($N = 63$) reported a significant reduction in pain intensity and an improvement in psychological well-being, quality of sleep, and physical functioning compared with baseline measures. The WL group ($N = 63$) had a statistically significant deterioration in most of these measures. The GP group showed ($n = 63$) a reduction in the use of short-acting opioids, but other measures of pain were not significantly changed. The interesting finding was that multidisciplinary treatment methods appear to be more effective than treatment by a general medical practitioner even though a pain diagnosis and management plan by a specialist had been established. These data are in contrast to a study which examined the 6-month results of an outpatient multidisciplinary rehabilitation program (MRP group; $n= 51$) versus the usual care (UC group; $n = 157$) by independent physicians.[110] The subjects in the study were a population of patients with chronic low back pain. Outcome was assessed from patients' responses in self-report questionnaires at baseline and after an interval of 6 months. The MRP group patients received 4 hours of treatment (exercise, cognitive behavioral treatment, muscle relaxation training, and in-office physical therapy and education) per day, 3 days per week for 20 days. Results showed that patients of the MRP group improved more in the physical and mental health domains of the SF-36 questionnaire, had fewer days off work, and reported higher overall success (54% vs. 24%) than patients in the UC group. However, the pain intensity, the pain-related interference with function, and the depression scores did not differ significantly between both groups.

16.2.D Pharmacologically based treatment

The medications often used for fibromyalgia are listed in Table 16.2. The medication most commonly used in this group of patients is a tricyclic antidepressant agent (e.g., nortriptyline or amitriptyline).[111] These medications are versatile and are effective in treating multiple symptoms associated with fibromyalgia; however, tolerability remains a problem and this is more so in the elderly. Conversely, SSRIs show improved tolerability and have demonstrated much clearer activity against depressed mood in the context of fibromyalgia compared with TCAs. However, their activity against other symptoms appears less robust. Sedative–hypnotic compounds, such as zolpidem (Ambian), appear to be useful adjuncts for the treatment of disturbed sleep, and the use of tramadol to treat fibromyalgia pain is supported by three trials. NSAIDs, on the other hand, have not been shown to be particularly effective in fibromyalgia.

Table 16.2 Medications for myofascial pain and fibromyalgia

Medication class	Comments about effect
1 TCA (e.g., nortriptyline)	Moderately to mildly helpful for pain, but high side effects
2 SSRI (e.g., citalopram)	Lower side effects than TCAs; more for depression than for pain
3 SNRI (duloxetine)	Moderately helpful for FMS-related pain (shown by several studies)
4 Low potency opioid (tramadol)	Moderately helpful for FMS-related pain (shown by several studies)
5 NSAID (e.g., ibuprofen)	Not particularly effective in FMS

FMS, fibromyalgia syndrome; NSAID, nonsteroidal anti-inflammatory drug; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, serotonin selective reuptake inhibitor; TCA, tricyclic antidepressant.

The previously cited meta-analysis by Rossy and colleagues (ref. 100) reviewed both pharmacological and nonpharmacological treatments for fibromyalgia and reported on multiple agents, including tricyclic antidepressants, two nutritional supplements, a benzodiazepine, two SSRIs, two NSAIDs, a corticosteroid, an insomnia drug, topical capsaicin, oral lidocaine, and a combination muscle relaxant agent. The authors, as they did with the nonpharmacological therapies, lumped all the pharmacological therapies together and concluded that they were not better than nonpharmacological therapy and there were not enough high-quality studies to recommend pharmacological therapy as evidence-supported therapy for fibromyalgia. A more recent review also examined multiple studies testing medications for regional musculoskeletal pain and concluded that the medication studies are generally of lower quality and had several methodological problems, so no specific recommendations could be made.[112] In spite of these two relatively negative overview reviews of pharmacological therapy, this form of therapy is worthy of further review and this chapter

individually examines the most recent studies of specific drugs that are used to help control chronic muscle pain symptoms.

Topical medications for musculoskeletal pain

Description, mechanism of action, and primary indications

See Chapter 5 for details on topical medications used for chronic pain.

Starting dose

See Chapter 5.

Metabolism, side effects, and adverse drug reactions

See Chapter 5

Efficacy for fibromyalgia

As was discussed in Chapter 5 there are multiple topical medications that are used for chronic pain. These include anesthetics, NSAIDs, rubefacient combined with salicylates, and multiple others. The best data supporting the use of topical agents is that, when these agents are used for cutaneous pain conditions such as postherpetic neuralgia, they have lower efficacy (if any) for myofascial pain of the orofacial region. There have been two reviews published in the Cochrane Library database which examined topical medications for the treatment either of chronic musculoskeletal pain or of acute and chronic pain of all types. The topical medications examined contained either a nonsteroidal anti-inflammatory agent[113] or a rubefacient combined with salicyclate.[114] Unfortunately, the disease groups covered in these two reviews are not limited to chronic myogenous pain, but are a mixed group of acute and chronic musculoskeletal and arthritic pain patients. Nevertheless, these two reviews concluded that topically applied NSAIDs and rubefacients containing salicylates may be efficacious in the treatment of acute pain but for chronic musculoskeletal and arthritic pain the results varied from moderate to poor efficacy. The good news is that these two topical agents are relatively safe and can be used with low risk for 2 weeks to see if the patient has benefit or not. Certainly for the pharmacosensitive patients with chronic musculoskeletal conditions they can be used for a short period. The same group that conducted these two reviews also performed a review on topical capsaicin for chronic musculoskeletal and/or neuropathic pain and concluded that it was not shown to be an effective stand-alone topical treatment.[115]

Tricyclic antidepressants

Description, mechanism of action, and primary indications

As discussed in Chapter 8, the use of antidepressant medications in the tricyclic–tetracyclic category for musculoskeletal pain and for skeletal muscle relaxants is only partially supported by results from controlled clinical trials. There was one review on the use of various antidepressants for fibromyalgia and it concluded there was enough evidence to support the use of tricyclic antidepressants in fibromyalgia.[116]

Starting dose

When used, the tricyclic antidepressants are mostly used in low dosage to improve sleep and to enhance the effects of analgesics. The largest experience is available for amitriptyline in low doses (10–25 mg) given at night to improve sleep.

Metabolism, side effects, and adverse drug reactions

The major disadvantage of the tricyclics is that they strongly interact with adrenergic, cholinergic, and histaminergic receptors and therefore have many side effects.

Efficacy for fibromyalgia

An early meta-analysis[117] assessed nine placebo-controlled trials of the cyclic drugs that inhibit the reuptake of both serotonin and norepinephrine, including the tricyclics amitriptyline,[118–121] dothiepin (which is structurally similar to amitriptyline and doxepin),[122] cyclobenzaprine[123–125] (which possesses structural and pharmacological properties of other tricyclics),[126] and clomipramine and the tetracyclic maprotiline.[127] Seven outcome measures were assessed, including: the patients' self-ratings of pain, stiffness, fatigue, and sleep; the patient's and physician's global assessment of improvement; and tender points. The largest effect was found for measures of sleep quality, with more modest changes in tender-point measures and stiffness. Thus, the most consistent improvement could be attributed to the sedative properties of these medications. The results of another meta-analysis of randomized, placebo-controlled studies of cyclobenzaprine was consistent with the meta-analysis by Arnold and colleagues.[128] Cyclobenzaprine treatment resulted in moderate improvement in sleep, modest improvement in pain, and no improvement in fatigue or tender points.[129] Like the previously cited meta-analysis by O'Malley et al. in 2000, this meta-analysis also described the overall effect of the cyclic drugs on most symptoms of fibromyalgia as modest. This

review suggested that if larger doses were used, the effect might be better.

Selective serotonin reuptake inhibitors

Description, mechanism of action, and primary indications

When the SSRIs came to be used for depression, they more or less replaced the cyclic medications because they were found to be effective for depression without the many side effects that were seen with cyclic antidepressants. For a more detailed discussion of SSRIs we refer the reader to Chapter 8.

Starting dose

Not applicable.

Metabolism, side effects, and adverse drug reactions

The details on the SSRIs are covered in Chapter 8.

Efficacy for fibromyalgia

It is safe to say that the SSRIs have not been found helpful for the painful symptoms associated with chronic muscle pain.[130] Overall, trials of SSRIs in fibromyalgia have shown mixed results, suggesting that medications with selective serotonin effects are less consistent than those with dual effects on norepinephrine and serotonin in the relief of pain associated with fibromyalgia. Citalopram, which has the highest selectivity for the serotonin reuptake transporters among the SSRIs, was not effective for the treatment of fibromyalgia in two small controlled studies.[131,132]

Serotonin and norepinephrine reuptake inhibitors (SNRIs)

Description, mechanism of action, and primary indications

A newer class of drugs, the serotonin and norepinephrine reuptake inhibitors (SNRIs), has emerged that is attracting interest for the treatment of chronic muscle pain. The rationale for using these drugs in fibromyalgia is that increasing the activity of serotonin and norepinephrine may correct a functional deficit of serotonin and norepinephrine neurotransmission in the descending inhibitory pain pathways and, therefore, help reduce pain. For a more detailed discussion of these medications we refer the reader to Chapter 8.

Starting dose

Duloxetine 60 mg 1–2 times per day is claimed to be moderately effective in controlling fibromyalgia pain whether or not the patient is depressed.[133]

Metabolism, side effects, and adverse drug reactions

The details regarding metabolism, side effects, and adverse drug reactions (ADRs) for duloxitine are covered in Chapter 8.

Efficacy for fibromyalgia

Three recent meta-analyses of fibromyalgia pharmacological trials assessed the efficacy of medications that inhibit the reuptake of serotonin and/or norepinephrine. One specific medication available in the United States and approved for neuropathic pain has exhibited nearly equal serotonin and norepinephrine reuptake inhibitor activity. This drug is generally well tolerated by most fibromyalgia patients, with nausea, dry mouth, constipation, diarrhea, and anorexia reported more frequently with active drug than with placebo. A randomized, placebo-controlled, double-blind, parallel-group, multisite, 12-week monotherapy study of duloxetine titrated to 60 mg twice a day included 207 patients with fibromyalgia with or without current major depressive disorder.[134] Duloxetine-treated patients compared with placebo-treated patients improved significantly more on a total overall fibromyalgia questionnaire but not so on the pain subscale of the questionnaire. Nevertheless, the study's data suggests that SNRIs have efficacy in fibromyalgia and will improve pain and other important symptom domains of fibromyalgia in addition to improving function, quality of life, and global well-being. These medications appear to be well tolerated by most patients, but additional study is needed as these medications are still considered off-label for fibromyalgia by the FDA.

NSAIDs

Description, mechanism of action, and primary indications

For a more detailed discussion of NSAID medications and there role in chronic pain, we refer the reader to Chapter 3.

Starting dose

NSAIDs are not applicable for primary masticatory myogenous pain, but would be useful for acute direct injury muscle pain. In this case, use 400 mg three times daily unless contraindicated.

Metabolism, side effects, and adverse drug reactions

See Chapter 3 for details about the NSAIDs.

Efficacy for fibromyalgia

NSAIDs have not been found to be efficacious for primary myalgia, myofascial pain, or fibromyalgia. These medications also cause substantial gastrointestinal disease and the risk of myocardial infarctions is elevated in the cyclooxygenase-2 (COX-2) selective NSAIDs. Exactly how much myocardial risk elevation exists for nonselective COX-inhibiting agents is not clear, but given the limited efficacy it would be illogical to use NSAIDs long term for myogenous pain. The efficacy of oral NSAIDs has been examined in several Cochrane reviews of various regional musculoskeletal pain conditions. Unfortunately, as with the topical agent studies described earlier, studies of the effect of systemic NSAIDs have not been performed on a subset of patients who had regional musculoskeletal pain, but only on a mixed group with arthritis and chronic musculoskeletal pain. These reviews have generally concluded that systemic NSAIDs are not effective as monotherapy for chronic pain.

Tramadol

Description, mechanism of action, and primary indications

Tramadol was a drug designer's improvement on the cyclic antidepressants. This unique drug exhibits a combination of serotonin and norepinephrine reuptake inhibition and it is a weak μ-opioid agonist. The combination of these two actions is that antinociceptive effects occur within both the ascending and descending pain pathways. For a more detailed discussion we refer the reader to Chapter 3

Starting dose

A typical maintenance dose for fibromyalgia patients is 300–400 mg/day in 3–4 divided dosages, concomitant with acetaminophen at 2–3 g/day in divided dosages.

Metabolism, side effects, and adverse drug reactions

Nausea and dizziness can be limiting at first in approximately 20% of patients, but initiating therapy with just one tablet at bedtime for 1–2 weeks can reduce that frequency and allow progressive increasing of the dosage by approximately 1 tablet every 4 days to full therapeutic levels.

Efficacy for fibromyalgia

Tramadol has been shown to reduce the impact of pain in fibromyalgia patients. As monotherapy, it significantly reduces the severity of experienced pain but has trivial effects on insomnia or depression. In combination with acetaminophen, a substantial synergy has been noted (see below). Three controlled studies have evaluated the efficacy of tramadol in fibromyalgia. The first small study used a double-blind crossover design to compare single-dose intravenous tramadol 100 mg with placebo in 12 patients with fibromyalgia. Patients receiving tramadol experienced a 20.6% reduction in pain compared with an increase of 19.8% of pain in the placebo group.[135] The second study of tramadol began with a 3-week, open-label phase of tramadol 50–400 mg/day followed by a 6-week double-blind phase in which only patients who tolerated tramadol and perceived benefit were enrolled.[136] The primary measure of efficacy was the time to exit from the double-blind phase because of inadequate pain relief. One hundred patients with fibromyalgia were enrolled in the open-label phase; 69% tolerated and perceived benefit from tramadol and were randomized to tramadol or placebo. Significantly fewer patients on tramadol discontinued during the double-blind phase because of inadequate pain relief. This study is limited by the possible unblinding of patients in the double-blind phase after open-label treatment with tramadol. Finally, a multicenter, double-blind, randomized, placebo-controlled, 91-day study examined the efficacy of the combination of tramadol (37.5 mg) and acetaminophen (325 mg) in 315 patients with fibromyalgia. Patients taking tramadol and acetaminophen (4 ± 1.8 tablets per day) were significantly more likely than placebo-treated subjects to continue treatment and experience an improvement in pain and physical function.[137] Treatment emergent adverse events were reported by significantly more patients in the tramadol/acetaminophen group (75.6%) than the placebo group (55.8%). The most common side effects in the tramadol/acetaminophen group were nausea, dizziness, somnolence, and constipation. A *post hoc* analysis of the data from this trial revealed that the patients who had the most reduction in pain severity (≥25 mm on the 0–100 mm visual analog scale) from baseline had significantly greater improvement in health-related quality of life than those with less reduction in pain. When comparing treatment groups, improvements in the SF-36 physical functioning, role–physical, bodily pain, and physical component summary scores were significantly greater in the tramadol/acetominophen than the placebo group.[138] For example, although tramadol is currently marketed as an analgesic without scheduling under the United States Controlled Substances Act, it is under review for possible control, and it should be used with

caution because of recent reports of classic opioid withdrawal with discontinuation and dose reduction and of increasing reports of abuse and dependence.[139]

Opioids

Description, mechanism of action, and primary indications

For a more detailed discussion of these medications we refer the reader to Chapter 4 and here we simply say that, although the efficacy of moderate to strong opioid medications is well established from clinical practice, they are not recommended for fibromyalgia or myofascial pain.

Starting dose

Not applicable, but for more information about opioids, see Chapter 4.

Metabolism, side effects, and adverse drug reactions

See Chapter 4.

Efficacy for fibromyalgia

The bias of most experts is that opioids should not be used in fibromyalgia patients until well-designed, controlled, clinical studies show unequivocal benefit. However, a survey of academic medical centers in the United States reported that about 14% of fibromyalgia patients were treated with opiates.[140] A small, double-blind, placebo-controlled study found that intravenous administration of morphine in nine patients with fibromyalgia did not result in a reduction of pain intensity.[141] A 4-year, nonrandomized study of opiates in fibromyalgia discovered that the fibromyalgia patients taking opiates did not experience significant improvement in pain at the 4-year follow-up compared with baseline, and reported increased depression in the last 2 years of the study.[142] These results suggest that opiates may not have a role in the long-term management of fibromyalgia and may even cause unintentional harm to patients.[143]

Anticonvulsants

Description, mechanism of action, and primary indications

Anticonvulsant medications are used frequently in patients with chronic neuropathic pain where central neuronal sensitization is suspected. Pregabalin is a new drug, similar in effect to gabapentin, that binds to a subunit of calcium channel and reduces neuronal activity; it has been approved by the FDA for neuropathic pain and for fibromyalgia. This drug has analgesic, anxiolytic, and anticonvulsant activity in animal models.[144,145] It reduces the release of several neurochemicals, including glutamate, norepinephrine, and substance P.

Starting dose

Pregabalin is given (300–600 mg/day) in 2–3 divided doses and is generally well tolerated, with adverse effects including dose-related dizziness and somnolence that do diminish in intensity after several days of continuous use.

Metabolism, side effects, and adverse drug reactions

Weight gain and peripheral edema occur in 5–10% of patients without evidence for an effect of the drug on the heart or kidneys. There are certainly other stronger opioids, but they have generally not been used for musculoskeletal pains of any kind.

Efficacy for fibromyalgia

Pregabalin has been found to be effective in reducing the severity of body pain, improving quality of sleep, and reducing fatigue in fibromyalgia.[146] Gabapentin is also used for treatment of neuropathic pain, but its effect on different somatic pain modalities and integrative mechanisms are not completely understood. A recent double-blind, placebo-controlled experimental pain study, conducted on 20 healthy volunteers, examined the effect of a single dose of 1200 mg gabapentin on multimodal experimental cutaneous and muscle pain.[147] The authors reported that gabapentin significantly increased the pain threshold in skin compared with a placebo medication. It also significantly reduced pain due to hypertonic saline injections in the muscle, suggesting it could be used in myofascial pain and fibromyalgia. Anticonvulsant medications and their role in chronic pain are discussed in more detail in Chapter 6.

NMDA receptor antagonists

Description, mechanism of action, and primary indications

As the pathophysiology underlying central neuronal sensitization became understood, the receptor *N*-methyl-D-aspartate (NMDA) became a target for drug development since it plays a critical role in this process. Several experimental drugs exist but, clinically, there are only four commercially available NMDA receptor antagonists in the United States:

the antitussive, dextromethorphan; the dissociative anesthetic, ketamine; the antiviral drug, amantadine; and a drug approved for the treatment of Alzheimer's disease, memantine. Among these drugs, only ketamine has found some success in treating chronic neuropathic pain.

Starting dose

Ketamine can be given by multiple routes: intravenous, intramuscular, subcutaneous, oral, rectal, nasal, transdermal, epidural, or even intrathecal, although the optimal route of administration remains unclear due to a lack of good clinical trials and limited experimental studies.

Metabolism, side effects, and adverse drug reactions

The side effects of both ketamine and dextromethorphan are substantial and this severely limits their usefulness. In the case of ketamine, approximately 50% of fibromyalgia patients benefited with this agent but because of the frequent adverse effects, such as psychic disturbances like a feeling of unreality, altered body image perception, modulation of hearing and vision, dizziness, anxiety, aggression, and nausea, this drug is rarely used. Dextromethorphan exhibits a better side-effect profile than ketamine.

Efficacy for fibromyalgia

Ketamine and dextromethorphan have been studied in fibromyalgia and were both have been found to exhibit beneficial effects on pain and allodynia.[148] One study compared tramadol and dextromethorphan combined.[149] This study included 48 female patients with fibromyalgia who were treated with an open-label combination of tramadol 200 mg/day and increasing doses of dextromethorphan (50–200 mg/day), titrated to therapeutic effect or tolerability. The study reported that this mixture of agents achieved in 58% success in the treatment of fibromyalgia patients and the investigators concluded that this combination might have promise for a subgroup of fibromyalgia patients. Open-label studies are always questionable, so the study had the subjects who tolerated the medication and reported some success enter into a double-blind comparison. Patients were randomized to dextromethorphan plus tramadol or tramadol plus placebo. This study showed that significantly fewer patients on dextromethorphan plus tramadol discontinued treatment compared with patients on tramadol alone. Of course better tolerance of a drug regime is not a ringing endorsement of its efficacy and few clinicians are highly impressed with this agent. One study assessed the effects of an NMDA-antagonist (ketamine) fibromyalgia patients received by giving them either intravenous placebo or ketamine (0.3 mg/kg).[150] The authors established a subset of 17 fibromyalgia pain patients as ketamine-responsive (defined as a 50% decrease in pain intensity at rest on two consecutive assessments). Fifteen out of 17 ketamine-responders were included in the second part of the study and they had muscle pain induced via an intramuscular infusion of hypertonic saline (0.7 mL, 5%) into the tibialis anterior (TA) muscle. The saline-induced pain intensity was assessed on an electronic VAS. The authors reported that local and referred pain areas were significantly reduced by ketamine compared with a placebo. The authors concluded that ketamine has value in suppressing central mechanism causing referred pain, temporal summation, muscular hyperalgesia, and muscle pain at rest. This study was not a true clinical trial on chronic fibromyalgia and ketamines used in this situation are not yet proven.

Muscle relaxants and sedative agents

There are multiple muscle relaxants used for musculoskeletal pain. Cyclobenzaprine is the most commonly utilized for myofascial pain and fibromyalgia.

Description, mechanism of action, and primary indications

Cyclobenzaprine is FDA approved for relief of muscle spasm associated with acute, painful musculoskeletal conditions. Cyclobenzaprine's chemical structure, dosing, and side-effect profile are very similar to other tricyclic antidepressants (TCA), even though it is not classified as such. [151] Like the TCAs it has a strong anticholinergic effects and long elimination half-life (12–24 hours). Its site of action is thought to be in the brainstem level of the central nervous system rather than the spinal cord level. Cyclobenzaprine is an antagonist at one or more of the serotonin 5-HT2 receptor subtypes and thus it reduces muscle tone via its antagonism of 5-HT2C receptors. See Chapter 7 for a description of the various other muscle relaxants.

Starting dose

This will vary based on the muscle relaxant being used. For cyclobenzaprine the typical dosing is to start with 5 or 10 mg at bedtime and increase dose by 10 mg every 3–7 days and switch to a three-times-a-day dosing schedule. See Chapter 7 for a details on the various muscle relaxants.

Metabolism, side effects, and adverse drug reactions

See Chapter 7 for the common side effect and serious adverse reaction associated with muscle relaxants.

Efficacy for fibromyalgia

There are four systematic reviews on muscle relaxant studies for musculoskeletal pain. Two were focused on acute and nonspecific low-back pain and both were in the Cochrane Library database.[152,153] These reviews examined randomized placebo-controlled drug studies that used cyclobenzaprine, benzodiazepines, carisoprodol, or metaxalone. These two studies conclude that, for this population, all of these medication showed positive short-term benefit, but cautioned that these medications, especially carisoprodol and the benzodiazepines, had to be used with great caution due to their abuse potential. The previously cited meta-analysis of Tofferi et al. (2004) examined the effect of cyclobenzaprine on fibromyalgia patients. They reported that cyclobenzaprine-treated patients were 3 times as likely to report overall improvement and to report moderate reductions in individual symptoms within the first few days of use and particularly in sleep improvement. They suggested that this medication did not produce any change in tender-point palpation and the effect might be short-lived, but with these cautions, it was recommended as being an evidence-based treatment for fibromyalgia. In contrast cyclobenzaprine was not rated in the top 12 by the patients on the remedyfind.com website. Finally, there was a non–Cochrane Library review of muscle relaxants for myofascial face pain published in 2004.[154] This systematic review concluded that the use of muscle relaxants in patients with myofascial pain involving the masticatory muscles seems to be justified but that current research can only be judged as weak and consideration must be made of the risk-to-benefit ratio of these medications. The combination of alprazolam and ibuprofen has been found somewhat beneficial in a pilot trial of fibromyalgia.[155] Most clinicians dealing with chronic pain avoid sedative medications due to their moderate abuse or dependence potential and safer alternatives for the management of insomnia associated with chronic muscle pain include low-dose tricyclic agents, and, more recently, the alpha 2 delta ligand pregabalin or a related compound, gabapentin, which have sedative properties, improve slow-wave sleep, and relieve pain.[156,157]

16.3 Six final recommendations on the diagnosis and treatment of chronic masticatory myogenous pain

Deciding which treatment is appropriate for myogenous pain of the masticatory system begins with having a correct diagnosis. To do this it is necessary to understand or at least try to understand the etiology and mechanism underlying the pain. If the correct etiology-mechanism-based diagnosis were available, then the appropriate treatment choice should logically follow. Unfortunately, there are many forms of therapy identified in this chapter and only a few have had systematic reviews conducted on the published data. Given these limitations, the best recommendations that can be made are as follows.

Final treatment recommendations for myogenous pain

1. For the patient with traumatic-onset local myalgia with secondary trismus, the common sense recommendations for treatment are rest, ice, short-term nonsteroidal anti-inflammatory drugs (NSAIDs), and then frequent daily active mobilization of the jaw until normal motion is achieved again.
2. For the patient with secondary local or regional myalgia it is appropriate to manage or minimize the local pathology first and then re-examine the myogenous pain for resolution or persistence.
3. For those patients with local myalgia that appears secondary to self-reported parafunctions, the use of an occlusal appliance seems indicated. The evidentiary basis for occlusal splints as a method of treatment is generally modest.
4. For the patient with all forms of nontraumatic, nonsecondary chronic myogenous pain, namely, local, regional, or widespread myalgia (or myofascial trigger points and/or fibromyalgia), where daily stress is the suspected etiology, it is likely that several treatments are appropriate, including self-directed treatment. This would include education plus absolute avoidance of harmful behaviors, regular daily thermal treatments, repeated (every 2 hours) jaw and neck stretching, and a daily nonimpact aerobic exercise program. Unfortuanately these methods have no good evidentiary basis beyond common sense.
5. In general the data on pharmacologically based treatment approaches are modest at best:
   - (a) Topical medications for musculoskeletal pain seem to be good only for short-term use and mostly for acute pain.
   - (b) Tricyclic antidepressants (TCAs) are generally considered one of the better agents for myogenous masticatory pain and even then the effects on pain are modest and many patients find the side effects intolerable.
   - (c) Selective serotonin reuptake inhibitors (SSRIs) have little to no benefit for musculosketal pain but can be helpful in those cases where substantial depression coexists with the pain, as in the most severe cases.
   - (d) Serotonin and norepinephrine reuptake inhibitors (SNRIs) are a new class of drugs, and there is some

preliminary evidence that would make them equivalent to the TCAs with potentially fewer side effects. These drugs need to be compared directly with TCAs on a population of fibromyalgia patients in the future.

- **(e)** Systemic NSAIDs are generally not effective as monotherapy for chronic musculoskeletal pain, and long-term side effects (gastritis and myocardial risk) limit this drug to short-term use if used at all.
- **(f)** Tramadol has some evidence suggesting modest-to-moderate efficacy when used in fibromyalgia; when used in combination with acetaminophen, the combination substantially reduces body pain more than a placebo medication. Again, because this drug is an opioid agonist, it has some potential for opioid tolerance and even long-term habituation or dependence. Most agree this drug is more appropriately used as a short-term pain agent.
- **(g)** The use of traditional opioids in fibromyalgia patients is controversial and generally not recommended by experts.
- **(h)** Anticonvulsant medications such as gabapentin and pregabalin have shown some promise as effective agents to reduce the severity of body pain, improving quality of sleep, and reducing fatigue in fibromyalgia. However, the effect is modest at best and may not even be as good as the TCAs, although they have far fewer side effects.

6 Finally, there are many behavioral therapies suggested for treatment of local and regional myalgia or myofascial pain as well as fibromyalgia, and they generally help patients cope with their chronic pain but do not provide pain reduction or improvement in function.

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Chapter 17

Diagnosing and managing chronic trigeminal neuropathy

Glenn T. Clark, DDS, MS

17.1 Chronic trigeminal neuropathy

When the phrase chronic trigeminal neuropathy is used this could mean several things, so it is appropriate to define it before talking about diagnosing and managing patients with such a problem.[1,2] By "chronic" we mean that the problem is ongoing in spite of treatment and there is usually a minimum period of 3–6 months before a pain is labeled as chronic or persistent. By "trigeminal" we mean it is localized to the region of the trigeminal nerve, which in most cases means pain in the teeth, alveolar bone, or gingival mucosa. Occasionally this pain may be extraoral, if some form of neural injury occurs. By "neuropathy" we mean a continuous noxious activity generated within the nervous system without adequate stimulation of its peripheral sensory endings. The International Association for the Study of Pain (IASP) introduced the term neuropathic pain and defined it as "pain initiated or caused by a primary lesion or dysfunction in the nervous system." Other names for a chronic trigeminal neuropathy are chronic trigeminal neuropathic pain, persistent orodental pain, atypical odontalgia,[3,4] and phantom tooth site pain.[5] When the term atypical or idiopathic is added in front of the phrase "chronic trigeminal neuropathy," this usually means that the cause of the pain is unknown or not yet identified. The background history and prior names used to describe this problem are reviewed later in this chapter. What is not covered in this chapter is the episodic trigeminal nerve pain known as trigeminal neuralgia. This disorder is reviewed and discussed in the chapter on anticonvulsants.

17.1.A Prevalence of chronic trigeminal neuropathy

A 2008 article put forth the following definition for neuropathic pain: "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system."[6] They also suggested a grading system for neuropathic pains using the terms (1) definite, (2) probable, or (3) possible neuropathic pain. They proposed that the grades probable and definite require confirmatory evidence from a neurologic examination. Of course, such a system needs to be evaluated and then adopted by group like the IASP. Even with a definition and a grading system it is still moderately difficult to determine when an idiopathic chronic trigeminal neuropathic pain exists. This is because there are no "disease defining" physical examination or radiologic features and there are multiple other sources of pain in the dental–mucosal–alveolar region, such as failing dental restorations, tooth fractures, pulpitis, pulpal necrosis, or periodontal and maxillary sinus inflammation or infections. Fortunately, most of these other pain-inducing problems do not produce continuous chronic pain (lasting greater than 3–6 months) since either the cause is transient, so the problem goes away, or successful treatment is initiated. These other problems will also have physical examination or radiologic evidence of the pathology that is causing the pain.

By default, treatment failure is often the single most common defining feature for chronic trigeminal neuropathy. A far too common story told by patients seeking help in a chronic pain center is that they have seen multiple dentists and have had multiple unsuccessful irreversible procedures performed (root canal therapies, apical surgeries, or extractions) and they still have pain. It is usually at this point that a diagnosis of neuropathy is considered.[7] Unfortunately, while the number of patients with chronic orodental pain that have had failures in usual and customary treatment are many, the number of reports in the literature are few. While this could mean there are few cases of treatment failure, a more likely explanation for this is that no one likes to broadcast their failures. There are, however, a few such reports; a 2003 article described 38 patients (32%) who had failed invasive therapies for their orofacial pain, taken from a case series of 120 consecutive patients. These patients all attended

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a university-based hospital pain center for treatment of their orofacial pain.[8] The report categorized patient self-reports of prior irreversible dental procedures for their pain (e.g., endodontics [30%], extractions [27%], and apicoectomies [12%]). By definition, all 38 of these failed patients still had pain and 21 of 38 (55%) of them further reported that these treatment interventions actually exacerbated their pain. A more recent 2007 study described 44 of 100 (44%) consecutive nondental orofacial pain patients who had previously received inappropriate extractions or endodontics.[9] To some degree these seemingly inappropriate treatments happen because of a lack of understanding of the disease and the lack of authoritative disease criteria.[10]

As could be expected, the actual prevalence of patients in the general population who suffer with this problem has not been determined. Most studies in the pain literature have focused on other neuropathic conditions, such as trigeminal neuralgia, postherpetic neuralgia, painful diabetic neuropathy, and phantom limb pain.[11] One approach to solving the neuropathic trigeminal pain prevalence dilemma would be to develop a validated questionnaire. For example, a 2006 article described a validated screening questionnaire that claimed to be able to identify neuropathic pain in patients with low back problems without a physical examination, imaging, or diagnostic tests.[12] The study involved prospective, multicenter data collected from approximately 8000 low back pain (LBP) patients. They claimed the questionnaire had high sensitivity and specificity and an excellent positive predictive accuracy (85%, 80%, and 83%, respectively). While a questionnaire, if it is designed properly, can identify with reasonable probability that segment of the population with definite neuropathic pain and who have probably already suffered treatment failure. Used alone such questionnaires will never provide a definitive method for "early" diagnosis of neuropathic pain problems. Early identification of trigeminal neuropathy will require a disease-defining biologic marker that has yet to be identified. While they are not population-based studies using defined criteria, opinions in the existing literature suggest that atypical odontalgia prevalence varies between 3% and 12% of the patients who undergo seemingly successful endodontic treatment.[13–15] Consistent with these opinions is a 2007 report on the diseases and demographic patterns of 1049 consecutive patients attending a university-based orofacial pain and oral medicine center that reported chronic trigeminal neuralgia made up 3% of the total.[16] Of course convenience samples are not prevalence data, but a consistent finding in these studies it that all report a high female preponderance, with the onset starting in the fourth decade of life and with a peak in the fifth or sixth decades. Finally, molars and premolars are more frequently involved, with the maxilla being more often affected than the mandible.[17] It is still unclear why females are more commonly affected than males or why the maxilla is more commonly affected than the mandible. A commonly offered explanation for why some patients get chronic pain and others do not is that they might have a genetic polymorphism that makes them susceptible to neuropathic pain.

17.1.B History and prior terminology

Chronic trigeminal neuropathic pain is not a new phenomenon. In 1932, Wilson described a group of patients with atypical facial neuralgia and among them were patients who had dental pain of unknown origin.[18] Since then many others have coined terms for these patients such as idiopathic periodontalgia and atypical odontalgia.[19–23] The term phantom tooth pain (PTP) was applied to the subgroup of these patients who had unexplained chronic dental pain even after the suspected tooth was extracted.[24–27]

17.1.C Clinical characteristics

The lack of a set of disease-defining criteria does not mean chronic neuropathic trigeminal pain is not a real disease or that we know nothing about it. On the contrary, we know quite a lot about this disease. We know women in their 40s are more likely to suffer this disease, we know the most common site of pain is maxillary molars and premolars. We now know that atypical odontalgia and phantom tooth pain are most likely the same disease with the main difference being that an unsuccessful pain-relieving extraction has occurred in the cases of phantom tooth pain. What is also known is that patients with phantom tooth pain have lower somatosensory thresholds in the pain region. While the data is sparse, a 2002 study measured the threshold levels for light touch sensation using an intraoral site in clearly defined group of phantom tooth pain subjects.[28] This involved a case–control experimental on 10 PTP patients (mean age 56, range 32–71, 9 females) and 10 controls. The authors found the PTP complaints were predominantly reported in the upper jaw (ratio 8:2), with the majority in the molar region (ratio 5:3). In addition, PTP subjects showed significantly lower threshold levels for light touch sensations on the affected side. While limited in quantity, the data suggests that PTP subjects demonstrate measurable mechanical hyperalgesia and, among all tests performed, mechanical pain threshold was significantly altered on both sides with the greatest change being on the pain side.

Atypical odontalgia patient characteristics

Atypical odontalgia presents as a continuous pain located in a tooth, gingiva, or extraction site, and can often involve

wider areas of the face. Several reports indicate that the pain usually begins and persists long after a dental or surgical procedure.[29,30] Typically, no obvious tooth or periodontal pathologies are evident and no radiographic signs of pathology are present as a cause of this pain. Local anesthetic block of the involved tooth produces modest to equivocal pain relief.[31] Atypical odontalgia includes cases with an identifiable causeof the chronic tooth pain, such as a dental abscess that was correctly treated but the patirnt's pain did not resolve after endodontic therapy. In some of the atypical odontalgia cases a chronic pain develops without clear-cut cause (e.g., no evidence of clear tooth fracture, no dental caries, no periapical lesion, and the teeth test vital with cold testing). In these cases the two explanations most often offered include incomplete tooth fractures and clenching-induced pulpitis (discussed later in this chapter). One study did report that 74% of the atypical odontalgia sufferers were women in their 40s at initial onset, and the pain was usually present in posterior teeth or alveolar arch, with molar teeth affected 58.8% of the time, premolars 26.8%, canines 4.2%, and incisors 12%.[32] A second study, which evaluated 120 subjects complaining of atypical odontalgia, had 80.8% women between the ages of 23 and 60 years, with a mean age of 43 ± 13.9 years.[33] Making the assumption that inflammation of the pulp is an underlying mechanism for the pain, an explanation is needed regarding why the pulpal tissue of women over 30 years of age would cause pain in the their posterior teeth. The above data suggests that changes in both the nervous system and in the teeth themselves with age must play a role in producing tooth pain or pulpal inflammation. Moreover, given the predilection of the posterior teeth to show this disease it seems again that some factor related to bite force, which is far greater on the posterior teeth than the anterior, might play a role. Finally, some factor that is more evident in women than men must be involved and fortunately the literature sheds some light on these issues.

Phantom tooth pain patient characteristics

When tooth pain becomes chronic and root canal treatment is unsuccessful in stopping the pain, the treating dentist commonly elects to extract the tooth hoping that the pain symptoms will stop. If the tooth is the source of the pain and extrapulpal trigeminal neuropathic changes have not occurred, then the pain should stop. If, however, there are extrapulpal neuropathic changes, this results in chronic tooth-site pain that is commonly called phantom tooth pain. It should be stated that while the phrase "phantom tooth pain" is commonly used, it would be more accurate to describe it as chronic, unexplained pain at the site of the extracted tooth. There are no patients who describe feeling the phantom presence of their tooth as occurs in phantom limb patients, where they actually feel the missing limb. Instead what would be a more accurate analogy is that these patients are experiencing tooth stump pain, which is the term used to describe chronic limb pain when a phantom limb presence is not part of the clinical pain pattern.

Other characteristic of trigeminal neuropathic pains

While this chapter focuses on the above two chronic trigeminal neuropathies, this category would also include burning mouth syndrome[34] and autoimmune trigeminal neuropathic pain.[35] Trauma can also induce a chronic trigeminal nerve pain, which is presumably neuropathic. For example, chronic nerve pain is reported with implant inferior alveolar nerve impingement[36] and chronic dysesthesia is reported after a local anesthetic injection into the nerve.[37] Nerve pain can occur after mandibular fracture or after orthognathic-surgery-related nerve injury.[38] Nerve compression is known to occur after osseous growth compression injury,[39] neoplastic perineural invasion injury, and infection-related damage to the nerve itself such as with a trigeminal herpes zoster and herpes simplex infection.[40] In addition, neuropathic pain can be caused by diabetic-related neural injury and altered sympathetic nervous system related neuropathy. The literature describes several medications and other chemical toxins that cause neuropathic pain and all branches of the trigeminal nerve can be involved including the lingual,[41] inferior alveolar, mental nerve, auriculotemporal, and infraorbital nerves,[42] as well as trigeminal neuroma pain after surgical transaction of a nerve.[43]

Finally, some patients with temporomandibular joint (TMJ) pain develop a chronic TMJ pain that is resistant to anti-inflammatory medications and may be neuropathic. Sensitization of the auriculotemporal nerve may account for the reason some patients have sustained unchanging pain even after direct corticosteroid injection into the joint itself. Proof of auriculotemporal nerve change was provided in recent study that used quantitative sensory testing on 72 patients (44 who had arthralgia and 28 who had chronic myalgia) and 22 healthy controls.[44,45] Nerve response threshold was tested with electrical stimulation applied bilaterally in three trigeminal nerve sites (cheek, temple, and chin). By comparing the affected-side threshold with the control (non-affected) side, the authors found that the electrical detection threshold ratio for the three sites did not vary from the expected value of 1 in the controls. However, for the patients with arthralgia the mean ratio obtained for stimulation at the temple site was significantly lower compared with the other sites, and this was not so for the cheek or chin sites. This data suggests that the auriculotemporal nerve, which

innervates both the TMJ and the temple, was sensitized and had a lower threshold.

17.1.D Psychiatric co-morbid disease

Psychiatric assessment of chronic pain subjects with failed treatment was described in a 1983 case series report on 21 patients with atypical facial pain.[46] These patients had had a total of 65 irreversible dental and oral surgical treatments (3 per patient) trying to solve their pain; only one patient reported showing less pain as a result of the treatment. Each of the patients in this report also had a full psychiatric assessment. Based on these data, these authors concluded that failed-treatment patients with chronic trigeminal pain suffered a high degree of psychiatric illnesses. The authors recommended psychiatric assessment before repeated dental and surgical procedures are performed in this population. While the need for a psychiatric assessment by a mental health professional is easy to comprehend and implement in the patient with chronic multiple treatment failures, it is harder to justify and implement if the patient has not yet failed treatment and presents with a single symptom such as toothache and no obvious behavioral abnormalities. Whether psychological pathoses in this population precedes, or is a consequence of, chronic pain is unknown. Consistent with this case series is a 2007 study that reported on the clinical and psychosocial characteristics of 46 consecutive atypical odontalgia patients compared with 35 age- and gender-matched control subjects.[47] The patients were found to have significantly more TMD pain, tension-type headaches, and widespread pain than the controls. They also had significantly higher scores for somatization, depression, and limitations in jaw function and significantly lower scores on quality of life.

Of cours, observing that two problems are strongly associated does not prove that one is the cause of the other. The relationship between psychological factors and future chances of neuropathic pain was examined in a study on knee surgery patients.[48] This study looked to see if any preoperative psychological characteristic would predict the presence of chronic pain following total knee arthroplasty. These authors studied 77 patients having this surgery and all completed a battery of psychometric tests assessing various characteristics. They reported that patients with higher preoperative anxiety scores and more preoperative pain predicted the presence of chronic regional pain syndrome symptoms at follow-up. However, a high tendency for anxiety was not a strong predictor of postsurgical complications (sensitivity of 73% and a specificity of 56%). What these numbers imply is that it is not easy to predict who will get neuropathic pain. Moreover, pretreatment depression or anxiety as a psychological characteristic does not dictate that the individual to become a neuropathic pain sufferer in the future.

An alternate explanation for the strong association between psychological disturbance and neuropathic pain is that the unrelenting nature of the pain itself alters the patient's personality. In fact,a more recent study examined the relative contribution of catastrophic thinking (i.e., rumination, magnification, helplessness) to the pain experience in 80 neuropathic pain patients.[49] This study reported that individuals who scored higher on a measure of catastrophic thinking also rated their pain as more intense, and rated themselves to be more disabled due to their pain. Catastrophizing thinking predicted pain-related disability over and above the variance accounted for by pain severity; combined, these data suggest that unrelenting pain without highly effective treatment methods may induce helplessness in patients and shift them to express more psychopathology and mood disorders.

17.2 Neuropathic pain mechanisms

This section of the chapter reviews the neuronal changes (categorized by mechanism) that are known to occur when a patient has neuropathic pain. This is important to know because if you knew exactly how the nerve was injured and how it has changed as a result of the injury, you would understand which ion channels or receptors have also changed. With this knowledge you might be able to better select an appropriate therapy or medication based on the neuropathic mechanism. Unfortunately, while we know how nerves change with experimental injury and we even how and where the various anticonvulsant medications act on nerve transmission, this does not mean we have designer medications that can be targeted to a specific neuropathic mechanism, but this may occur in the future. Designer pain medications are what the drug manufacturers and pain doctors trying to help their patients hope for, but it is still an elusive target.[50–52] What is now known is that painful neuropathic pain will occur with quite different clinical manifestations (e.g., stimulus-independent constant pain; stimulus-dependent paroxysmal pain). Moreover, one or several types of pain may be present in the same patient. These different types of pain may be caused by distinct pathophysiologic mechanisms, such as spontaneous activity of damaged C-nociceptors, increased sensitization of afferent nerves and neurons to noxious and non-noxious stimulation, sympathetic hyperactivity, or a loss of central inhibition.[53] Given this, it is unlikely that a single drug with a single mechanism of action will relieve neuropathic pain, especially if we are not sure which of the above pathophysiological processes are present in the patient.

17.2.A Local nerve injuries

All neuropathic pain begins with a nerve injury and, unfortunately, there are many ways a nerve can be injured. In some clinical situations we know exactly what the injury was (e.g., an infected tooth pulp or an improperly positioned implant), but in most cases we are only guessing at the type of injury. Injuries to the trigeminal nerve can be due to injection of a neurotoxic substance into or very near the neural sheath, traumatic or even iatrogenic crush, inadvertent neural transection, hypoxia, strangulation, abrasion, compression, bacterial or viral insult, neurodegenerative disease, tumor-induced compression, or neural invasion of a tumor into the nerve, autoimmune-related inflammation, and chemical- and medication-induced toxicity to name a few. In the specific case of postherpetic neuralgia the injury is a viral-induced damage to the nerve itself. In the case of dental implant pain, the surgical removal of bone, if too deep, can surgically burr and cut the nerve or the implant, when placed into the bone can crush the nerve in the inferior alveolar canal. Third-molar extraction is a common cause for inferior alveolar nerve and lingual nerve damage, causing altered sensation on the distribution of the nerve affected.[54–58]

After injury, there are a variety of changes in the gene and in the proteins produced by the gene that occur within a first-order nerve. A recent study examined the issue of the tetrodotoxin-resistant voltage-gated sodium channel Nav1.8 (SNS1/PN3) in human pulp tissue associated with irreversible pulpitis.[59] This receptor is expressed by nociceptors and may play a role in pain states and using specific antibodies for immunohistochemistry, we studied Nav1.8 immunoreactivity in human dental pulp in relation to the neuronal marker neurofilament. Human tooth pulp was extracted from teeth harvested from a total of 22 patients (14 without dental pain, 8 with dental pain). Fibers immunoreactive for Nav1.8 were significantly increased on image analysis in the painful group: median (range) Nav1.8 to neurofilament percentage area ratio, nonpainful 0.059 versus painful 0.265; this fourfold difference is statistically significant and is likely why the alveolar nerve supplying the tooth has spontaneous activity and is more difficult to block with a local anesthetic.

17.2.B Nerve sprouting and ectopic neural activity

After crushing or cutting a nociceptive nerve, the nerve will attempt to restore its continuity through axonal sprouting. These new nerve sprouts and neuromas are unusually sensitive to mechanical, thermal, and chemical stimulation and even are known to have spontaneous discharge. These new nerve sprouts and neuroma are also spontaneously active, forming what is called an ectopic generator causing tingling, itching, or electrifying dysesthetic sensations in patients.[60] Sometimes, these nerve sprouts mature and normal sensitivity to stimuli returns but in some cases, especially with neuromas, the sensitivity is ongoing.

17.2.C Demyelination of nerves

Painful ectopic neuronal discharges occur secondary to demyelination that results from a neurodegenerative disease such as multiple sclerosis or due to a vascular-compression-related nerve injury as in trigeminal neuralgia. Neuropathic pain due to multiple sclerosis, such as trigeminal neuralgia, painful spasms, and painful dysesthesias and paresthesias, are usually treated with anticonvulsants. Carbamazepine has proven to be efficient in controlling the trigeminal-neuralgia-like symptoms. Oxcarbazepine can be used as the alternative drug for carbamazepine. The other anticonvulsants are often used as the second line of treatment.[61] A randomized, double-blind, placebo-controlled, two-period, crossover, pilot trial of lamotrigine showed no difference in comparison with placebo group in the treatment of central pain in multiple-sclerosis patients.[62]

17.2.D Peripheral sensitization

If a peripheral nerve starts to fire spontaneously and continuously, this causes the nerve to start to release inflammatory and other excitatory mediators (e.g., substance P, calcitonin gene–related peptides) at the terminus of the nerve. These chemicals further stimulate the nerve and keep the nerve firing.[63] In addition to inflammation induced neuronal activity, the nerve begins to change. The most commonly described change is that the fast-firing, hard-to-block atypical sodium channels are upregulated and begin to populate the nerve axon and the axon in the ganglion itself.[64–66] Blockage of these sodium channel subtypes may be an important issue in treating patients with neuropathic pain. While the number of atypical sodium channels are known to increase in response of nerve injury and continuous activity, this same phenomenon is not proven for calcium channels. Nevertheless, the entry of calcium ions into the nerve endings through calcium channels regulates growth-related proteins. Recently N- and L-type calcium channels have been found to contribute to calcitonin gene–related peptide (CGRP) release from injured nerve endings *in vitro*.[67] Blockade of N-, T-, and P-type calcium channels has been found to block experimental neuropathic pain.[68,69] These results suggest that calcium channels may play a role in the expression of the neuropathic state. Selective calcium channel blockers, such as gabapentin, oxcabazepine, and lamotrigine may have significant potential in the treatment of neuropathic pain. Conotoxins are neurotoxic peptides that block the activity

of ion channels. The mu subtype of these conotoxins has been shown to specifically block tetrodotoxin-resistant voltage-gated sodium channel Na(v)1.8 and to decrease allodynia and hyperalgesia in an animal model.[70]

Neuropathic pain can be also be induced by inflammation and, while some of the above injury-induced neuroplastic changes are similar to inflammation, some are dissimilar.[71,72] For example, one study examined the effect of interleukin-1-beta (IL-1β) exposure on modulation of the voltage-dependent sodium currents and tetrodotoxin-resistant (TTX-R) sodium channels in capsaicin-sensitive neurons.[73] They report that a brief exposure (5 minutes) led to a 28% reduction of TTX-R sodium currents in these neurons, while a 24-hour exposure led to a 67% increase in sodium currents and increased mRNA transcripts of Na(v)1.8. These data demonstrate that prolonged inflammation causes an increase in both the slowly inactivating TTX-R currents in DRG neurons and more Na(v)1.8 sodium channels being produced, rather than the usual downregulation of this sodium channel seen with direct nerve injury. These results suggest the participation of Na(V)1.8 channels in the development and maintenance of chronic inflammatory hyperalgesia.

17.2.E Increased sympathetic to afferent sensory neuron activity

Normally sympathetic neurotransmitters do not activate sensory nerves because they are not populated with adrenergic receptors. However, when a nerve has been sensitized due to injury or sustained activity, the nerve upregulates these receptors and therefore participates in the development of sympathetically maintained pain (SMP).[74–77] This pain is usually burning in character and it is associated with one of the following signs: sweating; swelling; abnormal skin temperature in the painful area; changes in skin color (red, purple-bluish). There are several drugs that have been shown to suppress sympathetic activity and that have been used in the treatment of SMP. Alpha-adrenergic antagonists such as phentolamine, phenoxybenzamine, and prazosin are used for the treatment of pain where the involvement of the autonomic nervous system has been demonstrated.[78,79] Clonidine, which is an α-adrenergic agonist also has been used for treatment of this condition;[80–82] however, there is lack of controlled trials for these medications.

17.2.F Cytokines in neuropathic pain

There are many different types of cytokines, including those that promote or inhibit inflammation. The role that cytokines play in neuropathic pain has been clarified in several publications.[83,84] Two specific cytokines that are considered important in promoting neuropathic pain are interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α). When an irritating substance is injected into an animal this triggers the development of allodynia and hyperalgesia; it has been shown that giving the animal an endogenous IL-1 receptor antagonist or antibodies to IL-1 will block the hyperalgesia.[85,86] In patients with neuropathy, there is evidence that TNF is elevated also.[87] Furthermore, there is a difference in the cytokine profile of patients who present with painful neuropathy and those with painless neuropathy. In patients with painful neuropathy there is a increase in the proinflammatory cytokines TNF-α and interleukin-2 (IL-2). In contrast, in patients with painless neuropathy the anti-inflammatory cytokines IL-10 and IL-4 are found in higher levels than in patients with painful neuropathies or in healthy control subjects.[88]

17.2.G Central sensitization and plasticity

The more extensive or longer lasting the peripheral neuronal changes are, the more likely there will be central neuroplastic changes. The location of these central changes can be throughout the afferent pathway to the cortex and may even involve DNA changes to the neurons themselves. Most scientists have focused on the second-order neurons and most specifically on the *N*-methyl-D-aspartate (NMDA)[89,90] and the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)–kainite receptors. Normally, activation of the NMDA receptor causes an influx of calcium ions and production of the gaseous neurotransmitter nitric oxide (NO). NO is an important neurotransmitter since it is able to diffuse out of the second-order neurons to activate nearby neurons. If the NMDA and the AMPA–kainate receptors, which are normally not easy to activate, undergo change such that they are continuously or very easily activated, this then constitutes central sensitization. With central sensitization, secondary allodynia (pain in response to nonpainful stimuli) and secondary hyperalgesia (exaggerated pain in response to painful stimuli) develop and, moreover, local anesthetic applied to the peripheral pain site does not block the pain.[91–95]

17.2.H Central inhibitory pathway deficiency

Normally, ongoing pain signals in a normal nervous system will trigger endogenous inhibitory systems. However, it is believed one of the mechanisms involved in neuropathic pain is malfunction in this built-in inhibitory system. For example, sensory information is usually controlled by inhibitory interneurons, and incoming spinal and trigeminal pain signals are under continuous inhibitory control from signals originating at the brainstem centers located in the periaque-

ductal gray and in the locus ceruleus, causing release of inhibitory neurotransmitters and endogenous opioids. Experiments in animals have demonstrated that, after peripheral nerve injury, there is a decreased production of gamma-aminobutyric acid (GABA) and glycine, the inhibitory neurotransmitters, along with loss of the inhibitory interneurons located in the spinal cord. The end result of these changes is an increased excitability of the neurons, leading to pathological pain states.[96,97] Moreover, a decrease in the expression of mu opoiod receptor has been found in animals that had experimentally induced nerve injury.[98] Paradoxically, endogenous dynorphin has been shown to be involved in morphine tolerance and pain development in animal models.[99,100]

17.3 Differential diagnosis of chronic trigeminal pain

For most chronic trigeminal neuropathy patients, unless a psychiatric illness is obvious and necessitates immediate referral for mental health assessment, the dentist seeing a patient with suspected chronic trigeminal neuropathic pain would begin by first ruling in or out infection and/or inflammation as a source of the pain. If the teeth and surrounding oral tissues have a healthy appearance and probing of the gingival tissues reveals no obvious pathology, the next consideration is that there is pathology under the site of pain. This can usually be evaluated with periapical dental films and a panoramic film of the jaw. When these are also negative, the dentist must consider disorders further afield (e.g., sinus infection, myofascial pain, and TMJ pain) and any local maxillofacial pathology (e.g., neoplastic disease). Depending on the situation, sometimes irreversible diagnostic treatments (e.g., root canal or extraction) are performed to see if they will have any beneficial effect. These are labeled diagnostic treatments when they are performed even though the usual and customary signs of infection or inflammation are not present. If these treatments fail to help, before performing a second diagnostic treatment on a second tooth or oral tissue site, the possibility that the patient has a neuropathic pain must be considered.

To minimize incorrect conclusions, the diagnostic process should be performed in a systematic fashion whenever a patient is suspected of having a chronic trigeminal neuropathic pain. As a baseline this workup would likely include the following:

1. cold testing for pulpal nonvitality
2. periapical radiographic examination for apical change
3. a panoramic radiograph looking for other maxillofacial disease
4. a head and neck examination looking for other potentially causative diseases
5. a cranial nerve examination (assessing for allodynia and hyperalgesia)

Next there are three additional steps that might be taken to assess the patient who has a suspected trigeminal neuropathy disorder:

1. microscopic inspection of the tooth with all restorations removed
2. using an occlusal adjustment or orthotic device to reduce loading on the tooth
3. anesthetic testing of the intraoral pain site

If a crack in the tooth is identified after removing all restorations, this is definitive. The final two procedures in the diagnostic workup would be to order an MRI examination and, if clinical history is suggestive of any psychopathology or a mood disorder order (e.g., depression, anxiety), a behavioral health assessment. These last two tests are not required in many cases, but they would be indicated if the pain does not respond to treatment in a reasonable time frame. Your index of suspicion for all deadly diseases, including cancer, should elevate when you are dealing with any patient with a history of prior cancer, when dealing with a patient with exposure to risk factors (e.g., smoking), or when the pain disorder is not within the expected sites or age group of the commonly affected.

17.3.A Lidocaine inefficacy in neuropathy

Systemically administered local anesthetics such as intravenous lidocaine, oral mexilitine, and oral tocainamide, are effective in a number of chronic pain conditions.[101] Such regimens produce analgesia in diabetic neuropathy,[102] neuralgias,[103,104] peripheral nerve injury,[105,106] and reflex sympathetic dystrophy.[107] However, despite this efficacy in different clinical pain conditions, systemic local anesthetics are limited by their adverse central nervous system (dizziness, lightheadedness, somnolence) and cardiac effects. It is moderately common to find that after an inferior alveolar nerve (IAN) anesthetic nerve block the patient still experiences pain during dental surgery. This finding could be because the location of the deposited solution was not correct or because the IAN has undergone a change that makes it less responsive to the anesthetic agent. Long-lasting neuroplastic changes are known to occur both as a result of chronic inflammation and following direct nerve injury. With pulpal disease, the predominate change that is seen inside the pulp is inflammation; therefore the chronically inflamed pulps are more likely to have upregulation of TTX-resistant Na(v)1.8 sodium channels. When a nerve upregulates a receptor or

ion channel these changes occur not just on the terminal branches of the nerves (e.g., those inside the pulp chamber) but all along the sensory nerve axon, in the ganglion of the nerve, and at the central terminus of the nerve—and sometimes on the second-order neuron as well. This means that removing the pulpal portion of the nerve does not remove all of the neuropastic changes that have developed and it is not surprising that the patient still has spontaneous pain and is hyper-responsive to light nonpainful stimuli. The other bad news is that these phenotypic switches in sensory neurons are not always reversible with time.

Note that with an increase in the number of TTX-resistant sodium channels (Na(v)1.8) local anesthetics have a 2–6 times lower affinity for these sodium channels. This means that more local anesthetic is needed to block a nerve populated with TTX-R channels.[108] The experimental prediction that an inflamed nerve should be harder to anesthetize is in fact supported by clinical data from anesthetic efficacy studies on patients with irreversible pulpitis. For example, one study involved a prospective, randomized, double-blind comparison of the degree of pulpal anesthesia obtained with 1.8 mL of 4% articaine with 1:100,000 epinephrine and 1.8 mL of 2% lidocaine with 1:100,000 epinephrine in inferior alveolar nerve blocks on 57 normal patients.[109] A pulp tester was used to test for anesthesia, in 4-minute cycles for 60 minutes, of the molars, premolars, and central and lateral incisors. Anesthesia was considered successful when two consecutive high current readings (≥80) were obtained within 15 minutes and the 80 reading was continuously sustained for 60 minutes. Using the lidocaine solution, successful pulpal anesthesia ranged from 2% to 48% of the tested teeth. Examining the data closely showed that the percentage of patients with anesthetic failure in the first and second molar region with conventional lidocaine was 7% for the second molar and 18% for the first molar. Although pulp testing is a sensitive pain-assessment tool, it does not measure whether the level of anesthesia achieved is adequate to perform dental procedures such as tooth preparation, endodontics access opening, or tooth extraction. There has been at least one published study that used clinical markers rather than a pulp test response to assess anesthetic efficacy and failure. The authors described 56 healthy patients who were having lower molar extraction. They performed a comparison on two methods of mandibular nerve block (28 subjects in each group).[110] With the conventional inferior alveolar nerve block using 1.8 mL of 2% lidocaine with 1:100,000 epinephrine these subjects exhibited an anesthetic failure rate of 10.7%.

In contrast to the above studies, there have been two reports that have examined the efficacy of 1.8 mL of 2% lidocaine with 1:100,000 epinephrine in teeth diagnosed with irreversible pulpitis. In the first, 51 patients with symptomatic, vital maxillary, and mandibular posterior teeth diagnosed with irreversible pulpitis received conventional infiltrations or inferior alveolar nerve blocks.[111] Pulp testing was used to determine pulpal anesthesia after "clinically successful" injections. Patients who were positive to the pulp tests, or were negative to the pulp tests but felt pain during endodontic access, received an intraosseous injection using 1.8 mL of 2% lidocaine with 1:100,000 epinephrine. The results demonstrated that 42% of all patients who tested negative to the pulp tests reported pain during endodontic access and required supplemental anesthesia. In addition, 81% percent of the mandibular teeth exhibited a failure to gain adequate pulpal anesthesia. Finally, there was a second study on irreversible pulpitis assessing anesthetic efficacy with IAN block.[112] They used a prospective, randomized, double-blind study and the same pulp testing method described above to assess the relative efficacy of 1.8 mL of 4% articaine with 1:100,000 epinephrine with 1.8 mL of 2% lidocaine with 1:100,000 epinephrine. The anesthetic procedure used was an inferior alveolar nerve block and the subjects were 72 patients experiencing irreversible pulpitis in mandibular posterior teeth. Endodontic access was begun 15 minutes after solution deposition, and all patients were required to have profound lip numbness. Success was defined as none or mild pain on endodontic access or initial instrumentation. The failure rate for the inferior alveolar nerve block using lidocaine solution was 77%. These studies suggest that anesthetic failure rate in irreversible pulpitis is clearly higher than the 10–20% failure rates seen with normal teeth.

17.3.B Anesthetic challenge test in neuropathy diagnosis

A test that can be used along with the clinical neurosensory examination when a trigeminal neuropathy is suspected is to perform a local anesthetic challenge test.[113] This involves isolating the painful area, asking the patient to rate their ongoing spontaneous pain, and then applying either a topical anesthetic (Orobase-B) or a nonanesthetic placebo agent (orobase cream without anesthetic) topically to the painful site. This test is best done in double-blind fashion and therefore it must be done on two separate days with the order of the test agents being applied randomly. Otherwise anesthetic testing can be done in a single-blind fashion with a 30-minute washout period between agents, but the placebo agent must be used first. In either case, the patient will rate the pain change (if any) using the visual analog scale (VAS). The effect of topically applied benzocaine on spontaneous toothache without obvious cause was examined in 60 patients in a 2003 study.[114] This study used a randomized, double-blind, placebo-controlled clinical trial to see the effi-

cacy of intraoral benzocaine delivered by via a patch could suppress pain in spontaneous toothache pain of at least a moderate intensity. They 12 mg of benzocaine or a matching placebo was applied approximately 2 mm apical to the mucogingival junction of the symptomatic tooth and left in place for 60 minutes. Using a survival analysis they found that the percentage of patients reporting meaningful pain relief by 30 minutes was significantly ($p < 0.05$) greater in the benzocaine group than in the placebo group (77% for benzocaine and 47% for placebo). Complete resolution of the chronic otherwise unexplained trigeminal pain with a topically applied anesthetic indicates neuropathic pain with peripheral sensitization. Of course, this conclusion assumes all other local pathologies are not present and a strong placebo effect is not present. In such cases, a custom-fabricated vacuum-formed tissue stent that covers the painful area can be made to hold the topical benzocaine in place for an extended time (Colgate Orabase-B®).[115] The purpose of the stent is to hold the medication at the painful site.[116–119]

In the anesthetic test protocol, if the pain does not resolve with topical anesthetic, this lowers the chances of sustained application being therapeutic and reversing the neuropathic changes. In these cases the next step is to perform a local infiltration of 2% lidocaine with epinephrine in the area to see if the pain can be stopped. As mentioned earlier, the neural changes are considered more substantial and more it is more likely that central sensitization has developed (i.e., 2nd and 3rd order neuronal changes) when a single anesthetic infiltration or nerve block fails. This suggests that the magnitude of peripheral and central change are such that the patients will require systemic (usually anticonvulsant) medications in addition to the topical anesthetics to manage the chronic pain.

17.4 Etiology of spontaneous chronic trigeminal pain in the otherwise healthy tooth

There are two common theories that are used to explain spontaneous tooth pain in a caries-free patient with no periapical lucency. Both are discussed next.

17.4.A Clenching-induced pulpitis

There is a collection of circumstantial data that suggests that clenching-induced pulpitis is a reasonable hypothesis for the causation for dental neuropathic pain. First, in this line of evident is that as teeth age, the pulpal chamber and canals get smaller, which might compromise pulpal blood flow. Specifically, one study examined the effect of age on the diameter of the apical third of root canals from extracted teeth.[120] Using 40 first upper molars they found that the of the palatal and mesiobuccal root canal diameters exhibited significant narrowing with age. The above noted aging-related changes in root canal diameter do not prove that canal narrowing alone compromises pulpal circulation and leads to a higher chance of pulpal ischemia. The second piece of circumstantial evidence is that age is known to modify pulp circulation. This has been studied using laser Doppler assessment to measure pulpal blood flow (PBF) on 22 clinically healthy upper central incisors in 22 healthy subjects who varied in age from 8 to 75 years.[121] This study showed that the resting PBF was significantly decreased with increasing age of the participants. Of course this type of recording has not yet been performed on posterior teeth but the data taken from the central incisor should generalize to all teeth. The third piece of circumstantial evidence is that with increasing attrition (which is an analog of clenching and grinding behavior) the root canal dimensions also decrease. This has been examined in a study using 100 extracted canines, 50 of which had advanced tooth wear (attrition) and 50 were without it.[122] The dimensions of root canal were investigated at the light microscope level. They reported the nonworn teeth had a significantly greater root canal diameter in the cervical 1/3 than the teeth with advanced wear. Again, the study of root canal size changes with tooth wear does not prove that clenching can compromise pulpal circulation, cause ischemia, and induce inflammation within the pulp; it is only suggestive. A fourth piece of circumstantial evidence shows that intrusive tooth loading can compromise human pulpal blood flow. This has been examined in a 2002 study that recorded PBF, using a laser Doppler flowmeter, from 13 vital upper left central incisors in 13 healthy subjects.[123] Eight of these subjects had a very low continuous intrusive force (0.5 N) applied to the tooth using an orthodontic archwire. Pulpal blood flow measurements were made before, during the force application, and after removal of the wire, and five of the subjects had all of the same procedures performed and measurements made but no force was applied. This study reported that the pulpal blood flow in the experimental group was significantly reduced during the period of continuous intrusive force application compared with the control subjects. This finding was actually surprising since the force level used in this study (0.5 N) was well below what would occur if a patient had a sustained tooth clenching habit. For example, in research on the posterior tooth force levels achieved in nocturnal bruxism patients, one study reported that the typical levels were between 50 and 150 N and even these levels are still well below maximum force levels of 500 N.[124] Unfortunately, as was noted above, the laser Doppler flow data has been performed exclusively on anterior teeth and not on posterior teeth. The fifth and final piece of circumstantial

evidence comes from a study that reported on the effect of a continuous intrusive force on the pulpal tissues of healthy premolars in teenagers (11- to 17-year-olds).[125] While this study did not look at pulpal blood flow they did examine the histologic effects of intrusion on 20 healthy premolars that were scheduled for extraction. As a control they had 20 homologous premolars that did not have intrusion. The 20 premolars that were intruded via an orthodontic archwire had a load of 150 g (or approximately 1.5 N) applied for a period of 15–20 days. Light microscopy observation of the pulpal tissues in the intruded teeth revealed alterations in predentin, calcium deposition, fibrohyalinosis, congestion, inflammation, and hamorrhage. Interestingly, pulpal inflammation because of sustained intrusion was present in young patients, but undoubtedly it is even more likely in older patients.

In combination, the preceding experimental and observational data taken from extracted teeth as well as recorded *in vivo* from healthy human subjects suggests that age and heavy function narrow the canal and decrease resting blood flow. The data also suggests that sustained clenching could also substantially reduce intrapulpal blood flow, potentially producing an ischemic injury and inflammation of the pulpal tissues in the absence of tooth fracture or pulpal tissue infection. While the above literature offers only circumstantial or indirect evidence, it would explain why a seemingly spontaneous onset atypical odontalgia pain is more prevalent in posterior teeth and in patients over 30. What is not yet clear is the reason women are over-represented in the atypical odontalgia population. Clearly additional laser Doppler pulpal blood flow research on posterior teeth is needed and cofactors such as gender, attrition, habitual clenching behavior, apical canal diameter, and age need to be included and examined.

17.4.B Incomplete tooth fractures in chronic trigeminal pain

As was mentioned above, a common alternative hypothesis that must be considered with chronic trigeminal pain is that a tooth has an incomplete crack or fracture. Sometimes this diagnosis is excluded by performing what has been termed a diagnostic root canal or diagnostic extraction. Since no one would elect to have an irreversible procedure be the first choice of diagnosis, we need to discuss alternative methods for diagnosis beyond pulp testing and periapical imaging. One promising method would be to perform a direct microscopic examination of the tooth for incomplete fractures.[126] One 2002 study assessed the value of direct visual examination of 46 chronically painful teeth in 32 patients after removal of all restorations was performed for evidence of incomplete fracture.[127] They found evidence of incomplete tooth fracture in one or more teeth from 29 of the 32 patients. While this study suggests that, if you look hard enough, 90% of teeth with persistent pains will have an incomplete tooth fracture as the underlying cause, this finding is not consistent with other literature since the long-term outcomes for patients seeking care in a chronic orofacial pain clinic suggest that less 25% have complete relief with irreversible dental and oral surgical treatment. Clearly additional research data on this method of diagnosis (direct visualization using an operating microscope) and the long-term results is needed; however, in the meantime, this method should be considered to confirm the presence of a structural abnormality of the tooth before a "diagnostic" root canal or "diagnostic" extraction is performed.

17.5 Treatment of chronic trigeminal neuropathy

The pharmacotherapy of chronic and neuropathic pain states has been described extensively in several reviews.[128–131] Unfortunately confusion still exists as to which medication is best for the treatment of chronic trigeminal neuropathic pain, due in large part to the large number of pharmacologic medications that can be used to treat both pain symptoms and the co-morbid diseases. In addition, there are no neuropathic-activity-suppressing medications that affect only the damaged, sensitized nerves without having a powerful effect on normal sensory nerve systems. This means that high side effects are likely to be associated with these medications. Direct medication-to-medication trials are not commonly performed, and therefore it is difficult to compare medications for relative efficacy. It is, however, common to use two numbers calculated from a randomized blinded controlled clinical trials to help rate and compare drugs. The first is the number needed to treat (NNT), which is defined as the number of patients needed to treat with a certain medication to obtain one patient with a defined degree of pain relief (usually 50%).[132,133] The second is the number needed to harm (NNH). This is defined as the number of patients that need to be treated for one patient to drop out due to an adverse effect. The characteristic of a good medication is a low NNT and a high NNH. Several meta-analyses of medication trials have reported these two numbers for medications commonly used in the management of neuropathic pain.[134–141] Using the preceding meta-analysis information, plus the NNT and NNH calculations, the neuropathic-suppressing medications have been ranked as first-, second-, third-, or fourth-line medications (Secs. 17.5.A–17.5.D).

17.5.A First-line treatment for chronic trigeminal neuropathy

Using these rankings, the first and safest approach to treating chronic neuropathic trigeminal pain is to apply topical anesthetics (a first-line medication) for a prolonged period of time to attempt to suppress nociceptive activity and reverse the neuropathic changes. Usually these medications are applied to the focal pain site using a tissue-covering oral stent as a holding device. The most common topical anesthetic medication is benzocaine 20% in Orobase® paste to control the patient's pain. Other first-line orally administered medications might be added to the treatment protocol: for example, by including a tricyclic-antidepressant-type medication (e.g., nortriptyline) and/or a mild anticonvulsant-type medication (gabapentin or pregabalin).

17.5.B Second-line treatment for chronic trigeminal neuropathy

If adequate control is not achieved with these two agents and the topical anesthetics, another, second-line medication would be added: an atypical antidepressant (e.g., duloxetine). This medication is used if the tricyclic antidepressant/anticonvulsant combination does not work or if the side effects are not acceptable to the patient. In all situations, the above medications would be supplemented with a nonopioid analgesic for breakthrough pain (another second-line medication).

17.5.C Third-line treatment for chronic trigeminal neuropathy

In some cases, a moderate or strong opioid (third-line medication) is used if the nonopioid analgesic is not adequate. In some select neuropathic pain conditions (e.g., trigeminal neuralgia, chronic daily headache [CDH], burning mouth syndrome [BMS]) individual neuropathic medications that would be third- or fourth-line medications for trigeminal pain might be first-line medications; although these medications are not the focus of this chapter, they are included for completeness.

17.5.D Fourth-line treatment for chronic trigeminal neuropathy

Finally, in cases where the patient has substantial co-morbid depression a fourth-line neuropathic pain medication such as a selective serotonin reuptake inhibitor (SSRI) would be used as part of the treatment protocol. In addition, behavioral methods of pain suppression are used in cases were medications are not adequate. This chapter does not cover the nonpharmacologic methods used to treat pain (e.g., behavioral and physical medicine) but without question a comprehensive approach to assessment and treatment of pain is paramount. As a general rule, the clinician also must try to avoid polypharmacy, which sometimes is impossible in the treatment of chronic pain. Theoretically the use of a single medication that is directed toward the responsible pain receptor is preferred over a combination of medications that are nonspecific for the condition being treated. Likewise, the use of multiple medications with different mechanisms of action should increase effectiveness for conditions where more than one receptor needs to be targeted. The clinician's goal should be to alleviate pain and distress while keeping medications to a minimum effective dose.

17.6 Long-term prognosis for chronic trigeminal neuropathy

All patients with a neuropathic pain disorder ask about the future in that they wish to know: "How long with the pain last?" and "Will it go away with time?" In addition, when they are having irreversible treatments they usually want to know the odds of the treatment working. Extensive data on the prevalence of how often irreversible dental treatments (e.g., endodontics and extractions) completely solve a patient's chronic trigeminal pain without pretreatment evidence of nonvitality and or periapical lucency is based only on retrospective analyses of cases. While such reports are valuable they make it difficult to reliably predict the future for an individual patient. There are only two studies that examine the long-term prognosis of patients suffering facial pain that does not fit with the traditional diagnostic criteria and does not respond to dental treatment. One 2004 article described the long-term results of a cohort of 74 patients suffering chronic idiopathic facial pain who were seen a minimum of 9–19 years prior.[142] Of the 74, 13 had died and 16 did not wish to participate. Of the 45 remaining study participants 10 (22%) were free of orofacial pain. In a subset of 14 of these patients who had undergone multiple extractions (7.1 per patient), only 3 (21.4%) reported permanent pain relief, which is no higher than the rate seen in nonextraction cases. Overall these authors reported a very low success rate for the invasive dental treatments that were performed and suggested they may be contraindicated in patients suffering from idiopathic orofacial pain. Their data was consistent with a prior study on persistent facial pain.[143] This study followed up 109 consecutive patients seen in a dental school pain clinic. The patients had between 4 and 9 years elapsed from their first visit to the follow-up; of the 109, 85% responded to the questionnaire. The data

suggested only 27% of the patients experienced total disappearance of pain. These two studies suggest that between 21% and 27% of patients who have chronic orofacial pain will have pain relief with time. It may also suggest that the treatments provided in the late 1980s and early 1990s were not highly effective.

Based on this data, the best that can be said is that, assuming no obvious dental infection or cracked tooth is identified, the odds of stopping a patient's atypical odontalgia pain or phantom tooth pain (after failed root canal therapy or extraction has not stopped the pain) is 25% for full pain remission in 5-plus years. Moreover, the odds of a positive psychiatric diagnosis being made (e.g., anxiety, depression, somatization) in a failed treatment for atypical odontalgia or phantom tooth pain is 67%. It seems logical to hope that with a logical plan, a more defined diagnosis, and some of the newer medications and methods of treatment that the percentage of patients having full remission will increase and more patients overall will feel better managed. With earlier treatment and better pain control using the best neuropathic suppressing medications, this the rate of remission hopefully will increase and it should also prevent secondary psychiatric disease from developing.

17.7 Seven final recommendations for persistent atypical odontalgia and/or phantom tooth pain disorders (also known as chronic trigeminal neuropathy)

Recommendations regarding persistent atypical odontalgia and/or phantom tooth pain disorders (also known as chronic trigeminal neuropathy)

1. If pain is modulated by topical anesthetics, then applying these medications (benzocaine 20% in Orobase® paste) for a prolonged duration using a medication stent is the first method of treatment.
2. If topical anesthetics are not sufficient, the initial treatment protocol would be to use either a tricyclic-antidepressant-type medication (e.g., nortriptyline) and/or a mild anticonvulsant-type medication (gabapentin or pregabalin).
3. If adequate control is not achieved with these two agents and the topical anesthetics, the next medication that should be tried is an atypical antidepressant (e.g., duloxetine).
4. In some cases, a moderate or strong opioid (tramadol) is needed to manage the pain.
5. In cases where the patient has substantial co-morbid depression, fourth-line neuropathic pain medications would be a selective serotonin reuptake inhibitor (SSRI; citalopram) and a strong opioid.
6. The data on the long-term prognosis for chronic trigeminal neuropathy with treatment suggests that between 25% and 27% of patients experienced total disappearance of pain.
7. Invasive dental treatments (repeated endodontics, apical surgery, alveolectomy) for atypical odontalgia or phantom tooth pain (assuming no obvious dental infection or cracked tooth) yields a very low prognosis, with a potential for pain exaggeration as a result of the treatment.

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Chapter 18

Temporomandibular joint arthritis: implications, diagnosis, and management

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18.1 The normal temporomandibular joint

18.1.A General considerations

The temporomandibular joint (TMJ) is a complex synovial joint. It is the only joint in the human body where the condyle slides completely out of its socket and yet is not considered dislocated. This unique joint contains a disk composed of dense fibrous connective tissue, and the temporal and condylar articular surfaces are also covered with the fibrocartilage rather than the more typical hyaline cartilage seen in other joints.[1,2] Synovial fluid lubricates the joint, and loading of the articular fibrocartilage and subchondral bone causes chondrocytes in the articular cartilage to synthesize and secrete collagen and proteoglycans and other proteins necessary for cartilage and subchondral bone repair.[3–7] Proteoglycan molecules consist of a protein core with negatively charged glycoaminoglycan side chains composed of keratin sulfate and chondroitin sulfate. Aggregates of proteoglycans are linked to a core hyaluronic acid. The twisted structure of this molecule is such that it creates space where water molecules can be bound inside this complex molecule, and compression of the cartilage releases this fluid. It is recaptured as compression is removed. This fluid movement allows cartilage to undergo reversible deformations.

18.1.B Synovial fluids and the temporomandibular joint

Like all synovial joints, the fibrocartilage and TMJ disk are largely acellular and are maintained in health and repaired and lubricated by the synovial fluid in the joint. With either excessive loading or loading without adequate lubrication there is a surface breakdown, leading to microfracture of the cartilage and osteoarthritis. In synovial joints, it has been reported that aging induces articular cartilage thinning and the cartilage actually has a color change (white to a dull yellow). In addition, the fluid that lubricates and protects the joint surface changes with age. With aging, there is reduced accumulation of this synovial fluid and smaller proteoglycans are synthesized, which therefore hold less water and have less compressive ability, and there is more breakdown in the surface of the joint. This produces an increase in keratin sulfate and reduces chondroitin sulfate content in the synovial fluid. These changes are partly caused by the decrease in water content that accompanies aging and a change in cartilage proteoglycan. These changes are considered one of the earliest signs of articular cartilage loss in osteoarthritis. This was clearly demonstrated by a 2002 study[8] which examined normal synovial fluid and measured the concentrations of chondroitin 6-sulfate (C6S), chondroitin 4-sulfate (C4S), and hyaluronic acid (HA) in healthy subjects of different ages. The subjects were 82 healthy volunteers ranging in age from 20 to 79 years. They found that the concentrations of CS and HA varied with age. Their values were highest between 20 and 30 years of age, and thereafter they showed a tendency to decrease. The ratio of C6S to C4S was significantly lower in the group aged 60–70 years compared with the group aged 20–30 years. In fact, multiple regression analysis demonstrated that age was, strongly, negatively correlated with the C6S concentration and the C6S:C4S ratio.

18.1.C Age profiling of TMJ disease

Arthralgia, arthritis, and arthrosis are among the most common conditions that affect the TMJ. With trauma and time, starting in the early 30s, the cartilaginous surfaces of

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the TMJ start to show wear-and-tear deterioration, which is then called osteoarthritis. When this wear-and-tear process starts to affect more than one or two joints, this is described as a polyjoint arthritic disease process and it is more common in patients over the age of 50. As might be expected considering this high prevalence, the social and economic impact of rheumatic diseases taxes our healthcare systems. Adults over the age of 65 have more patient visits for these diseases than any other age group.[9] In addition to clear-cut rheumatologic disease, there are more than 100 medical conditions that affect the muscles and tendons and joints that are classified as musculoskeletal related diseases. It is postulated that approximately nearly 1 in 5 adults of the US population is also demonstrating signs and symptoms of musculoskeletal disease.[10] Moreover, $118.5 billion per year was spent by US citizens on the care of musculoskeletal diseases. Over $86.2 billion is spent annually on rheumatic diseases. The percentage cost of the US gross national product used to treat musculoskeletal disease has increased each decade since the 1960s. When these diseases are severe, mobility and functional limitations cause increased work loss, disability, nursing care, and premature retirement. Musculoskeletal disorders are second only to heart diseases as a cause of work disability. Work-loss costs associated with rheumatic diseases account for 50–76.5% of all indirect costs. Therefore, it is important to understand the disease process and to develop new therapeutic strategies.

18.2 Arthritic disease of the TMJ

18.2.A Description and prevalence

Osteoarthritis is considered a disease of the bone, cartilage, and supporting tissues and is the result of both mechanical and biologic events that destabilize the normal coupling of degradation and synthesis of articular cartilage and subchondral bone.[11] It is characterized by degeneration of joint cartilage with osseous erosion and sclerosis and sometimes osteophyte formation occurring at the joint margins.[12] Age is considered to be the primary risk factor for osteoarthritis and the increase in prevalence with age that is observed in patients with osteoarthritis is likely a consequence of biological changes that occur with aging.[13,14] When an elderly patient attends a dentist's office with a complaint of jaw pain, the most likely diagnosis is localized arthritis (assuming they do not exhibit polyjoint arthritic disease). This can usually be discovered with palpation, auscultation, and radiographic examination of the joint. Occasionally the reason for the jaw joint pain is related to a disk derangement of the jaw (clicking, locking, and/or dislocation), but osteoarthritis is the more prevalent problem in the elderly. In a study based on a European population, it was reported that the prevalence of osteoarthritis is approximately 12% for subjects between 25 and 50 years of age, but in the subset of patients over 60 years this prevalence reaches as high as 95%.[15] Fortunately, osteoarthritic changes in the TMJs of an elderly population are much less prevalent than the above data might suggest for all body sites. In a random sample (n = 88) of elderly subjects (between the ages of 76 and 86 years) living in Helsinki the most frequent radiographic finding in the TMJ was flattening of the articular surface, indicating osteoarthritis. This was found to occur in 17% of the population.[16]

Still, 17% of the population over 65 with TMJ osteoarthritic change is a large group of patients. It is likely that as many as 50% of those with radiographic change have a mild to moderate (or worse) level of pain and dysfunction in their jaw. Aging in-and-of-itself is not thought to cause osteoarthritis, but if a combination of several age-related changes occurs in the same individual, then osteoarthritis will result. Specifically, forceful repetitive function (e.g., bruxism) and/or disk displacement along with synovial fluid alterations of the TMJ will predispose an individual develop osteoarthritis. Localized osteoarthritis is usually thought to be traumatic (either macrotrauma or repetitive microtrauma) in nature but could also be due to a rare infective arthritic disease. Chondrocytes in human articular cartilage collected from patients whose age ranged from 1 to 87 years showed that there is an age-related increase in the accumulation of senescent chondrocytes in the articular cartilage. Furthermore, *in vitro* studies have demonstrated that chondrocytes subjected to repetitive exposure to peroxide or that have grown under superphysiologic oxygen tension undergo premature aging and that excessive mechanical stress applied to cartilage results in significant increased production of oxidants.[17]

18.2.B Pathophysiology of osteoarthritis

Susceptibility to develop osteoarthritis increases and is determined when local factors, such as joint deformity and previous damage to important protective structures in the joint, which leave the joint vulnerable to normal activities, are combined with systemic vulnerabilities.[18] Nonetheless, despite the nature of the initiating factors of osteoarthritis, the pathological progression follows a typical pattern.[19] The onset of osteoarthritis tends to be insidious and the progression of the disease tends to take a chronic course. Loss of articular cartilage is the hallmark event in osteoarthritis, therefore is the structure that has attracted most attention in relation to the pathogenesis of this condition. However, the pathophysiology of osteoarthritis involves the whole joint, and other associated structures can also be affected, such as the subchondral bone, the soft-tissue structures in and around the joint, such as ligaments, capsule, and muscles. Besides

progressive cartilage loss, the structural changes observed include increased subchondral plate thickness, formation of new bone at the joint margins (osteophytes), and development of subchondral bone cysts.[20] In the earliest phases of osteoarthritis there is chondrocyte clustering as a result of increased cell proliferation and a general upregulation of synthetic activity leading to a hypertrophic repair of the joint tissue, which results in a thicker than normal cartilage appearance, a phase which can last for decades. As the disease progresses there is a decrease in proteoglycans.[21] The loss of proteoglycans causes the softening and reduction in the thickness of the joint cartilage. The ultimate result is the appearance of vertical defects or gaps, a process called fibrillation. At this stage, the underlying bone is exposed due to the disappearance of the cartilage. Subsequently the exposed bone remodels and hypertrophies, leading to sclerosis, new bone formation at the joint margins (osteophytes), and subchondral cyst formation.[22]

Osteoarthritis traditionally has been regarded as a noninflammatory process, but recent studies using improved detection methods have shown the involvement of altered inflammatory pathways. These observations provide strong evidence for inflammation as one of key mechanisms in the pathogenesis of osteoarthritis, at least in some patients and some phases of the disease process. In a recent study significantly lower levels of the inflammatory mediator peroxisome proliferator-activated receptor gamma (PPARγ) were found in the cartilage of patients with osteoarthritis in comparison with cartilage from healthy individuals.[23] This study also demonstrated that interleukin 1(IL-1), tumor necrosis factor alpha (TNF-α), interleukin 17 (IL-17), and prostaglandin E2 (PGE2) induce downregulation of PPARγ, suggesting that downregulation of this chondroprotective molecule might be one of the mechanisms involved in cartilage degeneration. Moreover, it has been suggested that inflammation and cartilage destruction may be two separate pathogenic events: IL-1 has been shown to be responsible for the infiltration of inflammatory cells into the joint and the loss of proteoglycans from cartilage. On the other hand TNF-α, which has many of the properties of IL-1, also induces the infiltration of inflammatory cells into the joint; however, it fails to cause significant cartilage destruction. Since TNF-α, has effects on chondrocytes similar to the effects of IL-1, in combination these two cytokines yield a strong synergistic effect.[24,25] In fact, IL-17, TNF-α, and IL-1 have been considered potential targets in arthritis therapy.[26] Furthermore, previous studies have demonstrated that there is a correlation between increased synovial fluid levels of TNF-α in patients with chronic inflammatory disease of the TMJ and pain levels on the TMJ during mandibular movement and upon palpation of the posterior aspect of the TMJ capsule.[27,28]

18.2.C Signs and symptoms

Common symptoms experienced by patients early in the course of arthritis include joint pain that worsens with activity but is relieved at rest. However, if the disease has reached an advanced, severe stage the patients might experience pain even at rest. Additionally, another sign of advanced disease is internal derangement which might lead to "locking" of the joint. Another common symptom is morning stiffness or following inactivity which, unlike other types of arthritis, rarely exceeds 30 minutes. Characteristic signs of clinically evident osteoarthritis are decreased range of motion, bony enlargement, occasional effusion, variable degrees of inflammation, and crepitation which is considered to be a late manifestation of the disease. The usual presenting symptom is pain, which can involve one or only a few joints. Tenderness on palpation at the joint line and pain on passive motion are also common, although not unique to osteoarthritis. The presence of osteophytes is not only the most specific radiographic marker of osteoarthritis but is also indicative of advanced disease. Additionally, other radiographic findings found in osteoarthritis include decreased joint space, subchondral sclerosis, and subchondral cysts.[29]

The most common form of arthritis that affects the TMJ is osteoarthritis. The spectrum of clinical signs and symptoms found in osteoarthritis are equal in all the joints including the TMJ. Therefore, the affected patients present with pain, crepitus, joint space narrowing—symptoms which may only be evident at late stages of the disease (Figs. 18.1 and 18.2).[30] Martinez et al. studied the clinical and radiological features of patients with osteoarthritis of the TMJ. They identified crepitation as the most relevant clinical finding (93% of cases), along with limited mandibular movement range. Furthermore, the most relevant finding on radiographic examination was alteration of joint surface morphology (62–68% of cases). The most frequent radiographic finding in the TMJ was flattening of the articular surface, which occurred in 17% of the population.[31] Another study investigated the prevalence of jaw pain in patients that presented with rheumatoid arthritis (RA) and osteoarthritis. After analyzing 4,011 patients with osteoarthritis they found that 18.6% of the patients presented with pain. They concluded that patients who experienced jaw pain may have decreased functional ability, as well as decreased quality of life.[32]

18.2.D Treatment of TMJ osteoarthritis

When management of joint pain symptoms is required, the principles governing treatment of the TMJ are no different than those used with any other body joints with painful osteoarthritis. A table listing the all common treatment of TMJ osteoarthritis is provided (Table 18.1).

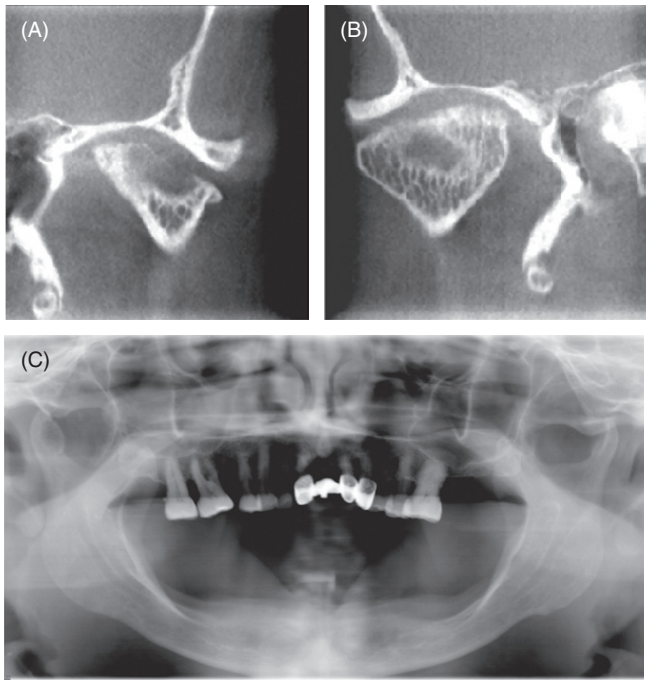

Figure 18.1 Osteoarthritis affecting the temporomandibular joint (TMJ). Computed tomographic scan of left TMJ (A) and right TMJ (B); panoramic radiograph (C) of the same patient, showing erosive and irregular cortical outline of the surface of the condylar head characteristic of degenerative changes secondary to osteoarthritis in both TMJs.

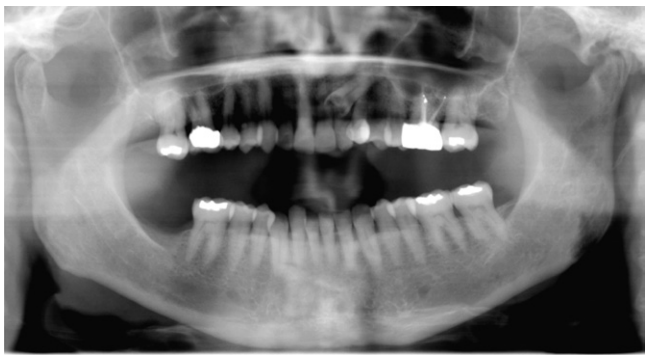

Figure 18.2 Another case of TMJ osteoarthritis. Panoramic radiograph showing a left TMJ with extensive degenerative changes on the left condyle with loss of structure, loss of articular joint space, and involvement of the articulating surface.

Nonpharmacologic treatments

The elements of the nonpharmacologic treatment approach are education, avoidance of harmful behaviors, and in-office physical therapy including daily exercise and use of an occlusal appliance (when tooth clenching or an unstable bite is evident).

Table 18.1 Treatment methods for TMJ arthritis

Nonpharmacological	
Education	• Reduce stressful jaw function • Reduce or eliminate aggravating factors (clenching, opening wide, gum chewing)
Physical therapy	• Apply heat or ice packs to jaw • "N" position exercise (placing jaw and tongue in the position achieved when pronouncing letter "N" and holding for count of 6, six times, repeated six times daily) • Jaw hinge exercise (move jaw in a strict hinge motion to a point about 15 mm open and then close it again)
Occlusal appliance	• Stabilization acrylic appliance
Pharmacological	
Nonopioid analgesics and NSAIDs	• Usual and customary treatment
Corticosteroid injection (triamcinolone)	• With any inflammatory TMJ pain problem that is unresponsive to the usual treatments • Early treatment intervention in patients with gastritis, GERD, or other indications for not using a nonsteroidal anti-inflammatory medication • Injected in a single jaw joint, 10 mg, targeted to the superior joint space; usually mixed with local anesthetic to make the joint injection more comfortable
Intra-articular hyaluronic acid injection (Synvisic and Hyalgan)	• For patients who have only a transient response to the corticosteroids • Given in a series of three injections, 1 month apart; currently approved for knee joints

GERD, gastro-esophageal reflux disorder; NSAIDs, nonsteroidal anti-inflammatory drugs; TMJ, temporomandibular joint.

Education

One consistent feature of TMJ arthritic disease management is that the patient must be taught about the chronic nature of the disease. It is sometimes difficult for the patient to accept that the damaged joint tissues cannot be repaired or replaced. For instance, it has been shown that patients that have a high degree of jaw function inference show a poorer prognosis when treated with self-directed physical therapy and over-the-counter nonsteroidal anti-inflammatory drugs.[33] Depending on what medical information the patient has been exposed to they might have unrealistic treatment expectations that can lead to frustration and depression.

Avoidance of harmful behaviors

The patient must be taught to identify and avoid stressful jaw function (e.g., chewing hard foods) and reducing or eliminating aggravating factors such as teeth clenching, opening wide, and gum chewing.

In-office physical therapy

A combined systematic guided musculoskeletal therapy program including exercises, how to properly apply heat and/or ice packs to the jaw, and cognitive self-management skills has been shown to reduce self-reports of pain in a population of patients with chronic myofascial pain.[34] The most important exercises are the "N"-position exercise, which involves placing the jaw and tongue in the position achieved when the letter "N" is said and holding it for a count of 10. The patient is instructed to perform this exercise every 2 hours each day (or 6 times a day). The goal is to put and hold the jaw in the most relaxed jaw position where the teeth are apart and the lips not touching. Once the patient's initial pain symptoms are shown to be reducing, the next exercise is called the jaw hinge exercise. This involves instructing the patient (using mirror feedback) to carefully move the jaw in a strict hinge motion to a point about 15 mm open and then back closed again. This movement promotes synovial fluid movement without any translation of the condyle. The motion is usually performed done 15 times on a 2–3 hour schedule or 6 times a day. When the N-position and hinge exercises help reduce strain on the joint, it is also advisable to use 20 minutes of heat therapy (hot towels, or a moist heating pad) applied to the sorest muscles. Heat helps to reduce pain and stiffness by relaxing aching muscles and increasing circulation to the area. Finally, nonopioid analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) can be used.

NSAID treatments

Indications

When and how to use NSAIDs for inflammation and pain control is discussed in detail in Chapter 3 and is not covered here.

Dosage and adverse effects

This is information is provided in Chapter 3.

Efficacy

Pharmacologic treatment of arthritis (of all types) aims to decrease pain and inflammation and includes non-narcotic oral analgesics, such as acetaminophen, in those with pain complaints. With regard to selection of an NSAID versus a nonopioid analgesic medication for osteroarthritis, the American College of Rheumatology (ACR) guidelines emphasize that acetaminophen should be the first-line treatment for osteoarthritis of the hip and knee.[35–37] We also suggest this is the case for TMJ osteoarthritis, but the dose of acetaminophen that has been used in the studies on which this recommendation is based is 4000 mg per day—a dose that is closer to the toxicity level than many practitioners and patients are comfortable with. Moreover, the magnitude of the pain reduction this dose of acetaminophen induces in osteoarthritis is only minimal. In cases where the patient cannot or will not take this much acetaminophen or where the pain is not effectively controlled, an alternative is to use NSAIDs. Several medications in this drug class are reasonable options (e.g., ibuprofen, naproxen sodium, and nabumetone) and if the patient has a gastric sensitivity making it more logical to use cyclooxygenase-2 (COX-2) selective medications, they have three options here also (celecoxib, meloxicam, etodolac). These medications are reviewed in detail in Chapter 3 and they have reasonable efficacy for arthritic disease, although they must be used with caution.

Nutritional supplements

Indication

A method of treatment that patients experiment with is the use of "nutraceutical" supplements such as glucosamine and chondroitin sulfate. Chondroitin sulfate is a major component of aggrecan, and glucosamine sulfate is a normal constituent of glycoaminoglycans; both are believed to be involved in restoring the balance in cartilage metabolism.

Dosage and adverse effects

It is commonly recommended that a patient consume 1500 mg of glucosamine and 1200 mg of chondroitin sulfate daily. There are very few adverse events associated with this supplement.

Efficacy

The Glucosamine/chondroitin Arthritis Intervention Trial (GAIT), a 24-week, randomized, double-blind, placebo- and celecoxib-controlled, multicenter trial, evaluated the effect of these two supplements, given as 1500 mg of glucosamine and 1200 mg of chondroitin sulfate daily.[38] The results showed that treatment with glucosamine and chondroitin sulfate in combination may be effective in the subgroup of patients with moderate-to-severe knee pain; however, their

effect failed to be superior to celecoxib. Studies evaluating the efficacy of glucosamine and chondroitin in osteoarthritis of the TMJ remain lacking. A recent (2009) study suggested that these two agents are better when combined versus monotherapy, but noted that research is lacking on this issue.[39]

Corticosteroid injections

Indications

Corticosteroid injections are clearly helpful with any inflammatory-based TMJ pain problem when it is unresponsive to the usual treatments and in those patients with gastritis or gastro-esophageal reflux disorder (GERD). In such a situation, the corticosteriod agent is injected directly into the TMJ.

Dosage

When a corticosteroid intra-articular injection is indicated, several different corticosteroids can be used; a common one is triamcinalone.[40,41] The usual dose of medication injected in a single jaw joint is 10–20 mg. The injection is targeted to the superior joint space and usually the corticosteroid is mixed with an equal amount of local anesthetic to make the joint injection more comfortable. After the injection, it is wise to recommend ice packs as needed and a completely soft diet for 48 hours until the injection has an effect on the inflammation. The general guideline suggested is that the TMJ should not be injected more than twice in a 12-month period.

Adverse effects

The issue of whether there are any long-term adverse effects of repeated corticosteroid injections on the TMJ has been examined in several studies. In a study using computed tomography (CT) examination of 36 patients before and after TMJ injection of either corticosteroid or hyaluronate, there were found no changes of osteoarthritic abnormalities in the treated joint after 6 months post-treatment.[42] Additionally, in a long-term (12 years) follow-up of 21 patients with rheumatoid arthritis (RA) and symptomatic TMJs who received either an intra-articular injection of a steroid ($n = 11$) or a local anesthetic agent ($n = 10$), 14 patients reported no pain arising from the TMJ. Radiographic follow-up examination was performed on 12 of these patients and all but 4 of the 24 joints had structural bone changes. Interestingly the magnitude and prevalence of change was no different for the two groups. They concluded that the odds of long-term progression of joint destruction for the steroid and the nonsteroid injected joints were equivalent in this patient group with RA.[43] Presumably these results would be generalizable to osteoarthritic disease in the TMJ also. Moreover, a more recent retrospective chart review of 25 patients with juvenile idiopathic arthritis affecting the TMJ who had received one or more intra-articular joint injections showed that these patients tend to have only minimal adverse events.[44] Another study, on effects of CT-guided injections of corticosteroids, no adverse effects were reported after 1 year of the corticosteroid injections and the only side effect reported was a short-term facial swelling in 2 of the 13 patients studied.[45] Conversely, other clinicians have reported adverse effects on the TMJ as a result of chronic corticosteroid administration, although the generalizability of such isolated data is highly suspect.[46,47]

Efficacy

In a 4-week study of three treatment groups totaling 41 patients with temporomandibular disorders (TMDs), a corticosteroid, hyaluronic acid, or placebo was injected directly into the TMJ. All groups showed reduced clinical signs of dysfunction, but the corticosteroid and hyaluronic acid groups showed a greater decrease in the number of painful muscles and a marked increase in the ability to open.[48] In another study of 16 patients who were treated with intra-articular injections of corticosteroid and then followed up for 8 years, the authors reported an improvement in clinical signs of TMD. In addition, they reported radiographic findings suggesting remineralization of areas of condylar erosion.[49] The long-term effect (2 years) of intra-articular injections consisting of corticosteroids and local anesthetic were compared in two groups of 15 patients and were found to have a prolonged palliative effect on pain and TMJ dysfunction. A Cochrane review of the efficacy of intra-articular corticosteroid injection in the knee concluded that corticosteroid injection is more effective that placebo in alleviating pain at 1, 2, and 3 weeks postinjection.[50] However, there was no evidence of pain-reduction efficacy in the period from 4 to 24 weeks postinjection. Moreover, no statistical short-term difference was noted between intra-articular joint injections with corticosteroid and with hyaluronic acid (HA), an injectable agent used in arthritis and discussed in the next subsection. The study concluded that corticosteroid injections provide short-term benefit with few adverse effects in treatment of osteoarthritis.

Hyaluronic acid injections

Indications

If the patient has only a transient response to the corticosteroids, hyaluronic acid injections have been used with moderate success for new-onset osteoarthritis with crepitation.

Intra-articular hyaluronic acid injection can provide symptomatic relief lasting for several months. These drugs are currently approved for knee joints.[51,52] These substances have been approved for osteoarthritis of the knee and are also helpful for TMJ pain and dysfunction.

Dosage

There are currently two approved drugs, Synvisc and Hyalgan. The medications are given by injection in a series of three injections, one month apart.

Adverse effects

One study examined for effects and complications of corticosteroid injections of the TMJ versus sodium hyaluronate injections in 40 patients with TMJ osteoarthritis.[53] The authors reported only transient local pain after the injection in both groups. They did find that both medications may reduce pain and improve function in patients with osteoarthritis. The injections were more effective in patients with only TMJ pain versus patients with both joint and myofascial pain. Sodium hyaluronate was significantly more effective in deceasing pain intensity than corticosteroids in this study.

Efficacy

One of the first studies on the use of hyaluronic acid in the TMJ was performed nearly two decades ago.[54] Specifically they looked at 121 patients, who were studied at three test sites using a randomized, double-blind, placebo-controlled experimental design. Patients were selected on the basis of a confirmed diagnosis of degenerative joint disease (DJD), reducing displaced disk (DDR), or nonreducing displaced disk (DDN); and nonresponsiveness to nonsurgical therapies; and a severe jaw dysfunction using several measures. Subjects received a unilateral upper joint space injection of either 1% sodium hyaluronate in physiologic saline or a USP physiologic saline injection. They reported no differences for degenerative joint diseases and only minor difference for DDN. However, for DDR they found a statistically significant within-group and between-group improvement throughout the 6-month test period. More recently, a study evaluated the effect of sodium hyaluronate (HA) on TMJ degenerative and derangement disorders using a prospective randomized controlled clinical trial.[55] They provided HA injections in the upper compartments of the involved TMJs, with 35 receiving 1% HA 6 mg and 28 receiving prednisolone (PS) 12.5 mg administered in 3–4 injections across a 2-month treatment period. They concluded that the intra-articular injection of HA is effective and safe to treat TMJ degenerative disorders with mild adverse reactions. The results reported in a 2009 retrospective study comparing 33 TMJ osteoarthritis patients aged over 65 years versus 17 TMJ osteoarthritis patients under 65 years found both groups had significant decrease in functional limitation and masticatory pain when treated with TMJ injections of hyaluronic acid. The over-65 group had a greater decrease in functional limitation than the under-65 group. The under-65 group report less minimum pain at rest compared with the over-65 group.[56]

Topical medications

Indications

Topical creams (e.g., capsaicin, corticosteroids, NSAIDs) have been described as being helpful if the patient does not tolerate oral medications and does not want an injection-based therapy. This issue is covered in detail in Chapter 5. Another method of delivery of mediations is to use iontophoresis. This technique pushes medication through the skin at the application site using an electric current to ionize drug solutions.

Dosage and adverse effects

There are multiple over-the-counter products sold to patients to help them with arthritis pain. Detailed information on topical medications is provided in Chapter 5.

Efficacy of topical medications for arthritis

The experimental data for transdermal therapy in arthritis is weak. Reid et al.[57] compared iontophoresis with dexamethasone in a lidocaine vehicle versus placebo for TMD following three sessions of drug administration over 5 days with 7- and 14-day follow-up. Both groups of subjects showed improvement over the course of therapy and continued to report less pain and improved range of motion at the 7- and 14-day follow-up compared with placebo. These data illustrate the dichotomy of opinion that often exists between clinical observations and the results of a controlled clinical trial. If one compared the pain and dysfunction reported by all patients before treatment and at the follow-up appointments, it would appear logical to conclude that the improvement was the result of the treatment being evaluated, in this case the iontophoretic application of a steroid to the TMJ. Evaluation of the drug therapy in the context of a controlled trial, as illustrated by the dexamethasone and placebo groups, leads to the opposite conclusion, that the drug had no detectable therapeutic effect. Alternative interpretations include cyclic fluctuations in symptomatology over time and patient expectations of improvement from receiving

medications applied by a novel method in a therapeutic environment. Another study examined the effect of topical application of capsaicin on localized pain in the TMJ area.[58] In a randomized, double-blind, placebo-controlled study of 30 patients suffering from unilateral pain in the TMJ area, patients received either 0.025% capsaicin cream or its vehicle and were instructed to apply the cream to the painful TMJ area 4 times daily for 4 weeks. Capsaicin cream produced no statistically significant difference in the outcome measures when compared with placebo. This general result was also supported by another more recent study that examined the effects of a topical analgesic and placebo in treatment of chronic knee pain.[59] This double-blind, randomized, placebo-controlled clinical trial in 46 men and women with chronic knee pain showed that both groups experienced improved pain scores, but there were no differences between groups over the treatment period for any of the dependent variables. Another topical medication (transdermal lidocaine patch) has become available for neuropathic pain and was recently evaluated for osteoarthritis. The effectiveness of a 5% lidocaine patch on pain, stiffness, and function in patients with pain due to osteoarthritis was evaluated in a prospective, multicenter, open-label effectiveness trial. They concluded that the lidocaine patch 5% appears to be effective as an add-on therapy for osteoarthritis pain. It is recommended by the authors that use of up to four patches, with the patches changed every 24 hours, provides effective analgesia without anesthesia, reduces stiffness and disability, and improves quality of life in polyjoint arthritis patients, especially those who have responded incompletely to prior medication therapy. The advantage is that this approach offers an effective topical analgesic option for osteoarthritis with a minimal risk of systemic toxicity or drug–drug interactions. Additional evidence on the efficacy and safety in controlled clinical trials is needed to confirm the clinical utility of lidocaine patch therapy.

Joint lavage or arthrocentesis treatment

Indications

Arthrocentesis-based lavage is useful for TMJs with limited mobility but is controversial as a treatment for joint pain without any joint mobility. The primary goal of this procedure is to attempt to mobilize the TMJ and involves infusing and washing the joint with saline solution and conducting manual manipulation of the jaw when it is anesthetized. Its role is primarily in those patients who do not respond to pharmacologic treatment and present with limited opening. The long-term benefits of arthrocentesis lavage are still unknown and very limited good-quality comparative therapy studies have been done.

Dosage and adverse effects

While rare in their prevalence, the following complications are usually listed on a consent form that the patient signs before having an arthrocentesis procedures: Temporary or permanent facial muscle weakness resulting from motor nerve injury during the injection of which the most common problem resulting is the inability to wrinkle the brow, raise the eyebrow, or gain tight closure of the eyelids. Other, less common complications include numbness (temporary or permanent) of certain areas of skin in the region of the joint and sometimes in more remote areas of the face or scalp; bleeding within the joint that cannot be adequately controlled and could require immediate intervention by open joint surgery; ear problems, including inflammation of the canal, middle or inner ear infections, perforation of the ear drum and temporary or permanent hearing loss; instrument separation, which may require open joint surgery; facial scarring from the entry injection; damage to the joint surface during the arthrocentesis or needle procedure, usually of a reversible nature but which could permanently affect joint function. Moreover, there can be unsuccessful entry into the joint or inability to accomplish the desired procedure because of limited motion of the joint or scarring and changes in the bite after arthrocentesis which may affect chewing functions. In addition, there may be temporary or permanent limited mouth opening; postoperative infection requiring additional treatment as well as adverse or allergic reactions to any of the medications used in the procedure.

Efficacy

One study retrospectively examined the use of arthrocentesis for the treatment of osteoarthritic TMJs.[60] The patients were 29 females and 7 males (ages 16–54 years) presenting with 38 dysfunctional joints that exhibited osteoarthritis and had not responded to conservative treatment. The patients were evaluated after arthrocentesis and at time points ranging from 6 to 62 months. It was reported that 26 joints reacted favorably to the treatment and stated that in many instances the osteoarthritic TMJs returned to a healthy functional state. A prospective study reported on the effect of intra-articular irrigation injection therapy on osteoarthritis of the TMJ.[61] They treated 37 patients (the test group) with an intra-articular irrigation (arthrocentesis) and 26 with an intra-articular injection of steroid only. The percentage of patients rated as having excellent or good in the two groups was 86% in the arthrocentesis group versus 65% in the steroid group and they claimed this difference was statistically significant. Of course, a single study without randomization and substantial bias control measures in place is not conclusive. Overall, the above data suggests that arthrocentesis-based lavage of the TMJ can be effective to increase range of

motion and decrease pain in disk displacement without reduction (DDWR), and cases not responding to medical management, but it should be restricted to those cases with recent-onset hypomobility; however, use of this procedure for osteoarthritis is both illogical and yet unproven by quality research. In fact, the conclusion from a 2007 review of the literature on arthrocentesis stated that the majority of the reviewed publications were prospective case series with flawed methodology and, despite the impression that arthrocentesis may be beneficial for patients with TMJ closed lock, there have been no good prospective randomized clinical trials that confirm the efficacy of this procedure.[62] Unfortunately this review did not examine the efficacy of this procedure for osteoarthritis patients.

18.3 Polyjoint or generalized osteoarthritis and rheumatic diseases

Polyjoint osteoarthritis is by far the most common of the rheumatic diseases, affecting an estimated 20.7 million Americans. Polyjoint osteoarthritis is responsible for over 7 million patient visits per year.[63–65] When all of the arthritic diseases are added together over 70 million US citizens (1 in 3 adults) reported a rheumatic disease.[66] In those over 75 years of age, a majority of individuals reported having arthritis. Polyjoint or generalized osteoarthritis is generally classified as being primary or secondary. The most common sign of a primary polyjoint osteoarthritis is when the patient demonstrates the formation of Heberden's nodes on the distal interphalangeal joint of the hand. The proximal interphalangeal joint, the first carpometacarpal joint, spine, knee, and hip joints are also common osteoarthritis sites. McGonagle et al. offer a viewpoint that generalized osteoarthritis (GOA) may be primarily a disorder of ligaments. A review of high-resolution magnetic resonance imaging (MRI), microanatomical studies, and animal models supported the concept that the earliest structural abnormalities in GOA may be present in ligaments.[67] Primary polyjoint osteoarthritis is more or less considered idiopathic, although genetic defects are suspected strongly in this disease especially when a familial pattern of osteoarthritis is present.[68,69] Secondary polyjoint osteoarthritis is defined as joint damage or cartilage changes characteristic of osteoarthritis caused by other disorders.[70] Secondary polyjoint osteoarthritis may present in congenital and developmental disorders. Prior trauma, surgery, inflammatory disease, bone disease, blood dyscrasias, neuropathic joint diseases, excessively frequent intra-articular steroid injections, endocrinopathies, and metabolic disorders may damage joint surfaces and cartilage. Finally, with severe and very aggressive polyjoint osteoarthritis, it is necessary to also have a negative serologic test for rheumatoid factors before the diagnosis of polyjoint or generalized osteoarthritis is proven.

It is likely the genetic defects that will be discovered with involve the type 2 cartilage collagen binding proteins. This molecule forms a three-dimensional cross-linked fiber network with proteoglycan, allowing compressibility and elasticity of the joint surface. In addition to an overt genetic defect, aging appears to decrease the ability of articular cartilage to withstand loading pressures, and thus more degradation of cartilage occurs. Only recently have formal studies of the genetics of osteoarthritis been undertaken.[71] Unfortunately the various studies have not always agreed on the genetic factors that are to blame. In 2006, Carroll hypothesized two major phenotypes of polyarticular osteoarthritis. He proposed a nexus between the *HFE* gene, most commonly mutated among Caucasians, and a subset of polyarticular osteoarthritis patients with a clinically recognized phenotype. He hypothesized at least two major polyarticular osteoarthritis phenotypes, each associated with discrete genotypes. Type 1 is characterized by Heberden's or Bouchard's nodes with distal interphalangeal (DIP) joint, proximal interphalangeal (PIP) joint, knee, and great toe–metatarsophalangeal (MTP) joint involvement resembling generalized osteoarthritis. Type 2 is characterized by involvement of the index and/or middle finger metacarpophalangeal joints resembling the arthropathy associated with hereditary hemochromatosis, also the elbow, ankles and possibly intertarsal, tarsometatarsal, hip, and knee joints[72] Furthermore, a study published in 2009 reports confirmation of this hypothesis. Sixty-seven patients were assigned to the putative Type 1 POA (39 with 6M, 33F) or Type 2 POA (28 with 18M, 10F) based on predetermined clinical criteria for osteoarthritis in the hand and other joints if radiographic criteria were met. Heberden's nodes were found in 34 of 39 Type 1 subjects versus only 9 of 28 in Type 2 subjects. The human hemochromatosis gene mutations were found in 9 of 39 Type 1 subjects; 21 of the 28 Type 2 patients had a single *HFE* gene mutation.[73] Genetic researchers interested in osteoarthritis will continue to search for a complex of additional genetic defects, with the hope it will lead to new therapies, prevention, and/or genetic therapeutic strategies in the future.

18.3.A Polyjoint osteoarthritis affecting the TMJ

The TMJ is less likely to show aging-related deterioration than other major body joints, possibly because the TMJ it is less of a load-bearing joint than the knee, shoulder, or spine. Even though several treatment modalities are available for patients suffering with osteoarthritis, controlling symptoms and preventing or even slowing down the progression of the disease is still a challenge in these patients. Many efforts are

being made for the development of disease-modifying osteoarthritis drugs (DMOADs) that could be used to treat patients with osteoarthritis. Due to better understanding of the pathophysiological mechanisms of osteoarthritis that has been achieved, many promising agents have been identified. IL-1β antagonists, doxycycline, calcitonin, metalloproteinase inhibitors, compounds that inhibit inducible nitric oxide, and bisphosphonates are among the compounds that are beeing considered and investigated as potential DMOADs.[74–80] However, despite the progress made so far the approval of a true DMOAD with demonstrated efficacy for TMJ arthritis remains unfulfilled.

18.3.B Rheumatic arthritis and other systemic diseases affecting the TMJ

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune, inflammatory disorder. Rheumatoid arthritis is characterized by joint inflammation, erosive properties, and symmetric multiple joint involvement. Rheumatoid arthritis can involve other body organs. It is an aggressive disease causing joint damage within 2 years, decreased function, and increased impairment. It shortens life spans by 5–7 years and if severe the quality of life can be seriously altered.[81,82] The main serologic marker, rheumatoid factor (RF), an immunoglobin M (IgM) autoantibody against the Fc portion of an IgG molecule, is found in 75–80% of patients. While etiology is unknown, certain genetic markers, HLA-DR4 and DR1, are found in approximately 30% of patients with RA. Familial studies suggest strong evidence for genetic factors. There is some evidence that an infectious agent (virus, bacteria) may trigger the disease in genetically predisposed individuals. Edema, hyperplasia of synovial lining, and inflammatory infiltrate are early components of RA onset. Chronic RA is characterized by hyperplasia of Type A synovial cells and subintimal mononuclear cell infiltration resulting in the massive damage of cartilage, bone, and tendons by the pannus, an infiltrating inflammatory synovial tissue mass.[83]

Rheumatoid arthritis is found in the TMJ (Fig. 18.3). Fortunately, the TMJ appears to be one of the last joints attacked by RA, but it is affected in more than 50% of adults and children with RA. A recent observational study reported that, clinically, involvement of the TMJ is observed in about 65% and radiologically in 76% of patients diagnosed with RA.[84] The signs and symptoms include dull aching pain associated with function, joint edema, and limited mandibular range of motion. Anterior open bites are common. Morning stiffness or stiffness at rest lasting longer than 1 hour is common. Radiographic findings range from flattening of the condylar head to severe, irregular deformity. Multiple joints are typically involved. Symmetric polyarthritis of at least 3 joints in 14 areas is found in 50% of patients. Laboratory tests for serum rheumatoid factor (RF) are positive.

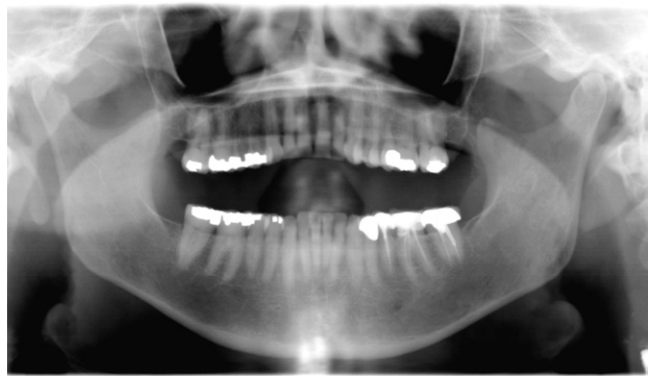

Figure 18.3 Rheumatoid arthritis affecting the TMJ. The panoramic radiograph of this patient shows evidence of degenerative changes on the right TMJ, exhibiting flattened condyle and narrowing of the right joint space. Clinically the patient presented with a 2-mm posterior open bite.

Several other rheumatic diseases such Lyme disease, psoriasis, ankylosing spondylitis (AS), mixed connective tissue disorders (MCTD), spondyloarthropathies (SPA), among others are known to affect the TMJ, which can also lead to pain, limited mouth opening, and dysfunction. Helenius et al.[85] reported a case–control study and they found TMJ tenderness upon palpation in patients 38% diagnosed with MCTD, 32% with AS, 33% with SPA in comparison with 4% of the control group. Crepitation was found in 63%, 79%, and 71% of the patients diagnosed with MCTD, AS, and SPA, respectively, as opposed to only 21% of control patients.

18.3.C Pharmacologic treatment of polyjoint inflammatory TMJ arthritis

For the more aggressive RA cases, where medications such as NSAIDs are not strong enough to manage, the current standard is to utilize one or more disease-modifying antirheumatic drugs (DMARDs) and a short course of oral or intra-articular steroid. DMARDs act slowly over 1–3 months. The early use of DMARDs in treating RA may lead to long-term control and remission and is a cost-effective treatment. On the other hand, the use of biologic agents, such as TNF inhibitors, are reserved for treatment of resistive RA.[86] They appear to alter RA by causing erosive healing, controlling inflammation, and improving function. In practice, DMARDs' effectiveness varies with each patient. DMARDs are available in two forms, nonbiologic and biologic. Nonbiologic DMARDs include antimalarial drugs, sulfazalazine, intramuscular gold, methotrexate, hydroxychloroquine, cyclosporine, azathioprine, leflunomide, and cyclophosphamide.[87] They can be used in combination to

find an effective regimen. Biologic DMARDS (anti-TNF agents) include etanercept, infliximab, and adalimumab. These agents can be conbined with nonbiologic DMARDS. The ACR published guidelines in 2008 on the use of these agents. Treatment goals in RA include the following: control of immunologic and inflammatory disease processes; prevention of joint damage and normalization of function and life span; complete relief of symptoms and return to normal daily activities; avoidance of complications of the disease and its treatments; education; counseling; physical and occupational therapy.[88,89] Complications of DMARDs are medication specific. Alteration of the immune system leading to increased susceptibility to infection, kidney, liver damage, and suppression of bone marrow activity can occur. Therefore, blood chemistry, kidney function, and liver function must be evaluated regularly.

18.3.D Genetic-based diagnosis and treatment of TMJ arthritis

Development of new and combined medication regimens is leading to better management. Unique and progressive regimens, such as the use of TNF-α antagonists in refractory RA, is giving hope to patients with severe disease. Despite these exciting advances in the treatment of such cases the indiscriminate use of this type of drug should be avoided. The use of TNF blockers has been correlated with an increase in tumor risk in patients with RA compared with the untreated population. This risk is particularly higher for the development of lymphomas.[90]

Recent work with tissue engineering is producing an exciting look into the future.[91] These researchers harvested three tissue-engineered TMJ condyles from host mice. The harvested condyles formed from adult stem cells stimulated to form either bone or cartilage. While this is early research, someday it may be possible to grow "new" condyles to replace those diseased. By understanding, the influence of genetics, function, and trauma in the initiation of rheumatoid disorders, practitioners can establish clear, reasonable, and attainable treatment goals. Time must be taken to empower our patients to manage their disease through education, understanding, and reasonable expectations.

18.4 When pain in the TMJ becomes neuropathic

One of the cardinal symptoms of osteoarthritis is pain. Even though, normally, pain is present on function and alleviated at rest there are patients in whom the pain becomes intractable, leading to greater disability. The exact mechanism for this phenomenon is still unknown. Knowing that cartilage is not sensitive to pain since it is deprived of nerves and blood vessels, it can be suggested that in addition to the local inflammation there is also a neuropathic component to the pain in osteoarthritis, with peripheral and even central sensitization of the afferent nerves. In clinical experience, several patients with osteoarthritis affecting the TMJ present with hyperalgesia of the surrounding areas. Furthermore, scientific evidence for the sensitization of the TMJs as well as central nociceptive pathways has been provided. In one study the electrical and heat thresholds over the skin of the TMJ and adjacent muscles were evaluated. The inclusion criteria for patients with osteoarthritis were pain on function, tenderness to palpation, and radiographic evidence of structural changes. In addition, they could present with limited range of motion, jaw deviation to the affected site, and/or crepitus. In this subset of patients the electrical and heat thresholds were assessed on the auriculotemporal nerve (AUT) on the skin overlying the TMJ, the buccal nerver territory (BUC) on the skin over the masseter, and in the mental territory (MNT) area on the skin overlying the chin. The results demonstrated that patient with TMJ arthralgia presented with decreased electrical thresholds in the AUT area in comparison with the BUC and MNT, suggesting that arthralgia might affect the large myelinated fibers that supply the skin overlying the TMJ.[92] Moreover, further studies, by Ayesh et al. (2007), on 20 patients who had also been diagnosed with TMJ arthralgia demonstrated that these patients present with increased sensitivity to tactile and pinprick stimuli and lower pressure thresholds on the TMJ in comparison with their healthy counterparts.[93] It has been suggested that the afferent sensitization observed in these patients might be secondary to inflammatory process. This has been tested using a rat model. These studies have shown by experimentally inducing inflammation in the TMJ of rats that the threshold to mechanical stimuli is decreased, that there is an increase in the decreased sensitivity to heat, and that these results are due to alteration in the excitability of the nerves in located in the trigeminal root ganglion which are responsible for the innervation of the facial skin.[94,95] These results together suggest that inflammation of the TMJ may be one of the contributory factors underlying the mechanism of trigeminal inflammatory allodynia in the TMJ disorders.

18.5 Seven final recommendations on the use of medications for TMJ arthritis

Recommendations on the use of medications for arthritis of the temporomandibular joint

1 When self-applied physical medicine therapy (e.g., exercises plus heat or ice, and general advice about reduced

jaw function) is used, these methods have produced a positive response in approximately 75% of patients.

2. The use of occlusal appliances for temporomandibular joint (TMJ) pain is indicated in the patient with a clear-cut jaw-muscle clenching or grinding behavior or an unstable occlusion.
3. We endorse the American College of Rheumatology (ACR) guidelines for medications that are used for primary osteoarthritis: acetaminophen first, followed by a nonsteroidal anti-inflammatory drug (NSAID) if not successful.
4. Judicious use of corticosteroid injections into the superior joint space of the painful TMJ is also a safe and logical therapy for many patients with low risk of morbidity and a high likelihood of symptom reduction.
5. When arthritis symptoms linger in spite of treatment using the above methods, it is likely that some etiologic factor is still present (e.g., strong bruxism or tooth clenching habit, a generalized stress reaction, or an autoimmune disease process).
6. For TMJ pain due to a polyarthritic disease process (e.g., rheumatoid arthritis) more specific disease-modifying drugs (e.g., immunosuppressive medications) would be in order.
7. For select cases, sodium hyaluronate injections have a substantially albeit transient beneficial effect with a predictable reduction of pain and an increase of jaw motion.

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Chapter 19

Five oral motor disorders: habitual tooth clenching and other involuntary oral motor disorders

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Multiple disorders that affect the motor system need to be considered when the trigeminal, facial, or genioglossal muscles become dysfunctional. For instance, involuntary tremor suggests Parkinson's disease; weakness suggests Bell's palsy or stroke-related paralysis; involuntary jaw and tongue motions suggest dystonia or dyskinesia; daily jaw pain and temple headaches suggest clenching or bruxism. The focus of this chapter is on five motor disorders: (1) tooth clenching, which is presumably a learned and voluntary behavior, and the most commonly seen involuntary orofacial motor disorder (OMD): (2) sleep bruxism; (3) focal orofacial dystonia; (4) oromandibular dyskinesia; and (5) medication-induced extrapyramidal system muscle activation.[1–4] Table 19.1 provides a brief definition, the main clinical features, and management approaches for these OMDs.

19.1 Habitual tooth clenching

Many patients reporting to an orofacial pain center with a complaint of pain also report an oral parafunction such as tooth clenching, habitual cheek chewing, gum chewing, and other oral habits. In fact, sometimes patients can be seen repeatedly clenching and bulging their masseter muscles during the interview. This chapter begins with tooth clenching as it is the most common of the oral parafunctions. From a scientific perspective, the problem with tooth clenching is that little data is available on how frequently this behavior occurs in the natural environment and we do not know at what point it becomes damaging to the patient. This lack of information is because most habitual behaviors are not highly deliberate acts, but an act that someone performs at the edge of their consciousness. This means their recollection of this behavior may be inaccurate and as soon as you ask someone to self-observe how often they perform this act, they change their behavior. Alternatively, if you attach electrodes to the subject's face and jaw muscles so that you can physically record this behavior, you also raise the subject's awareness of the behavior and possibly change its pattern of occurrence. To accurately gather information about tooth clenching you must (1) record masseter muscle electromyograph (EMG) over a long period of time in the natural environment, (2) prove that the subject does not alter his or her behavior as a result of the recording process, and (3) you must be able to separate chewing, talking, laughing, and facial expressions, which all have a functional purpose, from those behaviors that have no obvious functional value, such as tooth clenching.

19.1.A Habitual tooth clenching studies in the natural environment

There have been several attempts to study habitual tooth clenching in the natural environment. In the 1970s a portable EMG recording device was developed to record masseter muscle activity in the subject's natural environment and provide auditory feedback which would let the subject know they were clenching. The first report using this device described it as a daytime use device that provided tooth clenching subjects an audio sound every time they clenched their teeth above threshold.[5] This device was triggered and it recorded cumulative totals of electrical activity above a 20-μV threshold. Unfortunately, because only a single cumulative value of activity was available for each recording period, this did not distinguish between the types of oral activity the subject performed while awake (e.g., chewing, talking, laughing, clenching). This device was used almost exclusively during sleep since the other normal behaviors were less likely during sleep (see Sec. 19.2, on bruxism).

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Table 19.1 Five oral motor disorders

Oral motor disorders	Definition	Clinical features	Management
Clenching (no ICD number)	• Involuntary • Repetitive • Nonfunctional tooth contact	• Tooth pain • TMJ dysfunction • Headaches	• Majority of cases managed with an occlusal appliance and habit therapy
Sleep bruxism (ICD-9-CM #306.8)	• Stereotyped movement • Grinding or clenching of the teeth during sleep	• Dental attrition • Tooth pain • TMJ dysfunction • Headaches	• Pharmacologic treatment data not convincing • Majority of cases managed with an occlusal appliance • Only most severe cases treated with botulinum toxin injections
Oromandibular dystonia (ICD-9-CM #333.6)	• Involuntary • Repetitive • Briefly sustained muscle contraction • Results in an abnormal posturing of structure	• Involuntary jaw opening • Lateral or open jaw motion • Protrusion of the tongue • Present during the day • Disappears during sleep • Dystonic spasms increase in intensity during stress, emotional upset, or fatigue.	• Pharmacologic treatment • Transient help with botulinum toxin injections • Select use of neurosurgical treatment
Orofacial dyskinesia (ICD-9-CM #333.82)	• Repetitive and stereotypic oral movements • Onset with neuroleptic medications • Persists or worsens after withdrawal of neuroleptics	• Facial grimacing • Tongue protrusion • Puckering, smacking, and licking of lips • Side-to-side jaw motion	• No effective treatment
Drug-induced dystonic-type extrapyramidal reactions (ICD-9-CM #333.9)	• Medication induced • Illegal-drug induced • Unspecified extrapyramidal syndrome reaction	• Dystonic • Akasthasia • Parkinsonism	• Withdraw offending drug

ICD, International Classification of Diseases; TMJ, temporomandibular joint.

In the late 1980s and 1990s, digital technology improved dramatically, allowing better, more-detailed (second-by-second) recording of jaw muscle activity using portable equipment. One such device was developed and tested for its ability to perform long-term EMG recordings of the masseter muscle in healthy subjects in their home environment.[6,7] This device was used initially to capture sleep-related jaw muscle activity and these results are described below in the section on bruxism. Several years later this device was used to examine the habitual daily masseter muscle activity of short-face versus long-face subjects as assessed in their natural environment and the data reported on how much, how often, and how long normal nonpain subjects clench their teeth.[8] Specifically the study described 14 long-face and 16 short-face subjects who were selected for long-term masseter muscle activity monitoring (8 hours per day) in the natural environment over three working days. The data outcomes included the number of activity periods per hour above threshold and the mean amplitude and duration of these periods. The authors reported that the maximal EMG activities seen with experimental clenching did not differ significantly between the short-face and the long-face subjects and they also reported no significant difference between the two groups regarding the amplitude and duration of activity seen in the natural environment. The mean duration for each activity period was also not different by group and averaged 4.2 seconds in duration. What was not known is how often, how long, and how much do patients with facial muscle pain clench their teeth.

Using a somewhat similar recording apparatus ambulatory daytime and sleep period jaw motor activity was recorded bilaterally from 15 young adult patients with a clear-cut skeletal jaw deformity and 15 healthy controls (without jaw deformity).[9] The surface EMG activities were averaged, rectified, and normalized to a reference task which involved a 98-N bite force. The focus was on bilateral symmetry of right and left masseter and anterior temporal muscles in the controls and the craniofacial deformity patients. The authors showed a 15–30% right-versus-left side EMG signal difference in their controls during the day, chewing, and even when sleeping. The control subject data showed that daytime nonchewing activity (presumably clenching, talking, etc.) was 5–9 times lower than the level of jaw muscle activity generated during chewing and just

slightly lower than the sleeping masticatory activity levels being generated. Again no data is available on the frequency, duration, or amplitude of jaw muscle activity in myogenous-pain-reporting subjects who self-acknowledge "clenching" behaviors.

19.1.B Habitual tooth clenching studies in the laboratory

Kato et al. (2006) gathered the frequency of spontaneous functional and nonfunctional orofacial activities (under direct observation) in subjects without pain under laboratory conditions.[10] Sixteen asymptomatic subjects who were instructed to read silently for 30 minutes while polygraphic recordings (including audio–video monitoring) were made of their jaw and facial muscles. Orofacial behaviors were scored based on the polygraphic and audio–video records and the magnitude and duration of masseter EMG bursts were calculated for each behavior. The number of orofacial behaviors varied widely between subjects, and the most frequently observed behavior was swallowing. Approximately half of the orofacial behaviors that occurred were closely associated with body movements but 45% of all masseter muscle EMG bursts was regarded as nonfunctional activity. More than 80% of these masseter bursts were <2 seconds in duration and had an amplitude of less than 20% of maximal voluntary contraction (MVC). Overall, the authors concluded that spontaneous orofacial motor activity is variable and even asymptomatic subjects can exhibit substantial masseter bursts during wakefulness that are not associated with purposeful, function-driven activity. Unfortunately, a comparison group of subjects with facial pain of myogenous origin was not available.

19.1.C Self-reported frequency of habitual tooth clenching

There are several studies in the literature which have described the frequency of self-reported clenching events in healthy controls and in patients with facial pain. For instance, Glaros et al. (2005) reported on the number of times during the day normal subjects and facial pain subjects self-reported they had their teeth in contact.[11] Specifically this study included 3 groups of temporomandibular dysfunction (TMD) patients and a group of normal controls who were asked to carry pagers for one week. Subjects were contacted approximately every two hours by an automated calling system; when contacted they would complete a questionnaire assessing if they had tooth contact, facial tension, and facial–jaw pain. Results showed that patients with myofascial pain with or without arthralgia reported more frequent tooth contact, higher intensity contact, and more tension than patients with a TMJ disk displacement or the normal controls.

Asking the same question, Chen et al. (2007) examined the number and frequency of nonfunctional tooth contacts in healthy controls and patients with myogenous-based facial pain.[12] Specifically the study was performed on 24 subjects (15 controls and 9 patients with myogenous facial pain). Data on tooth clenching was gathered for more days and at more frequent intervals than the previously described study by Glaros et al. (2005). Recordings were made for 10 days the subjects were alerted by a radio-wave-activated wrist vibrator approximately every 20 minutes during the day to report whether the teeth were in contact. Subjects also completed two stress assessment questionnaires that were designed to measure perceived stress levels. Similar to the earlier study, these authors also reported that there was a significantly higher frequency (more than four times) of wake-time nonfunctional tooth contact in the myogenous pain patients than in controls (median of 34.9% versus 8.9%) of the day. In both groups the frequency of nonfunctional tooth contact did not significantly differ among the various days or between the genders. The pain patients had significantly higher stress scores and reported having experienced more stressful situations than the controls. The above two studies suggest that increased masticatory muscle activity responsible for tooth contact may be an important mechanism in the etiology of myofascial pain and arthralgia of TMJ.

19.1.D Harmfulness of habitual tooth clenching

Certainly the data above suggests that putting your teeth together with a sustained low-level force is not unusual and in most cases it is also not harmful to the jaw system. The question that must be answered is, "When does clenching turn harmful?" This question has also received moderate attention by researchers over the last few years. Widmalm et al. (1995) examined the relationship between oral parafunctions and jaw pain or dysfunction using data gathered by both questionnaire and examination.[13] The study sample included 203 children between the ages of 4 and 6 years. The authors found statistically significant correlations between reported bruxism, nail biting, thumb sucking, and most of the signs and symptoms associated with TMDs. A significant relationship between oral parafunction, temporomandibular disorders, and emotional status was observed in a similar study of 502 children between the ages of 3 and 7 years.[14] These authors gathered information (both subjective and objective) about the signs and symptoms of temporomandibular disorders, including attrition, oral parafunction, and emotional status in preschool children which was confirmed by parental questionnaire. The results showed significant associations between (1) attrition and emotional status,

as well as several temporomandibular joint symptoms and (2) the reported habit of tooth grinding and jaw pain. A serious limitation of the above two studies is the age of the subjects since self-report of bruxism, facial pain, and clinical examination is not of proven reliability in children between 3 and 7 years of age.

There are several studies on adults which have examined whether oral habits are related to TMD. Moss et al. (1995) used self-rating of oral habits over a 7-day period in subjects with and without facial pain.[15] The results indicated a significant relationship between TMD and self-reported teeth clenching. As with the two studies on children, there was a statistically significant association between pain status and TMD. Glaros et al. (2005) examined the role of parafunctions, emotions and stress in predicting facial pain in 96 subjects who had been diagnosed with either (1) myofascial pain, (2) myofascial pain and arthralgia, (3) disk displacement, or (4) a healthy control group.[16] The authors asked patients to record their pain, current activity/behavior and emotional level each time they were paged (approximately every two hours) during their waking hours. The authors reported that two myofascial pain groups scored higher than did the groups with disk displacement or controls on the following: pain; masticatory muscle tension; and a composite variable measuring time and intensity of contact; mood; and stress. A linear regression analysis showed that masticatory muscle tension and the composite variable was able to predict jaw pain and accounted for 69% of the variance in jaw pain.

One must be skeptical when reading studies that collect data on parafunctional habits of children or adults based on self-reporting or parental reports and not on direct measurement of jaw function. Even if the study can show an association between myogenous pain and self-reported oral parafunctions, this does not prove causality. Nevertheless, the conclusion derived from the above studies suggest that indeed parafunctional behaviors, especially those that are associated with emotional states, increased muscle tension, and sustained tooth clenching can be harmful in patients with myogenous facial pain.

19.1.E Experimental tooth clenching, injected algesic agents, and jaw pain

Several researchers have examined the question, "Does experimental clenching actually produce sustained pain in the jaw?" The approach used was based on the idea that if tooth clenching is harmful, then it should be possible to experimentally produce pain in patients by having them mimic this behavior. Several prior studies have looked at jaw clenching exercise, endurance, and postexercise pain and recovery of maximum bite force ability following exercise. Specifically, the studies reported the effect of repeated sustained isometric contractions of the jaw-closing and protrusive muscles on jaw pain and stiffness during the week following the experiment.[17,18] These two studies examined the pressure pain threshold of masticatory muscles, maximum active pain-free jaw opening, and overall jaw pain level before, during, immediately after, and 1, 2, 3, and 7 days after higher force muscle sustained contraction tasks were performed by healthy male volunteers (aged 24–39 years). They reported that jaw pain level significantly increased during and immediately (1 hour) after the experimental task. However, these subjects demonstrated only very low levels of postexperimental jaw muscle pain and soreness at 1, 2, and 3 days after the contraction tasks. This result was surprising given that it is common to induce postexercise muscle soreness in limb muscles with sustained exercise. The study did not include women in the experiment. One report in the literature that did include women in a postexercise jaw-muscle soreness study included 7 male and 7 female healthy subjects (aged 25 ± 3 years) who performed various intermittent and sustained high-force contraction tasks.[19] The main difference with the Plesh et al. (1998) study and the prior two studies by Clark et al. (1989, 1991) was that there was far more postexercise overall jaw pain level on the first and second days after the exercise, and a significant decrease in pain-free jaw opening distance on the second day in females than in males.

Svensson et al. (2001) tried to induce fatigue and pain in the jaw motor system by using a lower level sustained-force clenching task.[20] Eleven healthy men were asked to clench on a bite-force meter for 60 minutes at 10% of the maximum voluntary contraction (MVC). The authors described that all participants reported an increasing sensation of jaw fatigue and 7 out of 11 reported mild facial pain in the jaw-closing muscles during the task but all were able to maintain the required force without drop-off. Unfortunately, they did not assess if the pain lasted for any substantial length of time beyond the actual experimental task and they did not include females in the study sample. Torisu et al. (2006) conducted a similar type of study using a low-level experimental sustained clenching task to see its effect on muscle pain, fatigue, and resting jaw-muscle activity in 12 healthy men and 11 healthy women.[21] This experiment supplemented the change induced by the low-level tooth-clenching with an injection of glutamate (an algesic substance) at the end of the clenching task. Pain and EMG data were recorded before and at 3 points after a 30 minute tooth-clenching task at 10% of maximal force. The first postclenching data was preinjection (Post-1), the second postclenching data (Post-2) was after a glutamate (Glu) or isotonic saline (Iso) injection into the left masseter, and the last data set (Post-3) was collected at 60 minutes after the end of the tooth-clenching task. The authors reported that sustained low-level tooth-clenching

consistently produced some muscle pain and headache-like symptoms in both genders. The authors found that there was a larger increase in the resting EMG activity in women than in men in the masseter muscles, suggesting more pain-induced muscle-guarding behavior in the female subjects. Finally, there was no significant difference by gender for the perceived amount of experimental pain induced by the glutamate injection. Again proof of long-lasting pain was not provided by this experiment.

19.2 Bruxism

Sleep bruxism (SB) is a stereotyped movement disorder characterized by grinding or clenching of the teeth during sleep. This definition is from the American Academy of Sleep Medicine Classification of Sleep Disorders, which considers clenching a part of sleep bruxism. It involves strong contractions of the jaw muscles during sleep; these contractions can be rhythmical or continuous isometric contractions lasting from several seconds to as much as 10 minutes each night.[22] Bruxism commonly involves two basic patterns: (1) rhythmic, chewinglike movements and (2) prolonged, maximal isotonic contractions of the jaw muscles. Periods of sustained contractions have been observed to continue for up to 300 seconds. Abnormal wear to the teeth is the most often mentioned clinical sign of bruxism and is often used to determine whether a subject is a strong bruxer or not. Unfortunately, wear of the teeth is not a good measure of active ongoing bruxism and may be moderately influenced by the amount of saliva the subject produces during sleep.[23]

19.2.A Prevalence of bruxism

The prevalence of chronic bruxism is unknown because no large probability-based random sample study has been performed using polysomnography (PSG), which is needed to measure bruxism. The prevalence in the general adult population has been reported to be between 3% and 90% and, among children, prevalence ranges from 7% to 88%.[24–32] Of course, many bruxers do not have substantial attrition and many also do not make tooth grinding sounds during sleep, so sleep partners or parental reports are not always accurate. However, it is not clear that bruxing among children is the same problem as in adults.[33,34] In younger children, bruxism may be a consequence of the immaturity of the masticatory neuromuscular system. The complications of bruxism reported in children include dental attrition, headaches, and masticatory muscle soreness.[35] Sleep bruxism in children has been shown to occur more frequently in stage 2 and rapid-eye-movement (REM) sleep, with arousals in 66% of the cases. The high arousal index in children with bruxism has been moderately correlated with increased incidence of attention–behavior problems.[36] Children who brux also have high-anxiety-prone personalities.[37]

19.2.B Pathophysiology of bruxism

The pathophysiology of bruxism is unknown. Various factors have been associated with bruxism. The most cogent theories describe bruxism as a neuromotor dysregulation disorder. This theory proposes that bruxism occurs due to the failure to inhibit jaw motor activity during a sleep state arousal. There are numerous clear-cut neuromotor diseases that exhibit bruxism as a feature of the disease (e.g., cerebral palsy). The disorder of periodic limb movements is thought to be quite similar to bruxism except that it occurs in the leg muscles rather than in the jaw.[38] Bruxism has been reported during each stage of sleep; however, the majority of episodes appear during stage 2 sleep.[39,40] Bruxism also occurs frequently when the patient moves from a deeper to a lighter stage of sleep and can be induced by attempts at waking the sleeping subject.[41] Consequently, some bruxism episodes appear to be part of an arousal phenomenon including an increase in heart rate and respiration, galvanic skin resistance changes, and the appearance of the K-complex on the electroencephalogram. Although most bruxism episodes appear to occur during stage 2 sleep and during arousal, others have reported that bruxism may occur during REM sleep.[42–44]

Although, patients with SB show a higher incidence of rhythmic masticatory muscle activity (RMMA) during sleep than matched normal controls, they are good sleepers. Sleep macrostructure (e.g., total sleep time, sleep latency, number of awakenings or sleep stage shifts, and sleep stage duration) is similar between groups. Differences in sleep microstructure between SB patients and normals have been investigated in only a few studies. Lavigne et al. (2002) quantified the number of microarousals, K-complexes, K-alphas, EEG spindles, and the density of slow wave activity, in both bruxers and control groups, in order to better understand the pathophysiology of SB. SB patients showed 6 times more RMMA episodes per hour of sleep than controls, with a higher frequency in the second and third non-REM to REM cycles. SB patients presented 42.7% fewer K-complexes per hour of stage 2 sleep, but only normals showed a decline from the first to fourth non-REM episode. Only 24% of SB–RMMA episodes were associated with K-complexes in 60 seconds. The number of K-alphas was 61% lower in SB patients, no change across non-REM episodes was noted. While no difference in electroencephalographic (EEG) spindles or slow wave activity (SWA) was observed between groups, EEG spindles increased and SWA decreased linearly

over consecutive non-REM to REM cycles. The authors concluded that good sleep in SB patients is characterized by a low incidence of K-complexes or K-alphas and by the absence of any difference in other sleep microstructure variables or sleep wave activity.[45] In 2006, a study showed a shift in sympatho-vagal balance toward increased sympathetic activity started 8 minutes preceding SB onset. In moderate to severe SB subjects, a clear increase in sympathetic activity precedes SB onset.[46] Moreover, the onset of RMMA and SB episodes during sleep were shown to be under the influences of brief and transient activity of the brainstem arousal–reticular ascending system contributing to the increase of activity in autonomic–cardiac and motor modulatory networks.[47]

19.2.C Actual frequency, duration, and amplitude of sleep bruxism

Data is available from the early single-channel EMG recorders that captured cumulative nocturnal masseter muscle activity, which was presumably due to bruxism.[48–51] The disadvantages of using this method were that second-by-second levels of muscle activity during sleep were not available and correlations between motor activity and sleep status were not possible. Nevertheless, these single-channel EMG–based home measurement systems have helped researchers achieve a greater understanding of bruxism. Since then several studies have examined what are the correct features of a masseter muscle EMG activity recording that define bruxism (e.g., EMG amplitude, rhythmicity, and duration).[52–54] Gallo et al. (1999) used their long-term sleep EMG recording device to record masseter muscle activity in healthy subjects in their home environment.[55] The study was performed on 21 healthy subjects selected after telephone and questionnaire screenings and clinical examination from among randomly selected inhabitants of Zürich. The masseter EMG was recorded across seven nights in each subject's natural environment. The signal was analyzed for number, amplitude, and duration of contraction periods. The signal amplitude was expressed as a percentage of the amplitude recorded during maximum voluntary contractions (%MVC) and it was determined that an average of 10.5 ± 3.8 per hour contraction episodes above threshold occurred for all subjects with men having more episodes than women. They also reported that the average mean amplitude was 26.2 ± 6.4% of MVC again with men having a consistently high level of contraction than women. Finally, the duration of the episodes had a mode of 0.5 second. They concluded that healthy subjects showed intermittent periods of masseter activity during sleep which, on average, were of rather low intensity and short duration. This finding was in agreement with data provided by Nishigawa et al. (2001), who measured bruxism forces using strain gauge tranducers in occlusal splints during sleep in known bruxers.[56] In their study, the mean amplitude of all bruxism events was 22.5 kgf (kilogram force) and the duration was 7.1 seconds. The highest amplitude of nocturnal bite force in individual subjects was 42.3 kgf (15.6 ± 81.2 kgf). Maximum voluntary bite force during the daytime was 79.0 kgf (51.8 ± 99.7 kgf) and the mean ratio of nocturnal to daytime maximum bite force was 53.1%. These data indicate that nocturnal bite force during bruxism can exceed the amplitude of maximum voluntary bite force during the daytime.

In 2003, Baba et al. described a device which recorded tooth contact patterns on an occlusal splint using a piezoelectric film embedded in the splint.[57] Specifically, the study examined the reliability and utility of an intrasplint, force-based, bruxism detection system for multiple night recordings of forceful tooth-to-splint contacts in sleeping human subjects in their home environment. Bruxism type forces, i.e., forceful tooth-to-splint contacts, during the night were recorded with this system in 12 subjects (6 bruxers and 6 controls) for 5 nights in their home environment; a laboratory-based nocturnal polysomnogram (NPSG) study was also performed on one of these subjects. All 12 subjects were able to use the device without substantial difficulty on a nightly basis. The bruxer group exhibited bruxism events of significantly longer duration than the control group (27 s/h vs. 7.4 s/h). The PSG study performed on 1 subject revealed that, when the masseter muscle EMG was used as a "gold standard," the intrasplint force detector system had a sensitivity of 0.89. The correlation coefficient between the duration of events detected by the force based system and the EMG method was also 0.89. Watanabe et al. (2003) described the frequency of bruxism levels and examined if this behavior was being influenced by daily behaviors from daily diary data and from tooth contact recordings made over a 3-week period using the intrasplint force detection system described previously.[58] Specifically, the study included 12 patients (6 females and 6 males) with a sleep bruxism disorder to see if any daily behaviors (stress, physical activity, anger), jaw-pain/headache symptoms, or sleep quality were correlated with their sleep bruxism levels. Bruxism was defined as a force applied to the occlusal surface of the splint at or above a level of 10% MVC. VAS scales were used by the subjects to rate their daily behaviors, sleep quality, and jaw-pain/headache symptoms in a diary. The authors reported that bruxism and sleep disturbance, and the mean bruxism score for the male subjects was significantly higher than that seen for the female subjects. Overall, no single daily diary variable was consistently correlated with the bruxism levels in these subjects. They concluded that bruxism is not strongly related to any of the subject's self-monitored daytime activities or sleep quality.

19.2.D Harmfulness of bruxism

Sleep-state motor behaviors such as bruxism have been suggested as an important etiology causing TMD, pain and morning-onset tension-type headache. Bruxism is a potential contributor to the cause of both tension-type headaches and temporomandibular disorders. Clark et al. (1981) conducted one of the first studies which examined an association between nocturnal masseter muscle activity and severity of myofascial pain symptoms.[59] Specifically, the study evaluated the level of nocturnal masseter activity and the symptoms of jaw dysfunction in 85 subjects who varied with respect to degree of jaw dysfunction. A combined jaw dysfunction index was employed which evaluated both the patients' subjective report of pain as well as the clinical examination evidence of jaw dysfunction. Using this combined index, a significant correlation was found between the level of nocturnal masseter activity and the signs and symptoms of jaw dysfunction. Molina et al. (1999) examined the relationship of bruxism (based on subjective reports by the patient) and TMJ signs and symptoms. The study reported 207 patients who were subdivided into mild, moderate, and severe bruxism categories using a questionnaire and clinical examination. They found the smallest mean jaw opening (39.2 mm) and the highest prevalence of capsulitis (97.8%) in the severe bruxism patients. They concluded that that severe bruxers are more impaired by muscular and joint disorders as compared to mild and moderate bruxers.[60]

Many clinicians feel that nocturnal bruxism is partially responsible for many of the spontaneous onset TMJ internal derangements but few studies have actually measured this behavior in any detail. One notable study collected EMG based recordings for 6 nights on 103 young adult subjects (age range, 22–32 years) who also had a careful examination of the jaw for signs and symptoms of temporomandibular disorders.[61] The EMG data were considered dependent variables, while the questionnaire and examination data were considered independent variables. Multiple stepwise linear regression analysis was utilized and TMJ sound scores were found to be significantly related to the duration of EMG activity (i.e., the longer the EMG duration, the more likely the subject would exhibit joint sounds). None of the other independent variables were found to be related to any of the muscle activity variables.

19.2.E Treatment methods for bruxism

Occlusal appliances for bruxism

The primary management method for strong bruxism and clenching is still a full arch occlusal appliance plus clear instructions to the patient to make sure they try to avoid any and all clenching habits.[62] In some cases it is advisable to have the patient use the occlusal appliance a few hours each day during which they consciously never close their teeth on the appliance. The literature is clear that at best the appliance does not stop the bruxism behavior but limits its dental damage.

Contingent feedback devices for bruxism

An innovative new method to suppress bruxism was developed and reported in 2001. This method involved using a vibratory stimulation-based inhibition system for nocturnal bruxism.[63] For the single subject tested to date, the bruxism-contingent vibratory-feedback system for occlusal appliances effectively inhibited bruxism without inducing substantial sleep disturbance. Whether the reduction in bruxism would continue if the device no longer provided feedback and whether the force levels applied are optimal to induce suppression remain to be determined. All occlusal appliances alter the behavior for a few weeks when first used, but this treatment only offers a brief respite from some headaches and bruxism-induced TMJ derangement and/or arthritis problems.

Medications for bruxism

Clonazepam was mentioned as an effective bruxism suppression agent; however, its therapeutic values is limited due to the known dependency issues induced by this class of drug and the short-term nature of its proven effect. Actually, the article, which examined the effect of clonazepam using PSG recordings, was based on 10 middle-aged bruxism subjects (6 females, 4 males; 46.5 ± 13.1 years old) and employed a single-blind, nonrandomized study design.[64] In addition, this study included patients with substantial insomnia and anxiety/depression. Moreover, 6 of the 10 subjects also had a concomitant movement disorder (6 with restless legs syndrome, 4 with periodic leg movement disorder). These facts make it highly difficult to generalize any positive findings of bruxism suppression due to clonazepam in this population to younger populations without other sleep or motor disturbances. Nevertheless, the authors concluded acute clonazepam therapy significantly improved not only the bruxism index but also objective and subjective sleep quality.

Botulinum toxin type A injections for bruxism

For only the most severe cases of bruxism and clenching, botulinum toxin injections can be used to suppress jaw motor activity. By severe, what is usually meant is when the bruxism disorder is so strong that the damaging consequences are well beyond the teeth. In these cases, one option is to inject the masseter and/or temporalis with botulinum

toxin about every 3–6 months to minimize the power of the bruxism activity. The literature support for this treatment is mostly dealing with brain-injured patients with severe bruxism during a coma.[65–67] In cases of non-brain-injury-related sleep bruxism, Tan and Jankovic (2000) reported on the long-term treatment of 18 severe bruxism cases with botulinum toxin type A.[68] These cases all had severe bruxism, which had been causing symptoms for an average of 14.8 ± 10.0 years and all had no success with prior medical or dental treatment procedures. Similar to prior reports, they injected the masseter muscle with a mean dose of the 61.7 ± 11.1 units per side. The efficacy of these injections was rated by the subjects as a 3.4 on a scale from 0 to 4 (with 4 being equal to total cessation of the behavior). They did describe one subject who experienced dysphagia as a side effect of the injections.

Comparison studies on bruxism treatment

Two related studies examined the relative efficacy of various treatments for sleep bruxism.[69,70] Specifically this review compared and contrasted 10 clinical randomized studies on sleep bruxism, 3 involving oral devices, and 7 involving pharmacologic therapy. These studies concluded that sleep bruxism can be managed by mandibular advancement devices, clonidine, and standard occlusal splints. Moreover, when these authors included information such as adverse effects of various treatments they concluded that the standard occlusal splint was the treatment of choice for bruxism.

19.3 Oromandibular dystonia

Oromandibular dystonia (OMD) is one form of a focal dystonia that affects the orofacial region and involves the jaw openers (both lateral pterygoids and anterior digastrics), tongue muscles, facial muscles (especially orbicularis oris and buccinator), and platysma. When this occurs in association with blepharospasm (focal dystonia of the orbicularis oculi muscles), it is called Meige's syndrome.[71] Dystonia is considered present when the patient exhibits repeated, often asynchronous, spasms of muscles.

19.3.A Prevalence of oromandibular dystonia

Most dystonias are idiopathic and the focal form of dystonia occurs 10 times more often than the generalized systemic form. The prevalence of all forms of idiopathic dystonia ranges between 3 and 30 per 100,000.[72] Focal dystonias can be primary or secondary and the secondary form of dystonias occurs as a result of a trauma (peripheral or central), brainstem lesion, systemic disease (e.g., multiple sclerosis, Parkinson's disease), vascular disease (e.g., basal ganglia infarct), or drug use.[73] The majority of dystonias are primary, or "idiopathic," and demonstrate no specific central nervous system (CNS) disease. Of course, various pathophysiologic mechanisms which have been proposed to explain dystonia (e.g., basal ganglia dysfunction, hyperexcitability of interneurons involved in motor signaling, reduced inhibition of spinal cord and brainstem signals coming from supraspinal input, and dysfunction of neurochemical systems involving dopamine, serotonin, and noradrenaline).[74] All dystonias are involuntary but tend to be more intermittent than dyskinesias (described later) and comprise short but sustained muscle contractions that produce twisting and repetitive movements or abnormal postures.[75,76]

Almost pathognomonic for dystonia in the orofacial region is that many patients can partially control or suppress the movement with the use of tactile stimulation, such as touching the chin in the case of orofacial dystonia or holding an object in their mouth. This suppressive effect has been called *geste antagonistique*.[77] These tactile maneuvers may mislead physicians to the erroneous diagnosis of malingering or hysteria. Other examples of sensory tricks include placing a hand on the side of the face, the chin, or the back of the head or touching these areas with one or more fingers, which at times will reduce neck contractions associated with cervical dystonia. Sometimes patients will have discovered that placing an object in the mouth, such as a toothpick or a piece of gum, may reduce dystonic behaviors of the jaw, mouth, and lower face (oromandibular dystonia). Finally, the vast majority of the focal and segmental dystonias only occurs during waking periods and disappears entirely during sleep.

19.3.B Management of dystonia

For most OMDs, there is no well-defined treatment protocol except: (1) rule out CNS disease and local pathology; (2) try one or more of the medications that may be helpful in these cases; (3) if the disorder is severe enough and focal enough to consider, and the medications are not adequate, then consider botulinum toxin injections; (4) for those who cannot be helped using options 1–3 it is reasonable to consider neurosurgical therapy or implanted medication pumps that can deliver intrathecal medications. The use of motor-blocking injections (botulinum toxin) has proven to be most helpful for the focal dystonias and dyskinesias. In these disorders, injection of botulinum toxin is used successfully to block the transmission from the motor nerve to the motor end plate on the muscle for a period varying from 2 to 3 months (until the nerve sprouts and reconnects to the muscle). In the specific case of bruxism, some of the damage done by this behavior can be mitigated with the use of an

intraoral appliance. For the subgroup of hemifacial spasm of spontaneous origin, occasionally intracranial surgical microvascular decompression surgery is used to remove the source of the irritation on the nerve.

19.3.C Management of dystonia with botulinum toxin

For management, there are several medications that can be used to suppress hyperkinetic muscles. After medications, the other primary method for treating dystonia is chemodenervation using botulinum toxin. Blitzer et al. (1989) first described the injection of botulinum toxin for oromandibular dystonia.[78] In their article, they described injecting many of the orofacial muscles in 20 OMD patients and claimed that masseter and temporalis injections helped with suppressing the overall OMD. These early reports failed to report on tongue movement changes and botulinum toxin injections were not given in the tongue. In 1991, Blitzer et al. described the first use of botulinum toxin in patients with lingual dystonia but cautioned clinicians that dysphagia was a problem in some of their cases. Unfortunately, doses and injections sites were not carefully described by the authors.[79] Charles et al. (1997) reported on a series of 9 cases with repetitive tongue protrusion resulting from OMD or Meige's syndrome.[80] They were treated with botulinum toxin injections into the genioglossus muscle at four sites via a submandibular approach. Six of these patients were helped and the average dose injected was 34 units, producing a 3- to 4-month period of relief. Clearly, there is a need to explore when, where, and to what degree botulinum toxin may become useful in management of the galloping tongue and tongue-based severe dyskinesia patient. There are many variations of oromandibular dystonia, but a common one is involuntary jaw-opening dystonia. One complication of jaw-opening dystonia is that the TMJ can become physically locked in the wide-open position so that, even after the dystonic contraction stops, the jaw will not easily close back to the normal position. Moore and Wood (1997) described the management of recurrent, involuntary TMJ dislocation using botulinum toxin A.[81] The injected target was each of the lateral pterygoid muscle and the injections were performed using EMG guidance. The authors describe that the effect lasted for 10 months. The lateral pterygoid is the muscle most responsible for opening and it is a difficult injection, which has a high potential for misplacement of the solution into other adjacent muscles.

19.3.D Anticholinergic therapy

The anticholinergic drugs, such as trihexyphenidyl hydrochloride, biperiden, or benztropine, are the first line of motor-suppressive medications used for dystonia, although they are only partially effective when compared with botulinum toxin injections.[82,83] It is critical to start at a low dose and increase the dose very slowly to try to minimize the adverse effects (dry mouth, blurred vision, urinary retention, confusion, memory loss).

19.3.E Dopamine therapy

A specific subset of dystonias that have a childhood onset have been shown to respond remarkably well to low-dosage L-dopa such as Carbi/levodopa. These dystonias are referred to as dopa-responsive dystonias (DRD) and have been shown in recent years to encompass adult parkinsonism, adult-onset parkinsonism, adult-onset oromandibular dystonia, spontaneously remitting dystonia, developmental delay and spasticity mimicking cerebral palsy, and limb dystonia that is not only diurnal but clearly related to exercise.[84,85]

19.3.F Miscellaneous drugs for movement disorder therapy

There are several miscellaneous drugs that have been reported to suppress motor disorders. One medication used to suppress motor activity is buspirone, which is a nonbenzodiazepine anxiolytic drug.[86,87] Another drug where the mechanism is unclear is amantadine, which is used to suppress extrapyramidal reactions.[88] Other drugs which suppress motor activity are diphenhydramine,[89] and clonidine.[90]

In 2003, a randomized, double-blind, placebo-controlled three-way crossover study was performed to investigate the effect of two muscle relaxants (tolperisone hydrochloride and pridinol mesilate) on experimental jaw-muscle pain and jaw-stretch reflexes.[91] Fifteen healthy men participated in three randomized sessions separated by at least 1 week. In each session 300 mg tolperisone, 8 mg pridinol mesilate, or placebo was administered orally as a single dose. One hour after drug administration 0.3 mL hypertonic saline (5.8%) was injected into the right masseter to produce muscle pain. Subjects continuously rated their perceived pain intensity on an electronic 10-cm visual analog scale (VAS). The pressure pain threshold (PPT) was measured and short-latency reflex responses were evoked in the precontracted (15% maximal voluntary contraction) masseter and temporalis muscles by a standardized stretch device (1 mm displacement, 10 ms ramp time) before (baseline), 1 hour after medication (post-drug), during ongoing experimental muscle pain (pain post-drug), and 15 minutes after pain had vanished (postpain). Analysis of variance demonstrated significantly lower VAS peak pain scores (5.9 ± 0.4 cm) after administration of tol-

perisone hydrochloride compared with pridinol mesilate (6.8 ± 0.4 cm) and placebo (6.6 ± 0.4 cm). Administration of pridinol mesilate was associated with a significant decrease in PPT compared with tolperisone hydrochloride and placebo after medication, but not after experimental jaw-muscle pain. The normalized peak-to-peak amplitude of the stretch reflexes were not significantly influenced by the test medication, but were in all sessions significantly facilitated during ongoing experimental jaw-muscle pain. In conclusion, tolperisone hydrochloride provides a small, albeit significant, reduction in the perceived intensity of experimental jaw-muscle pain whereas the present dose had no effect on the short-latency jaw-stretch reflex.

19.4 Oral dyskinesia

Risk factors for the development of tardive dyskinesia are older age, female gender, and the presence of affective disorders.[92] For spontaneous dyskinesias, the prevalence rate is 1.5–38% of elderly individuals, depending on age and definition. Elderly women are twice as likely to develop the disorder.[93] When this disorder is associated with a drug use, the medications most commonly implicated are the neuroleptic medications now in widespread use as a component of behavioral therapy.

19.4.A Prevalence of oral dyskinesia

The prevalence rate of drug-induced dyskinesia (tardive form) is approximately 15–30% in patients who receive long-term treatment with neuroleptic medications.[94] These medications chronically block dopamine receptors in the basal ganglia. The result would be a chemically induced denervation supersensitivity of the dopamine receptors leading to excessive movement. However, other neurotransmitter abnormalities in GABA-ergic and cholinergic pathways have been suggested as underlying changes. There are isolated reports in the literature that implicate dental treatment as an etiologic factor for the onset of spontaneous orofacial dyskinesia. By definition, orofacial dyskinesias are involuntary, repetitive, stereotypical movement of the lips, tongue, and sometimes jaw during the day.[95,96] Sometimes the dyskinesia is medication induced (called tardive) or it can occur spontaneously. The spontaneous form of dyskinesia often affects the elderly. The tardive form of dyskinesia typically occurs in mentally ill patients who have had long-term exposure to medications used to treat the mental illness.[97] By definition, tardive dyskinesia requires at least within 3 months of total cumulative drug exposure, which can be continuous or discontinuous. Moreover the dyskinesia must persist more than 3 months after cessation of the medications in question. Most dopamine receptor antagonists cause oral tardive dyskinesia to one degree or another. The typical antipsychotics and in recent years even the atypical antipsychotics, including clozapine, olanzapine, and risperidone, have been reported to cause both tardive dystonia and tardive dyskinesia. No adequate epidemiologic data exist regarding whether any particular psychiatric diagnosis constitutes a risk factor for the development of tardive reactions to medications; however, the duration of exposure to antipsychotics required to cause tardive reaction is from months to years. Exposure to antipsychotics need not be long, and a minimum safe period is not apparent. This duration of neuroleptic exposure seems to be shorter for women. A longer duration of exposure to neuroleptics does not correlate with the severity of the reaction. Treatment of orofacial dyskinesia is largely with medications which unfortunately are not highly successful.

A review of the published studies where medications were used to manage benign essential blepharospasm and Meige syndrome was conducted in 1985.[98] These authors noted that most of the studies were of low quality (open, unblinded studies) and even then the effectiveness of various medications was quite poor. They reported that <10% of patients experienced sustained benefit from anticholinergic agents and, although neuroleptic medication may have better efficacy, the side effects and the risk of tardive manifestations prevented their general use. These authors reported that benzodiazepines, particularly clonazepam, seemed particularly promising, with sustained benefit in 67% of patients from one study. They described mixed results for dopamine-depleting agents (e.g., tetrabenazine); they also reported that dopaminergic agents were not particularly effective nor was baclofen. Finally, there is one report in the literature that reports an 11% spontaneous remission rate for benign essential blepharospasm.[99]

19.4.B Treatment of dyskinesia

If the dentist chooses to become involved in medicating patients with OMDs, it is essential that he or she be familiar with the pharmacodynamic and pharmacokinetic effects of medications prescribed along with risk-versus-benefit considerations. For both dystonia and dyskinesia that have undergone a confirming medical differential diagnosis, it would be preferable for the dentist to work in conjunction with a movement-disorder-specializing neurologist or psychiatrist, as pharmacologic management can be exceedingly complex and frustrating. This frustration is that while the medications described below sometimes work effectively, more often only a small effect is seen and side effects can be substantial. Only a dentist well versed in pharmacological

approaches should attempt drug management, albeit als with continuing medical interaction. As for surgical approaches to managing movement disorders, these are reserved only for the most severe cases.

The general rule is that (1) you withdraw the offending medication and (2) hope that the dyskinesia or dystonic reaction will go away.[100] If the suspected medication cannot be stopped or the case is severe, the following methods are used: (1) diphenhydramine 50 mg; benztropine 2 mg intravenously or intramuscularly.[101–103] The preferred route of administration is intravenous. If this is not feasible, intramuscular drug administration can be used. Finally, both amantadine 200–400 mg/day orally[104] and diazepam 5 mg intravenously[105] have been shown to be effective for recurrent neuroleptic-induced dystonic reactions.

19.4.C Differential diagnosis of dystonia and dyskinesia

The most important aspect of any clinician's skill is the ability to provide a differential diagnosis. With the exception of bruxism, all of the other motor disorders will require a neurologic consultation to achieve a definitive diagnosis. This includes Bell's palsy, essential tremor, the focal and multifocal dystonias, the dyskinesias, the motor and vocal tics, and hemifacial spasm. While the dentist will not be doing this examination, it is necessary to identify whether a patient has had a correct assessment before participating in the management of the patient. A proper initial diagnostic workup for a movement disorder involves a full clinical examination including a thorough neurologic examination. This is necessary in order to rule out the possibility that the motor dysfunction may be due to a central degenerative, demyelinating, or sclerotic lesion of the nervous system. Depending on the exact nature of the motor disorder, the examining physician may add to the workup a thorough medication and illegal-drug history. The physician (1) will order standard, enhanced, and angiographic-type magnetic resonance imaging of the brain and spinal cord to rule in or out a neurologic infarct or tumor or compression of these tissues, (2) may order an EMG assessment to specifically identify which muscles are involved and to assess the patient for a motor nerve or sensory nerve conduction deficit or a peripheral-origin myopathic disease or motor neuron abnormality, and (3) may, for the most severe forms of bruxism and some myoclonic-type bruxism problems, find it necessary to conduct a nocturnal PSG that includes an electroencephalogram. For the dystonias that affect a specific motor system (e.g., blepharospasm or torticollis) it is necessary to assess that system thoroughly to ensure that no local infection, neoplastic, or arthritic diseases are present, to name only a few of the considerations.

19.5 Drug-induced dystonic-type extrapyramidal reactions

There are patients who develop a medication-induced oral motor hyperactivity which does not fit into the dyskinesia category.[106] These medications and illegal drugs produce a motor response that is better classified as an unspecified extrapyramidal syndrome (EPS) reaction. EPS responses typically have 3 presentations: dystonia, akathisia, and parkinsonism. Dystonic reactions consist of involuntary, tonic contractions of skeletal muscles.[107–109] Akathisia reactions occur as a subjective experience of motor restlessness.[110,111] Patients may complain of an inability to sit or stand still, or a compulsion to pace or to cross and uncross their legs. Parkinsonian reactions manifest themselves as tremor, rigidity, and akinesia, which shows as a slowness in initiating motor tasks and fatigue when performing activities requiring repetitive movements (bradykinesia). When a medication or drug induces a dystonic EPS reaction, it typically involves the muscles of the head, face, and jaw producing spasm, grimacing, tics, or trismus. Most of the literature has focused on the more severe acute dystonic EPS reactions which occur with the use of antipsychotic medications. In addition to the antipsychotics, several antiemetics with dopamine receptor blocking properties have also been associated with tardive dystonia/EPS. These include prochlorperazine, promethazine, and metoclopramide. Of course, other less severe reactions do occur which vary in intensity and even wax and wane over time. The most commonly reported offending agents that are not neuroleptics are the selective serotonin reuptake inhibitors (SSRIs), stimulant medications, and illegal drugs.

Yang et al. (2005) examined the relationship between antidepressants and periodic leg movements (PLM) during sleep.[112] Specifically a total of 274 consecutive patients taking antidepressants and 69 control subjects not taking antidepressants met criteria among patients referred for overnight diagnostic PSG. The PLM index (PLMI) was calculated after visually counting the periodic leg movements. The venlafaxine and SSRI groups had significantly higher mean PLMIs than control and bupropion groups. Periodic leg movement indexes at thresholds considered to be of potential clinical significance were more statistically prevalent in the SSRI and venlafaxine groups compared with the control and bupropion groups. The odds ratio of having a PLMI greater than 20 was 5.15 for the SSRI group and 5.24 for the venlafaxine group compared with the control group. Venlafaxine and SSRI-induced PLM are likely to be the result of enhanced serotonergic availability and secondarily decreased dopaminergic effects. The results of this study might assist in the selection of antidepressants, especially in patients with pronounced sleep complaints.

19.5.A Serotonergic agents that cause extrapyramidal reactions

Selective serotonin reuptake inhibitors, such as fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram, are used for depression and a variety of other mental illnesses. Unfortunately, these drugs are reported to produce the side effect of increased clenching and bruxism.[113–116] The term "SSRI-induced bruxism" has been used to describe this condition, but it may not be accurate in that the actual motor behavior does not present as the brief strong sleep-state-related contractions seen in bruxism. The motor abnormalities are more of an increased sustained nonspecific activation of the jaw and tongue musculature. Patients generally describe an elevated headache and tightness in their jaw, tongue, and facial structures. Berry et al. (1999) examined the acute effects of paroxetine on genioglossus activity in obstructive sleep apnea.[117] They found that 40 mg of paroxetine produced a clear augmentation of peak inspiratory genioglossus activity during NREM sleep. The recent widespread use of SSRIs is based on a perception that these drugs have a lower side-effect profile than other categories of antidepressant medications (e.g., tricyclics and monoamine oxidase inhibitors [MAOIs]). Unfortunately, only case-based literature exists at this time and further PSG studies on the motor effects of SSRIs are necessary in order to define prevalence and risk factors and to establish a causal relationship between SSRI use and OMDs.

19.5.B Stimulant drugs and other medications that cause extrapyramidal reactions

Illegal drugs such as methamphetamine, cocaine, and 3,4-methylenedioxymethamphetamine (MDMA; Ecstasy) and legal prescription stimulants such as methylphenidate, phentermine, pemoline, dextroamphetamine, amphetamines, and diethylproprion have all been reported to induce bruxism and dystonic extrapyramidal reactions.[118–122] All stimulant drugs have the potential to cause extrapyramidal reactions and they are being used in greater numbers to treat obesity and as stimulants for children with attention deficit hyperactivity disorder (ADHD) or narcolepsy and even severe depression.[123]

19.5.C Treatment of drug-induced extrapyramidal reactions

The primary approach is either removing medications (if a suspected drug-related motor disorder is present) or adding additional medications that suppress the motor system. If a patient has a proven tardive dyskinesia that does not stop with withdrawal of the offending medications, or if these medications cannot be stopped, this is managed as a spontaneous movement disorder with motor suppressive medications. These medications work well for acute-onset spasms of the jaw but often only a small effect is seen and side effects can be substantial in patients with hyperkinetic oral movement disorders. Fortunately, acute dystonic reactions secondary to neuroleptic drugs are infrequent and disappear upon discontinuation of the medication; however, this may take days to months, depending upon the drug, its dose, and the patient. The same goes for less severe dystonic EPS reactions associated with SSRIs and stimulant drugs. If the suspected medication cannot be stopped or if the case is severe, the following methods are used to treat them: diphenhydramine 50 mg; benztropine 2 mg intravenously or intramuscularly. The preferred route of administration is intravenous. If this is not feasible, intramuscular drug administration can be used. Finally, both amantadine 200–400 mg/day orally and diazepam 5 mg intravenously have been shown to be effective for recurrent neuroleptic-induced dystonic reactions. Some patients with SSRI-induced dystonic EPS have relief when the dose of SSRI or the other stimulant drug is reduced (e.g., fluoxetine changed from 20 mg/day to 10 mg/day). Other patients respond to the addition of buspirone in doses of 5–15 mg/day.[124] Other patients developed bruxism within the first few weeks of SSRI therapy; however, they were successfully treated with buspirone in doses of 10 mg twice daily to three times daily. Buspirone appears to be an effective treatment based on a few case reports. This drug may have an additional benefit of relieving anxiety if it is present. It is usually well tolerated and carries a low risk of significant side effects. Finally, the patient may be switched to antidepressants that have not been associated with bruxism, such as mirtazapine or nefazodone.

19.6 Final recommendations

Recommendations on the management of clenching

1. Habitual tooth clenching for nonfunctional purposes is a common behavior; it appears to be of short duration and low amplitude and is exhibited several times per hour in healthy controls.
2. Daytime habitual jaw muscle activity studies suggest that the peak amplitude of these activities probably ranges between 5% and 20% of maximum voluntary contraction (MVC) and the duration of tooth contact periods is probably low (sub-5-second range per event) in nonpain, healthy controls.
3. In myogenous pain subjects, this behavior increases substantially in frequency, duration, and amplitude, but at present we do not have adequate data to understand or

describe the range of values (frequency, duration, and amplitude) that is exhibited by these subjects.

4. We do know based on self-reported tooth contact data that patients with muscle pain may exhibit probably 4 times more tooth contact related activities than controls without pain.
5. Experimental studies of clenching at high- or low-level force can produce pain during and for a short time after the clenching task; they do not support the idea that clenching alone produces any long-term pain and the process of myogenous pain must be more complex than simple clenching-induced muscle injury.
6. These data suggest that, although it is difficult to induce chronic muscle pain with 30–60 minutes of exercise, it appears that women might be slightly to moderately more susceptible to postexercise pain in the jaw muscles than men.
7. For management of tooth clenching, logic would dictate that any method applied to this problem must make the patient more aware of his or her behavior.
8. Hardly any treatments that are claimed to reduce tooth clenching in the long term have data to back up these claims. The most common approach used to treat daytime tooth clenching behaviors is as follows:
   (a) Advise the patient to wear his or her occlusal appliance during the day.
   (b) Advise the patient to pay close attention to when they close their teeth together and avoid this as much as possible.
   (c) Refer the patient to a therapist who will provide relaxation-training therapy and then have the patient practice these skills during the day in his or her natural environment.
9. As the technology improves, the ability to collect information on long-term daytime habits will provide new information about what treatments are more effective and when they are necessary.

Recommendations on the management of sleep bruxism

1. Most agree that the single most effective way to protect the teeth from progressive attrition, fracture, or clenching-induced pulpitis is to fabricate an occlusal appliance and have the patient use it at night.
2. The problem with an occlusal coverage appliance is that it does little or nothing to actually stop the bruxism in the long term, but recent work on vibration splints offers some hope for longer term suppression of the behavior.
3. The use of botulinum toxin (BoNT) should be restricted only to severe cases.
4. Medications have not been shown to be remarkably effective, but clonazepam if used judiciously can be supplemental to other treatments.

Six final recommendations for diagnosis and management of oromandibular dystonia

1. Oromandibular dystonia is considered present when the patient exhibits repeated (but not continuously present), often asynchronous, involuntary spasms of one or more orofacial muscles during waking periods, but not sleep.
2. Assuming it is a focal dystonia, it is most commonly idiopathic in origin, but central nervous system pathology must be ruled out.
3. Many patients can temporarily control or suppress the movement with the use of tactile stimulation (e.g., touching the chin or holding an object in their mouth).
4. There is no well-defined treatment approach and, although some oral medications can help, they rarely fully suppress the disorder:
   (a) The anticholinergic drugs, such as trihexyphenidyl hydrochloride (Artane™), biperiden (Akineton™), or benztropine (Cogentin™), are the first line of motor-suppressive medications used for dystonia, although they are only partially effective.
   (b) A specific subset of dystonias that have a childhood onset have been shown to respond remarkably well to low-dosage L-dopa such as such as carbi/levodopa (Sinemet®).
   (c) There are several miscellaneous drugs that have been reported to suppress motor disorders, including buspirone (Buspar™), amantadine (Symmetrel™), diphenhydramine (Benadryl™), and clonidine. The efficacy data for these drugs is lacking.
5. Botulinum toxin type A (BoNT/A) is usually very helpful in oromandibular dystonia (see Chapter 11 for specifics).
6. In some cases, neurosurgical therapy or implanted medication pumps should be considered.

Four final recommendations for diagnosis and management of oromandibular dyskinesia

1. The characteristics of patients who are most likely to have an oromandibular dyskinesia, whether it is drug induced or spontanenous, are older age, female gender, and having a chronic psychiatric disorder.
2. Spontaneous dyskinesias have prevalence rates varying from 1.5% to 38% of elderly individuals, depending on age and definition.
3. For drug-induced dyskinesia (tardive form) the prevalence reported varies from 15% to 30% in patients who

receive long-term treatment with neuroleptic (antipsychotic) medications (e.g., both typical and atypical).

4 Medications used to suppress the dyskinesia actions are usually ineffective (e.g., tetrabenazine, Sinemet, baclofen).

Six final recommendations for drug-induced extrapyramidal reactions

1 Extrapyramidal syndrome or reactions (usually the dystonic type) cause tightening, spasm, grimacing, tics, or outright trismus to occur in the orofacial region due to prescribed and illegal medications.

2 The difference between an extrapyramidal syndrome (EPS) and a tardive dyskinesia is that the latter diagnosis is only made if the motor disorder is still present 3 months after the suspected medication has been withdrawn.

3 Common offending prescription medications for EPS include antipsychotic medications, several antiemetics with dopamine receptor blocking properties, and serotonin–norepinephrine reuptake inhibitor (SNRI) and selective serotonin reuptake inhibitor (SSRI) medications.

4 Stimulant medications (some are prescribed and some are illegal drugs) also cause EPS activity in the orofacial region: methamphetamine, cocaine, 3,4-methylenedioxymethamphetamine (Ecstasy), and legal prescription stimulants such as methylphenidate [Ritalin™], phentermine [Adipex-P™], pemoline [Cylert™], dextroamphetamine [Dexedrine™], amphetamines [Adderall™], and diethylproprion [Tenuate™]).

5 The primary approach is to remove medications and/or protect the teeth with an occlusal appliance if the cessation of the medication is not appropriate.

6 In some cases, adding a second motor-suppressive medication may be necessary to treat drug-induced EPS if the medication cannot be stopped or lowered in dose.

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Chapter 20

Diagnosis and treatment of temporomandibular joint internal derangements

Glenn T. Clark, DDS, MS

20.1 Description of internal derangement of the temporomandibular joint

The term "internal derangement" implies an anatomical abnormality of the relationship of the disk–condyle components, with resulting changes in the smooth movement of the joint causing clicking, popping, locking, or momentary catching with or without associated pain and muscular disturbance.[1,2] When this term is used, it usually implies that these tissues have not yet undergone any degeneration and that when osteoarthrotic damage is visibly evident on a radiograph, then this diagnosis supercedes a diagnosis of internal derangement. Internal derangements of the temporomandibular joint (TMJ) can be differentiated into the following three clinically distinguishable problems: (1) disk displacement with reduction (DDWR), (2) disk displacement without reduction (DDNR), and (3) condyle open locking and dislocation.[3] This chapter focuses on the differential diagnosis and treatment of these three conditions.

20.1.A Disk displacement with reduction (also known as disk–condyle incoordination)

This condition is manifested clinically as a brief interference with the jaw opening movement which usually has an associated distinct brief joint sound or click. If the displacement is substantial, the patient may experience a momentary or intermittent restriction of condyle translation before the disk reduces to a normal position and full translation is achieved. Achieving full condyle translation after the click or lateral shift of the jaw joint occurs implies either a release or reduction of the momentarily jammed disk. This release allows the disk to continue its normal rotational movement about the condyle during opening. During closure, the disk will return to its original starting position relative to the condyle. Typically the opening click is loudest and this is thought to be due to the increased condyle pressure that is present during an opening motion. There is a much less noticeable reciprocal or closing click just before full intercuspation.[4] In some patients, however, the opening movement produces a less noticeable click while the closing movement produces a severe jamming and loud click. The best explanation for a loud closing click is that the disk is more deformed and its shift back to an anterior position is more difficult, with more friction and more noise.

Since the most commonly observed anatomic abnormality is a physical displacement of the disk from its normal position, this clinical condition has been most frequently called a disk displacement with reduction (DDWR) disorder. The term "reduction" means that the disk is out of place in the closed mouth position and that during opening it returns, or reduces, to a normal position. To confirm that the patient's complaints are related to a true DDWR, the TMJs are palpated bilaterally with very light pressure while the patient opens widely and closes several times. Any significant joint movement interference (especially if sound is produced) will be palpable. To document the problem, the timing of the joint movement interference relative to mouth opening is measured with a millimeter ruler. Many varied patterns of disk–condyle interference exist. Unfortunately, no definitive statement can be made regarding the severity, prognosis,

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or even the specific nature of the anatomic deformity based on these various patterns of joint sound or movement interference.[5]

20.1.B Disk displacement with no reduction (also known as closed locking)

This disk displacement with no reduction (DDNR) disorder is sometimes described as "closed locking."[6] The mechanism of this condylar movement restriction is also thought to be either disk perforation, condyle or disk deformation, disk–articular surface adhesion, or disk displacement without reduction. If the disk does not fully rotate from an anterior to a posterior position relative to the condyle during mandibular movement, a clear restriction of jaw opening will result; this is described as a nonreducing disk. To confirm that a true condylar restriction exists, maximum active mouth opening is measured with a millimeter ruler. Confirmation can also be obtained by palpating the lateral pole of the condyle during opening. Movement anterior to the crest of the articular eminence will not be felt if a restriction exists. Finally, a passive stretch manipulation of the jaw by the examiner will not produce normal opening. When associated pain occurs, it probably results either secondarily from a protective jaw closing muscle trismus or a muscle splinting response. This trismus response is an attempt to prevent either pinching or stretching of the disk tissue, or impingement on the vascular, highly innervated disk attachment tissues which are sometimes drawn into an area of articular loading. Of course, the pain could also be from a primary masticatory muscle disorder or any number of other orofacial pain conditions. Because full, friction-free movement of the disk does not occur, this condition can eventually lead either to a perforation of the disk or, more likely, to fibrosis of the disk-attachment tissues. In either case, there is usually a subsequent osseous remodeling (flattening) of the condyle and articular eminence.[7–9] These changes are essentially adaptive attempts to restore increased movement in a highly frictional joint. Neither the incoordination phase nor the restriction phase of an internal derangement is accompanied by obvious radiographic osseous change of the condyle or eminence.

20.1.C Open condyle locking and open dislocation

Although in most cases, when the jaw locks open, there really is not a dislocation of the condyle, even though the patient complains they cannot close their mouth. It would be better to simply call such cases an open locking until it is proven the condyle has traveled outside or beyond its normal range of travel. The mechanisms for open locking are several. First, there could be a simple jamming of the entire disk–condyle complex in a position anterior to the crest of the articular eminence due to jaw closing muscle trismus. The onset is often associated with extreme yawning or a dental treatment intervention where the jaw was open for an extended period of time. In the absence of ongoing pain, infrequent momentary open locking upon wide opening is not a serious clinical problem for most patients. The reason for this jamming is not because of any dislocation of the condyle beyond its normal open translation position, but simply because the friction in the joint is such that the condyle and disk are momentarily stuck anterior to the eminence. In the wide open jaw position the jaw closing muscles are maximally stretched which increases the friction forces between the eminence and the disk. In normal patients, this situation would not cause an open jamming, but if there is any increased stiffness in the jaw closing muscles or the intra-articular fluids are not lubricating the joint surface adequately, then once the condyle passes to the anterior of the eminence it may be more difficult to initiate the closing movement. It has been determined that the joint reaction forces during jaw opening are greatest in the open jaw position, and any increase in stiffness or any co-contraction of the jaw closers can magnify the joint reaction forces 3- to 10-fold in magnitude.[10]

Second, there are cases of true hyperextension of the disk–condyle complex well beyond its normal maximum translation. This condition is a true dislocation and fortunately it is rare. When it has been reported it has always been due to a traumatic insult to the jaw (e.g., intubation or surgery on the facial or jaw structures) and it is almost always in the frail elderly. Third, another form of "I can't close my teeth together" is best described as a partial open locking situation where the patient is at least halfway closed or more, and it truly means they cannot get their teeth to come together. This clinical complaint is almost always a posterior disk jamming or folding problem which prevents the mandible from closing. In the last situation, the disk has difficulty returning to its usual more anterior position relative to the condyle on closure. Sometimes this derangement is momentary and therefore self-reducing; other times it may require manual manipulation of the mandible by the doctor to reduce the disk position abnormality.

20.2 Mechanism and etiology of internal derangement

The above conditions have been accompanied by a list of probable mechanisms which might explain anatomically and functionally how a joint movement interference occurs, but mechanisms are not the same as etiology. A table of etiolo-

Table 20.1 List of potential etiologies for internal derangement

Macrotrauma	• Significant external force trauma can damage bony TMJ structures. • Overstretching can damage soft-tissue TMJ structures. • Injury forms include blows to the jaw, iatrogenic stretching during dental and surgical treatment, and an impact to the jaw sustained during a motor vehicle accident.
Parafunction or microtrauma	• Repeated strain on the joint due to parafunctional activity is injurious. • This most commonly causes an internal derangement. • Parafunction includes repetitive behaviors such as tooth grinding (bruxism), chronic tooth clenching, and atypical chewing habits such as chronic gum chewing.
Arthritic disease	• Sometimes, especially in patients over 40, derangement symptoms are associated with arthritic disease of the TMJ. • The term osteoarthrosis implies the breakdown of joint articular surface.
Hypermobility	• Joint hypermobility can be one cause of internal derangement of TMJ. • Cause is discal and joint ligament laxity (local or generalized). • Prevalence of polyjoint hypermobility is less than 3% of the population.
Abnormal biomechanical loading	• Increased joint load can be due to a severely unstable occlusion. • Most commonly seen instability is severe open bite. • Experimental high crowns have been shown to cause TMJ clicking.

TMJ, temporomandibular joint.

gies is provided (Table 20.1) and, with regard to mechanism, there are several proposed anatomic alterations that might produce a joint sound or a complete displacement of the disk and its associated brief movement disturbance. The most common mechanism is a simple displacement of the disk which produces a click or pop because the disk is jammed in front of the condyle as it moves and sound occurs once the jamming is released.[11] The most likely abnormality of anatomy that allows the TMJ disk to displace is an elongation of the lateral collateral ligament.[12,13] Other explanations are (1) disk and joint capsule and ligament hypermobility, (2) articular surface abnormality, such as flattening, erosion, or bony spur development,[14] (3) disk–articular surface adherence due to altered (less lubricating) synovial fluids,[15] and (4) disk perforation.[16]

With regard to etiology and in common with general orthopedic problems, the etiology of a TMJ internal derangement is often multifactorial and difficult to determine clearly. Nevertheless, the major causes which can be considered as the most likely etiologies of a TMD are macrotrauma, parafunction–microtrauma, arthritic disease, hypermobility, and abnormal biomechanical loading. Each etiology is discussed in the following subsections.

20.2.A Macrotrauma to the temporomandibular apparatus

If a significant external-force trauma occurs from either impact or overstretching, the joint structures can be damaged.[17] The predominant causes are blows to the jaw, iatrogenic stretching during dental and surgical treatment, or an impact to the jaw sustained during a motor vehicle accident. While trauma is not the most frequent cause of an internal derangement, patients complaining of a jaw function problem (e.g., clicking and locking) to a specialty clinic are more likely to have a history of major trauma (30%) than a nonpatient population of individuals with varying observed TMJ symptoms (13%).[18,19]

20.2.B Parafunction

Repeated strain on the joint due to parafunctional activity is probably the most common cause of internal derangement and is sometimes thought of as microtrauma to the temporomandibular articulation. Parafunction includes any repetitive behaviors, such as tooth grinding (bruxism), chronic tooth clenching, or atypical chewing habits such as chronic gum chewing These behaviors can be highly injurious and produce painful TMJ and masticatory muscle disorders and joint dysfunction.[20–24] A more detailed discussion of bruxism and how this behavior is associated with TMJ clicking is presented in Chapter 19.

20.2.C Arthritic disease as a primary cause of disk displacement

Many people consider that TMJ derangements are merely an early manifestation of an osteoarthritic process. The term "osteoarthrosis" implies the breakdown of the joint articular surfaces and probably synovial fluid alterations. These changes would predispose the disk to abnormal function.

20.2.D Joint hypermobility of the temporomandibular joint

Joint hypermobility or joint laxity means excessive mobility of the mandible and it is caused by discal and joint ligament laxity. When present, these patients can exhibit associated symptoms such as disk–condyle incoordination or open condyle dislocation. The issue of whether joint tissue laxity

is present in a high percentage of patients with temporomandibular dysfunction is dependent on the definition of joint laxity. When a conservative definition is used, the prevalence of polyjoint hypermobility is less than 3% of the population and certainly does not explain the majority of internal derangements.

20.2.E Abnormal biomechanical loading

This is defined as an unstable occlusion (e.g., severe open bite or loss of posterior tooth support). The evidence that dental occlusal abnormalities are related to disk displacement comes from a 1976 study where researchers placed a "high" gold onlay on the occlusal surface of a mandibular molar in 8 healthy subjects.[25] This interference was approximately 250 μm above the contacting plane, thus putting the tooth in supracontact. The experimental occlusal interference was in place for 14 days and the authors described via qualitative observations that the experimental occlusal interference produced noticeable changes in jaw muscle EMG symmetry during clenching. They described that these 6 subjects complained of TMJ tenderness and muscle tenderness as a result of the experimental occlusal interference. Finally, new spontaneous TMJ clicking was reported during mandibular opening bilaterally in 3 subjects during this experiment (these symptoms occurred at 7–14 days after insertion of the inlay). In one of these subjects there were still severe irregularities of the movement in both joints near maximal mandibular opening 1 week after the removal of the inlay. This symptom persisted for 9 months and abated after treatment with a stabilization splint. This theory has substantial merit in some cases when clicking is associated with new dental work or orthodontic care, but overall this association is weak at best and cannot explain many other cases of TMJ clicking or locking.

20.3 Diagnostic tests for temporomandibular joint internal derangements

Even though the previously described TMJ internal derangements involve specific articular pathologic conditions, identifying the probable etiology of the problem is not always straightforward. This is especially true for intracapsular condyle restrictions, which are easily mimicked by jaw muscle pain and stiffness problems. Historical factors such as the onset, duration, character, and location of the jaw dysfunction and its relationship to pain in the region are of essential importance in the diagnostic process. When combined with physical signs such as joint noises, jaw movement patterns and restrictions, and the passive stretch and joint manipulation tests, they are of greater clinical importance than any other diagnostic test, including radiographs, in the differential diagnostic process.[26] A table of the various diagnostic procedures used for internal derangement is provided (Table 20.2). In spite of the many diagnostic

Table 20.2 Diagnostic tests and patterns helpful for internal derangement

Passive stretch test	• Used when patient has an active limitation of motion less than 40 mm. • Performed by first cooling skin over masseter and temporalis muscles with ice. • Ice or cold spray transiently blocks pain and protective muscle trismus. • Examiner gently stretches the jaw opening (finger pressure to incisors). • If an opening is not achieved with stretch, this suggests a DDNR. • If mild trismus is causing restriction, jaw opening will increase to a normal distance with passive stretch.
Pattern of locking	• If pattern is locking in the morning, this suggests sleep-related bruxism or clenching as cause of locking.
Anesthesia and joint mobilization test	• Used when passive stretching is unsuccessful. • Procedure is done at an outpatient office visit. • Involves a combination intra-articular anesthetic and steroid injection. • After injection, jaw is manually mobilized (stretched open gently). • Patient is taught self-stretching exercises to be performed at home. • It is best to ogtain images of the joint before performing test. • Sometimes manual mobilization with anesthesia will release stuck disk.
Open MRI	• MRI is the technique of choice for visualizing TMJ disk. • Most important image is open MRI as disk may appear displaced when closed but reduce to normal position when open.
Panoramic radiographs of the TMJ	• Panoramic radiograph can assess for substantial arthritic change of the TMJ. • Early changes are often not seen on panoramic film of TMJ.
Cone beam CT	• Cone beam CT scans are the preferred method of imaging TMJ bony tissues. • TMJ internal derangements are usually free of overt arthritic change.

CT, computed tomography; DDNR, disk displacement with no reduction; MRI, magnetic resonance imaging; TMJ, temporomandibular joint.

instruments which are used for research which can also be applied clinically to document jaw motion or muscle activity levels, the TMJ internal derangement is still best discovered and documented with a thorough history and a clinical examination. The clinical examination items which are most important for this discovery process are (1) the passive stretch test and (2) the joint manipulation test (when indicated). Additional diagnostic tests (e.g., MRIs or tomograms) should only be ordered if they will either confirm or rule out specific recognized pathologic entities which are suspected from the clinical findings. Further, these tests should only be requested when they will definitely influence the diagnostic, prognostic, or treatment-decision process.

20.3.A Passive stretch test

The differentiation between a muscular cause of limited jaw movement versus a true intracapsular restriction may require two diagnostic tests, passive stretch and joint manipulation; this concept is presented in Chapter 10. The passive stretch test is performed by first rubbing the masseter and temporalis muscles with ice to help transiently block the protective muscle trismus response which prevents opening. The second step of this test is for the examiner to immediately stretch the jaw opening by applying a mild to moderate force between the maxillary and mandibular teeth with the fingers. If a muscular induced limitation is present, jaw opening will increase to a normal distance.[27]

20.3.B Images and radiographs

The primary purpose of this diagnostic procedure is to assess the degree (if any exists) of osteoarthrosis in the symptomatic joint.[28–30] Except when associated with osteoarthritis signs (e.g., joint tenderness and crepitation noises), most TMJ restrictions are usually free of overt radiographic signs. The most acceptable radiographs include panoramic films of the TMJ[31] and cone beam computerized tomographic (CT) scans.[32] Cone beam CT scans are preferred over the other radiographic films of the TMJ but, because of their cost, magnetic resonance images (MRIs) of the TMJ are an optional diagnostic procedure.[33] Except when associated with osteoarthrosis, TMJ internal derangements are usually free of overt radiographic signs. As previously mentioned, radiographs should be made only when indicated by the clinical examination. Clinical signs such as severe joint tenderness, repeatable joint noises on palpation, crepitation, or a progressive deterioration of TMJ movement indicate a need for radiographs of the TMJ. Cone beam CT procedures have great merit and have surplanted conventional tomographic radiographic techniques for hard-tissue imaging of the TMJ structures. Cone beam CTs provide clearly superior images versus MRI for hard-tissue imaging. Magnetic resonance imaging is rapidly becoming the technique of choice for visualizing the intra-articular soft tissues because it is not invasive, does not involve ionizing radiation, and does not cause distortion of the intra-articular structures. Now multiple MRI images at different jaw openings can be linked to give a more dynamic view of TMJ and disk function.[34–37]

20.4 Treatment of DDWR disorder

Patients with a diagnosis of a nonpainful DDWR disorder can be separated further into those with a nonprogressive nonfunctional disk interference problem and those with a intermittent locking of the jaw joint. For the former group, avoidance therapy is usually adequate for managing the problem.[38,39] If and only if they exhibit clinical signs of active bruxism, then a stabilization appliance should be fabricated. For the latter group, those who are having intermittent locking, additional therapies such as a device to restrict lateral motion and viscoelastic supplementation are therapies to consider. Regardless of its severity, the most likely anatomic alteration that would produce a disk displacement is elongation of the lateral collateral ligament. Each of these methods is discussed in the following subsections.

20.4.A Avoidance therapy for DDWR

Avoidance of TMJ clicking is the primary approach used for the treatment of both the nonpainful and slowly progressing disk–condyle incoordination disorders. This therapy usually involves using a model to explain how the TMJ works, showing the patient how to open the mouth without translation (in a hinge fashion) most of the time, and helping him or her find a place to chew without inducing a click in the joint. Strict avoidance of all clicking is required. If the patient exhibits intermittent locking or has substantial pain in the joint when the click is produced, they should have panoramic films, cone beam CT radiographs of the TMJ, or magnetic resonance imaging of the disk itself, depending on the severity of the patient's problem. In fact, a 2003 study examined the effect of therapeutic exercises on clicking due to DDWR in the temporomandibular joint.[40] The study was a randomized controlled clinical trial to compare jaw exercise with a no-treatment control condition. There were 42 subjects who all had an MRI-confirmed DDWR diagnosis. The authors reported that success in 61.9% of the 21 subjects in the exercise groups and none in the control condition. The authors concluded that therapeutic exercise for clicking due to DDWR was effective

and more conservative and cost-effective than splint therapy or surgery.

20.4.B Intra-articular injection of sodium hyaluronate for DDWR

In those patients with painful joint clicking and intermittent morning locking of the joint due to a DDWR, another method of reducing friction is to inject into the superior joint space (up to four times at a frequency of once a month) 1.0 cc of sodium hyaluronate. Sodium hyaluronate (HA), a naturally occurring polysaccharide, was first discovered in 1934 in the vitreous fluid of the eye and later found in synovial fluid, umbilical cord, rooster combs, and, in lesser amounts, in the extracellular matrix of connective tissue throughout the body.[41,42] Based on its biological and physical properties, HA is considered to be an important biologic tissue lubrication.[43,44] It has also been proposed that synovial fluid, which contains high concentrations of HA, acts as a nutrient source for the avascular articular cartilage cells and synovial membrane.[45–49] Recent research indicates that when high-molecular-weight hyaluronate is utilized in symptomatic human temporomandibular joints, it has the potential to be a conservative, safe, and efficacious therapy. Although substantive data is lacking, one placebo-controlled, randomized double-blind study examined DDWR patients who were treated with either a saline injection or a sodium hyaluronate injection.[50] This study included 120 patients with various temporomandibular disorders in a 6-month study. In the subgroup of 50 patients with DDWR, the results showed a statistically significant within-group and between-group improvement in pain and joint sounds. Further, only 3% of patients with DDWR who were treated with hyaluronate relapsed compared with 31% of patients with DDWR given placebo. More recently a 2006 study reported on the long-term changes in condylar mobility and radiographic alterations after sodium hyaluronate injection based treatment in patients with nonreducing disk displacement of the TMJ.[51] Specifically this study examined and compared changes in condylar mobility and morphological changes in the affected condyles after treatment in patients with nonreducing disk displacement of the TMJ. They include 55 patients who had a diagnosis of DDNR and performed joint mobilization and injection of a sodium hyaluronate solution into the joint. The authors reported that clinical signs and symptoms improved after treatment in the patients and condylar mobility significantly increased after treatment in patients although it did not reach the levels expected for a normal subject. They also noted that, although radiographic changes of the condyle increased after treatment, the magnitude of these changes was mild or none and the changes were likely due to the inherent joint disease process itself. They concluded this method of treatment was reasonably successful and without great risk to the patient.

20.4.C Nighttime use of lateral motion restriction appliances for DDWR

Finally in the special case of a patient who wakes up in the morning and reports that their jaw is locked and after a few moments it releases, the presumption is made is that some parafunctional behavior during sleep is causing the disk to displace. The association between bruxism and clicking has been confirmed by a study (cited earlier in this chapter) by Baba et al. (2005) that examined bruxism levels (via EMG recordings) and clinical symptoms in 100 young adult patients. In these morning locking cases, it is important to examine the teeth for wear facets on the anterior teeth, indicating that the patient is performing wide lateral motion bruxism. This motion is thought to contribute to stretching of the lateral collateral ligaments and this is one explanation for the disk displacement during sleep. One way of stopping this morning locking is to use one of the interlocking double (maxillary and mandibular) appliances that restrict wide lateral jaw motions. This device can be used alone or in conjuction with a series of intra-articular sodium hyaluronate injections (described previously). These appliances have commonly been used to anteriorly reposition the mandible during sleep to reduce snoring and obstructive apnea events. Of course in DDWR cases with intermittent locking it is not necessary, nor desired, to reposition the mandible forward, only to restrict wide lateral jaw motion during sleep. No study exists currently in the literature that demonstrates that this method is any more than a palliative approach.

20.5 Treatment of DDNR

Assuming the patient's limitation of joint motion is of recent vintage and not due to an acute trismus and the passive stretch test has failed to yield full or nearly full translation of the restricted joint, then it is likely that the restriction is due to a DDNR disorder. There are several methods for treating this problem if the joint dysfunction causes a significant disability and functional impairment. The four main methods are (a) medications and self-applied physical therapy, (b) a joint injection with anesthetic and steroid followed by manual joint mobilization, (c) sedation plus an arthrocentesis lavage of the joint followed by manual mobilization of the joint, and (d) an arthroscopic surgical intervention to mobilize the joint. Each method is described below, along with a section comparing the relative efficacy of these methods.

20.5.A Anti-inflammatory, muscle relaxant, self-applied physical therapy for DDNR

Anti-inflammatory therapy for joint pain consists of the following: (1) a prescription of a nonsteroidal anti-inflammatory agent (e.g., ibuprofen 400 mg three times a day) and if needed a muscle-relaxant agent (e.g., cyclobenzaprine 10 mg at bedtime); (2) cessation of any jaw clenching and elimination of all hard or chewy foods from the diet; (3) the application of a small ice pack on the involved joint several times a day for 20 minutes at a time followed by gentle self-stretching of the jaw open using tongue blades between the teeth. If the patient's pain is due to true inflammation of the joint, then this approach will reduce pain and joint swelling within 1–2 weeks. As the pain subsides the joint motion will improve, but if the disk is truly displaced and folded, the jaw opening will not return to full opening.[52] If the patient has a strong bruxism or clenching habit, it may be necessary to fabricate an occlusal appliance, but occlusal appliances do not return the disk to its normal position. Of course, definitive occlusal evaluation during the acute phase of joint inflammation should be avoided because the intracapsular swelling may cause a dramatic acute change which will return to normal after the joint inflammation subsides.

20.5.B Anesthetic-assisted joint mobilization for DDNR

If the above medication–self-treatment approach fails to yield an improvement in two or three weeks, the next procedure to be considered would be a local anesthetic assisted mobilization of the TMJ. This procedure can be done at an outpatient office visit; a combination anesthetic and steroid injection is administered to the joint, the jaw is manually mobilized (stretched open gently) to increase mobility, and the patient is taught self-stretching exercises to be performed at home. The basic concept underlying this procedure is that the disk is adherent or mechanically stuck and with some mechanical assistance (when pain does not stop the procedure), the joint motion can be increased. Although it is not possible to state the position of the disk without imaging of the disk with an MRI, it is frequently assumed that the disk is positioned slightly anterior or medial and is not rotating around the condyle during an opening movement. If the disk is not greatly damaged or scar tissue (adhesions) is not too strong, it may be possible to release the disk by manual mobilization of the jaw in the acute stages (< 1–2 months) of condyle restriction.

The procedure is typically performed as follows:

- *Step 1* Anesthetize the cutaneous tissues overlying the joint capsule, and block the auriculotemporal nerve with a local anesthetic (lidocaine with epinephrine).
- *Step 2* Manually manipulate the TMJ, pulling the restricted TMJ down and forward in an attempt to mobilize the disk that is not moving properly.
- *Step 3* Assuming a successful manipulation, infuse a long-acting corticosteroid solution into the superior joint space.

Joint mobilization is most successful in patients with acute (less than 1 month) restriction who have a previous history of incoordination. The test first involves the manual inferior distraction of the condyle, followed by a mildly forced slow translation of the restricted condyle in a forward and slightly medial direction. Typically this procedure is done without sedation. If the patient is anxious and does not want to have a joint injection/mobilization procedure performed without sedation, this can be added. Preinjection screening should include an open mouth panoramic radiograph of the jaw to confirm that no pathology or substantial arthritic disease of the TMJ is present. Recently, this procedure has become the primary form of DDNR treatment for such cases. It is generally acknowledged that anesthetic-assisted is a highly successful procedure for DDNR patients with acute (less than 1 or 2 months) restriction of motion. If the jaw joint fails to increase its translation, the next therapeutic intervention is arthroscopic exploration of the joint to see if substantial adhesion exists. In most cases, arthroscopic exploration of the TMJ is performed in an operating theatre and general anesthesia is the sedation method used. Finally, in Japan the common method of treatment of DDNR is to anesthetize the joint with a single needle and then infuse and withdraw several cc's of fluid into the superior joint compartment and then mobilize the joint. This procedure has been dubbed "pumping" and it requires a much larger needle (e.g., 20 guage). In a 2008 study it was done using 36 females who had an MRI-confirmed diagnosis of DDNR.[53] In this study they examined if the efficacy of the pumping method was helped by having the patients perform an additional mouth opening exercise at home after the procedure. Twenty-three female patients with nonreducing disk displacement of the TMJ underwent pumping of the TMJ and did mouth opening exercise after this treatment (rehabilitation group), and 36 female patients with nonreducing disk displacement of the TMJ underwent pumping of the TMJ but did not do mouth opening exercise (nonrehabilitation group). There were various outcomes collected, including pain and mouth opening. The end result reported by these authors based on outcomes collected at 12 months after the pumping procedure showed no group differences. They concluded that in both groups, the clinical signs and symptoms improved and the overall rate of improvement was not significant. In summary these data suggest that anesthetic-assisted mobilization of a closed lock (DDNR) is

logical, is safe, and should be the first-line therapy for this problem.

20.5.C Arthrocentesis for DDNR

Joint pumping with a single needle or with the double-needle technique dubbed "arthrocentesis" does not require that the patient be sedated to do either procedure, but it is usually desirable since these procedures are more complex and the needles are substantially larger that those use for simple anesthesia of the joint. Arthrocentesis is the method that is typically used when the patient's jaw restriction is more chronic and/or anesthesia-assisted mobilization of the jaw does not help. In these cases, the next step in therapy is to use a short-acting sedative agent via intravenous infusion and then insert two needles in the superior joint space to perform a lavage of the joint. Typically, after the lavage, the jaw is manually mobilized to see if increased opening is possible. This lavage–mobilization procedure is called an arthrocentesis-assisted joint manipulation.[54–56] It is not expected that the displaced disk will be reduced by this procedure, only that the jaw will have increased motion.

The procedure is typically performed as follows:

- *Step 1* As before, anesthetize the cutaneous tissues overlying the joint capsule, and block the auriculotemporal nerve with a long-acting local anesthetic (bupivacaine and epinephrine).
- *Step 2* Infuse into the superior joint space with 3–5 cc of lactated Ringer's solution. This infusion is typically done with a 20-gauge needle.
- *Step 3* Manually manipulate the TMJ, pulling the restricted TMJ down and forward in an attempt to mobilize the disk that is not moving properly.
- *Step 4* Assuming a successful manipulation, infuse a long-acting corticosteroid solution into the superior joint space.
- *Step 5* If the joint does not easily mobilize, place a second needle into the superior joint space (18 gauge) and flow an additional 100 cc of lactated Ringer's solution through the joint.
- *Step 6* Repeat the manual manipulation procedure as described in Step 3.
- *Step 7* Prescribe analgesic for the next 2–3 days and ice packs to be applied to the TMJ for the first 2 hours postoperatively.

For those patients where increased movement is demonstrated immediately after this treatment, re-examine them in 1 month and, if they still have pain symptoms of a temporomandibular disorder (e.g., myofascial pain), then manage these symptoms appropriately. If the patients are greatly improved, place them on a recall examination schedule (every 3 months for 1 year) to reinforce the exercises and self-treatment protocol prescribed and to insure that they do not have a recurrence of their symptoms. For the patients who do not show a substantial increase of motion after this procedure, the diagnosis of a prolonged TMJ restriction is now appropriate. With regard to the efficacy of arthrocentesis, a recent uncontrolled study on arthrocentesis examined if the disk would ever be recaptured as a direct result of this procedure.[57] The authors performed arthrocentesis and mandibular manipulation as an initial treatment in 33 patients (unilateral involvement) with a variable duration of closed lock. They also performed magnetic resonance imaging of the TMJ disk before and 1 month after the procedure. The authors described an overall success rate of 72.7%; but the disk was recaptured (defined as interposed between the condyle and the eminence on closed and open MRI images) in only 3 (10%) acute locking (<1 month) cases.

20.5.D Arthroscopic treatment of DDNR

If arthrocentesis-assisted mobilization does not work, then an arthroscopic-assisted manipulation is the next recommended procedure. Before attempting any procedure more invasive than an arthrocentesis-assisted manipulation, a clear image of the TMJ disk is recommended. This can be performed with an MRI,[58] since it has become the technique of choice for visualizing the intra-articular soft tissues because it is not invasive, does not involve ionizing radiation, and does not cause distortion of the intra-articular structures as occurs with arthrography. The arthroscopic technique recommended involves inducing general anesthesia, locally anesthetizing the involved joint with local anesthetics, then placing two trochars with cannulas into the superior compartment of the TMJ.[59] Into one cannula, the arthroscope is inserted; the other serves as an exit port for the fluid flushed through the joint. This compartment is flushed with a physiologic saline solution or lactated Ringer's solution. Arthroscopic probing of the compartment and lysis of any adhesions is then carried out in the upper joint space to mobilize the TMJ disk. Success of this procedure is quite good, especially if the disk is not perforated, torn, or severely distorted, and if the joint surfaces are not severely damaged. The results of this therapeutic approach seem quite good.[60–62] Usually, the prognosis is poorer in more prolonged cases of locking and those in which osteoarthrotic change exists. This treatment should be followed by a comprehensive management program that includes exercises to maintain the regained mobility and an occlusal appliance to help reduce clenching and bruxing. As with arthrocentesis, the primary goal of arthroscopy is to mobilize the TMJ. For those patients where increased movement is demonstrated,

re-examine them in 1 month after the procedure and, if they still have symptoms of a temporomandibular disorder (other than limitation), then manage these symptoms appropriately. If the patients are greatly improved, place them on a recall examination schedule at every 3 months for 1 year to insure that they do not have a recurrence of their symptoms. For the patients who do not show a substantial increase of motion after this procedure, the diagnosis of a chronic TMJ pain and dysfunction is now appropriate.

20.6 Chronic temporomandibular joint dysfunction and joint arthrosis

By the time they present for help, some patients will already have sustained substantial damage to their TMJ structures. This damage may occur in the form of extensive adhesions, disk deformation and displacement, or substantial arthrotic changes in the TMJ hard tissues. These cases will not typically benefit from arthroscopy or, if they benefit initially, they will have a return of pain and loss of motion within a few weeks after the arthroscopic procedure. In some cases, the patient develops joint pain that has transformed from an acute inflammatory process and is not a chronic neuropathic pain disturbance. In these cases, anti-inflammatory therapy will not produce substantial change in symptoms and complete recovery is not to be expected; a discussion with the patient about expected limitations of jaw function and chronic pain modulating medications is in order. If a more aggressive surgical approach is taken in these cases, it can turn into the well-known problem of multiple surgical failure. Unfortunately, while there are several cases of multiple spinal surgery failure in published reports, only 1 case in the literature describes a patient case of multiple TMJ surgical failure.[63] For patients who have a joint dysfunction problem (usually limitation of opening due to adhesion and scarring in and around the joint), surgical treatment does not necessarily improve the patients' mobility.

Recommendations for a chronic joint dysfunction case include

- *Step 1* A periodic recall for monitoring of further joint and/or occlusal changes
- *Step 2* Continued jaw mobilization exercises and wearing an occlusal appliance at night if it has been shown helpful
- *Step 3* Use of pain-modulating medications up to and including opioids as needed
- *Step 4* Consultation with a pain specialist
- *Step 5* Explanation of necessary dietary limitations
- *Step 6* Explanation of the possible long-term occlusal effects of progressive joint remodeling and adaptation

20.7 Which interventions are most efficacious for DDWR and DDNR?

For DDWR, the primary choice of treatment is always a strict avoidance protocol. Only in painful clicking and intermittent morning locking would it be appropriate to try a combination of lateral motion restriction device and joint injections using sodium hyaluronate. For DDNR the primary choice of therapy is medications followed by self-applied gentle stretching. If this does not work, the next approach is anesthesia-assisted joint mobilization. Of course the literature is replete with single-treatment studies claiming success, but one critical study was performed and published in 2007 that provides greater insight on this topic. This study examined and compared the relative effectiveness of four different methods of treating DDNR.[64] This study was a randomized prospective parallel treatment group study that evaluated the effectiveness of (1) medical management, (2) rehabilitation, (3) arthroscopic surgery with postoperative rehabilitation, and (4) open joint surgery (arthroplasty) with postoperative rehabilitation on DDNR patients. The authors concluded that, although all groups improved, there were no between-group differences at any follow-up time point on pain or jaw dysfunction measures, suggesting that primary treatment should be medical management or rehabilitation (occlusal appliances and exercises). These findings are consistent with multiple other studies in the literature suggesting that a conservative nonsurgical therapy is successful for management of DDNR.[65–67] In agreement with these data is a 2009 article by a British oral surgeon who stated that "there is no longer a perceived need to correct internal derangement with disc repositioning surgery."[68] This review article also stated that the primary management of acute restriction of opening and joint pain is now with arthrocentesis and arthroscopy. This opinion is in agreement with data from a 2007 research article that compared high condylectomy and surgical disk repositioning versus an arthroscopic surgery involving lysis, lavage, and capsular stretching for the treatment of chronic closed lock of the TMJ.[69] These researchers randomly assigned 20 patients with a clinical and radiologic diagnosis of chronic closed lock to have one of these two methods of treatment. They collected data presurgery and 1 year postsurgery on pain levels and mandibular functional impairment, with a questionnaire. Statistical analysis demonstrated that both methods (open surgery and arthroscopic) significantly reduced pain and improved mandibular function. The severity of pain was significantly reduced in both groups. They concluded that, because of the minimally invasive character of the arthroscopic procedure, it should be considered as the first choice in the surgical treatment of the TMJ.

The above recommendations that arthroscopy should be a first-line therapy need to be contrasted with a study that examined nonsurgical therapy versus arthrocentesis and arthroscopy in 1995 support this position.[70] Specifically this study divided consecutive patients into three groups treated either nonsurgically ($n = 18$), with arthrocentesis ($n = 20$), and treated with arthroscopic surgery ($n = 25$). They reported a success rate of 55.6%, 70%, and 91% in these three groups, respectively. These authors concluded that arthrocentesis was indicated for acute TMJ closed lock patients who were refractory to medication and mandibular manipulation. Of course, this study did not examine the effect of injection-assisted joint mobilization, only medication and mobilization. Finally, there was a 2002 report that described the 10-year follow-up results of nonsurgical treatment for DDNR.[71] The authors collected long-term data on 50 cases and reported that 80% (40 out of 50 cases) had an excellent result. They concluded that the long-term (10-year) outcomes of nonsurgical treatment for TMJ DDNR were considered to be acceptable and stable when compared with those of results reported for other treatment modalities (such as arthroscopic treatment).

20.8 Final recommendations

Recommendations on the treatment of internal derangement (DDWR and DDNR)

1. The internal derangements of the temporomandibular joint (TMJ) include disk displacement with reduction (DDWR), disk displacement with no reduction (DDNR), open jaw locking, open dislocation of condyle, and posterior disk displacement.
2. The mechanism of disk displacement is multifactorial but must involve some alteration of the disk attachment to the condyle, namely, the lateral collateral ligaments.
3. Etiologies for internal derangement include macrotrauma, parafunction–microtrauma, arthritic disease, hypermobility, and abnormal biomechanical loading.
4. In most cases, the clinical and historical findings will suffice to determine which type of internal derangement the patient presents with, but absolute confirmation of disk position requires magnetic resonance imaging of the TMJ.
5. For the patient with a diagnosis of a nonpainful DDWR disorder, the primary choice of treatment is always a strict avoidance protocol.
6. In those patients with painful joint clicking and intermittent morning locking of the joint due to a DDWR, another method of reducing friction is to inject into the superior joint space (up to 4 times at a frequency of once a month) 1.0 cc of sodium hyaluronate.
7. In the special case of a patient who reports waking up in the morning and finding his or her jaw is locked and after a few moments it releases, use of an interlocking double (maxillary and mandibular) appliance that restricts wide lateral jaw motion is logical and a palliative treatment.
8. The four main methods for treating a DDNR include the following:
   - **(a)** NSAID or acetaminophen medications followed by self-applied gentle daily jaw stretching is the first-line approach for DDNR.
   - **(b)** If the preceding medication–self-treatment approach fails to yield an improvement in 2 or 3 weeks, the next procedure to be considered would be to inject the joint with anesthetic and corticosteroid, followed by manual joint mobilization.
   - **(c)** If joint-anesthetic–mobilization treatment does not help, the next step of treatment is intravenous sedation plus an arthrocentesis lavage followed by manual mobilization of the joint.
   - **(d)** Only in cases of significant restriction of motion where arthrocentesis has failed is it appropriate to use an arthroscopic surgical intervention to mobilize the joint.

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Appendix

Drug list

Chapter 1

Vincristine
Cisplatinum
Nitrofurantoin
Amiodarone
ddC (dideoxycytidine)
ddI (dideoxyinosine)
Dapsone
Clozapine
Olanzapine
Risperidone

Chapter 2

Morphine
Oxycodone
Methadone
Codeine
Hydrocodone
Tramadol
Acetaminophen
Aspirin
Ibuprofen
Naproxen
Nabumetone
Piroxicam
Sodium diclofenac
Celecoxib
Meloxicam
Methylprednisolone
Triamcinolone
Fluocinonide
Lidocaine
Benzocaine
Carbamazepine
Oxcarbazepine
Lamotrigine
Levetiracetam
Zonisamide
Gabapentin
Pregabalin
Valproate
Topiramate
Tizanidine
Sumatriptan
Eletriptan
Frovatriptan
Rizatriptan
Butalbital
Dihydroergotamine
Timolol
Propranolol
Verapamil
Amitriptyline
Nortriptyline
Venlafaxine
Duloxetine
Escitalopram
Citalopram
Fluoxetine
Metaxalone
Methocarbamol
Carisoprodol
Cyclobenzaprine

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Botulinum toxin
Baclofen
Tiagabine
Diazepam
Clonazepam
Alprazolam
Indomethacin
Ketamine
Antivirals
Antibiotics
Benzodiazepine
Paracetamol
Doxylamine
Caffeine
Ketoprofen
Etodolac
Rofecoxib
Etoricoxib
Valdecoxib
Lumiracoxib
Clobetasol propionate
EMLA cream
Prilocaine
Valproic acid
Dihydroergotamine (D.H.E. 45)
Desipramine
Milnacipran
Paroxetine
Carisoprodol
Triazolam
Botulinum toxin type A
Fentanyl
Capsaicin
Acyclovir
Valacyclovir
Prednisolone
Azithromycin

Chapter 3

Acetaminophen
Tramadol
Aspirin
Diflunisal
Ibuprofen
Naproxen
Ketoprofen
Meclofenamate sodium
Piroxicam
Diclofenac
Nabumetone
Celecoxib
Meloxicam
Etodolac
Prednisolone
Methylprednisone
Naproxen sodium

Chapter 4

Codeine
Hydrocodone
Morphine
Oxycodone
Fentanyl
Hydromorphone
Oxymorphone
Methadone
Propoxyphene
Zoloft
Paroxetine
Fluoxetine
Warfarin
Rifampin
Zidovudine
Sennoside
Docusate
GlycoLax
Phenytoin
Lamotrigine
Cocaine
Heroin
Ecstasy
Marijuana
Clonidine
Naltrexone

Chapter 5

Topical benzocaine
Topical lidocane
Topical capsaicin
Topical diclofenac
Topical ibuprofen
Topical ketoprofen
Topical clonidine
Topical ketamine hydrochloride
Topical tetracaine
Topical prilocaine
Aspercreme®
Voltaren®

Emugel
Pluronic lecithin organogel

Chapter 6

Methylprednisolone
Vincristine
Cisplatinum
Nitrofurantoin
Amiodarone
ddC (dideoxycytidine)
ddI (dideoxyinosine)
Dapsone
Carbamazepine
Oxcarbazepine
Lamotrigine
Levetiracetam
Zonisamide
Phenytoin
Gabapentin
Pregabalin
Baclofen
Valproic acid
Topiramate
Lidocaine
Felbamate

Chapter 7

Dantrolene
Baclofen
Tizanidine
Dantrolene
Tiagabine
Diazepam
Lorazepam
Alprazolam
Clonazepam
Cyclobenzaprine
Methocarbamol
Metaxalone
Ophendrine
Chlorzoxazone
Carisoprodol
Meprobamate
Rituximab
Ciprofloxacin
Fluvoxamine
Clozapine
Fluconazole
Nefazodone
Rifamycin
Theophylline
Pramlintide
Secretin

Chapter 8

Amitriptyline
Imipramine
Doxepin
Clomipramine
Nortriptyline
Protriptyline
Desipramine
Venlafaxine
Milnacipran
Duloxetine
Fluoxetine
Citalopram
Escitalopram
Paroxetine
Sertraline
Fluvoxamine
Methylphenidate
Donepezil
Levorphanol
Levomethorphan
d-Propoxyphene
Maprotiline
Naloxone
Bupropion
Trazodone
Nefazodone
Haloperidol
Prochlorperazine maleate
Quetiapine
Risperidone
Chlorpromazine
Thioridazine
Fluphenazine
Olanzapine
Ziprasidone
Midazolam
Flumazenil
Lorazepam
Oxazepam
Temazepam
Diazepam

Phentermine
Dextroamphetamine
Amphetamines
Diethylpropion
Modafinil
Armodafinil
Donepezil

Chapter 9

Penicillin
Amoxicillin
Chloramphenicol
Doxycycline
Pethidine
Gentamicin
Neomycin
Kanamycin
Streptomycin
Minocycline
Doxycycline hyclate
Spicamycin
Tetracyclines
Clavulanate potassium
Cephalosporin

Chapter 10

Bupivacaine
Lidocaine
Mexiletine
Benzocaine
Ibuprofen
Nabumetone
Triamcinolone acetonide
Ketoprofen
Carisoprodol
Chlorzoxazone
Cyclobenzaprine hydrochloride
Metaxalone
Methocarbamol
Orphenadrine citrate
Pentafluoropropane
Tetrafluoroethane
Amantadine
Dextromethorphan
Ketamine
Sumatriptan
Zolmitriptan
Naratriptan
Rizatriptan
Carbamazepine
Indomethacin

Chapter 11

Botulinum toxin A
Bupivacaine
Etidocaine
Lidocaine
Naloxone
Glycerin
Phenol
Buprenorphine
Morphine
Phenol/glycerol
Botulinum toxin B

Chapter 12

Imatinib
Methotrexate
Pentoxifylline
Thalidomide
Chlorhexidine
Viscous lidocaine
Liquid diphenhydramine
Kaopectate
Magnesium aluminum hydroxide
Sucralfate
Gelclair®
Caphosol®
Polyvinylpyrrolidone
Sodium hyaluronate
Oxethazaine
Aluminum hydroxide
Magnesium hydroxide
Calcium phosphate
5-FU
Palifermin
Benzydamine hydrochloride
Amifostine
Glutamine
L-Glutamine
Furosemide
d-Penicillamine
Hydrogen peroxide
Nystatin

Prednisolone
Triamcinolone
Methylprednisolone
Dexamethasone
Fludrocortisone acetate
Betamethasone
Fluocinonide
Clobetasol propionate
Cyclosporine
Tacrolimus
Pimecrolimus
Dapsone
Azathioprine
Cyclosporine
Diamino-diphenyl sulfone
Dapsone
Azathioprine
Acitretin
Topical retinoids
Methoxypsoralen

Chapter 13

Vinca alkaloids
Paclitaxel (Taxol)
Platinum-derived compounds
Suramin
Thalidomide
Bortezomib
Cisplatin
Oxaliplatin
Vincristine
Botulinum toxin (BoNT)
Pentoxifylline
Diclofenac sodium
Ketorolac
Acetaminophen
Amitriptyline
Nortriptyline
Desipramine
Paroxetine
Citalopram
Venlafaxine
Bupropion
Dexamethasone
Prednisone
Tizanidine
Gabapentin
Topiramate
Lamotrigine
Carbamazepine
Levetiracetam
Oxcarbazepine
Pregabalin
Tiagabine
Zonisamide
Phenytoin
Valproic acid
Ketamine
Dextromethorphan
Memantine
Amantadine
Baclofen
Valproate
Imipramine
Doxepin
Clomipramine
Duloxetine
Methadone
Dextropropoxyphene
Ketobemidone
Orphenadrine
Cyclobenzaprine
Carisoprodol
Metaxalone
Methocarbamol
Diazepam
Morphine
Hydromorphone
Fentanyl
Meperidine
Levorphanol
Oxycodone
Oxymorphone
Lidocaine (1%)
Bupivacaine (0.25%)
Lidocaine 5% patch
Oral tetrahydrocannabinol (THC)
Dronabinol
Nabilone
Cannabis medical extract

Chapter 14

Tetracycline
Lithium carbonate
D-penicillamine
Captopril
Clonazepam
Trazodone
Duloxetine
Olanzapine

Amisulpride
Gabapentin
Pregabalin
Alpha-lipoic acid
Nortriptyline
Topical lidocaine
Tramadol
Hydrocodone
Paroxetine
Sertraline
St. Johns wort (*Hypericum perforatum* extract)
Levosulpiride

Chapter 15

Carbamazepine
Lamotrigine
Topiramate
Gabapentin
Indomethacin
Acetaminophen
Aspirin
Ibuprofen
Naproxen
Hydrocodone
Codeine
Fiorinol
Fioricet
Sumatriptan (Imitrex)
Rizatriptan (Maxalt)
Naratriptan (Amerge)
Zolmitriptan (Zomig)
Eletriptan (Relpax)
Frovatriptan (Frova)
Dihydroergotamine
Promethazine
Prochlorperazine
Chlorpromazine
Droperidol
Valproate
Methysergide
Propranolol
Timolol
Divalproex sodium
Amitriptyline
Fluoxetine
Tizanidine
Botulinum toxin type A
Clonazepam
Verapamil
Nifedipine
Candesartan
Olmesartan
Predonisone
Lithium
Octreotide
Psilocybin
Methylprednisolone

Chapter 16

Nortriptyline
Amitriptyline
Zolpidem (Ambien)
Tramadol
Citalopram
Duloxetine
Dothiepin
Cyclobenzaprine
Clomipramine
Maprotiline
Gabapentin
Pregabalin
Dextromethorphan
Ketamine
Amantadine
Memantine

Chapter 17

Carbamazepine
Oxcarbazepine
Lamotrigine
Gabapentin
Conotoxin
Phentolamine
Phenoxybenzamine
Prazosin
Clonidine
Lidocaine
Oral mexilitine
Oral tocainamide
Articaine
Topical anesthetic (Orobase-B)
Topical benzocaine
Nortriptyline
Pregabalin
Duloxetine
Tramadol
Citalopram

Chapter 18

Triamcinolone
Synvisic
Hyalgan
Acetaminophen
Ibuprofen
Naproxen sodium
Nabumetone
Celecoxib
Meloxicam
Etodolac
Glucosamine
Chondroitin sulfate
Topical capsaicin
Topical corticosteroid
Topical voltaren
Dexamethasone
Transdermal lidocaine patch
Doxycycline
Calcitonin
Sulfazalazine
IM gold
Methotrexate
Hydroxychloroquine
Cyclosporine
Azathioprine
Leflunomide
Cyclophosphamide
Etanercept
Infliximab
Adalimumab

Chapter 19

Botulinum toxin A
Clonidine
Clonazepam
Trihexyphenidyl hydrochloride
Biperiden
Benztropine
Carbi/levodopa
Buspirone
Diphenhydramine
Clonidine
Tolperisone hydrochloride
Pridinol mesilate
Tetrabenazine
Amantadine
Diazepam
Venlafaxine
Fluoxetine
Fluvoxamine
Paroxetine
Sertraline
Citalopram
Escitalopram
Ecstasy
Methylphenidate
Phentermine
Pemoline
Dextroamphetamine
Amphetamines
Diethylproprion
Mirtazapine
Nefazodone

Chapter 20

Sodium hyaluronate
Cyclobenzaprine
Bupivacaine

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Note: Page entries referring to figures are in *italics*; tables are noted with *t*.

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