Orofacial Pain
Guidelines for Assessment, Diagnosis, and Management

The American Academy of Orofacial Pain
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The American Academy of Orofacial Pain (AAOP) was founded in 1975, and its goal was to improve the understanding and quality of education in temporomandibular disorders (TMDs) and orofacial pain. The mission of the AAOP remains to be an organization of health care professionals dedicated to alleviating pain and suffering through the promotion of excellence in education, research, and patient care in the field of orofacial pain and associated disorders.

Five publications have preceded this current edition of what commonly is referred to as the AAOP Guidelines. Dr Charles McNeill spearheaded the first two editions called *Craniomandibular Disorders: Guidelines for Evaluation, Diagnosis, and Management* (Quintessence, 1990) and *Temporomandibular Disorders: Guidelines for Classification, Assessment, and Management* (Quintessence, 1993). These publications focused predominantly on TMDs. As health care professionals and researchers became more conscious of the relationship between TMDs and other disorders of the head and neck, there was a need to expand the Guidelines to include disorders presenting as or related to TMDs. These disorders included not only headaches and neck disorders but several neuropathic pain conditions as well as biobehavioral factors. In 1996, under the editorship of Dr Jeffrey Okeson, the third version of the AAOP Guidelines was published, titled *Orofacial Pain: Guidelines for Assessment, Diagnosis, and Management*. That edition used the term *orofacial pain* to echo the rapidly changing and expanding field of orofacial pain and to reflect the fact that TMDs and orofacial pain should not be regarded as separate conditions, but that TMDs should be considered part of the disorders that fall under the umbrella of orofacial pain. Under the editorship of Dr Reny de Leeuw, the fourth edition of the Guidelines was published, which started to express evidence-based concepts. This edition included a separate chapter on cervical disorders to emphasize the close relationships between some orofacial pain disorders and cervical pain disorders, and—more importantly—to call attention to the differences and similarities associated with these disorders. The fifth edition, published in 2013, adopted the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) and the expanded TMD taxonomy based on the work of the International RDC-TMD Consortium. An updated definition of bruxism based on another international consensus work group was also adopted. Moreover, a new chapter was added in the fifth edition dedicated to the relationship between pain disorders and sleep.

While the structure of the present work resembles previous editions, significant changes have been implemented in this current edition. All chapters contain essential updates, and some have undergone more changes than others. References have been updated throughout to reflect the most current literature. When available, evidence-based material has been included to provide the reader with scientifically sound and effective diagnostic procedures and treatment options. All references to the *International Classification of Diseases, Ninth Edition* (ICD-9) codes have been removed, and *ICD-10* codes have been updated or added. In addition, references to the *International Classification of Headache Disorders, third edition* (beta version) (ICHD) have been updated in chapters 4 and 5 and added to chapter 6. Chapter 1 has been updated with the most recent knowledge from the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) studies, regarding genetics and epigenetics as well as expanded information about glial cells, neuropeptides, and their implications for pain. In chapter 2, the relationship between TMDs and otalgia has been elaborated upon, and additional measures for sleep apnea assessment have been included. In chapter 3, the newest versions of classification systems have been included. Chapters 4 and 5 contain various general updates as well as updates to management. Chapter 6 was completely renewed and now follows the ICHD. As a result, the description of superior laryngeal neuralgia was eliminated. Chapter 7 contains general updates to the references as well as management strategies for several disorders. The sections on viral infections, candidiasis, and pain due to cancer treatment contain the most notable updates. In chapter 8, the section on epidemiology was updated and expanded to
include more information on TMDs and comorbid conditions. The section on genetic factors has also been updated to reflect the work from the OPPERA studies. The section on diagnostic classification has been updated to more accurately describe the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for the most common TMDs and the expanded taxonomy including less common TMDs. General updates have been provided for the management section of this chapter, and new sections include but are not limited to gabapentinoids, glucosamine and chondroitin, and topical medications. A summary of pharmacologic treatments is also new. Under the physical agents section, a separate paragraph is dedicated to the potential use of botulinum toxin for myofascial pain, indicating that there is currently insufficient evidence for its use. The layout for chapter 9 has been changed, and sections emphasizing genetics and peripheral and central sensitization have been added. Sections have also been renamed to reflect the most up-to-date terminology. In chapter 10, benign disorders of the eyes and ears have been expanded on. A description of first-bite syndrome has also been added. The descriptions of various connective tissue diseases have undergone major edits, and the section on blood vessels contains major improvements as well. The content of chapter 11 has been updated, specifically regarding comorbidities and bruxism. Chapter 12 provides updates on brief, ultra-brief, and comprehensive screening tools for biobehavioral factors in line with the recommendations from the DC/TMD. The chapter also includes major updates in the description of several psychiatric diseases in line with the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Lastly, the glossary has undergone major updates to reflect the emerging and expanding field of orofacial pain. New terms have been added, and obsolete and superfluous terms have been removed.

Finally, a word of caution: This is not intended to be an all-encompassing textbook including complete details regarding all aspects of orofacial pain. Instead, it is meant to provide insight in and to assist the reader with the procedures of evidence-based assessment, diagnosis, and management of orofacial pain conditions, based on the latest scientific knowledge.

Reny de Leeuw and Gary D. Klasser
Co-chairs, AAOP Guidelines Committee

Acknowledgments

Over the years, numerous AAOP members and nonmembers have participated in the evolution of the AAOP Guidelines, resulting in the sixth edition of this publication. The contributors to the current edition of the AAOP Guidelines are listed on a separate page. Each new edition has reflected the emerging and expanding field of orofacial pain. Based on these developments, new and evidence-based materials have been added. However, this ever-evolving work has built on and edited the work others have done in the past. As such, some parts of previous contributions may still be intact. We therefore want to extend our sincere appreciation to all of you who have contributed to any of the past editions, and especially to those of you who laid the foundation of this publication. We also would like to offer much gratitude to the publishers for providing us with timely advice and guidance so that deadlines could be met. The staff support at Quintessence has been incredibly accommodating and meticulous in their efforts and should be applauded. We truly hope that you will get great enjoyment and practical help from this new edition.
Introduction to Orofacial Pain

Key Points

◊ Orofacial pain remains a prevalent and debilitating condition with significant social and economic impacts.
◊ Many of the risk factors associated with a temporomandibular disorder (TMD) involve mechanical, chemical, or environmental stressors that increase the likelihood of developing and maintaining a chronic pathologic state.
◊ TMDs are not caused by a single gene mutation but are a result of changes in the expression of many genes that contribute to the pathology and nature of the pain.
◊ Sensitization and activation of trigeminal nerves and the subsequent development of peripheral and central sensitization are key pathophysiologic events that lead to allodynia and hyperalgesia.
◊ A decade of discovery from the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study helped to clarify specific risk factors and genes implicated in the development of a TMD.
◊ Given the complex nature of orofacial pain conditions, treatment should involve multiple modalities including pharmaceuticals, physical therapy, behavioral modifications, diet, and exercises that emphasize proper breathing and increasing flexibility.

Orofacial pain refers to pain associated with the hard and soft tissues of the head, face, and neck. These tissues, whether skin, blood vessels, teeth, glands, or muscles, send impulses through the trigeminal nerve to be interpreted as pain by the brain circuits that are primarily responsible for the processing that controls complex behavior.¹ The complaint of orofacial pain encompasses a diagnostic range from neurogenic, musculoskeletal, and
psychophysiologic pathology to headaches, cancer, infection, autoimmune phenomenon, and tissue trauma. Evaluation and management of orofacial pain requires collaboration among all fields of medicine because pain has the potential to arise from multiple trigeminal receptive fields.

The quest to better manage pain problems involving the trigeminal system such as TMDs and headaches has led to the establishment of orofacial pain as a discipline in the field of dentistry. There are residency training programs in orofacial pain, board certification processes, and increasing cooperation among advocacy groups, universities, professional organizations, and federal agencies. A huge step in the recognition of orofacial pain as a discipline in dentistry occurred in 2009 when the Commission on Dental Accreditation (CODA) approved orofacial pain as an area of advanced education. Since 2011, several programs in the United States have received accreditation from CODA. Furthermore, the International Association for the Study of Pain developed a core curriculum on this subject for all health care professionals in a clear acknowledgment of the need for orofacial pain as a component of professional education.

This revised edition is a collaborative effort derived from reviews of refereed literature spanning the spectrum of conditions that are at the root of orofacial pain. It is intended for health care professionals who evaluate and treat patients with orofacial pain and face the daunting task of keeping up with the literature in the rapidly emerging arena of pain management in clinical practice.

The Health Care Professional’s Responsibility in Orofacial Pain

It is every clinician’s responsibility to remain unbiased during evaluation and differential diagnosis. Orofacial pain complaints involve diverse, complex physiologic interrelationships, and all clinicians must be able to judge when their diagnostic acumen requires consultation; otherwise, treatment may not target the appropriate source.

The clinician’s responsibility is threefold. First, the clinician must combine a current working knowledge of the clinical science of orofacial pain with an ability to obtain a complete relevant history from the patient. Appropriate questions must be asked, answers must be analyzed, and findings must be synthesized into an initial differential diagnosis. Second, the clinician must perform a thorough clinical assessment, including a physical examination and indicated laboratory testing, imaging studies, neurologic testing, and consultations. Accurate diagnosis may require insight from other health care professionals. Third, the clinician must be able to explain to the patient all findings as well as the details of the treatment plan, which must be consistent with standards of care based on scientific literature. When the scope of care falls beyond individual expertise, an interdisciplinary team approach may be developed. The clinician should discuss appropriate referral options with the patient.

Epidemiology of Orofacial Pain

Pain is a common experience that has profound societal effects. Results from a cross-sectional Internet-based survey found that the weighted point prevalence of chronic pain was 30.7% in adults in the United States. This prevalence was greater in women and increased with age. Based on results obtained from the 2012 National Health Interview Survey, the National Center for Complimentary and Integrative Health from the National Institutes of Health (NIH) reports that nearly 50 million American adults suffer from significant chronic or severe pain. Not surprisingly, the study found that individuals in more severe pain required more health care services and experienced greater disability when compared with individuals re-
porting lower levels of pain. About half of the individuals in the worst pain still reported their overall health as good or better, while both sex (women) and ethnicity (non-Hispanics) were associated with a higher frequency of reporting painful conditions. Findings from this report highlight the need for a better appreciation of the subjective nature of pain and the challenge of personalizing the treatment to achieve a successful outcome for each pain patient.

Chronic pain costs the United States billions of dollars annually due to loss of work, decreased productivity, disability compensation, and expenses for health care services including more emergency room visits, higher medication costs, and greater psychologic treatment expense. Chronic pain is economically costly because it requires medical intervention and makes it more difficult to treat other ailments. The cost of pain is actually estimated to be greater than the annual costs of heart disease, cancer, and diabetes.

Lipton et al surveyed 45,711 American households and reported that nearly 22% of the general population had experienced at least one of five types of orofacial pain in the past 6 months. The most common type of orofacial pain was toothache, reported by 12.2% of the population. Temporomandibular joint (TMJ) pain was reported by 5.3%, with face or cheek pain being reported by 1.4%. Orofacial pain seldom appears to be an isolated complaint. More than 81% of patients reporting to an orofacial pain center had pain sources apart from the trigeminal system, but few patients mention these other pain sources. Conditions that seem to coexist with TMDs include fibromyalgia (FM), chronic fatigue syndrome, headache, panic disorder, gastroesophageal reflux disorder, irritable bowel syndrome (IBS), multiple chemical sensitivity, and posttraumatic stress disorder. Symptoms of such comorbid conditions differentiate orofacial pain patients from those who seek routine dental care. If the true pain sources are not revealed during the evaluation, the prognosis may be adversely affected by the continued barrage of brain circuits as the result of chronic nociception.

Results have been published from the OPPERA study funded by the National Institute of Dental and Craniofacial Research (NIDCR) to identify risk factors involved in the initiation and maintenance of TMDs and to develop treatments for managing TMD-associated pain. The major objectives of this longitudinal, multidisciplinary study were to determine psychologic and physiologic risk factors, clinical characteristics, and associated genetic and cellular mechanisms that influence the development of TMDs. Based on findings from these studies, the investigators presented a model that includes genetic, physiologic, and environmental factors that increase the risk for an individual to experience TMD pathology. More recently, NIDCR funded an additional study, OPPERA II, with the goal of further investigating risk factors for the development of TMDs and understanding their relationship with often-reported comorbid pain conditions including IBS, headache, and lower back pain. A summary of the major findings from a decade of research from the OPPERA studies has recently been published. Those individuals seeking more information from the OPPERA studies are encouraged to visit the Journal of Pain website.

Importantly, both the US Congress and NIH now recognize coexisting pain conditions characterized by a set of disorders that include, but should not be limited to, TMDs, FM, vulvodynia, IBS, interstitial cystitis/painful bladder syndrome, endometriosis, chronic tension-type headache, migraine headache, myalgic encephalomyelitis/chronic fatigue syndrome, and chronic lower back pain. Taken together, these conditions are gradually being referred to as chronic overlapping pain conditions. The discussion of these overlapping pain conditions produced by the Chronic Pain Research Alliance can be found at their website.
Pain constructs

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Nociceptors are polymodal, high-threshold nerve endings that send impulses in response to damaged tissue on fast-conducting Aδ fibers and slow-conducting C-fibers to the central nervous system (CNS). Although pain is an interpretation of nociception, many orofacial pain patients lack apparent tissue damage, and anatomical changes such as TMJ disc displacement without reduction do not predict continuing pain.

About 25% of free nerve endings in skeletal muscle that transmit impulses to the CNS on Aδ fibers and C-fibers are chemo- and mechanoreceptive but not nociceptive. Some of these low-threshold receptors, called metaboreceptors, appear to be uniquely stimulated by the metabolic products generated during muscle activity, while others sense the relative distension of post-capillary bed venules. These receptors display background activity at rest, accelerate impulse transmission as behavior intensity increases, and may affect the same central modulatory systems as nociception. The CNS uses this input to coordinate respiratory and cardiovascular changes during dynamic muscle behavior. Future consideration of the role of these receptors in pain etiology may help us better understand pain conditions in which there is no apparent tissue damage.

Anatomical and Physiologic Considerations of Orofacial Pain

Orofacial pain may be defined as pain and dysfunction affecting motor and sensory transmission in the trigeminal nerve system. From a sensory perspective, the trigeminal system...
oversees the efficacy and tissue integrity of the highly integrative orofacial behaviors that are controlled by cranial nerves and modulated by the autonomic nervous system (ANS) and the greater limbic system.26 Orofacial nerves transmit information about pressure (touch), position, temperature, and potential pain to the trigeminal nuclei, which have extensive bidirectional connections throughout the brain.27–29 These trigeminal connections affect the sensory, motor, and autonomic-endocrine changes that occur during orofacial behaviors, and orofacial pain may result when these behaviors are impaired. The next sections briefly discuss peripheral and central trigeminal neuroanatomy to explain how the trigeminal system affects physiology and pain.

**Neuroanatomy of the orofacial structures**

*Cranial nerves* are extensions of the brain that directly or indirectly innervate tissues involved with the trigeminal system.4 The specialized neurons of the olfactory, optic, and vestibulocochlear nerves that send smell, sight, sound, and balance information to the CNS do not travel through the trigeminal nuclei. However, nerves associated with the nose, eye, and ear tissues do transmit proprioceptive, pressure, and potential pain impulses into the trigeminal nuclei. A comprehensive orofacial pain evaluation should include a basic assessment of the function of all cranial nerves (see chapter 2). Five of these nerves (V, VII, IX, X, and XII) are reviewed here.

**Trigeminal nerve**

The trigeminal nerve, which provides sensory innervation to most of the head and face, is the primary nerve involved in TMDs, migraine, sinus, pulpal, and periodontal pathology. It is the largest cranial nerve and consists of three peripheral divisions: the ophthalmic, maxillary, and mandibular.30–33 These branches receive sensory input that is conveyed on first-order neurons through the trigeminal ganglion, where most neuronal cell bodies are located. Although these neurons enter the ganglion on three branches, they exit in one large sensory root that enters the brainstem at the level of the pons before reaching the trigeminal nuclei.34

**Ophthalmic branch (V1).** This branch of the trigeminal nerve leaves the skull through the superior orbital fissure and transmits sensory information from the scalp and forehead, upper eyelid, conjunctiva, and cornea of the eye, nose (including the tip of the nose), nasal mucosa, frontal sinuses and parts of the meninges (the dura and blood vessels), and deep structures in these regions. It also carries postganglionic parasympathetic motor fibers to the glands and sympathetic fibers to the pupillary dilator muscles.34

**Maxillary branch (V2).** This branch exits the skull at the foramen rotundum. It has a sensory function for the lower eyelid and cheek; the nares and upper lip; the maxillary teeth and gingiva; the nasal mucosa; the palate and roof of the pharynx; the maxillary, ethmoid, and sphenoid sinuses; and parts of the meninges. Near its origin, it divides to form the middle meningeal nerve, which supplies the middle meningeal artery and part of dura mater. The terminal V2 branches—the anterior and greater palatine nerves and the superior, middle, and anterior alveolar nerves—innervate the soft palate, uvula, hard palate, maxillary gingiva and teeth, and mucous membranes of the cheek.34

**Mandibular branch (V3).** This branch leaves the skull through the foramen ovale and functions in both sensory and motor transmission. V3 carries sensory information from the lower lip, mandibular teeth and gingiva, floor of the mouth, anterior two-thirds of the tongue, the chin and jaw (except the angle of the jaw, which is supplied by C2 and C3), parts of the external ear, parts of the meninges, and deep structures. The auriculotemporal nerve is a branch of V3 that innervates most of the TMJ. The motor nuclei use V3 to provide motor fibers to the muscles of mastication (ie, mas-
seter, temporalis, medial pterygoid, lateral pterygoid, anterior digastric, and mylohyoid) as well as the tensor veli palatini involved with Eustachian tube function and the tensor tympani, which attaches to the malleus bone in the eardrum.  

**Trigeminal sensory nuclei.** The trigeminal sensory nuclei lay in bilateral columns on either side of the brainstem. They originate in the midbrain and terminate in the dorsal horn of the cervical spinal cord (Fig 1-2). All touch, position, and temperature sensory input from the face is sent to the trigeminal nuclei, as is potential pain input from the face, head, and neck. They are, in a rostrocaudal orientation, the mesencephalic nucleus, the main sensory nucleus, and the spinal trigeminal nucleus.

The mesencephalic nucleus, which is more a ganglion than a nucleus, houses the cell bodies of the proprioceptive neurons that convey input from the apical periodontal ligament and the muscle fibers that connect during the jaw-closing reflex. The proprioceptive neurons and possibly the blink reflex nerves represent the only peripheral nerves with cell bodies located within the CNS. The neurons are monosynaptic and pass through the mesencephalic nucleus to synapse in the trigeminal motor nuclei located medially to the much larger main sensory nucleus. The main sensory nucleus receives the facial proprioceptive and pressure input for orofacial behaviors (eg, chewing, kissing, smiling, and light touch) other than the jaw-closing reflex.
These neurons have their cell bodies in the trigeminal ganglion and synapse in the main sensory nucleus, where input is conveyed to the motor nuclei by arrays of small interneurons. The spinal trigeminal nucleus consists of three subnuclei: subnucleus oralis, subnucleus interpolaris, and subnucleus caudalis. Subnucleus oralis and subnucleus interpolaris receive some peripheral nociceptive fibers, but they mostly receive temperature information on Aδ fibers and touch impulses on Aβ fibers from the periphery and convey this input via interneurons to the motor nuclei. In response to nociceptor activation, neuropeptides and other inflammatory agents are released in the spinal trigeminal nucleus and can cause excitation of neurons and glial cells. This promotes development of central sensitization, allodynia, and hyperalgesia, which are physiologic events associated with acute and chronic pain.

The subnucleus caudalis is the main terminus for most slow first-order neurons that convey potential pain from trigeminal receptive fields. Figure 1-2 illustrates the “onion peel” somatotopic organization of the face (areas 1 to 5) and the corresponding laminae (1 to 5) in the subnucleus caudalis, where first-order nociceptive neurons terminate regardless of their division of origin. For instance, A- and C-fiber neurons from area 5 in the face all synapse with second-order nociceptive neurons in the most caudal aspect of the subnucleus caudalis, lamina 5, whether they start in V1, V2, or V3. Such convergence means that a dural blood vessel, masseter muscle, or a tooth or tongue nociceptive afferent could excite the same second-order neurons.

This convergence, the anatomical basis for referred pain, is not just a facial phenomenon. Cervical spine nociceptive afferents also synapse in the subnucleus caudalis, meaning that trapezius or sternocleidomastoid nociceptive afferents can excite second-order neurons that also receive input from facial tissues. Recent findings from the OPPERA study have provided evidence that pain in the neck and shoulder muscles is highly correlated with both acute and chronic TMDs. Thus, this type of neuronal organization may help to explain the high prevalence of comorbid pain conditions associated with tissues in the head and face (eg, headache and sinusitis, headache and TMDs). Another construct to consider is that all of the CNS structures affected by trigeminal nociceptive input are also contacted by second-order neurons from the dorsal horn of the spinal cord. Therefore, potential pain input from regions outside trigeminal receptive fields may excite CNS structures that communicate with trigeminal nuclei and modulate their functions.

**Facial nerve**

The seventh cranial nerve is a mixed nerve that has five branches (temporal, zygomatic, buccal, mandibular, and cervical) that course through the parotid gland but do not innervate the gland. Its main function is motor control of most of the muscles of facial expression and the stapedius muscle of the middle ear. The facial nerve supplies parasympathetic fibers to the sublingual and submandibular glands via the chorda tympani and to the lacrimal gland via the pterygopalatine ganglion. In addition, it conveys taste sensations from the anterior two-thirds of the tongue to the solitary tract nucleus and transmits cutaneous sensation from the skin in and around the earlobe via the intermediate nerve.

**Glossopharyngeal nerve**

The ninth cranial nerve is a mixed nerve comprising somatic, visceral, and motor fibers. It conveys sensory information from the posterior third of the tongue, tonsils, pharynx, middle ear, and carotid body. Taste sensation from the posterior third of the tongue as well as carotid body baroreceptor and chemoreceptor information are transmitted to the solitary tract nucleus. Nociceptive input from the ear is sent to the spinal trigeminal nucleus. From the inferior salivatory nucleus, the glossopharyn-
The glossopharyngeal nerve delivers parasympathetic control to the parotid and mucous glands throughout the oral cavity, while motor fibers from the nucleus ambiguous project to the stylopharyngeus muscle and upper pharyngeal muscles. An altered gag reflex indicates glossopharyngeal nerve damage.34

**Vagus nerve**

The tenth cranial nerve originates in the brainstem and extends to the abdomen and innervates virtually all organs from the neck to the transverse colon except the adrenal glands. It supplies visceral afferent fibers to the mucous membranes of the pharynx, larynx, bronchi, lungs, heart, esophagus, stomach, intestines, and kidneys, and it distributes efferent or parasympathetic fibers to the heart, esophagus, stomach, trachea, bronchi, biliary tract, and most of the intestine. The vagus nerve also affects motor control of the voluntary muscles of the larynx, pharynx, and palate and carries somatic sensory fibers that terminate in the skin of the posterior surface of the external ear and the external acoustic meatus.34 Through these connections, the vagus affects activities as varied as respiration, cardiac function, sweating, digestion, peristalsis, hearing, and speech.

**Spinal accessory nerve**

The eleventh cranial nerve innervates the cervical muscles, the sternocleidomastoid and trapezius, which are coactivated during masticatory behaviors. Like the trigeminal motor nucleus, the accessory motor nuclei are rich in norepinephrine receptors, which can facilitate vigilant behaviors.39 Nociceptive afferents from the cervical muscles converge onto the spinal trigeminal nucleus. It is notable that cervical myofascial pain seems to be prominent in patients with orofacial pain.

**Upper cervical nerves**

Spinal nerves C1 to C4 and possibly C5 are important considerations in orofacial pain because their sensory fibers converge onto the trigeminal subnucleus caudalis.28,29,38 As C1 to C4 leave the spine, they combine to form the cervical plexus, which yields cutaneous, muscular, and mixed branches. C1 forms the suboccipital nerve that supplies motor control to the muscles of the suboccipital triangle. The cutaneous branches are the lesser occipital (C2, C3), the greater auricular (C2, C3), the transverse cervical (C2, C3), and the supraclavicular (C3, C4). These nerves innervate the back of the head and neck, the auricle and external acoustic meatus, the anterior neck and angle of the mandible and the shoulders, and the upper thoracic region. The muscular branch—the ansa cervicalis—innervates the sternohyoid, the sternothyroid, and the omohyoid muscles and is composed of a superior root (C1, C2) and an inferior root (C2, C3). The mixed branch is the phrenic nerve (C3, C4, and C5), which innervates the diaphragm.34

**Autonomic nervous system**

The ANS, which is commonly viewed as a largely involuntary motor system, is composed of three peripheral divisions—the sympathetic, parasympathetic, and enteric—that function to maintain homeostasis.34 The peripheral ANS is controlled by the central ANS, which comprises cortical, limbic, and reticular formation structures and nuclei.39 Stimuli that activate the central ANS induce increased sympathetic activity initially in the brainstem and then in the periphery.39,40 The sympathetic system is involved in vigilance, energy expenditure, and the flight-or-fight response, while the role of the parasympathetic system is to counterbalance sympathetic arousal with rest-and-digest actions.41 The sympathetic and parasympathetic systems have preganglionic neurons that originate in different parts of the CNS and postganglionic neurons that deliver impulses to target tissues. Preganglionic neurons release acetylcholine at the autonomic ganglia. The postganglionic sympathetic neurons release the primary neurotransmitters norepi-
nephrine and epinephrine, while parasympa-
thetic neurons are cholinergic and therefore
secrete acetylcholine at the target sites.

The enteric system provides local sensory
and motor fibers to the gastrointestinal tract,
the pancreas, and the gallbladder. This system
can function autonomously but is regulated
by CNS reflexes. Its control of gastrointestinal
vascular tone, motility, secretions, and fluid
transport plays a vital role in homeostasis.
Persistent sympathetic arousal that impairs
parasympathetic function and leads to disturb-
bances of the enteric system may be related
to orofacial pain because functional disorders
of visceral organs controlled by the ANS seem
to be common comorbid conditions.9,11,41

Sympathetic input to the orofacial re-
gion. Sympathetic preganglionic neurons
originate in the spinal cord. Their cell bodies
are found in the intermediolateral gray matter
at the level of the T12 and L1 to L3 vertebrae.
They exit the spinal cord via the ventral horn at
the segmental level where their cell bodies are
located, but they can synapse with any of the
sympathetic ganglia in the bilateral paraverte-
bral chains. The superior portion of the sympa-
thetic chain contains four cervical ganglia. In a
rostrocaudal orientation, they are the superior
cervical, middle cervical, intermediate cervical,
and stellate ganglia. Postganglionic fibers leav-
ing these sympathetic ganglia transmit motor
input to the blood vessels in the head and
neck, various glands, and the eyes. The skin
of the face and scalp receive sympathetic in-
nervation from the superior cervical ganglia via
plexuses extending along the branches of
the external carotid artery.34,41

Parasympathetic input to the orofacial
region. Parasympathetic preganglionic neu-
rons originate in the brainstem nuclei, where
their cell bodies are located, or in the lateral
gray columns of the sacral spinal cord (S2
to S4). Cranial nerves III, VII, IX, X, and the
splanchnic nerve in the pelvic region carry para-
sympathetic preganglionic neurons, which are
considerably longer than the postganglionic
fibers because ganglia are generally located
close to or embedded in the target organ.

Neurophysiology of Orofacial Pain

Orofacial pain pathways

Nociceptive impulses generated by potential
or actual tissue damage are just one of the
types of input that are continually assessed
and evaluated throughout the various levels
within the CNS. The senses (smell, sight,
hearing, touch, and taste) alert the brain
to stimuli through thalamic-amygdala and
thalamic-cortical-amygdala circuits, and those
data streams are analyzed and compared with
what the brain already knows to sequence ef-
cient behavior.42,43 Ongoing proprioceptive,
nociceptive, thermoreceptive, baroreceptive,
chemoreceptive, and vestibular inputs tell the
brain how effectively its tissues are conduct-
ing responses and enables the brain to make
ongoing behavioral adjustments aimed at
maintaining efficiency. Nociception provides
the brain an opportunity to interpret pain and
make behavioral adjustments to avoid further
potentially damaging stimuli.44

First-order nociceptive nerves, whether
they synapse in the spinal trigeminal nucleus
or in the dorsal horn, excite the same type of
second-order neurons that respond to nocici-
ptive signals as well as a variety of sensory
stimuli and are therefore called wide-dynamic
range neurons. These neurons conduct no-
ciception and other sensations through the
brainstem and display varying degrees of ar-
borization with structures throughout the re-
ticular formation where baseline physiologic
processes are controlled before reaching the
third-order neurons in the thalamus (see Fig
1-2).4,45-47 Second-order neurons, stimulated
by the faster-conducting Aδ fibers that release
glutamate, arborize less than those receiving
impulses from the slower-conducting C-fibers
that release a wide variety of neurotransmit-
ners.\textsuperscript{4,48,49} Thus, information from \(\alpha\) fibers allows for a much faster nocifensive response (i.e., reflex response) than that elicited by C-fiber input, which is important in maintaining persistent pain and coordinating reparative and behavioral responses.

With sufficient temporal and/or spatial summation, third-order circuits, which start in the thalamus and connect the sensory cortex with the basal ganglia and the limbic system, interpret nociceptive input.\textsuperscript{1,4} This is how pain is perceived.\textsuperscript{1,4} Even when pain is felt, it is sometimes difficult to locate the actual source. Sites of cutaneous stimuli are easier to recognize than stimuli from the muscles and visceral organs because the dermis has more nociceptive free nerve endings than deep tissues to assess integument integrity.\textsuperscript{4} In response to pain interpretation, multilevel behavioral responses are coordinated, and descending motor commands are created. Whether nociception is delivered to the CNS through the spinothalamic tract or the trigeminal thalamic tract, pain perception evokes ANS-modulated cranial nerve responses.\textsuperscript{4,50,51} Because the tissues under cranial nerve control will continue to excite the trigeminal nociceptive pathways, an orofacial pain prognosis may be poor if ongoing pain sources beyond the trigeminal receptive fields cannot be controlled.

**Nociception and pain modulation**

Organisms need to be able to recognize and avoid pathologic pain to prevent potential tissue damage; however, normal daily activities should not be significantly altered by transient physiologic pain. Therefore, nociception has a biphasic effect in the CNS. Low-intensity nociceptive impulses are facilitated first through the CNS and then by stimulation of the cortex and a variety of brainstem regions, while inhibition may be facilitated via activation of the rostral ventromedial medulla and the peri-aqueductal gray regions.\textsuperscript{52,53} If nociception is relatively minor, inhibitory mechanisms will minimize the impact of transient nociceptive barrages in the CNS that affect cognitive function and task performance. Simultaneously, low-intensity nociception via second-order neuron arborization stimulates reticular formation structures to coordinate adjustments in motor and vascular behavior.\textsuperscript{51} Because of net inhibition, such adjustments can occur almost below the level of consciousness, and efficient behavior will continue. In addition, data from human and animal studies support a role for diffuse noxious inhibitory controls (DNICs) in modulating response to painful stimuli.\textsuperscript{4,54,55} This occurs at the level of the spinal cord and is mediated when some neurons are strongly inhibited in response to a nociceptive stimulus applied to any part of the body, distinct from their excitatory receptive fields. For example, stimulation in more remote areas of the body is reported to induce inhibitory reflex movements in the jaw and tongue in response to noxious craniofacial stimulation.\textsuperscript{56,57} Thus, the inhibitory effects of DNIC are observed in nociceptive neurons and wide-dynamic range neurons in the spinal trigeminal nucleus as well as in sensorimotor behavioral responses involving the spinal trigeminal nucleus.\textsuperscript{58–61} Because the term DNIC, although still widely used, describes a specific inhibitory mechanism at the lower brainstem level, a group of clinicians and basic scientists has proposed a new term that could be used for psychophysical testing in humans. This new term, *conditioned pain modulation*, can be used to describe the neuronal mechanism where pain inhibits pain at all levels in the CNS.\textsuperscript{62,63} Importantly, dysfunction of these inhibitory control mechanisms is likely to be involved in promoting and maintaining chronic orofacial pain. Of clinical relevance, dysfunction in DNIC may make those individuals more likely to progress to a chronic pain state following tissue injury or infection in the orofacial region.

When nociception persists to excite third-order neurons and pain is realized, the brain’s inhibitory capacity, *stimulation-
produced analgesia (SPA), must work harder to counteract facilitation. By both noradrenergic and serotonergic pathways, SPA inhibits nociceptive transmission at many sites but initially where first- and second-order neurons synapse in the spinal trigeminal nucleus or in the dorsal horn. This descending inhibition is mediated by endogenous opioids, γ-aminobutyric acid (GABA), and various inhibitory amino acids that are located in the periaqueductal gray. These same inhibitory compounds are released when stressors induce anxiety, fear, or depression. Brain circuits that interpret pain and direct descending inhibition also send signals to direct alterations in motor behavior and ANS functions. These descending commands reach structures throughout the reticular formation and, by vast pools of interneurons, affect all cranial nerve motor nuclei and alter behavior in response to pain (Fig 1-3). Alternatives motor pathways are recruited, and protective changes in respiration and cardiovascular mechanisms are engaged. In the case of trigeminal motor activity, premotor interneurons deliver messages to the main sensory nucleus, the subnucleus oralis, and the subnucleus interpolaris, which, through interneurons, alter motor neuron sequencing in the motor nuclei. These same nuclei mediate the minor motor adjustments when net inhibition minimizes minor nociceptive volley intrusion on circuits where pain is perceived.

**Sensitization**

With persistent nociception, excitation can exceed inhibitory capacity, and a spectrum of neuroplastic changes occurs, first peripherally and then centrally. These changes are called peripheral and central sensitization. The following changes are characteristic of neuronal...
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sensitization: nerve thresholds are lowered, receptive fields are enlarged, gene expression is changed, and pain is persistent and evoked by nonpainful stimuli. In the transition from acute to chronic pain, nociceptive neurons can change the type and level of expression of receptors and ion channels, leading to the development of a primed state. In the primed state, lower levels of inflammatory mediators are required to generate nociception, and sensitizer agents can become stimulatory agents. The transformation of nociceptors to the primed state is implicated in persistent pain conditions. High-threshold peripheral nociceptors do not fire unless exposed to noxious stimuli. However, repeated stimulation can quite rapidly reduce firing thresholds by the actions of a variety of inflammatory molecules acting on various receptors. The antidromic release of neurogenic inflammatory compounds by perivascular afferents at the location of the pain also enhances peripheral nociceptor sensitization. This increase in the transmission frequency of noxious action potentials to second-order neurons is called long-term potentiation and, if persistent, leads to central sensitization.

The development of sensitization is a time-and intensity-dependent progression. Initially, low-intensity nociceptive volleys carried on Aδ neurons release glutamate and activate postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors in the spinal trigeminal nucleus or dorsal horn. Higher-intensity stimuli induce C-fibers to release neuropeptides and other inflammatory mediators that cause changes in the expression and activity of neuronal receptors and ion channels that result in lower activation thresholds in second-order neurons.

In nonpainful states, Aβ fibers release only glutamate and deliver tactile sensations to the subnucleus oralis and subnucleus interpolaris or dorsal horn lamina 3 and 4. These tactile sensations are important for coordination of motor behaviors. As central sensitization develops, the thresholds where second-order neurons arborize to the subnucleus oralis and subnucleus interpolaris are lowered, and Aβ fibers can begin to sprout axons into the adjacent nociceptive lamina. As a result of this structural reorganization in the CNS, nonpainful stimuli that converge onto a sensitized CNS will be interpreted as painful (see Fig 1-3). Reduction of inhibition and reorganization of synaptic connectivity are other mechanisms by which Aβ fibers may be recruited to mediate pain. Patients thus suffer allodynia (pain induced by stimuli that normally would not be perceived as painfull), pain exacerbations, and hyperalgesia (an exaggerated pain response to painful stimuli).

In acute pain states such as posttraumatic wounds, these mechanisms are vital to help avoid contact that would slow wound healing; survivability of the species improves as a result. However, in chronic pain states with glial cell activation augmenting CNS cytokine release, maintenance of central sensitization requires minimal nociceptive input. Understanding central sensitization is essential to pain practice because it explains light-touch pain symptoms that once were considered psychosomatic. Sensitization may also affect symptoms associated with a variety of diagnoses such as migraine, gastroesophageal reflux disease, IBS, and FM, which are often comorbid with facial pain. It is vital to abort acute pain and eliminate pain sources as quickly as possible because once central sensitization is firmly established, it becomes exceedingly difficult to diminish with current pharmacologic and nonpharmacologic therapies.

Pain in the head and face, which can be very severe and debilitating, often involves activation of the trigeminal ganglion nerves and the development of peripheral and central sensitization. The craniofacial symptoms can manifest as acute or transient conditions such as toothaches and headaches, or they can transform into more chronic conditions such as migraine, rhinosinusitis, TMDs, or trigeminal neuralgia. It is well established that peripheral
tissue injury or inflammation leads to excitation of trigeminal nerves, resulting in the release of inflammatory molecules in the periphery and within the CNS at the level of the spinal trigeminal nucleus. Calcitonin gene-related peptide (CGRP), which is an abundant neuropeptide in trigeminal ganglion neurons, is implicated in the underlying pathology of diseases involving trigeminal nerve activation given its ability to promote neurogenic inflammation as well as peripheral and central sensitization (Fig 1-4).\textsuperscript{77–79} However, peripheral tissue injury or inflammation also leads to increased interactions between neuronal cell bodies and satellite glial cells within the trigeminal ganglion.\textsuperscript{80} These cell-to-cell interactions, which involve the transfer of key regulatory mediators via channels or gap junctions as well as paracrine signaling, are thought to play an important role in the induction and maintenance of peripheral sensitization of trigeminal nociceptive neurons.

Under normal conditions, neuron-glial interactions in the trigeminal ganglia are involved in information processing, neuroprotection, and regulation of neuronal activity including the basal rate of spontaneous firing and threshold of activation to maintain homeostasis. While a transient increase in neuron-glial communication is associated with an acute response to inflammatory signals, stable gap junctions are formed between trigeminal neurons and satellite glia in response to sustained inflammation that is implicated in TMDs.\textsuperscript{81}

Specialized glial cells found in the CNS, namely astrocytes and microglia, perform functions similar to satellite glia.\textsuperscript{82} Astrocytes are the most abundant type of cell found in the CNS and perform a diverse array of important functions, including regulation of neuronal development, synaptic coupling, repair, and even nutritional support. In addition, astrocytes monitor and control the concentration of inflammatory mediators and maintain the extracellular environment necessary for normal neuronal function.
of ions, neurotransmitters, and metabolites, as well as water movement, and thus play a key role in modulating the excitability state of neurons both in the brain and the spinal cord. The other prominent glial cells in the CNS are the microglia that function as immune cells to remove cellular debris and dead cells; they also release inflammatory mediators to promote healing. Glial cells are responsible for regulating the extracellular environment around neurons and hence neuronal activities, and their importance in regard to the underlying pathology of many inflammatory diseases is now becoming recognized. Thus, glial cells have emerged as important cellular targets for therapeutic intervention given their role in promoting peripheral and central sensitization and persistent pain.

**Heterotopic pain**

A common phenomenon associated with orofacial pain that may confuse both patients and clinicians is heterotopic pain. When reporting chief complaints, patients often describe the site where they feel the pain, which may differ from the actual pain source. For treatment to be effective, clinicians must determine the sources of pain. Primary pain is that which occurs at the source, as is often the case in acute injury or infection. Primary pain is not a difficult problem to diagnose and treat when other pain sources are absent, but diagnostic difficulties may be presented when the source of pain is not located in the region of pain perception. Such pain is said to be heterotopic. In the spinal system, heterotopic pain commonly involves impulses projected along a common nerve distribution. For instance, in the L4 distribution, a patient may feel pain in the big toe when the source is a hip muscle impingement or foraminal stenosis. Projected nerve pain also occurs in the trigeminal system. A good example is the pain related to trigeminal neuralgia, which is felt throughout the peripheral distribution of the affected nerve. Another diagnostic challenge is referred pain, in which the pain is felt at a location served by one nerve but the source of nociception arrives at the subnucleus caudalis on a different nerve (see Fig 1-3). A common example is temple pain in the V1 distribution caused by trapezius input delivered to the subnucleus caudalis on C4.

The neuroanatomical basis for referred pain is provided by the convergence of multiple sensory nerves carrying input to the trigeminal spinal nuclei from cutaneous and deep tissues located throughout the head and neck. As opposed to dermatomal projected pain in the spinal system, primary nociceptive afferents from tissues served by V1, V2, V3, C2, C3, and C4 can excite some of the same second-order neurons in the spinal trigeminal nucleus. In addition, first-order nociceptive neurons carried by C5, C6, and C7 and cranial nerves VII, IX, and X can synapse in the spinal trigeminal nucleus as well as the paratrigeminal nuclei.

Further, data clearly show that trigeminal second-order neurons converge on multiple brainstem locations involved in motor, ANS, and hypothalamic-pituitary-adrenal (HPA) activity. Convergence explains how intracranial, neck, shoulder, or throat nociception may excite the second-order neurons that receive input from facial structures. This convergence of input from tissues controlled by multiple motor nerves and delivered by multiple different sensory nerves to trigeminal nuclei helps to illustrate the important role of the trigeminal system in integrating nocifensive behaviors involving head, neck, and shoulder tissues. Because nociceptive afferents from the cervical muscles converge in the spinal trigeminal nucleus, the same location as trigeminal nociceptors, it is not surprising that cervical myofascial pain appears to be a prominent orofacial pain problem.

As important as convergence of peripheral afferents is to understanding orofacial behaviors and referred pain, it is perhaps even more significant to appreciate descending convergence from cortical, limbic, hypothalamic, and ANS regions into the vast interneuronal pools of the brainstem. These interneurons not only
reach the trigeminal motor nuclei through the spinal trigeminal nucleus; they also simultaneously convey directives to the other cranial nerve motor nuclei. When pain is felt, the CNS adapts, trying to minimize continued nociceptive barrages by altering patterns of movement involving the highly integrative behaviors controlled by the cranial nerves. For example, the CNS restricts jaw movement in response to pain in the sternocleidomastoid, resulting in reduced jaw range of motion or cocontraction. The muscles of the jaw, tongue, face, throat, and neck work synergistically to execute multiple orofacial functions, but pain in these areas alters the movements. Neck or shoulder pain may result in impaired jaw or neck movement just as a sore tooth alters chewing and swallowing or a severe headache compels retreat from light and sound, but these sources will also contribute to central sensitization. While convergence is the anatomical construct for referred pain, sensitization with its allodynic and hyperalgesic responses underlies the neurophysiologic changes that make it challenging to diagnose and treat persistent pain involving the trigeminal system.

The Biopsychosocial Model: Allostasis and the Emotional Motor System

Mind/body dualism is a concept that views the mind and mental phenomena as nonphysical, something apart from the body. This concept has existed since 1641, but many physicians and patients still believe that disease and pain must be the result of a detectable physical malady or injury. A mechanistic or biomedical model of medicine discounts the effects of the mind and society on disease processes. It views pain as the result of tissue damage, and if such organic disease or injury cannot be detected, then pain is explained as psychosomatic. Engel challenged the traditional biomedical model of disease as shortsighted in its assumptions that correcting the somatic parameters of disease defined the scope of physicians’ responsibilities and that the psychosocial elements of human malfunction lie outside the responsibility and authority of medicine. After rejecting the biomedical approach that all clinicians need to do to resolve pain is to find and repair the offending tissues, Engel developed the biopsychosocial model. This model views biologic, psychologic, and sociologic issues as body systems just like the musculoskeletal or cardiovascular systems, with no separation of mind and body. Pain arises as a symptom that results from the combination of biologic, psychologic, and sociologic factors that continuously affect all individuals, and no two people experience the same spectrum of factors. Psychologic and sociologic differences are why equal degrees of nociception, a measurable biologic parameter, can produce vastly different pain and behavioral responses.

The biopsychosocial model also makes a distinction between (1) disease associated with demonstrable pathology and (2) illness in which poor health is perceived but biologic parameters do not show disease pathology. As science evolves, imaging techniques and biologic and genetic markers continue to be discovered that show the adverse effects of psychologic and sociologic issues on physiology, thus redefining disease. The mechanisms for central sensitization or the modification of neuroendocrine parameters that have been found to characterize abuse victims, who often suffer from many comorbid illnesses, are examples of science revealing markers for conditions previously considered as lacking biologic basis.

Another theory that considers chronic pain a multidimensional experience is the neuromatrix theory put forth by Dr Melzack. This novel theory of pain associated with persistent pain syndromes, which are often characterized by severe pain with little or no discernible in-
jury or pathology as well as chronic psycho-logic or physical stress, provides a new con-ceptual framework to examine orofacial pain conditions. In this model, pain is perceived in response to activation of perceptual, homeo-static, and behavioral programs after injury, pa-thology, or chronic stress, rather than directly only by sensory input evoked by injury, inflam-mation, or other pathologic events. Thus, al-though the neural pattern that produces pain is primarily established by genetics and modi-fied by sensory experience, the output pattern is determined by multiple influences including neural-hormonal mechanisms of stress.

Allostasis is the adaptation of neural, neuroendocrine, and immune mechanisms in the face of stressors. Allostatic load refers to the physiologic changes that continued stressors produce as organisms attempt to maintain homeostasis. The changes in HPA axis func-tion and brain cytokine activities that underlie cardiac disease and diabetes are examples of allostatic load. Allostasis intersects with the controversial concept known as the emotional motor system. The emotional motor system maintains that thoughts and emotions create neuroendocrine-mediated motor re-sponses. When an organism hears, sees, or smells, its limbic system (amygdala and hippocampus) acquires primary sensory stimuli and compares their relevance with prior knowl-edge in a matter of 15 to 30 milliseconds to help sequence dynamic behavior. Input analy-sis and the emotional motor system facilitation of autonomic and cranial nerve motor behavior involve the full spectrum of brain neurochemis-try and endocrine function.

Two scenarios not uncommon in orofacial pain practice illustrate how sociologic experi-ence may alter supraspinal physiology and pain experience. Consider an excessively worried patient who awakes with neck pain, the same initial complaint reported by his uncle who died from cancer, or a headache patient experienc-ing a panic attack when a smell rekindled the fear physiology associated with an assault 7 years earlier. For these patients, investigating only acute biomedical parameters may not help and may even contribute to a deepening state of illness as the pathologic processes continue without recognition and treatment. These are patients for whom the biopsychosocial approach may prevent increased allostatic load. Taking sufficient time to obtain a thorough history and to explain the physiologic effects as they relate to psychosocial problems can help patients control factors that affect illness symptoms.

Although there is an increasing awareness of the need to assess all three systems out-lined by Engel, many barriers described in a 2005 study prevent its widespread utiliza-tion. The study found that physicians and residents avoided approaching psychosocial issues because of inadequate training, lack of time, insufficient monetary incentive, and a large cultural ethos that favors "quick fixes." The Research Diagnostic Criteria for TMDs (RDC/TMD) represent an attempt to apply both biologic (Axis I) and psychosocial (Axis II) factors to better understand a patient’s condition. However, the RDC/TMD have met resistance because Axis I fails to account for how referred pain and central sensitization affect physical findings, and Axis II is per-ceived by many as indicating that TMDs are psychosomatic despite evidence of disease. Yet, a 5-year follow-up study showed that in the 49% of TMD patients whose pain remitted, baseline psychologic measures were the same as found in the general population. Of the remaining 51%, the 14% who experienced high pain improvement had improved psychologic parameters but minimal change in physical findings. In the 37% who did not get better, neither psychologic nor physical find-ings improved. Such data, which suggest that psychologic issues affect prognosis, demand that the physiology of psychosocial parameters be better addressed. Otherwise, advances in managing chronic orofacial pain problems and the conditions that may be comorbid with facial pain complaints may not be achieved.
Although a great deal of effort is dedicated to understanding genetic predisposition for disease, it is equally if not more important to realize that environmental stressors alter the expression of genetic codes and behavior. An animal model has shown that placing an identical twin in a harsher environment causes downregulation of GABA receptors and increases locus coeruleus (noradrenergic) modulated stress behaviors.\textsuperscript{105} It is important to understand that each individual will interpret nociception differently, depending on the influence of cognitive processes on pain perception and allostatic adaptations in response to its lifetime experiences.

A TMD is not caused by a single gene mutation but is a result of changes in the expression of many genes that contribute to the pathology and pain characteristic of this prevalent medical condition. As documented in the OPPERA study, many of the risk factors associated with TMDs involve mechanical, chemical, or environmental stressors that increase the likelihood of developing and maintaining a chronic pathologic state.\textsuperscript{106,107} Epigenetics is an emerging area of research that focuses on understanding the impact of environmental factors on the global expression of genes and thus overall health.\textsuperscript{108} Epigenetics determines how changes in one’s diet; the quantity and quality of sleep; and the amount of exercise, tobacco use, and exposure to drugs and toxins influence the packaging of DNA.\textsuperscript{109–111} Thus, epigenetic changes ultimately control genes that can either protect from or render one more susceptible to disease progression.\textsuperscript{109–111}

### Suffering and Pain: Comorbid Conditions

Suffering and pain are different. Though the term is notably absent in most medical dictionaries, Fordyce\textsuperscript{112} defined suffering as the negative emotional or psychologic state that occurs in response to or in anticipation of nociception, while pain was defined as perceived nociception. But suffering is not exclusive to pain, as it also characterizes sadness, sorrow, and grief. Anticipation of intense and protracted pain, sadness, or grief does affect the intensity of suffering. Moral and societal premises such as secondary gain also influence how much suffering an individual may demonstrate. Regarding sadness, time may improve some wounds. But in the case of pain from uncontrolled etiology, sensitization of the anterior cingulate cortex with limbic system and endocrine modulation may make suffering a progressive experience to the individual and those who are touched by that person’s struggle.\textsuperscript{113}

Acute pain, a biologic adaptive pain, is associated with quick onset and short duration. It may be very intense as in postsurgical pain, but the cause-and-effect relationship is usually apparent and the stimuli are not repeated. Central sensitization is induced only as a protective element to protect wound sites. As tissues heal, pain reduces, sensitization resolves, and duration of suffering is short.

Acute and chronic pain can be distinguished by the duration of pain; acute pain can become chronic pain if it lasts longer than 3 to 6 months, or the time it would take connective tissue to heal. Chronic pain is persistent pain that becomes part of the patient’s daily routine. It is resistant to medical treatment because of neuroplastic changes throughout the CNS and in primary nociceptors.\textsuperscript{69,114} Chronic pain may present with psychopathology such as depression, but this is not always the case.\textsuperscript{4} What seems to be true in patients with chronic pain is persistent central sensitization and an increased possibility of comorbid conditions. Although conditions like conversion disorders may exist, the links between stressor effects on the CNS and the digestive, respiratory, musculoskeletal, cardiovascular, endocrine, and immune systems are redefining what used to be called somatoform disorders.\textsuperscript{91,115–118} Chronic nociception, unrelenting stressors, or horrific experiences as in posttraumatic stress disor-
under can all cause central sensitization, sympathetic upregulation, and endocrine abnormalities, which may explain why conditions such as headaches, TMDs, IBS, gastroesophageal reflux disease, and FM are so prevalent in chronic pain states.\textsuperscript{119–121}

The role of the clinician is changing as science clarifies how CNS dysfunction caused by uncontrolled inflammatory processes and chronic stressors leads to a maladaptive chronic pain state that affects all the major physiologic systems. The fast-paced, ever-changing nature of society unfortunately creates an environment in which people experience the fight-or-flight response multiple times on a daily basis. This lifestyle promotes a state of hyperexcitability characterized by mental exhaustion and a feeling of helplessness that favors sympathetic drive and suppresses parasympathetic function. Practitioners must see the patient’s whole story, not just the portion seen through the biomedical model. For example, exposure to violence is a common experience, and in patients with chronic pain, exposure to abuse may be three-fold greater than that experienced in the general population.\textsuperscript{122} Patients may not always reveal these experiences given the cultural taboos associated with abuse or the repression induced by the sheer horror of the abuse or another catastrophic event. Clinicians must be aware that severe pain and comorbid conditions due to maladaptive CNS function may be the only indications of psychosocial distress. It is often a delicate subject to approach, but if pain improvement is to be achieved, clinicians must first recognize patients with problematic psychosocial histories and then refer them to skilled therapists.

A primary goal of the health care provider should be to prevent the transition from an acute episodic disease that is reversible with common pharmaceutical and behavioral treatments to a chronic pain state that is not easily altered and is often comorbid with anxiety, depression, and IBS. The risk factors for this transition need to be evaluated and reduced. In particular, the patient should be encouraged to incorporate activities that naturally evoke a parasympathetic response such as walking, swimming, yoga, tai chi, Pilates, meditation, or mindfulness training. These exercises emphasize proper breathing and increasing flexibility, and incorporating them into the patient’s daily routine will reduce the negative effect of key risk factors and help to empower the patient to become an active participant in the management of his or her disease.

### Chronic Orofacial Pain Disorders: TMDs and Comorbid Conditions

The 1996 NIH Technology Assessment Conference defined a TMD as “a collection of medical and dental conditions affecting the [TMJ] and/or the muscles of mastication, as well as contiguous tissue components.”\textsuperscript{123} This definition was similar to that published in the third edition of \textit{Orofacial Pain: Guidelines for Assessment, Diagnosis, and Management} (Quintessence, 1996), which referred to contiguous tissue components as “associated structures.” It is not yet clear what constitutes \textit{contiguous tissue components} for TMDs, and this question strongly influenced the NIH conference’s major conclusions: “diagnostic classifications for TMD are flawed as they were based on signs and symptoms and not etiology; etiology was not known, no consensus on what or when to treat existed, and no therapies had proven efficacy although behavioral approaches offered the best outcomes with the least risks.” The consensus on TMD etiology and the scope of signs and symptoms has not been achieved, but research on TMDs has provided information that may help with patient care.

Many if not most patients with a TMD will recover with no or minimal care.\textsuperscript{16,17} A minority of TMD problems become chronic, and of those that do, one-third seemed to resolve over an 8- to 10-year period.\textsuperscript{124,125} TMD patients
who significantly improve may have minimal psychologic issues, while patients with chronic TMDs, like those with chronic musculoskeletal pain, have psychologic comorbidity similar to other chronic pain patients.\textsuperscript{104,126–129} Chronic TMD pain, like headache and most other chronic pains, is more prevalent among women, especially when multiple symptoms are present.\textsuperscript{130–133} It is well known that women with orofacial pain displayed more medical problems than female controls.\textsuperscript{11} Over a 12-month period, 73% of adults experienced headache, 56% had back pain, 46% had stomach pain, and 27% had dental pain.\textsuperscript{133,134} These findings coincide with data suggesting that preexisting headache or back, abdominal, or chest pain were better predictors than depression for the onset of facial pain experienced by 12% of the population.\textsuperscript{135} More than 81% of patients with facial pain also report pain in regions below the head.\textsuperscript{78} TMD patients frequently have symptoms of FM, chronic fatigue syndrome, headaches, panic disorder, gastroesophageal reflux disease, IBS, multiple chemical sensitivity, posttraumatic stress disorder, and interstitial cystitis.\textsuperscript{9} Unfortunately, TMD patients may avoid care when symptoms carry psychosomatic stigma.\textsuperscript{136}

Heart rate variability is a measure of the beat-to-beat time interval that reflects the CNS control of the ANS tone.\textsuperscript{137} Low heart rate variability, when the beat-to-beat time interval becomes inflexible, occurs when high sympathetic tone impedes parasympathetic (vagal) dampening of cardiac activity.\textsuperscript{138} Low heart rate variability is a common finding for conditions such as cardiovascular disease, diabetes, depression, anxiety, cognitive problems, IBS, gastroesophageal reflux disease, posttraumatic stress disorder, migraine, FM, and sleep apnea.\textsuperscript{139} High heart rate variability, when parasympathetic control modulates a variable beat-to-beat time interval, is associated with health and improved cognitive capacity.\textsuperscript{140,141}

TMD patients have been differentiated from controls by pain, anxiety, depression, sleep disturbance, and measures of ANS reactivity, and behavioral therapies have been shown to treat these conditions more successfully than traditional dental therapies.\textsuperscript{142–144} Orofacial pain patients with TMDs and other comorbid conditions such as headaches, gastroesophageal reflux disease, and FM demonstrated low heart rate variability when subjected to stressors compared with controls. Three months after patients were exposed to self-regulation skills aimed at controlling stress, associated jaw, neck, and breathing behaviors and pain scores improved, and measures of heart rate variability no longer differentiated patients from pain-free controls. The improved heart rate variability scores correlated with decreased pain interference scores, suggesting enhanced self-efficacy in the face of stressors.

Patients with orofacial pain report a high degree of exposure to traumatic events and significant disability.\textsuperscript{120,121} In the past, disabling chronic pain was attributed to the failure of coping skills related to personality type.\textsuperscript{145,146} The heart rate variability study data suggest that, for some orofacial pain patients with multiple comorbid conditions, specific self-regulation skills may enable patients to cope with previously unrecognized and therefore uncontrollable physiologic disturbances associated with the pain. Acceptance of a biopsychosocial approach by the patient may largely be dependent on his or her previous psychosocial experiences.\textsuperscript{147}

Persistent elevation of sympathetic tone and impaired parasympathetic tone may be responsible for many comorbid conditions that affect orofacial pain patients. Heart rate variability is a noninvasive measurable parameter that may track the physiology of ANS problems in patients with trigeminal pain and shed light on its cause.\textsuperscript{148} Reducing upregulated sympathetic activation, which may drive an out-of-control emotional motor system, may reduce central sensitization that underlies the refractory nature of the spectrum of conditions seen in orofacial pain practice.
Headache and orofacial pain disorders

Recurrent headache may occur in as many as 80% of TMD patients compared with a 20% to 23% occurrence rate in a general population.\(^{149–153}\) One-third of the population has been estimated to suffer from severe headache at some point in their life, a lifetime incidence similar to the 34% rate estimated for TMDs, but only 5% to 10% of North Americans have sought medical advice for severe headache.\(^{135,154,155}\) Although earlier studies have shown associations between TMDs and headache, causal interrelationships have not been demonstrated.\(^{131,151,156–159}\) However, in a study in which 61% of orofacial pain patients had headache complaints and 38% fulfilled the criteria for migraine, higher migraine disability assessment (MIDAS) scores correlated with masticatory and cervical myalgia but not with the presence or absence of intracapsular TMJ problems.\(^{160}\) More recently, an association of sleep bruxism and painful TMDs was reported to greatly increase the risk for the development of episodic migraine, episodic tension-type headache, and especially for chronic migraine.\(^{161}\) Interestingly, in women experiencing both TMDs and migraine, the migraine condition only significantly improved when both conditions were treated. Furthermore, women suffering from migraine are likely to have more muscular and articular TMDs, which supports the notion that both disorders are clinically associated.\(^{162}\) This also highlights the importance of physical therapy assessment in the multidisciplinary team approach to managing complex pain patients.\(^{162}\)

Headaches and TMDs are major complaints associated with trigeminal pain, leading to significant suffering and absenteeism from work or school.\(^{134,163}\) Traumatic stressors may play a significant role in this suffering and pain.\(^{120,121}\)

The head and neck muscles are responsible for orienting organisms to collect primary sensory input and executing orofacial behaviors. According to the myalgia correlation, these muscles may affect the overwhelming input that might contribute to the states of ANS dysfunction and central sensitization that characterize headache and other comorbidities.\(^{50,160,164–167}\)

Data are emerging from human genetic linkage analysis and association studies supporting the notion that mutations in genes involved in modulation of the nervous system predispose individuals to a hyperexcitable nervous system and thus play an important role in the initiation and maintenance of chronic pain.\(^{168}\) The genes responsible for regulating neurotransmission in both the ascending and descending nociceptive pathways seem to be the ones augmented in all the chronic pain conditions examined thus far, including TMDs and migraine. For example, mutations have been identified in ion channels and receptors on neurons and glial cells that are associated with increased neuronal excitability and an enhanced sensitized state of nociceptors. Collectively, results from these studies have begun to provide a clearer understanding of how genetic variants influenced by environmental factors lead to the development of multifactorial pathologic conditions that share overlapping etiologies. There is clearly a need for more specific treatment options for the diverse array of chronic pain conditions. Findings from these genetic studies may help to direct development of more personalized strategies for managing chronic pain patients, including pharmacologic and nonpharmacologic methods. Finally, it should be noted that there are several novel therapeutic approaches that are showing efficacy in the treatment of migraine, including monoclonal antibodies that target CGRP, vagal nerve stimulation, and the use of cannabinoids.\(^{169–171}\) Given the underlying pathologic nature of orofacial pain conditions, these therapies are likely to be useful in relieving pain associated with TMDs, neuropathic pain, and other diseases involving sensitization and activation of trigeminal nociceptive neurons.
References

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