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The Classification of Orofacial Pains

Jeffrey P. Okeson, DMD

Department of Oral Health Science, University of Kentucky, College of Dentistry, 800 Rose Street, Lexington, KY 40536-0297, USA

Pain diagnosis

This article is dedicated to the subject of orofacial pain and dysfunction. The orofacial structures are complicated, so there are many sources that can produce pain. It is imperative that the clinician be able to identify the precise source of pain to be effective in its management. This process is called ''diagnosis'' and is the most critical task for the clinician, for only by establishing the correct diagnosis can the appropriate and successful therapy be selected. Diagnosis is by far the most difficult aspect of managing a patient's pain problem. Because of this difficulty, many therapists fail to make the proper diagnosis. In fact, the majority of treatment failures arise directly from misdiagnoses. This article presents a means of assessing the pain complaint and describes a diagnostic road map that will lead the examiner toward an accurate classification of the pain disorder.

There are many methods by which pain disorders can be classified. The most elementary classification of pain is that which lists the anatomic locations where pain is felt. An example of such a classification would be head and neck pain, thoracic pain, abdominal pain, or extremity pain.

Subdivisions of head and neck pain would include orofacial pains, headaches and cervical pains. This article primarily discusses orofacial pains; however, the clinician must have an appreciation for other pain conditions of the head and neck so that proper diagnosis is possible. Other texts should be reviewed for a more complete understanding of headaches and cervical pain disorders.

A simple classification of pain disorders is often used to record the patient's subjective complaint. For example, it might list the complaint as a headache, toothache, chest pain, backache, or leg pain. It should be understood, however, that this type of classification identifies only the site where pain is felt, not the location of its true source. A pain listed as a ''toothache'' could be of dental origin and require dental therapy. But it could also be a heterotopic manifestation of some myogenous, vascular, or neuropathic condition that would require treatment using a completely different strategy. Therefore, such a classification has very little diagnostic or therapeutic value.

More refined pain classifications require additional knowledge of pain behavio and require a greater diagnostic effort. To classify pain by the location of its source requires an understanding of heterotopic pains and entails the need for diagnostic differentiation between primary pain and its secondary effects. Thus, ''toothache'' in such a classification might become pulpal pain, periodontal pain, or heterotopic pain when its true site of origin is determined. It should be obvious that this more accurate classification of the patient's complaint implies important therapeutic considerations.

In 1988, the International Headache Society published the first edition of the ''Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain'' [1]. In 2004, this classification was revised [2]. This classification attempts to separate all headaches according to etiology and involved structures. Although this classification has been most useful in unifying

E-mail address: okeson@uky.edu

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international groups, it relies heavily on the clinician's preexisting knowledge of each condition. In this classification (Box 1), the area of orofacial pain and temporomandibular (TMD) disorders fall mostly in section 11, which is listed as "Headache or facial pain attributed to disorders of cranium, neck, eyes, nose, sinuses, teeth, mouth or other facial or cranial structures." Although this section includes TMD and orofacial pain disorders, it falls short in helping the clinician diagnose and ultimately manage the patient's pain condition. Part of this failure is attributed to the lack of definitive etiology commonly associated with orofacial pain conditions [3]. This classification also fails to consider the psychologic aspect of the pain condition.

Box 1. The important categories of the International Headache Society's Classification of Headache

Part One: The primary headaches
Migraine
Tension-type headache
Cluster headache and other trigeminal autonomic cephalalgias
Other primary headaches

Part Two: The secondary headaches
Headache attributed to head or neck trauma
Headache attributed to cranial or cervical vascular disorder
Headache attributed to nonvascular intracranial disorder
Headache attributed to substances or their withdrawal
Headache attributed to infection
Headache attributed to disorder of homoeostasis
Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures
Headache attributed to psychiatric disorder

Part Three: Cranial neuralgias, central and primary facial pain and other headaches
Cranial neuralgias and central causes of facial pain
Other headache, cranial neuralgia, central or primary facial pain

Data from Olesen J. The international classification for headache disorders. Cephalalgia 2004;24(Suppl 1):1–160.

An understanding of the genesis of pain can add more refinement to a pain classification. An important concept for the clinician to appreciate is that the clinical characteristics of the pain can be useful in identifying the tissues or structures that are responsible for the pain. A reasonable classification for pain disorders, therefore, would be based on the structures that are responsible for producing the nociceptive input (the true origin of the pain). However, even this type of classification does not consider the psychologic factors that may influence or even cause the pain disorder. In order for the clinician to fully classify the pain disorder, he or she must consider both the somatosensory input (nociception from the body tissues) and the psychosocial input (influence from the higher centers). A complete pain classification must assess the pain condition on two levels or axes. One axis represents the physical factors that are responsible for the nociceptive input; the other axis represents the psychologic factors that influence the pain experience. In this article, "Axis I" will depict the physical factors and "Axis II" will depict the psychologic factors. In evaluating any pain disorder, both axes must be considered, for only then can a diagnosis be established and proper therapy selected. Therapy that addresses only one axis will likely fail if the other axis is a major contributor to the pain disorder.

Some pain disorders are influenced by one axis more than the other: for example, acute pains are commonly related more to Axis I factors than Axis II factors. Therefore acute pains often respond well to therapies directed toward the somatosensory input. Chronic pains, however, often have significant Axis II factors, and therefore therapies directed only to somatosensory inputs will likely fail. This concept is essential to successful management of pain.

Axis I: physical conditions

Axis I represents the physical conditions that are responsible for the initiation of nociceptive impulses. These conditions can be classified according to the tissues that produce the nociception. The following is a list of orofacial structures

that make up the basis for a classification of orofacial pains:

Cutaneous and mucogingival pains.
Mucosal pains of the pharynx, nose, and paranasal sinuses.
Pains of dental origin.
Pains of the musculoskeletal structures of the mouth and face.
Pains of the visceral structures of the mouth and face.
Pains of the neural structures of the mouth and face.

Axis II: psychologic conditions

Axis II represents the psychologic conditions that can either produce or influence the pain experience. The American Psychiatric Association has developed a comprehensive classification for mental disorders [4]. Only the categories that may be associated with pain will be discussed in this article. For a more complete review of all mental disorders the clinician should review this document. Mental disorders that need to be considered as Axis II factors are anxiety disorders, mood disorders, somatoform disorders, and other conditions, such as psychologic factors affecting a medical condition.

Categories of orofacial pains

In order for the clinician to begin classifying orofacial pain disorders, he or she must first be able to differentiate the signs and symptoms associated with each category. Symptoms are those complaints reported by the patient during a history-taking session. Signs are the specific findings identified by the clinician during the clinical examination. Signs and symptoms may not always be the same. In this section, physical and psychologic factors will be separated and identified. This begins the process called ''diagnosis'' and represents the most important process for the successful management of pain. Without proper diagnosis, appropriate therapy cannot be rendered.

A reliable pain classification needs to be based on symptomatology. This requires an understanding of the clinical characteristics displayed by the different categories of pain. It is on the basis of the subjective symptoms and objective signs of the nociceptive condition under examination that proper identification is made. If one fully appreciates the concept of pain modulation, understands and can differentiate primary from secondary pain, has some knowledge of pain genesis, can identify the categories of pain by their clinical characteristics, and appreciates psychologic factors, a truly sophisticated and useful classification of orofacial pain is possible. As concepts have evolved in recent years, this pain classification has undergone considerable metamorphosis. It represents a logical classification for orofacial pain that conforms well to current knowledge of nociceptive mechanisms and psychologic factors. Box 2 outlines these classification categories.

Axis I categories: physical conditions

The various tissues of the body make up the physical conditions that are responsible for nociceptive input that can eventually produce pain. These tissues can be divided into two broad categories: somatic and neurogenous. Neurogenous tissues are those tissues that comprise the communication or control system, while somatic tissues refer to all other body tissues. The somatic structures are subdivided into the superficial somatic structures, the musculoskeletal structures, the structures of the supply system, and the special sensory organs. The neurogenous structures are the brain and brainstem, including the spinal cord, the peripheral nervous system, and the autonomic nervous system. It is important to appreciate that the manner by which each system communicates with the neurologic system is perceived differently by the brain and brainstem. Therefore, pain felt from each type of somatic tissue can be differentiated from the other somatic tissues by unique clinical characteristics. Understanding these characteristics is essential in establishing the proper diagnosis.

Somatic pain

Somatic pains occur in response to the stimulation of normal neural receptors. Local conditions, such as inflammation, increase the receptivity of the neural structures so that stimulation becomes more pronounced. As nociception becomes prolonged the central nervous system responds with increased sensitization of spinal track neurons, increasing the excitability of these neurons. This process is referred to as central sensitization and can have profound effects on the processing of nociception. At this same time, reduced central inhibitory control of the passage of peripheral impulses to the higher centers also

Box 2. Orofacial pain classification

Axis I: Physical conditions
Somatic pain
- Superficial somatic pain
  - Cutaneous pain
  - Mucogingival pain
- Deep somatic pain
  - Musculoskeletal pain
    - a. Muscle pain (*see the article by Clark in this issue*)
      - i. Protective co-contraction
      - ii. Local muscle soreness
      - iii. Myofascial pain
      - iv. Myospasm
      - v. Myositis
      - vi. Centrally mediated myalgia
      - vii. Central mediated movement disorders (*see the article by Balasubramaniam and Ram in this issue*)
    - b. Temporomandibular joint pain (*see the article by de Leeuw in this issue*)
      - i. Ligamentous pain
      - ii. Retrodiscal pain
      - iii. Capsular pain
      - iv. Arthritic pain (*see the article by Mercuri in this issue*)
    - c. Osseous and periosteal pain
    - d. Soft connective tissue pain
    - e. Periodontal dental pain
  - Visceral pain
    - a. Pulpal dental pain
    - b. Vascular pain
      - i. Arteritis
      - ii. Carotidynia
    - c. Neurovascular pain (*see the article by Nixdorf, Velly, and Alonso in this issue*)
      - i. Migraine
      - ii. Tension-type headache
      - iii. Cluster headache and other trigeminal autonomic cephalalgias
      - iv. Other primary headaches
      - v. Neurovascular variants
    - d. Visceral mucosal pain
    - e. Glandular, ocular, and auricular pain

Neuropathic pain
- Episodic neuropathic pains (*see the article by Benoliel and Eliav in this issue*)
  - Paroxysmal neuralgia pain
    - a. Trigeminal neuralgia
    - b. Glossopharyngeal neuralgia
    - c. Geniculate neuralgia
    - d. Superior laryngeal neuralgia
    - e. Nervous intermedius
    - f. Occipital neuralgia
  - Neurovascular pain (already listed under visceral pain)
- Continuous neuropathic pains
  - Peripheral mediated pain
    - a. Entrapment neuropathy
    - b. Deafferentation pain
    - c. Neuritic pain
  - Central mediated pain
    - a. Burning mouth syndrome (*see the article by Klasser, Fischer, and Epstein in this issue*)
    - b. Atypical odontalgia (phantom pain)
    - c. Postherpetic neuralgia
    - d. Chronic regional pain syndromes
    - e. Sympathetically maintained pain
  - Metabolic polyneuropathies
    - a. Diabetic neuropathy
    - b. Hypothyroid neuropathy
    - c. Alcoholic neuropathy
    - d. Nutritional neuropathies

Axis II: Psychologic conditions (see the article by Carlson in this issue)
Mood disorders
- Depressive disorders
- Bipolar disorders
- Mood disorders because of a medical condition

Anxiety disorders
- Generalized anxiety disorders
- Posttraumatic stress disorders
- Anxiety disorders because of a medical condition

Somatoform disorders
- Undifferentiated somatoform disorders
- Conversion disorders
- Pain disorders
- Hypochondriasis

Other conditions
- Malingering
- Psychological factors affecting a medical condition
  - Personality traits or coping style
  - Maladaptive health behavior
  - Stress-related physiologic response
- Any other mental disorders not mentioned in this classification

Data from Olesen J. The International Classification for Headache Disorders. Cephalalgia 2004;24(Suppl 1):1–160.

causes less intense peripheral stimulation to become more noxious. The end result is that the degree of pain reported by the patient no longer relates proportionally to the intensity of the stimulus.

The neural structures involved in such pain reception and transmission are presumed to be normal, and the sensation serves to warn, alert, or inform the individual of the noxious stimulation. The conscious sensation of pain under such conditions is an added component to the voluminous sensory input the brain receives constantly, and it serves the purpose of preparing the patient for the appropriate response. Afferent neurons of both the peripheral (somatic) and autonomic (visceral) nervous systems participate in this mechanism.

The clinical characteristics of pain that originates in superficial structures are distinctly different from those of deep origin. It is by these differences that the two types of somatic pain are distinguished.

Superficial somatic pain. The external surface of the body is richly innervated with receptors and sensory fibers of different types. These constantly feed information to the somatosensory cortex concerning the organism's environment. Not only does such sensation establish full conscious contact between the organism and its surroundings, it also furnishes the impetus for involuntary reflex activity. Superficial sensation serves a protective function so the organism may react appropriately to the constant and varied environmental threat to its well-being, comfort, and survival.

The sensory system provides input at conscious levels that allow precise definition of the physical characteristics of the stimulus, including its modality, location, duration, and intensity. Pain emanating from these superficial structures presents characteristics at a conscious level of the definition of the physical properties of the noxious stimulus. These qualities are inherent in superficial somatic pain and furnish the examiner a means of identifying it.

Superficial pains have a bright, stimulating quality [5–7]. This probably results from the alarm reaction that such discomfort tends to create. As part of the environmental threat, superficial pain causes the patient to react in such a way as to escape such threat (fight or flight response). The more severe the superficial pain, the more pronounced this stimulating quality becomes. Superficial pains can be correctly located by the patient so that the patient is precisely aware of where the hurt is. They are able to describe the location of the pain with anatomic accuracy.

Because the source of superficial pain is noxious stimulation of the very structures that hurt, the location of the pain clearly identifies where to look for its cause: the site of pain and the origin of the pain are identical. In fact, if the cause of the pain is not immediately evident or reasonably explicable, the diagnosis of superficial pain should be questioned.

Because superficial somatic pain is the result of a lowered pain threshold, and because the site of pain and the location of its true source are the same, the discomfort that results from provocation at the site of pain relates faithfully to the stimulus. This means that the reaction is immediate, it is proportional to the intensity of the stimulus, it lasts as long as the stimulus, and there is no referral of pain to other normal structures. Superficial pain responds faithfully to provocation. Effects of central sensitization, such as referred pain, secondary hyperalgesia, local autonomic effects, and secondary muscle co-contraction are not observed.

Because superficial pain emanates from the surface tissue, application of a topical anesthetic interrupts the pain. It should be noted that neither neuropathic pain felt in superficial tissues nor pain referred from deeper structures to the surface is arrested by the application of topical local anesthesia.

Two types of superficial orofacial pain are recognized: namely, cutaneous pain and mucogingival pain. To summarize, the following clinical characteristics are displayed by superficial somatic pain:

The pain has a bright, stimulating quality.
Subjective localization of the pain is excellent and anatomically accurate.
The site of pain identifies the correct location of its source.
Response to provocation at the site of pain is faithful in incidence, intensity, and location.
The application of a topical anesthetic at the site of pain temporarily arrests it.

Deep somatic pain. Sensory innervation of the deeper structures of the body supplies the somatosensory cortex with a constant inflow of information, monitoring all the internal functioning of the body. No doubt the information has a certain precision of definition as to the physical

characteristics of the stimulus, including its modality, location, duration, and intensity, but this information is normally below conscious levels unless volition brings it to the attention of the subject. Functions that require precise definition of the physical characteristics of the stimulus, such as the action of skeletal muscles, are attended by some conscious sensation that is fairly precise for location. Most functions that operate at an involuntary level, such as the action of smooth muscle, are attended by sensations that remain below conscious levels unless unusual conditions prevail, such as distension, pressure, sustained hyperemia, or inflammation [8,9]. In such cases, the conscious sensation usually is that of diffusely located and poorly defined discomfort or pain.

Deep pain has a dull, depressing quality [5,7,8], sometimes causing a sickening sensation of nausea. The background sensation may be punctuated by momentary lancinating pains that the patient describes as "stimulating" and "exciting." Such lancinating pain is usually initiated by sudden traction, distension, or distortion of deep tissues.

The depressing effect of pain arising in deeper body structures and mediated by either deep somatic or visceral afferent fibers is likely to be a manifestation of withdrawal reaction. In contrast to the alarm effect from an environmental threat, as witnessed in superficial pain, the usual reaction to discomfort emanating from deeper structures is to prepare the subject for conservation and recovery. Therefore, a decrease in somatic skeletal activity occurs in favor of increased visceral function [10]. The characteristic quality of deep pain is that the discomfort induces a depressing effect leading to inactivity and withdrawal, sometimes accompanied by weariness, depression, weakness, or lowered blood pressure [11].

Deep pain is less accurately localizable by the patient. Some pains of deep origin, such as those from skeletal muscle or from the periodontal ligament, are fairly localizable. However, such localizing sensation is considerably less accurate and the ability of the patient to describe the painful site anatomically is less certain than with the superficial pain. The area where pain is sensed is usually larger than the site from which it arises. Many deep pains, such as those emanating from the dental pulp or from blood vessels, are hardly localizable, and the patient's anatomic description of where he feels the pain may be diffuse indeed. Some deep pains produce central sensitization so that the pain may be referred to otherwise normal structures, and the descriptive location of the pain is nonanatomic.

Because of the variable and inconsistent localizability of deep pain, the site of pain may not indicate the true origin. This applies especially to pains that occur spontaneously or in response to normal function. Pain provoked by manual palpation and manipulation more accurately identifies its true location, and this diagnostic maneuver often can be useful to isolate otherwise vague and diffusely located pain sites. Muscle and organ pains especially show this trait. It is true that the site of some deep pains may clearly identify the origin, but even then it is considerably less precise and dependable than with superficial pain. Although some deep pains are felt in sites much larger than the true source of pain, others may be felt in entirely normal structures.

Because these variables are characteristic of deep pain, it is important for the examiner to take measures to prove the location of the pain source and not to depend on the patient to report the site of pain. In those cases when local provocation of the location the patient feels the pain does not increase the pain, the clinician should be suspicious that this is a site of pain but not the source of the pain. In those instances it can be very diagnostic to inject local anesthetic into the site. If the pain is not eliminated, the clinician should strongly consider that this is not the true source of the pain and that therapy should not be extended to these structures [12]. The clinician is then obligated to find the true source of the pain before therapy is begun.

Deep pain may not be proportional to the stimulus. Although some deep pains (usually those with better localization behavior) respond rather faithfully to a stimulus, the response is not as faithful as with superficial pain. In contrast, some deep pains manifest little relationship between stimulus and response, and others cannot be provoked by manual palpation or the demands of function. Although the lack of faithful response to provocation is characteristic of deep pain (sometimes greater, sometimes less than the intensity of provocation would suggest), true summation effects are not seen. Therefore, triggering of intense pain by light touch or superficial movement is not characteristic of deep pain disorders.

One of the most important identifying clinical characteristics of deep pain is its tendency to display effects caused by central sensitization or hyperexcitability [5,8,13]. Deep pain input tends

to provoke referred pains, secondary hyperalgesia (allodynia), localized autonomic effects, and secondary muscle co-contraction. This tendency relates to the continuity, severity, and duration of the deep pain input. When diagnostic evidence of such central excitatory effects is observed, a deep pain disorder must be suspected and a serious diagnostic search made for the primary pain source. Great care must be exercised not to confuse secondary pain effects (which may actually be the patient's clinical complaint) with the primary pain source, which may be relatively silent and therefore nonsymptomatic to the patient. It is the manifestation of such secondary effects that creates much of the diffuse variableness and spreading effect of some deep pains. Certainly, these effects are largely responsible for the confusion that surrounds many deep pain disorders and the therapeutic failure that sometimes occurs.

Deep pain usually is not arrested by the application of a topical anesthetic, except when it arises from visceral mucosa, such as the nasal mucosa in so-called "sinus headache." Analgesic blocking of the nerve that mediates the primary painful impulses usually arrests deep pain, and this technique is useful diagnostically in localizing the source of such pain [12]. Vascular pains, however, may not respond well to ordinary analgesic blocking.

To summarize, the following clinical characteristics are displayed by deep somatic pain:

The pain has a dull, depressing quality.
Subjective localization of the pain is variable and somewhat diffuse.
The site of pain may or may not identify the correct location of its true source.
Response to provocation at the source of pain is fairly faithful in incidence and intensity.
Secondary central excitatory effects frequently accompany the deep pain.

There are two distinct types of deep somatic pain, namely, musculoskeletal pain and visceral pain. Musculoskeletal pain involves the action of receptors that respond to varying degrees of stimulation. Such pain therefore yields a graduated response to stimulation. Musculoskeletal pain relates intimately to biomechanical function. It can be localized to the degree that such a sense of localization is required in the course of normal functioning. Musculoskeletal pain is further subdivided into (1) muscle pain, (2) temporomandibular joint pain, (3) osseous and periosteal pain, (4) connective tissue pain, and (5) dental pain of periodontal origin. Muscle pains include protective co-contraction, local muscle soreness, myofascial pain, myospasm, myositis, and centrally mediated myalgia. These muscle pain disorders are common and will be discussed in more detail in the article by Clark in this issue.

Another type of muscle disorder includes orofacial movement disorders, which are centrally mediated. These disorders are characterized by uncontrolled and spontaneous contraction of specific orofacial muscles, resulting in involuntary movement. These muscle disorders are relatively uncommon in the general population and will be discussed in detail in the article by Balasubramaniam and Ram in this issue.

Temporomandibular joint pain includes ligamentous pain, retrodiscal pain, capsular pain, and arthritic pain. Ligamentous, retrodiscal, and capsular pains are sometimes involved with internal derangements. A discussion regarding internal derangements and arthritic pain is presented in the article by de Leeuw and the article by Mercuri in this issue.

It is important to appreciate that all the orofacial pain conditions that have their source in and emanate from the musculoskeletal structures of the masticatory system are collectively called temporomandibular disorders [14]. This field of study has grown greatly over the years and is a primary interest of many dentists. As interest has grown, so has our technology. The article by Gonzalez, Greene, and Mohl in this issue discusses the use of technologic devices to aid in the diagnosis of TMD.

Visceral pain involves the action of high-threshold receptors of the interoceptive type. Such pain is not usually felt until the threshold is reached. Unless inflammatory, it does not present a graduated response to stimulation. It has little or no relationship to biomechanical function, and is poorly localizable by the subject. Visceral pain is further subdivided into (1) neurovascular pain, (2) vascular pain, (3) dental pain of pulpal origin, (4) visceral mucosal pain, and (5) glandular, ocular, and auricular pain. Neurovascular pains are common and can be subdivided into (1) migraine, (2) tension-type headache, (3) cluster headache and other trigeminal autonomic cephalalgias, (4) other primary headaches, and (5) neurovascular variants.

Neuropathic pain

Neuropathic pain is a broad term depicting any pain condition that has its source in the

neurologic structures [15]. The clinician needs to be acutely aware that pain felt in somatic structures may actually be originating in neurogenous tissues, both peripherally and centrally. When this occurs managing the peripheral somatic tissues will fail. In fact, examining the peripheral tissues will fail to find any pathology, other than the report of pain. Stimulation of sensory receptors and primary afferent neurons is therefore unnecessary. Stimulation may cause summation effects so that the evoked response may be wholly disproportionate to the stimulus. A common clinical characteristic of neuropathic pain is the lack of any obvious source of the nociception. Because the pain originates in the neural structures the somatic structures appear normal. This clinical presentation is a real challenge for the clinician because neuropathic pains and psychogenic pains both present with no obvious clinical findings.

In earlier years, before neuropathic pains were appreciated, most of these patients were labeled as having a psychologic problem causing the pain. This was a very unfortunate assumption and very frustrating for patients. In fact, even today, many patients are given a primary psychiatric diagnosis by the naive, uninformed clinician. Most experienced pain clinicians agree that true psychogenic pain is rare. This does not mean that a psychologic disorder cannot coexist (Axis II). In fact, the longer one suffers with pain the greater the likelihood of having a coexistent condition, such as depression, anxiety, hostility, and frustration. But these conditions may be secondary to the pain and not the primary diagnosis [16,17]. Informing a neuropathic pain patient that his or her pain condition is ''all in his or her head'' can be a devastating blow.

Neuropathic pains are commonly reported as a burning sensation and may be associated with other neurologic symptoms, such as burning, hyperalgesia, paresthesia, and even sometimes anesthesia. Heterotopic pain is also common. Neuropathic pain can present as either episodic pain or continuous pain. Because this characteristic is useful for classifying neuropathic pains, it will be used in this article.

Episodic neuropathic pains. Episodic neuropathic pains are characterized by periods of very intense pains followed by total remission. These pains may last from seconds to hours, depending on the type. Usually, the individual is able to localize the site of pain quite well. The site, however, does not identify the correct source, as many of these pains are projected heterotopic pains. Response to provocation at the site of pain is unfaithful. Because these pains will demonstrate periods of total remission, secondary symptoms associated with central excitatory effects are not usually seen. Episodic neuropathic pains are classified into one of two categories: paroxysmal neuralgic pains and neurovascular pains.

Paroxysmal neuralgic pains are characterized by a bright, stimulating, burning quality that simulates superficial somatic pain from which it must be differentiated. These pains are said to be paroxysmal and therefore the name paroxysmal neuralgia. The pain is extremely intense, usually lasting only a few seconds. On occasion it may last minutes, but this is rare. In between episodes the individual is usually pain free; however, if the episodes are frequent there may be a lingering dull aching pain. Neuralgic pains are categorized according to the affected nerve, for example trigeminal neuralgia. Other neuralgias are glossopharyngeal neuralgia, geniculate neuralgia, superior laryngeal neuralgia, and nervous intermedius. Some of these more common neuralgic pains are reviewed in the article by Benoliel and Eliav in this issue.

Neurovascular pains are characterized by periods of intense, debilitating, pulsating pain that typical lasts from 4 to 72 hours [18]. These pains have already been classified under the visceral pain category. They are mentioned here because of studies that have demonstrated their etiology is likely to begin with a neurovascular mechanism. Neurovascular pains will be discussed under the category of visceral pains because their clinical characteristics are more typical of visceral pains. These pain disorders are discussed in more detail in the article by Nixdorf, Velly, and Alonso in this issue.

Continuous neuropathic pains. Continuous neuropathic pains result from interference with the normal transmission of afferent impulses by primary sensory neurons. Many of these pains are felt as a persistent, ongoing, unremitting, burning, tingling sensations [19]. These pains may have some fluctuation in intensity but no periods of total remission. These will often present as enlargement of the receptive field and diminished central inhibitory activity. They occur from a variety of conditions, but trauma or some other form of damage to the neuron is common. Continuous neuropathic pains are classified

into three categories: peripheral mediated pain, central mediated pain, and metabolic polyneuropathies. The peripheral mediated neuropathic pains are further subdivided into three categories: entrapment neuropathies, deafferentation pains, and neuritic pains. Understanding the mechanisms of these pain disorders is not simple and management can be very challenging. These continuous neuropathic pain disorders are discussed in detail in the article by Benoliel and Eliav in this issue.

Central mediated neuropathic pains are subdivided into two subcategories: burning mouth syndrome and atypical odontalgia (phantom pain). Probably the most common of these is burning mouth syndrome, and this is discussed in the article by Klasser, Fischer, and Epstein in this issue.

In some instances a continuous neuropathic pain can be influenced by activity of the sympathetic nervous system in the area of the problem. When this occurs, the neuropathic condition is referred to as a ''sympathetically maintained pain.'' In other conditions the sympathetic nervous system has no obvious influence on the pain condition, and this is referred to as ''sympathetically independent pain.'' This is also discussed in the article by Benoliel and Eliav in this issue.

When neuropathic pain conditions become more chronic they can present with additional clinical signs and symptoms, such as extreme allodynia, tissue erythema, temperature and trophic changes, and swelling. In an attempt to better study and understand these conditions, investigators have developed clinical criteria and termed these conditions ''complex regional pain syndromes'' (CRPS) [20]. CRPS has been described primarily in the limbs and with few reports involving the orofacial structures [21]. CRPS is discussed briefly in the article by Benoliel and Eliav in this issue. It is recommended that the clinician refer to other sources for more information on this continuous neuropathic pain condition [22–26].

Axis II categories: psychologic conditions

Psychologic conditions influence all pains. These conditions have their greatest effects on chronic pains. The longer a patient suffers, the greater the influence of these factors. All clinicians treating pain disorders must be familiar with certain important psychologic factors, so that when indicated these conditions can be properly addressed.

Psychologic intensification of pain may proceed until the suffering is wholly disproportionate to the peripheral nociceptive input. Although the original pain complaint may have displayed the usual clinical characteristics of somatic or neuropathic pain, as psychologic intensification converts it into a chronic pain disorder, the clinical symptoms take on additional features. Such features are that the pain lacks an adequate source of input that is anatomically related to the site of pain. It may be felt in multiple and sometimes changeable locations. Pain bilaterally may become evident in the absence of bilateral sources of noxious input. The complaint may display unusual or unexpected responses to therapy. It may respond too quickly or too slowly. It may respond in an exaggerated way or with unusual side effects or complications. The response may be followed by a relapse without organic justification, or the condition may remain refractory in spite of otherwise effective therapy. Pains that are greatly influenced by psychologic factors may display changeableness in location, intensity, or temporal behavior without a reasonable, identifiable organic cause.

To summarize, the following clinical characteristics are common to pain conditions that are greatly influenced by psychologic factors:

The site of pain lacks an adequate, anatomically related source of nociceptive input.
Its clinical behavior and responsiveness to reasonable therapy is unusual, unexpected, and nonphysiologic.

The psychologic influence of orofacial pains can be categorized into certain identifiable mental disorders [4]. Although there are numerous disorders, the clinician needs to be familiar with the following common mental disorders as these can greatly influence the individual's pain experience: mood disorders, anxiety disorders, somatoform disorders, and a fourth category that includes many other mental conditions or psychologic factors that affect the outcome of a medical condition.

Each of these major categories can be separated into subcategories. Mood disorders are divided into the depressive disorders, bipolar disorders, and a general category in which the mood disorder is the result of a medical condition.

Anxiety disorders are subdivided into the generalized anxiety disorders, posttraumatic stress disorders, and anxiety disorders that are caused by a medical condition.

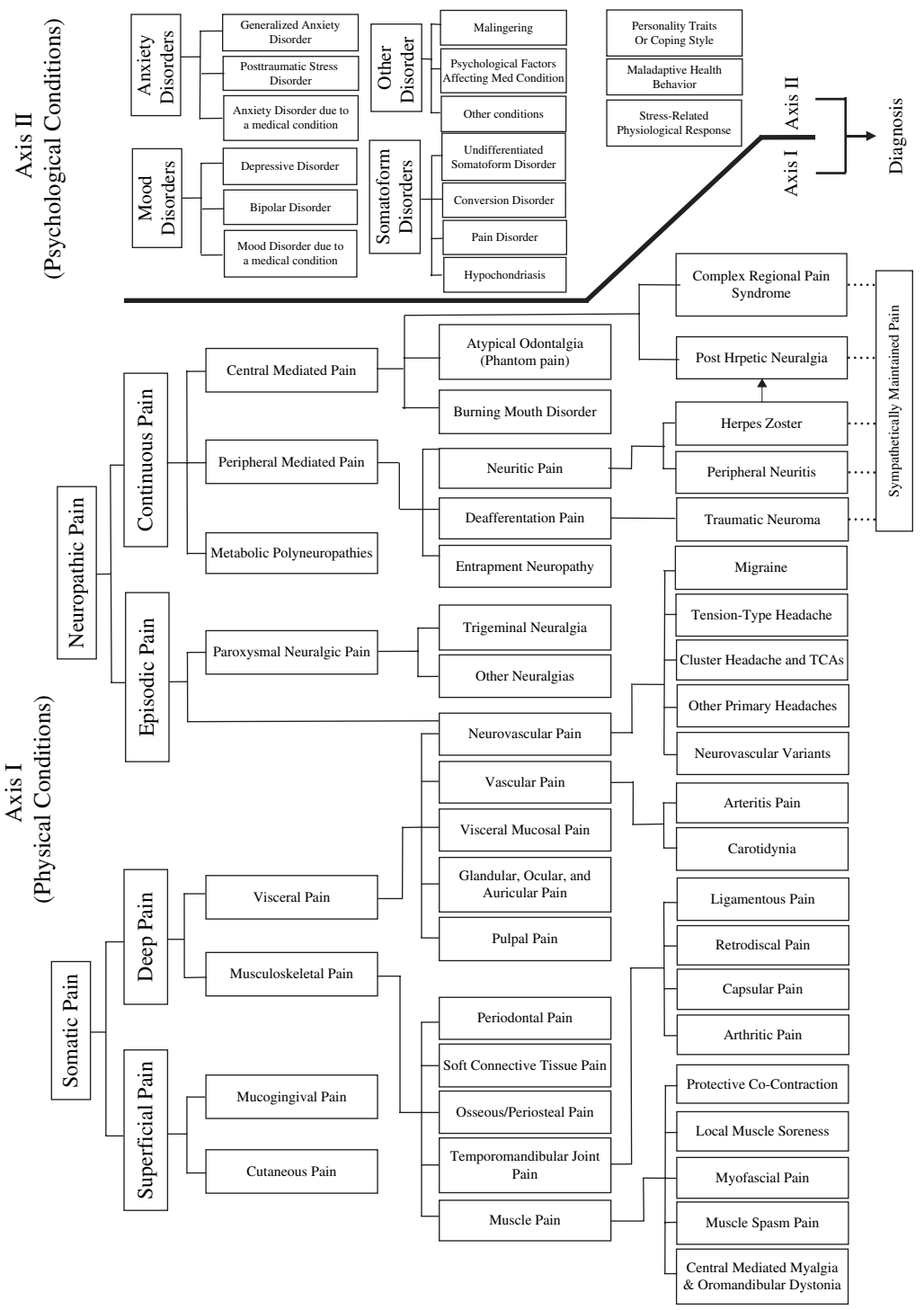

Fig. 1. The classification of orofacial pain. (*Modified from* Okeson JP. Bell's Orofacial Pains. 6th edition. Quintessence Publishers, Chicago Ill, 2005; with permission.)

Somatoform disorders are a group of disorders that are characterized by physical symptoms, suggesting a physical disorder for which there are no demonstrable organic findings of known physiologic mechanisms. Strong positive evidence that the symptoms are linked to psychologic factors or conflicts is important. The somatoform disorders are subdivided into undifferentiated somatoform disorders, conversion disorders, pain disorders, and hypochondriasis.

The last category is a broad group of mental disorders that may be related to pain conditions. This category includes malingering, psychologic factors affecting a medical condition, such as certain personality traits, coping styles, maladaptive health behavior, and stress-related physiologic responses.

Axis II conditions can play a significant role in the chronic pain patient; however, most clinicians have very little training in diagnosing and managing these conditions. This can be a very frustrating aspect of managing chronic pain. The clinician who routinely manages chronic orofacial pain should have access to a behavioral medicine practitioner with understanding and expertise in the unique aspects of orofacial pain. The article by Carlson in this issue addresses these considerations.

There are two additional articles in this issue aimed at helping the clinician diagnosis and manage orofacial pain. The article by Hersh, Balasubramaniam, and Pinto in this issue reviews pharmacologic aspects of managing orofacial pain. In some instances the clinician will need to use pharmacologic therapy, either as a primary treatment or as an adjunct to other therapies. Therefore the oral and maxillofacial surgeon involved in the management of orofacial pain patients needs to understand pain pharmacology.

Another chapter in this issue is directed to understanding of the association between orofacial pain conditions and symptoms of primary tumors, metastatic disease, systemic cancer, or distant nonmetastasized cancer. Additionally, each clinician needs to be able to recognize and appreciate the potential acute and chronic oral complications induced by head and neck cancer therapies. These issues will be reviewed in the article by Fischer, Klasser, and Epstein in this issue.

Summary

The management of orofacial pain is certainly a challenge to the clinician. The difficultly arises from the complexity of the many structures that make up the orofacial region. Pain can arise from many sources. Establishing the correct diagnosis is essential for successfully managing the pain condition. This article has laid out a framework to organize the data collected in the history and examination that will categorize the specific pain condition. The classification is based on the clinical characteristics of the pain complaint and the structure by which it emanates. It is meant to serve as a road map for the clinician that will help him or her establish the correct diagnosis, thereby allowing appropriate management. The entire classification is summarized in Fig. 1.

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Classification, Causation and Treatment of Masticatory Myogenous Pain and Dysfunction

Glenn T. Clark, DDS, MS

Department of Diagnostic Sciences, University of Southern California, School of Dentistry, 925 West 34th Street, Los Angeles, CA 90089-0641, USA

Understanding muscle pain classification and causation

The common subcategories for masticatory muscle pain include: (1) focal masticatory myalgia, (2) those with 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, which also involves the masticatory system. For local and regional myalgia, if some additional anatomic features are added, such as taut bands, trigger points within the taut band, and referred pain sensations upon sustained compression of the trigger point, then the term "myalgia" can be changed to "myofascial pain." For widespread chronic musculoskeletal pain, if the appropriate criteria are satisfied, then the term "fibromyalgia" (FM) is used [1]. Note that the palpation pressure used in the masticatory system varies (1 kg–2 kg), but is generally lower than that used when palpating large leg, arm, shoulder, or neck muscles [2]. Of course an anatomic-based-classification of masticatory muscle pain does not account for the etiology, and when it is known it must be appended to the diagnostic term being used. It is always cleaner if a single etiology exists, but in most patients this is not reality. When multiple etiologic factors are possible, then it is best to select the one or two most prominent etiologies. Etiologies often prove far more difficult to discover than "where the pain is located and what physical characteristics are revealed by palpation."

Classifying the different types of myalgia based on causation

Focal and regional masticatory myalgia may be caused by one of the following etiologies: direct muscular trauma, parafunction induced or stress-related primary myogenous pain, or secondary myogenous pain (eg, associated with local temporomandibular(TM) joint disease). Focal myalgia can develop as a result of muscle damage resulting in histologically evident changes within the muscle called myositis [3,4]. Such injuries are not common in the masticatory system, but when they do occur they are quite dramatic. Patients typically exhibit strong focal pain and severely limited opening because of secondary trismus [5]. The most common traumatic cause of myositis in the jaw system is an inadvertent intramuscular injection of local anesthetic during dental treatment [6–9]. Other forms of local muscle injury can occur (eg, neck musculature can be injured during a low-velocity rear-end collision) that produce a regional cervical muscle strain and secondary cervical and masticatory myalgia. It is assumed that the jaw closing and opening muscles themselves are not stretched or torn during a low velocity rear-end motor vehicle collision, but may become involved as a secondary phenomenon after the craniocervical muscles are injured. The standard treatment for traumatic focal or regional myalgia is rest, ice or moist heat, nonsteroidal anti-inflammatory drugs (NSAIDs), and then frequent, daily active mobilization of the jaw and neck muscles until normal range of movement is reestablished and maintained [10].

Often focal and regional myalgias are not strongly associated with a traumatic event or

E-mail address: gtc@usc.edu

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any other local pathologic problems in the masticatory system. In these cases, the clinician is usually asked about medications, stress, and parafunctions (both waking and sleeping) in a search for the cause of the pain. When a patient admits to these behaviors the clinician will typically diagnose a primary myalgia resulting from stress or parafunction. Oral parafunctions include both diurnal and nocturnal clenching and tooth grinding, as well as other oral habits such as chronic gum chewing [11]. Several studies have reported that there is a moderately strong positive association between self-reported clenching and chronic masticatory myofascial pain [12–14]. One study performed a questionnaire based on an epidemiologic cross-sectional study, and another used a clinical based case-controlled design [15,16]. These two studies found a positive relationship between self-reported nocturnal tooth grinding and self-reported jaw pain. The standard ways of modifying parafunction include oral appliances and a thorough review of these methods has been recently published [17]. Stress, can be treated pharmacologically or behaviorally.

Sometimes focal, and even regional myalgia, will develop in response to a local painful pathologic process, such as acute arthritis affecting the TM joint. In these 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, but it may generate an equal or greater degree of tenderness to palpation. The fact 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 by the literature [18,19]. The most likely secondary jaw and cervical motor activation occurs with a painful arthritis or internal derangement of the TM joint [20]. In some cases, acute traumatic trismus can convert to chronic contracture of the involved muscle [21].

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 [22]. Essentially the term ''myofascial pain'' is used only when specific criteria are satisfied. These criteria are both subjective (history based) and objective (examination based) in nature. The three subjective criteria that patients should endorse include: (1) spontaneous, dull aching pain and localized tenderness in the involved muscles, (2) stiffness in the involved body area, and (3) easily induced fatigue with sustained function. The four objective criteria are as follows: (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 neurologic deficit explaining this weakness. Many have included the presence of referred autonomic phenomena upon compression of the hyperirritable spot or a twitch response to snapping palpation of the taut bands as additional diagnostic criteria [23–27].

Myofascial pain appears to be a completely different entity than localized traumatic myalgia, in that the former is not associated with any histologically evident tissue damage or inflammation. Several investigators have attempted to biopsy the muscles of patients who have myofascial pain without finding any unique tissue-based evidence of inflammatory disease. Several investigators in recent years have offered explanations for the referred pain phenomena [28–32]. Needle electromyography (EMG) based studies have reported that a sustained spontaneous EMG activity can be found within one to two millimeters of the hyperirritable or ''trigger'' point in a muscle, but not from control nonpainful sites or from the surface above the muscle [33]. 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. Recently, after reviewing the literature on myofascial trigger points, one study concluded that the electrical activity characteristics of trigger points are similar to those described from needle EMG recording in and around a motor endplates [34]. They speculated that the spontaneous activity recorded from the trigger point is probably related to excessive release of acetylcholine at the endplate. They also speculated that these endplates were abnormal because the sensory nerve fibers that surrounded these endplates 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 endplate.

Finally, there is a small percentage of the population that develops widespread chronic

musculoskeletal pain. Based on epidemiologic studies, syndromes of diffuse musculoskeletal pain are reported to occur in 4% to 13% of the general population [35–37]. 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, TM disorders, and headaches. In general, FM is treated using multimodal approaches that simultaneously target the biologic, psychologic, and environmental or social factors that maintain the pain.

The American College of Rheumatology (ACR) has set forth criteria for the diagnosis of FM [38]. These criteria include specific duration, location, and examination findings that must be satisfied. The duration criteria specify that a history of widespread pain has to be present for at least 3 months. Moreover, for pain to be considered widespread, it must involve both sides of the body and be located above and below the waist. The location criteria states that the pain must involve the 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 criteria for below the waist pain. Finally, the examination finding 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 and also specify that a manual finger palpation force of approximately 4 kilograms is to be used during the examination to elicit a pain response to palpation.

The most likely difference between focal or regional myalgia and myofascial pain versus FM is that there is substantial evidence that FM sufferers have central neuronal changes in their pain system. Functional central nervous system (CNS) changes can be demonstrated in FM by several different imaging techniques. For example, one study reported that FM has a decreased thalamic and caudate blood flow when compared with healthy controls on single-photon-emission-computed tomography imaging [39]. FM patients often develop an increased response to painful stimuli (hyperalgesia) and experience pain from normally nonnoxious stimuli (allodynia) [40]. Both hyperalgesia and allodynia reflect an enhanced CNS processing of painful stimuli that is characteristic of central sensitization [41]. FM 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 [42,43]. Recent muscle nociceptor sensitization discoveries in FM [44–46] are known to be important contributors to pain pathogenesis. Note that etiology is more relevant when discussing focal and regional myalgia, but for widespread chronic myalgia (eg, FM), the patient's pain is usually so long-standing by the time FM has developed and is diagnosed that the original etiology is not discoverable and the central sensitization is the predominant issue.

Treatment of masticatory myogenous pain

This third section of the article covers self-applied treatment, office-based treatment, pharmacologic treatments, and behavioral treatments. 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 RBCT assessing the same method, whereby conclusions can be drawn across several RBCT studies and 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 of studies which promotes evidence based reviews of the literature (http://www.cochrane.org). This article endeavors to find review articles that specifically deal with local or regional myogenous pain in the craniocervical or TM region. However, if such information was not available, other chronic pain treatment outcome reviews were looked at, in the hope of generalizing the data to masticatory myogenous pain. While such collecting together of disparate information has it disadvantages, the advantages and overall conclusions will hopefully outweigh the limitations of the data. Where no substantive scientific evidence is available, current best clinical practice, as understood by the author, is described and identified clearly as clinical opinion.

Self-directed treatment

Whether the masticatory musculoskeletal pain is localized, regional, or generalized, the first line of treatment is almost always self-treatment. Self-treatment always includes education about the specific masticatory muscle disorder the patient is

experiencing and an individualized self-treatment program. The self-treatment program generally includes four elements:

1. Identify and avoid activities that are potentially harmful to the masticatory 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 when the patient is able to
4. Encourage the patient to start a daily nonimpact exercise program.

With regard to education about the disease process of chronic musculoskeletal pain, there are several patient driven self-help groups which host helpful Web sites and meetings. Of course, the extent to which a patient incorporates these self-directed treatments into their life will largely depend on the training they receive and the severity of their problem.

Avoidance therapy

This treatment approach also has three elements and is one of the treatment methods that has little or no hard scientific evidence. Recommendations are largely based on common sense, which dictates that if it hurts, avoid the behavior that causes the pain. In the case of jaw pain, the three elements of avoidance behaviors are clenching, TM joint clicking, and other oral habits. Clenching avoidance is best done by instructing the patient to hourly find a relaxed position of the jaw, tongue, and lips. The appropriate instructions to achieve this position are to have the patient place their relaxed tongue on the floor of the mouth (without pressure exerted on the tip of the tongue), have their teeth not touching (clenching), and have their lips relaxed (not touching). Most importantly, patients are told that they should bring the 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 or when concentrating on a specific task, such as driving, watching television, working on computers, or exercising). Next, the patient should be advised that it is prudent to avoid any jaw motion or food that induces TM joint clicking, presumptively to reduce wear 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. The health care provider needs to insist that the patient only take small food bites and eats only soft foods. Educate the patient about avoiding any "other oral habit." 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 ear pressure."

Increased intramuscular blood flow therapy

With regard to self-applied methods of stimulating blood flow in the masticatory system, most patients report benefit from either heat or ice packs applied to the painful site. These methods increase intramuscular blood flow, reduce muscle tension, and generally relieve muscle pain for a period of time. As with avoidance therapy, no study has systematically examined the long-term benefits of 3 weeks of daily 20-minute hot bath soaking on masticatory muscle pain, but this treatment recommendation makes common sense. 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 [47]. The results of this review suggested that this form of treatment produces a consistent positive result. Caution must be exercised in those patients that are hypotensive and heat intolerant. The specific thermal methods used to increase blood flow in a patient with jaw and neck muscle pain include hot baths and showers and local heat and ice packs. With all forms of local thermal therapy (hot or cold packs), leave it on the painful muscle site for 20 minutes, and do this two to three times per day. It is somewhat paradoxical that ice and heat are used for the same purpose, namely 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. This occurs because when skin is acutely heated or cooled, the blood vessels beneath the thermal pack have a reactive vasodilation to attempt to warm or cool this site back to body temperature. 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 on the surface, then always, ice packs are preferred.

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. 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 to 60 minutes, once a day at most, and if this is how often stretching were performed, it would be unsuccessful. Common sense and clinical experience suggest stretch therapy is critical to treatment of spontaneous muscle pain disorders (myofascial and FM) where the muscles exhibit taut band and stiffness. Daily (every 2 hours) stretch therapy is certainly worthy of separate review from traditional exercise therapy, such as nonimpact aerobics or water-exercise therapy, unfortunately such data do not exist.

The two essential elements of a stretch program for masticatory muscle pain are the n-stretch and chin-chest stretch. The first is done by placing the tip of 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 so they should hold this open position for about 5 or 6 seconds and repeat the stretch five or six times every 2 hours. Chin-to-chest stretching involves having the patient slowly tilt their chin to their chest. Alternative versions of this stretching exercise would involve a slight turning (approximately 20 degrees) 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 having the patient place their hand on top of their head during the stretch; this exercise should be avoided in patients with osteoarthritis of the neck.

Exercise therapy

There have been two systematic reviews available which offer a consistent point of view on the data of exercise therapy. One review is a Cochrane Library review that examined 16 clinical trials, which included a total of 724 subjects [48]. Of these 16 studies, seven studies were judged to be of high scientific quality and included four studies on aerobic training; one study on a mixture of aerobic, strength, and flexibility training; one study on strength training; and two studies on exercise training as part of a composite treatment for FM. The other review was not a Cochrane Library review but did examine 17 clinical trials that studied the effect of exercise treatment in a FM population [49]. Both of the systematic reviews endorsed aerobic exercise as a beneficial evidence-based treatment for FM, though this evidence is weak. One problem with all self-applied treatment methods is patient compliance, and long-term adherence with exercise programs after completion of studies has been consistently low in the FM studies [50,51].

Office-based physical medicine treatment

There are many physical medicine methods that are recommended for treatment of local and regional myalgia and myofascial pain as well as FM. 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 placebo therapies provided in the context of a clinical experiment are active behavioral therapies and both have value. The following discussion of physical medicine treatment methods for masticatory muscle pain is based on the available literature on which most studies have been conducted. For a more extensive discussion on pharmacotherapy for muscle pain, see the article by Hersh, Balasubramaniam, and Pinto in this issue.

The most common treatments provided by a trained clinician include local trigger-point injection therapy and manual physical therapy procedures, including therapeutic massage, acupressure, acupuncture therapy, and other forms of manual therapy, such as osteopathic or chiropractic mobilization and manipulation. In the domain of physical medicine the topic of botulinum toxin injections has been included for review. As with self-directed therapies, the extent to which a patient pursues these treatments will depend on the severity of their problem. At this point, no medical or dental society has endorsed botulinum toxin injections as efficacious for FM. The systematic literature reviews on physical

medicine for myogenous pain include one study on trigger-point injections or needling and three on acupuncture.

The Wheeler and colleagues [52] review on trigger-point therapy does offer an endorsement of this method, but it suggests that dry-needling is a viable therapy and injecting a local anesthetic or corticosteroid solution into the trigger point was not needed for improved efficacy. Moreover, they suggested that the needling effect may not be more than a powerful placebo treatment. Several systematic reviews on acupuncture deal with different disease entities and reach different conclusions. The one review that focused on FM was not a Cochrane Library review and it endorsed acupuncture as better than sham-acupuncture [53]. The second review on acupuncture and chronic pain (of all types) was also not a Cochrane Library review and it stated that the available studies were not of sufficient methodologic quality to offer an endorsement [54]. The third review on acupuncture for management of acute and chronic low back pain was a Cochrane Library review and it examined 11 clinical trials, but stated that only two were of high quality [55]. It also concluded that the available studies were not of sufficient methodologic quality to offer an endorsement.

While no systematic multiple study literature review has yet been performed, there was one article in the literature which examined botulinum toxin in a randomized double-blind study on 33 subjects with refractory myofascial pain (11 subjects in each group) [56]. One group received normal saline and the other two groups received either 50 or 100 units of botulinum toxin injections into trigger points in the cervicothoracic paraspinal muscle area. They were not able to demonstrate statistically significant improvement between the groups and it cannot be endorsed as evidence supporting treatment for trigger points based on current research.

A meta-analysis examined both pharmacologic (33 studies) and nonpharmacologic treatment (16 studies) of FM completed between 1966 and 1996 [57]. The nonpharmacologic therapies reviewed included exercise, education, cognitive-behavioral therapy, electroacupuncture, acupuncture, and hypnotherapy, and the review did not individually analyze these methods but considered them as a group. The investigators concluded from their review that both pharnamcologic and nonpharmacologic treatments were associated with improvement in physical status, FM symptoms, and psychologic status, but only nonpharmacologic treatment improved daily functioning. Nonpharmacologic treatments were found to be superior to pharmacologic treatment on FM symptoms.

A different systematic review of randomized, controlled trials of several nonpharmacologic treatments for FM completed between 1980 and 2000 examined 25 studies that included exercise therapy, educational intervention, relaxation therapy, cognitive-behavioral therapy, acupuncture, and forms of hydrotherapy [58]. This review did not lump these methods together and reported individually on aerobic exercise (nine studies), education (four studies), and relaxation (four studies). The investigators concluded that no strong evidence existed supporting any single intervention; however, moderate strength existed for aerobic exercise, but as the sample sizes were small, they were compelled to say that data is still inconclusive because of the methodologic limitations of most of the studies.

Pharmacologic-based treatment

The previously cited meta-analysis by Rossy and colleagues [59] reviewed both pharmacologic and nonpharmacologic treatments for FM. They reported on multiple agents, including tricyclic antidepressants (TCAs), nutritional supplements, a benzodiazepine, two selective serotonin reuptake inhibitors (SSRIs), NSAIDs, a corticosteroid, an insomnia drug, topical capsaicin, oral lidocaine, and a combination muscle relaxant agent, among others. They concluded that pharmacologic treatments for FM were not better than nonpharmacologic therapy and there were not enough high quality studies to recommend it as an evidence-supported therapy for FM. A more recent review [60] also examined multiple studies testing medications for regional musculoskeletal pain, and they concluded that the medication studies are generally of lower quality and had several methodologic problems, so no specific recommendations could be made. Considering the above studies, the data on pharmacologic-based treatment approaches for FM are not strong.

Topical agents

There were two reviews on topical agents available in the Cochrane Library database that examined topical medications for the treatment of either chronic musculoskeletal pain or for acute and chronic pain of all types. The topical

medications examined contained either a nonsteroidal anti-inflammatory agent [56] or a rubefacient combined with salicyclate [61]. 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.

Tricyclic antidepressants

The use of antidepressant medications in the tri- and tetracyclic category for muscle pain is only modestly supported by results from controlled clinical trials. For example, there was one review on the use of various antidepressants for FM and it concluded the use of TCAs had enough evidence to support their use in FM [62]. When used, the TCAs are mostly used in low dosage to improve sleep and to enhance the effects of analgesics. The major disadvantage of the tricyclics is that they strongly interact with adrenergic, cholinergic, and histaminergic receptors, and therefore have many side effects. The largest experience is available for amitriptyline in low doses (10 mg–25 mg) given at night to improve sleep.

An early meta-analysis [63] assessed nine placebo-controlled trials of the cyclic drugs. These investigators concluded that the largest effect of the cyclic medications was found for measures of sleep quality, with only modest changes in tender-point measures and stiffness. Like the previously cited meta-analysis by O'Malley and colleagues [62] in 2000, this meta-analysis also described the overall effect of the tricyclic drugs on most symptoms of FM as modest, but also speculate that if larger doses were used, the effect might be better. Overall, the best evidence is for the cyclic antidepressant medications, and even then the effects are modest and many patients find the side effects intolerable.

Selective serotonin reuptake inhibitors

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. However, it is safe to say that the SSRIs have not been found helpful for the painful symptoms associated with chronic muscle pain [64]. Overall, trials of SSRIs in FM 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 FM [65,66].

Serotonin and norepinephrine reuptake inhibitors

The serotonin and norepinephrine reuptake inhibitors (SNRIs) are a new class of drugs that have some preliminary evidence that would make them equivalent to the TCAs with fewer side effects: hence, attracting interest for the treatment of chronic muscle pain. The rationale for using these drugs in FM is that by increasing the activity of serotonin and norepinephrine, this may correct a functional deficit of serotonin and norepinephrine neurotransmission in the descending inhibitory pain pathways and, therefore, help reduce pain. Three recent meta-analyses of FM pharmacologic trials assessed the efficacy of medications that inhibit the reuptake of serotonin and norepinephrine. One specific medication available in the United States and approved for neuropathic pain has exhibited nearly equal SNRI activity.

Duloxetine, 60 mg, one to two times a day, is claimed to be moderately effective in controlling FM pain, whether or not the patient is depressed [67]. This drug is generally well tolerated by most FM patients, with nausea, dry mouth, constipation, diarrhea, and anorexia reported more frequently with the 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 subjects with FM, with or without current major depressive disorder [68]. Duloxetine-treated subjects compared with placebo-treated subjects improved significantly more on a total overall FM questionnaire, but not so on the pain subscale of the questionnaire. Nevertheless, the above data suggests that SNRIs have efficacy in FM and will improve pain and other important symptom domains of FM in addition to improving function, quality of life, and global well-being, but additional study is needed as these medications are still considered off-label for FM by the Food and Drug Administration (FDA).

Systemic nonsteroidal antiinflammatory drugs

The efficacy of systemic NSAIDs has been examined in several Cochrane reviews of various regional musculoskeletal pain conditions. Unfortunately, as with previously described studies on topical agents that contain NSAIDs, studies of the effect of systemic NSAIDs have not been performed on a subset of patients who had regional

musculoskeletal pain only, but 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. Perhaps the more important role of such agents is to contribute synergy with other medications; however, on the negative side is that NSAIDs have been found to cause substantial gastrointestinal disease and the risk of myocardial infarction is elevated in the cyclooxygenase (COX)-2 selective NSAIDs [69]. Exactly how much cardiovascular risk elevation exists for the older nonselective COX inhibiting agents is not clear, but given the data, which shows a limited efficacy, it would be illogical to use NSAIDs long term for chronic myogenous pain.

Tramadol

Tramadol has a modest to moderate efficacy when used in FM, and when used in combination with acetaminophen substantially reduces body pain more than a placebo medication. This agent exhibits a combination of serotonin and norepinephrine reuptake inhibition and 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. Tramadol has been shown to reduce the impact of pain in FM patients. As monotherapy, it significantly reduces the severity of experienced pain but has trivial effects on insomnia or depression. Nausea and dizziness can be limiting at first in approximately 20% of patients, but initiating therapy with just one tablet at bedtime for 1 to 2 weeks can reduce that frequency and allow progressive increasing of the dosage by approximately one tablet every 4 days to full therapeutic levels. A typical maintenance dosage for FM patients is 300 mg to 400 mg per day in three or four divided dosages, concomitant with acetaminophen at 2 g to 3 g per day in divided dosages.

Three controlled studies have evaluated the efficacy of tramadol in FM. The first small study used a double-blind crossover design to compare single-dose intravenous tramadol of 100 mg with placebo in 12 subjects with FM. Subjects receiving tramadol experienced a 20.6% reduction in pain, compared with an increase of 19.8% of pain in the placebo group [70]. The second study of tramadol began with a 3 week open-label phase of tramadol 50 mg/day to 400 mg/day, followed by a 6-week double-blind phase in which only subjects who tolerated tramadol and perceived benefit were enrolled [71]. The primary measure of efficacy was the time to exit from the double-blind phase because of inadequate pain relief. One hundred subjects with FM were enrolled in the open-label phase; 69% tolerated and perceived benefit from tramadol and were randomized to tramadol or placebo. Significantly fewer subjects on tramadol discontinued during the double-blind phase because of inadequate pain relief. This study is limited by the possible unblinding of subjects 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 subjects with FM. Subjects taking tramadol and acetaminophen (4 plus or minus 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 [72]. Treatment-related adverse events were reported by significantly more subjects in the tramadol/acetaminophen group (75.6%) than the placebo group (55.8%). A post hoc analysis of the data from this trial revealed that the subjects who had the most reduction in pain severity (greater or equal to 25 mm on the 0-mm to 100-mm visual analog scale) from baseline had significantly greater improvement in health-related quality of life than those with less reduction in pain [73].

Opioids

The efficacy of analgesic medications is well established from clinical practice. However, opioid analgesics are associated with adverse reactions and also with dependency and abuse. 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 increasing reports of abuse and dependence [74]. Thus, the use of traditional opioids in FM patients is controversial and generally not recommended by experts. The bias of most investigators is that opioids should not be used in FM patients until well-designed, controlled, clinical studies show unequivocal benefit. A recent, 4-year, nonrandomized study of opiates in FM discovered that the FM subjects taking opiates did not

experience significant improvement in pain at the 4-year follow-up when compared with baseline, and reported increased depression in the last 2 years of the study [75]. These results suggest that opiates may not have a role in the long-term management of FM and might even cause unintentional harm to patients [76].

Anticonvulsants

Anticonvulsant medication, such as gabapentin and pregabalin, have shown some promise as a modestly effective agent (equivalent to TCAs) to reduce the severity of body pain, improving quality of sleep, and reducing fatigue in FM. In fact, pregabalin was recently approved by the FDA for use in the treatment of FM. Gabapentin is approved for epilepsy but his commonly used off-label for FM because central neuronal sensitization is suspected.

A new drug, similar in effect to gabapentin, that binds to a subunit of calcium channel, reduces neuronal activity, and has been approved by the FDA for neuropathic pain, is pregabalin. This drug has analgesic, anxiolytic, and anticonvulsant activity in animal models [77,78]. It reduces the release of several neurochemicals, including glutamate, norepinephrine, and substance P. Pregabalin was found to be effective in reducing the severity of body pain, improving quality of sleep, and reducing fatigue in FM [79]. This drug is given (300 mg/day–600 mg/day) in two to three 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. Weight gain and peripheral edema occur in 5% to 10% of patients, without evidence for an effect of the drug on the heart or kidneys. Similar to duloxetine, these drugs need to be compared in a head-to-head comparison with TCA-based medications on a population of FM patients.

Behavioral therapies

There are many behavioral therapies suggested for treatment of local and regional myalgia and myofascial pain, as well as FM. These treatments include various forms of therapy with a psychologist, with the most common being cognitive behavioral therapy (CBT). Sometimes these methods are a component of a combined multidisciplinary program and sometimes they are stand-alone treatments. A systematic review has been published that focused only on mind-body therapies (MBTs), such as autogenic training, relaxation exercises, meditation, cognitive-behavioral training, hypnosis, guided imagery, biofeedback, or education for FM [80]. 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 MBTs 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 importantly, the review determined that strong evidence exists that exercise was more effective than MBTs for short-term improvement in pain intensity or tender-point pain threshold and physical function [51,81]. Third, patients with FM who were also severely depressed were not responsive to MBTs, and these MBTs that used cognitive restructuring and coping components were not significantly better than education or attention controls [82], and neither method produces a substantial improvement in pain intensity [83].

More recent studies have generally agreed with the above reviews. Specifically, in a 2002 study, 145 subjects with FM were randomized to either standard medical care (pharmacologic treatment and advice to engage in aerobic fitness exercises) or standard medical treatment and a six-visit program of cognitive behavioral therapy [84]. Significantly more (25%) of the 62 subjects 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 FM.

In 2005, a coping skills training (CST) intervention for adolescents with FM was developed to include developmentally appropriate explanation and training guidelines, as well as a parent training component [85]. In an 8-week study, 30 adolescents with FM were randomly assigned to either CST or a self-monitoring condition in which subjects monitored daily symptoms without instruction. After 8 weeks, subjects 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 greater pain-coping skills.

Final treatment recommendations

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 article 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:

- For the patient with traumatic onset local myalgia with secondary trismus, the common sense recommendations for treatment are rest, ice or moist heat, short term NSAIDs, and then frequent daily active mobilization of the jaw until normal motion is achieved again.
- 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.
- Although not reviewed in this manuscript, 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 appliances or splints as a method of treatment is generally modest.
- For the patient with all forms of nontraumatic, nonsecondary chronic myogenous pain, namely local, regional or widespread myalgia (or myofascial trigger points and FM), where daily stress is the suspected etiology, it is likely that several treatments are appropriate.
- Self-directed treatment is the first line of therapy and includes education plus absolute avoidance of harmful behaviors, regular daily thermal treatments, repeated (every 2 hours) jaw and neck stretching, and a daily nonimpact aerobic exercises program. Unfortunately, these methods have no good evidence basis beyond common sense.
- For those patients with myofascial pain and local trigger points that generate referred pain when compressed, the use of injections with a local anesthetic or dry-needling of the most hyperirritable spots appears better than no treatment, but may not be better than a credible placebo. In addition, for myofascial trigger points, the data on botulinum toxin injections into the trigger points is not sufficient yet to make a recommendation. For FM patients, acupuncture treatments have been found better than sham acupuncture, but here the data is also limited.
- In general, the data on pharmacologic based treatment approaches are modest at best.
- Topical medications for musculoskeletal pain seem good for only short-term use and mostly for acute pain.
- TCAs are generally considered one of the better agents for myogeneous masticatory pain and even then the effects on pain are modest and many patients find the side effects intolerable.
- SSRIs have little to no benefit for musculoskeletal pain but can be helpful in those cases where substantial depression coexists with the pain, as in the most severe cases.
- SNRIs are a new class of drugs that have 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 FM cases in the future.
- Systemic NSAIDs are generally not effective as monotherapy for chronic musculoskeletal pain, and long-term side effects (gastritis and cardiovascular risk) limit this drug to short-term use, if used at all.
- Tramadol has some evidence that suggests modest to moderate efficacy when used in FM, and when used in combination with acetaminophen this 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 that this drug is more appropriately used as a short-term pain agent.
- The use of traditional opioids in FM patients is controversial and generally not recommended by experts in masticatory muscle pain.

Anticonvulsants medications, such as gabapentin and pregabalin, have shown some promise as an effective agent to reduce the severity of body pain, improving quality of sleep and reducing fatigue in FM. Still, the effect is modest at best and may not even be as good as the TCAs, although they have far fewer side effects.

There are many behavioral therapies suggested for treatment of local and regional myalgia and myofascial pain as well as FM, and they generally help patient cope with their chronic pain but do not provide pain reduction or improvement in function.

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Internal Derangements of the Temporomandibular Joint

Reny de Leeuw, DDS, PhD

Orofacial Pain Center, University of Kentucky, College of Dentistry, 800 Rose Street, Lexington, KY 40536-0297, USA

Definition of various internal derangements

Internal derangement is defined as any interference with smooth joint movement. Although the term therefore includes all types of intracapsular interferences that impede smooth functional joint movements, with regard to the temporomandibular joint (TMJ) the term is typically used interchangeably with disc displacement. In this article, several other types of internal derangements are discussed. Besides the common derangements, disc adherences, disc adhesions, subluxations, and dislocations of the disc–condyle complex are also discussed (Table 1).

Stegenga and de Bont [1] most recently made a case for a name change of the phenomenon of disc displacement. They argued that adhering to the so-called ''12 o'clock position'' as the normal position of the posterior band of the disc relative to the condyle might lead to overdiagnosis of this particular disorder, because a displaced disc does not always lead to clinical symptoms. They therefore proposed to replace the word ''displacement'' with ''derangement,'' which would indicate that the displaced disc actually interferes with smooth joint movement and causes some type of dysfunction to the individual. Imaging studies have found disc displacements in 23% to 33% of asymptomatic volunteers [2–4].

A disc derangement is defined as a malpositioning of the articular disc relative to the condyle and eminence. Theoretically, a disc may be displaced to varying degrees and in any direction (ie, anterior, posterior, lateral, or medial). Rarely is a disc displaced purely in one direction, with the possible exception of anterior displacement. Posterior displacements have been described but are infrequent [4–7]. Pure sideways displacements seem to be rare also [2,8] and may be related to more advanced stages of derangement [9]. The most common type of disc derangement is an anterior displacement [4]. Controversy exists about which type of displacement is next most common. Some studies report more often anteromedial derangements [10,11], some found more often anterolateral derangements [2,8], and others report an even distribution of anteromedial and anterolateral derangements in patients and healthy volunteers [4].

With regard to clinical diagnosis and treatment, two predominant stages of disc derangements are distinguished. The respective conditions are called disc derangement with reduction and disc derangement without reduction. In a normal TMJ, the disc is positioned over the condylar head with the posterior band situated in the 12 o'clock (superior to the condyle) position and the intermediate zone situated in the 1 o'clock (superior-anterior to the condyle) position. On opening the disc–condyle complex translates in a forward direction. Although the condyle also rotates forward, the disc relatively rotates in a posterior direction over the condyle. Disc derangement with reduction is typically defined as a condition in which the articular disc of the TMJ is (most often anteriorly) displaced while the mouth is closed and the teeth are together in maximal occlusion. On opening, the condyle pushes against the posterior band of the disc until the condyle is able to slide or snap under the posterior band of the disc, and the disc reduces to its position on top

E-mail address: rdele0@email.uky.edu

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Table 1
Definitions of internal derangements of the temporomandibular joint

Disc derangement	A malpositioning of the articular disc relative to the condyle and eminence
With reduction	The articular disc resumes its normal position on top of the condyle on opening
Without reduction	The articular disc remains malpositioned on opening attempts, resulting in restricted mouth opening in acute cases
Disc adherence	A temporary sticking of the disc either to the fossa or to the condyle
Disc adhesion	A fibrotic connection between the disc and the condyle or the disc and the fossa
Subluxation (hypermobility)	An overextension of the disc–condyle complex on opening beyond the eminence
Joint dislocation	A dislocation of the entire disc–condyle complex beyond the eminence combined with the inability to return passively into the fossa

of the condyle. Overcoming the thick posterior band of the disc is believed to be responsible for the clicking or popping sound. On closing the mouth, the disc stays behind and slips off the condyle, which may be accompanied by a clicking sound. Typically, the opening click occurs later during the opening movement, whereas the closing click often occurs close to maximal occlusion.

Disc derangement without reduction is defined as a condition in which the condyle is unable to slide or snap back underneath the disc. The (anteriorly) displaced disc thus does not reduce to its position on top of the condyle during the opening movement. The disc is obstructing further translation of the condyle and consequently the opening and contralateral movements are impaired.

Disc adherence is defined as a temporary sticking of the disc either to the fossa or to the condyle. This adherence can be caused by prolonged static loading or lack of lubrication or a combination thereof. Oftentimes patients report difficulties with jaw opening on awakening. On attempts to move the jaw, generally the adherence can be overcome; this is often accompanied by a loud single pop or click. The condition should not be confused with disc derangement with reduction or subluxation. Another condition that has similar characteristics has been termed anchored disc phenomenon [12]. It is believed that the disc is stuck to the fossa because of compromised lubrication. A strong adhesive force prevents the disc from being separated from the fossa or condyle by simply moving the jaw. This phenomenon may resemble a disc derangement without reduction, although a history of clicking is frequently absent and the limitation of mouth opening is said to be more severe [12]. Disc adhesion is defined as a fibrotic connection between the disc and the condyle, or the disc and the fossa. This condition is characterized by limited jaw movements. In contrast with an adherence, an adhesion cannot be overcome by simple jaw movements. This condition should be distinguished from disc derangement without reduction or fibrous ankylosis. For disc adherence or adhesion to occur the disc does not have to be deranged.

Subluxation (sometimes referred to as hypermobility) is defined as an overextension of the disc–condyle complex on opening. On opening, the disc–condyle complex passes beyond the eminence. Typically, this is accompanied by a dull thud-like sound. The sound may be reciprocal (ie, may occur on opening and on closing). The sound typically occurs, unlike in the case of disc derangement, late in the opening phase (almost at maximum opening) and early in the closing phase. The subluxation may be habitual, meaning that the disc–condyle complex passes the eminence back and forth without causing pain, discomfort, or dysfunction during routine opening. Several cross-sectional studies have attempted to relate generalized joint hypermobility to TMJ hypermobility, yet the results of a systemic review revealed that controversies about this continue [13].

A joint dislocation is similar to a subluxation in that the condyle–disc complex passes beyond the eminence. In this case, however, the patient is unable to close the mouth because the disc–condyle complex is trapped in front of the eminence.

Etiology/pathophysiology

The most common etiologic factor in the development of internal derangements is trauma. Macrotrauma, such as a hit or blow to the face, may result in direct tissue injury and immediate derangements of the TMJ components. Oral intubation and dental/surgical procedures that involve prolonged mouth opening or excessive forces, such as difficult extractions, also have the

propensity to cause direct tissue injury. In addition, such trauma could result in elongation of ligaments, creating internal joint laxity, which may set the TMJ up for a slower development of derangement. Under normal physiologic conditions, a balance exists in synovial joints between tissue breakdown and repair. When the balance is disturbed by a mechanical, biomechanical, or inflammatory insult the internal cartilaginous remodeling system may fail, resulting in accelerated tissue breakdown [14]. The intrinsic changes in the joint components may induce a disc derangement.

Microtrauma may be another etiologic factor in the development of internal derangements. Microtrauma is defined as application of prolonged repetitive forces, such as in clenching or grinding. The repetitive forces may result in tissue failure in several ways. When the force is within physiologic limits, but is applied to articular cartilage that has a reduced adaptive capability, or when the force exceeds the adaptive capability of normal cartilage, tissue degeneration may ensue [15].

Under normal physiologic conditions, a balance also exist between formation of free radicals and neutralizing mechanisms [16,17]. Mechanical loading of the joint may result in local hypoxia. Reperfusion of hypoxic cells can lead to an explosive increase in free radicals [16]. These free radicals may lead to degradation of hyaluronic acid, which is an important component of synovial fluid. Degradation of hyaluronic acid in turn may impair the lubrication of the TMJ [18]. The impaired lubrication may increase friction between the surfaces of the different joint components. Not only could this lead to adherences or an anchored disc but also it may precipitate a disc derangement [19]. In addition, it has been proposed that adhesions may be formed by free radical–mediated crosslinking of fibrinogen and fibronectin [20].

Indirect trauma, such as that related to acceleration-deceleration (whiplash) injuries in the absence of a direct trauma to the face, has been related to symptoms of temporomandibular disorder (TMD). The most recent prospective controlled study indicated that 1 out of 3 patients who had whiplash accidents without direct trauma to the head developed TMJ pain or associated symptoms within 1 year of the accident compared with 1 out of 16 of the control group [21]. In contrast, a previous prospective study showed that there were no differences between whiplash patients and controls at 6 months regarding TMJ pain and clicking [22].

Clinical diagnosis, including imaging and differential diagnosis

The most salient sign of a disc derangement with reduction is a repeatable, audible click on opening. Often there is also a click on closing, but this may be less noticeable. When there is a closing click it is called reciprocal clicking. On occasion the click is not audible but may be heard by auscultation. In addition, the shift in disc position may be felt by palpation. The click may coincide with a momentary deviation from the midline during the opening movement. Other signs of disc derangement with reduction may include a click on protrusion or lateral movements. Typically, the mouth opening is not restricted and this condition usually is not painful by itself [23].

Conventional radiographs may be used to rule out degenerative joint diseases. Generally, a disc derangement with reduction presents with no to mild radiographically visible degenerative changes. These changes are mostly limited to flattening and sclerosis [24]. The clinical diagnosis of disc derangement can be confirmed by soft tissue imaging, although the mild nature of this condition does not necessitate routine soft tissue imaging. Differential diagnosis may include adhesions, deviation in shape, or arthritis.

The most salient sign of an acute disc derangement without reduction is sudden limited mouth opening. The patient's history in the case of disc derangement without reduction is essential and usually includes a sudden cessation of clicking accompanied by a limitation of mouth opening. The clinical signs are related to the obstruction of translation of the condyle by the disc. They include a limited mouth opening, limited contralateral movement, deflection on protrusion, and opening to the ipsilateral side [23,25]. This condition is often accompanied by pain. Palpation of the affected joint may be painful and reveals a limited translation of the obstructed condyle.

Generally, an acute disc derangement without reduction presents with no to mild radiographically visible degenerative changes. If the derangement persists and becomes chronic, usually pain subsides and joint mobility increases, even without treatment [26,27]. Mobility-related clinical signs and symptoms may gradually fade, although crepitus may emerge [28]. At the same time, degenerative changes may become radiographically visible [24]. These changes are generally moderate, consist predominantly of flattening and sclerosis of the load-bearing areas of the joint, and most

often stabilize over a few years [24,29,30]. In cases with severe degenerative changes, occlusal disturbances, such as anterior open bite or a unilateral open bite, may develop. In general, the visible osteoarthritic changes should be seen as articular remodeling in an attempt for the joint to establish a new balance between form and function [30]. Conventional radiographs may be used to identify degenerative changes. The position and shape of the disc can be observed with soft tissue imaging, but unless surgery is planned, routine imaging is not warranted. Differential diagnosis may include arthritis, disc adherences or adhesions, fibrotic ankylosis, myospasm, and neoplasia.

Adherences are difficult to diagnose clinically. The most important information, the transient inability to open the mouth wide after a period of static loading, resolved by moving or manipulating the jaw, and the accompanying single pop, may be derived from the history. Rarely do these types of adherences occur while the patient is in the clinic. The disc may be anchored for a more prolonged time when the patient is unable to overcome the adhesive force between the surfaces of the disc and the fossa [12]. In such cases, the patient presents with limited mouth opening, deflection to the ipsilateral side on opening and protrusion, and restricted contralateral movements. The restriction of the mouth opening may be more severe than in the case of disc derangement without reduction because the adhesive force prevents any translation in the joint and mobility is strictly dictated by rotation of the condyle. Technically speaking, adherences can occur in the lower joint space also, in which case rotation of the condyle is impaired. The clinical presentation of a patient who has an adherence in the lower joint space is similar to that of a patient who has an upper joint space adherence. Because movement of the condyle is now dictated by translation, the movement may be irregular with a sensation of stiffness.

Conventional radiography is not indicated to detect adherences but may be used to rule out degenerative changes. Magnetic resonance imaging may be used to depict a static (ie, nonmoving) disc. Differential diagnosis may include disc derangements.

Persistence of adherences and articular tissue changes related to osteoarthritis may result in adhesions [20]. Adhesions are common in painful TMJs with limited mobility that are refractory to conservative therapies [31]. Adhesions are difficult to diagnose clinically, and the history and clinical findings obtained from the patient who has adhesions may not differ from those of a patient who has disc derangement without reduction or anchored disc.

Adhesions can be detected by arthroscopy, magnetic resonance arthrography, and plain film arthrography, although medial adhesions seem to be more difficult to discern with the latter technique [32]. Differential diagnosis may include disc derangement without reduction, prolonged adherence, and fibrous ankylosis.

A joint dislocation is commonly known as an ''open lock.'' The patient is unable to close the mouth or fully occlude. There may be considerable variability in the extent that the mouth remains open. The patient may present with a prognathic profile and class III malocclusion attributable to the protrusion of the mandible.

A conventional radiograph, such as a transpharyngeal or transcranial projection with ''closed'' mouth, reveals that the condyle is dislocated in front of the eminence.

Treatment and prognosis

If a disc derangement with reduction is asymptomatic (ie, the patient is not bothered by it) this condition does not warrant treatment [33]. Clicking and disc derangement may persist for several years without any progression and without development of radiographically visible degenerative changes [24,28]. In addition, signs and symptoms of temporomandibular disorders in the general population fluctuate considerably over time and rarely result in significant dysfunction [34,35]. Taking into account the possibility of spontaneous resolution, the initial treatment should be limited to nonaggressive measures, such as counseling (reassurance and education, rest, instructions to avoid loading, control of contributing factors, such as parafunctional habits) and mild analgesic or anti-inflammatory medicines [36].

Several authors report the use of anterior repositioning appliances for the treatment of disc derangement with reduction with variable rates of success [37–41]. An anterior repositioning appliance is indicated in a patient who has painful clicking or frequent locking, if the clicking can be eliminated by having the patient close down in a protrusive position [42]. The patient is instructed to open the mouth; on doing so the deranged disc reduces to its position on top of the condyle. The patient is then allowed to close the mouth while keeping the mandible protruded, which prevents the disc from deranging again.

The ultimate treatment position is defined by the least protrusive position in which the disc remains in place. The correctness can be checked by having the patient open and close in the chosen position. The click should not reoccur when the position is chosen correctly. The anterior repositioning appliance should be worn at nighttime only. The goal of this treatment is to allow the retrodiscal tissues to recover and adapt and to bring the patient back to a pain-free clicking state. This procedure is not intended to recapture the disc or eliminate clicking permanently, because this has been shown to be unattainable [38,39,43–45].

In the case of an acute disc derangement without reduction, an attempt should be made to unlock the patient. This can be done by gently manipulating the affected TMJ in a downward and then medial direction. During this manipulation the disc may snap back onto the condylar head. Sometimes this procedure is sufficient and the patient may not lock for some time. If the patient locks again immediately on closing, however, an anterior repositioning appliance may be indicated. In such a case, after the patient has been unlocked, the appliance should be made immediately and worn full time for about 5 days, after which the patient should gradually reduce the use of the appliance to avoid malocclusion. Several surgical options are available for disc derangement with reduction; however, they are rarely indicated. These procedures are described below because they may apply to disc derangement with and without reduction.

If in the case of an acute disc derangement without reduction manipulation is unsuccessful to unlock the jaw, there are many nonsurgical and surgical options to choose from. Studies show that if minimal treatment is provided [28,29,46], or even if nothing is done [26,27,47], the signs and symptoms gradually improve. Treatment speeds up the natural progression process, however, and is primarily aimed at restoring the balance between form and function, also called adaptation [30]. Similar to disc derangement with reduction, nonaggressive measures, such as reassurance and education, rest, instructions to avoid loading, control of contributing factors (such as parafunctional habits), and mild analgesic or antiinflammatory medicines, should be provided as first-line treatment [36]. An interocclusal appliance (ie, a stabilization appliance) may also be helpful if the patient complains of pain that is worse on awakening. Physical therapy aimed at reduction of pain and dysfunction may be indicated also [48]. Once the patient is pain free, additional treatments aimed at reducing the limited mouth opening should be implemented. These may consist of simple stretching exercises within a pain-free range performed by the patient, or manipulation techniques performed by a physical therapist. In rare cases the restriction of mouth opening is persistent and more aggressive therapies may be needed. Several studies show that a disc derangement without reduction responds well to nonsurgical treatment [28,30,49,50]. If these nonsurgical treatments fail, however, an evaluation for the appropriateness of surgical intervention is indicated.

As outlined in the Clinical Practice Guidelines for TMJ surgery of the American Association of Oral and Maxillofacial Surgeons, TMJ surgery is only indicated when nonsurgical therapy has been ineffective. TMJ surgery is not indicated for asymptomatic or minimally symptomatic cases and should not be performed in an attempt to prevent TMD [51]. Indications for surgery include moderate to severe pain or dysfunction that is disabling [51]. Most often surgery is indicated for persistent painful intracapsular conditions. When clicking is interfering significantly with the patient's quality of life, however, and nonsurgical procedures have been ineffective to improve the patient's quality of life, surgical procedures may also be indicated.

Although the guidelines state that surgical procedures are indicated only after reasonable efforts with nonsurgical modalities have failed, there may be one exception. When it is debatable whether the diagnosis is disc derangement without reduction or disc adherence, an arthrocentesis may be performed. An arthrocentesis is a minimally invasive procedure typically associated with good outcomes for patients who have a closed lock [52]. A disc adherence may be instantly released by such a procedure and recurrence of the adherence seems to be infrequent [53]. A locked jaw because of a deranged disc may also be resolved, although most frequently the improvement of dysfunction and mouth opening are not related to an improved disc–condyle relationship [54–58]. Although there are studies promoting the use of sodium hyaluronate during arthrocentesis, there are no controlled trials indicating that the use of sodium hyaluronate results in significantly better treatment outcomes than arthrocentesis alone [59].

Most surgical procedures for disc derangements are aimed at improving the disc–condyle

relationship. Such procedures include modified condylotomy, discoplasty, and disc repositioning. Another procedure includes discectomy with or without replacement of the removed disc.

Discectomy has long been advocated to reduce the mechanical problems related to disc derangements. Discectomies have resulted in elimination of pain and improvement of function. Success rates vary from 43% to 93% for this procedure [60–66]. Significant radiographically visible degenerative changes, which resemble those associated with degenerative joint disease, may occur with this procedure [61,66]. There seems to be no advantage to replacing the disc with temporary or permanent implants or grafts [61,67–70]. Evidence of the formation of a pseudodisc after discectomy has been reported [65,71].

The modified condylotomy consists of an intraoral vertical ramus osteotomy, in which the condylar segment is allowed to move slightly inferiorly [72]. This supposedly creates space to allow for a better disc–condyle relationship. The advantage of this procedure is that it avoids intracapsular surgery. The disadvantage of the procedure is that it is hard to predict what the position of the condyle will be and whether the condyle–disc relationship will improve. This procedure is generally only recommended in early stages of disc derangements with reduction [73], when it is more likely that the disc still has its original saddlelike shape. Disc derangements in the absence of pain generally do not warrant treatment, and several more conservative treatment options have proven successful in the treatment of early disc derangements. The indications and use of this particular procedure are therefore limited.

Discoplasty is a surgical open-joint procedure in which the disc is repaired or its shape improved. Oftentimes this procedure is used concomitant with disc repositioning techniques. Although reports on pain and dysfunction are favorable, relapse of disc position is frequent [74,75]. Disc repair and disc repositioning can also be achieved with arthroscopy [76]. Similar positive treatment outcomes were obtained in a randomized study wherein one group of patients received open-joint surgery with disc repositioning and the other group was treated arthroscopically with lysis, lavage, and capsular stretch [75]. Note that in the latter case the arthroscopic procedure did not aim to improve the disc–condyle relationship.

Arthroscopy is a minimally invasive closed-joint procedure. It has proven successful for treatment of different stages of derangements, even if the main goal was not aimed at improving the disc–condyle relationship [77–82]. Mobilization seems of more importance for reduction of signs and symptoms of derangements. With arthroscopy, the deranged disc can be repositioned or reshaped [83].

Adherences may be treated with reassurance and education, instructions to avoid static loading of the TMJs, and control of parafunctional habits. If the patient reports that the jaw is also locked on awakening, an interocclusal appliance (ie, a stabilization appliance) may be indicated. If the patient and the health care provider are unable to unlock the jaw, arthrocentesis is indicated. Adherences can also be alleviated with arthroscopy [83], although this procedure may rarely be indicated in lieu of arthrocentesis.

Adhesions are difficult to manage with nonsurgical measures. To break adhesions lysis, lavage, and hydraulic distention may be sufficient. More likely, arthroscopy will be necessary to release or ablate adhesions [83].

An acute joint dislocation is treated by manipulation of the jaw in a slightly forward, then downward, direction. Once sufficiently cleared from the eminence, the condyle-disc complex snaps back into the fossa. Sometimes it is sufficient to ask the patient simply to yawn, on which the joint may overcome the eminence and return to the fossa. The manipulation technique should be taught to the patient in addition to instructions to avoid opening wide. In case of a chronic dislocation, the patient may need to be put under general anesthesia to unlock the jaw. In addition, intermaxillary fixation may be needed to avoid relapse. When a patient suffers from uncontrollable repeated dislocations, treatment depends on the cause of these dislocations. Eminectomy, by way of arthroscope or the traditional open-joint surgery, has been a widely used method to treat recurrent or habitual dislocations [84–86]. Although this method was originally described in 1951 by Myrhaug [87], estimates of its efficacy are mostly based on small sample case series or case reports. Other methods used to reduce the recurrent or habitual dislocations include techniques aimed at creating a barrier to limit condylar translation [88–91] and injection of sclerosing agents [92]. Downfracturing of the eminence, placement of miniplates or screws, or cranial bone or other autografts have been used to create barriers. No randomized controlled trials or comparative trials were found in the English

literature regarding the efficacy and safety of these procedures. If dystonia or spasm of the lateral pterygoid is responsible for the dislocations, injections with botulinum toxin may be useful [93,94].

Summary with an emphasis/impact on oral surgeons

TMJ internal disc derangements most often respond well to nonsurgical methods. An asymptomatic click does not warrant treatment. In line with the Clinical Practice Guidelines for TMJ Surgery, surgical options should only be used in cases of moderate to severe persistent pain or dysfunction, after reasonable conservative treatment has proven ineffective. Possible exceptions are acute disc adherences, and adhesions, in which surgical methods, such as arthrocentesis and arthroscopy, may be the first treatment of choice. For disc derangements, a multitude of surgical procedures are available, but recent advances in technology and philosophy direct the surgical procedures of choice toward the minimally invasive technique, arthrocentesis, with arthroscopy as the next alternative.

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Osteoarthritis, Osteoarthrosis, and Idiopathic Condylar Resorption

Louis G. Mercuri, DDS, MS[a,b]

[a]*TMJ Concepts, 1793 Eastman Avenue, Ventura, CA 93003, USA*
[b]*Division of Oral and Maxillofacial Surgery, Department of Surgery, Loyola University Chicago, Stritch School of Medicine, 2160 South First Avenue, Maywood, IL 60153, USA*

Definitions

The term "osteoarthritis" has classically been defined as a low-inflammatory arthritic condition, either primary or secondary to trauma or other acute or chronic overload situations, characterized by erosion of articular cartilage that becomes soft, frayed, and thinned resulting in eburnation of subchondral bone and outgrowths of marginal osteophytes. Pain and loss of joint function result [1].

The term "osteoarthrosis," a synonym for osteoarthritis in the medical orthopaedic literature, has recently come to be identified in the dental temporomandibular joint (TMJ) literature with any low-inflammatory arthritic condition that results in similar degenerative changes as in osteoarthritis. In the dental TMJ literature, however, osteoarthrosis has also come to be identified with abnormal disc position or unsuccessful adaptation of the TMJ to the mechanical forces placed on it with disc derangement or disc interference disorders [2]. Because the basic etiology, pathology, and management involved are the same, the terms osteoarthritis and osteoarthrosis are used synonymously in this article.

The term "idiopathic condylar resorption" (ICR), also known as "progressive condylar resorption" (PCR), is described by Arnett and colleagues [3,4] as a dysfunctional remodeling of the TMJ manifested by morphologic change (decreased condylar head volume), decreased ramal height, progressive mandibular retrusion in the adult, or decreased mandibular growth in the juvenile. Arnett and colleagues [3,4]. proposed an explanation for the pathophysiology of this condition as one that results from dysfunctional articular remodeling attributable to (1) excessive or sustained physical stress to the TMJ articular structures that exceeds the normal adaptive capacity (Box 1), or (2) a decreased adaptive capacity of the articulating structures of the joint (Box 2).

Whether the pathology of ICR is a form of osteoarthritis is still debated. Because the clinical features of ICR are comparable to those found in other low-inflammatory arthritic TMJ conditions, until the etiology of this entity is completely elucidated, it should be included in the same context of osteoarthritic disease for the sake of the discussion of its management.

General principles

Temporomandibular joint (TMJ) arthritic conditions can be classified as low-inflammatory or high-inflammatory types (Table 1).

Low-inflammatory arthritic conditions, such as osteoarthritis, begin in the matrix of the articular surface of the joint, with the subcondylar bone and capsule secondarily involved. The classic low-inflammatory arthritis type is primary osteoarthritis, produced by intrinsic degeneration of articular cartilage typically the result of functional overloading. Patients who have low-inflammatory type have low leukocyte counts in the synovial fluid and laboratory findings consistent with low-level inflammatory activity, with the affected joint showing focal degeneration on imaging. Despite that low-inflammatory arthritic conditions often involve the TMJ, these conditions seldom require

E-mail address: lmercur@lumc.edu

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Box 1. Mechanical stress–related factors capable of initiating change in temporomandibular architecture

Occlusal Therapy
Internal derangement
Parafunction
Macrotrauma
Unstable occlusion

Data from Arnett GW, Milam SB, Gottesman L. Progressive mandibular retrusion—idiopathic condylar resorption. Part I. Am J Orthodont Dentofac Orthop 1996;110:10.

invasive surgical intervention if they are managed appropriately nonsurgically in their early stages [5].

Signs and symptoms of arthritic changes in the temporomandibular joint

The most common symptom of any TMJ arthritic condition is painful joints. The pain arises from the soft tissues around the affected joint that are under tension and the masticatory muscles that are in protective reflex cocontraction as the result of Hilton's Law [6]. This orthopaedic principle states that the nerves that innervate a joint also innervate the muscles that move that joint and the overlying skin. This self-preservation physiologic reflex provides for the protection of an injured or pathologically affected joint by causing the surrounding musculature to reflexly contract in response to intra-articular injury or pathology, thus protecting it from further damage. Pain may also arise from the subchondral bone that is undergoing destruction as the result of the arthritic process.

Other common and significant signs and symptoms of TMJ arthritis are loss of joint function or late-stage ankylosis, joint instability, and facial deformity attributable to loss of posterior mandibular vertical dimension as pathologic osteolysis decreases the height of the condyle and condyloid process resulting in an apertognathia [5].

Box 2. Host adaptive capacity factors capable of initiating change in TMJ architecture

Age
Systemic illness
  General
  Autoimmune diseases
  Hyperparathyroid
Hormones
  Sex hormones
Estrogen
Prolactin
  Corticoids

Data from Arnett GW, Milam SB, Gottesman L. Progressive mandibular retrusion—idiopathic condylar resorption. Part I. Am J Orthodont Dentofac Orthop 1996;110:10.

Table 1
Classification of arthritic conditions affecting the temporomandibular joint

Low-inflammatory arthritic disorders	Osteoarthritis (osteoarthrosis, degenerative joint disease), posttraumatic arthritis
High-inflammatory arthritic disorders	Infectious arthritis Rheumatoid arthritic conditions Adult and juvenile Gouty arthritis Psoriatic arthritis Lupus erythematosus Ankylosing spondylitis Reiter syndrome Arthritis associated with ulcerative colitis

Diagnosis

The diagnosis in late-stage arthritic TMJ disease is usually obvious, especially in the late-stage high-inflammatory arthritic diseases when the disease process manifests in other joints. The problem in diagnosis comes with the uncommon patient whose arthritic disease first manifests itself as TMJ pain and mandibular dysfunction. A history of joint overload because of habits (eg, excessive gum chewing, unilateral chewing) or parafunction (eg, bruxism, clenching) and clinical examination are important. Because of the lack of correlation between the signs and symptoms and the history and physical findings, however, the most helpful approach to diagnosis may be derived from information provided by appropriate imaging and laboratory examination.

The characteristic imaging features of low-inflammation osteoarthritis in which normal joint mechanics have been disrupted (eg, disc

derangement, disc interference) are focal degeneration and the appearance of osteophytes (Fig. 1). The image may be characterized by hypertrophic changes about the affected joint rather than atrophic changes seen in high-inflammatory types of arthritis. Subchondral focal degeneration, the so-called ''Eli cyst'' may be seen in low-inflammatory arthritis (Fig. 2).

Principles for management of temporomandibular joint osteoarthritis

Management of TMJ osteoarthritis may be divided into noninvasive, minimally invasive, and invasive or surgical modalities. Finally, in end-stage disease, salvage modalities must be considered (Box 3).

The decision to surgically manage any TMJ arthritic condition must be based on evaluation of the patient's response to noninvasive management, the patient's mandibular form and function, and the affect the condition has on the patient's quality of life [5].

The management goals in any TMJ arthritis should be

- Decreasing joint pain, swelling, and reflex masticatory muscle cocontraction
- Increasing joint function
- Preventing further joint damage
- Preventing disability and disease-related morbidity

Fig. 1. Right TMJ osteoarthritis on orthopantomogram in a 78-year-old female.

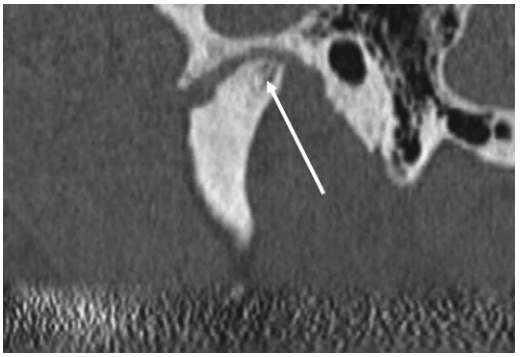

Fig. 2. Left TMJ in CT scan. Arrow indicates Eli cyst.

Using a classification scheme based on clinical signs and symptoms and imaging, modified from that developed by Steinbrocker [7] and Kent and colleagues [8], this article presents an evidence-based discussion for the management of osteoarthritis affecting the TMJ (Table 2).

Noninvasive management modalities

The noninvasive modalities of management include medications, oral appliances, and especially physical therapy [9–15].

Box 3. Modalities for the management of temporomandibular joint osteoarthritis

Noninvasive modalities
Medications
- Anti-inflammatories
- Muscle relaxants

Minimally invasive modalities
Intra-articular injections
- Hyaluronic acid
- Corticosteroids

Arthrocentesis
Arthroscopic surgery

Invasive surgical modalities
Bone and joint procedures
- Arthroplasty

Autogenous hemiarthroplasty
Alloplastic hemiarthroplasty
- Osteotomy

Salvage procedures
Total joint reconstruction
- Autogenous
- Alloplastic

Table 2
Classification of osteoarthritis based on symptoms, signs, and imaging with management options

Stage	Symptoms	Signs	Imaging	Management options
I: Early disease	Joint/muscle pain Limited function Crepitus	Little or no occlusal or facial esthetic changes	Mild to moderate erosive changes of condyle/fossa/eminence	Noninvasive (1°) Minimally invasive (2°)
II: Arrested disease	Little or no joint pain Muscle pain Some joint dysfunction Crepitus	Class II malocclusion Apertognathia	Flattened condyle/eminence	Bone and joint (1°) Salvage (2°)
III: Advanced disease	Joint/muscle pain Loss of function ±crepitus Progressive retrognathia	High-angle class II malocclusion Apertognathia Developing fibrosis/ankylosis	Gross erosive changes Loss of condyle and eminence height Ankylosis Hypertrophy of coronoid	Salvage (1°)

Data from Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. JAMA 1949;140:659–62; and Kent JN, Carlton DM, Zide MF. Rheumatoid disease and related arthropathies. II. Surgical rehabilitation of the temporomandibular joint. Oral Surg 1986;61:423–39.

Medications

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, should be used on a time-contingent basis to take advantage of their pharmacokinetics. Oral corticosteroids on a short-term basis (5–7-day course) may be considered to "jump start" the anti-inflammatory process, and would then be followed by a longer course of NSAIDs. Muscle relaxants may be helpful to control the reflex masticatory muscle cocontraction and pain [9].

Oral appliance

Oral appliances assist in decreasing frequency and duration of muscle activity in some patients; they may also provide relief from masticatory muscle cocontraction/pain and along with a soft diet decrease the loads delivered across the TMJ articulation under function [10]. Reconstruction of the occlusion to provide bilateral occlusal stability temporarily during the early stages of management also decreases the potential for unilateral joint overload.

Physical therapy

Physical therapy should be considered a potential treatment of TMD. The use of modalities can assist with the provision of treatment. Physical therapeutic modalities act as counterirritants to reduce inflammation and pain. Superficial warm and moist heat or localized cold may relieve pain sufficiently to permit exercise. Therapeutic exercises are designed to increase muscle strength, reduce joint contractures, and maintain a functional range of motion. Ultrasound, electrogalvanic stimulation, and massage techniques may help reduce inflammation and pain but their therapeutic value remains unanswered [11].

Active and passive jaw movements, manual therapy techniques, correction of body posture, and relaxation techniques were used in the management of 20 consecutive patients who had TMJ osteoarthritis. After treatment (mean 46 days) pain at rest was reduced 80% and there was no impairment in 37% [12].

In pursuing physical therapy, patients should avoid heavy loading exercises that compress the joint [13]. For this reason most muscle-strengthening exercises are best done isometrically in a position that does not cause pain [14]. Assisted, passive range-of-motion [15] exercises, such as with the Therabite Jaw Exerciser (Atos, Milwaukee, Wisconsin), may also be recommended.

Maxillomandibular fixation has no role in the management of TMJ osteoarthritis or ICR and can result in joint contractures, increase the potential for ankylosis, and promote masticatory muscle atrophy and fibrosis.

Minimally invasive modalities

Hyaluronic acid

Hyaluronic acid (HA) as an injectable, large, linear glycosaminoglycan has been studied in other body joints. In double-blind studies in hips, shoulders, and knees after 2 months, HA has been shown to provide significantly better

results than saline. These results were sustained for 1 year. No significant differences were noted in radiographic progression of the disease, however [16–18].

Bertolami and colleagues [19] reported that when using sodium hyaluronate in TMJ osteoarthritis there was no difference in outcomes among the placebo and saline control group measured variables. The authors concluded that sodium hyaluronate did not seem to be an effective means of treating TMJ osteoarthritis.

Neo and colleagues [20] concluded that HA may have a role in preventing the progression of TMJ osteoarthritis from a study in sheep that underwent five repeated injections of sodium hyaluronate over 14 months into their experimentally induced TMJ osteoarthritis. The HA-injected joints revealed minimal osteoarthritic anatomic and histologic changes when compared with control joints injected similarly with saline.

Alpaslan and Alpaslan [21] reported in a 24-month follow-up study after TMJ arthrocentesis with and without the addition of sodium hyaluronate that although both benefited from the procedures, those patients having arthrocentesis with the addition of sodium hyaluronate had superior results.

An in vivo rabbit study reported that in a comparison of intra-articular injections of 1.6 mg prednisolone verses 1.3 mg hyaluronate weekly for 1 month into pain-induced TMJ osteoarthritis that the hyaluronate-injected joints demonstrated limited cartilage change, less fibrillation, and the presence of clusters of chondrocytes in deficit areas. The prednisolone-treated joint exhibited worsening of the cartilage destruction [22].

HA has to date not been approved as a safe and effective medication in the management of arthritic disease in the TMJ by the US Food and Drug Administration.

Corticosteroids

Intra-articular injections of corticosteroids are of limited use in other joints of the body [23]. The main limitations of repeated intra-articular steroid injections are the risks for infection and the destruction of articular cartilage, and tendon or ligament attachments. Repeated intra-articular corticosteroid injections have been implicated in the ''chemical condylectomy'' phenomenon in the TMJ [24–27].

Toller's [25] clinical study indicates that single injections of steroids into the TMJ may be helpful for patients older than 30 years of age but are not indicated in younger patients. He advocates that all nonsurgical management options should be used before injecting steroids into the TMJ, however.

Friedman and Moore [28] have questioned the efficacy of intra-articular steroid injections. They showed that the effects were transient after 4 weeks.

In 1953 Hollander [29] reviewed his experience of more than 7000 injections of hydrocortisone into synovial cavities and concluded that such treatment was a safe and effective palliative procedure in the local treatment of arthritis; but in 1958 Chandler and Wright [30] recommended caution with this treatment because the steroid might interfere with a local protective mechanism and encourage further damage with joint function.

In 1970, Poswillo [24] reported experimental evidence of histologic damage to the articular surfaces of the mandibular condyles of healthy *Macacus irus* monkeys after six injections of hydrocortisone.

Intra-articular injections of steroids are not routinely recommended in patients who have low-inflammation arthritic conditions. Injections should be considered only with evidence of acute high inflammation of the joint and should be limited to no more than two injections in 6 months. Multiple injections of steroids should not be used, except in rare instances when previous injections have been successful. In all cases after intracapsular injection of steroids, decreased activities within pain-free limits should be recommended to prevent acceleration of the degenerative process from overactivity and joint overload. Prednisolone trimethylacetate (25 mg) is the usual injection dose [31].

Arthrocentesis

Nitzan and Price [32] presented a 20-month follow-up study of 36 patients who had 38 dysfunctional joints that had not responded to nonsurgical management to determine the efficacy of arthrocentesis in restoring functional capacity to their osteoarthritic joints. They reported that 26 joints (68%) responded favorably to arthrocentesis. Subjective pain and dysfunction scores significantly decreased and objective maximum interincisal opening (MIO) and lateral excursions significantly increased.

These authors concluded that arthrocentesis is a rapid and safe procedure that may result in the osteoarthritic TMJ returning to a functional state. Failure of arthrocentesis (32%) suggested that

painful limitation of TMJ function might be the result of fibrous adhesions or osteophytes that require arthrotomy for management.

There are no reports of the results of arthrocentesis in ICR.

Limitations of these studies are the small sample size, the inability to generalize the results to a male population because the overwhelming majority of the patients in these studies were female, lack of a control group, the influence of concomitant anti-inflammatory or other analgesic agents, and the short follow-up.

Arthroscopy

The value of TMJ arthroscopy may be in the early diagnosis and management of arthritic processes affecting the TMJ, especially early-stage arthritic disease, to avoid the complications of open bite and ankylosis [33–35].

Holmlund [33] describes the arthroscopic picture as varying widely depending on when in the stages of the arthritic process the procedure is performed and whether disease-modifying therapeutic agents have been given. For example, in rheumatoid arthritis early features of synovial involvement may be increased vascularity and capillary hyperemia; the more severe the disease, the more features are found. The same is true of the cartilage, in which the findings may vary from early superficial changes, such as localized areas with fibrillation, to lesions and exposure of subchondral bone. Late-stage marked fibrosis or ankylosis makes arthroscopy impossible and contraindicates its usefulness.

There are no reports as to the efficacy of arthroscopic procedures in the management of ICR.

Invasive surgical modalities: bone and joint procedures

Arthroplasty

Henny and Baldridge [36] described arthroplasty (high condylar shave) as a limited removal of the damaged articular surface of the condyle that maintains the height of the ramus, the articular disk, and the surrounding soft tissue, including the lateral pterygoid muscle attachment. Its use was advocated in severe, unremitting osteoarthritis pain.

Reshaping the articular surfaces to eliminate osteophytes, erosions, and irregularities found in osteoarthritis refractory to other modalities of treatment was described by Dingman [37].

Although arthroplasty reportedly provided pain relief, concerns about the resultant mandibular dysfunctions, dental malocclusions, facial asymmetries, and the potential for development of further bony articular degeneration, disk disorders or loss, and ankylosis led to the development of techniques for interposing autogenous tissues and alloplastic materials.

The need for replacement of the articular disk in such cases remains controversial [38,39]. The literature on TMJ anatomy and function suggests that the articular disk serves many functions [40]. These include shock absorption, congruency between the articulating surfaces of the condyle/fossa/eminence complex, facilitation of movements, distribution of functional loads, and dispersion of synovial fluid. To date, however, there is little scientific evidence to substantiate any of these inferences. It is therefore impossible to objectively define the ideal properties and requirements of a disk replacement material.

According to Moriconi and colleagues [41], TMJ replacement grafts should fulfill the following criteria: biologic compatibility, adequate strength, good biomechanics, and resistance to the adverse effects of the biologic environment.

Autogenous hemiarthroplasty. Several different autogenous tissues have been advocated as a replacement for the TMJ articular disk [42]; however, the literature on the use of the vascularized local temporalis muscle flap seems to present the most applicable data to the management of the arthritic TMJ [43–51].

The advantages of the temporalis muscle flap are its reliable blood supply [50,51] and its proximity to the TMJ. Feinberg and Larsen [45] stated that one of the most important roles of the temporalis muscle flap is the maintenance of functional movements. Because the flap is attached to the coronoid process, when the mandible translates the movement of the mandible pulls the muscle flap in an anterior direction, simulating the natural functional movements of the disc. Investigators who performed follow-up studies on patients who had temporalis muscle replacement demonstrated the presence of viable muscle tissue within the joint [40,51,52].

Tong and Tideman [53] reported the reformation of a disclike interpositional structure with use of the pedicled temporalis muscle flap in four discectomized rhesus monkeys that had osteoarthritis after 18 months. They also reported that a milder degree of osteoarthritis was observed histologically in the joints in which the graft survived (three of the four monkeys).

Henry and Wolford [54] presented the contraindications for the use of the temporalis muscle/fascia graft: failed Proplast-Teflon (Vitek, Houston, Texas) or Silastic (Dow Corning, Midland, Michigan) with continuing foreign body giant cell reaction [55,56], progressive osteoarthritis [57], and two or more prior surgeries [58,59].

Alloplastic hemiarthroplasty. Hemiarthroplasty, an alloplastic bearing surface articulating with bone, either diseased or normal, has been used in orthopaedic surgery for fractures of the hip and shoulders in geriatric patients. This surgery can be successful in such cases wherein functional demands are low. It has been demonstrated that under normal functional loading, however, a metal articulation causes breakdown of articular cartilage leading to failure of the hemiarthroplasty, pain, and progression to total joint replacement [60–62]. For this reason, hemiarthroplasty is generally not performed in young patients or in patients who have osteoarthritis [63,64].

In all low-inflammatory (eg, osteoarthritis) and high-inflammatory (eg, rheumatoid) arthritic conditions both articulating components of any joint are involved in the pathology; therefore, orthopaedists recommend total joint replacement, not hemiarthroplasty, for such cases. Comparison studies have demonstrated that total joint replacements have significantly better outcomes than hemiarthroplasties relative to pain, stability, function, failure rates, and requirement for further revision [65–68].

Several different alloplastic implantable materials have been advocated for hemiarthroplasty reconstruction of the temporomandibular joint. Among these were Silastic (Dow-Corning, Midland, Texas) and Proplast-Teflon (Vitek, Houston, Texas), both of which have been determined to be inappropriate for use in the TMJ because of their poor wear characteristics and resultant foreign body giant cell osteolysis they caused [69].

Park and colleagues [70] reported an 8-year retrospective pilot study using a metal alloplastic hemiarthroplasty in advanced TMJ osteoarthritis in 112 joints treated over more than 12 years. The mean follow-up was 3 years. The authors concluded that their findings of significant relief of pain and increased TMJ function warranted further investigation of this treatment modality.

In light of the orthopaedic literature showing the long-term poor experience with hemiarthroplasty in low- and high-inflammatory arthritic disease, it would seem logical that using this method in management of TMJ arthritic disease might only lead to the same outcome. It should not be recommended until further long-term, well-designed clinical trials with larger populations are published demonstrating the safety and efficacy of hemiarthroplasty in the management of TMJ arthritic conditions [5].

Osteotomy

Patients who have active TMJ disease and either concomitant or resultant maxillofacial skeletal discrepancies treated only with orthognathic surgery often have poor outcomes and significant relapse [71–78]. Preexisting TMJ pathology, with or without symptoms that can lead to unfavorable orthognathic surgery outcomes, include internal derangements, progressive condylar resorption, condylar hyperplasia, osteochondroma, congenital deformities, and nonsalvageable joints [72].

Examples of nonsalvageable TMJ conditions are severe low-inflammatory arthritic conditions refractory to nonsurgical management, high-inflammatory arthritic diseases, neoplasms, multiply operated joints, joints previously exposed to failed alloplastic devices materials, and ankylosed joints. Patients who have these conditions and concomitant or resulting facial deformities may benefit from TMJ reconstruction with total alloplastic TMJ reconstruction and concomitant orthognathic surgical procedures [54,79–81].

Because the TMJs are the foundation of orthognathic surgery, the resultant pathology offers a poor base on which to build any maxillofacial functional skeletal reconstruction in conditions where there are gross erosive changes in the articulating components of the fossa and condyle resulting in loss of vertical height.

Further, the degenerative and osteolytic changes the joint components are undergoing in these conditions make these components of the TMJ highly susceptible to failure under the new functional loading resulting from orthognathic surgical repositioning of the maxillofacial skeleton. Successful outcomes have been reported, however, using orthognathic surgical procedures to manage maxillofacial skeletal discrepancies in patients who have ICR (Fig. 3) [80,81].

Wolford and Cardenas [80] reported 12 patients who had active ICR who underwent combined TMJ (disc repositioning and stabilization with the Mitek anchor [Mitek Surgical Products Inc., Westwood, Massachusetts]) and bimaxillary orthognathic surgery followed 33 months who

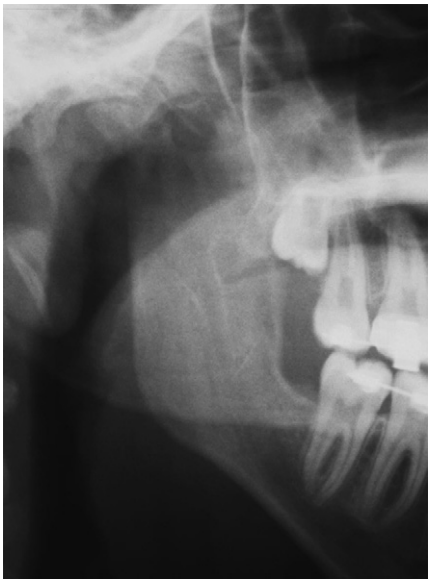

Fig. 3. Right TMJ idiopathic condylar resorption on orthopantomogram in a 15-year-old female.

had stable skeletal and occlusal results and significant pain relief.

Morales-Ryan and colleagues [81] evaluated 44 patients who had ICR, 10 of whom underwent bimaxillary orthognathic surgery but no TMJ surgery and 34 of whom underwent the management recommended in the Wolford and Cardenas [80] paper. The former 10 patients followed 37 months were reported to have statistically significant relapse attributable to PCR, whereas the latter 34 patients followed 25.5 months had no statistically significant relapse attributable to PCR.

Osteodistraction. Van Strijen and colleagues [82] reported a case of ICR 1 year following distraction osteogenesis to advance the mandible in a 15-year-old male. Although there was associated postdistraction trauma in this case, the authors advise that because osteoclastic activity in the TMJ has been reported after gradual distraction of the mandible, distraction osteogenesis may make its own contribution to ICR. They suggest that in the future patients being considered for surgical management of mandibular hypoplasia be critically evaluated for any traumatic, functional, or metabolic risk factors for ICR.

Based on the experience reported in the literature, it is recommended that the management of the maxillofacial skeletal discrepancies resulting from active or advanced arthritic TMJ disease would be most predictably managed using the orthopaedic principles of total joint replacement safely and effectively used for more than 4 decades in other joints for these osteoarthritic conditions.

Salvage procedures—total joint replacement

Autogenous total joint replacement procedures

Several autogenous tissues have been used to reconstruct the mandibular condyle to regain facial form and return mandibular function in cases of developmental abnormalities, postneoplastic/posttraumatic discontinuity defects, and ankylosis.

In 1909, Bardenheuer [83] performed a mandibular condylar replacement with the fourth metatarsal. The use of the metatarsal head to reconstruct the mandibular condyle was also reported by Gillies [84] in 1920, Dingman [85] in 1964, Glahn [86] in 1967, and Spiessl and colleagues [87] in 1972. Use of a nonvascularized metatarsophalangeal joint to correct a facial deformity was reported by Entin [88] in 1958 and Datillo and colleagues [89] in 1986; Dierks and colleagues [90] in 2000 reported the use of a vascularized metatarsophalangeal joint to reconstruct the temporomandibular joint. None of these reports involved patients reconstructed because of inflammatory arthritic conditions.

Mandibular condyle reconstruction has also been reported performed by using vascularized rib [91,92], iliac crest [93], and fibular free flaps [94,95]. Other autogenous tissues, such as iliac bone free-grafts [96–100], clavicle, and sternoclavicular joint have also been used [101,102]. None of these reports provided data on management of cases with inflammatory TMJ arthritic disease.

The costochondral graft has been the most frequently recommended autogenous bone for the reconstruction of the temporomandibular joint because of its ease of adaptation to the recipient site, its gross anatomic similarity to the mandibular condyle, the low morbidity, reported low morbidity rate at the donor site, and its demonstrated growth potential in juveniles [103–108].

Lindqvist and colleagues [109] in 1988 presented a clinical 10-year mean follow-up study of 16 of the 60 patients he previously reported [110]. Of the 16, all were unilateral and 4 had the preoperative diagnosis of severe TMJ arthritis. There was no indication as to whether these 4 cases were low-inflammatory or high-inflammatory arthritis, although based on the pathophysiology of these diseases processes one might suspect

that these patients had a low-inflammatory TMJ arthritic disease (osteoarthritis) because that category of arthritis is demographically more common unilaterally than are the high-inflammatory forms of TMJ arthritis. The authors concluded that the long-term clinical results of autogenous costochondral TMJ reconstruction in adult patients are "fairly good."

Obeid and colleagues [111] retrospectively reported in a mean 5-year (range 2–11 years) clinical follow-up study the results of the reconstruction of 22 patients (14 unilateral) and none were for management of arthritic disease. These authors concluded, despite a 10% infection rate and an unpredictable growth rate in younger patients requiring later corrective osteotomies, that autogenous free costochondral grafting was a successful method for reconstruction of portions of the mandible and its temporal articulation.

Perrot and colleagues [112] in 1994 presented a retrospective study of 26 patients, 7 growing and 19 nongrowing, with a mean follow-up of approximately 4 years. One of the nongrowing patients had a prereconstruction diagnosis of "autoimmune arthritis" and 2 others "DJD" (degenerative joint disease—osteoarthritis). When reviewing the data, it can be seen that the patient who had autoimmune arthritis (high-inflammatory arthritis) on follow-up radiographic measurement showed one of the most significant total bilateral losses of posterior mandibular vertical dimension and the only incidence of a decrease in MIO. The follow-up data for the 2 patients who had DJD shows, however, that their radiographic measurements and MIO correspond with the other prereconstruction diagnoses. These authors concluded that the results of their study indicate that costochondral grafting may be used to successfully construct/reconstruct the ramus–condyle unit.

Several other reports discussed the use of the autogenous costochondral graft for reconstruction of the TMJ, but specific reference to its use in the management of the functional, pain, and esthetic problems associated with high-inflammatory arthritis cannot be found [113–118].

MacIntosh [42,107,108,118] discusses a rationale and provides clinical examples for the use of autogenous costochondral grafting in the management of the functional and esthetic consequences of osteoarthritis, rheumatoid arthritis, and juvenile arthritis, but offers no clinical data to evaluate.

Freitas [119] and colleagues reported on 12 arthritic nongrowing patients (24 joints) requiring total TMJ reconstruction. Six were managed with autogenous sternoclavicular or costochondral grafts and 6 with total alloplastic TMJ prostheses. The groups were followed for a mean of 48.8 months and 58.5 months, respectively. The authors reported that based on the criteria established for the study, the patients who had alloplastic TMJ reconstruction had statistically significant better subjective and objective results than did those reconstructed with autogenous bone. They concluded that in light of these results and that the alloplastic reconstruction avoided the need for another operative site and potential morbidity, decreased operating room time, and allowed for simultaneous mandibular advancement with predictable long-term results and stability [120], alloplastic TMJ reconstruction was more appropriate for total TMJ reconstruction in patients who had low-inflammatory or high-inflammatory arthritic conditions.

Troulis and colleagues' [121] report on 10 patients (17 joints) followed a mean of just 17 months (range 8–38 months) who underwent endoscopic condylectomy and autogenous costochondral grafting. They report satisfactory clinical results with low morbidity over the short period of this initial study and state they are pursuing long-term follow-up studies.

Saeed and Kent [122] retrospectively reviewed 76 costochondral grafts (57 patients) after a mean of 53 months (range 24–161 months). Nine patients (3 with ankylosis and 6 without ankylosis) had a preoperative diagnosis of "arthritis" but it was never stated whether they were low-inflammatory or high-inflammatory arthritic conditions. They concluded that in patients who had no previous TMJ surgery, "arthritic disease," or congenital deformity, the costochondral graft performed well. Further, a preoperative diagnosis of ankylosis was associated with a high complication rate suggesting caution in arthritic patients using the autogenous costochondral graft.

None of the textbooks of orthopaedic surgery nor any journal articles published recently discuss the use of autogenous bone in the reconstruction of any joint of a nongrowing patient affected by either low-inflammatory or high-inflammatory arthritic disease. Alloplastic reconstruction is the recommended management modality when total joint replacement is required in such cases [123,124].

Alloplastic total joint replacement procedures

In orthopaedic surgery, resection arthroplasty introduced in the 1960s was an uncertain procedure with recurrent deformity and limited motion as common complications. It was for this reason that joint prostheses were developed [125]. Reconstructive surgery of peripheral joints affected by arthritis is performed for relief of pain, correction of deformities, and increase in joint function to decrease physical impairment. The patient's prognosis and magnitude of joint involvement influence surgical intervention [126].

Successful reconstructive surgery in large joints involves alloplastic replacement. Early problems of material failure have been resolved and most designs, regardless of their implantation sites, involve the use of convex (condyle) metal (cobalt-chrome) against concave (fossa) ultrahigh molecular weight polyethylene. Earlier materials were stabilized to host bone surfaces with rapid curing polymethylmethacrylate cement yielding unacceptable failure rates from latent cement–bone interface loosening and host bone osteolysis, but newer femoral implants are made to be press-fitted to achieve osseointegration and longer-term wear even in younger individuals [127].

In the TMJ, alloplastic reconstruction has been discussed at length [128–132]. All these authors agree that when the mandibular condyle is extensively damaged, degenerated, or lost, as in arthritic conditions, replacement with either autogenous graft or alloplastic implant is an acceptable approach to achieve optimal symptomatic and functional improvement. Dissatisfaction with some of the facets of autogenous costochondral grafting, however, particularly in patients who have high-inflammatory arthritic disease and ankylosis, led to the development and use of total alloplastic TMJ devices with data that can be evaluated to support good results.

Before the mid-1980s reports of the use of alloplastic materials for TMJ reconstruction were primarily related to their use in management of ankylosis or reconstruction of the TMJ after trauma or ablative tumor surgery [131].

Stern and colleagues [133] published a case report specifically dealing with the use of an alloplastic total TMJ system (Vitek II, Kent, Houston, Texas). Although this paper discussed using this modality to manage arthritic TMJ conditions, it was not until 1986 when Zide and colleagues [134] and Kent and colleagues [8] published their comprehensive review of rheumatoid arthritis and its surgical management that the subject was specifically addressed.

In another publication, Kent and colleagues [135] presented 57 cases of low-inflammatory arthritic disease (osteoarthritis) and 14 cases of high-inflammatory arthritic disease (rheumatoid arthritis) that were treated by either partial or total alloplastic reconstruction. Unfortunately, the results using these data are difficult to interpret and apply because the partial and total alloplastic prostheses all contained Proplast-Teflon.

In 1994, Kent and Misiek [129] provided a comprehensive review of partial and total temporomandibular joint reconstruction. They concluded that when there is a major vertical dimension problem, loss of disc and entire condylar head with chronic pain, hypomobility, or malocclusion, such as in advanced arthritic conditions, total joint reconstruction with an alloplastic prosthesis is indicated.

In 2000, Speculand and colleagues [136] published a report of 86 total alloplastic joints (27 VK II [Houston, Texas] and 59 TMJ, Inc. [Golden, Colorado]) used to reconstruct degenerative joint disease and rheumatoid arthritis with a median follow-up of 14.5 months (range 1–120 months). Using the subjective (pain and diet) and objective (interincisal opening) criteria they established for this study, they reported an overall success rate of 94%. Four patients required replacement of the VK II devices, however, because of foreign body giant cell reactions.

Saeed and colleagues [137] in a 2001 publication reported on a series of seven patients who had rheumatoid arthritis whose TMJs were replaced with TMJ, Inc. (Golden, Colorado) devices. After the mean follow-up of 30 months (range 8–50 months), they report improved subjective (pain and diet) and objective (interincisal opening) scores in these patients and concluded that patients who had severe rheumatoid arthritis affecting the TMJ should consider alloplastic total TMJ reconstruction to restore some normal function and appearance.

Long-term follow-up studies include patients who have diagnoses consistent with low- and high-inflammatory arthritic TMJ in their total alloplastic reconstruction data sets [131,138–143], but to date only the studies discussed above [5,143] directly deal with arthritic disease affecting the TMJ and alloplastic reconstruction results.

Mercuri [5] reviewed the records of 494 patients who had total alloplastic TMJ replacement

with a patient-fitted system (TMJ Concepts, Ventura California); 60 patients (12%) had diagnoses consistent with a low-inflammatory TMJ arthritic condition. Twenty-seven (5%) had diagnoses consistent with high-inflammatory TMJ arthritic conditions.

After a mean follow-up period of 31.8 months (range 2–48 months), the data revealed a significant improvement ($P < .0003$) in subjective variable (pain, function, diet) visual analog scores in the high-inflammatory diagnosis group. There was a significant improvement ($P < .005$) in subjective variable (pain, function, diet) visual analog scores and improvement in measured MIO ($P < .05$) in the low-inflammatory diagnosis group.

In light of these findings, previously published experience in the orthopaedic and oral and maxillofacial surgery literature, and the literature comparing autogenous versus alloplastic total TMJ replacement in arthritic conditions, it seems that total alloplastic TMJ reconstruction should be considered appropriate management for advanced-stage arthritic disease and ICR of the temporomandibular joint.

In conclusion, it is essential that TMJ osteoarthritis be presented as the pathologic entity it is in the same terms as our colleagues discuss osteoarthritis in orthopaedic circles. To not do this only exacerbates the problem that everyone dealing with this entity—patients, clinicians, insurance carriers, and so forth—has with TMJ osteoarthritis, because they do not consider it as the orthopaedic (medical) pathology that it is, but rather a purely dental TMJ problem.

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Psychological Considerations for Chronic Orofacial Pain

Charles R. Carlson, PhD, ABPP

Department of Psychology, University of Kentucky, 106 Kastle Hall, Lexington, Kentucky 40506-0044, USA

Many acute temporomandibular disorders can be managed effectively within traditional dental practice settings using standard dental procedures. Recent evidence also suggests that early and effective multidisciplinary biobehavioral interventions with patients who have acute trigeminal pain problems are effective and reduce the incidence of chronic pain [1]. When chronic disorders develop or referred patients who have ongoing chronic pains present for treatment, it is even more important to initiate a comprehensive treatment that is informed by the biobehavioral model. The biobehavioral model for management of temporomandibular disorders recognizes the importance of nonphysical factors, such as past history of pain or trauma, ongoing emotional states, health beliefs, and coping skills, that interact with the actual physiologic disturbances in determining the pain experience for individual patients. When behavioral, social, and psychologic factors are included in the clinician's treatment delivery, the probability of long-term symptom management is enhanced [1,2].

The interrelationships between biologic and behavioral facets of human activity are captured by the term *biobehavioral*. This term integrates the important roles biologic factors play in governing human functioning with the influences of behavioral factors, including principles of learning, interpersonal processes, and techniques for self-change. Biobehavioral domains are thus complementary to biomedical domains and help create an understanding of human functioning. Engel [3] introduced the term *biopsychosocial* as a broad construct to convey the importance of considering the interacting roles that biologic, psychologic, and sociologic factors play in human functioning. The use of the word *biobehavioral* is on a par with the use of the term *biomedical*, so that both represent dimensions of the biopsychosocial model. The use of *biobehavioral* directs attention to the specific assessment and treatment strategies that clinicians use to integrate the biologic and behavioral components of human functioning.

Dworkin [4] has discussed the biobehavioral approach using a dual-axis model that integrates the biologic components of the presenting problem (axis I) with psychologic responses or adaptations to the physiologic changes mediated by behavioral and social issues (axis II). Thus, the biobehavioral perspective enables a broader understanding of presenting complaints and provides more avenues for treatment intervention. The foundation of this approach is the recognition and appreciation of the distinction between nociception (actual neuronal signaling of noxious pressure, temperature, chemical, or tissue change) and pain perception (complex subjective experience involving sensory, physiologic, psychologic, historical, and social factors). Physical disease factors are important to address as the physical sources of nociception, but biobehavioral factors are equally important to consider if the individual is to return to normal functioning, especially in the case of chronic dysfunction. Biobehavioral factors, such as behaviors that may promote or prolong physical dysfunction, thought processes (thinking) that may be distorted, or emotions that may be disabling, require evaluation first and then inclusion in the treatment plan as targets for specific interventions.

E-mail address: ccarl@uky.edu

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Importance of practice worldview

One of the primary foci of dental training is to teach dental students to identify the cause of a problem through careful history taking, examination, and diagnosis. Generally speaking, once a cause is identified then treatment begins to restore normal functioning. This linear model is based on a mechanistic worldview in which a clear cause-and-effect relationship is operating. For many dental problems, this worldview is well justified and its abandonment would be most unfortunate for the patient. In the case of an impacted third molar, for example, appropriate diagnosis can lead to a straightforward procedural fix that will eliminate pain and generally enable rapid return to normal functioning. With more complex problems that have multiple etiologic factors, however, the mechanistic mindset may not be the best perspective from which to approach treatment. Consider the same situation of an impacted third molar that has not been treated because the patient has a long history of delaying treatment because of fear associated with receiving dental care. During this delay, the patient may have developed behavioral habits (eg, altered chewing patterns) to minimize the pain, but these behavioral habits may be fatiguing motor units of certain muscle groups that are also mediated by the trigeminal nerve. This muscle fatigue and, if not addressed, the resulting microscopic physiologic changes create additional sources for nociception that may not diminish even when the impacted third molar is treated with the appropriate dental procedures. If so, the patient may still complain of pain despite the original source of the pain being adequately addressed. The biobehavioral perspective provides clinicians with the option to develop a multicomponent management plan for chronic pain that can be introduced to the patient at the outset of treatment. This approach assumes that multiple facets of a problem can be addressed simultaneously rather than in the linear, step-by-step manner characteristic of the mechanistic model. The biobehavioral approach also recognizes that patient beliefs, perceptions, emotions, and learned behaviors are critical to understand and account for in the long-term management of chronic pain conditions.

Foundations for management

One of the challenges for clinicians working with individuals who have an orofacial pain complaint is grappling with the paradigm shift required by the biobehavioral model. This paradigm shift involves not asking when is the biobehavioral model appropriate for guiding evaluation and treatment, but how can it enhance the delivery of clinical care, which means thinking about multiple, interacting systems involving biologic, psychologic, and social factors as a normal part of everyday routines. Biopsychosocial systems are important from the moment clinicians initially encounter patients, develop rapport, take the history, perform the clinical examination, formulate the treatment plan, and perform treatment. This approach permeates everything in the orofacial pain practice, from the structure of the clinical environment, the nature of the initial examination and how information is recorded, how long a period is allotted for the initial examination, who delivers the treatment, what professional colleagues are affiliated with the clinical practice and how that affiliation is characterized, and what is communicated to the patient through the clinician's own words and actions. Clinicians who use the biobehavioral approach consider the initial encounter with patients a significant component of the treatment process itself. The effective use of the biobehavioral model often requires a considerable revolution in a clinician's thought processes and practice behaviors.

Change is as difficult to achieve in clinicians as it is in patients. Change is often a process that unfolds over time and involves five important steps: precontemplation, contemplation, preparation, action, and maintenance [5]. Precontemplation is the initial phase in which individuals are not aware of the need for change and have no intentions of changing their behavior. In the precontemplation phase, resistance to suggestions or recommendations for change is expected. The contemplation phase involves a clear awareness that a problem exists and efforts are being made to think about ways to address the problem, but no specific actions are taken to deal with the problem. Contemplation is also often characterized by reflection on the costs and benefits associated with pursuing change in the desired direction. The preparation phase involves making decisions and small changes in behavior because specific plans are being made to invoke significant change within the next month. In the action phase, behaviors, thoughts, and surroundings are changed according to the decisions formalized in the preparation phase. Finally, maintenance requires efforts to preserve the changes that have been made and to forestall relapse into old patterns. It is not uncommon for change to follow a pattern of gains and

reversals as efforts are made to develop new habits. The process of change often requires considerable time and energy for alterations in thought, feelings, and behavior to emerge.

Readiness to change involves two elements: importance and confidence. Importance involves the "why" of change that is characteristic of the contemplation phase. Questions such as, "Is change worthwhile?," "What will be the cost of change?," and "Do I really want to change?" are part of determining importance. Goals have a way of motivating people; the importance ascribed to change captures a dimension of the individual's goals. Confidence reflects an assessment of capability and self-efficacy; capability involves the mastery of skills required for the performance of behavior and self-efficacy involves beliefs about one's ability to perform or change. Both capability and self-efficacy are necessary components of confidence that will lead to change.

Clinicians must be willing to add the challenge of incorporating assessment of change into their repertoire of skills, because it will inform the nature and process of the clinical exchange with patients. Clinicians must also assess the extent to which biopsychosocial variables must be addressed. The clinical examination and relevant questions are crucial in determining this. Using screening questionnaires as a part of the evaluation process is also helpful. The use of screening questionnaires ensures that all relevant domains are sampled and an individual's scores can be compared with a normative distribution for an actuarial interpretation of level of dysfunction. The use of more objective indices to evaluate important behavioral and psychosocial functioning can improve diagnostic reliability and inform treatment planning. The relevant domains include pain behavior, psychologic functioning (depression, anxiety, personality disorders), sleep habits, physical activity, interpersonal relationships, and work functioning. Screening questionnaires are available that can be readily used (just as imaging or blood study would be ordered) for these domains and include instruments such as the Multidimensional Pain Inventory [6], Short Form-36 [7], Symptom Checklist 90-R [8], Pittsburgh Sleep Quality Index [9], Multidimensional Fatigue Scale [10], Graded Chronic Pain Scale (GCPS) [11], and the Posttraumatic Stress Disorder Checklist [12]. These instruments provide clinicians with a standardized method of reliably assessing a patient's current level of functioning on a broad array of domains. Additionally, the availability of these data during the initial evaluation provides a baseline standard of comparison for evaluating the efficacy of treatment in the short-term and over an extended period.

The Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) uses a pain history and previous responses to treatment; assessment of parafunctional oral behaviors; the SCL-90R depression, somatization, and anxiety scales; and the Graded Chronic Pain Scale to gauge patient functioning. Readers are encouraged to look elsewhere for specific reviews of these strategies [13,14], but the GCPS provides a way to readily measure interference with psychosocial functioning. The GCPS assesses three domains that include pain ratings (present, worst, and average), pain interference (work, recreational, social, and family), and days lost from work. In combination with data from the clinical examination and history, using standard assessments such as the GCPS and the SCL-90R provide clinicians with a set of convenient measures for baseline assessment of an individual's current level of functioning.

Biobehavioral interventions

The goal of biobehavioral interventions is to return patients to adaptive or as near to normal functioning as quickly as possible. Given that chronic pain conditions have generally been refractory to previous treatments, clinicians should be mindful of the multiple determinants of pain that may be operating to maintain the patient's current status and must be addressed to obtain optimal symptom relief. Managing the presenting complaints therefore requires applying various strategies in a coordinated manner to address the symptoms in a systematic way. Care administered within a systems model includes multiple interventions offered in a coordinated fashion, often simultaneously, and not in a linear fashion over time. The concept of simultaneous treatments is valuable and may require a paradigm shift for patients and clinicians. These intervention strategies should be based on treatment outcomes studies that used randomized clinical trial methods to obtain results. Moreover, clinicians should also use appropriate measurement instruments to evaluate the efficacy of the clinical treatments they are providing to patients. Thus, clinicians are providing patients with a means to make informed decisions about the efficacy of the care being received while also evaluating the progress of therapy.

Biobehavioral approaches are designed to address both excitatory factors for pain (eg,

expectancies, negative emotions, parafunctional behaviors) and inhibitory factors (eg, confidence, relaxation, positive emotion). These approaches are designed to provide patients with skills to understand and manage their pain experience. Pain is generally a very useful biologic signal indicating a temperature, pressure, or chemical disturbance in normal functioning [15]. However, in a small number of cases the pain source can be supraspinal (eg, conversion disorder), but the incidence of true conversion disorders is relatively low [16]. Therefore, management with biobehavioral approaches is designed to enable most patients to acquire skills to address the pain condition in ways that will allow them to return to normal or near-normal functioning, thereby empowering patients with self-efficacy or the belief that they can manage their own lives and their pain. Without helping patients develop this sense of control over their own lives, clinicians may be inadvertently fostering helplessness that may hamper any meaningful long-term change in presenting complaints and adaptive functioning [17].

Education and self-care

One of the most important biobehavioral interventions is to provide accurate information to patients about their conditions. This measure includes providing (1) an understandable diagnosis and information about the nature of the physical structures involved (eg, function of the temporomandibular joint, muscles, and nerves associated with temporomandibular function), (2) information about the physiologic basis for nociception and interpretation of pain by higher brain centers, (3) discussion of the role of biobehavioral factors (eg, guilt, anger, sleep, stress) in pain interpretation, (4) the purpose of treatment (management of symptoms), and (5) instruction on the importance of self-care as the foundation for symptom management.

Once the basic rationale for self-care is introduced, specific methods for self-care should be offered. One of the first strategies is to eat without increasing pain. This step involves avoiding hard or chewy foods that may strain the muscles of mastication. It also means limiting the size of food bites so that opening the jaw does not increase pain or the length of chewing time does not create discomfort. Chewing gum should generally be avoided, except in some individuals for whom short bouts of chewing may actually facilitate muscle function, improve mood, and reduce pain [18,19]. Learning to chew on both sides of the teeth, or at least alternating from side to side, is also important [20]. Additionally, chewing should be performed primarily with the back teeth rather than the front teeth. Eating habits should not result in increased pain and should be an early target for self-care.

Another strategy for self-care involves monitoring and controlling parafunctional activities. Patients must develop an awareness of oral habits that may contribute to dysfunction and learn ways to manage these habits. Teeth clenching or grinding is a common problem that can be managed during waking hours by learning appropriate rest positions for the mandible and tongue. Research data indicate that the muscles of mastication are most at rest when the teeth are not touching, the lips are relaxed (often not touching), and the tongue is relaxed with no pressure exerted on the tip of the tongue. Although the rest position of the tongue is commonly believed to be on the roof of the mouth, no scientific data support that assertion. In contrast, when the tongue is relaxed on the floor of the mouth, electromyographic (EMG) data indicate that the muscles of the temporalis and suprahyoid groups are more relaxed than when the tongue is on the roof of the mouth [21]. Patients can be instructed to self-monitor lip-teeth-tongue position regularly, stop clenching/grinding, and assume more relaxed positions as often as they are aware of the need to do so. Additional parafunctional activities to alter include nail biting, pencil chewing, cheek biting, or any other habit that may increase the activity of the jaw muscles. These learned habit patterns are important to control because they may contribute to orofacial pain and dysfunction.

The cervical muscles provide the platform on which masticatory muscles perform. Patients should be reminded that monitoring head and shoulder position is equally important for managing muscle activity in structures associated with jaw function. Just as prolonged usage of the masticatory muscles may lead to fatigue and pain, sustained forward head position may contribute to pain and dysfunction in the cervical/masticatory (trigeminal) system.

Self-care of the temporomandibular region also involves managing sustained activity of the jaw such as from singing, teaching/speaking, or playing a musical instrument. Along with sustained activities that may provoke or aggravate pain, opening the jaw wide should be avoided (eg,

oral surgery, yawn) until pain subsides. Although gentle stretching of the muscles can promote relaxation and reduction of pain [22], care should be taken when doing so to avoid tissue damage and the provocation of more pain. Patients must avoid actions or movements that strain or torque the mandible, such as when resting the chin on a hand or sleeping facedown on a pillow.

Another component of self-care is for patients to monitor pain symptoms to determine what influence environmental or personal factors may have. Pain diaries in which patients record level of pain and critical incidents may be particularly useful. Through self-monitoring, patients may become aware of daily routines or weather patterns (particularly temperature and atmospheric pressure) that may either reduce or incite pain. Moreover, patients may also identify behavioral or emotional triggers. Self-monitoring data often must be reviewed with patients because they may not be skilled at identifying patterns from their own data when they start treatment. One goal of self-care training is for patients to become careful students of their own behavior.

Three important dimensions of general functioning should be communicated to patients. First, these include the value of maintaining good nutrition through a well-balanced diet and controlling the problems associated with excessive caffeine use. If diet seems to be disrupted, nutritional consultation with a dietician or nutritionist may be appropriate. A small amount of caffeine (one to two cups of coffee in the morning) may not have a discernible effect on function, but significant amounts (three or more caffeinated beverages daily) may increase physiologic activation and negatively influence sleep. If patients are drinking excessive amounts of caffeine (caffeinated soft drinks are often overlooked as a source), care should be taken to help them slowly reduce the amount over a period of weeks to avoid withdrawal effects. Alcohol consumption should also be reviewed, as should smoking. If an individual is smoking, a smoking cessation program and support should be recommended. Obtaining adequate restorative sleep is the second domain of general functioning. Sleep onset and duration may be enhanced through the use of relaxation techniques; a recent National Institutes of Health (NIH) consensus panel affirmed the value of relaxation strategies for improving sleep in patients who have chronic pain [23]. Sleep environment should be quiet and comfortable; pillow and mattress should be conducive to good rest and multiple pillows may need to be used to obtain some measure of pain relief. Patients must understand that adequate sleep quality and duration (7–10 hours) are necessary to maintain optimal functioning. Finally, the value of regular physical activity should be introduced as a third dimension of good overall functioning. Clinicians managing patients who have orofacial pain should not ignore the fact that routine walking or other regular physical activities that improve aerobic capacity provide a physiologic foundation for restoring healthy functioning is an important biobehavioral intervention.

The regular use of brief relaxation techniques and diaphragmatic breathing are also important ways to control physical functioning. Brief relaxation strategies include resting the body in relaxed positions [24] and taking periodic relaxation breaks (ranging from a few moments to 20–30 minutes) throughout the day. These relaxation strategies can be introduced in a short time, and patients can readily incorporate these strategies into daily routines. When patients find relaxation a significant challenge, more extensive training and coaching in relaxation are necessary and are discussed later. Diaphragmatic breathing is a powerful relaxation strategy that has been used for many centuries. Patients experiencing pain are often not using the diaphragm in their normal breathing patterns and may derive substantial benefit from diaphragmatic breathing entrainment. Readers are referred elsewhere for more extensive discussion of breathing entrainment [25], because relearning diaphragmatic breathing as the primary means of respiration may require technical coaching and deliberate practice. Moreover, medical conditions (eg, diabetes, cardiovascular disease, epilepsy) may be very sensitive to changes in respiratory function and require knowledge and consent of primary physician, especially when medications are needed for control. Although diaphragmatic breathing may be readily adopted as a primary self-care strategy, it is not easily acquired by many patients who have chronic pain unless they are carefully trained.

Another valuable dimension of self-care involves appropriate medication, both prescribed and over-the-counter. Several issues should be discussed with patients, including the use of complementary or herbal medicines, because of the potential for interactions with medications that might be prescribed. The first issue involves using medication to potentially treat symptoms of the disorder rather than the cause, such as when extensive parafunctional behavior is present. Medication can inadvertently prolong inappropriate and dysfunctional

activity through pain-relief without altering the pain-producing activity itself. Sometimes this situation is inevitable and required for job function or maintenance of personal responsibilities. As a long-term management strategy, however, this approach may not be in the patient's best interests, and effective self-care instructions must include this discussion so that patients understand the appropriate function of medication and attempt to alter behavioral habits that may be creating or maintaining pain conditions. Another dimension of appropriate medication self-care is compliance with prescribed medication regimen. Under- or overuse of medications must be monitored carefully so that patients can obtain maximum benefit from the medication. Clinicians must be sensitive to the significant problem of noncompliance with medication use and discuss this with their patients. Although medications may offer substantial promise for pain relief, they must be used judiciously and with appropriate patient education [2,26].

Relaxation training

Relaxation training involves instruction to achieve deep levels of both physiologic and psychologic rest. The most common approach to relaxation is progressive relaxation training, wherein individuals learn to relax systematically the major muscle groups in the body [27]. This technique is typically performed using muscle tension exercises (10–15 seconds) followed by periods (60 seconds) of muscle relaxation [28]. These exercises are introduced by a trained therapist over 4 to 12 sessions and generally include daily home practice exercises. Several variants exist to the basic progressive relaxation methods [29], including the mindfulness approach [30]. Each technique, whether it involves one or multiple sessions, however, requires the presence of a trained therapist to introduce the skills to the patient. The goal of relaxation training is to provide individuals with skills to control levels of muscle activity during daily activities. The method of relaxation is not as important as its acceptance to the patient; it is important to find a match between the patient and technique.

Muscle stretching procedures provide an alternative to muscle tension exercises for teaching progressive relaxation [22]. With this approach, individuals use gentle muscle stretches (15–20 seconds) rather than tensing the muscles to learn how to systematically manage muscle tension. Data from clinical studies of the stretch-based approach to progressive muscle relaxation indicate that persons who have temporomandibular disorders are able to relax important cervical/masticatory muscles using this technique [22]. Its use also improves salivary immune activity (immunoglobulin A) that may enhance first-line defense against infections involving the oral cavity [31]. Review of available clinical research by an NIH consensus panel found that relaxation training is an efficacious clinical management strategy for patients experiencing chronic pain [23].

Biofeedback training

Biofeedback training involves the use of an external monitoring device to provide information to individuals about some aspect of body function. This feedback can take the form of muscle activity (EMG), sweat gland activity (electrodermal activity), skin temperature (generally hand or foot temperature), or respiration (end-tidal carbon dioxide level, oxygen saturation, or respiration rate) to learn volitional control over that particular physiologic function. The most common biofeedback strategy used in orofacial pain is EMG training [32,33]. This approach consists of attaching sensors to a target muscle group, most commonly the masseter, and teaching individuals over a series of sessions to relax the muscle group for an extended period. Consistent practice with the biofeedback monitor provides patients with volitional control of physiologic functions. The use of biofeedback training is predicated on the value of an individual generalizing the skills of relaxation from the target muscle group used for the training to other muscle groups so that an overall skill of relaxation is achieved. Biofeedback training is essentially a way for covert activity to be brought to conscious awareness. It is valuable for patients who do not seem to have an awareness of body functions that may be dysregulated and contributing to the maintenance of their pain conditions. Research data on the efficacy of EMG biofeedback training for patients who have chronic pain indicates that its use is appropriate and can offer patients significant symptom relief [23,34]. It is important, however, to distinguish the use of biofeedback as an approach to teach conscious management of muscle tone during diurnal activities from its use during nocturnal activities in which long-term effectiveness has not been shown [35].

Cognitive therapy training

Links exist between the thought patterns of an individual and their physical and emotional

functioning. The central tenet of cognitive therapy training is to become aware of ongoing thought processes and then restructure thinking in a direction of greater adaptability and positive emotional functioning [36]. Cognitions or thoughts serve as the rules or guides for behavior and feelings. For patients who have chronic pain, the patterns of thoughts linked to feelings and behaviors associated with the ongoing pain experience must be identified. Often, cognitive patterns that develop or are intensified because of pain can contribute to the maintenance or magnification of the pain conditions. Cognitive therapy is directed toward teaching an individual improved self-awareness of ongoing cognitive functioning and strategies for altering dysfunctional thought processes. This approach to helping patients experiencing pain is generally performed by professionals with considerable training and experience in cognitive therapy, although an understanding of the basic processes may enable clinicians treating patients who have orofacial pain to make a more informed referral for cognitive therapy.

Dysfunctional thought processes in patients experiencing chronic pain may be related to the pain itself, depression related to or independent of the pain, somatization, or other emotional states (eg, anxiety). These dysfunctional thought processes are automatic in that patients engage in them as a matter of habit without deliberation. They often occur so rapidly that patients initially have no awareness of their presence or influence. These automatic thoughts include loss of objectivity (''the pain is from a disease they haven't found yet and is going to kill me''), overgeneralization (''the doctor says it is all in my head''), catastrophizing (''I am going to be suffering with this for the rest of my life''), selective attention (''I cannot do anything to ease this pain''), and ''all or none'' (dichotomous) thinking that interprets life events from an extreme point of view (''pain medicine never works for me''). The purpose of cognitive therapy is to teach individuals to recognize these types of dysfunctional thoughts and make deliberate changes in them, thereby asserting personal control. For example, if people hear themselves say, ''The pain is from a disease they haven't found yet and is going to kill me,'' they would first rate the strength of the belief in that statement. They would then explore the evidence for this belief; state an alternative, such as ''The doctors have said this is a condition that is not life-threatening but will follow an up-and-down course over time''; and act in a manner consistent with the latter statement. In cognitive therapy, patients are taught to listen for and challenge automatic statements and then substitute an appropriate alternative statement that will generate new patterns of actions and feelings. Jensen and colleagues [37,38] have shown that changes in cognitions are associated with improvement in the management of chronic pain.

Research data on using strictly cognitive therapies with patients who have chronic pain are generally confounded by the use of behavioral techniques, such as relaxation training and habit changes [39,40]. Hence, the common phrase seen in the literature is *cognitive behavioral therapy* (CBT). Research data on CBT methods in patients who have chronic orofacial pain indicate efficacy, especially over 6- to 12-month periods [40]. The efficacy of CBT programs are often similar to standard orofacial pain treatments (education, medication, oral appliance) immediately after treatment. As the time lengthens from the last treatment, however, CBT has shown significantly improved gains in patient functioning compared with standard orofacial pain treatments only [39–41].

Examples of programmatic biobehavioral interventions

Dworkin and colleagues [40] developed a brief CBT-based treatment program based on the foundations for cognitive therapy outlined earlier. This program consists of six sessions delivered by a trained health care provider. These sessions include introduction and enlistment of patients (session one); education on the biobehavioral model, behavioral training in self-care and relaxation skills, including diaphragmatic breathing training, cognitive therapy (restructuring, control of thoughts and feelings along with training for depression and somatization management using an ABCD approach that includes focusing on activating events, beliefs/thoughts, consequences or emotions/physical consequences that beliefs evoke, disputing or challenging maladaptive thoughts), and coping skills that include strategies for managing relationships with health care providers (sessions two to five); and follow-up to assist in long-term maintenance of cognitive/behavioral change and to develop strategies to manage expectations and relapse (session six). This CBT training is typically added to a program of standard treatment that includes use of an intraoral appliance, medications (typically nonsteroidal anti-inflammatory drugs), jaw range-of-motion exercises, habit

change (parafunctional activities and eating behavior), and use of heat/cold packs. Results from clinical trials that include long-term follow-up (6–12 months) data showed that CBT-intervention causes a significant decrease in pain self-reports and pain interference in daily activities. These decreases are in addition to those obtained with standard treatment.

Turk and colleagues [39] evaluated the combination of an intraoral appliance, stress management and biofeedback (eg, relaxation and stress coping training), and cognitive therapy (recognition of dysfunctional thoughts and strategies for changing those thoughts) for treating patients who have temporomandibular disorders who are identified as having high levels of pain and interference in normal activities caused by pain, emotional distress, and limited personal control. The stress management and biofeedback intervention consisted of six sessions of relaxation training, EMG biofeedback from the masseter muscle region to assist in learning relaxation skills, and information and training in using specific self-regulation skills for controlling pain. The cognitive therapy involved recognizing distortions in cognitions and maladaptive thought process that would intensify helplessness, hopelessness, and lack of personal control. Moreover, patients were taught strategies to alter and decrease these dysfunctional thoughts. Treatment results showed that persons undergoing this combined program experienced reductions in pain, depression, and medication use that continued to improve during long-term (12 months) follow-up.

In a recent randomized clinical trial, Carlson and colleagues [2] evaluated an alternative biobehavioral intervention model. Based on clinical research examining the characteristics of individuals who had chronic masticatory muscle pain [42], a physical self-regulation protocol was developed to provide (1) an explanation of pain processes using recent neuroscience findings and help patients develop personal ownership of the pain problem; (2) proprioceptive awareness training (use of posturally relaxed positions; recognition and control of nonfunctional tooth contact, clenching, and grinding; gentle flexion/extension movement of head; and reduction of upper back muscle tension); (3) regular use of relaxation training in normal routines; (4) sleep hygiene instructions; (5) fluid, nutrition, and exercise management; and (6) diaphragmatic breathing entrainment. This program was presented within two 50-minute sessions and participants were evaluated at 6 and 26 weeks after treatment. Results indicated that significant reductions in pain severity and life interference from pain were obtained, along with improvements in perception of control and incisal opening without pain at 6 weeks after treatment initiation. These results were maintained or improved at the 26-week evaluation and were obtained without any other physical treatments from the orofacial pain practitioner. The physical self-regulation program provides additional evidence that short-term biobehavioral interventions can provide significant relief of temporomandibular dysfunction.

Stepped model for biobehavioral care

As in other areas of medicine, the use of a stepped management plan has a place in the biobehavioral treatment of orofacial pain conditions. The use of self-care and brief interventions to address biobehavioral issues could be regarded as a first step in the management of orofacial pain conditions. The second level of intervention might include more advanced training in self-regulation through exposure to alternative relaxation techniques, such as autogenic training, skin temperature biofeedback, or end-tidal carbon dioxide feedback. These strategies represent time-limited interventions for acquiring skills to improve self-control of physical and mental functioning. For some individuals, a third level of intervention might be appropriate. As indicated earlier, a significant number of persons who have orofacial pain also have comorbid psychological dysfunction that may persist even after level one and two therapies have been provided. For those individuals, more in-depth individual or group psychotherapy may be warranted to address issues that may contribute to the maintenance of the orofacial pain condition. When persons who have severe depression, anxiety conditions (generalized anxiety, phobias, or post-traumatic stress disorder), personality issues, or other identifiable problems continue to experience unmanageable orofacial pain, medications or psychotherapy may be indicated. Management of psychologic issues (eg, grief, conflict, fear, inappropriate boundaries) can often best occur within the context of a therapeutic relationship in which a trained therapist enables individuals to work through problems using a set of techniques and principles (psychotherapy) based on sound clinical research. Psychotherapy to address biobehavioral issues would not be appropriate nor would it be cost-effective for every patient experiencing orofacial pain. However, some patients must have access to and engage in treatment for their specific

psychosocial issues. Therefore, psychotherapy can be viewed as an adjunct to other self-care and short-term interventions that have been unsuccessful in symptom management [43].

To take full advantage of biobehavioral care, whether to clarify diagnostic issues or deliver many of the specific interventions, including psychotherapy, clinicians treating orofacial pain who are not working in a multidisciplinary environment with biobehavioral specialists available may want to refer patients to these experts (eg, clinical psychologist, psychiatrist) for evaluation and treatment. The referral process is important for successfully incorporating biobehavioral specialists into the treatment team, and requires patients to actually follow-up with the evaluation and pursue treatment from these experts. A first step to successful referral is helping patients develop a biobehavioral understanding of their orofacial pain condition, which often means providing a clear and direct explanation of how cognitive, behavioral, and emotional issues influence pain perception. It is important for clinicians to acknowledge that patients' pain experience is real and not "all in their head." In communicating this to patients, clinicians must listen and let patients know they have listened. Although listening requires significant time and energy, it is essential to providing optimal patient care and successful referral to biobehavioral specialists. The next step in the process is to communicate to patients that they have problems (eg, learning to manage life stress) and working with someone who is skilled at helping to solve these problems can be helpful. Clinicians can then describe the expertise of the biobehavioral clinician and take the steps necessary to foster successful referral. These steps would include making the appointment with the biobehavioral specialist and then helping patients plan how they can keep that appointment. To address psychosocial issues that may be maintaining or intensifying orofacial pain conditions, clinicians may need to enlist the aid of colleagues in clinical psychology, psychiatry, or behavioral medicine.

Cost of biobehavioral management

The cost of incorporating biobehavioral principles into the management of orofacial pain conditions has two dimensions. The first dimension involves who will pay for the biobehavioral clinician's services. In the case of third-party reimbursements, the task is to provide insurance companies with appropriate diagnostic and clinical procedure codes. Working within the patient's insurance coverage is challenging because it often has differential reimbursement schedules for medical versus psychologic services. One issue that cannot be ignored is the question of medical offset costs. Without appropriate biobehavioral treatments, patients may seek care from multiple medical practitioners which will result in substantial medical costs that may dwarf the costs associated with even an extensive course of biobehavioral interventions. For example, in a recent randomized clinical trial of a biobehavioral/self-regulation strategy for chronic orofacial pain compared with standard dental care, the cost of the biobehavioral intervention was less than half the cost of the traditional dental approach. Moreover, a greater long-term reduction in pain and improvement in functioning was seen among patients who were exposed to the biobehavioral intervention [2]. The costs of a biobehavioral intervention are generally more than offset by a reduction in total medical costs.

A second dimension is the cost to the patient of initiating and maintaining change. In a recent study of the cost of self-regulation, participants were asked to exert self-control for a brief period in a challenging situation [44]. After exposure to this situation (eg, not being able to eat when encountering a powerful stimulus to do so), participants were notably fatigued and less efficient in performing cognitive and physical tasks. Similarly, the act of self-regulation for a patient experiencing orofacial pain probably has cognitive, emotional, and physiologic costs. Patients should be forewarned that the costs of self-regulation, or change, are significant. Although arguably continuing to experience orofacial pain is also costly, patients may be reluctant to engage in the process of change because the perceived costs may be too much. The author is reminded of the expression, "everybody wants to grow; nobody wants to change," which communicates the challenge of helping patients negotiate the transitions from their current situations to better management of their presenting complaints.

Summary

This article presents an overview of treatment planning for psychologic and behavioral issues related to chronic orofacial pains. These chronic pain conditions require considerable professional skills to deliver effective long-term care. Clinicians managing patients experiencing pain must have an understanding of the role that biobehavioral

issues play in the onset and maintenance of orofacial pain. Even more important is for clinicians to have skills that enable effective biobehavioral interventions to be directed toward managing the pain condition, whether those skills involve making an effective referral or providing professional skills directly. Successful outcomes in chronic orofacial pain management often require a multidimensional approach to treatment because of the complexity of dysfunctions within the trigeminal system. The principles and procedures outlined in this article can serve as a guide for the development of a biobehavioral management approach for orofacial pain conditions.

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Pharmacologic Management of Temporomandibular Disorders

Elliot V. Hersh, DMD, MS, PhD[a,*],
Ramesh Balasubramaniam, BDSc, MS[b], Andres Pinto, DMD, MPH[b]

[a]*Department of Oral Surgery and Pharmacology, University of Pennsylvania, School of Dental Medicine, 240 South 40th Street, Philadelphia, PA 19104-6030, USA*
[b]*Department of Oral Medicine, University of Pennsylvania, School of Dental Medicine, 240 South 40th Street, Philadelphia, PA 19104-6030, USA*

The pharmacologic management of pain related to temporomandibular disorders (TMDs) should ideally be driven by therapeutic efficacy and safety established in one or more well-controlled randomized clinical trials [1]. For the US Food and Drug Administration (FDA) approval of new analgesic agents, this typically implies the use of a double-blind, placebo-controlled design in which medication is randomly allocated to study patients. Evidence supporting the analgesic efficacy and tolerability of nonsteroidal anti-inflammatory drugs (NSAIDs) and combinations of aspirin, acetaminophen, or ibuprofen with opiates for relieving acute postsurgical dental pain is abundant throughout the scientific literature and these studies have often been significant parts of successful new drug applications submitted to the FDA in obtaining general acute pain indications for these agents [2–10].

As illustrated in Fig. 1 [11], although there are theoretically numerous targets for relieving TMD-associated pains, evidence-based literature clearly establishing the efficacy and safety of any of these drugs in the TMD population is limited at best [12]. Often decisions regarding the use, type, and dose of medication to use in these patients are made from uncontrolled clinical reports claiming efficacy, poorly controlled clinical trials, and well-controlled clinical trials in a completely different pain population, such as those having acute postsurgical dental pain, arthritic pain, chronic lower back pain, and neuropathic pain.

The goal of prescribing drugs in the management of chronic TMD pain is not to cure the disorder but is aimed at helping patients manage their discomfort or dysfunction for extended periods of time often in concert with other therapies (ie, physical therapy, appliance therapy) or until a more definitive treatment (ie, surgery), or simply time itself, either eliminates the pain or reduces it to a level at which it is not overly burdensome to the patient [13]. The remainder of this article is devoted to pharmacologic agents that have been used in the treatment of TMD with a special emphasis on clinical trials that either support or refute their efficacy.

Nonsteroidal anti-inflammatory drugs

NSAIDs can be grouped as being nonselective COX inhibitors (that is, they inhibit cyclooxygenase-1 [COX-1] at least as readily if not more so than they inhibit COX-2), semiselective COX-2 inhibitors (meaning they are two- to threefold more selective in blocking COX-2 over COX-1), or highly selective COX-2 inhibitors (meaning they are sevenfold or more selective in their COX-2 blocking activity) (Box 1) [14]. Although chronic use of highly selective COX-2 inhibitors (because they spare COX-1 cytoprotective prostaglandins) have been associated with a significantly lower incidence of serious gastrointestinal (GI) events, including ulcerations, perforations, and

* Corresponding author.
E-mail address: evhersh@pobox.upenn.edu (E.V. Hersh).

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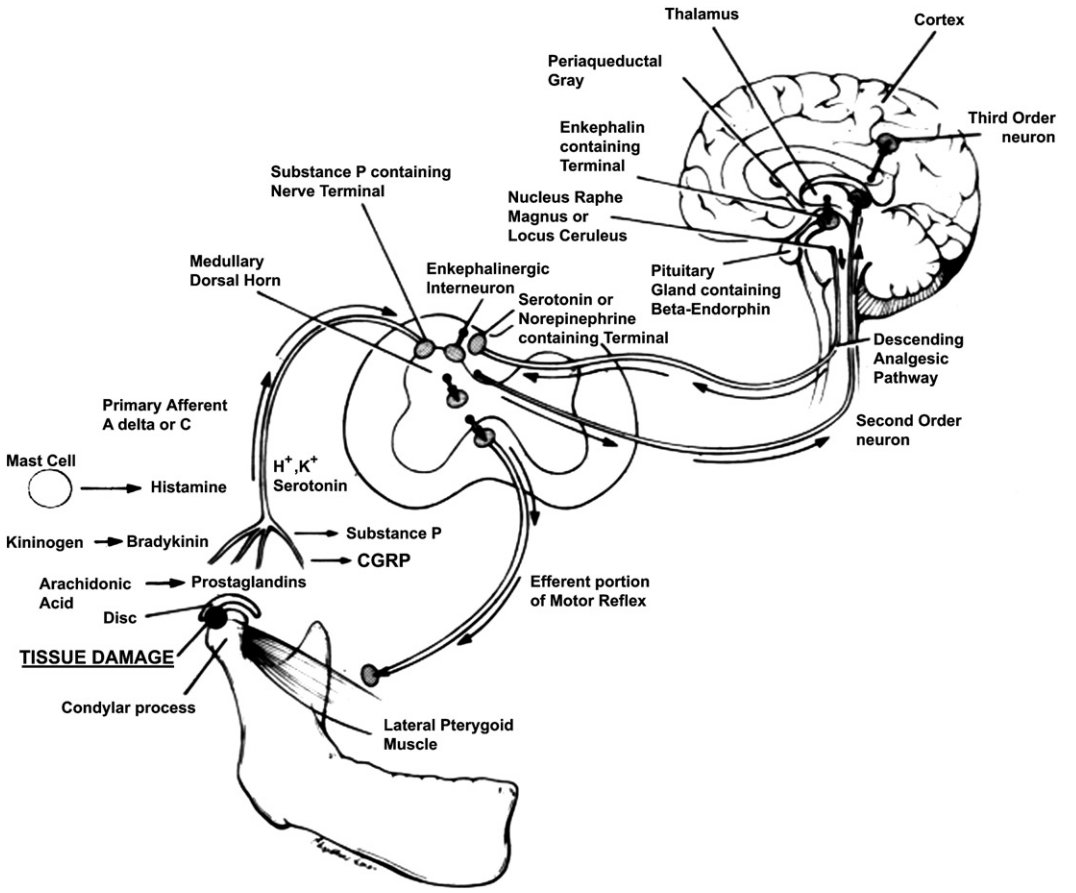

Fig. 1. Peripheral inflammatory mediators, ascending neuronal pathways, central neurotransmitters, neuromuscular reflex arcs, and descending opiate pathways that influence TMD pain. Potential targets of drug action include an inhibition of peripheral prostaglandin synthesis for NSAIDs and corticosteroids, an inhibition of peripheral substance P and calcitonin gene–related peptide release for capsaicin, a blockade of neuronal transmission by C and A delta pain fibers for transdermal lidocaine, a reduction of spinal and medullary substance P release and an activation of descending analgesic pathways for opioids, a decrease in efferent motor reflexes to muscles of mastication for benzodiazepines and skeletal muscle relaxants, an increase in CNS serotonin and norepinephrine for TCAs, and a diminution of second- and third-order neuron hyperactivity for gabapentin. (*From* Hersh EV. Mechanisms of pain. In: Pertes RA, Gross SG, editors. Clinical management of temporomandibular disorders and orofacial pain. Carol Stream (IL): Quintessence Publishing Co., Inc.; 1995. p. 35–44; with permission.)

bleeds, than nonselective or semiselective NSAIDs [15–17], their chronic use compared with placebo is associated with increased cardiovascular risk, especially in patients who have comorbid factors of older age, hypertension, coronary artery and atherosclerotic disease, and previous cardiovascular events [18,19]. In the most fragile of these patients (those who had just undergone coronary artery bypass surgery), even short-term administration of highly selective COX-2 inhibitors was associated with a significantly higher incidence of serious cardiovascular events [20] than those not treated with these drugs for postoperative pain. The results of these studies, along with an unusually high incidence of serious skin reactions for valdecoxib, have lead to the removal of rofecoxib and valdecoxib from the worldwide marketplace. The recent FDA disapproval of etoricoxib further validates the FDA's safety concerns for this class of drugs.

Although the efficacy of NSAIDs for acute postsurgical dental pain and chronic arthritic pain has been supported by numerous well-designed clinical trials, only a single recently published study by Ta and Dionne [21] has clearly demonstrated efficacy with one of these agents compared

Box 1. Some commonly prescribed nonsteroidal anti-inflammatory drugs

Nonselective COX inhibitors
Aspirin
Diflunisal (Dolobid)
Ibuprofen (Motrin, Advil)
Ketoprofen (Orudis)
Naproxen (Naprosyn, Aleve)
Meclofenamate (Meclomen)
Piroxicam (Feldene)

Semiselective COX-2 inhibitors
Diclofenac (Voltaren, Cataflam)
Etodolac (Lodine)
Meloxicam (Mobic)

Highly selective COX-2 inhibitors
Celecoxib (Celebrex)
Etoricoxib[a] (Arcoxia)
Lumiracoxib[a] (Prexige)
Rofecoxib[b] (Vioxx)
Valdecoxib[b] (Bextra)

[a] Available in Europe
[b] Removed from worldwide marketplace

with placebo. Patients who have pain attributable to temporomandibular joint (TMJ) disc displacement were randomized to a 6-week course of either naproxen 500 mg twice a day, celecoxib 100 mg twice a day, or placebo twice a day. From weeks three through six, pain intensity as measured on a visual analog scale (VAS) was significantly reduced in the naproxen compared with placebo, whereas the reduction in pain with celecoxib was no different than placebo. In addition naproxen was significantly more efficacious than celecoxib at week four. Maximal comfortable mouth opening at week six was also significantly greater in the naproxen group than the two other treatment groups [21]. The authors did note that there was approximately a 40% increase in nonserious GI events (dyspepsia, pain) in the naproxen group compared with celecoxib or placebo.

Other studies, however, have not been able to distinguish ibuprofen 2400 mg/d for 4 weeks or piroxicam 20 mg/d for 12 days from placebo in TMD patient populations who had chronic myogenous pain [22,23]. Although the authors of another study reported that topical diclofenac formulated with dimethyl sulfoxide applied four times a day was equally as efficacious as oral diclofenac sodium 50 mg twice a day in subjects who had pain and tenderness attributable to osteoarthrosis of the joint [24], the study was not placebo controlled or blinded, and thus it is impossible to ascertain whether the reduction in pain and the improved function experienced by patients in both groups was truly an effect of the drug.

Because NSAIDs do represent first-line drugs for many clinicians treating TMD pain, additional well-designed clinical trials are needed. Patients who have early painful disc displacement, capsulitis, synovitis, and arthritis associated with the TMJ may benefit the most from these drugs. These medications may also be used as supplemental treatments to an overall management strategy in cases of masticatory myalgia and myofascial (trigger point) pain. An around-the-clock dosing regimen, especially during the first few weeks of treatment, better facilitates the analgesic/anti-inflammatory effects of these drugs. These drugs, especially when used chronically at relatively high doses, are not without toxicity. Besides the increased risk for cardiovascular toxicity with highly selective COX-2 inhibitors and serious gastrointestinal events with nonselective and semiselective NSAIDs, the entire group can also decrease renal function leading to water and sodium retention with concomitant hypertension, especially in individuals already taking antihypertensive drugs [3,25,26]. Of special note, because chronic pain patients are often taking antidepressant drugs, the results of recent epidemiologic studies have indicated a startling increase of up to 16-fold in the risk for upper GI bleeds in patients concomitantly taking NSAIDs and selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine (Prozac), paroxetine (Paxil) and sertraline (Zoloft) [27,28].

Corticosteroids

Corticosteroids are powerful anti-inflammatory agents that can be administered orally or injected directly into the joint space. They have multiple actions that contribute to their anti-inflammatory effects, including a blockade of phospholipase A_2, which decreases the production of proinflammatory prostaglandins and leukotrienes, and decreases the number and activity of proinflammatory cells, including lymphocytes, eosinophils, basophils, and macrophages. Like NSAIDs, there is a relative dearth of well-controlled clinical trials

demonstrating their therapeutic benefit in the TMD population. A recent study concluded that in patients who have TMJ closed lock, medical management with a 6-day regimen or oral methylprednisolone (Medrol DOSEPAK) followed by 3 to 6 weeks of NSAID therapy worked equally as well over a 5-year period as arthroscopy or open joint therapy in reducing jaw pain and dysfunction as measured by the Craniomandibular Index [29]. Although the results of this study suggest a trial of nonsurgical conservative therapy benefits many of these patients, the lack of a placebo control group makes it difficult to discern how much the drugs and the surgical interventions really contributed to the therapeutic effect reported.

In uncontrolled case studies of arthritic TMJs, intra-articular steroids, including 0.7 mL of methylprednisolone acetate 40 mg/mL (Depo-Medrol) combined with local anesthetic in children or 1 mL of triamcinolone acetonide (Kenalog-40) or 1 mL triamcinolone hexacetonide (Aristospan-20) in adults, seemed to significantly reduce pain and improve function [30,31]. Reports of articular cartilage destruction, infection, and disease progression because of the overly aggressive use of intra-articular steroids confirm that this mode of drug delivery should only be used for the most severe cases and frequent injections must be avoided [32]. Likewise, oral corticosteroid use should be limited to no more than 2 weeks because of the well-known risks of decreased resistance to infection, elevations in blood glucose, osteoporosis, and suppression of the hypothalamic-pituitary-adrenal axis. Patients who have severe disc interference disorders and inflammatory conditions, such as capsulitis, synovitis, and TMJ osteoarthritis/rheumatoid arthritis, may benefit the most from this class of drugs.

Opioids

The use of opioids (narcotic analgesics) in chronic nonmalignant pain remains controversial because of their potential for dependence, abuse, and diversion, yet their use by many chronic pain experts is considered not only acceptable but also warranted in carefully selected patients [33,34]. The chronic use of oral morphine, oxycodone, hydromorphone, and transdermal fentanyl patches has demonstrated effectiveness in patients who have chronic lower back pain from degenerative arthritic and disc disease, although bouts of breakthrough pain are still common in these patients [35]. In addition, the development of tolerance during chronic use of these agents is common; thus an increase in opioid dosage may be required to maintain analgesic efficacy.

Most state dental boards consider the routine prescribing of chronic opioid therapy in patients who have TMD to be a "red flag," and their use as first-line drugs in any patient who has TMD is strongly discouraged. The lack of clinical trials evaluating opioids in the chronic orofacial pain population further compounds this problem. In addition, it is well known by many oral and maxillofacial surgeons and general dentists that drug-seeking patients often complain of TMD pain. The round-the-clock use of opiates in patients who have documented intractable TMD pain when surgery and implants have failed seems reasonable in skilled hands, however [36]. Before prescribing an opioid, the patient's level of pain and its interference with the quality of life should be determined. It is imperative that an assessment of previous drug use and past and current psychiatric status also be determined, often in consultation with a behavioral medicine specialist. Long-acting or sustained-released formulations of opiates, such as morphine sulfate (MS Contin) and oxycodone (OxyContin) should limit cycles of breakthrough pain and opiate withdrawal symptoms. Careful upward dose titrations to achieve efficacy and downward titrations to reduce side effects require frequent follow-up visits, at least once every 2 weeks at the outset [37]. One classic opioid side effect that often does not diminish with chronicity of use is constipation, and the oral and maxillofacial surgeon must be prepared to deal with this through diet modification (plenty of fluids and fiber), exercise, and occasional stool softeners and laxatives. The establishment of an "opioid contract" between patient and doctor wherein the responsibilities of both are clearly outlined is also recommended [37].

One novel use of morphine in the patient who has TMD is its intra-articular injection as part of an arthrocentesis or arthroplasty procedure, or as the sole treatment for intracapsular disorders [38–40]. It has been reported that a peripheral subtype of the mu opiate receptor exists in the TMJ tissues, possibly explaining the benefits of this treatment modality [41]. Although clinical observations have lead to claims of long-term reductions in pain with a combination of arthrocentesis and 10 mg morphine infused into the joint [38], clinical trials that also used saline controls have at best only shown a short-term benefit [39,40].

Another opiate-like drug that deserves discussion is tramadol, which is formulated as both a single entity (Ultram) and combined with acetaminophen (Ultracet). Although the efficacy of tramadol 100 mg in the absence of acetaminophen has been disappointing in postsurgical dental pain patients [42,43], the combination of acetaminophen 650 mg plus tramadol 75 mg seems efficacious in this patient population [43,44]. In various chronic pain syndromes, including osteoarthritis, lower back, fibromyalgia, and diabetic neuropathy, both formulations of tramadol seem effective [45–50]. Whether there is a true advantage of one formulation over the other in patients who have chronic pain has not been adequately studied, nor have there been any randomized controlled trials published in the TMD pain population. It has been suggested that when tramadol is combined with acetaminophen an opiate-sparing effect occurs compared with using tramadol alone resulting in better tolerability [51].

There are some important pharmacokinetic nuances of tramadol that the oral and maxillofacial surgeon should be aware of. It is now widely accepted that both the parent molecule through inhibition of 5-HT and NE neuronal reuptake, and its demethylated metabolite (*O*-desmethyl tramadol or M-1) through opiate receptor activation, contribute to the analgesic efficacy of the drug [52–54]. Because the cytochrome P-450 2D6 (CYP2D6) isoenzyme is responsible for the conversion to the active demethylated metabolite, any drug that is a CYP2D6 inhibitor, including the antiarrhythmic quinidine and antidepressants of the SSRI class, such as paroxetine (Paxil), could reduce the analgesic activity of tramadol [55,56]. Of equal importance is that tramadol must be used with extreme caution in patients taking any of the antidepressant classes, including tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and SSRIs, because of case reports implicating the combinations of producing a serotonin syndrome manifested by tremors, convulsions, muscle rigidity, and hyperexia [57,58].

Benzodiazepines

Benzodiazepines bind to specific receptors in the central nervous system (CNS) and increase the efficiency of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) for its receptor resulting in the inward movement of negatively charged chloride ions through nerve cell membranes. The resulting hyperpolarization and neuronal inhibition is believed to contribute to the anxiolytic, sedative, and hypnotic properties of these drugs, and also may explain their ability to reduce polysynaptic reflex pathways innervating skeletal muscle. Some benzodiazepines, most notably diazepam (Valium) and clonazepam (Klonopin) possess potent anticonvulsant activity. The potential benefits of these drugs in reducing muscle contraction that can lead to pain in the patient who has TMD are thus attributable to actions within the CNS and not to direct relaxation of skeletal muscle. Improvement of sleep patterns in subjects who have chronic pain also seems to be beneficial in breaking the pain cycle [59]. Some members of this class, such as diazepam and clonazepam, have long half-lives and are first metabolized to active metabolites, which greatly increases their duration of action. Others, like oxazepam (Serax), alprazolam (Xanax), and triazolam (Halcion), have short half-lives and are either devoid of or are converted to short-lived active metabolites [60].

There are several well-designed studies that support the efficacy and safety of benzodiazepine use in patients who have a significant muscular component to their TMD pain. In one double-blind, placebo-controlled study of subjects who had chronic myogenous jaw pain, those taking diazepam 5 mg four times a day for 4 weeks displayed a significantly greater decrease in their pain than those taking placebo [22]. In the same study ibuprofen 600 mg four times a day seemed devoid of benefit, whereas the combination of ibuprofen and diazepam provided somewhat better pain relief than ibuprofen alone. In another placebo-controlled trial in patients who had TMD who had failed appliance therapy and physical therapy, 1 month of clonazepam therapy (mean dose 0.375 mg) taken at bedtime also seemed effective compared with placebo [61]. In a cross-over study, however, short-term use of triazolam 0.25 to 0.5 mg over a period of 4 days, although significantly improving sleep patterns, did not improve pain intensity or muscle tenderness compared with placebo [62]. The results of these studies taken together may suggest that longer-acting benzodiazepines with documented anticonvulsant activity, such as diazepam and clonazepam, may be more beneficial in relieving muscle pain in patients who have TMD than shorter-acting members of the group. It is evident, however, that more research concerning drug selection, drug dosage, and duration of therapy is needed.

Clinicians prescribing oral benzodiazepines should be aware of the likelihood of drowsiness

and psychomotor impairment induced by these agents. Peak blood levels of these drugs occurs when the patient is asleep if dosing is performed immediately before bedtime. Careful dose titration upward may also limit side effects [22,61]. The geriatric population is especially sensitive to the CNS depressant and memory impairment effects of this class of drugs because of a combination of decreased biotransformation, decreased clearance, and increased receptor sensitivity [63]. Reducing typical doses at least in half seems prudent in this population. In addition, several benzodiazepines, most notably alprazolam, diazepam, midazolam (Versed), and triazolam, are cytochrome P-450 3A4 (CYP3A4) substrates. Concomitant foods, such as grapefruit juice and Seville oranges, and drugs including azole antifungals, erythromycin, clarithromycin (Biaxin), and calcium channel blockers that inhibit the CYP3A4 isoform, can significantly reduce the metabolism of these benzodiazepines leading to elevated blood levels and enhanced CNS depression [55]. Although physical and psychologic dependence is known to occur with these agents, this potential can be minimized by limiting the course of therapy to no more than 4 weeks.

Nonbenzodiazepine sedative hypnotics

Improving sleep patterns in patients who have chronic pain may be beneficial in breaking the pain cycle [59], and sleep disturbances seem to correlate with the degree of pain severity and psychologic distress reported in patients who have TMD [64]. Eszopiclone (Lunesta), zolpidem (Ambien), and zaleplon (Sonata) represent several recently approved nonbenzodiazepine sedative hypnotics that seem to specifically bind to benzodiazepine receptors associated with the α-subunit of the $GABA_A$ receptor [65]. In addition to inducing sleep, sedative doses of eszopiclone and zaleplon seem also to be associated with muscle-relaxing activity [65]. Their abuse potential seems similar to that of benzodiazepines, however, and there is currently no evidence that directly supports their usefulness in the TMD population. In addition, reports of sleepwalking have occurred in patients taking zolpidem [66–68].

Ramelteon (Rozerem) represents the first FDA-approved melatonin receptor agonist indicated for the treatment of insomnia [69]. Although it seems to have little potential for abuse, its usefulness in patients who have chronic pain needs to be explored before any recommendations concerning its use can be made.

Centrally acting muscle relaxants

Familiar members of this class of drugs include carisoprodol (Soma), chlorzoxazone (Paraflex), cyclobenzaprine (Flexeril), metaxalone (Skelaxin), methocarbamol (Robaxin), baclofen (Lioresal), and tizanidine (Zanaflex). Like benzodiazepines, their muscle relaxation action takes place within the CNS by way of inhibition of polysynaptic pathways. Generally speaking these drugs have lower therapeutic indices than benzodiazepines [60], and thus must be used with extreme caution in patients who have significant comorbid depression. Although there are several double-blind, placebo-controlled trials that have demonstrated efficacy of these agents in patients who have lower back pain [70], these drugs have not been well studied in the TMD population [12]. In one open-label study lacking a placebo control, although patients who had TMD seemed to benefit from 1 week of orphenadrine citrate (Norflex) therapy, they did equally well with appliance therapy or diazepam [71]. As in previously described studies of other drug groups, the lack of a placebo control makes it difficult to ascertain the true benefit of the active treatments. Cyclobenzaprine has been shown to be superior to placebo in treating pain and reducing electromyographic recordings of muscle spasm in the cervical and lumbar back regions [72,73], suggesting a potential benefit in patients who have TMD with muscle contraction and spasm. In addition, a 3-week randomized controlled clinical trial in patients who had TMD reported that cyclobenzaprine 10 mg taken at night was statistically superior to either placebo or clonazepam 0.5 mg when added to self-care and education in the management of jaw pain on awakening [74] in the absence of any improvements in sleep quality.

Sedation is a prominent side effect of all members of the skeletal muscle relaxant class. With carisoprodol in particular, concerns of abuse potential are on the increase. During the year 2000, carisoprodol was ranked 14 on the list of 20 most-abused mood-altering substances in the United States [70], and thus should only be used in carefully selected patients. Cyclobenzaprine, unlike other members of this class, has a structure that resembles tricyclic antidepressants, and thus carries some additional side-effect liabilities that are prominent with this class of drugs, including xerostomia and tachycardia, both attributable to anticholinergic activity [60]. Like all drugs with prominent anticholinergic activity, cyclobenzaprine must be avoided in patients who have

narrow-angle glaucoma. To limit side effects it is recommended that muscle relaxants be titrated upward gradually, starting with bedtime use only.

Topical medications

FDA-approved topically applied agents that have potential usefulness in TMD pain include capsaicin 0.025% to 0.075% and the 5% lidocaine transdermal patch. Capsaicin is a derivative of the chili pepper and several randomized double-blind trials in osteoarthritis [75–77] and neuropathic pain [78] have demonstrated efficacy in these chronic pain populations. Its proposed mechanism of action involves a depletion of substance P and calcitonin gene–related peptide from peripheral afferent nerve endings. These neuropeptides have been isolated in the synovial fluid and tissues of patients who have symptomatic joints [79,80], as has the recently characterized capsaicin receptor known as the transient receptor potential channel–vanilloid subfamily 1 (TRPV1) whose activation is believed to be necessary for the release of these inflammatory and pain-provoking compounds [81]. Although the use of topical capsaicin has been proposed in patients who have TMD [37,82], surprisingly there are no clinical trials or even case-controlled studies evaluating its therapeutic effect (or lack of therapeutic effect) in the TMD population. From a safety profile the topical application of the drug is devoid of systemic toxicity, although patients must be counseled to expect a burning feeling during the initial applications of the drug; with continued application this unpleasant feeling will dissipate. Combining capsaicin with a topical anesthetic, such as benzocaine 20% in pluronic lecithin organogel may help reduce this burning sensation [83]. Capsaicin is probably best used as an adjunct to NSAIDs, benzodiazepines, or other systemic modalities.

The 5% lidocaine transdermal patch (Lidoderm) is currently FDA approved for the treatment of pain associated with postherpetic neuralgia. The patch is 10×14 cm in area and contains 700 mg of lidocaine, although only about 3% of this dose is absorbed resulting in peak blood levels of 130 ng/mL during the recommended 12-hour application, slightly more than that achieved following an injection of one-half cartridge of 2% lidocaine with epinephrine [84,85]. According to the manufacturer the patch can be cut into smaller sizes with scissors before removal from the release liner, which almost invariably has to be done for application to the TMJ dermal site. In addition to placebo-controlled trials in postherpetic neuralgia [86,87], the drug has also proven efficacious in other neuropathic pain states [88]. More recently, open label studies of the lidocaine patch have reported improvements in various pain qualities in patients who have chronic lower back pain and osteoarthritis [89,90]. Although there are no reported studies of its effectiveness in patients who have TMD, the onset of pain relief in other chronic pain syndromes is often seen within a few days, and thus it is possible that some patients who have TMD will benefit from this therapy.

Antidepressants

Antidepressants are grouped into three main categories: TCAs, MAOIs, and SSRIs (Box 2). Duloxetine (Cymbalta) and venlafaxine (Effexor), although classified as dual selective NE/5HT reuptake inhibitors (SNRIs), have activity that closely resembles that of the older tricyclic antidepressant drugs. TCAs and SNRIs block the

Box 2. Pharmacologic groupings of various antidepressants with common trade names

TCAs/SNRIs
Amitriptyline (Elavil)
Nortriptyline (Pamelor)
Desipramine (Norpramin)
Doxepin (Sinequan)
Duloxetine[a] (Cymbalta)
Imipramine (Tofranil)
Protriptyline (Concordin)
Venlafaxine[a] (Effexor)

MAOIs
Isocarboxazid (Marplan)
Phenelzine (Nardil)
Tranylcypromine (Parnate)
Selegiline (Eldepryl)

SSRIs
Fluoxetine (Prozac)
Paroxetine (Paxil)
Sertraline (Zoloft)
Citalopram (Celexa)
S-Citalopram (Lexapro)

[a] Duloxetine and venlafaxine are classified as dual selective serotonin and norepinephrine reuptake inhibitors.

reuptake of the central biogenic amines NE and 5HT back into presynaptic nerve terminals, allowing the neurotransmitters to stay in contact with their respective postsynaptic receptors longer, and over time (a few weeks) causing a down-regulation of these postsynaptic receptors. This relatively slow change in CNS receptor density is believed to correlate with the onset of antidepressant activity. Although the SSRIs have become the most widely prescribed group of agents for depression [91], largely because of a better side-effect profile than the TCAs and the lack of food restrictions (those containing tyramine) necessary with MAOI therapy, it is the TCAs and SNRIs that have shown the greatest benefit in patients who have chronic pain [92].

Although depression is often a comorbid feature found in chronic pain patients, in placebo-controlled trials of chronic lower back pain and postherpetic neuralgia, the TCAs imipramine and amitriptyline have demonstrated efficacy in depressed and nondepressed individuals [93–95], arguing for a distinct mechanism of action besides their antidepressant activity. Also supporting this notion is that their analgesic onset in patients who have chronic pain is often is more rapid than their mood-altering effects, and analgesic dosages have been reported to be lower than antidepressant dosages of these drugs [96–98]. Of 17 placebo-controlled trials reviewed by Monks and Merskey [96] in patients who had various chronic pain syndromes, including arthritic, diabetic neuropathy, low back, migraine headache, tension headache, psychogenic, neoplastic, and postherpetic neuralgia, in all but 2 of 3 lower back pain trials the tricyclic antidepressant produced clinically significant pain relief compared with an identical looking placebo. The trials lasted a minimum of 4 to 8 weeks and the time required for a statistically significant analgesic effect varied from 1 week until the end of the trial. Two recently published randomized placebo-controlled trials in patients who had painful diabetic neuropathy or fibromyalgia also demonstrated that the analgesic effect of the SNRI duloxetine was rapid (within 1 week), occurred at a relatively low dose (60 mg/d) and was independent of patient mood [97,98]. Of note is that duloxetine was recently granted FDA approval for the treatment of painful diabetic neuropathy. Whether the mechanism of analgesic action of TCAs and SNRIs involves increased central norepinephrine and serotonin availability, activation of endogenous opiate systems, improved sleep patterns caused by the sedative antihistaminic and anticholinergic effects of these drugs, peripheral modulation of inflammatory mediators and their receptors, or a combination of these processes is still open to debate [92,99].

Several placebo-controlled randomized clinical trials have reported efficacy of the TCA drug amitriptyline in patients who have TMD. In one study, 14 days of treatment with low-dose amitriptyline (25 mg/d) was significantly more effective than placebo in reducing pain intensity in women who had chronic TMD pain [100]. A second placebo-controlled study of low-dose amitriptyline (10–30 mg/d) also demonstrated significant improvement in pain intensity as measured by a VAS and the McGill Pain Questionnaire at 6 weeks and 1 year of treatment [101]. Both depressed and nondepressed subjects demonstrated improvement in this study.

Common side effects of TCAs and SNRIs include nausea, sedation, psychomotor impairment, xerostomia, and constipation [96–101]. These drugs must be absolutely avoided in patients taking concomitant MAOIs because the combination can lead to a potentially lethal serotonin syndrome consisting of confusion, fever, shivering, diaphoresis, ataxia, myoclonus, and severe hypertension [102].

Anticonvulsants

Although anticonvulsant medications haves typically been reserved for neuropathic pain, including that in the orofacial region, as TMD pain persists CNS changes, including the wind-up phenomenon of second- and third-order afferent neurons leading to central sensitization, may occur, making this class of drugs a potential therapeutic option [12]. Gabapentin (Neurontin) in particular is an attractive agent because of its relatively low side-effect profile compared with other anticonvulsants and its efficacy in placebo-controlled trials of various chronic pain syndromes [103–111]. The structurally related anticonvulsant pregabalin (Lyrica) has also demonstrated efficacy and favorable tolerability in neuropathic pain [112–117]. Both drugs are currently FDA approved for the treatment of pain associated with postherpetic neuralgia with pregabalin also being approved for the treatment of painful diabetic neuropathy.

A recently published randomized controlled trial in patients who had TMD of myogenous origin demonstrated that gabapentin significantly reduced spontaneous pain as reported on a VAS,

along with the number of tender sites in the temporalis and masseter muscles, compared with placebo [118]. The initial dose of gabapentin was 300 mg, with dose titrations upward of 300 mg every 3 days until pain relief was achieved or a daily maximum dose of 4200 mg was reached. Statistically significant reductions in spontaneous pain intensity occurred by week 8 and the number of tender sites by week 12 when the average dose of gabapentin was 3315 mg/d and 3426 mg/d, respectively. Although there were no statistically significant differences in the incidence of any particular side effect, dizziness, drowsiness, and memory impairment occurred somewhat more frequently in the gabapentin group than the placebo group, especially during dose titrations upward. These side effects, in addition to xerostomia, peripheral edema, and weight gain, have been the most frequent adverse events reported in other clinical trials of gabapentin and pregabalin [103,104,107–109,111–117]. Anticonvulsants may be particularly useful as adjuvant analgesics in TMD in patients who have a history of failed TMJ surgeries or those who have longstanding unremitting pain.

Summary

Although several pharmacologic strategies have been used in patients who have TMD pain, few have undergone the rigors of randomized controlled clinical trials. Based on the few trials that have been reported and the efficacy and safety of various agents in other chronic pain states, the following recommendations regarding drug therapy are made. In patients who have inflammatory pain, such as arthritis, capsulitis, or TMJ disc interference disorders, NSAIDs remain a rational first choice of drugs. Although naproxen currently is the only drug that has demonstrated efficacy in this patient group, there is no reason not to believe that other NSAIDs will show efficacy. If a particular NSAID does not show some benefit within 4 weeks, the drug should be discontinued because of the risk for significant GI or renal side effects in the absence of therapeutic benefit. In patients who experience GI distress with nonselective NSAIDs or who are at greater risk for serious GI events, semiselective COX-2 inhibitors, such as etodolac, provide a rational alternative. Because of the increased cardiovascular risk for all highly selective COX-2 inhibitors and the lack of proven efficacy of celecoxib in this patient population, this drug should be avoided in any patient who has cardiovascular risk factors.

In patients who have TMD with a significant muscular component to their pain, cyclobenzaprine seems effective; however, it is likely to induce side effects related to its anticholinergic activity. Nighttime dosing should limit psychomotor impairment complaints. Benzodiazepines that are long acting with anticonvulsant properties, such as diazepam and clonazepam, may be used in patients for whom cyclobenzaprine and other muscle relaxants are ineffective. These drugs are best dosed right before bedtime to avoid peak psychomotor impairment when patients are awake. Short-term, once-a-day use should limit dependency issues.

Although the topical agents capsaicin and transdermal lidocaine produce few if any systemic side effects, there is virtually no published information regarding their effectiveness in the TMD population. Because of their extremely favorable therapeutic index, however, their use is encouraged either as monotherapy or combined with systemic therapeutic interventions.

TCAs or anticonvulsants may be considered in patients who do not respond to NSAIDs, benzodiazepines, or muscle relaxants. Theoretically these drugs may be of greatest benefit in patients who have long-lasting pain in whom the phenomena of wind-up and CNS sensitization have occurred. TCAs and anticonvulsants, especially early in dosing, are likely to induce sedation, psychomotor impairment, and xerostomia.

The injection of corticosteroids directly into the joint space should only be used in patients who have severe pain and limitations in function attributable to intracapsular inflammation. Their overzealous use can result in joint destruction. Narcotic therapy should be reserved for the patient who has truly intractable pain. Because of the potential for abuse patients must be carefully selected and closely monitored.

If some clinical benefit is achieved, how long should patients be maintained on drug therapy? Patients for whom therapy, such as behavioral modification, appliance therapy, physical therapy, or TMJ surgery, greatly improves the quality of life should only use drugs on an as-needed basis. In other cases, however, when surgery is not an option (or required) or occlusal appliance therapy, behavioral modification, or physical therapy do not provide enough pain relief to allow the patient to experience a favorable quality of life, how long should a patient remain on

pharmacotherapy? Is it "forever," like many osteoarthritis patients, or are there groups of patients who can be weaned off drugs after several weeks or months and still maintain a high quality of life? Only additional well– thought-out studies in the TMD population will truly answer these questions.

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Technological Devices in the Diagnosis of Temporomandibular Disorders

Yoly M. Gonzalez, DDS, MS[a,*], Charles S. Greene, DDS[b], Norman D. Mohl, DDS, PhD[a,1]

[a]*Department of Oral Diagnostic Sciences, State University of New York at Buffalo, School of Dental Medicine, 3435 Main Street, Buffalo, NY 14214, USA*

[b]*Department of Oral Medicine and Diagnostic Sciences, University of Illinois at Chicago, College of Dentistry, 801 South Paulina Street, Chicago, IL 60612, USA*

The subject of using electronic diagnostic devices as adjunctive diagnostic instruments for orofacial pain patients has been controversial for many years, and it remains so today. The three main types of devices are electromyography (EMG) machines, jaw movement trackers, and joint sound recorders (sonography or vibratography). All of these have been used for many years in research studies of normal and abnormal jaw function in animals and in humans. Attempts to use them in a clinical situation on individuals presenting with orofacial pain conditions have had mixed results at best. A large number of clinical studies and review papers have found poor discriminative qualities and technological problems when these instruments are used in a clinical situation. Nevertheless, some dental clinicians continue to use them for assessing pain patients and for ''discovering'' problems in nonsymptomatic individuals. In this article we briefly summarize the literature on this topic, with a special focus on how these devices might affect the practice of oral and maxillofacial surgery.

The main argument offered for using technologic diagnostic devices to diagnose temporomandibular disorders (TMDs) is an appeal to scientific modernity. The developers and promoters of this technologic approach usually are willing to acknowledge that physical examination and history taking are still important in the diagnosis of TMDs and other orofacial pain (OFP) problems. They insist, however, that modern dentists also must use technology as an adjunctive part of the diagnostic process, in the same way as our medical colleagues have done for so many years. According to them, the failure to accept this concept means that dentists are being stubbornly traditional and old-fashioned. Analogies are made to electrocardiography, echosonography (ultrasonography), or ballistocardiography in the diagnosis of heart problems. A more appropriate analogy for TMDs and OFP disorders would be to compare them to orthopedic disorders and headaches, which are medical conditions for which imaging technology has become somewhat useful, but other technologies have failed to add much to the differential diagnostic process.

In this article, we hope to offer practicing oral and maxillofacial surgeons enough information to appreciate the current controversy and also to enable them to communicate with other dental colleagues who may be using electronic diagnostic devices in their practices. Inevitably, some of the patients in those dentists' practices will be referred to oral and maxillofacial surgeons, with the expectation that a major surgical procedure (eg, temporomandibular joint [TMJ] surgery or orthognathic surgery) may need to be performed. Although this may be true and obvious in some cases, in others the referral may be based on one or more positive findings obtained from the use of certain electronic devices. For example, the results

* Corresponding author.

[1] Present address: 7631 Uliva Way, Sarasota, FL 34238.

E-mail address: ymg@buffalo.edu (Y.M. Gonzalez).

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from EMG or jaw tracking may suggest to the clinician that the mandible needs to be repositioned because it is not in a proper neuromuscular relationship to the maxilla. Obviously, the uncritical acceptance of such a conclusion could lead to major irreversible procedures being performed on a naïve patient.

We briefly discuss the current status of EMG and jaw-tracking devices in the diagnosis and monitoring of TMDs. Our main focus, however, is on the sonography and vibratography machines, because they are used to record TMJ sounds that might be of specific diagnostic interest to oral and maxillofacial surgeons who treat intracapsular TMJ problems. These technologies are claimed to aid in the differential diagnosis of such disorders, with specific sound patterns, frequencies, and wavelengths described as being characteristic of specific disorders. The question, however, is whether these technologies can provide acceptable levels of technical and diagnostic validity; if not, they cannot be relied on for making important clinical decisions.

Jaw tracking

Because impairment of jaw mobility and function are often among the main signs or symptoms of TMDs, it is not surprising that various parameters of jaw movement have been considered to be of diagnostic value. In addition to pantography and axiography devices that track jaw movement at the condylar level, several types of recording machines have been developed to track the movement of the entire mandible relative to the maxilla. Using various machines to study mandibular movements in patients who have TMDs, several investigators have examined jaw movement parameters that are considered to be of potential diagnostic value. These include amplitude of jaw movement in all three planes of space, reproducibility or consistency of jaw movements, and velocity and smoothness of jaw trajectories.

There have been reports that the velocity of voluntary jaw movements is less in patients who have TMDs. For example, Cooper and Rabuzzi [1] stated that a maximum vertical velocity of less than 300 mm/sec is "not healthy," but Feine and colleagues [2] found that all of their healthy subjects had measurements below this limit (as did 80% of Cooper and Rabuzzi's asymptomatic subjects). The mean scores for TMD patients were somewhat lower than in normal individuals, but not at a significant level, and as usual there were wide variations in individual performances.

In two other studies evaluating the reliability and accuracy of jaw-tracking devices, Balkhi and Tallents [3] reported measurement errors in the range of 1% to 66%, whereas Tsolka and colleagues [4] reported errors in the range of 9% to 30%. They also showed that these instruments consistently underestimated large mandibular movements, which inevitably leads to the false-positive diagnosis of limited mandibular movement, resulting in potential overtreatment of healthy people. As Mohl and colleagues [5] concluded in their first review article, "At the present time, the claim that jaw-tracking devices have diagnostic value for TMD is not well supported by the scientific evidence." This conclusion still seems to be valid almost 20 years later, but unfortunately the advocacy for using such devices has not disappeared.

Electromyography

Surface EMG of the muscles of mastication has been advocated by some dentists as a modern scientific approach to the diagnosis and treatment of patients who have TMDs, because the output from such devices is presumed to be quantitative and objective. The use of EMG devices is based on the assumption that certain pathologic or dysfunctional conditions can be identified by abnormal activity of the masticatory muscles. A large body of literature describes the outcomes of many studies that have looked at possible EMG differences between patients who have TMDs and normal subjects. An analysis of that literature, conducted by Mohl and colleagues [6], uncovered several major deficiencies in a large percentage of the clinical trials, and these severely limit the interpretation of the results. Among their major criticisms were: the lack of adequate control groups, the lack of studies showing reliability and validity of the methods, the inadequacy or nonexistence of statistical comparisons, and the declaration of conclusions that were not supported by the study results. The most significant problem, however, was the large interindividual variability in normal and patient groups, resulting in considerable overlap between them.

In review articles by Lund and colleagues [7,8], several specific methodologic problems are described to explain why EMG results cannot be taken at face value and then simply interpreted

as demonstrating normal or abnormal muscle behaviors. There must be experimental controls for age, sex, facial form, skin thickness, electrode positioning, and a history of bruxism or other parafunctions, before absolute EMG levels can be compared [9–13]. In addition, the researchers emphasized that the muscles of facial expression are a source of confounding signals when jaw muscles are being recorded with surface electrodes [14,15]. Despite all of these complicating factors, the manufacturers of surface EMG devices to be used for diagnosing and monitoring TMDs provide purchasers with cutoff values for normal resting muscle activity, which oddly are the same for all masticatory muscles in all people.

As is the case with jaw-tracking instruments, the clinical usefulness of EMG devices seems to be severely limited by all sorts of technical problems, methodologic concerns, questions of data interpretation, and overlap between normal and patient groups. It has been more than 20 years since Majewski and Gale [16] reported not only that EMG results failed to discriminate between these two groups but also that there was no consistent difference between symptomatic and asymptomatic sides in patients who had unilateral myofascial pain. One might expect that these and other widely reported negative findings would have dampened the enthusiasm of advocates for the clinical use of EMG machines. Instead, these devices continue to be marketed and sold to practicing dentists in several countries.

Sonography and vibratography

Sonography is the technique of recording and graphically representing sound. Some investigators have attempted to use this technique to obtain a more objective measurement that could link the sound characteristics produced during jaw movements to a specific pathologic state in the temporomandibular joint. Generally, there are three intracapsular TMJ conditions that need to be differentiated:

Anterior disk displacements with reduction, a condition that usually is associated with reciprocal clicking or popping sounds as the disk is reduced and displaced during opening and closing movements;

Anterior disk displacements without reduction, a condition that may produce less-discrete soft tissue sounds. It is described as an altered disc-condyle structural relation that is maintained during condylar translation.

Degenerative joint disease, also described as osteoarthrosis or osteoarthritis. This condition may produce grating noises as altered hard and soft tissue surfaces pass over one another.

When using any diagnostic instrumentation, the first point to establish is its technical validity (ie, to determine whether the instrument or device actually measures what it claims to measure) [17]. As summarized in Table 1, several investigators have assessed temporomandibular joint sounds using spectral analysis and Doppler instrumentation to determine the characteristics of the sounds per se. In the late 1980s, however, Gay and Bertolami [18,19] concluded that TMJ sound patterns share "significant common spectral characteristics among intra-capsular disorders, and that noises at extreme movements have a wide range of variability."

Other investigators have addressed the technical differences between various types of instrumentation, which can confound the interpretation of results obtained from different devices. Based on the outcomes of their studies, they have reported a high degree of variability in those results, and even more importantly they have questioned their clinical relevance [20–22]. In an attempt to study reproducibility of individual patients' TMJ sounds, Wabeke and colleagues [23] concluded that, in a 3-month period, the variance found in most subjects is attributable to the natural variation in joint sounds. This variation may be caused in part by the physical impossibility of performing identical jaw movements, thus questioning the instruments' reliability in addition to their potential clinical application.

More recently, clinical studies have been conducted to evaluate the clinical application of these modalities by addressing their diagnostic validity [24–27]. Deng and colleagues [24] reported moderate to acceptable levels of sensitivity and specificity for detecting various intracapsular conditions using electrosonography. In comparing their findings with the gold standard findings seen on arthrograms, however, they also noted that among the "normal" joints only 60% showed "no obvious anterior disc displacement." Other investigators have reported that, although the sensitivity of Doppler sonography for detecting disc displacements is acceptable, the specificity is low,

Table 1
Characterization of temporomandibular joint sounds

Title	Authors	Objective	Methods	Results	Conclusions	Comments
The spectral properties of temporomandibular joint sounds	Gay T, Bertolami CN [18]	To conduct spectral analyses of sounds obtained from TMJs with specific disorders	This observational study evaluated the sound characteristics from 47 patients (55 TMJs) during natural opening and closing and during extreme vertical movements.	Characterization of the sounds by diagnostic group	Intracapsular TMJ disorders can be differentiated by sound energy patterns, but they share "significant" common spectral properties. The information contained in the spectra of TMJ-propagated sounds reflects physical or frictional properties but with limited application in the differential diagnosis.	Lack of standardization of the unilateral versus bilateral assessment. No sensitivity or specificity provided Gold standard diagnosis was not necessarily the same for all patients. Unable to discriminate among the diagnostic groups based on sound's properties
The acoustical characteristics of the normal temporomandibular joint	Gay T and Bertolami CN [19]	To determine the conditions under which TMJ noises may arise	In this observational study joint sounds and mandibular movements from 200 asymptomatic individuals were recorded.	Asymptomatic TMJs are acoustically quiet during opening and closing. More than 80% of the subjects presented sounds during maximum vertical movements.	Noises present at extreme movements have a wide range of variability. In addition, normal joint sounds are characterized by a low energy at a subsonic level.	Definition of normal based on self-reported status, which in turn is based on lack of history of symptoms or past treatment of "TMJ"

Evaluation of a technique for recording temporomandibular joint sounds	Wabeke KB, Spruijt RJ, van der Weyden KJ, et al [23]	To distinguish between random variations and structurally produced sounds by studying sound reproducibility during 1-day and 3-month periods	Variables: peak to peak amplitude, energy of the sound, and mean power frequency of the signals Subjects: 12. The only sign was the presence of a joint sound on opening and sometimes during closing. Reliability of the recording technique was estimated by calculating Cronbach's α	Reliability 0.91 to 0.98 calculated from the day 1 data Long-term change in the sound characteristics occurred.	The variance is due to natural variation in joint sounds and may be caused by the physical impossibility of performing identical jaw movements, except within the small time interval of four successive movements.	No inclusion of control subjects. One subject had bilateral sounds, another only unilateral. Authors pointed out that changes over time may be due to changes in the protocol. Range of the frequency data varies among investigators. No sensitivity or specificity presented
Power spectral analysis of temporomandibular joint sounds in asymptomatic subjects	Gallo ML, Airoldi R, Ernst B, et al [20]	To determine the power frequency spectrum of TMJ sounds at rest and during jaw movement in asymptomatic subjects	Observational study including 40 asymptomatic subjects without past history of TMJ myoarthropathies	Baseline spectrum was approximately 10 dB above system noise. On movement the spectrum peaked at 66 dB.	Asymptomatic TMJs produced sounds that were distinctly different from baseline and background noise at lower frequencies.	The authors addressed the technical difficulties for evaluating joint sounds, their potential confounding qualities, and their clinical relevance.
Resonant characteristics of the human head in relation to temporomandibular joint sounds	Prinz JF [22]	Characterization of the resonant frequency of the human skull	This observational study compared the vibratory characteristics among skulls vs subjects with TMJ sounds.	There were no significant differences in the average spectra between clicks and crepitus.	Frequency vibration near 180 Hz may be due to a resonance in the tissues of the external ear often seen in asymptomatic populations.	Author attributes poor low-frequency response to the instrumentation used in the study.
The frequency range of TMJ sounds	Widmalm SE, Williams WJ, Djurdjanivic D, et al [21]	To establish the time frequency distribution of TMJ sounds obtained by different methods	This observational study gathered data from three subjects (172 sounds) by a microphone in the ear canal and skin contact transducer on the same side and a microphone in the contralateral ear.	The ranges of the energy peak locations were different among the recording techniques.	A microphone placed in the ear canal has the advantage of being as close as possible to the TMJ sound source.	No normative values for vibration were established. Energy content is sensitive to technique.

Table 2
Temporomandibular joint sounds clinical studies

Title	Authors	Objective	Methods	Results	Conclusions	Comments
Electrosonographic characteristics of sounds from temporomandibular joint disc displacement	Deng M, Long X, Dong H, et al [24]	To evaluate the wave form and electrosonographic characteristics of sounds emanating from internal derangement (DD) of the TMJ and compare findings with arthrographic images	Case-control study design with a total of 40 patients. Sound from 10 normal joints, 10 joints with DD with reduction, and 20 joints with DD without reduction. Fast Fourier transfer and electrosonographic techniques were used.	There was ''very little'' difference in sound frequencies between the diagnostic groups. Amplitude characteristics of DD with reduction were higher than among normal or DD without reduction individuals.	The sensitivity and specificity for DD with reduction were 77% and 93% and for DD without reduction 81% and 64%, respectively.	Gold standard: clinical symptoms and arthrographic evidence. Among the ''normal'' joints only 60% showed ''no obvious anterior disc displacement.'' No reference made to blinding of the examiners No calibration for the clinical examinations The authors stated that a total of 139 sounds were selected to assess sensitivity and specificity, although no selection criteria are described. Cases were ''selected'' and controls were ''chosen''

Comparison of Doppler sonography to magnetic resonance imaging and clinical examination for disc displacement	Puri P, Kambylafkas P, Kyrkanides S, et al [25]	To evaluate the accuracy of Doppler sonography to compare joint sounds with MRI and clinical findings	This cross-sectional study included 11 controls accepted into the study based on the negative self-reported history of pain, joint sounds, locking, and treatment. ROM $\geq$ 40 mm. Cases: patients were ''selected'' from the TMD clinic and had positive response to the clinical variables presented above.	The sensitivity of the Doppler compared with MRI was 90% and the specificity was 49%. In contrast, the sensitivity and specificity of clinical examinations compared with MRIs were 70% and 73%, respectively.	The sensitivity of Doppler diagnosis for disc displacements was acceptable but the specificity was low, producing many false positives.	Researchers did not use the RDC/TMD as gold standard for classification. Blindness and calibration of the examiners not done Mild crepitation was present in 46% of the asymptomatic joints and in 26% of symptomatics. Presence of mild crepitation alone was considered normal to reduce the number of false positives.
Sound analysis of temporomandibular joint internal derangements with phonographic recordings	Ögütcen-Toller M [26]	To assess the value of joint sound analysis in the diagnosis of internal derangements	Case-control study; 64 patients and 12 controls matched by gender and age ratios.	There were no differences in the sound patterns between disc displacements with or without reduction. Sounds during excursive movements indicated the diagnosis and establishment of severity.	Absence of sounds in the TMJ should not be regarded as a normal joint. The gold standard for assessment of disc conditions in the TMJ is MRI.	No consistency of diagnostic criteria. Some patients diagnosed with MRI and others with arthrography. Imaging criteria of disc position is not clear. RDC/TMD not used for gold standard diagnosis Characterization of the sound based on 20 cycles. Reproducibility of the cycles is not presented, nor are the criteria used. No data are shown to support the increasing validity or severity index based on sound characteristics. There is an inconsistency in the ''N'' value for different tables presented.

(*continued on next page*)

Table 2 (*continued*)

Title	Authors	Objective	Methods	Results	Conclusions	Comments
Amplitude and frequency spectrum of temporomandibular joint sounds from subjects with and without other signs/symptoms of temporomandibular disorders.	Sano T, Widmalm SE, Westesson PL, et al [27]	Evaluation of the amplitude and power spectrum of the TMJ sounds among symptomatic and asymptomatic individuals	Case control study; 49 participants with recognized TMJ sounds on auscultation by three clinical examiners. Control group had absence of any other sign or symptom associated with TMD. Cases had at least one other sign or symptom associated with TMD.	Sounds for symptomatic individuals have larger amplitude.	No differences were found between the amplitude of opening and closing sounds within the groups. Distribution of the sounds among the groups occurred at similar distance of the open/close cycle.	No calibration of examiners. No reliability data regarding clinical assessments, including joint sounds. Range of amplitude of TMJ sounds during opening and closing overlap among the experimental and the control groups.

producing many false positives [25]. In addition, the absence of sounds in the TMJ should not be regarded as sufficient evidence for identifying a normal joint, because of the poor diagnostic concordance between joint sounds and the MRI gold standard [25,26]. In general, these studies share certain shortcomings because they do not address methodologic issues, such as calibration and blinding of the examiners, use of research diagnostic criteria for classifying various TMDs, and selection bias (Table 2).

In summary, although the technical validity of various sonographic techniques has been addressed, the mixed outcomes of the clinical studies involving TMD patients fail to support the diagnostic validity of these instruments at this time. The methodologic shortcomings of most of those studies cast even more doubt on the value of using such instruments in clinical practice. There is obviously a need for further investigations with more rigorous design to more credibly test the applicability of these instruments and their potential integration into clinical practice. For now, however, the evidence presented in this article suggests that oral and maxillofacial surgeons should not rely on sonographic methods for establishing accurate TMJ diagnoses.

Summary

With regard to the temporomandibular joint, it is appropriate that oral and maxillofacial surgeons seek methods to enhance their ability to differentiate between pathology and normal variation. In addition, they need to be able to discriminate between the various pathologic or dysfunctional conditions that may afflict the various components of this joint complex. Among these are fractures, neoplasms, developmental anomalies, traumatic injuries, ankylosis, osteoarthrosis, osteoarthritis, and derangements of the articular disc. The classic sequence of differential diagnosis (chief complaint, history, clinical examination) is often followed by a diagnostic test or procedure, based on the presumptive but preliminary diagnosis. The most common adjunctive procedure used for diagnosing disorders of the TMJ is imaging, the type of which (plain film, CT Scan, MRI, and so forth) is determined by information gained from the history and the clinical examination. The technical and diagnostic validity of these imaging techniques have been

well established and are the current state of the art.

There is a general rule that governs all types of adjunctive diagnostic testing, especially if the test itself carries any risk (eg, radiation from X-rays) or if the test outcomes carry a high risk for being incorrect. The rule is as follows: The results obtained from diagnostic testing should have a high probability of affecting either the correctness of the diagnosis, the selection of appropriate treatment, or both. Despite these factors, claims have been made that certain TMD diagnostic devices should be routinely used because they have the ability to differentiate between jaw dysfunction and normal variation, and between the various pathologic or dysfunctional conditions of the TMJ. The claims that jaw-tracking devices have diagnostic value for TMD are not well supported by the scientific evidence, and the clinical usefulness of EMG devices is severely limited because of technical, methodologic, and data interpretation problems, along with significant overlap between asymptomatic and symptomatic groups.

As for sonography and vibratography machines that are used to record TMJ sounds, the analysis of which can presumably be used as an aid in the differential diagnosis of intracapsular disorders, those claims have not been substantiated by well-designed basic and clinical research. The diagnostic validity of sonography in the evaluation of temporomandibular joints sounds is questionable because of the variability of joint sounds, the poor intra- and interexaminer reliability in their assessment, and the poor sensitivity and specificity of the sounds per se in discriminating among intracapsular conditions.

Until acceptable levels of technical validity and diagnostic validity have been clearly established, sonography and vibratography cannot be relied on as an aid in differential diagnosis or in clinical decision making for the management of patients who have TMDs.

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Neurovascular Pains: Implications of Migraine for the Oral and Maxillofacial Surgeon

Donald R. Nixdorf, DDS, MS[a,b,*], Ana M. Velly, DDS, MSc, PhD[a], Aurelio A. Alonso, DDS, MS[c]

[a]*Division of TMD and Orofacial Pain, University of Minnesota, School of Dentistry, 515 Delaware Street SE, Minneapolis, MN 55455, USA*
[b]*Department of Neurology, University of Minnesota, Medical School, 420 Delaware Street SE, Minneapolis, MN 55455, USA*
[c]*Oral Biology PhD Program, University of Minnesota, Brain Sciences Center VAMC, One Veterans Drive, Minneapolis, MN 55417, USA*

Neurovascular pains, otherwise known as headaches, are a group of pain disorders that are felt as cephalalgias, or pains in the head. Likely they are a heterogeneous group of disorders that share a common anatomic region of presentation, the head, but have somewhat separate pathophysiologic mechanisms. For the most part, neurovascular pains are currently viewed as arising from neuronal firing of nociceptors associated with intracranial blood vessels and dura. For this reason these pain disorders were historically referred to as vascular pains [1], but further research has identified that peripheral and central aspects of the nervous system are playing crucial roles in the initiation and perpetuation of these pains [2,3]. This finding brought about a change in nomenclature regarding headaches, which are now referred to as neurovascular pain disorders, stressing the neuropathic aspect of migraine (Box 1).

Research has continued to more closely associate headache disorders with neuropathic mechanisms, which is starting to result in a shift in how headaches are viewed from clinical and research perspectives. In the midst of this paradigm shift this article provides an overview of the epidemiologic data and pathophysiologic mechanisms of one type of neurovascular pain, migraine headache. Migraine headaches are known to be common in the population [4,5] and have been reported to have the most disability associated with them [6,7], making migraine headache the prototypic neurovascular pain disorder. Migraine headache in the United States has resulted in $13 billion in lost productivity and $1 billion in direct health care costs [8]. For these reasons migraine headache likely has a significant impact on the practice of oral and maxillofacial surgery and dentistry as a whole despite this relationship not being systematically investigated. This article seeks to clarify what migraine headache is and is not, outline who in the population presents with migraine, and superficially review key underlying pathophysiologic mechanisms.

Although this article focuses specifically on migraine headache, clinicians should be aware of the various other headache disorders that have been defined and can impact care in a similar fashion as migraine headache. For readers interested in the specific diagnostic criteria of these other headache disorders, please refer to *The International Classification of Headache Disorders*, 2nd edition [9]. For information beyond the diagnostic criteria, the reader may wish to consult with any number of available textbooks, such as *Wolff's Headache and Other Head Pain*, 7th edition [10] and *The Headaches*, 3rd edition [11].

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* Corresponding author. Division of TMD and Orofacial Pain, School of Dentistry, University of Minnesota, 6-320 Moos Tower, 515 Delaware Street SE, Minneapolis, MN 55455.

E-mail address: nixdorf@umn.edu (D.R. Nixdorf)

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Box 1. Primary headache disorders

Migraine headache
Tension-type headache
Cluster headache
Paroxysmal hemicrania
SUNCT (Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing)
Stabbing headache
Cough headache
Exertional headache
Headache associated with sexual activity
Hypnic headache
Thunderclap headache
Hemicrania continua
New daily persistent headache

Box 2. Diagnostic criteria for migraine headaches

Diagnostic criteria for episodic migraine

A. At least five attacks fulfilling criteria B–D
B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity
D. During headache at least one of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
E. Not attributed to another disorder

Diagnostic criteria for chronic migraine

A. Headache fulfilling criteria C and D above for episodic migraine on $\geq$15 days per month for >3 months
B. Not attributed to another disorder

What is a migraine headache?

The case definition of migraine headache has been established by a panel of experts and presented within *The International Classification of Headache Disorders*, 2nd edition [9]. This disorder is characterized by the repeated occurrence of these paroxysmal head pains and is not an isolated event, much in the same way epilepsy is defined. An additional similarity is the presentation of aura in about 10% of people who experience migraines. The aura experienced with migraines is defined as a focal neurologic symptom that usually precedes or accompanies the onset of headache. The most typical type of aura experienced is visual aura, such as scintillations or scotoma, but other types of auras may occur, such as aphasia, hemiplegia, and hypoesthesia. These auras are believed to be related to a wave of spreading hyperexcitability and then depression over areas of cortical neurons. Although these varied presentations have been recognized, the disorder of migraine headaches seems to be consistent with one syndrome with the presentation of aura symptomatology being related to the neuroanatomic region involved in susceptible individuals (Box 2).

A single occurrence of intense, unilateral, throbbing head pain made worse with physical activity, with or without aura, is not considered strictly a migraine headache. Such an occasional migrainelike headache can be experienced by anyone, but the condition of having migraine headaches is the repeated occurrence of headache attacks that fit the specific diagnostic criteria. This requirement prevents the misclassification of potentially life-threatening events, such as a subarachnoid bleed (see later discussion), from being inappropriately diagnosed as a migraine headache.

Primary versus secondary headache diagnoses

Overall, all headache disorders are classified into two groups based on whether there is an identifiable underlying pathologic cause. Any headache disorder identified to have an underlying causative factor, such as associated with an aneurysm or hyponatremia, is referred to as a secondary headache; this is an important distinction. All headache types can arise from mechanical impingement of some component of the trigeminal nociceptive system, central or peripheral, or an imbalance in homeostasis, infectious or otherwise. Furthermore, when these secondary causes of headache mimic migraine headache [12], they also can respond to typical migraine headache treatments [13]. These migrainelike head pains likely involve some of the same pathophysiologic mechanisms as primary migraine headache, such as triggering the same primary afferent nociceptors

(see later discussion of pathophysiology), but may be initiated by a life-threatening event, such as a subarachnoid hemorrhage or the impingement by a space-occupying lesion. To guard against misdiagnosis, clinicians should follow the defined International Headache Society (IHS) diagnostic criteria and be aware of the typical red flags that may signal the presence of an ominous reason for head pain (Box 3) [14]. If the individual's clinical presentation is consistent with a secondary cause of headache, appropriate and timely referral for further diagnostic work-up is mandated. For these reasons, clinicians need to assess their patients for the possibility of such secondary causes when considering a headache diagnosis.

Episodic versus chronic migraine diagnoses

The most recent version of the diagnostic criteria of headache further separates migraine by duration, termed episodic migraine for those that are intermittent as discrete headaches and chronic migraine for those that seem to be daily and continuous in nature [9]. This separation was instituted because chronic migraine and other continuous headache disorders were being referred to as chronic daily headache in the literature, and difficulty investigating the pathophysiologic aspects of this heterogeneous disorder was being encountered [15,16].

Box 3. Signs and symptoms of secondary headache

- Abrupt onset or first experience of intense head pain, especially in adults >35 years old
  - ''First or worst'' headache
- Progressive worsening of head pain, especially over a short period of time, such as hours to days
- Absence of typical migraine-provoking factors
- Presence of abnormal other physical finding or symptoms
  - Stiff neck, papilledema, neurologic deficits, fever, changes in level of consciousness or mental function
- Refractoriness to appropriate interventions

This concept is relatively new, with the underlying premise that individuals who have chronic migraine first experienced episodic migraine and then transformed into the chronic version [17], also sometimes referred to as analgesic rebound or medication overuse headache [18]. A proposed transforming factor is frequent use of short-acting analgesics and vasoconstricting agents daily or near daily for 2 years or more [19,20], which has clinical implications for clinicians who regularly prescribe such medications. Other transforming factors have been suggested [21], but at present only anecdotal evidence has been reported from basic science research.

Important differences between episodic and chronic migraine are that individuals who have chronic migraine have fewer pronounced features classically defined as migraine, such as nausea, photophobia, aura, and significant pain reduction with analgesic intake that was effective in the past [17]. The significant aspect of this is that transformation to chronic migraine is believed to be associated with greater disability and worse prognosis [22–24], but this remains to be thoroughly investigated. The classification of episodic and chronic migraine was revised to specifically draw the clinician's attention to the greater understanding that these two headache presentations are believed to be migraine headaches, with the assumption that similar underlying pathophysiologic mechanisms are present [17].

Where are headaches located?

The term ''headache'' is defined by Dorland's Illustrated Medical Dictionary as ''pain in the head; cephalalgia'' [25]. It is our understanding from interactions with patients and colleagues that headache, as a construct, is most consistently thought of as a pain in the head felt above the orbitomeatal line and posterior to include the entire back of the head, thereby excluding the orofacial regions of the nose, sinuses, jaws, temporomandibular joints, and ears. This unstated assumption can be misleading, especially because such an anatomic distinction has not been made by the IHS classification subcommittee, as recently revised in their published diagnostic criteria for headache disorders [9]. Within this review the definition of headache encompasses the entire head, including the orofacial region, and is therefore consistent with the recognized diagnostic criteria.

The presentation of headaches within the orofacial region has been documented by several

case series [26–32]. This finding has obvious implications in clinical practice, requiring the clinician to consider the various headache disorders as part of the differential diagnosis when patients present with a complaint of orofacial pain. Understanding which individuals are most likely to present with a headache disorder (ie, epidemiology) and what characteristics of these headache disorders are (ie, diagnostic criteria), and having some knowledge of the underlying pain mechanisms (ie, pathophysiology) are helpful in arriving at a definitive diagnosis and appropriate treatment plan. From clinical experience the most common odontogenic neurovascular presentation of ''toothache'' is migraine headache, which is consistent with existing epidemiologic research.

There is a concept that such neurovascular pains can arise in extracranial tissues, such as by the interaction of blood vessels and nerves within tooth dental pulps. This concept is opposed to the accepted belief that pain arises from intracranial tissues and is then referred and perceived within the extracranial tissues. This concept of extracranial mechanism of neurovascular pains has been termed ''vascular toothache'' or ''vascular-type craniofacial pain'' [33–35]. Currently this is not a concept that is firmly accepted by most pain clinicians because treatment targeting this peripheral blood vessel/nerve interface, such as dental extractions, has not been observed to palliate these pains. This clinical evidence thereby suggests the likely source of pain is intracranial and referred to be perceived in the periphery by the individual who is experiencing such pain. The practicing oral and maxillofacial surgeon therefore needs to be familiar with these concepts to accurately diagnose and treat patients who have such a presentation.

Epidemiology of migraine headache

Prevalence of migraine

The 1-year-period prevalence of migraine in adults has been noted to range between 10% and 14%, with females experiencing migraines three times more often than males (Fig. 1) [7,36–38]. The prevalence increases from infancy until around 40 years of age, as does the occurrence of new people developing migraine, and then decreases with aging [39–43].

These prevalence estimates are similar across studies in the Americas and Europe [39,40,42,44–46], but some racial differences have been observed. Within the United States, migraine has been shown to be more prevalent among Caucasians (~15%), followed by African Americans (~12%) and Asian Americans (~7%) [47]. Similar differences were observed between these racial populations by continent, with the Americas and Europe having the higher prevalence (~13%) and Asia and Africa having lower prevalence (~5%) [4].

Cross-sectional and longitudinal studies have noted an association of low education and low income with migraine [7,36,43,44,48,49]. This association has been explained to be because of lack

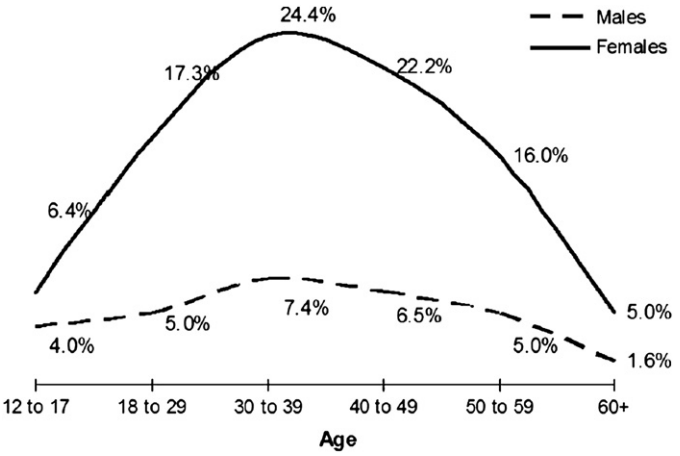

Fig. 1. Prevalence of migraine headache separated by gender. The presence of migraine is considerably higher in females, especially between the ages of 20 to 50 years. (*From* Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and the need for preventative therapy. Neurology 2007;68:345; with permission.)

of access to health care, stress, and poor living conditions [48]. Lower educational attainment, however, could be a consequence of a migraine disposition's influencing the ability to obtain vocational education even before the onset of migraine attacks [43].

Risk factors in migraine headache

There are two components that accompany the idea of risk factors related to migraine headache: (1) the risk for developing the condition of experiencing migraine headaches, and (2) the risk for triggering a migraine headache attack. Although the literature does not always distinguish consistently and clearly between these two types of risk factors, they are presented separately based on our understanding of the literature.

Risk factors for having the condition of migraine

An increased risk for having migraine headache has been noted among people who have a first degree relative who has migraine [43,48,50] and between twins, with a pairwise concordance rate being significantly higher in monozygotic twins (43%) compared with dizygotic twins (12%) [51]. These findings suggest that there is some underlying genetic factor that predisposes people to developing the condition of migraine headaches. This is becoming an explosive area of research in the post-genomic era. The evidence of genetic mutations resulting in pathophysiologic mechanisms has been scant. What is known and accepted is briefly outlined here.

A rare subtype known as familial hemiplegic migraine, named from its clinical presentation of transient hemiplegic aura, is believed to have a prominent hereditability [52]. Research has shown it to be an autosomal dominant disorder involving multiple mutations of P/Q-type voltage gated calcium channels (for specific information about mechanisms, see section on pathophysiology of migraine elsewhere in this article) [53,54]. Preliminary reports suggest other genetic mutations are somehow involved with increased risk for having the condition of migraine. Recently an endothelial nitric oxide synthase polymorphism, homozygous Asp298, was found to have a threefold increased risk for migraine [55], whereas MTHFR C677T genotype, which is known to be associated with an increase risk for stroke, had a twofold increase for migraine [56].

Even with all these positive relationships between migraine and genetic factors, the current opinion is that genetics alone cannot explain the presence of the condition, and therefore migraine is considered a multifactorial disorder [57]. Many nongenetic factors, such as stress, psychic tension, depression, and sleep problems, have been implicated in increasing the risk for having the condition of migraine headaches [58–62]. Research has not determined the exact nature of this association because it has two directions: depression increases the risk for developing migraine, and the risk for having depression increases with having migraine [48]. The description of such risk factors continues to be ambiguous and the diagnosis of having migraine headaches remains as a description of clinical features and not genotyping.

Risk factors for triggering migraines

Changes in hormone levels (eg, menstruation, ovulation, oral contraceptives), sleep disturbance, weather changes, psychologic factors, alcohol, and nutrition (eg, chocolate) are suggested to be risk factors for triggering migraine headaches [58–67]. More specifically, the risk for occurrence and persistence of headache despite treatment increases with menstruation [61], whereas hormone replacement therapy seems to contribute to prolongation of migraine headaches into older age [68]. Finally, few studies have investigated factors associated with a reduction in risk for migraines being triggered, such as daily sunshine duration of 3 hours or more (Table 1) [61].

Comorbidity disorders with migraine headache

Comorbidity of migraine with other pain conditions

Migraine has been noted to be associated with other chronic pain conditions, including temporomandibular disorders (TMD). In a cross-sectional study, based on reviewing the records of one medical insurance population, almost 28% (n = 115) of those 408 subjects who had a TMD diagnosis had a diagnosis of migraine headaches [69]. In a population-based study, subjects who had TMD pain were 1.8 times more likely to report headache than subjects who did not have TMD pain (95% CI, 1.1–3.2) [70]. Furthermore, the presence of headaches was shown to increase the risk for developing TMD over a 3-year time period within a population study of 1996 11-year-olds (odds ratio [OR] = 2.65; 95% CI, 1.6–4.4) [71].

Table 1
Risk for migraine headache expressed as an odds ratio

Variable	% with risk factor	Migraine (n = 453) OR	95% CI[a]
Gender (female versus male)	42.6	6.6[b]	3.0, 14.8
Mean age (per decennial increase)	42.7	0.6[b]	0.4, 0.8
Familial disposition (yes versus no)	32.9	3.1[b]	1.6, 6.2
Vocational education (none versus any)	26.9	2.9[b]	1.5, 5.7
Marital status (single versus married)	17.0	1.2	0.5, 2.8
Employment (not working versus working)	12.8	0.6	0.2, 1.8
Self-rated health (bad versus good)	15.9	1.8	0.8, 3.8
Problems at home or at work (yes versus no)	43.3	0.7	0.4, 1.4
Having a close friend (no versus yes)	39.3	1.9	0.9, 3.9
Regular physical exercise (no versus yes)	62.5	1.1	0.5, 2.3
Snoring (yes versus no)	39.7	2.0	0.9, 42
Feelings of fatigue (yes versus no)	38.6	0.9	0.5, 1.9
Sleeping problems (yes versus no)	21.0	1.3	0.6, 2.8
Feeling refreshed when awakening (no versus yes)	49.7	1.1	0.5, 2.1
Mean hours of sleep per night (per 1-hour decrease)	7.0	1.1	0.8, 1.6
Having a high work load (yes versus no)	34.9	2.2[b]	1.1, 4.3
Having too little time to do work (yes versus no)	20.5	0.9	0.4, 2.1
Being able to relax after work (no versus yes)	9.3	0.6	0.2, 1.9
Exposure to noise at work (yes versus no)	22.9	1.8	0.9, 3.9
Exposure to vapors at work (yes versus no)	16.3	1.6	0.6, 4.0
Use of oral contraceptives (yes versus no)	10.9	1.5	0.5, 4.5
Frequent tension-type headache (yes versus no)	25.6	2.5[b]	13, 5.0

Odds ratios, adjusted for age and gender, for incidence of migraine headache between 1989 and 2001 in relation to factors reported in a Danish population-based follow-up study.

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Subjects with migraine were not included in the at-risk group for tension-type headache.

[b] $P \leq .05$.

Adapted from Lyngberg AC, Rasmussen BK, Jorgensen T, et al. Incidence of primary headache: A Danish epidemiologic follow-up study. Am J Epidemiol 2005;161:1070; with permission.

Migraine has been associated with chronic pain conditions outside the head and neck region. In an adult population-based study it was found that migraine was strongly related to chronic spinal pain, such as chronic back or neck problems (OR = 5.2; 95% CI, 4.1–6.4) [72]. In another study a relationship was noted between headache frequency and comorbid musculoskeletal symptoms, defined as pain or stiffness in muscles and joints [73]. The magnitude of this association increased with the frequency of headache in individuals who experience headaches on 15 or more days per month (women: OR = 5.3; 95% CI, 4.4–6.5; men: OR = 3.6; 95% CI, 2.9–4.5). Furthermore, a high prevalence of fibromyalgia has been found among subjects who have migraine [74,75].

The increased odds of having comorbid musculoskeletal pain when diagnosed with migraine were also observed among children and young adults. A cross-sectional population-based study including more than 9000 adolescents and young adults revealed a strong association between headache felt more than 30 days per year and frequent low back pain (OR = 3.4; 95% CI, 2.3–5.0) [76]. In a prospective study, including 1756 third and fifth grade school children followed over 4 years, children who had headache were more likely to report persistent musculoskeletal pain at follow-up than children who did not have headache [77]. Such data support the emerging understanding that headaches, and likely migraines in particular, are a risk factor for the

development of musculoskeletal pain, including painful TMD (Table 2) [71,78].

Comorbidity of migraine and other diseases

The role of comorbidity with other diseases in the occurrence and persistence of chronic headache must be considered. Several comorbid diseases, such as clinical and subclinical cardiovascular disorders, epilepsy, and psychiatric disorders, such as depression and anxiety disorders, are frequently noted among people experiencing migraine headaches [79].

The association between migraine headache and coronary heart disease has been assessed by several studies. Hospital- and population-based epidemiologic studies have demonstrated that people who have migraines have an increased likelihood of several classic risk factors for cardiovascular disease, such as high blood pressure, negative cholesterol profile, and parental history of early myocardial infarction [79]. Furthermore, ischemic stroke occurs more frequently in migraineurs, with the association made worse by being female, older, smoking cigarettes, and using oral contraceptives [80,81]. Also, a relationship was found between family history of vascular disorders (ie, stroke, arterial hypertension, myocardial infarction) and migraine in a study including children (OR = 1.8; 95% CI, 1.0–3.5) [82].

Table 2
Conditions comorbid with migraine headache

Category	Condition
Psychiatric	Depression
	Anxiety
	Panic disorder
	Bipolar
Neurologic	Epilepsy
	Tourette syndrome[a]
Vascular	Raynaud phenomenon
	Blood pressure (inconsistent)
	Ischemic stroke, subclinical stroke, white matter abnormalities
Heart	Patent foramen ovale[a]
	Mitral valve prolapse[a]
	Atrial septal aneurysm[a]
Other	Snoring/sleep apnea[a]
	Asthma/allergy
	Systemic lupus erythematosus[a]
	Nonheadache pain

[a] Data from clinical samples only.

Data from Scher AI, Bigal ME, Lipton RB. Comorbidity of migraine. Curr Opin Neurol 2005;18:306.

A relationship between migraine and epilepsy has long been postulated, with recent clinical and epidemiologic studies having demonstrated that both are highly comorbid [83–85]. Although migraine prevalence in patients who have epilepsy is high (14% to 20%), only a few (1.7% to 3%) experience seizures in close temporal proximity to migraine [84,85].

Psychiatric disorders have been also investigated as comorbidities related to migraine. Cross-sectional, cohort, and bidirectional associations between migraine and various psychiatric and somatic conditions have been reported in the literature. In a cross-sectional study, magnitude of the associations of an odds ratio between 2.4 and 3.1 was found for three psychiatric disorders: depression (OR = 2.4; 95% CI, 1.8–3.1), anxiety (OR = 3.1; 95% CI, 2.0–4.9), and panic attacks (OR = 3.1; 95% CI, 2.2–4.3) [86]. A 2-year population-based cohort evaluated the bidirectional relations between migraine, severe nonmigraine headache, and depression. Results showed that depression increased only the risk for developing migraine (relative risk [RR] = 3.4; 95%CI, 1.4–8.7) over a 2-year period. In addition, migraine at baseline increased the risk for developing depression (RR = 5.8; 95% CI, 2.7–12.3) [66]. In another cross-sectional study, including more than 50,000 adults aged 20 years and older, migraine headache was positively associated with depression (OR = 2.7; 95% CI, 2.3–3.2) and anxiety disorders (OR = 3.2; 95% CI, 2.8–3.6) [62]. These associations are not specific to migraine, whereas nonmigraine headache was related to depression (OR = 2.2; 95% CI, 2.0–2.5) and anxiety disorders (OR = 2.7; 95% CI, 2.4–3.0) also. There is a linear trend associated with headache frequency: with migraine headache occurring on fewer than 7 days per month, 7–14 days per month, or 15 or more days per month, the associations with depression in odds ratios were 2.0 (95% CI, 1.6–2.5), 4.2 (95% CI, 3.2–5.6), and 6.4 (95% CI, 4.4–9.3), respectively [62]. This dose-response curve strongly implicates the involvement of migraine headache with mood disorders.

Pathophysiologic mechanisms of migraine headache

The pathogenesis of migraine is incompletely understood [87]. Currently, migraine is considered a disorder of trigeminal sensory processing, generated centrally, probably at the level of the brainstem. Recent discoveries demonstrated that the

neuronal events mediating migraine originate within the trigeminovascular system and its central projections (Fig. 2) [88].

The headache pain felt during migraine attacks is believed to be caused by the same nerves that are sensing pain, primary afferent nociceptive neurons. Antidromic transmission of nerve impulses results in a release of vasoactive neuropeptides, such as substance P, calcitonin gene–related peptide, and neurokinin, which promote vasodilation and plasma protein leakage [89]. This physiologic process has been termed neurogenic inflammation, because all the cardinal signs of inflammation result from neuronal impulses as opposed to infectious agents. Current opinion suggests that the release of such vasoactive peptides leads to the subsequent release of serotonin, histamine, bradykinin, and prostaglandins. These algogenic substances, which are brain generated and blood borne, further sensitize the primary afferent nociceptor [90–92].

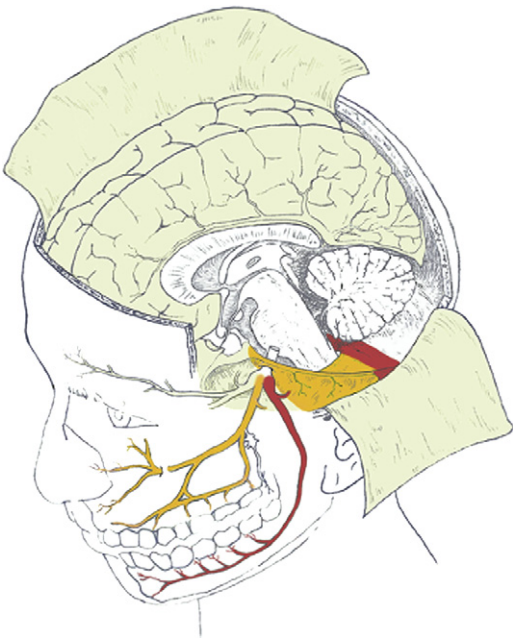

Fig. 2. Tissues innervated by the three branches of the trigeminal nerve. The vast majority of the brain and associated structures are innervated by branches of the ophthalmic branch nerve of the trigeminal nerve (yellow). A small portion are innervated by the maxillary branch (orange) and mandibular branch (red). Stimulation of intracranial nociceptive fibers in the colored areas is believed to result in pain being perceived in the corresponding trigeminal branches of the orofacial region, including the teeth and alveolar bone. (*From* Alonso AA, Nixdorf DR. Case series of four different headache types presenting as tooth pain. J Endod 2006;32:1111; with permission.)

This understanding of the pathophysiology has led to the development of a class of medications known as triptans. These medications are 5-HT_{1B} and 5-HT_{1D} receptor agonists, meaning they bind to specific subtypes of serotonin receptors located on blood vessels and nociceptive neurons within the brain, respectively. The resulting action is the inhibition of the neurogenic inflammation and vasoconstriction of the cerebral blood vessels and raising the depolarization threshold of the primary afferent neuron [93]. For these reasons they have proven to be more efficacious than analgesics and vasoconstrictors alone or in combination as an abortive medication [93]. As a greater understanding of migraine pathophysiology develops, novel treatment approaches will undoubtedly be developed that can exploit this knowledge (Fig. 3).

Animal studies exploring the implications of neurogenic inflammation revealed that intracranial and extracranial hypersensitivity are present [94,95]. This same type of hypersensitivity has been observed in humans experiencing migraine headache [96,97] and has been termed central sensitization. The clinical presentation of central sensitization is known as allodynia and hyperesthesia. These presentations have been shown to occur within and outside trigeminally innervated structures during migraine headache attacks [96,97]. Such hypersensitivity has been shown to occur in between migraine headaches also [98,99]. This occurrence is believed to be because of a temporary increase at least in the sensitivity of the second-order neurons that receive converging inputs from the skin in various body sites, such as the dura mater and the periorbital skin [100]. Allodynia has been demonstrated to be continuously present when episodic migraines have transformed into chronic migraines [22], likely representing synaptic strengthening of this pathway resulting in less chance for reversal of this hypersensitive state (Fig. 4).

The periaqueductal gray matter (PAG) is the center of a powerful descending antinociceptive pathway [101]. The PAG regulates nociceptive, autonomic, and behavioral responses to threat [102]. The potential for PAG dysfunction to be involved in migraine was observed when patients had electrode implantation into the PAG that provoked headaches resembling migraines [103]. Functional imaging studies performed during

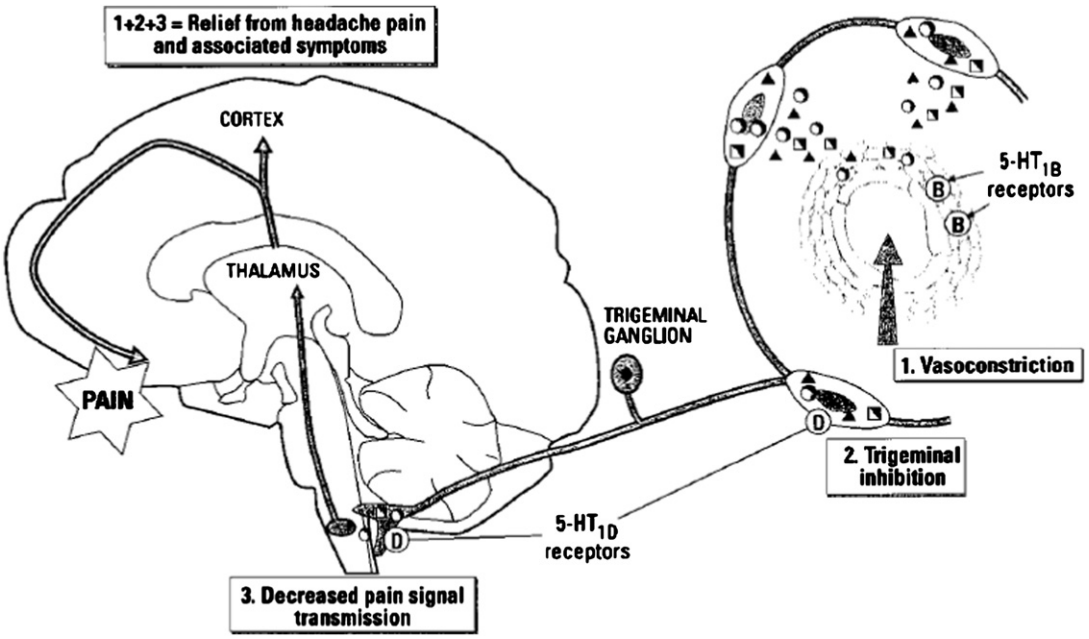

Fig. 3. Neurogenic inflammation and action of 5-$HT_{1B/D}$ agonists. Three actions of 5-$HT_{1B/D}$ receptor agonist activity: (1) Reducing vasodilation caused by the release of release of inflammatory mediators, (2) inhibiting the further neuronal release of these inflammatory mediators, and (3) decreasing the transmission of noxious stimuli at the level of the first synapse in the brainstem. (*From* Hargreaves RJ, Shepheard SL. Pathophysiology of migraine—new insights. Can J Neurol Sci 1999;26(suppl 3):S16; with permission.)

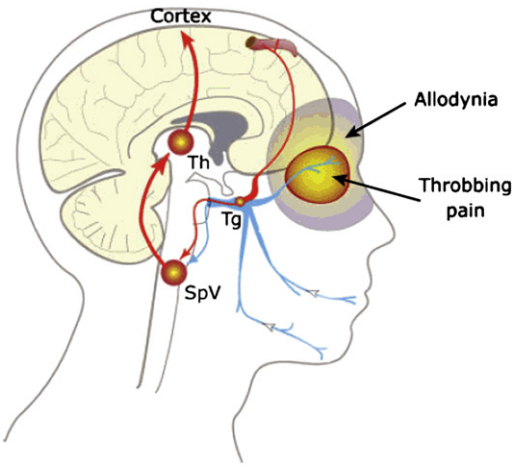

Fig. 4. Trigeminovascular pain pathway of migraine. Innervation of a cerebral blood vessel from a branch of the ophthalmic nerve (red) with pain referral and allodynia being present in the somatic distribution of the same trigeminal nerve, ipsilateral periorbital tissues. SpV, spinal trigeminal nucleus; Tg, trigeminal ganglion; Th, thalamic nuclei. (*From* Burstein R, Jakubowski M. Unitary hypothesis for multiple triggers of pain and strain of migraine. J Comp Neurol 2005;493:10; with permission.)

migraine headache attacks suggest that allodynia commonly seen in migraineurs involves the brainstem descending pain modulating system (eg, PAG dysfunction) [104,105]. Recent research has revealed that abnormal modulation of the brain nociceptive systems, specifically by way of dysfunction of the PAG, is further involved in the chronification of migraine headaches. This modulation is believed to occur with each migraine headache event, resulting in a shift from episodic migraines to chronic daily headache with whole-body hypersensitivity in individuals who experience frequent migraine for a protracted length of time (Fig. 5) [88].

The understanding of pathophysiologic mechanisms lacks information as to how or why the inciting event of antidromic transmission occurs along the afferent trigeminal fiber innervating the blood vessels and dura of the brain. Research on this issue has largely been at the cellular and genetic levels. Most researchers agree that susceptibility is inherited and that its clinical presentation is strongly modulated by internal and external factors. Pioneering research revealed polymorphisms in genes regulating ion translocation have been implicated in two subtypes of

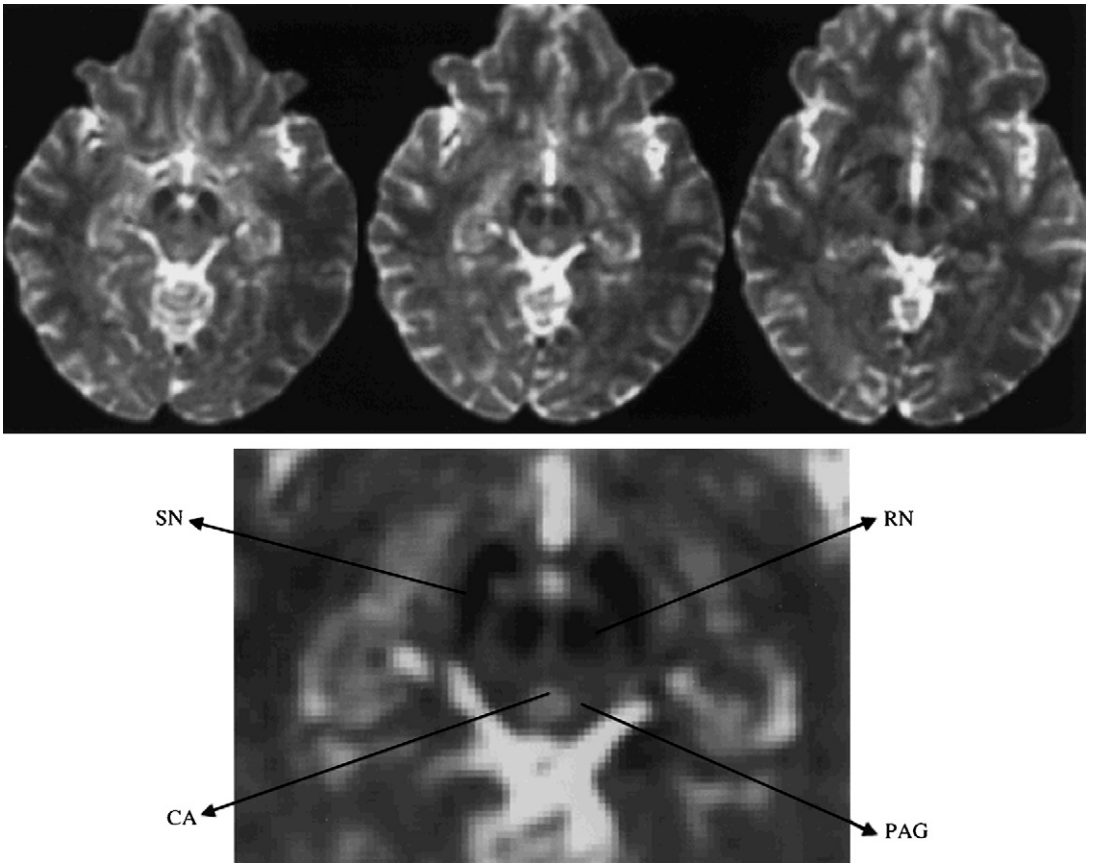

Fig. 5. Evidence of PAG and related nuclei involved in migraine. Three contiguous transverse slices, using functional magnetic resonance imaging, reveal changes in blood flow within the brainstem. Arrows pointing away from areas of hypointensity correspond to the substantia nigra (SN) and red nucleus (RN). The cerebral aqueduct (CA), which is hyperintense, is surrounded by the PAG, which also is hypointense. (*From* Welch KMA, Nagesh V, Aurora SK, et al. Periaqueductal gray matter dysfunction in migraine: Cause of the burden of illness? Headache 2001;41:632; with permission.)

familial hemiplegic migraine, which is a rare migraine disorder, and have been mapped to chromosome 19p13 [106]. Point mutations have been described that affect calcium channels and ATP-utilizing Na+/K+ ion pumps with these mutations being found on neurons and astrocytes [107,108]. This finding suggests multiple pathophysiologic mechanisms result in a specific, and rare, clinical presentation of familial hemiplegic migraine. Translating this information into the common migraine disorders, which are undoubtedly more heterogeneous in nature, explains why specific genetic abnormalities have not yet been identified.

The new cloned receptor for serotonin, 5-HT_7, attracts attention [109]. Recent research suggests that the receptor may play a role in migraine and other central nervous system disorders, including anxiety and cognitive disturbances. Furthermore, it may also be involved in other pain conditions, such as epilepsy, depression, memory, and sleep [110]. Development of knowledge along this line of research may yield a better understanding of these comorbid disorders and specific treatments.

In summary, migraine is regarded as a neurovascular disorder with alterations in trigeminal sensory processing. This disorder, which likely is associated with genetic alterations, such as calcium channel abnormalities [53,54] and serotonin receptor activity [109,110], has a centrally generated trigger [111] that results in vasodilatation and primary afferent nociceptor hypersensitivity [91]. This process results in lower sensory thresholds during the migraine headache attack [96,97]. Furthermore, individuals who have experienced

frequent migraine headaches show dysfunction of their descending antinociceptive pathway [88], which is believed to result in persistent whole-body hypersensitivity [22] and exaggerated pain response to stimulation.

Clinical relevance of migraine headaches

Epidemiologic data demonstrate that migraine headaches are common [6,36] and because of this migraineurs routinely present within the oral and maxillofacial clinical setting. The individuals who have migraine headache have specific issues unique to them that may alter the ultimate course of treatment. The two most compelling arguments for knowing about migraine and other headache disorders is that they may present as nonodontogenic reasons for toothache [29] and sinus pain [111], along with the possibility that life-threatening pathologic processes may be present. Such pains are known to motivate individuals to be evaluated by their dentists, suggesting that dental specialists should be familiar with these concepts and the diagnostic process. Furthermore, because migraine headache and secondary reasons causing migrainelike headache can be episodic or chronic in nature, both should be included in the differential diagnosis of intermittent and daily continuous orofacial pains when an odontogenic source is not readily identifiable.

Migraine has consistently been shown to be associated with other chronic pains, including TMD and other musculoskeletal pain disorders [70,74,75]. Emerging evidence suggests that migraine headaches may be a risk factor for the development of TMD [71,78], which implies that the phenotypic expression of migraine results in an alteration in central processing of stimuli, including nociception. Because the disorder of migraine headache actively uses the trigeminal nociceptive pathway, it may suggest that these individuals can be more sensitive to stimulation, such as may occur with oral surgical procedures. Procedures that cause acute pain within trigeminally-innervated structures are likely perceived as being more severe, longer lasting, and expressed as having a greater degree of interference in individuals who have migraine headaches. This finding is especially true of people who have chronic migraine, because continuous hypersensitivity is known to be present [22]. For this reason it is recommended that such patients be identified before the initiation of surgical treatment so that appropriate measures can be taken to improve their postprocedural outcome. One such measure may be to delay surgical treatment until better headache control is obtained, which is believed to be a clinical measure suggesting reversal of some of the hypersensitivity.

Migraine headaches have been strongly associated with depression and anxiety [43,44], similar to other chronic pain conditions. This association noted by clinical research is supported by neuroscience research that suggests common receptors are involved [109,110]. Together, these data suggest a close relationship between migraine headaches and mood disorders. Because a comorbid presentation of depression and anxiety is common, people who have migraine headaches should be screened for such mood disorders because such disorders are known to decrease compliance with prescribed pre- and postoperative directions.

Along similar lines, migraine headache has been associated with an increased risk for cardiovascular events, most notably stroke. This risk is increased in females who smoke and are taking exogenous estrogen supplements, such as for contraception. Migraine headaches are also known to be comorbid with seizure disorders. The presence of these comorbid disorders should be taken into account when prescribing medications, providing anesthesia services, and performing surgical treatments on these individuals.

Summary

Clinicians should be familiar with the concept that various neurovascular pain disorders, specifically migraine and secondary headaches, may present as pain anywhere within the trigeminally innervated tissues. For these reasons clinicians should consider including such diagnoses within the differential diagnosis when patients have a pain complaint that seems nonodontogenic in nature. Surgical procedures performed on individuals who have migraine headaches, especially the chronic migraine, may cause increased postoperative pain intensity, duration, and unpleasantness. Furthermore, individuals who have migraine are known to have an increased probability of comorbid conditions, most notably other chronic pains, depression and anxiety, seizures, and stroke.

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Neuropathic Orofacial Pain

Rafael Benoliel, BDS, LDS RCS Eng[a,*], Eli Eliav, DMD, PhD[b]

[a]*Department of Oral Medicine, Hebrew University-Hadassah, POB 12272, Jerusalem, Israel 91120*
[b]*Division of Orofacial Pain, Department of Diagnostic Sciences, University of Medicine & Dentistry of New Jersey-New Jersey Dental School, 110 Bergen Street, Newark, NJ 07103, USA*

Neuropathic pain is initiated by a primary lesion or dysfunction of the nervous system (Table 1) [1]. Neuropathic pain may be triggered by local trauma or systemic disorders, such as diabetes, that affect structures along the neuraxis from the central nervous system to peripheral structures. Based on symptomatology, neuropathic orofacial pain may be divided into two broad categories: episodic and continuous [2]. Episodic neuropathies are characterized by short electrical or sharp pain that may be paroxysmal, as in trigeminal neuralgia. Continuous burning pain is characteristic of posttraumatic neuropathy or inflammation in nerve structures (neuritis). Depending on the location of the initiating event, neuropathic pain may also be classified as peripheral or central. However, persistent peripheral neuropathies eventually involve maladaptive responses of the central nervous system.

Clinical approach to neuropathic pain

Occurrence of neuropathic pain may be spontaneous (stimulus-independent) or touch-evoked (stimulus-dependent), and these episodes may be superimposed on a background of constant pain. Typically neuropathies include positive (eg, hyperalgesia; see Table 1) or negative (eg, numbness) signs. Some sensory signs and symptoms, particularly thermal or mechanical allodynia, are frequently associated with neuropathic pain. Assessment of sensory changes is best performed by quantitative sensory testing (QST), usually using sophisticated equipment. However, when advanced QST equipment is unavailable, a simple pin, blunt instrument, warmed and cooled implements, and cotton wool may be used. This information may be complemented by mapping of areas with sensory changes; these should be documented with sketches or photographs and should be part of the patient evaluation and follow-up (Fig. 1A).

Quantitative sensory testing

QST uses noninvasive assessment and quantification of normal and abnormal responses of the nervous system to various stimuli. External stimuli are usually mechanical, thermal, or electrical; each selectively activates different sensory nerve fibers (eg, heat activates C-fibers and cold stimuli and punctuate mechanical stimuli activate A-delta-fibers and electrical stimuli A-beta fibers).

Clinical relevance

Extensive mechanical nerve damage is characterized by myelinated and unmyelinated nerve fiber hyposensitivity, clinically characterized by elevated detection thresholds to heat, electrical, and mechanical stimulation [3]. Partial damage may be followed by either hypo- or hypersensitivity [3]. In contrast, other specific nociceptive processes may provide a different, identifiable sensory signature. For example, neuritis (perineural inflammation) is characterized, particularly during its early phase, by a reduced detection threshold (hypersensitivity) in large myelinated A-beta nerve fibers [4,5]. Additionally, a measurable reduction in the interval between detection and pain thresholds has been shown to characterize centrally mediated pain conditions. Thus, data

* Corresponding author.
E-mail address: benoliel@cc.huji.ac.il (R. Benoliel).

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Table 1
Definition of commonly used terms

Term	Definition
Allodynia	Pain caused by a stimulus which does not normally cause pain
Analgesia	Absence of pain in response to normally painful stimuli
Anesthesia dolorosa	Pain in an area or region that is anesthetic
Dysesthesia	An unpleasant abnormal sensation, whether spontaneous or evoked
Hyperalgesia	An increased response (more pain) to a normally painful stimulus
Hypoalgesia	Diminished pain in response to a normally painful stimulus
Hypoesthesia	Decreased sensitivity to sensory stimulation (excludes the special senses)
Neuropathic pain	Pain initiated or caused by a primary lesion or dysfunction in the nervous system
Paresthesia	An abnormal sensation, whether spontaneous or evoked

Data from Merskey H, Bogduk N. Classification of chronic pain: descriptions of chronic pain syndromes and definition of pain terms. 2nd edition. Seattle: IASP Press; 1994.

obtained from QST may provide vital information for treatment decisions, such as in which cases to perform microsurgical repair and when to use centrally acting drugs.

Clinical syndromes

Trigeminal neuralgia

Trigeminal neuralgia (TN) is an excruciating, short-lasting, unilateral facial pain (Table 2). Two subsets of TN are recognized: classical and symptomatic. Symptomatic TN is related to various clear pathologies, including tumors, cysts, viral infection, trauma, and systemic disease [6]. Most patients (>85%) who have TN are diagnosed as having classical TN. Atypical TN cases that present with most but not all diagnostic criteria are unrecognized by any current classification.

Clinical features

Onset of TN may be abrupt or through a rarer preceding syndrome termed *pre-TN*. TN is a unilateral facial pain syndrome [6], but bilateral pain has been reported in 1% to 4% of patients [7,8]. Pain location is usually described according to the major branches of the trigeminal nerve. In 16% to 18% of patients, the singly affected branch will be the maxillary or mandibular branch, whereas the ophthalmic is affected singly in only approximately 2% of cases [8]. Most commonly the maxillary and mandibular branches are affected together (35%), and all three branches are involved in 14% of patients [8]. The jaws are therefore involved in most cases, explaining why patients who have classical TN often seek help from dentists. Although the features of TN vary across patients, they are highly consistent (stereotyped) within individuals.

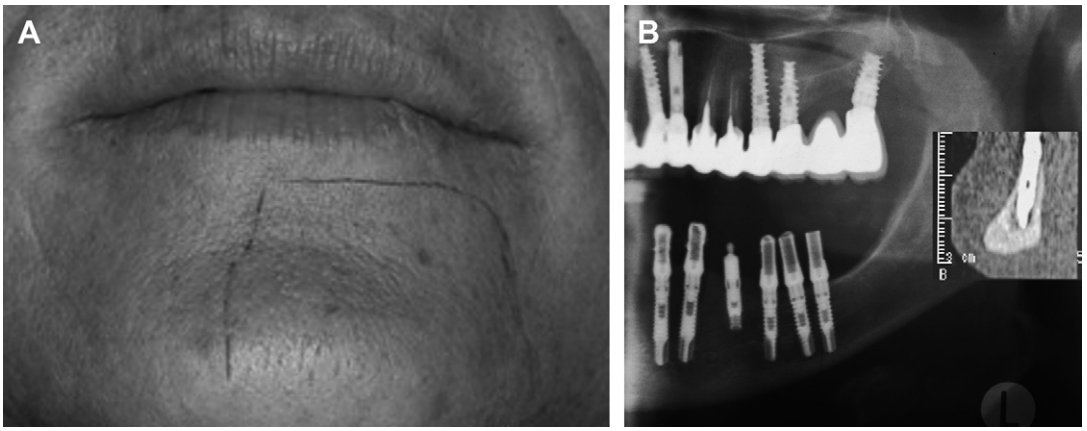

Fig. 1. Pain and neurosensory deficit after dental implants. (*A*) Mapped area of pain and disturbed sensation. (*B*) Implant placement. Insert is a CT section of an implant causing damage to the inferior alveolar nerve.

Table 2
Classical trigeminal neuralgia

Feature	Notes
Paroxysmal attacks of pain lasting from a fraction of a second to 2 minutes	Usually no pain is experienced between attacks, but some atypical cases have low-grade background pain or longer-lasting attacks Periods of remission from days to years may occur
May affect one or more divisions of the trigeminal nerve	Pain is mostly unilateral and does not cross the midline Pain is very rarely bilateral (1%–4%) Bilateral pain may indicate disease (eg, multiple sclerosis) Most patients experience pain in the distribution of the second or third division or both
Pain characteristics are electrical, intense, sharp, or stabbing; precipitated from trigger areas by innocuous stimuli; and precipitated by trigger factors	Pain may be accompanied by spasm of the facial muscles After an attack a refractory period occurs when pain cannot be triggered Innocuous stimuli include touch, wind, and shaving but may also be temperature, noise, lights, and taste Trigger points may however change location within the same patient A short gap between trigger and pain may be observed (latency)
Stereotyped attacks	Attack duration, distribution, and so forth may vary among patients but are highly consistent within cases
Usually no neurologic deficit is clinically evident	Particularly in longstanding cases sensory testing may show mild deficits in the distribution of the trigeminal nerve
Pathology that may mimic trigeminal neuralgia (TN) must be ruled out through history, physical examination, and special investigations. All patients who have TN should undergo brain imaging. Compression of the nerve root by a vascular malformation (tortuous or aberrant vessels) is considered classical.	

Data from Okeson JP. Orofacial pain: guidelines for assessment, classification, and management. The American Academy of Orofacial Pain. Hanover Park (IL): Quintessence Publishing Co., Inc.; 1996; and Olesen J, Bousser MG, Diener HC, et al. The international classification of headache disorders: 2nd edition. Cephalalgia 2004;24(suppl 1): 24–150.

Pain associated with TN is most often described as paroxysmal, shooting, sharp, piercing, stabbing, or electrical [9,10]. Pain severity is extreme, rating 9 to 10 on a 10-cm visual analog scale (VAS) [10,11]. Some patients may experience a dull background pain of varying duration, described as dull, throbbing, and burning [7,12]. Findings suggest that patients who have prominent background pain usually have detectable sensory loss, suggesting nerve damage [13].

The clinical characteristics of TN include the presence of trigger zones, and innocuous stimuli in these areas lead to pain. A short gap between the stimulation of a trigger zone and pain onset may be observed and is termed *latency*. However, TN attacks are often spontaneous and triggers are not always present or identifiable [14]. Triggers are usually in the distribution of the affected trigeminal branch, particularly around the lips but may be extratrigeminal and multiple, and even change location [11]. Triggering stimuli include talking, chewing, touch, temperature, wind, and shaving [11].

Pain in TN is characterized by a rapid onset and peak, lasting from 10 seconds to 2 minutes [11], followed by a refractory period during which pain is impossible or extremely difficult to trigger. Attacks occur mostly during the day, but nocturnal TN has been reported [12]. Contraction of the facial expression muscles typically accompanies the pain of TN, hence the terms *tic douloureux*/*tic convulsif*. Sensory disturbances such as hypoesthesia are rare and more readily detected when using sophisticated QST techniques [15].

A thorough history and clinical evaluation with adequate radiographs of oral structures are essential to rule out pathology. All patients who have TN should undergo imaging (CT or MRI) at least once during diagnosis and therapy [16]. Imaging techniques such as magnetic resonance tomographic angiography (MRTA or MRA) may indicate vascular compression of the nerve root. More sophisticated techniques, such as three-dimensional MRI with constructive interference in steady state sequence, are superior to MRTA/MRA in detecting venular compressions [17].

Prognosis

Long-term followup of patients who have TN shows that well-defined periods of pain attacks are variably followed by periods of remission [7,12]. However, TN bears a poor prognosis; approximately 90% of patients who have TN report

increased attack frequency and severity accompanied by a progressive and increasing resistance to pharmacologic and surgical treatment [11,18].

Atypical trigeminal neuralgia

Up to 30% of patients who have TN report atypical features, such as longer attacks and constant background pain [13,14], often associated with increased resistance to therapy. For example, only 47% of atypical TN cases reported absolute pain relief after microvascular decompression compared with 80% in classical TN. Additionally, a higher rate of recurrence was seen in atypical cases [19].

Pretrigeminal neuralgia. An early form of TN, termed *pretrigeminal neuralgia* (PTN), has been described in 18% of patients who have TN [20,21]. PTN is characterized by a dull continuous pain in one of the jaws that lasts from days to years before becoming typical [21]. Thermal stimuli may cause triggering at a higher rate, and a throbbing quality to PTN pain is sometimes present mimicking dental pathology [21]. These features and the success of regional anesthesia have led to misdiagnosis of PTN as pain of dental origin. The lack of clear and consistent diagnostic criteria makes this a problematic entity to recognize; it is usually diagnosed when all other possibilities are exhausted or in retrospect when classical TN develops [2].

Differential diagnosis

The differential diagnosis of TN includes dental pain, short-lasting unilateral neuralgiform headaches with conjunctival injection and tearing [9], an atypical (shorter) cluster-tic syndrome, and symptomatic TN. TN often mimics dental pain and a quarter of cases will initially consult a dentist [12,22,23]. Unfortunately, TN is often misdiagnosed and 33% to 65% of patients undergo unwarranted dental interventions; up to 12% eventually may be rendered edentulous [11,23].

Symptomatic trigeminal neuralgia

Multiple sclerosis (MS) is a common disabling disease affecting individuals between ages 20 and 40 years. MS-related demyelination of the trigeminal nerve leads to an increased risk for developing TN by a factor of 20 [7]. Clinical signs predictive of MS in patients who have TN are bilateral pain (14% in MS) and young age [24]. Very rarely (0.3%) is TN the presenting sign of MS onset; it usually (1.5%–4.9%) develops in patients diagnosed with MS [25,26].

Trigeminal nerve dysfunction has been observed in 33% of patients who have middle and posterior cranial fossa tumors, but in only 13% were these presenting symptoms [27]. Approximately 10% of cases with intracranial tumors report TN-like symptomatology, which are mostly posterior fossa tumors and meningiomas [28,29]. Cerebellopontine angle tumors may also cause TN, and this diagnosis is more likely when the patient is young and experiences pain in more than one trigeminal branch [16]. In patients younger than 29 years who have TN, the prevalence of intracranial tumor is extremely high (approximately 100%) but subsequently decreases with increasing age [16]. Overall, 10% to 13.4% of patients who have TN may have intracranial tumors and MRI is the most sensitive imaging modality [29,30].

Epidemiology

TN is a rare condition with a lifetime prevalence of approximately 70 TN cases per 100,000 population [31]. The crude annual incidence of TN is 4.3 to 8 per 100,000 and is higher in women (5.7) than men (2.5). However, among individuals older than 80 years, men have a very high incidence of 45/100,000 [31,32]. Peak incidence begins at 50 to 60 years and increases with age [7]. TN is extremely rare in children.

Pathophysiology

Several lines of evidence point to arterial or venous compression of the trigeminal root at or near the dorsal root entry zone as a major causative or contributing factor [13,33]. Imaging, surgical observations, and cadaver studies confirm a high rate of vascular compression of the nerve in patients who have TN [34–37]. Subsequent neuronal damage is suggested in biopsy specimens from patients who have TN, showing axonal loss and demyelination of trigeminal roots [33,38]. Degenerative hypermyelination and microneuromata in the trigeminal ganglion have also been shown [39].

Initiation of pain through an innocuous trigger is an intriguing feature of TN partly explained by the ignition hypothesis [40]. According to this hypothesis, injury renders axons and axotomized somata hyperexcitable, resulting in synchronized afterdischarge activity, cross excitation of nociceptors, and pain paroxysms [41,42]. Central nervous system neuroplasticity will undoubtedly occur in the presence of these changes and will ultimately affect the clinical phenotype and response to therapy.

Surgical and cadaver studies show that vascular contact is not invariably found in patients who have

TN [36,43], suggesting that additional pathophysiologic mechanisms are involved.

Treatment

Pharmacologic. A simple and useful way of expressing the efficiency of a drug relative to placebo is using the number needed to treat (NNT). Efficiency is most often measured as at least a 50% reduction in the patients' level of pain. For example, an NNT of three indicates that every third patient will obtain this reduction. Carbamazepine is highly efficacious in TN, with an NNT of 2.6 for significant pain relief, and is usually the first drug tested [44,45]. Its success in TN is often extrapolated to a diagnostic test, but up to 30% of patients may be initially resistant and up to 50% become refractory to carbamazepine therapy [14,46]. Oxcarbazepine, a carbamazepine derivative, is efficacious in TN with fewer side effects [18]. Baclofen has been successfully used in TN and, because of its low side-effect profile, may be titrated to high doses (80 mg/d) with an NNT of 1.4, but this recommendation is based on only one trial [47]. Moreover, few patients are actually able to tolerate high doses. A strong synergistic effect with carbamazepine is reported, also making baclofen suitable for combined therapy. The newer anticonvulsants have fewer side effects and may be effective for some patients either as mono- or add-on therapy. Lamotrigine is effective and has been rigorously tested as add-on therapy with an NNT of 2.1 [48]. Gabapentin has not been rigorously tested in TN but may be useful in selected patients who have TN.

Based on current evidence, the authors initiate therapy with carbamazepine and rapidly transfer patients to the controlled-release formulation that has fewer side effects. If carbamazepine continues to cause troublesome side effects, they reduce the dose and add baclofen, or may try oxcarbazepine. In refractory cases, add-on therapy with lamotrigine or baclofen should be tried before changing drugs. Gabapentin is probably the most promising alternative, but pregabalin, topiramate, or even the older anticonvulsants valproate and phenytoin may be tried in recalcitrant cases [49] (Table 3). All patients taking anticonvulsants need baseline and follow-up tests of hematologic, electrolyte, and liver function. Even in patients who undergo successful treatment, exacerbations (ie, breakthrough pain) may occur and require temporary dose adjustment.

Surgical. The decision to choose surgery is partly based on results obtained from medical treatment, the patient's age, and medical status. The choice of neurosurgical procedures is often limited by the surgical facilities and expertise available. Quality of life in patients treated medically is significantly lower than in patients after microvascular decompression, and successful surgery often relieves anxiety and depression associated with TN [10]. Therefore, patients who have typical classical TN who are physically able are prime candidates for surgery.

Peripheral procedures. Nerve blocks provide temporary but absolute pain relief in TN. Reported success rates for neurectomy conflict (50%–64%) and involve small series with short-term follow-up [50]. In any event, pain in TN invariably recurs after neurectomy within a mean period of 2 years [51]. Cryotherapy of peripheral branches may provide

Table 3
Antiepileptic drugs and dose schedules commonly used in the treatment of trigeminal neuralgia and other painful trigeminal neuropathies

Drug	Initial dose (mg)	Target or maximal dose (mg)[a]	Dose increase (titration)[a]	Schedule
Carbamazepine	100–200	1200	100–200 mg every 2 days	3–4 times per day
Carbamazepine CR	200–400	1200	Usually transfer from regular format at equivalent dose	2 times per day
Oxcarbazepine	300	1200–2400	300–600 mg/wk	3 times per day
Baclofen	5–15	30–60	5 mg every 3 days	3 times per day
Gabapentin	300	900–2400	300 mg every 1–2 days	3 times per day
Pregabalin	150	300–600	50 mg every 2–3 days	2–3 times per day
Lamotrigine*	25	400–600	25–50 mg/wk	1–2 times per day

Abbreviation: CR, controlled release.

[a] Titrate according to response and side effects.

* Lamotrigine has been tested as add-on therapy in trigeminal neuralgia.

pain relief for 6 months and may be repeated with good results [52]. Alcohol injections may be effective for about 1 year but are painful, and fibrosis makes repeat injections technically difficult [53]. Complications may include full-thickness skin or mucosal ulceration, cranial nerve palsies, herpes zoster reactivation, and bony necrosis [50]. A 60% success rate at 24 months after peripheral glycerol injection has been reported, but others report pain relapse by 7 months [53,54]. However, single reinjection is possible, with good results reported [54]. Peripheral procedures all have the goal of inducing nerve damage and therefore carry the attendant risk for patients to develop dysesthesias. Neurectomy, cryotherapy, and alcohol block have all resulted in neuropathic pain (sometimes termed *anesthesia dolorosa*; see Table 1). Peripheral procedures should be reserved for emergency use or patients who have significant medical problems that make other procedures unsafe [50].

Based on the theory that neuralgia-inducing cavitational osteonecrosis (NICO) may cause some cases of TN, curettage and packing of affected jaw areas have been described [55]. The concepts underlying the pathophysiology have developed over the years from an infective process to an inflammatory reaction and a disorder based on coagulation defects that may induce avascular necrosis [56,57]. However, rigorous scientific investigation has not established a cause-and-effect relationship [57]; NICO data are sparse compared with the rich laboratory, imaging, surgical, and cadaver studies underlying the etiologic hypothesis for TN. Moreover, imaging often shows no evidence for cavitation and diagnosis is based on nonspecific criteria, such as the presence of pain and its elimination with local anesthesia. Pathologic review of excised tissue often shows nonspecific findings. Therefore, the authors and many prominent oral and maxillofacial surgeons cannot currently endorse this mode of treatment [57–59].

Central procedures. ***Percutaneous trigeminal rhizotomy.*** These procedures are directed at the trigeminal ganglion and include radiofrequency rhizolysis, glycerol injection, or balloon compression. The three modalities provide approximately equal initial pain relief (around 90%) but are each associated with different rates of recurrence and complications [35,60]. Overall, radiofrequency rhizolysis consistently provides the highest rates of sustained pain relief but is associated with high frequencies of facial and corneal numbness.

Microvascular decompression. Microvascular decompression is based on the premise that TN is caused by vascular compression of the nerve root, and surgically separating them may offer a permanent cure. Surgical morbidity for this procedure has decreased to approximately 0.3% to 3% [61], making it a more attractive option than in the past. Complication rates are lowest in high-volume hospitals and when the surgeon performs a large number of these procedures yearly [61]. Initial success rates for microvascular decompression are very high (approximately 90%), but long-term follow-up shows that after 10 years 30% to 40% of patients will experience a relapse [62,63]. Notwithstanding, patient satisfaction with microvascular decompression is very high, particularly if it is the first intervention for TN [64]. Data suggest that the best results for microvascular decompression are obtained when performed within 7 years of TN onset [65] in patients who have no (or minimal) sensory loss [19].

Gamma knife. Gamma knife stereotactic radiosurgery (GK-SRS) is a minimally invasive technique that precisely delivers radiosurgical doses of 70 to 90 Gy to the trigeminal nerve root at the point of vascular compression as mapped using MRI. GK-SRS may be indicated in patients who are poor candidates for microvascular decompression, and provides good to excellent (60%–90%) initial pain relief [66,67]. Although posterior fossa surgery was shown to be superior to GK-SRS over a mean follow-up duration of approximately 2 years [68], some reports have shown that GK-SRS results may be improved through modifying the dose and delivery mode [69]. Additionally data suggest that GK-SRS may be the preferred procedure for recurrent classical TN [70]. This modality thus requires further investigation and review.

Trigeminal neuralgia: oral and maxillofacial surgery perspective

The numbers of TN cases with extensive and misguided dental interventions suggest a lack of awareness of many dentists to the features of classical TN or the existence of PTN. Oral and maxillofacial surgeons are often consulted for patients who have unexplained pain, which may be TN. Alternatively, patients experiencing TN pain may be referred to oral and maxillofacial surgeons for extractions. Invasive dental treatment must not be performed when it is not indicated by positive anamnestic, clinical, and radiographic signs. Additionally, oral and maxillofacial surgeons may be asked to help manage medically complex, elderly patients who have TN who are unsuitable for central

procedures. Several peripheral procedures are available that may offer temporary relief.

Glossopharyngeal neuralgia

Glossopharyngeal neuralgia (GN) is characterized by a milder natural history than that of TN. However, because of its location, clinical features, and rarity (0.7 cases/100,000 [32]) GN is difficult to diagnose and adequate treatment is often delayed several years [71]. Pain location in GN is dictated by which of the two sensory branches are affected [6]. Pain in pharyngeal-GN is usually located in the pharynx, tonsil, soft palate, or posterior tongue-base and radiates upward to the inner ear or the angle of the mandible. Tympanic-GN is characterized by pain that either remains confined to or markedly predominates in the ear but may subsequently radiate to the pharynx. Bilaterality is not uncommon and occurs in up to a quarter of patients [32].

Pain is usually described as sharp, stabbing, shooting, or lancinating and is stereotyped within patients [6]. Some patients may report a scratching or foreign body sensation in the throat. Attacks of GN are commonly mild but may vary in intensity to excruciating [32]. Usually no warning sign precedes an oncoming attack, but some cases report preattack discomfort in the throat or ear.

Typically GN trigger areas are located in the tonsillar region and posterior pharynx and are activated through swallowing, chewing, talking, coughing, or yawning [6]. Sneezing, clearing the throat, touching the gingiva or oral mucosa, blowing the nose, or rubbing the ear also trigger pain [32]. Topical analgesia to trigger areas will eliminate both trigger and pain and may help diagnose GN, although the areas may be difficult to reach.

Pain usually lasts from 8 to 50 seconds but may continue for up to 40 minutes or even recur in rapid succession [72]. Frequency of paroxysms may be 5 to 12 per hour, reaching 150 to 200 per day. After an individual attack a refractory period occurs [6]. Attacks may occur in clusters lasting weeks to months, then relapse for up to several years [6]. Spontaneous remissions are common, but some have no periods of pain relief. GN is reported to induce syncope, probably mediated by functional central connections between visceral afferents of cranial nerves (IX and X) and autonomic medullary nuclei. Cardiac arrhythmias are common, particularly bradycardia. Imaging of the head and neck to rule out pathology is indicated. An electrocardiogram should be performed before and after treatment.

Differential diagnosis

The most common differential is TN, particularly when pain of GN spreads to trigeminal dermatomes. Moreover, the co-occurrence of TN is reported in 10% to 12% of patients who have GN [73]. As observed in TN, a significant association between GN and MS has been reported [74]. Regional infectious or inflammatory processes and cerebellopontine angle or pontine lesions may cause GN-like symptoms [75]. Tonsillar carcinoma invading the parapharyngeal space and other regional tumors (tongue, oropharyngeal) may mimic GN [76].

Treatment

Pharmacotherapy for GN is based on drugs successfully used for TN. Microvascular decompression of the glossopharyngeal nerve root also has been used successfully. Life-threatening arrhythmias may require cardiac pacing.

Glossopharyngeal neuralgia: oral and maxillofacial surgery perspective

GN is an extremely rare syndrome that is difficult to diagnose. Although pain located in the ear may be confused with temporomandibular joint problems, the pain characteristics are very different.

Acute herpes zoster

Acute herpes zoster (HZ or shingles) is reactivation of latent HZ virus that causes a disease of the dorsal root ganglion with dermatomal vesicular eruption. Every year approximately 0.1% to 0.5% of the population develops HZ, with 1% occurring in individuals older than 80 years [77]. The overall lifetime risk of HZ is 10% to 20%, and more than 50% in patients older than 80 years. Trigeminal and cervical nerves are affected in 8% to 28% and 13% to 23% of acute HZ cases, respectively [78,79]. The ophthalmic branch is affected in more than 80% of trigeminal cases, particularly in elderly men, and may cause sight-threatening keratitis. Unilateral, intraoral vesicles may be observed in HZ of the maxillary or mandibular branches. These rapidly break down to small ulcers that may coalesce.

Acute HZ eruption begins with a prodrome of pain, headache, itching, and malaise [78]. Pain usually precedes the skin eruption by 2 to 3 days (<7 days) and may continue for up to 3 to 6 months with varying intensity. The acute stage is characterized by a unilateral, dermatomal, red maculopapular rash that develops into a vesicular eruption over 3 to 5 days; this usually dries out within another 7 to 10 days. Constant pain is

present, often with superimposed lancinating pains [79]. Stimulus-dependent pain, mechanical allodynia, and disturbed sensory thresholds are often seen and usually spread to adjacent dermatomes and bilaterally [79,80]. Descriptions of pain include burning, stabbing, shooting, tingling, and aching [78]. Intensity may be moderate to severe (VAS 6.2), but up to 25% of patients may report no pain [79,81]. High pain severity correlates with an increased incidence of postherpetic neuralgia (PHN) [81].

Pathophysiology

Viral DNA is found in most ganglion cells, with resultant cell degeneration, satellitosis, and lymphocytic infiltration of the nerve root. Acute inflammatory changes are maximal within the ganglion of the affected dermatome but also extend peripherally along the length of the sensory nerve (neuritis), followed by neuronal destruction [82]. These events lead to central sensitization. Viral-induced damage spreads within the spinal cord, involving adjacent segments (bilaterally) and in severe cases the ventral horn with resultant motor paralysis.

Treatment

Therapy is directed at controlling pain, accelerating healing, and reducing the risk for complications such as dissemination, PHN, and local secondary infection [83]. When antivirals are initiated early (<72 hours from onset of rash), particularly in patients older than 50 years, they decrease rash duration, pain severity, and the incidence of PHN [81]. Amitriptyline will provide analgesia, may shorten illness duration, and provides added protection from PHN [84]. When patients do not respond to analgesics, some experts recommend the use of corticosteroids [83]. However, all recent studies show that corticosteroids do not reduce the incidence of PHN [83]. Vaccinating individuals who are at risk, such as those who are elderly and immunocompromised, may be an efficacious technique to prevent HZ and PHN [85].

Herpes zoster: oral and maxillofacial surgery perspective

Oral and maxillofacial surgery departments often cover emergency rooms where some HZ cases may appear. The early detection of HZ cases and rapid initiation of antiviral and adjuvant therapy may substantially reduce long-term morbidity.

Postherpetic trigeminal neuralgia

A proportion (16%–22%) of patients who have acute HZ will report pain 3 to 6 months after initial onset, and these are categorized as having PHN. By 1 year, only 5% to 10% continue to experience pain. Several risk factors for persistent pain have emerged and include advanced age and severe prodromal pain, acute pain, and rash [86]. In the older age group (>60 years), 50% or more will continue to experience pain lasting more than 1 year.

Clinical features

Trigeminal PHN is a direct complication of acute HZ of the trigeminal nerve and will therefore localize to the affected dermatome, usually the ophthalmic branch. Pale sometimes red/purple scars may remain in the affected area. These scars are usually hypoesthetic or anesthetic and may paradoxically exhibit allodynia and hyperalgesia. Pain in PHN is burning, throbbing, stabbing, shooting, or sharp [87]. Itching of affected areas is common in trigeminal dermatomes and may be prominent and bothersome [88]. PHN is usually severe, with VAS ratings of 8 on a 10-cm scale, but is characterized by fluctuations [87].

Pathophysiology

PHN is a neuropathic pain syndrome resulting from viral-induced nerve injury. Scarring of sensory ganglia, peripheral nerves, and loss of large myelinated fibers is commonly found in patients who have PHN [89]. Skin biopsies from affected and contralateral sites show bilateral peripheral nerve damage that correlates with the persistence of PHN [90]. PHN is believed to progress from peripheral to central structures. Ongoing activity in peripheral nociceptors has been shown to be important in the early stages (<1 year) of PHN, whereas central mechanisms may become prominent in later stages [91]. The degree at which these processes are prominent define the clinical phenotype.

Treatment

Evidence-based treatment options for PHN include tricyclic antidepressant drugs, gabapentin, pregabalin, opioids, and topical lidocaine patches [92]. For PHN the overall NNT for effectiveness of antidepressants was 2.2; NNTs for amitriptyline vary from 1.6 to 3.2. Lidocaine patches are very effective in patients who have allodynia, with an NNT of 2. Gabapentin (NNT, 3.9–4.39), pregabalin (NNT, 3.3–4.93), and opioids (NNT, 2.5–3) are

beneficial [45,93]. More invasive modalities include epidural and intrathecal steroids and various neurosurgical techniques. Ophthalmic PHN is most resistant to treatment, but overall PHN carries a better prognosis than TN.

Postherpetic neuralgia: oral and maxillofacial surgery perspective

PHN is a chronic disease most often treated in pain clinics or neurology centers. Trigeminal PHN may be confused with dental or other orofacial pain, but the history is usually very clear.

Central causes of orofacial pain

Central pain may be caused by direct damage as in stroke and spinal cord trauma, secondary to centrally occurring diseases such as MS or other nervous system dysfunction. A central pain of particular interest to oral and maxillofacial surgeons is burning mouth syndrome, which is discussed extensively in the article by Klasser, Fischer, and Epstein in this issue.

Traumatic orofacial neuropathies

Micro- or macrotrauma (surgery, accidents) to orofacial structures may induce nerve injury that may ultimately result in chronic neuropathic pain. After zygomatic complex fractures, residual mild hypoesthesia of the infraorbital nerve is common, but chronic neuropathic pain is rare (3.3%) [94]. This rate of residual neuropathic pain is less compared with other body regions [95]. After dental implant and orthognathic surgery, 1% to 8% and 5% to 30% of patients, respectively, may have permanent sensory dysfunction, but the incidence of chronic pain is unclear [96–99]. Fig. 1B shows a case of nerve damage secondary to implant placement. Third molar extractions are associated with transient hypoesthesia [100]. Disturbed sensation may remain in 0.3% to 1% of cases for varying periods [101] but is rarely associated with chronic neuropathic pain [102]. Patient complaints of tongue dysesthesia after injury may remain in a small group of patients (0.5%) [103].

Persistent pain after successful endodontics was found to occur in 3% to 13% of cases [104,105], whereas surgical endodontics resulted in chronic neuropathic pain in 5% [106]. Factors significantly associated with persistent pain were long duration of preoperative pain, marked symptomatology from the tooth, previous chronic pain problems or a history of painful treatment in the orofacial region, and female gender [104].

Clinical features

Painful neuropathies often present with a clinical phenotype involving combinations of spontaneous and evoked pain. Positive (eg, dysesthesia) and negative symptomatology (eg, numbness) may be present, particularly if a major nerve branch (eg, infraorbital, inferior alveolar) was injured. Pain is of moderate to severe intensity and usually burning but may possess paroxysmal qualities. Pain is unilateral and may be precisely located to the dermatome of the affected nerve, but may be diffuse and spread across dermatomes. Patients may complain of swelling or a feeling of swelling, foreign body, hot or cold, local redness, or flushing.

Possible syndromes of painful traumatic trigeminal neuropathy

Persistent idiopathic facial pain (previously atypical facial pain). Much data collected on atypical facial pain (AFP) suggest a continuous neuropathic condition, and many patients who have AFP show some degree of sensory dysfunction [107]. The International Headache Society (IHS) criteria for persistent idiopathic facial pain (PIFP) include the presence of daily or near daily pain that is initially confined but may subsequently spread. The pain is not associated with sensory loss and cannot be attributed to any other pathologic process. This definition is rather loose and has not been field tested, and therefore it may misleadingly allow the classification of a large number of chronic facial pain disorders. Until specific data on PIFP accumulate, the features of AFP are briefly described.

Clinical features. Pain is usually poorly localized, radiating, and mostly unilateral, although up to 40% of cases may describe bilateral pain [12,108]. AFP is commonly described as burning, throbbing, and often stabbing [108,109]. Intensity is mild to severe and rated approximately 7 of 10 on a VAS [110]. Most patients report long-lasting (years) chronic daily pain, although pain-free periods have been reported [12,108]. Pain onset is often associated with surgical or other invasive procedures [108]. Although no sensory deficits should be present, they have been reported in up to 60% of cases [107,108]. The lack of a clear pathophysiologic basis precludes the establishment of a treatment protocol. The use of tricyclic antidepressants and anticonvulsants may be beneficial.

Atypical odontalgia. Atypical odontalgia is defined by the International Association for the Study of Pain as a severe throbbing pain in the

tooth without major pathology [1]; however, the IHS does not classify atypical odontalgia and suggests that it may be a subentity of PIFP. Whether atypical odontalgia is a neurovascular or neuropathic syndrome is the source of controversy, but most researchers consider atypical odontalgia to be neuropathic, most probably a subentity of AFP [111–114].

Complex regional pain syndrome. Complex regional pain syndrome (CRPS) has been previously termed *sympathetically maintained pain*, *reflex sympathetic dystrophy*, or *causalgia*. These early terms were based on observations of the clinical phenotype that often suggested involvement of the sympathetic nervous system. However, the link between nociceptive neurons and postganglionic sympathetic activity is inconsistent, with sympathetic blocks sometimes altering the syndrome at least temporarily and sometimes not [115]. Adrenergic mechanisms in some form seem to be involved in some of these conditions, but measurements of sympathetic responses have often shown normal results [116]. The current terminology attempts to solve these issues and is not suggestive of suspected etiologic mechanisms.

CRPSs are painful disorders that develop because of injury; CRPS I was previously referred to as reflex sympathetic dystrophy and CRPS II was previously referred to as causalgia [1]. Both entities present with spontaneous pain accompanied by allodynia and hyperalgesia that are not limited to dermatomal regions [117]. Additional signs include edema, abnormal blood flow in the skin, and abnormal sudomotor activity. CRPS I may develop as a consequence of remote trauma or after minor local trauma, such as sprains or surgery. These result in minor or no identifiable nerve lesions with disproportionate pain. The less frequent form, CRPS II, is characterized by a substantiated injury to a major nerve. Both syndromes may have clinical evidence to support the involvement of the sympathetic nervous system, in which case the term *sympathetically maintained pain* is added. However, this finding is not a prerequisite for diagnosing CRPS.

Clinical features. CRPS is most often reported in the extremities. Pain is usually of a burning or pricking character felt deep within the most distal part of the affected limb [118]. Most patients describe pain at rest, but movement and joint pressure will elicit or worsen pain [119]. Reduced sensitivity to thermal and mechanical stimuli is usually present and may spread to involve the adjacent body quadrant or even half of the body, suggesting central involvement. Other sensory abnormalities include mechanical/thermal allodynia and hyperalgesia not restricted to nerve territories [119]. Paresthesias are rare, but approximately one third will complain of a foreign, neglect-type feeling in the affected limb. Weakness, contraction, fibrosis, and tremor of the affected site are observed [119]. During the acute stage, more than 80% have edema and cutaneous vasodilation occurs, with the skin appearing red [119]. In the chronic stages, this may subsequently reverse into vasoconstriction, resulting in cold, bluish skin [120]. Increased sweating and trophic phenomena are common. Over time, atrophic changes appear in skin, nails, and muscles.

Therapy should be aimed at restoration of function and reduction of pain. Depending on the disease stage and symptomatology, steroids and sympathetic blocks may be indicated. Antidepressants and anticonvulsants may relieve neuropathic pain components, and opioids should be tried if these fail [119].

Complex regional pain syndrome in the orofacial region. The historical dependence on sympathetic involvement for diagnosing CRPS has probably prevented the identification and documentation of head and neck cases. Thus, reports have relied on cervical sympathectomy, clonidine, guanethidine, and stellate ganglion blockade to confirm CRPS [121]. Certain features, such as trophic changes and skin atrophy, are unreported in the trigeminal region and motor disturbances are rare. The particular clinical phenotype may reflect the trigeminal system's differential response to trauma [122].

Pathophysiology of complex regional pain syndrome. Research has suggested that particular processes are important in CRPS, including neurogenic inflammation, up-regulated neuropeptide release with impaired inactivation, and enhanced sensory sympathetic interactions [119].

Pathophysiology of painful traumatic neuropathies

Pain in neuropathy varies among patients, even after identical injuries. This variability is probably caused by a combination of environmental, psychosocial, and genetic factors. The pathophysiology of painful inflammatory or traumatic neuropathies involves a cascade of events in nervous system function that includes alterations in functional, biochemical, and physical characteristics [123–125], which are collectively termed *neuronal plasticity*. The prominent events are summarized in Fig. 2. Some of the pathophysiologic

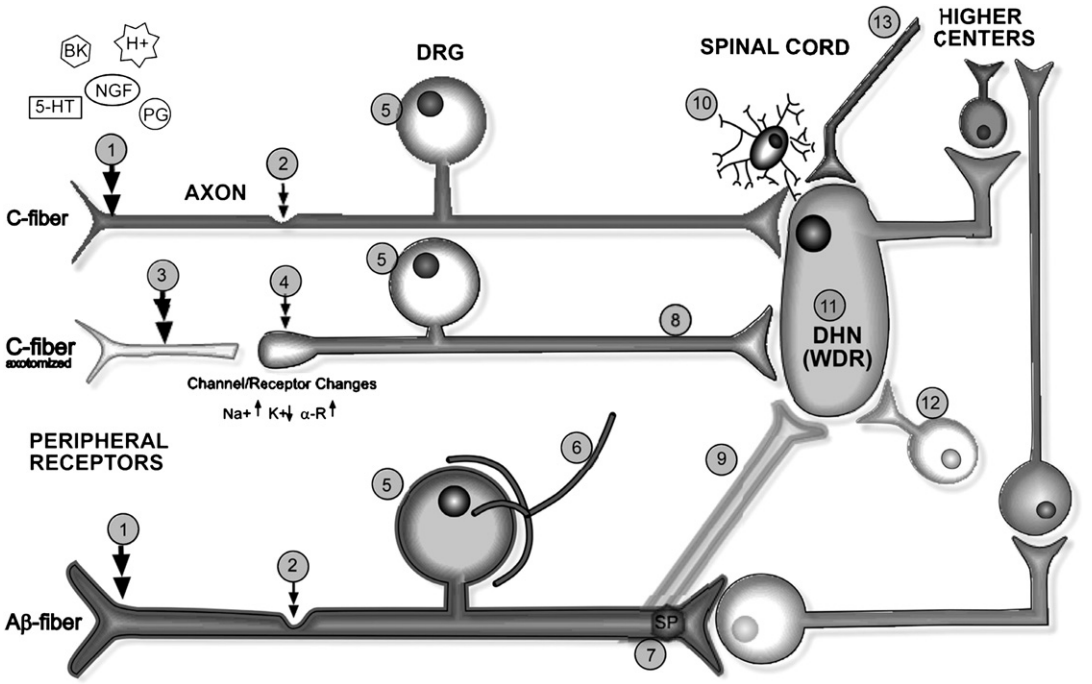

Fig. 2. Peripheral and central nervous system changes in chronic pain. In peripheral sensitization, tissue damage (1) releases inflammatory mediators, such as bradykinin (BK), nerve growth factor (NGF), serotonin (5-HT), prostaglandins (PG) and protons (H+). This "inflammatory soup" of bioactive molecules induces increased sensitivity of peripheral nociceptors leading to allodynia and hyperalgesia. Axonal injury (transection, crush, or chronic pressure and inflammation) induces increases in sodium (Na+) and α-adrenoreceptors (α-R) (2), initiating ectopic activity and increased sensitivity to mechanical and chemical stimuli. Axotomy may induce neuronal cell death. Alternatively, death of the distal part of the nerve may occur (3) while the proximal section survives with healing and neuroma formation (4). Neuromas may possess ectopic electrophysiologic activity, secondary to changes in specific ion channels. This activity leads to altered gene expression in the neuronal cell bodies located in the ganglia (DRG) and may induce ectopic activity origination from DRG cells (5). These phenomena explain spontaneous pain and the pain experienced when neuromas are touched. Nerve injury may lead to sympathetic nerve fiber sprouting (6), particularly around the larger DRG cells; this has not been detected in trigeminal ganglion cells. A-beta fibers undergo a phenotypic change (7), resulting in novel expression of neurotransmitters associated with nociceptors, such as substance P (SP). Injury-induced C-fiber degeneration (8) may result in sprouting of A-beta fibers from deep to superficial dorsal horn layers (9), augmenting allodynia. Primary afferents and dorsal horn neurons activate glial cells in the dorsal horn (10), and these compromise opioid analgesia and enhance dorsal-horn-neuron and primary afferent activity and excitability. Persistent nociceptive input also results in the direct sensitization of wide dynamic range (WDR) dorsal horn neurons (DHN) (11) and excitation of adjacent neurons (central sensitization). Central sensitization involves the activation and sensitization of the *N*-methyl-D-aspartate receptor. Glutamate released by nerve fibers is excitotoxic and reduces the number of inhibitory interneurons, augmenting excitation (12). Persistent pain initiates descending modulation, which in pathologic states tends toward facilitation (13). (*From* Benoliel R, Heir G, Eliav E. Neuropathic orofacial pain. In: Sharav Y, Benoliel R, editors. Orofacial Pain and Headache. Elsevier, in press; with permission.)

events are probably common to various neuropathies described earlier; each clinical entity is characterized by specific events and features, and these have been reviewed individually.

Indirect macrotrauma. Evidence shows that indirect macrotrauma may induce central nervous system damage. Even after minor head trauma, progressive and extensive axonal injury caused by widespread shearing occurs and is commonly known as *diffuse axonal injury* [126,127]. This phenomenon may underlie chronic pains associated with closed head trauma.

Treatment of painful traumatic trigeminal neuropathies

The inescapable progression of events after nerve or extensive tissue damage suggests that

early intervention is most important. With preemptive analgesia, preoperative treatment is designed to reduce or eliminate the initial sensory barrage and prevent central sensitization. The strategies include the use of preoperative local anesthetics and analgesics. In the dental setting, local anesthetics are routine and analgesics are usually ingested perioperatively, establishing the basis for a preemptive strategy.

Strategies for established painful trigeminal neuropathies. The goal of therapy is to reduce pain intensity and onset frequency. Research shows that approximately a 30% reduction represents meaningful pain relief for patients who have neuropathic pain [128].

The role of surgery in the management of painful TNs is unclear. In the authors' clinical experience, most patients who have undergone peripheral surgical procedures (exploration, further apicoectomies) for traumatic TN end up with more pain. Some cases reported in the literature were treated with peripheral glycerol injections with some success, but the authors have found no prospective controlled trials. Based on this experience, the authors recommend that patients who have painful traumatic neuropathies should not to undergo further surgery, but this has not been rigorously tested.

Some injuries to the lingual or inferior alveolar nerves may induce significant discomfort to patients, including liquid incompetence and untoward effects on speech, chewing, gustation, and swallowing. Several patients may present with pain and neurosensory dysfunction [129]. Most cases are secondary to surgical removal of impacted third molars [130–132]. Microsurgical repair may be warranted in these cases and an operative management protocol has been suggested [133]. Best results are probably obtained when nerve injuries are operated on early (<10 weeks). Surgery is more successful in inferior alveolar than in lingual nerve injuries [134], and the presence of a neuroma is a negative prognostic factor [129]. However, even in case series with repair within 1 year of injury, success rates as measured through sensory recovery are high [129–132]. Approximately 50% of repaired cases will recover full sensory function by 7 months [129]. Although most studies report sensory improvement, only a limited number of studies focus on pain accompanying nerve damage [129,132]. In some patients, microsurgery may offer successful management of pain and neurosensory dysfunction [129].

No prospective trials were found on central procedures for treating painful traumatic neuropathy. Anecdotal evidence suggests that central procedures may be useful for recalcitrant cases [135,136]. The authors suggest that the primary choice of operation should be minimally invasive, such as a trigeminal tractotomy nucleotomy (surgical division of the descending fibers of the trigeminal tract in the medulla effectively ablating pathways that carry sensation from the face). Trigeminal dorsal root entry zone operation (surgical damage to a portion of neurons in the trigeminal nerve root at brainstem level) may subsequently be performed for failures [136].

Available evidence confirms that successful pharmacotherapy of neuropathic pain relies on the anticonvulsant drugs and antidepressants, particularly the tricyclic antidepressants [137] (see Table 3; Table 4). Anticonvulsant drugs are heterogenous in their efficacy for the treatment of painful neuropathies [45]. Phenytoin (NNT, 2) has been shown superior to both carbamazepine (NNT, 3.3) and gabapentin (NNT, 3.8) but has significant side effects. For TN, anticonvulsant drugs, particularly carbamazepine, are preferred [45]. Based on the efficacy of pregabalin and gabapentin in peripheral neuropathies (PHN or diabetic neuropathy), they may also be good treatment options in traumatic neuropathy.

Table 4
Antidepressant drugs and dose schedules commonly used in the treatment of painful trigeminal neuropathies

Drug	Initial dose (mg)	Target or maximal dose (mg)[a]	Dose increase (titration)[a]	Schedule
Amitriptyline	10	35–50	10 mg/wk	Bedtime
Imipramine	12.5	25–50	12.5 mg/wk	Bedtime
Venlafaxine	37.5	75–150	75 mg every 4–7 days	2–3 times per day
Venlafaxine XR	37.5	75–225	75 mg every 4–7 days	1 per day
Duloxetine	20–40	60	20 mg/wk	1–2 times per day

Abbreviation: XR, extended release.
[a] Titrate according to response and side effects.

Analgesic trials with tricyclic antidepressants show that drugs with mixed serotonin/noradrenaline or specific noradrenaline reuptake inhibition are superior to the selective serotonin reuptake inhibitors, such as fluoxetine or paroxetine [138]. Calculations of the NNT show that tricyclic antidepressants such as amitriptyline benefit approximately every other patient (NNT, 2.2) experiencing painful polyneuropathies [139]. With careful dose titration, an NNT of 1.4 for imipramine may be attained in the treatment of traumatic neuropathies. In contrast, selective serotonin reuptake inhibitors have an NNT of 7 in painful polyneuropathies. Venlafaxine has an NNT of around 4 for painful polyneuropathy and duloxetine has an NNT of 4.1 for diabetic neuropathy; both have fewer side effects than the tricyclic antidepressants and may be attractive alternatives [137].

Based on a large literature review and the authors' clinical experience, tricyclic antidepressants or gabapentin/pregabalin would be the first drugs indicated in painful peripheral neuropathy. The efficacy of tricyclic antidepressants is counterbalanced by the excellent side effect profile of the newer anticonvulsant drugs. If initial tricyclic antidepressants or gabapentin are unsuccessful, patients should be transferred to their counterparts (ie, tricyclic antidepressants to gabapentin and vice versa) [137]. If individual drugs (tricyclic antidepressants, gabapentin) are partly successful, combination approaches may be used. Third-line monotherapy or add-on therapy may be attained with opioids or tramadol or newer agents such as duloxetine.

Combination therapies. Neuropathic pain involves multiple mechanisms at various sites with complex interactions. Theoretically, the use of drugs with different modes and sites of action may lead to improved efficacy with reduced side effects. For example, the combination of gabapentin and morphine produced significant analgesia in patients who had neuropathic pain (PHN and diabetic neuropathy) at a lower dose than each drug separately [140]. In patients who had painful diabetic neuropathy who did not respond to gabapentin monotherapy, the addition of venlafaxine in a double-blinded fashion resulted in significant pain improvement [141].

Neuropathy secondary to neuritis

The term *peripheral neuritis* was commonly used to describe generalized neuropathies related to chemical poisoning, autoimmunity, alcohol, or nutritional deficiencies that may have an inflammatory component. Currently, *neuritis* is used to describe localized nerve pathologies secondary to inflammation. Inflammation anywhere along a nerve can be a source of pain felt in the organ supplied by the nerve. Inflammation may affect the nerve either through direct effects of mediator secretion, mainly cytokines, or secondary to pressure induced by the accompanying edema [142]. Both processes can induce nerve damage if allowed to persist [3]. Studies have characterized the symptoms accompanying this condition and shown tactile allodynia with a dominant role for myelinated nerve fibers [3,143].

In the orofacial region, dental and other invasive procedures can generate temporary perineural inflammation, but it is usually asymptomatic. However, misplaced implants or periapical inflammation close to a nerve trunk can produce symptoms. Other conditions, such as temporomandibular joint pathologies [4], paranasal sinusitis [5], or early malignancies [144], can induce symptomatic perineural inflammation, pain, and other aberrant sensations.

The involvement of inflammation in a clinical painful neuropathy is a clear indication for anti-inflammatory therapy. Early treatment with anti-inflammatory medication (corticosteroids or nonsteroidal anti inflammatory drugs) can be beneficial because perineural and neural inflammation have a role in most neuronal pathologies.

Traumatic neuropathy: oral and maxillofacial surgery perspective

Although most surgical procedures heal with no residual problems, a small percentage of patients may present with continuing pain. Patients who have traumatic neuropathy must be separated from those who have recurrent pathology; the former may worsen with further surgeries. Additionally, careful surgical technique to avoid extensive tissue damage and direct neuronal injury is essential. Adequate local anesthesia and a comprehensive postoperative protocol for analgesia may be important in preventing chronic pain. Patients who have macrotrauma and fractures to the facial skeleton are often managed by oral and maxillofacial surgeons. Although early management is directed at life-saving interventions and restoring form and function, attention to pain and nerve injury is important. Early treatment of trauma-related pain probably allows a better prognosis. In selected cases, oral and maxillofacial surgeons may

be involved in the microsurgical reconstruction of damaged nerve trunks. Early distinction between sensory dysfunction secondary to nerve damage or operative edema is clinically difficult; QST may be crucial in these situations.

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Burning Mouth Syndrome: Recognition, Understanding, and Management

Gary D. Klasser, DMD[a,*], Dena J. Fischer, DDS, MSD, MS[a], Joel B. Epstein, DMD, MSD, FRCD(C), FCDS(BC), FDS RCSEdin[a,b]

[a]*Department of Oral Medicine and Diagnostic Sciences, University of Illinois at Chicago, College of Dentistry, 801 South Paulina Street, Chicago, IL 60612-7213, USA*

[b]*Interdisciplinary Program in Oral Cancer, University of Illinois at Chicago, Cancer Research Center, 801 South Paulina Street, Chicago, IL 60612-7213, USA*

Burning mouth syndrome (BMS) is defined by the International Association for the Study of Pain [1] as burning pain in the tongue or other oral mucous membrane associated with normal signs and laboratory findings lasting at least 4 to 6 months [2,3]. The International Classification of Diseases (version 9) has assigned the term glossodynia, which includes the adjunctive terms glossopyrosis and painful tongue, a specific identity code number (529.6) [4]. The International Headache Society in the International Classification of Headache Disorders II (ICHD-II) [5] classifies BMS in the category of cranial neuralgias and central causes of facial pain within the subcategory of central causes of facial pain. BMS (ICHD-II:13.18.5) is described as an intraoral burning sensation for which no medical or dental cause can be found. It is further noted that pain may be confined to the tongue (glossodynia) with associated symptoms that include subjective dryness of the mouth, paresthesia, and altered taste. Diagnostic criteria for BMS from ICHD-II are listed in Box 1. These definitions and classifications show the difficulty for the patient and the practitioner evaluating these individuals: the patient is experiencing continuous burning pain in the mouth without any obvious clinical signs, but the practitioner is unable to definitively diagnose these symptoms even with the use of diagnostic testing or imaging. This article aids the oral and maxillofacial surgeon in recognizing, understanding, and managing BMS.

Historically, BMS has been referred to by many names based on the quality or location of pain in the oral cavity. Some of these are: glossodynia, glossopyrosis, glossalgia, stomatodynia, stomatopyrosis, sore tongue, burning tongue, scalded mouth syndrome, oral dysesthesia, burning mouth condition, and burning mouth syndrome [6,7]. From these numerous descriptions it is not clear whether the oral mucosa appeared normal and, therefore, if these terms were describing BMS. The use of these multiple terms attests to the confusion and uncertainty that exists in the scientific literature and in clinical practice. This confusion has led to some discussion regarding the proper nomenclature for this condition. There is debate as to whether burning mouth is a syndrome or a disorder [6,8,9]. By definition, a syndrome (a disease unto itself) is a collection of several simultaneous signs and symptoms of varying intensity, which in the case of BMS is a normal-appearing oral mucosa with a burning sensation, a feeling of oral dryness, and taste disturbances [6,10–12]. A disorder is defined as a condition manifesting symptoms of other diseases, such as the complaint of dry mouth being the cause of the burning sensation often reported by patients who have BMS [9]. If burning mouth is a symptom of other local, systemic, or psychogenic diseases then this is referred to as oral burning disorder; otherwise the term burning mouth syndrome is used, making it a diagnosis of exclusion.

* Corresponding author.
E-mail address: gklasser@uic.edu (G.D. Klasser).

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Box 1. Diagnostic criteria for burning mouth syndrome

Pain in the mouth present daily and persisting for most of the day
Oral mucosa is of normal appearance
Local and systemic diseases have been excluded

Data from International Headache Society. The international classification of headache disorders. 2nd edition. Cephalalgia 2004; 24(Suppl 1):9–160.

Epidemiology

The prevalence of burning mouth symptoms reported from international studies ranges from 0.6% to 15% [8]. The considerable variation in prevalence among these studies may be because of different definitions of BMS leading to different criteria for the selection of the populations. Bergdahl and Bergdahl [13] performed a questionnaire survey study regarding oral burning complaints in a group of 1427 randomly selected subjects (669 male and 758 female) from 48,500 Swedish individuals between the ages of 20 and 69 years. All individuals who reported oral burning were clinically examined. It was found that 53 individuals (3.7%), 11 men (1.6%) and 42 women (5.5%), were classified as having BMS. In men, no BMS was found in the age groups of 20 to 39 years, whereas the prevalence in the 40- to 49-year-old age group was 0.7%, which increased to 3.6% in the 60- to 69-year-old age group. In women, no BMS was found in the 20- to 29-year-old age group, but in the age group 30 to 39 years the prevalence was 0.6% and increased to 12.2% in the 60- to 69-year-old age group. It seems the prevalence of BMS increases with age in both males and females, with this syndrome mainly affecting females in the fifth to seventh decade [13,14]. In an epidemiologic study conducted in the United States, the overall prevalence of burning mouth was found to be 0.7% in adults up to age 65 [15]. Interestingly, Riley and colleagues [16] repeated this telephone interview study in a subset of 5800 individuals aged 65 or older and reported a prevalence of only 1.7% for burning mouth pain. The difference between the lower prevalence of BMS in the Riley and colleagues study as compared with others may be related to methodologic errors, such as sampling bias, interview technique, question format, and lack of clinical examination. BMS usually first presents 3 years before to 12 years following menopause [3] and rarely before the age of 30 [13,17]. The ratio between females and males varies from 3:1 to 16:1 [3,18–21]. These gender differences may be explained by biologic, psychologic, and sociocultural factors; however, these factors are yet to be defined. It seems from these epidemiologic studies that menopausal females have a particularly high incidence of burning mouth. Despite these findings, no significant differences have been found between BMS and control subjects in any of the following factors: the number of years since menopause, the occurrence of surgical menopause, the use of hormone replacement therapy (HRT), the number of years of treatment with HRT, and the number of years passed since completion of HRT [3,22,23]. Santoro and colleagues [24] retrospectively studied the clinical and therapeutic experience of 28 patients who had BMS. They found that in a cohort of postmenopausal patients who had estrogen receptors of the oral mucosa (determined on biopsy of the buccal mucosa), hormone-replacing therapy had a positive effect on their symptoms. There has been only one study conducted on the prevalence of BMS in relation to ethnicity (Table 1). No studies have reported prevalence of burning mouth by social, educational, or occupational groups.

Table 1
Prevalence of burning mouth syndrome by demographic group

Demographic variable	Estimated prevalence (per 100,000)	Prevalence (%)
Ethnicity		
White, non-Hispanic	693	19
Black, non-Hispanic	531	15
Hispanic	786	22
Other non-Hispanic	1598	44
Age group		
18–34	609	19
35–54	696	21
55–74	757	23
75+	1184	36

Data from Lipton JA, Ship JA, Larach-Robinson D. Estimated prevalence and distribution of reported orofacial pain in the United States. J Am Dent Assoc 1993;124(10):115–21.

Classification

There have been several proposed classification schemes to better characterize and define BMS. One such classification [6,25] contains three subtypes according to variations in pain intensity over 24 hours. Type 1 is characterized by patients having burning every day. The burning is absent on waking but presents as the day goes on, being maximal in the evening. This type may be linked to systemic disorders, such as nutritional deficiencies and endocrine disorders [26]. Approximately 35% of patients who have BMS give such a history. Type 2 is characterized by burning that occurs every day, is present on awakening, and often makes falling asleep at night difficult. This subgroup of patients often report mood changes, alterations in eating habits, and decreased desire to socialize, which seem to be attributable to an altered sleep pattern [2,27]. Approximately 55% of patients who have BMS describe such a history. Type 3 is characterized by intermittent burning, present only on some days, with burning affecting unusual sites, such as the floor of the mouth, buccal mucosa, and throat. These patients frequently display anxiety and allergic reactions, particularly to food additives [28]. About 10% of patients who have BMS report this pattern of symptoms. A demographic study by Killough and colleagues [29] comparing BMS populations in the United Kingdom and United States has reported on identical prevalence rates using these subtypes within these two populations. The authors of this classification system believe that it is valid because they believe this system has prognostic significance and also indicates the necessity for specialist investigation to identify allergic components to the burning. This classification is not universally accepted, however, nor is it considered essential for management of the patient who has BMS.

A more pragmatic approach in classifying patients who have BMS is to divide patients into either primary (essential/idiopathic) BMS (no other evident disease) or secondary BMS (oral burning from other clinical abnormalities). Danhauer and colleagues [30] examined 69 patients who had BMS (83% female) with an average age of 62 years, pain duration of 2.45 years, and visual analog scale pain rating of 49 mm (rated from 0 to 100 mm). All patients completed the Multidimensional Pain Inventory (MPI) and Symptom Checklist 90-Revised (SCL-90R) questionnaires and had a clinical examination. The investigators found that there were no differences between the patients who had primary and secondary BMS with respect to age, pain duration, pain intensity, or levels of psychologic distress. There were substantial differences in burning symptom cessation with treatment; the patients who had secondary BMS improved if the underlying clinical abnormality was treated, whereas the primary BMS group did not report such positive results.

Symptomatology

Most individuals who have BMS describe their symptoms in the oral mucosa using the following words: burning, tender, tingling, hot, scalding, numb, and annoying. BMS is characterized by positive (burning pain, dysgeusia, and dysesthesia) and negative (taste loss and paresthesia) sensory symptoms [31]. The pain is mainly located bilaterally and symmetrically in the anterior two thirds of the tongue (71%–78%) followed by the dorsum and lateral borders of the tongue, the anterior aspect of the hard palate, and the labial mucosa of the lips, often occurring in multiple sites [3,10,20,32]. Other less commonly reported sites include the buccal mucosa, floor of the mouth, hard and soft palates, and the throat. The sites of pain do not seem to affect the course of the disorder or the response to treatments [28,33]. More than half the patients who have BMS experience a spontaneous onset of symptoms without any identifiable triggering factor [11,34]. About 17% to 33% of the patients attribute the onset of their symptoms to a previous illness, such as an upper respiratory tract infection, previous dental procedure, or medication use (including antibiotic therapy) [34–36], suggesting the possibility of neurologic alterations preceding the onset of burning in some patients [37–39]. Other individuals claim the onset of symptoms relates to traumatic life stressors [11,20,34]. Typically, the symptoms occur continuously for months or years without periods of cessation or remission [34], with some reports suggesting an average duration of 2 to 3 years [40,41]. There have been reports [34] of complete/partial remission (with or without intervention) in approximately 50% of patients and a complete spontaneous remission in approximately 20% of patients within 6 to 7 years of onset. The remission of symptoms, be it complete or partial, is often characterized by a change in pain pattern from a constant to an episodic form [34,42]. Contrary to these findings, Sardella

and colleagues [43], in an investigation to specifically evaluate the spontaneous remission rate in BMS, reported that a complete spontaneous remission was observed in only 3% of the patients within 5 years after BMS onset.

The pattern of daily symptoms is reportedly constant for the individual patient, with approximately one third of patients experiencing symptoms both day and night [3,13,20]. Most patients report minimal symptoms on awakening, after which the symptoms gradually increase during the day to culminate in the evening [2,3]. About one third of the patients have difficulty with sleep onset and some may awaken during the night because of the burning pain [20,44]. It has been suggested that these sleep disturbances and the presence of ongoing pain may explain the increased incidence of mood changes, irritability, and affective motivational disturbances among patients who have BMS [2,27]. The intensity of the burning pain has been described as moderate to severe and in some cases it is comparable to the intensity of toothache pain in regard to severity but not quality [27]. In most patients, the burning sensation intensifies in the presence of personal stressors, fatigue, and acidic foods (tomatoes and orange juice), and in about half the patients the intake of food or liquids and distraction seem to reduce or alleviate the symptoms [3,31]. It is unclear what the effects of tobacco, ethanol, or dietary factors are on the symptoms of BMS. Patients who have BMS have a significantly higher incidence of dry mouth, thirst, and taste disturbances, but they do not differ from healthy controls regarding changes in oral mucosa or dental problems [3,11,45,46]. More than two thirds of patients complain of dry mouth [3,10,13] and taste disturbances that manifest as a persistent alteration in taste (bitter or metallic) or a change in taste intensity [47]. Taste disturbances have been objectively demonstrated in patients who have BMS using electrical stimuli [48,49] and oral tastants [3,42,50] at threshold and suprathreshold levels. In contrast to these studies, Bergdahl and Bergdahl [51], in reviewing perceived taste disturbances from a large population-based study, found only a weak correlation between burning mouth and taste disturbances with perceived taste disturbances being more prevalent in females than males. Additionally, most studies have not objectively demonstrated decreased salivary flow rates despite the subjective complaints of dry mouth and thirst [26,36,52,53]. There have been several studies that have shown qualitative changes in salivary composition, however [36,53,54]. Furthermore, patients had no greater prevalence of medical conditions, such as diabetes, arthritis, or cardiovascular and gastrointestinal disorders, when compared with age- and sex-matched controls [3].

Patients who have BMS have more nonspecific health complaints and more severe menopausal symptoms as compared with healthy controls [3]. Headaches, dizziness, neck and back pain, dermatologic disorders, irritable bowel syndrome, anxiety, depression, personality disorders, and other psychiatric disorders are reported more frequently in these patients [20,35,45,46,55,56]. Many of these studies are unclear as to whether these symptoms are risk factors for development of BMS or a consequence of the syndrome, indicating a need for longitudinal cohort studies.

Etiology

The cause of BMS is currently unknown. The etiology is presumed to be multifactorial involving the interaction between biologic (neurophysiologic mechanisms) and psychologic factors [12]. A considerable number of local, systemic, and psychologic factors have been found related to BMS; however, several of these factors should be considered as conditions important to the differential diagnosis of oral burning rather than as an etiologic factor for BMS (Box 2).

Local factors

Various and multiple local factors have been implicated as causes of BMS. Some of these are: xerostomia, which is the subjective sensation of dry mouth and is found to be a frequent complaint (25% of patients who have BMS) [19,26,40] and may also include drug-induced xerostomia [40,48]; hyposalivation, which denotes objectively reduced salivary flow measured by sialometry [11,21,26]; taste disturbances involving either an alteration in taste perception, a persistently altered taste, or a combination [3,47,57]; oral infections involving bacterial, viral, or fungal (candidiasis) infection [58–62]; oral mucosal diseases, such as lichen planus [48]; parafunctional oral habits, such as clenching, bruxing, or tongue posturing [43,63]; mechanical and chemical irritations, such as galvanism and denture-related problems [26,64]; and allergic reactions [26,65]. Additionally, mucosal findings, such as benign migratory glossitis (geographic tongue), scalloped

Box 2. Reported etiologic factors for burning mouth syndrome

Local
Denture factors
Dental treatment
Mechanical factors
Parafunctional habits
  Clenching
  Bruxism
  Tongue posturing
  Myofascial pain
Allergic contact stomatitis
  Dental restorations
  Denture materials
  Foods
  Preservatives, additives, flavorings
Neurologic
  Referred from tonsils or teeth
  Trigeminal neuropathy
  Acoustic neuroma
Infection
  Bacterial
  Fungal
  Viral
Hyposalivation
  Radiation therapy
  Salivary gland disorders

Systemic
Deficiencies
  Iron (anemia)
  Vitamin B_{12}
  Folate
  Zinc
  B complex vitamins
Endocrine
  Diabetes
  Thyroid disease
  Menopause
  Hormonal deficiencies
Hyposalivation
  Connective tissue disease
  Sjögren syndrome
  Sicca syndrome
  Drug-induced
  Anxiety or stress
Medication
  Angiotensin converting enzyme (ACE) inhibitors
  Antihyperglycemic
Esophageal reflux

Psychologic
Depression
Anxiety
Obsessive compulsive disorder
Somatoform disorder
Cancerphobia
Psychosocial stressors

tongue, and fissured tongue, have also been considered [10,40,66]. Interestingly, Grushka [3] reported no significant differences on clinical examination between BMS and control subjects who had any intraoral soft or hard tissues findings. It is possible that the discrepancy between this study and the studies that found higher prevalences of oral changes may be attributable to the subjective nature of the diagnoses or may have developed as a result of the BMS rather than being the cause.

Systemic factors

There are many and varied systemic factors that have been considered as etiologic factors. Some of these are autoimmune, gastrointestinal, and endocrine disorders, such as connective tissue diseases, gastroesophageal reflux disease, diabetes, and thyroid disorders [11,18,31,42,67–70]; hormonal deficiencies and menopausal alterations [3,18]; drug-induced factors, especially involving angiotensin-converting enzyme (ACE) inhibitors, such as captopril, enalapril, and lisinopril [71,72]; and nutritional deficiencies involving vitamins and minerals, especially those associated with anemia (iron and vitamin B_{12} deficiency), zinc, and vitamin B complexes [73,74]. Despite some evidence from these studies supporting a possible association of these systemic factors as etiologic agents, there is much inconsistency within the literature [3,10,19,26,75–77]. Additionally, although more than 58% of people who have BMS display abnormal immunologic features, such as elevated rheumatoid factor and antinuclear antibody [78], no consistent relationship has been found between BMS and a connective tissue disorder. Other studies have reported a relationship between other facial pains [64], pains in other parts of the body [64], and headache pain [3] as being more frequent in patients who have BMS. The meaning and relevance of this association remains unclear, however.

Psychologic factors

Psychologic phenomena, such as alterations in states of anxiety and depression, somatization, and certain aberrant personality traits, are common findings in patients who have BMS [41,79–81]. At least one third of patients may have an underlying psychiatric diagnosis [40]. A phobic concern regarding cancer is also found in 20% of patients [26] and is often manifested as repeated self-examination by the patient [6]. Although BMS may be a somatic symptom of depression, the association does not always equate to a causal relationship. Carlson and colleagues [82] used the MPI and SCL-90R on 33 BMS cases and compared the data to those from population samples that included patients who had non-BMS chronic pain and a normal nonclinical sample. They concluded that there was no evidence for significant clinical elevations on any of the SCL-90R subscales, including depression, anxiety, and somatization. Moreover, patients reported significantly fewer disruptions in normal activities as a result of their oral burning pain than did a large sample of patients who had chronic pain. They did note that 21% of the BMS cases had substantially elevated psychologic distress. The presence of comorbid psychologic issues suggests the need for treatment of these problems but this is certainly not evidence of causality. Depression and psychologic disturbances are common findings in the chronic pain population and may be the result of the constant pain or may contribute to the cause, intensity, and urgency of complaint. Studies have reported similarities between the personality characteristics of chronic oral pain patients and other chronic pain populations [27]. In addition, many of the medications used to treat these psychologic conditions can cause side effects, such as dry mouth and taste alterations, that may induce or exacerbate BMS symptoms.

Salivary features

Xerostomia is a frequent complaint in patients who have BMS. No differences were identified in studies comparing the flow rates of whole saliva and parotid saliva between patients who had BMS and healthy controls [53,54,83–87]. There are many causes of xerostomia or hyposalivation, with the intake of certain medications being the most common causative factor. Because patients who have BMS take more medications, most likely because of issues regarding anxiety and depression, then it seems reasonable that this may account for the complaint of dry mouth in these individuals [69,88]. In a study by Lamey and colleagues [84] it was shown that stimulated parotid saliva flow rates were reduced in patients who had BMS who were taking antidepressants but normal in nonmedicated patients who had BMS.

Other possibilities for dry mouth symptoms found in BMS populations may be altered sensation or alterations in saliva composition or viscosity [89]. Some sialochemical studies in patients who have BMS have reported no alterations in the protein composition of whole or parotid saliva when compared with healthy age- and sex-matched controls [83,85,86]. Contrary to these findings, several studies have demonstrated, in stimulated and unstimulated whole saliva and stimulated parotid saliva, significant alterations in salivary compositions, such as proteins, immunoglobulins, inflammatory mediators, and phosphates, along with differences in salivary ions, pH, buffering capacity, electrical resistance, and conductance [46,54,87,90–94]. It has also been found that altered salivary composition is a common finding, possibly as a result of altered sympathetic tone at the time of menopause [22]. Although the significance of these findings is unknown, it is possible that these alterations represent a selective rather than a gross change in salivary flow rate related more to age or disease than BMS [95–97]. It does not seem that studies examining salivary flow rates or saliva composition in samples collected from the submandibular, sublingual, or minor salivary glands have been performed in the BMS population even though the location of BMS symptoms is frequently affected by areas exposed to the contents from these glands.

Evolving etiologic theories

The pursuit of a causal relationship is an extremely difficult task in science and association does not prove cause and effect. This distinction has not been purely adhered to as is evidenced by the vast array of potential etiologic factors reported by the many authors discussing BMS. For example, the observed elevated levels of psychologic issues, such as depression and anxiety, may be an effect of the chronic pain condition rather than a causative factor. Additionally, other local and systemic factors may purely be coincidental findings that are devoid of a cause-and-effect

relationship. Suarez and Clark [31] stated that to establish a causal link between two factors, one must have good consistency of data, meaning that the association investigated must be present in all cases regardless of the number of ways in which it is studied. They further comment that a biologically plausible explanation must be available regarding how the potential etiologic factor causes the outcome, and the suggested association must be independently verified. Using these criteria, there seem to be two current hypothetical etiologic theories for BMS, both involving neurologic processes.

Taste and sensory system interactions

Taste to the anterior two thirds of the tongue is innervated by a branch of cranial nerve (CN) VII (facial) by way of the chorda tympani nerve. Somatosensory innervation to this same area is supplied by a branch of CN V (trigeminal), the lingual nerve. The theory is that burning mouth pain symptoms occur when there is an abnormal interplay between the sensory function of these nerves within either the peripheral or central nervous systems [98,99]. This theory proposes that certain individuals, labeled as supertasters because of the high density of fungiform papillae present on the anterior aspect of the tongue, are more at risk for developing burning mouth pain. Supertasters are mainly females, who are able to perceive the bitter taste of a substance called PROP (6-n-propylthiouracil) and also experience a more intense burning sensation in the oral cavity, especially when stimulated with chili peppers [100,101]. Although supertasters may be at increased risk, those who are not supertasters may also develop symptoms of BMS following damage to taste wherein disinhibition of sensory input leads to burning symptoms. Svensson and colleagues [102] showed that patients who had BMS perceived a significantly more intense burning pain in the oral mucosa following exposure to capsaicin (the chemical irritant found in chili peppers) than did a matched control group. It has also been reported that unilateral anesthesia of the chorda tympani nerve intensifies the perception of burning pain on the contralateral anterior portion of the tongue, suggesting the presence of central inhibitory interactions between taste and oral pain [103]. A study by Eliav and colleagues [104] supports the concept of abnormal interplay between taste and sensory innervations by way of the chorda tympani and lingual nerves. Their study was composed of 48 patients: 22 patients had BMS, 14 had burning symptoms related to other diseases and were diagnosed as having secondary burning mouth syndrome, and 12 were healthy volunteers. The results of the study indicated an elevated electrical taste/tingling detection threshold ratio (lingual nerve) and taste detection threshold (chorda tympani) in the patients who had BMS, with 82% of these patients demonstrating chorda tympani dysfunction. This finding led to the conclusion that taste alteration may result in sensory hyperfunction. Additionally, the authors believe that this continuous input of pain may generate alterations in central nervous system processing and lead to pain that spreads beyond the affected nerve distribution. The taste and sensory system interaction theory speculates that damage (mechanical, chemical, or biologic) to the chorda tympani nerve impairs the normal ability of this nerve to inhibit sensations of pain from CN V. This impairment creates a type of disinhibition manifesting as an intensification of normal trigeminal sensations leading to spontaneous pain, altered sensations of touch, subjective sensations of oral dryness, and taste alterations (dysgeusia and phantom tastes) as observed in patients who have BMS [105]. It has also been suggested that interactions between taste and oral pain are not limited to BMS but may involve other orofacial pain complaints because patients who have persistent idiopathic facial pain also display taste damage [106]. Presently, this theory is lacking definitive data that a large proportion of patients who have BMS are indeed supertasters, and this theory is also unable to account for all the various manifestations that are clinically seen in the BMS population.

Neural alteration

Peripheral

The theory that alterations to the peripheral nervous system are an etiologic factor for BMS has been proposed in several studies. Jaaskelainen and colleagues [107] evaluated the possible neuropathic mechanisms underlying BMS by means of objective electrophysiologic examination of the trigeminofacial system. They studied the blink reflex response in 11 patients who had BMS and 10 controls with both groups undergoing a thorough clinical oral and neurologic examination. As a group, the patients who had BMS displayed definite alterations in their blink response to applied stimulation. The authors concluded from these

results that a possible pathologic involvement of the nervous system may be present in the BMS population. Forssell and colleagues [108] used quantitative sensory tests in addition to the blink reflex in 52 patients who had BMS. They found, based on electrophysiologic findings, that these patients in general have different types of neural changes (some with enhanced and some with reduced neural responses). Overall, the majority (90%) of those tested had some form of altered sensory threshold or blink reflex reaction. These studies suggest that peripheral or central nervous system alterations are present in BMS; however, they do not provide a definitive location for where in the somatosensory system these changes have occurred. The first study [109] to investigate whether damage of peripheral nerve fibers underlies the pathogenesis of BMS studied the innervation of the tongue epithelium. This study examined 12 patients who had clinically definite BMS for at least 6 months whereby superficial biopsies of the lateral aspect of the anterior two thirds of the tongue were performed on all patients who had BMS and 9 healthy controls. Immunohistochemical and confocal microscope colocalization studies were performed with cytoplasmatic, cytoskeletric, Schwann cell, and myelin markers for pathologic changes. Patients showed a significantly lower density of epithelial nerve fibers than controls, with a trend toward correlation with the duration of symptoms. Epithelial and subpapillary nerve fibers showed diffuse morphologic changes reflecting axonal degeneration. It was concluded that BMS is caused by a trigeminal small-fiber sensory neuropathy. Small-fiber neuropathy refers to a subtype of peripheral neuropathies characterized by the impairment of thinly myelinated A-delta and unmyelinated C fibers. This conclusion implies that both somatic and autonomic fibers may be involved, thus leading to sensory and autonomic neuropathies [110].

Central

Evidence from several studies alludes to a more centrally mediated alteration in modulation of nociceptive processing as an etiologic factor. These studies involve the dopaminergic function in the striatum (putamen and caudatus), which is part of the basal ganglia in the midbrain. The basal ganglia is purported to be involved in the processing and sensorimotor gating of nociceptive information. These studies indicate that inhibition of the nigrostriatal dopaminergic system is reduced in patients who have BMS compared with healthy controls resulting in reduced central pain suppression. It was also found that BMS participants involved in these studies displayed no signs of motor dysfunction or psychiatric disorders, which supports the hypothesis that pain sensation in BMS is exclusively a nociceptive projection [111–113]. Overall, these studies suggest that brain function in the processing of nociceptive input is altered in BMS cases. This theory was further evaluated in a study assessing the pathophysiology associated with BMS with the use of functional magnetic resonance imaging. Areas of brain activation following thermal stimulation of the trigeminal nerve in eight female patients who had BMS were compared qualitatively and quantitatively to matched pain-free controls. The authors concluded that patients who had BMS displayed brain activation patterns similar to those of patients who had other neuropathic pain conditions and seemed to process painful stimulation differently than pain-free individuals [114]. It has also been shown that areas in the brain that respond to taste are identical to those areas activated in response to pain, suggesting that taste and pain share overlapping neural substrates [115].

From these studies, it seems apparent that there are both central and peripheral mechanisms and a combination of such may be involved in the etiologic process leading to BMS. Additionally, it should be considered that these factors are not purely evident in all BMS cases, because BMS presents in multiple variations and themes.

Diagnosis

Taking a thorough and comprehensive history is the key to diagnosis of BMS. Important information to be ascertained by the practitioner relates to the past and current symptoms (pain, dry mouth, taste, and so forth), their duration, intensity, character, location, onset, and factors that improve or worsen the pain and its course. A numeric or visual analog scale measuring the patient's pain intensity and dry mouth should be used. Information should be obtained about current and past health status, including chronic systemic disorders, allergies, and immunologic disorders, and previous and current medications. This history should also include information on previous or current psychosocial stressors and psychologic well being. The diagnosis is based on the clinical characteristics and presenting symptomatology supplied by the patient. Important clinical characteristics that would provide

a diagnosis of BMS are: a sudden or intermittent onset of pain usually localized to the tongue, hard palate, and lips; bilateral presentation; a persistent and often progressive increase in pain during the day often not present on awakening and the remission of pain with eating (although some foods may exacerbate the pain) and sleeping; presence of abnormal or altered tastes (usually metallic or bitter); subjective sensations of a dry mouth and intraoral areas of roughness, irritation, or swelling; and parafunctional habits [116]. The clinical examination is more to rule out any possible local factors that may be responsible for the oral burning complaints. The clinical examination should therefore include an extraoral and intraoral examination of temporomandibular joint function; inspection and palpation of the masticatory muscles, oral mucosa, tongue mobility, and dental hard and soft tissues; and evaluation of any prosthetic devices. Objective measurements of salivary flow rates (whole stimulated and unstimulated saliva) and taste function should be taken [117]. Neurologic imaging and consultation should be a consideration if patients present with more complex, confounding, or atypical symptoms, including sensory, motor, and autonomic changes, to rule out any neurodegenerative disorders or central nervous system pathology. Additional clinical tests may be requested to rule out any local and systemic factors that may be responsible for the symptomatology (Box 3). As previously stated, BMS is a diagnosis of exclusion.

Box 3. Clinical tests for burning mouth syndrome

- Hematologic tests: Complete blood count/differential, glucose, thyroid studies, nutritional factors, autoimmune panel
- Oral cultures: fungal, viral, or bacterial if infections suspected
- Imaging: MRI, CT scans, and nuclear medicine, if deemed necessary to rule out systemic considerations
- Salivary flow rates for whole unstimulated (0.3–0.4 g/min) and stimulated (0.75–2.0 g/min) saliva
- Salivary uptake scans if low salivary flow rates and Sjögren syndrome suspected
- Allergy testing if needed, especially for a dental panel and allergens
- Trial of discontinuation of certain medications, including ACE inhibitors
- Psychometric tests: SCL- 90R, MPI, Hospital Anxiety and Depression Scale, and Beck Depression Inventory
- Gastric reflux studies

In a study by Mignogna and colleagues [118] it was reported that the average delay from onset of the symptoms to definitive diagnosis was 34 months. This delay in diagnosis may not only cause the oral pain to interfere chronically with normal daily lifestyle and sleep pattern but also could have a significant emotional impact on patients. The authors also found the average number of medical and dental practitioners consulted by each patient over this period (who initially misdiagnosed BMS) was 3.1. It is unclear whether this situation is the consequence of the complex and largely unknown nature of BMS or the expression of inadequate knowledge among the physicians and oral health care providers about non-dental orofacial pain conditions.

Burning mouth syndrome management

There is little research evidence to provide clear recommendations for management of patients who have BMS. Initially, the clinician must determine if the patient is suffering from primary (essential/idiopathic) BMS or secondary BMS in which symptoms are attributable to underlying local or systemic conditions, such as mucosal disease (ie, lichen planus, candidiasis), hormonal disturbances, psychosocial stressors, vitamin or nutritional deficiencies, diabetes, dry mouth, contact allergies, galvanism, parafunctional habits, cranial nerve injuries, or medication side effects [119]. Secondary BMS requires appropriate diagnosis and treatment of the underlying condition to manage symptoms. In primary BMS the cause is unclear, so treatment options are based on patients' symptomatology, often yielding unsatisfactory results. A retrospective study evaluated 53 patients who had BMS for at least 18 months. Various treatment modalities were administered, for which moderate improvement was reported in 28.3% of the subjects and spontaneous remission occurred in 3.7%. All other patients reported no change or worsening symptoms of BMS a mean of 5 years after having been diagnosed with the condition [43]. Three

Table 2
Summary of treatment interventions

Treatment (class of drug)	Dosage	Prescription	Evidence for use	Notes
Behavioral interventions				
Cognitive behavioral therapy			Two RCTs indicate decreased BMS symptomatology.	
Topical therapy				
Clonazepam (benzodiazepine)	1 mg tablet tid	Let tablet dissolve and hold fluid in mouth in area of most intense burning for 3 minutes, then expectorate.	One RCT indicates decreased BMS symptomatology.	This agent is approved by the FDA for seizures and panic disorders. It is used off-label for neuropathic pain and BMS in particular.
Lidocaine (anesthetic)	Viscous gel 2%	5 mL qid. Rinse for two minutes and expectorate.	No published evidence for BMS	This agent is FDA approved as a topical anesthetic agent but its use is specified as an aid for minor surgeries or skin abrasions.
Topical capsaicin	0.025% cream	Apply tid to qid	No published evidence for BMS	
Topical doxepin	5% cream	Apply tid to qid	No published evidence for BMS	
Systemic therapy				
Nortriptyline, amitriptyline (tricyclic antidepressants)	10–75 mg or more per day	10 mg at bedtime; increase dosage by 10 mg every 4–7 d until oral burning is relieved or side effects occur	No published evidence for BMS but used commonly for neuropathic pain	This drug is approved for treating the symptoms of depression, but it is used off-label for neuropathic pain.
Paroxetine, sertraline (SSRIs)	Paroxetine: 20 mg/d; sertraline: 50 mg/d	Paroxetine: maximum 50 mg/d; sertraline: maximum 200 mg/d	One RCT indicates decreased BMS symptomatology.	This agent is approved by the FDA for major depression and is used off-label for chronic pain.
Amisulpride, levosulpiride (atypical antipsychotic agents)	50 mg/d	50 mg tablets up to three times per day. Maximum dose not to exceed 400 mg/d	One RCT for amisulpride and open trial for levosulpiride indicate decreased BMS symptomatology.	This drug is FDA approved for schizophrenia. It is not available in the United States.

(*continued on next page*)

Table 2 (*continued*)

Treatment (class of drug)	Dosage	Prescription	Evidence for use	Notes
Clonazepam (benzodiazepine)	0.25–2 mg/d	0.25 mg at bedtime, increase dosage by 0.25 mg every 4–7 d until oral burning is relieved or side effects occur. As dosage increases, medication is taken as full dose or in three divided doses.	Open trial indicates decreased BMS symptomatology. No RCTs have been performed.	This agent is approved by the FDA for seizures and panic disorders. It is used off-label for neuropathic pain and BMS in particular.
Gabapentin (anticonvulsant)	300–2400 mg/d	100 mg at bedtime; increase dosage by 100 mg every 4–7 d until oral burning is relieved or side effects occur. As dosage increases, medication is taken in three divided doses.	One RCT indicates no decrease in BMS symptomatology. One case report suggests this agent may decrease burning in some patients.	This drug is FDA approved for partial seizures and for postherpetic neuralgia pain.
Alpha-lipoic acid (antioxidant)	200 mg tid	200 mg tid for 2 mo. Also prescribe gastroprotector.	Multiple RCTs indicate decreased BMS symptomatology.	This agent is considered a nutritional supplement.
Capsaicin (atypical analgesic)	0.25% capsules tid	0.25% capsules tid for 1 mo	One RCT indicates decreased BMS symptomatology.	It is not available in the United States.

Abbreviation: FDA, US Food and Drug Administration.

Data from Suarez P, Clark GT. Burning mouth syndrome: an update on diagnosis and treatment methods. J Calif Dent Assoc 2006;34(8):611–22.

approaches or combinations of these can be considered part of the management strategy.

Behavioral interventions

One randomized controlled trial (RCT) examined the effect of cognitive therapy on resistant BMS compared with a placebo program. Thirty participants underwent 12 to15 sessions of cognitive therapy lasting 1 hour once a week, and 30 individuals in the placebo group underwent motivational input three times during the 12- to 15-week period. The study showed a statistically significant reduction in pain intensity for those receiving cognitive therapy compared with placebo immediately following the therapy and a further reduction at the 6-month follow-up [120]. Another study showed some improvement of BMS resulting from psychotherapy treatment over 2 months, with significant improvement when combined with alpha-lipoic acid therapy (ALA) (600 mg/d) [121]. It seems from these studies that the practitioner may consider the involvement of a behavioral medicine practitioner as part of a multidisciplinary approach when managing patients who have BMS.

Topical medications

Three studies have assessed the efficacy of topical therapies on BMS symptomatology. A double-blind RCT was performed to evaluate the efficacy of topical clonazepam, a γ-aminobutyric acid (GABA) receptor agonist, compared with placebo. Patients were instructed to suck on a tablet containing either 1 mg clonazepam or placebo three times a day. After 14 days, the decrease in pain was significantly more

pronounced in the clonazepam compared with the placebo group. Sixty-six percent of patients who had BMS reported reduced pain intensity after 14 days, with residual partial improvement after 6 months in 29% [122]. In addition, benzydamine (not available in the United States) is a nonsteroidal drug with analgesic, anti-inflammatory, and antimicrobial properties that also has topical anesthetic properties. A small, double-blind RCT of benzydamine hydrochloride 0.15% oral rinse (15 mL used three times a day) compared with a placebo oral rinse solution and a no-treatment group was unable to demonstrate any statistically significant difference between the three groups at the end of the 4-week period. No adverse events were reported [123]. Furthermore, a single open-label RCT indicated topical lactoperoxidase oral solution (Biotene mouthwash) used five to six times daily for 60 days compared with placebo was not effective [124].

Systemic medications

Numerous studies have assessed systemic therapies for treatment of BMS, including antidepressants, anticonvulsants, GABA receptor agonists, and vitamin complexes. A prospective, randomized, single-blind study without placebo comparison was performed to compare the efficacy of amisulpride (not available in the United States), an antipsychotic medication, and selective serotonin reuptake inhibitor (SSRI) antidepressants sertraline and paroxetine in patients who had BMS. After 8 weeks of treatment, all three treatment regimens resulted in a significant improvement in BMS symptomatology [125]. In another study, 44 patients used levosulpiride (not available in the United States), an antipsychotic and antidepressant drug, at a dose of 100 mg daily (50 mg capsule, twice daily) for 8 weeks. Seventy two percent of the patients reported a partially effective result and 28% of the patients reported no benefit to the medication. This study did not include a control group [126]. Additionally, a double-blind, randomized, placebo-controlled study evaluated the efficacy of trazodone, a serotonin antagonist antidepressant medication, compared with placebo. After 8 weeks of trazodone 200 mg/d, the authors reported no statistically significant differences compared with placebo at any time point [127].

Thirty patients who had burning mouth symptoms ranging from 1 month to 12 years received clonazepam 0.25 mg/d, which was titrated on a weekly basis by 0.25 mg until symptoms resolved or to a maximum dosage of 3 mg/d in three divided doses. All subjects used clonazepam for a minimum of 2 months. Mild to moderate improvement of burning mouth symptoms was reported in 70% of the patients. Although using a convenience sample and providing evidence of effect, the strength of these data is limited by the lack of a control group [128]. Another study assessed 15 patients who had BMS prescribed gabapentin, an anticonvulsant medication, at a starting dose of 300 mg/d, slowly titrated up to a maximum of 2400 mg/d. Subjects were treated for 2 to 6 weeks. Gabapentin had no effect on pain ratings, mood scale, Beck Depression Inventory scores, or chemosensory functions following therapy [129]. Contrary to this, a case report suggests that gabapentin may be effective in reducing burning mouth symptoms [130].

ALA is the trometamol salt of thioctic acid and a potent antioxidant mitochondrial coenzyme. ALA may protect against damage mediated by reactive oxygen species and may be neuroprotective [131]. In patients who have BMS, multiple double-blind and open-label RCT studies conducted at one center have evaluated the efficacy of 600 mg ALA given daily compared with placebo [121,124,131,132]. In a Cochrane Database systematic review [133] these studies were unable to be pooled because of variation in the results. Regardless, all four trials showed a statistically significant improvement in BMS symptomatology with ALA. Another study compared ALA in patients who had BMS who had taken tranquilizer medication for treatment compared with those who had never used tranquilizers. Patients who were treated with tranquilizers responded poorly to therapy with ALA compared with those who had not received previous psychotropic therapy [134]. Given the subjective nature of the outcome assessment for all of these studies, the results should be interpreted with caution.

A triple-blind trial of systemic capsaicin was administered as 0.25% capsules three times per day for 4 weeks and compared with placebo. Results indicated that treatment with systemic capsaicin induced a statistically significant reduction of burning symptoms at the end of the study period. This study was limited by nonrandom allocation to the study groups, however, so results should be interpreted with caution [135]. Furthermore, a single open-label RCT indicated systemic bethanechol (which stimulates the parasympathetic system) 5 mg three times daily for 60 days

compared with placebo was not effective at improving symptoms of BMS [124]. In persisting cases of BMS, combinations of more than one agent with different mechanisms of action have been discussed, but no trials have been conducted.

It is apparent that a range of treatments has been used to alleviate symptoms of BMS resulting in an assortment of outcomes. The varying therapies, with different mechanisms of action, represent numerous suspected etiologies of the condition. Treatment interventions are summarized in Table 2.

Summary

Diagnosis and management of patients who have BMS is not an easy task. The scientific literature is ambiguous and equivocal about the classification, epidemiology, etiologic factors, clinical presentation, diagnosis, and management strategies regarding this condition. There is little evidence-based material to assist the practitioner when dealing with these individuals. There is no doubt that innovative and interdisciplinary research is required to elucidate and expand on the knowledge of the etiology and pathogenic factors involved in BMS. Oral and maxillofacial surgeons should therefore be cautious in diagnosis of a BMS case as to whether or not this individual should be managed within his or her scope of care, because the complaints represent a chronic pain condition wherein medical management is indicated and surgical approaches contraindicated. If there is uncertainty then the oral and maxillofacial surgeon may be wise to refer to an oral medicine/orofacial pain practitioner to assist in the management of these complex patients.

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Orofacial Movement Disorders

Ramesh Balasubramaniam, BDSc, MS[a,*], Saravanan Ram, BDS, MDS[b]

[a]*Department of Oral Medicine, University of Pennsylvania, School of Dental Medicine, 240 South 40th Street, Philadelphia, PA 19104, USA*
[b]*Division of Diagnostic Sciences, University of Southern California, School of Dentistry, 925 West 34th Street, Los Angeles, CA 90089, USA*

An understanding of orofacial movement disorders (OMD) is essential to the oral and maxillofacial surgeon interested in treating orofacial pain. It is not uncommon for OMD to be misdiagnosed as temporomandibular disorders (TMD) or to be mislabeled as a psychiatric manifestation resulting in inappropriate treatments. OMD should thus be a diagnostic consideration in patients presenting with orofacial pain.

OMD involves the motor aspects of cranial nerves V, VII, and XII and may present as hyperactivity or hypoactivity of the masticatory, facial, and tongue musculature or combinations of these voluntary muscles. These movement disorders are centrally mediated pathologic conditions involving the basal ganglia (the caudate, putamen, globus pallidus, subthalamus, and substantia nigra) and their communication with other areas of the brain. Along with the cerebral cortex, the basal ganglia are responsible for the performance of fine motor functions [1].

OMD may present in many forms. The discussion in this chapter is limited to three poorly recognized yet relatively common presentations of hyperactive OMD: oromandibular dystonia, orofacial dyskinesia, and drug-induced extrapyramidal syndrome reactions.

Oromandibular dystonia

Oromandibular dystonia (OD) is a focal dystonia whereby repetitive or sustained spasms of the masticatory, facial, or lingual muscles result in involuntary and possibly painful jaw opening, closing, deflecting, or retruding movements, or a combination of these movements [2–4]. Compared with dyskinesias, ODs are intermittent and present as short, sustained muscle contractions resulting in abnormal muscle movements and posturing. There have been numerous publications since French neurologist Henry Meige reported this condition in 1910 [5]. Nevertheless, OD is often misdiagnosed and subsequently patients are incorrectly managed by practitioners. Focal dystonias may be primary (idiopathic) or secondary. The primary form is more common and does not involve an underlying central nervous system pathology, such as infarctions and tumors [6–8].

The diagnosis of OD may well challenge the astute clinician [9–11], primarily because of the numerous forms and severities in the presentation of OD. In particular, the diagnosis is elusive in selected patients who have unrecognized triggers and present during periods of quiescence. Validity of the diagnosis for the different types of focal dystonias cannot be assessed because there is no available gold standard (a diagnostic test or biomarker) as yet [10]. Misdiagnosis commonly includes TMD [12] or spontaneous condylar dislocation [13,14], hemimasticatory [15] or hemifacial spasms [16], and psychologic manifestations [17].

Currently, OD affects approximately 3 to 30 per 100,000 persons in the United States [18,19]. Some studies suggest that OD affects more women than men, with a mean age of symptom onset between 31 and 58 years [20–23]. Although there is some evidence that genetic predisposition may be a factor in some patients who have OD [3,24]

* Corresponding author.
E-mail address: rbalasub@dental.upenn.edu (R. Balasubramaniam).

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in most cases the cause of OD is elusive. It is not uncommon for patients to report a precise onset of the first OD episode. Dental and oral and maxillofacial surgical procedures and orofacial trauma have been temporally and anatomically related to the onset of dystonia [25,26]. In studies by Tan and Jankovic [20], most ODs are idiopathic in etiology, accounting for 63% of cases reported. Other possible causes include drug-induced OD (22.8%), peripheral-induced OD (9.3%), postanoxic OD (2.5%), neurodegenerative disorder–associated OD (1.8%), and head injury–associated OD (0.8%). Pathophysiology for OD is unknown; however, it probably has multifactorial mechanisms involving basal ganglia dysfunction, hyperexcitability of motor neurons involved in signaling, reduced inhibition of spinal cord and brainstem signals coming from supraspinal input, and dysfunction of neurochemical systems involving dopamine, serotonin, and noradrenaline [19,27].

The clinical characteristics of OD are classified according to the affected muscles. The muscles involved may be the muscles of mastication, muscles of facial expression [28], or the muscles of the tongue. Patients may present with jaw-opening, jaw-closing, jaw-deflecting, or jaw-retruding dystonia, or a combination of any of these. The uncontrolled or involuntary mandibular movements may be repetitive or sustained [20,21]. The combination of OD and blepharospasm is known as Meige syndrome. Similarly, dystonic spasms may result in nasal contractions, facial grimacing, lip pursing, lip sucking or smacking, chewing, tooth clenching and grinding, tongue movements, retractions of corners of mouth, and platysma contractions [3,29,30]. Involvement of the laryngeal muscle groups may lead to dysarthria, dysphagia, dysphonia, breathing difficulties, and alteration in vocalization. For unknown reasons, patients often report triggers or exacerbating factors, such as stress, depression, glaring light, watching television, driving, reading, talking, praying, fatigue, and chewing [2–4,13,23,31]. Likewise for reasons unknown, patients also report that they have learned certain sensory tricks, or ''geste antagonistique,'' which are typically tactile stimulations of the orofacial region to control and suppress movements. Sensory tricks are more prevalent among jaw-opening OD [30]. Other means to help control the dystonia, such as sleeping, relaxing, talking, singing, humming, lip biting, tongue posturing, swallowing, chewing gum, and in some instances, alcohol intake, may be reported by patients [25,30,32,33].

Orofacial dyskinesia

Orofacial dyskinesia (ODk) is defined as involuntary, repetitive, stereotypical movement of the face, tongue, and jaw that may be painful [1,34–36]. Dyskinesias may be spontaneous (idiopathic) or tardive (medication-induced). Oral and maxillofacial surgeons should be aware of well-known complications of ODk, namely tooth wear and fracture, prosthesis damage and displacement, accelerated bone loss among edentulous patients, orofacial pain, temporomandibular joint degeneration, ulcers secondary to tongue and cheek biting, dysarthria, dysphagia, chewing difficulties, inadequate food intake and weight loss, and social embarrassment secondary to compromised facial esthetics [34,36–38].

Spontaneous orofacial dyskinesia

The less common spontaneous form of dyskinesia typically affects the elderly. The prevalence of spontaneous ODk varies depending on the population studied, ranging from 1% to 38% [34,39–43]. Specifically, it affects 1.5% to 4% of the healthy elderly [39,40], 18% to 31.7% of the elderly living in retirement homes [41–43] and 3.7% of the elderly in day care centers [34]. The difficulty in studying this condition is the need to rule out inadvertent exposure to an offending drug throughout the life of the patient and this may account for the large difference in prevalence rates between studies [44]. It has been suggested that antipsychotic drugs, which are often used in the elderly, may merely unmask dysfunctional subcortical circuits that predisposes the individual to ODk [34]. Previous studies have suggested a two- to threefold higher female to male ratio; however, this is likely attributable to the overrepresentation of females in these study populations [34,39–42,45]. The presence of spontaneous ODk occurring in various central nervous system conditions is well established and includes chronic schizophrenia [46], Alzheimer disease [41], dementia, autism, mental retardation [47], and Rett syndrome.

The clinical presentation of spontaneous ODk is typically milder in intensity compared with tardive ODk and involves various combinations of tongue, lips, and jaw movements [39,48,49]. Spontaneous ODk is also strongly associated

with ill-fitting removable prosthesis, so-called "prosthetic stereotypies," oral pain, and perception of inadequate oral hygiene. Whether ill-fitting prostheses are the cause or the effect of ODk is yet to be determined. It has been suggested that wearing ill-fitting prostheses is a greater risk factor for oral stereotypies than not wearing prostheses [34]. It has also been suggested that ODk and tardive dyskinesia (TD) are associated with edentulism [50,51]. One study reported 16% of subjects who had mild ODk, half of whom did not wear prostheses, questioning the association between ill-fitting prostheses and spontaneous ODk [48]. Further studies are required to ascertain the relationship between edentulism, dental prostheses, and ODk.

Tardive dyskinesia

TD represents rapid, repetitive, nonrandom, stereotypic movements involving the tongue, lips, and jaw areas. Combinations of tongue twisting and protrusion, lip smacking and puckering, and chewing movements occur secondary to exposure to an offending drug, typically conventional antipsychotic drugs, such as chlorpromazine, haloperidol, and perphenazine [52,53]. Other areas of the body may be involved, typically extremities and trunk. The diagnosis of TD requires a minimum of 3 months of cumulative exposure to the offending drug. Also, TD must persist for 3 months after withdrawal of the offending medication. Patients are often able to voluntarily suppress involuntary orofacial movements through activities such as eating or talking. Alternatively, TD can be exacerbated by stimulants, neuroleptic medication withdrawal, anticholinergic medications, emotional arousal, and distraction of other unaffected areas of the body during voluntary movements [54]. TD can be socially embarrassing and result in dysphagia and dysarthria in some cases.

The incidence and prevalence of TD varies with age (greater in the elderly), and sex (greater in females) [55–58]. Other known risk and predisposing factors for TD include greater drug exposure (specifically to conventional antipsychotics), poor response to treatment, genetics, affective disorders, brain damage and cognitive impairment, parkinsonism, diabetes mellitus, and alcohol and substance abuse [58–60]. The annual incidence for TD is 5% in the younger population (mean 28 years) [55] to 12% in the older population (mean 56 years) [61]. Reportedly, more than 20% of patients treated with neuroleptic medications develop TD [62]. The prevalence of TD has doubled over 20 years in patients who have schizophrenia and were treated with newer atypical antipsychotics, such as risperidone and olanzapine, that promised fewer extrapyramidal side effects, suggesting other mechanisms for the development of TD [63]. In a recent study involving hospitalized patients who had schizophrenia, TD occurred in 40% of those treated with antipsychotics, 39% of those treated with atypical antipsychotics, and 47% treated with both typical and atypical antipsychotics [64].

The cause of TD is chronic exposure to dopamine receptor–blocking drugs (ie, conventional antipsychotics) used in the treatment of psychosis and schizophrenia. To a lesser extent, other dopamine receptor–blocking agents, such as atypical antipsychotic drugs, antiemetics, tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRIs), among others, can cause TD (Table 1). The clinical course of TD is difficult to predict because it may persist [65], improve [66,67], or recur after a brief period of quiescence despite withdrawal of the offending drug [68].

The pathophysiology of TD remains elusive. The current theory posits that chronic blockade of

Table 1
Medications associated with tardive dyskinesia

Medication class	Medication
Conventional antipsychotics	Chlorpromazine
	Haloperidol
	Perphenazine
	Pimozide
	Trifluoperazine
Atypical antipsychotics	Clozapine
	Olanzapine
	Risperidone
Antiemetics	Metoclopramide
	Promethazine
Antiparkinsonian agents	Levodopa
	Benztropine
	Trihexyphenidyl
Anticonvulsants	Phenytoin
	Carbamazepine
Antihistamines	Diphenhydramine
	Ranitidine
Tricyclic antidepressants	Amitriptyline
	Doxepin
Selective serotonin reuptake inhibitors	Fluoxetine
	Paroxetine
	Sertraline

dopamine D2 receptors in the striatum results in increased receptor sensitivity and hence elevation of dopamine function. This concept fails to explain why the majority of patients are not afflicted by TD despite exposure to dopamine receptor–blocking drugs. One possible explanation for susceptibility to TD among select patients is the association between a serine-to-glycine polymorphism in exon 1 of the DRD3 gene and TD [58,69,70]. The effect of dopamine receptor–blocking agents on γ-aminobutyric acid (GABA), cholinergic and norepinephrine systems, and oxy-radical production causing neuronal degeneration are other possible explanations for TD [58,70–72].

Drug-induced extrapyramidal syndrome reactions

Drug-induced extrapyramidal syndrome (DiEPS) reactions are movement disorders that are commonly reported with use of prescribed medications and illicit or stimulant drugs. DiEPS reactions usually present as dystonia, akathisia, and parkinsonism (Table 2) [73].

Medication-induced extrapyramidal syndrome reactions

Medications, typically dopamine receptor–blocking agents for the treatment of psychosis, are the main culprit causing DiEPS. Despite the advent of newer atypical antipsychotic drugs that promised a lower side-effect profile than conventional antipsychotics, DiEPS continues to be a significant problem. Fewer than 5% of patients exposed to antipsychotics develop dystonic reactions, which manifest years after exposure to the medication [74]. The craniocervical region is the site most affected by these reactions [75]. Medication classes that can cause DiEPS include neuroleptics and conventional and atypical antipsychotics, among others [73].

Table 2
Drug-induced extrapyramidal syndrome reactions

Dystonia	Involuntary, sustained, patterned, and often repetitive muscle contractions causing twisting movements or abnormal postures
Akathisia	A subjective report and objective manifestations of restlessness in the form of movement of the limb
Parkinsonism	Bradykinesia (slowness of movement) associated with at least one of rigidity, tremor, or postural instability

Of particular interest to oral and maxillofacial surgeons is the side effect of tooth clenching and grinding associated with SSRIs. SSRIs, such as fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram are prescribed for the treatment of depression and anxiety. Strictly speaking the actual movement disorder is not the brief, strong, muscle contractions as seen in nocturnal bruxism; it presents more like an elevated and sustained jaw and tongue muscle contraction. Clinically, patients may present with jaw pain, tightness, fatigue, and headache similar to signs and symptoms of nocturnal bruxism [76–80].

Illicit or stimulant drug–induced extrapyramidal syndrome reactions

Tooth clenching and grinding, tics, and dystonic reactions have been reported with the use of illicit drugs, such as methamphetamine, cocaine, and 3,4-methylenedioxymethamphetamine (Ecstasy). Similar reactions have also been reported with legitimate stimulant medications (methylphenidate, phentermine, pemoline, dextroamphetamine, amphetamines, and diethylpropion) used for the treatment of obesity, attention deficit hyperactivity disorder, and narcolepsy; however, such drugs are often abused [81–87].

Management

The management of OMD is challenging and requires a thorough understanding of the various management options available today. The clinician should be well aware of the efficacy and limitations of these options and must educate the patient as to the underlying disorder, the available treatment modalities, and the expected outcome of the therapy. The first step is to take a thorough history, including a medication and illicit drug history. If the examination findings indicate a movement disorder, MRI should be performed to rule out a central degenerative, demyelinating, or sclerotic lesion of the nervous system. For those cases of hemifacial spasm, a magnetic resonance angiography may be performed to rule out vascular compression of the facial nerve. An algorithm highlighting the diagnostic work-up

for orofacial movement disorders is presented in Fig. 1.

Management of OMD can be broadly divided into medical management, chemodenervation using botulinum neurotoxin (BoNT), and surgical management (Fig. 2). Medical management involves the use of various centrally acting medications. The surgical management may range from a myectomy to a pallidotomy. Of all these approaches, injecting BoNT into the affected musculature has proved to be the most effective means of managing OMD [88]. The following section discusses the management of OMD; however, because of scarce information on OMD, many of the treatment recommendations may be based on movement disorders involving other areas of the body and less common OMD not previously discussed in this manuscript.

Medical management

Medical management is considered to be the least invasive approach in the management of OMD and involves administration of a medication (Table 3) or withdrawal of an offending agent (see Table 1).

Anticholinergics

Anticholinergic medications, such as trihexyphenidyl hydrochloride (Artane) and biperiden (Akineton), are approved by the US Food and Drug Administration (FDA) for the management of extrapyramidal reactions in Parkinson disease. They are also used as off-label medications for managing orofacial dystonias and are only effective in some patients. As a general rule, the anticholinergic medication is started at a low dose and gradually increased to achieve the

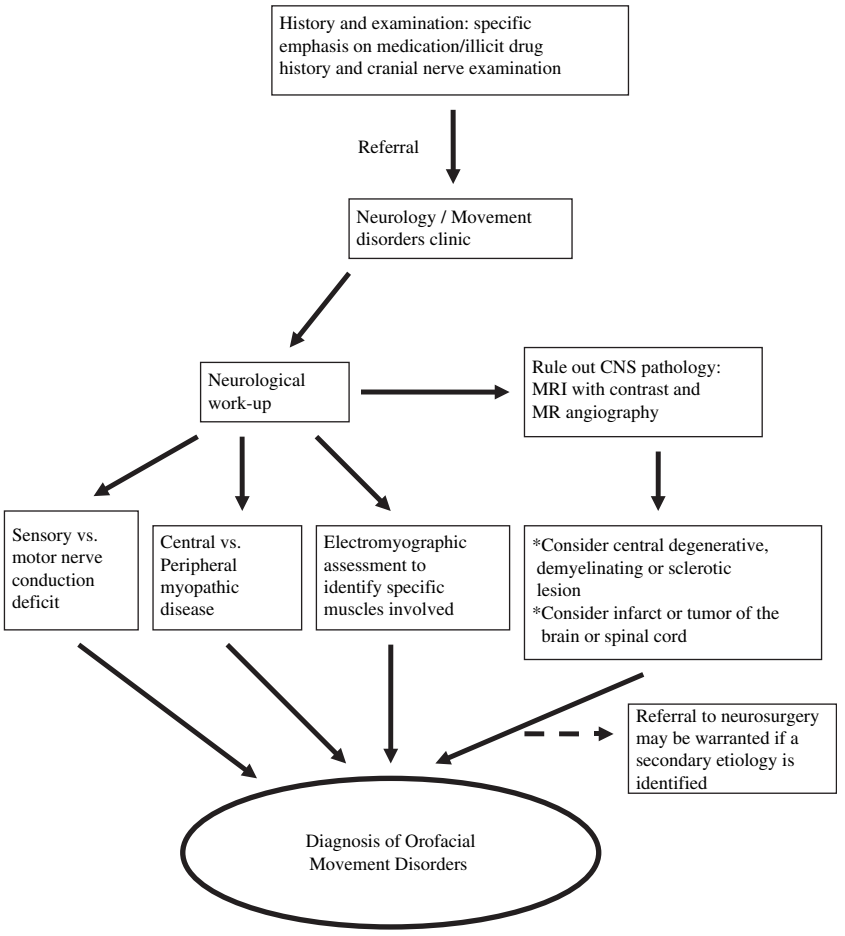

Fig. 1. Diagnostic work-up for orofacial movement disorders.

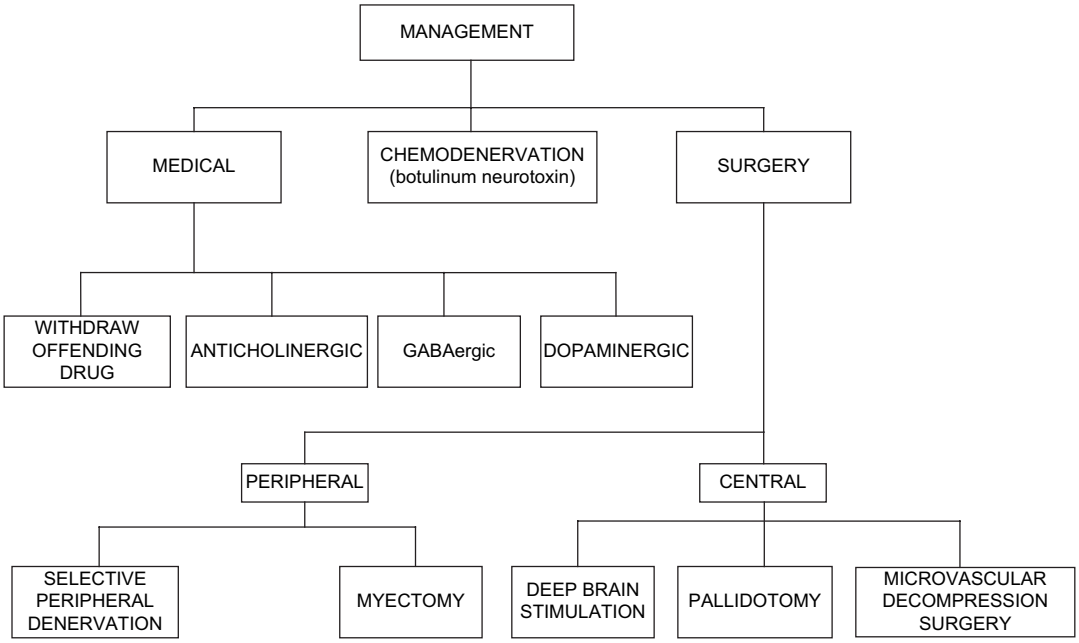

Fig. 2. Algorithm for management of orofacial movement disorders.

desired pharmacologic effect. This slow titration increases patient tolerability and decreases the incidence of side effects, such as dry mouth, blurred vision, urinary retention, and confusion [89].

GABAergic therapy

Baclofen (Lioresal), a GABAergic medication, is used either orally or intrathecally for patients who have dystonia and other spastic movement disorders. Intrathecal administration of baclofen is far more effective than oral administration and involves the use of an implantable infusion pump. The intrathecal catheters are placed under fluoroscopic guidance in the midcervical region for dystonia [90,91]. The catheter, pump, and surgical wound are subject to numerous complications at the time of implantation and throughout the life of the implanted system. These complications can be reduced with careful surgical technique and postoperative follow-up [92]. Baclofen, when administered orally, is started at a low dose of 10 mg at bedtime and increased to a maximum dose of 80 mg a day. The main side effects include drowsiness, confusion, dizziness, and weakness.

Table 3
Medications for management of orofacial movement disorders

Medication class	Medication
Anticholinergics	Trihexyphenidyl hydrochloride (Artane)
	Biperiden (Akineton)
GABAergics	Oral baclofen (Lioresal)
	Intrathecal baclofen
Benzodiazepines	Clonazepam (Klonopin)
	Diazepam (Valium)
	Lorazepam (Ativan)
Dopaminergics	Levo/carbidopa
Non-benzodiazepines	Buspirone (BuSpar)
Antiparkinsonians	Amantadine (Symmetrel)
	Benztropine (Cogentin)
	Diphenhydramine (Benadryl)

Benzodiazepines

Benzodiazepines, such as clonazepam, diazepam, and lorazepam, are often used as adjuncts for patients who fail to respond satisfactorily to anticholinergics [89]. Clonazepam (Klonopin) is the most popular benzodiazepine and is titrated from a dose of 0.25 mg once daily at bed time to a maximum of 1 mg four times daily. The side effects include drowsiness, confusion, trouble concentrating, and dizziness. Paradoxically, benzodiazepines and thiobenzodiazepine derivatives,

on prolonged administration, have been reported to cause blepharospasm [93].

Dopaminergic therapy

In general, dopaminergic agents, such as levo/carbidopa, have little therapeutic effect for dystonia except for a specific subtype called dopa responsive dystonia (DRD) that occurs in children. DRD constitutes approximately 5% of childhood dystonias and is often misdiagnosed as cerebral palsy. Response to the administration of low-dose levo/carbidopa aids in the diagnosis of DRD [94]. There have also been reports of the use of levo/carbidopa worsening symptoms of Meige syndrome [95].

Management of tardive dyskinesia and drug-induced dystonic extrapyramidal reactions

As a first step, the offending medication should be identified and withdrawn, bearing in mind that the dyskinesia or dystonia may not be reversible [96]. In general, it may take anywhere from few days to months for the movement disorder to disappear following withdrawal of the medication. If the suspected medication cannot be stopped or if the reaction is severe, then diphenhydramine (Benadryl) 50 mg or benztropine (Cogentin) 2 mg may be administered intravenously or intramuscularly [97–99]. Amantadine [100] (Symmetrel) 200 to 400 mg/d by mouth and diazepam [101] (Valium) 5 mg intravenously have been shown to be effective for recurrent neuroleptic-induced dystonic reactions. In the case of SSRI-induced tooth clenching and grinding, lowering the dose of the SSRI medication may be helpful; an alternative approach is to add buspirone 10 mg two to three times daily [102].

Chemodenervation

Chemodenervation with BoNT has become the management modality of choice for patients who have OMD because of its high-efficacy, albeit temporary, relief. Seven serologically distinct subtypes of BoNT (A to G) have been isolated, of which subtypes A and B are approved by the FDA for use in patients who have movement disorders. Botulinum neurotoxin type A (BoNT/A) is manufactured by Allergan Inc. (Irvine, California) as Botox and is the most potent and longest acting (8–16 weeks) of the seven subtypes. Botulinum neurotoxin type B (BoNT/B) is marketed by Solstice Neurosciences Inc. (San Diego, California) as Myobloc. BoNT/A is used off-label in the orofacial region to help treat primary and secondary masticatory and facial muscle spasm, severe tooth clenching and grinding/bruxism, facial tics, orofacial dyskinesias, dystonias, and idiopathic hypertrophy of the masticatory muscles [103]. Contraindications to the use of BoNT include allergy to the drug, infection or inflammation at the injection site, pregnancy, women who are lactating, inability of the patient to cooperate, and high levels of fearfulness toward the method.

The therapeutic benefit of BoNT is mainly attributable to its primary action of blocking the release of acetylcholine into the neuromuscular junction. More specifically, BoNT achieves this effect by cleaving SNARE proteins that are required for the docking of the acetylcholine vesicle to the presynaptic membrane [104]. Repeated injections of BoNT/A have been reported to cause immunoresistance or development of antibodies against the toxin, rendering it ineffective in some patients [105]. This outcome is frustrating for the patient and the practitioner. An alternative approach is to use BoNT/B or Myobloc for these patients, although there is a small risk for development of antibodies toward the B serotype toxin. A simple clinical test to determine whether a patient may be resistant to BoNT is to inject a small amount of BoNT (20 U of BoNT/A or 1000 U of BoNT/B) unilaterally into one corrugator-procerus muscle complex. A lack of frowning attributable to weakness of the injected muscles indicates lack of immunoresistance and is referred to as the unilateral brow injection test [89].

Side effects of BoNT injections can be divided into site-of-injection side effects and medication-related side effects. Site-of-injection side effects are rare and include local hematoma, infection, or persistent pain in the injection site. These complications are usually a result of injecting into infected or nonsterile skin. The medication-related side effects are transient and include muscle weakness (eg, weakening of the muscles of facial expression or swallowing). Lateral pterygoid muscle injections or palatal muscle injections may result in slurred speech and palatal weakness. Infrequently, patients may experience a thickening of the saliva, a desirable side effect in those who have excessive salivation.

Oromandibular dystonia

There are several forms of OD, such as the jaw-opening type, the jaw-closing type, lateral movement type, and so forth, of which the most common is the jaw-opening type. In this form of dystonia, the temporomandibular joint tends to

lock in a wide-open position, wherein the jaw fails to close easily on injecting the affected muscles with BoNT. Usually the lateral pterygoid muscles are injected under electromyographic guidance [106–108]. Occasionally, submandibular muscles, such as the anterior digastric and platysma, may be injected [109,110].

Hyperactivity of the tongue

Hyperactivity of the tongue is commonly seen in tardive or spontaneous dyskinesias and some forms of oromandibular dystonia. Management with BoNT injections involves injecting the genioglossus and intrinsic tongue muscles. Care should be taken to avoid injecting more than 15 to 20 U of BoTN per side of the tongue in the middle lateral aspect or the base of the tongue, to minimize the troublesome complication of dysphagia [111].

Tooth clenching and grinding

In cases of severe tooth clenching and grinding, an alternative approach to the use of an oral appliance at night is injecting BoNT in the masseter and temporalis muscles at intervals of 3 to 6 months. Only one pilot study has reported on the outcome of BoNT injections in the masseter muscles of 18 patients who had severe bruxism. The mean dose of injection was 61.7 ± 11.1 units per side. The mean total duration of response was 19.1 ± 17.0 weeks (range 6–78 weeks), and the mean peak effect, on a scale of 0 to 4, was 3.4 ± 0.9 (4 is equal to total absence of bruxism) [112]. Although the above study seems to report good results in bruxism patients with use of BoNT, further studies are required to thoroughly evaluate the efficacy of BoNT for tooth grinding and clenching as a movement disorder. Currently there remain many unanswered questions about the etiology and pathophysiology of tooth grinding and clenching, and the use of BoNT as a treatment alternative seems questionable. Based on the current evidence BoNT should be reserved as the last resort for only those severe cases of tooth grinding and clenching refractory to standard treatments.

Surgical management

Owing to the increased morbidity of surgery, it is usually reserved as a last resort for those patients who fail to respond to medications or for those who develop resistance to BoNT injections (Table 4).

Table 4
Surgical procedures for management of orofacial movement disorders

Type of surgery	Procedure
Peripheral	Selective peripheral denervation
	Myectomy
Central	Deep brain stimulation
	Pallidotomy
	Microvascular decompression surgery

Peripheral surgery

Peripheral surgery is usually indicated for those cases of blepharospasm and cervical dystonia that fail to respond to BoTN.

Selective peripheral denervation. Selective peripheral denervation is widely used in the management of cervical dystonias with well-established safety and efficacy [113]. There are two major procedures of surgical denervation: intradural ventral rhizotomy and extradural peripheral neurotomy (Bertrand procedure). Side effects, such as sensory loss in the C2 region and intraoperative bleeding, are minimized with the newer intradural ventral rhizotomy procedure [114].

Myectomy. Surgical removal of the affected muscle is referred to as myectomy and is usually done for patients who have blepharospasm who fail to respond to conservative management [115]. Eyelid protractor myectomy provides subjective benefit for patients who have essential blepharospasm and decreases the long-term need for BoNT injections in approximately 50% of these patients; those who have severe blepharospasm have been shown to benefit the most from myectomy [116]. There have also been reports of patients who had refractory jaw-opening OD who have had successful bilateral lateral pterygoid myectomy [26].

Central surgery

Abnormal electrical activity in the external and internal portions of the globus pallidus and the surrounding structures of the basal ganglia has been recorded in patients who have dystonia [117]. Central surgical management of dystonia has therefore focused on targeting the globus pallidus.

Deep brain stimulation. Deep brain stimulation (DBS) uses an implanted electrode to deliver continuous high-frequency electrical stimulation

to the thalamus, globus pallidus, or any part of the brain that is involved with the control of movement [118]. Unlike ablative surgery, such as thalamotomy and pallidotomy, DBS is reversible and adjustable, thus offering a viable alternative for patients who have disabling dystonia [119]. Vidailhet and colleagues [120] reported on the quality of life after bilateral deep brain stimulation of the globus pallidus in 22 patients who had generalized dystonia. A 16% increase in the general health, 21% increase in physical function, and 10% increase in vitality were observed, with no changes in mood or cognition at the end of 12 months following onset of DBS. Although the results of DBS seem promising, further studies are required to determine the long-term efficacy of this technique.

Pallidotomy. Pallidotomy is an invasive procedure that involves creating a surgical lesion in the globus pallidus and may be done unilaterally or bilaterally. Once a popular surgical modality for the management of movement disorders, pallidotomy is not so widely used currently because of the invasiveness of the procedure and associated surgical risks. Primary dystonias respond well to pallidotomy or DBS of the internal segment of the globus pallidus, whereas secondary dystonias seem to respond partially at best [121,122].

Microvascular decompression surgery. Hemifacial spasm secondary to compression of the facial nerve by a nearby blood vessel can be relieved by microvascular decompression surgery [123]. The most common vessel causing compression of the facial nerve is the posterior inferior cerebellar artery. This vessel must be sharply dissected free from the arachnoid and mobilized laterally away from the nerve so that a Teflon implant can be placed. In cases of atypical hemifacial spasm, the pathologic vascular entity is almost always located rostral to the nerve or between the seventh and eighth nerves [124].

Summary

OMD poses a great challenge to the clinician in diagnosis and management. The astute clinician should obtain a proper history and perform a clinical examination to avoid misdiagnosing or mislabeling patients who have OMD. A careful approach to diagnosis and management results in fewer inappropriate, irreversible and invasive procedures in these individuals.

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Cancer and Orofacial Pain

Dena J. Fischer, DDS, MSD, MS[a,*], Gary D. Klasser, DMD[a],
Joel B. Epstein, DMD, MSD, FRCD(C), FCDS(BC), FDS RCSEdin[a,b]

[a]*Department of Oral Medicine and Diagnostic Sciences, University of Illinois at Chicago, College of Dentistry, 801 South Paulina Street, Chicago, IL 60612-7213, USA*
[b]*Interdisciplinary Program in Oral Cancer, University of Illinois at Chicago, Cancer Research Center, 801 South Paulina Street, Chicago, IL 60612-7213, USA*

Pain is commonly associated with cancer, as it is the presenting symptom in 20% to 50% of all cancer patients and is significant in 75% to 90% of patients with advanced or terminal cancer [1]. In head and neck cancer (HNC) patients, pain has been associated with both disease and cancer treatment. Large surveys of HNC patients found that pain was frequently associated with the tumor (87%–92.5%), whereas in 17% to 20.8%, pain was secondary to therapy, and many patients reported pain from both disease and treatment [2,3]. Following treatment of HNC, 78% of patients reported pain in the head, face, or mouth and 54% in the cervical region or shoulder [3]. As many as 70% of patients may suffer pain from more than one site, involving inflammatory or neuropathic pain mechanisms [3].

Cancer pain correlates with increased morbidity, reduced performance status, increased anxiety and depression, and diminished quality of life [2,4]. Orofacial pain management may be particularly challenging as it is often multifactorial, differential diagnosis is complex, and the achievement of pain relief is compounded by cytotoxic treatment protocols. The present article reviews the clinical presentation of cancer-associated orofacial pain at various stages: initial diagnosis, during therapy, and in the posttherapy period.

Pain due to tumor

Pain due to primary head/neck tumor

Orofacial pain may be a presenting symptom of HNC and may motivate patients to seek care from an oral and maxillofacial surgeon. Primary squamous cell carcinomas of the oral mucosa are often associated with pain and other sensory disturbances when at advanced stage of disease, as they may interfere with oral function and induce nerve damage/dysfunction. In a retrospective case series [5], 66.5% of 322 patients with oral cancer reported localized discomfort within 6 months preceding cancer diagnosis. Another retrospective case series found pain to be the chief complaint at the time of oral cancer presentation in 19.2% of cases, with the most common pain complaints being sore throat and pain in the tongue [6]. Furthermore, a large case series of 565 salivary gland cancers found the most predominant complaint to be a lump (95%), with pain reported in 28% of the cases [7]. In rare circumstances, perineural spread of HNC may cause trigeminal neuropathy, paresthesias, and/or headaches [8].

Nasopharyngeal cancers may present with signs and symptoms that have been confused with, and treated as, temporomandibular disorders [9,10], parotid gland lesions [11], and odontogenic infections with trismus [12]. Signs and symptoms of nasopharyngeal carcinomas that mimic temporomandibular disorders include facial pain, limited jaw opening, deviation of the jaw on opening, earache, and headache [9,10,13,14]. In a retrospective case series, 44.2% of 52 patients diagnosed with nasopharyngeal carcinomas presented with orofacial pain described as aching, dull, pressing, or intermittent. Additionally, 13.5% of these patients complained of joint clicking, pain during chewing, and limited opening [9].

Osteosarcomas of the jaws are uncommon, representing 5% to 13% of all osteosarcomas

* Corresponding author.
E-mail address: fischerd@uic.edu (D.J. Fischer).

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[15–17]. For primary jaw tumors, the most common presenting feature is painless extraoral or intraoral swelling [16]. However, pain may develop in as many as 50% of the cases, and neurosensory disturbances of the trigeminal nerve have been reported in 21.2% of cases [17].

Intracranial malignancies may give rise to orofacial pain and/or headache, with the most common presentation being similar to that of classic trigeminal neuralgia (TN) [18]. The oral and maxillofacial surgeon must be cautious in the presence of these symptoms so as to not misdiagnose and mismanage these patients for TN when a central lesion is present. In a large series of patients presenting to neurology clinics with facial pain, the incidence of intracranial tumors has been found to be 0.8% to 5.9% [18,19]. Further evaluation of presenting symptoms associated with intracranial tumors has revealed that peripherally located tumors tend to cause an unusual facial pain presentation associated with sensory loss [19]. Middle fossa tumors may present as TN, but usually cause severe pain of an atypical nature and are associated with progressive neurologic deficits [19]. Posterior fossa tumors are most likely to cause TN-like symptoms, often accompanied by subtle neurologic deficits [19]. Furthermore, in a prospective study of cancer patients, new or changed headache was the presenting symptom for 32.4% of 68 cancer patients with intracranial metastases. Factors such as non–tension-type headache pain or new or changed headache [20] with duration of less than 10 weeks and vomiting were individually predictive of intracranial metastatic disease, although no information from the neurologic examination significantly contributed to diagnosis [21]. The clinical presentation is therefore often misleading and neurologic assessment may be of limited value. Ultimately, neuroimaging is required for diagnosis of intracranial tumors and should be considered for all patients presenting with symptoms of trigeminal neuralgia, neurologic deficits, and new or changed headaches [21].

Orofacial pain associated with metastatic malignancy

Metastatic orofacial tumors are rare, though they affect jaw bones more often than the oral soft tissues [22]. The breast is the most common primary source for tumors metastasizing to the jaw bones, followed by lung and prostate, and metastatic lesions most commonly occur in the posterior mandible, angle of the jaw, and ramus [22,23]. In the oral soft tissues, the lung in males and breast in females are the most common primary sources for metastases, and the attached gingiva is the most common affected site followed by the tongue [22,24]. Pain is a rare complaint in soft-tissue metastases [24], whereas in metastatic disease of the jaw bones, pain has been reported in 39% and paresthesias in 23% of patients [25]. In a retrospective case series of metastatic disease in the jaws, 60% of 114 cases reported the metastatic lesion in the oral region to be the first indication of an undiscovered primary malignancy at a distant site [23].

Orofacial pain in systemic cancer

Manifestations of systemic cancers may affect the head and neck structures, causing pain and loss of function. Lymphoma is the second most common neoplasm occurring in the oral region [26] and accounts for less than 5% of all head and neck malignancies [27]. Over 71,000 new cases of lymphoma, 44,000 new cases of leukemia, and 19,000 new cases of multiple myeloma are expected in 2007 [28]. Extranodal lymphoma may present as a local mass, with most common sites being the tonsil and sinuses, which may or may not be ulcerated, and is associated with discomfort in approximately one half of patients [29]. Lymphomas and leukemias may also induce pain by infiltration of pain-sensitive structures such as periosteum and gingiva [30]. Multiple myeloma may present with osteolytic lesions of the skull and/or jaw and is typically unaccompanied by oral symptoms [31]. However, when such lesions are adjacent to teeth, odontogenic pain is common and presents a radiologic diagnostic challenge as the osteolytic lesions appear to be associated with teeth but are actually related to systemic disease [32]. Consequently, histologic analysis of osteolytic lesions is recommended to obtain an accurate diagnosis [31].

Orofacial pain secondary to non-metastatic malignancy at a distant site (referred pain)

Rarely, orofacial pain has also been reported in patients suffering from a distant non-metastasized cancer, most commonly from the lungs [33–37]. In such circumstances, the facial pain is almost always unilateral, frequently described as severe and aching, and usually is continuous and progressive. Reviews of the literature have revealed that the pain is most commonly localized

to the ipsilateral ear (84%–91%), the jaws (48%), and the temporal region (38%). An elevated erythrocyte sedimentation rate has also been reported [33,36]. The mechanism by which a mass in the lung can refer pain to the face presumably involves either direct tumor invasion or compression of the vagus nerve by malignant lymph nodes [34,35]. Additionally, orofacial pain may be caused by activation of nociceptive pathways in mediastinal or head and neck structures [37].

Acute pain during cancer therapy

Surgical procedures

Acute pain is common secondary to surgical procedures for head and neck cancer. Surgery-related pain usually involves acute inflammatory responses related to the extent of the surgery and may be associated with a variable degree of concomitant nerve injury.

Acute pain secondary to chemotherapy/radiation therapy (mucositis)

Oral mucositis is a common acute complication of chemotherapy (CT) and/or radiation therapy (RT) and typically manifests as erythema and/or ulceration of the oral mucosa (Figs. 1 and 2). Chemotherapy-induced mucositis affects the labial and buccal mucosa, tongue, floor of mouth, and soft palate, all of which are more severely affected than attached, heavily keratinized tissues such as hard palate and gingiva. Unlike CT damage, radiation damage is anatomically site-specific, and toxicity is localized to irradiated tissue.

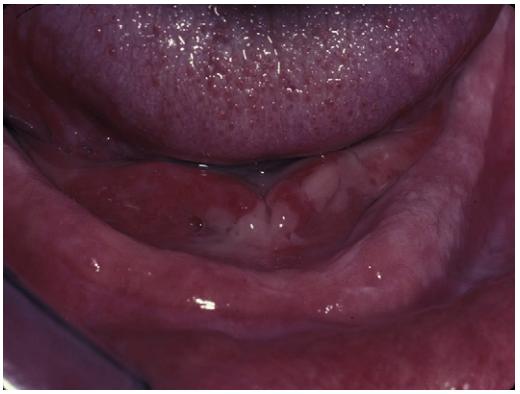

Fig. 1. Oral mucositis on the floor of mouth secondary to cancer chemotherapy.

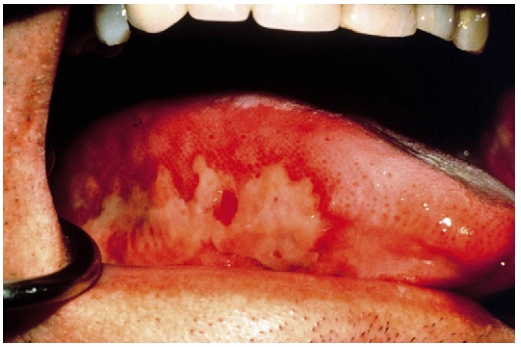

Fig. 2. Ulcerative and erythematous mucositis on the right lateral tongue secondary to radiation and chemotherapy for a right-sided base of tongue squamous cell carcinoma.

In chemotherapy-induced mucositis, erythematous mucositis typically appears 5 to 14 days after initiation of treatment, and ulcerative mucositis initially emerges approximately 2 weeks after initiation of treatment [38,39]. However, the biologic tissue changes begin immediately, as cytotoxic cancer therapy causes direct injury to replicating basal epithelial cells and disturbances in mucosal immunity [39,40]. Ulcerative mucositis occurs in approximately 40% of patients receiving standard CT and about 75% of patients who undergo hematopoietic stem cell transplants receiving high-dose CT. In about half of the patients with ulcerative mucositis, the lesions are severe and painful [40,41] and the breakdown of the epithelial barrier is a potential portal for systemic infection [39,42]. Medical intervention is often required with severe ulcerative mucositis and may lead to a modification or interruption of cytotoxic therapy, which may negatively affect treatment outcome and increase morbidity and mortality [41,43]. Mucositis is self-limiting when uncomplicated by infection and typically heals within 2 to 4 weeks after cessation of cytotoxic CT.

In RT, oral mucositis is the result of cumulative tissue dose and is almost universal in patients undergoing treatment involving the oropharynx. The degree of damage is dependent on treatment regimen-related factors, including type of radiation used, total dose administered, field site, and field size/fractionation. Mucositis pain is common (58%–75%) and may be severe, interfering with daily activities and oral function that affect the patient's quality of life [44–46]. Pain often escalates at week 3, peaking at week 5, and persisting

for weeks with gradual remission of signs and symptoms [45]. Duration of radiation-induced oral mucositis typically extends for 6 to 8 weeks [38,45]. Radiation-induced damage also differs from CT-induced changes in that irradiated tissue tends to manifest permanent damage that places the patient at continual risk for oral sequelae. The oral tissues are thus more easily damaged by subsequent toxic drug or radiation exposure, and normal physiologic repair mechanisms are compromised as a result of permanent cellular damage [42]. A retrospective cohort study of 204 patients who underwent RT found that oral mucositis was associated with increased weight loss and an incremental increase in treatment costs, depending on the severity of mucositis [47]. Combined CT and RT has been documented to result in increased frequency, severity, and duration of mucositis [47–49].

Treatment for oral mucositis involves meticulous oral hygiene and symptomatic management in a stepped approach beginning with bland rinses such as 0.9% saline and/or sodium bicarbonate solutions, followed by topical anesthetics, mucosal coating agents (eg, milk of magnesia, liquid Amphogel, Kaopectate, Gelclair), and then systemic analgesics [42,50–53]. However, these management approaches have not been subjected to controlled clinical trials. Oral care protocols generally include atraumatic cleansing of the oral mucosa, maintaining lubrication of the lips and oral tissues, and relieving pain and inflammation. As has been evaluated in Cochrane database systematic reviews [54,55], many agents and protocols have been promoted for prevention of mucositis or palliation of symptoms and have been found to provide some benefit at preventing or reducing the severity of mucositis associated with cancer treatment.

Oral infection

Acute oral infections of the mucosa (eg, bacterial, viral, and fungal), dentition/periapices, and periodontium may occur due to exacerbation of latent or prior chronic infection, changes in flora that occur secondary to cancer treatment, or indirect damage to oral structures and tissues, all of which may contribute to oral pain [56–59].

Bacterial

Both indigenous oral flora and hospital-acquired pathogens have been associated with bacteremias and systemic infection during myelosuppression secondary to high-dose CT [60]. Other oral sites, including the dentition, periapices, and periodontium, can also become acutely infected. Cancer patients undergoing high-dose CT who have chronic periodontal or pulpal/periapical disease may develop acute infections with associated systemic sequelae, and inflammatory signs may be masked due to the underlying myelosuppression [56,57,61]. Frequency and severity of bacterial infections typically begin to decrease approximately 3 to 4 weeks after cessation of CT and generally coincide with immune reconstitution [59]. Dental management of potential odontogenic and periodontal infection before initiation of CT can substantially reduce the risk of acute infectious flares [58,62,63], and mouth-care protocols that reduce microbial colonization of the dentition and periodontium are important during myelosuppression [62,63]. Bacterial infections may occur throughout the course of head and neck radiation and should be treated as soon as possible to reduce pain and the spread of infection.

Fungal

Candidiasis is a common clinical infection of the oropharynx in patients during and following CT and/or RT (Fig. 3). A number of variables contribute to its clinical expression, including immunocompromised status, mucosal injury, and xerostomia [64]. In addition, antibiotics used during prolonged neutropenia and/or concurrent steroid therapy typically alter oral flora, thereby creating a favorable environment for fungal overgrowth [65]. In irradiated patients, candidiasis develops secondary to the hyposalivation caused by

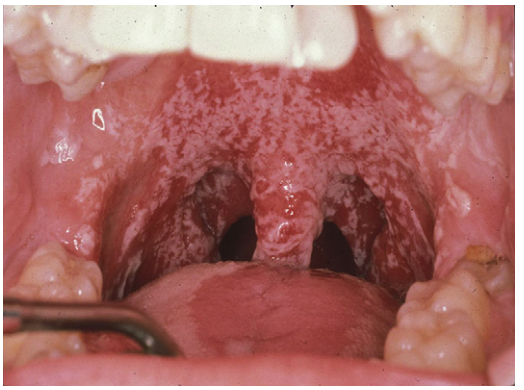

Fig. 3. Oropharyngeal pseudomembraneous candidiasis secondary to cancer therapy.

RT. Although superficial fungal infections may be treated with topical antifungal agents, systemic medications are often indicated for treating fungal infections in the oral cavity. Deep fungal infections may develop in immunocompromised cancer patients, including infection by aspergillosis, histoplasmosis, and mucormycosis [66]. The clinical presentation is not pathognomonic; lesions may appear similar to other oral toxicities and are painful. Microbiologic documentation is essential, and systemic therapy must be instituted promptly owing to high risk for morbidity and mortality.

Viral

Viral infections can cause a variety of diseases that range from mild to serious conditions in patients receiving cancer therapy. The severity and impact of these lesions, including risk for systemic dissemination, dramatically increases with worsening immunosuppression [67]. The ulcerations caused by viral infections can be painful and persistent. In most instances, herpes simplex virus (HSV), varicella zoster virus (VZV), and Epstein-Barr virus (EBV) infections result from reactivation of latent virus, whereas cytomegalovirus (CMV) infections can result from either reactivation of a latent virus, or via a newly acquired virus [68]. Prophylaxis with antiviral medications (eg, acyclovir, valacyclovir, gancyclovir, famciclovir, foscarnet) for patients receiving high-dose CT and undergoing hematopoietic stem cell transplantation has considerably reduced the incidence of these diseases. In high-dose CT and hematopoietic stem cell transplantation patients not receiving antiviral prophylaxis, HSV lesions typically emerge during the period of most significant immunosuppression, from a few days before transplant through day 35 posttransplant [67]. Orofacial VZV lesions are typically observed from approximately 3 to 12 months posttransplant, with allogeneic transplant recipients being at highest risk [69]. Oral lesions associated with CMV have been documented in patients who have undergone marrow transplantation [70,71]. EBV does not appear to be clinically significant in CT recipients, although hairy leukoplakia has been reported in stem cell transplant patients. However, hematopoietic stem cell transplant patients who are immunocompromised for a prolonged period may be at risk for development of EBV-related lymphomas (posttranplant lymphoproliferative disorders) of the head and neck region, especially when T-cell–depleted grafts are used for allogeneic transplant [72]. Current studies indicate that patients receiving head and neck RT are not at increased risk of viral reactivation specifically related to therapy, although occasional instances of simultaneous oral HSV lesions occurring during therapy have been reported [69,73].

Acute graft-versus-host disease

Patients who have received allogeneic or matched unrelated hematopoietic stem cell transplants are at risk for graft-versus-host disease (GVHD), which is the result of donor cells that react with and destroy recipient tissue. Acute GVHD can occur at the time of white cell recovery, as early as 5 days posttransplant, ranging from 5 to 47 days [74], and most commonly presents as a pruritic rash on the skin, followed by involvement of the liver and gut. Oral mucosal lesions occur in only about one third of acute GVHD cases and constitute a minor component of this problem [75,76]. Acute oral GVHD has been described as erythematous, desquamative and ulcerative lesions and/or lichenoid lesions that may be symptomatic and can involve multiple areas of the oral cavity [76].

Chronic pain secondary to cancer treatment

Chronic mucosal changes

Chronic changes involving oral mucosa are the result of hypovascular, hypocellular, and hypoxic changes that occur during cancer treatment, most commonly RT [40,77]. Types and severity of these changes are directly related to radiation dosimetry, including total dose, fraction size, and field size.

Chronic mucosal sensitivity

Chronic mucosal sensitivity may persist long after oral tissues heal following cancer treatment. In a survey of patients who have undergone RT, results indicated that 43% of 65 respondents reported at least mild sensitivity 1 year following treatment [48]. This chronic pain may result from permanent damage to oral tissues, including epithelial atrophy, submucosal fibrosis, neurologic sensitization, and/or neuropathy.

Slow-healing mucosa

The chronic mucosal changes may lead to an atrophic, friable mucosal barrier [40,77], which may predispose oral tissues to ulceration following trauma or injury. Soft-tissue necrosis may

then ensue due to reduced vascularization of the tissue and poor wound healing. Pain will generally become more prominent as soft-tissue necrosis progresses. Infection secondary to tissue injury increases the risk. Soft-tissue necrosis can involve any mucosal surface in the mouth, though nonkeratinized surfaces appear to be at moderately higher risk.

Chronic graft-versus-host disease

Chronic GVHD usually arises as an extension of acute GVHD in which the disease evolves directly from acute GVHD (progressive) or following a period of recovery from acute GVHD (quiescent). However, chronic GVHD may also develop in patients with no history of acute GVHD (de novo) or as an abrupt onset of multisystem involvement and manifestations of both acute and chronic GVHD (explosive) [20,74]. Chronic GVHD changes can be recognized as early as day 70 posttransplant [75,76], with recognition earlier in patients receiving nonidentical related or unrelated donor transplants [74]. Chronic GVHD can affect oral tissues and often mimic autoimmune conditions [75–78]. Common oral findings include atrophy, erythema, and lichenoid lesions, possibly with an erosive component and fibrosis consistent with progressive systemic sclerosis, as well as persistent reduction in salivary function (Fig. 4). Oral GVHD has also been linked with oral precancerous and malignant lesions [79]. Oral symptoms of GVHD include xerostomia and increased pain and sensitivity to acidic or spicy foods, alcohols, and flavoring agents, especially mint flavors in toothpaste and oral care products. Management of chronic GVHD may include topical or systemic steroids and/or immunosuppressants as well as management of hyposalivation, increased caries risk, and infection associated with hyposalivation.

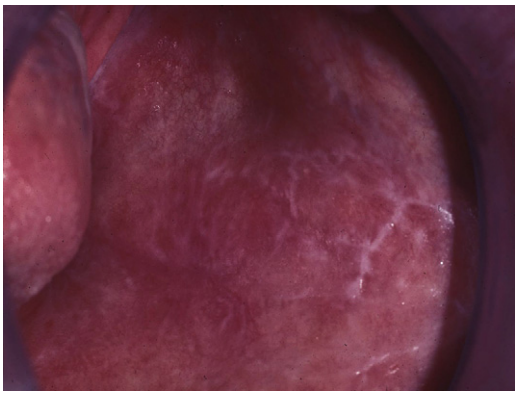

Fig. 4. Lichenoid changes to the buccal mucosa in a patient with chronic graft-versus-host disease.

Neuropathic pain

Neuropathic pain is defined by the International Association for the Study of Pain as pain initiated or caused by a primary lesion or dysfunction in the nervous system [80]. This dysfunction in the nervous system may be exacerbated by persistent, unrelieved nociceptive (inflammatory) pain associated with the tumor or cancer treatments, such as surgical procedures and neurotoxicities due to CT and RT or combinations of these treatments. Neuropathic pain is an extremely debilitating form of pain that occurs when peripheral, autonomic, and/or central nerves are affected. Additionally, changes occur in the immune system that modifies the normal function of nociceptors. These alterations in pain processing at the peripheral and central levels produce characteristic symptoms such as hyperalgesia, allodynia, and paresthesia [81]. The International Association for the Study of Pain [80] defines hyperalgesia as an increased response to a stimulus, which is normally painful; allodynia as pain due to a stimulus, which does not normally provoke pain; and paresthesia as an abnormal sensation, whether spontaneous or evoked.

Grond and colleagues [3] in a study involving 377 patients diagnosed with HNC found that 11% of the patients had neuropathic pain related to treatment. Unfortunately, in HNC patients, neuropathic pain has not been well characterized in terms of sensory report (location, intensity, quality, and pattern) or sensory quantification (allodynia and hyperalgesia).

Neuropathic pain secondary to surgical procedures

Surgical procedures used in the treatment for HNC commonly result in acute orofacial pain and may lead to painful posttraumatic neuropathy. Resection of the mandible for tumor excision will inevitably lead to sensory impairment [82], with 50% experiencing regional hyperalgesia or allodynia. At 2 to 5 years postmaxillectomy, approximately 90% of patients reported persistent pain [83]. The severity of the neuropathic pain may be increased following RT. In addition to tissue injury at tumor resection, morbidity has been found to be increased by neck dissection [84]. Sist and colleagues [85] evaluated 25 patients

with persistent pain for at least 1 month following neck dissection. The sample consisted of patients with moderate to severe pain ranging from 1 month to 27 years in duration. They found that all patients had at least one type of neuropathic pain: spontaneous, continuous burning pain (81%), shooting pain (69%), and/or allodynia (88%). A study by van Wilgen and colleagues [86] found that neck pain was present in 33% of their sample of which 96% reported some form of neuropathic pain. Contrary to these studies, Talmi and colleagues [87] described three groups of patients after neck dissection procedures and found neck pain to be an uncommon finding and the most frequently affected cranial nerve is the trigeminal nerve—in particular, the sensory component. This most often results in reduced or altered sensations in a dermatomal distribution with the presence of allodynia and hyperalgesia [88].

Treatment-related toxicity (chemotherapy, radiotherapy)

Chemotherapeutic agents used in the treatment of HNC often initiate painful peripheral neuropathies that often affect the orofacial region. This debilitating adverse effect may result in the inability to provide the patient with the full chemotherapeutic regimen and limit ideal dosing, thereby greatly affecting survival rate. This side effect known as chemotherapy-induced peripheral neuropathy (CIPN) is commonly seen during CT cycles [89]. Typically, the neuropathic pain resolves with or without symptomatic treatment. However, in some patients, this resolution does not occur and may evolve into a chronically painful condition. In these patients, the symptoms cause a notable decrease in functional capacity and overall quality of life [90]. Prevalence during treatment is variable among agents, the intensity of treatment (dose intensity and cumulative dose), other ongoing therapies (such as surgery and RT), age of the patient, and the use of combinations of CT agents [91]. Estimates of prevalence range from 4% to 76% during CT [92,93]. Preexisting nerve damage such as that caused by diabetes, alcoholism, inherited neuropathy, or paraneoplastic syndrome may increase the incidence and severity of CIPN [94]. Commonly used neurotoxic agents such as the taxanes (paclitaxel, docetaxel), vinca alkaloids (vincristine, vinblastine), platinum-based compounds (cisplatin, oxaliplatin), thalidomide, and bortuzamib appear to be the most responsible for precipitating CIPN. The majority of the CIPN demonstrate a mixed sensory (positive and negative symptoms) and motor (muscle weakness and atrophy) signs [95]; however, autonomic dysfunction (hypotension, cardiac conduction irregularities, impotence, and bowel and bladder involvement) may also be present. Interestingly, both small-diameter sensory fibers—unmyelinated C fibers and thinly myelinated A-delta fibers—and large myelinated A-beta fibers are affected by chemotherapeutic agents, with the large fibers being preferentially injured by CT agents such as vinca alkaloids, taxanes, and platinum-based compounds [89,96,97]. Unfortunately, at present, little is known about the cellular and molecular mechanisms responsible for CIPN and prevention is not available.

Radiation therapy plays an important role in the management of HNC. Most patients treated with a curative intent currently receive a dose between 50 and 70 Gy (Gray unit—absorbed dose of radiation) given over a 5- to 7-week period, once a day, 5 days a week, with 1.8–2.2 Gy per fraction. This regimen is not without toxicity [98]. The early or acute effects depend on the radiated fields and include skin/mucosal reactions, nausea, diarrhea, and neutropenia and are usually self-limiting. Late effects, including connective tissue fibrosis, neural damage resulting in neuropathic pain, and secondary malignancies, can occur long after completion of RT [99]. The radiation tolerance of normal tissues depends on total dose, dose per fraction, total time of exposure, volume, radiation quality, and adjunctive therapies [100]. Acute toxicities are more prevalent with higher doses per fraction, altered fractionation (hyperfractionation), concomitant boost, higher total dose, and when combined with chemotherapy [101]. The frequency and size of each treatment (fractionation) have been shown not to affect the occurrence in a brachial plexopathy model; however, it has been shown that there is an elevated morbidity to neural tissues with high-dose regimens [94,102].

Taste is altered as an early response to RT and may present as a reduction in taste sensitivity (hypogeusia), an absence of taste sensation (ageusia), or a distortion of normal taste (dysgeusia) [103]. Taste impairment greatly impacts the quality of life of the patient and, coupled with other RT-related comorbidities such as mucositis, hyposalivation, dysphagia, and reduced food enjoyment, RT may affect the nutritional status and overall health of the patient [98,104–106]. During a curative dose of RT, taste function becomes

impaired during the first week for bitter flavor and gradually worsens. Taste loss may begin with radiation doses of 20 Gy and decreases with cumulative doses; with 30 Gy all taste qualities are affected. Ninety percent of all patients experience a loss of taste when the cumulative dose has reached 60 Gy [107–109]. Direct radiation damage to the taste buds or innervating fibers is the proposed caused of taste loss [107,109]. Histologically, taste buds show signs of degeneration and atrophy at 10 Gy (2 Gy/day), whereas at therapeutic levels the architecture of the taste buds is almost completely destroyed [107]. It has been found that taste loss is usually transient, gradually returning to normal or near normal levels within 1 year following RT; however, it can take as long as 5 years [110]. The loss of taste is a result of the damage to the neural component of taste and is related to the reduction in salivary flow rate.

Musculoskeletal pain

Postradiation osteonecrosis

Postradiation osteonecrosis (PRON) is another well-recognized complication of head and neck RT that may be associated with pain. Loss of bone vitality occurs secondary to injury to osteocytes, osteoblasts, and osteoclasts as well as relative hypoxia owing to reduction in vascular supply [77,111]. These changes can lead to a reduced capacity of soft tissue and bone to recover from injury, predisposing to soft-tissue necrosis and osteonecrosis [111,112].

The risk for PRON is directly related to radiation technique, dose, and volume of tissue irradiated. Patients who have received high-dose radiation (>60 Gy) to the head and neck are at risk for PRON for life, with an overall risk of approximately 4% to 15% after standard fractionation [111–113]; the risk increases more significantly after 66 Gy [114]. PRON more frequently involves the mandible versus the maxilla, likely owing to greater bone density and unilateral vascular supply to each half of the mandible [111,112]. Presenting clinical features include symptomatic or asymptomatic exposure of necrotic bone or bone sequestrae, diminished or complete loss of sensation, fistula, and infection (Figs. 5 and 6) [111,115,116]. Pathologic fracture can occur as the compromised bone is unable to appropriately undergo repair at the involved sites.

Prevention of PRON begins with comprehensive oral care and assessment before head and neck RT. Dentition that exhibits poor prognosis and is within high-dose fields should be extracted before radiation therapy, and patients should be educated regarding excellent compliance with oral care. Patients who develop PRON should be comprehensively managed to include removal of bony sequestrae and topical antibiotics (ie, tetracycline) or antiseptics (ie, chlorhexidine) that may contribute to wound resolution [111,112]. Analgesics for pain control are often effective. In cases associated with pain and progression, hyperbaric oxygen therapy is recommended for management of PRON [112]. Hyperbaric oxygen therapy increases oxygenation of irradiated tissue, promoting angiogenesis and enhancing osteoblast repopulation and fibroblast function. Hyperbaric oxygen therapy is usually prescribed as 20 to 30 dives at 100% oxygen and 2 to 2.5 atmospheres of pressure. If surgery is needed, 10 dives of postsurgical hyperbaric oxygen therapy are recommended [112].

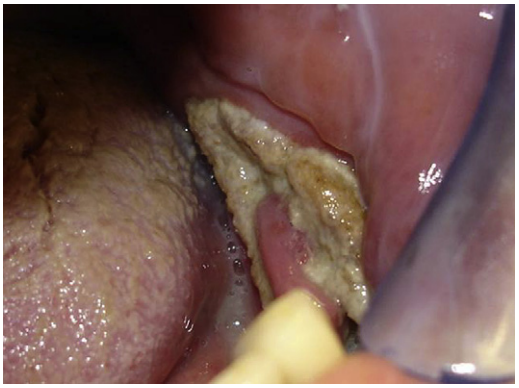

Fig. 5. Postradiation osteonecrosis of left mandible following standard fractionation radiation treatment.

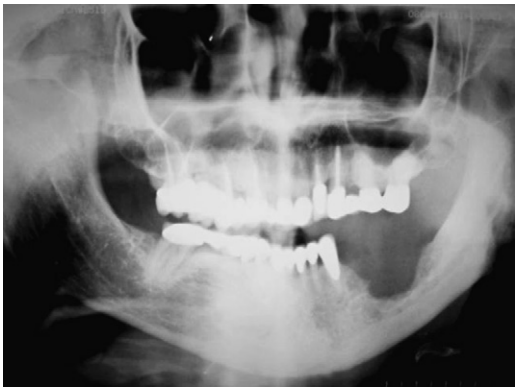

Fig. 6. Postradiation osteonecrosis of left mandible following standard fractionation radiation treatment.

Bisphosphonate-associated osteonecrosis

Oral bisphosphonates are commonly used in the management of osteoporosis, and high potency, intravenous bisphosphonates are important agents in cancer treatment, including malignancies, metastatic disease of bone, and hypercalcemia of cancer. Bisphosphonates are synthetic analogs of inorganic pyrophosphate that have a high affinity for calcium and are generally divided into two main classes based on the presence or absence of a nitrogen side chain. Those that contain nitrogen are the most potent, as the nitrogen side chain prevents these drugs from being metabolized, allowing them to accumulate with ongoing effects. The main pharmacologic effect of bisphosphonates is the inhibition of bone resorption, mediated by a decreased function of osteoclasts [117–119]. They inhibit both osteoclastic activity and osteoclast recruitment and diminish the lifespan of these cells [120], thereby causing an increase in bone deposition and mineralization [121,122]. Bisphosphonates also have antiangiogenic effects, further contributing to a decrease in bone remodeling [123,124]. Recently, osteonecrosis and osteomyelitis of the jaws have been recognized in patients treated with bisphosphonate medications (Fig. 7). Bisphosphonate-associated osteonecrosis (BON) appears to occur only in the oral and maxillofacial region and not elsewhere in the body skeleton. This may be due to the jaws having a greater blood supply than other bones and a more rapid bone turnover rate related both to their daily activity and the presence of teeth, consequently causing bisphosphonates to be highly concentrated in the jaws [125,126].

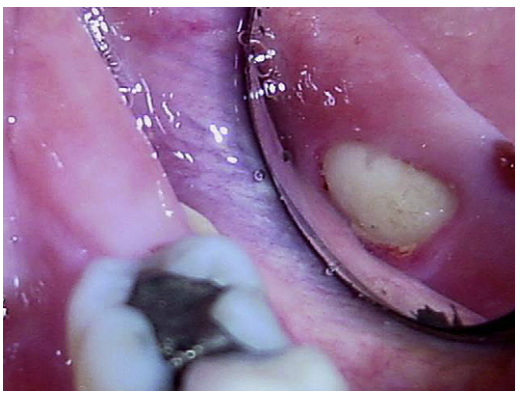

Fig. 7. Bisphosphonate-associated osteonecrosis involving the mylohyoid area (mirror image).

On the basis of retrospective surveys of patients treated with intravenous bisphosphonates, the prevalence of BON ranges from 7% to 10% for patients with multiple myeloma and 3% to 4% for those with breast cancer [127,128], whereas the prevalence of BON in patients taking oral bisphosphonate medications is much lower [129]. The risk of BON appears to be related to duration of therapy and type of bisphosphonate medication. The cumulative hazard of developing BON increased from 1% after 12 months of intravenous bisphosphonate infusion treatments up to 11% to 13% at 4 years [127,128]. Furthermore, the cumulative hazard of developing BON was significantly higher in those who received zoledronic acid alone (1% at 12 months, 15%–21% at 48 months) compared with the group with pamidronate alone or with subsequent zoledronic acid (0% at 12 months, 5%–7% at 48 months) [127,128]. A possible explanation for the difference in these findings is the more potent inhibitory effect of zoledronic acid on bone turnover and a stronger antiresorptive activity compared with pamidronate [127,128].

Prior to initiation of bisphosphonate therapy, patients should have a dental examination, and therapy should not be initiated until all dental treatment is completed [125,126,130]. Dental treatment is aimed at eliminating infections and preventing the need for invasive dental procedures in the near and intermediate future. For patients receiving bisphosphonate therapy, management should include avoidance of surgical procedures, including tooth removal, if at all possible. If patients develop BON, current guidelines do not recommend surgery beyond superficial debridement, such as rounding-off sharp bony projections that produce soft-tissue inflammation and pain [125,129,131]. However, recent literature has reported successful surgical intervention in cases of BON that are refractory to conservative management [132]. Long-term antibiotics, if indicated, and 0.12% chlorhexidine are recommended [125,126,130]. Treatment should be directed at eliminating or controlling pain and preventing progression of the exposed bone. There is no scientific evidence to support discontinuation of bisphosphonate therapy to promote healing of necrotic osseous tissues in the oral cavity, owing to the extensive half life and effect in bone [130,133]. Hyperbaric oxygen therapy may be beneficial in patients with bisphosphonate-induced exposed bone, though cessation of bisphosphonate medication is necessary to achieve remission.

A randomized controlled trial to evaluate the efficacy of hyperbaric oxygen therapy in treating BON is currently in progress [134].

Trismus and other musculoskeletal presentations

In HNC, trismus may develop due to tumor invasion, surgical treatment, and/or RT, if the masticatory muscles and/or the temporomandibular joint (TMJ) is involved, or a combination of these factors [135–137]. The prevalence of trismus after HNC treatments ranges from 5% to 38% [138,139]. Surgical treatment may induce scar tissue, which reduces mouth opening due to scar contraction and fibrosis of the masticatory muscles. Additionally, RT may induce fibrosis and atrophy in the masticatory muscles and/or TMJ as a late radiation effect [135,136,140,141]. This muscle fibrosis, on the basis of animal studies, evolves over several years and is most likely the result of increased cytokine production, proliferation of fibroblasts, synthesis of matrix proteins, and loss of vascular supply due to RT [142–144]. Dijkstra and colleagues [145], in a cross-sectional study, determined that 35 mm or less was the appropriate criterion for trismus, on the basis of the extent of the restrictions perceived in mouth opening and mandibular function by HNC patients. Trismus may increase morbidity because the limitation in opening interferes with oral hygiene, speech, nutritional intake, examination of the oropharynx, and dental treatment.

Trismus occurs with unpredictable frequency and severity. Generally, it is a late-treatment effect that develops 3 to 6 months after RT, often becoming a lifelong problem [136,146]. It has been suggested that the severity of the trismus is dependent on the configuration of the radiation field (unilateral or bilateral), the radiation source, and the radiation dose [135]. Contrarily, Steelman and Sokol [137] reported no correlation between reduced interincisal distance and total radiation dosage to the TMJ region. Nguyen and colleagues [147] also did not find a relationship between dosage and postradiotherapy complications, including trismus. However, other authors reported that trismus as a result of alterations to the TMJ develops only after high radiation doses [136], whereas others support the finding that trismus involving the masticatory muscles may develop after fairly low doses and worsens with increasing doses [135,141]. Goldstein and colleagues [135] suggested that the most critical factor in the development of postradiation trismus is probably due to the inclusion of the pterygoid muscles in the treatment field. This may explain the differences observed among the various studies reported in the literature.

Masticatory and/or cervical muscle pain may be found in HNC patients owing to tumor invasion and/or cancer therapy. Morbidity of these structures is not very well described in the literature. Shah and colleagues [148], in a retrospective study of 51 patients having different types of neck dissection, found that neck tightness was reported in 71% of the cases together with shoulder discomfort reported in 53% of the cases. They concluded the reported muscle pain had a substantial negative effect on quality of life. In an assessment of quality of life study following surgical management, it was found that neck and shoulder symptoms commonly followed neck dissection and decreased pain was seen in selective neck versus modified radical neck dissection [149]. In another study, of 25 patients with persistent neck pain after neck dissection, it was found that 72% of the patients reported cervical muscle pain [85]. In a study assessing patients who underwent neck dissection, with and without RT at least 1 year before the study, it was found that cervical muscle pain was present in up to 46% of the patients and was associated with a significant reduction in range of motion [86]. It is possible that the mechanisms responsible for trismus may also be responsible for the muscle pain.

It is important for the oral and maxillofacial surgeon to be aware of these conditions as he or she may be involved in the treatment of these adverse effects. In patients who present with trismus and/or muscle pain, the goal would be to restore lost interincisal opening and to alleviate pain and dysfunction. Exercises to increase mouth opening and improve mandibular mobility, including the use of prosthetic appliances (dynamic bite openers), rubber plugs, and tongue blades, may be used to treat trismus; however, once established, limited increase in range of movement can only be achieved. Involvement of orofacial pain practitioners and physical therapist to establish muscle pain control and restore function may be warranted. Regardless of the approach, patient compliance and perseverance are essential for success because dramatic results are not achieved immediately [98].

Summary with an emphasis/impact on oral and maxillofacial surgeons

Cancers involving the head and neck may originate in the oral cavity, salivary glands,

paranasal sinuses, nasal cavity, nasopharynx, pharynx, larynx, and/or lymph nodes in the upper neck. The close proximity and dense arrangement of blood vessels, nerves, and the central nervous system make these head and neck structures susceptible to nerve damage and pain. Classification of orofacial pain in cancer patients is complex and may be based on numerous pain mechanisms (eg, nociceptive/inflammatory, neuropathic), the location and extent of tumor, and the stage of treatment. Since orofacial pain is a well-recognized symptom associated with systemic and distant cancer and its treatment, it is imperative that the oral and maxillofacial surgeon has an understanding of various pain presentations. Successful pain management requires knowledge of, and attention to, multiple pain mechanisms that may contribute to the patient's pain presentation.

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