Mechanisms Associated with Unusual Orofacial Pain

Gilles Lavigne, DMD, MSc, PhD
Professor and Director of the Quebec Oral Health Research Network (FRSQ)
Faculties of Dentistry and Medicine
Université de Montréal
Montréal, Québec, Canada

Alain Woda, DDS, PhD
Professor and Vice-Dean for Research, EM INSERM Neurobiologie de la Douleur Trigéminale
Faculty of Dentistry
Université d'Auvergne
Clermont-Ferrand, France

Edmond Truelove, DDS, MSc
Professor and Chair
Department of Oral Medicine
University of Washington
Seattle, Washington

Jonathan A. Ship, DMD, FRCS(Edin)
Professor, Department of Oral Medicine
Director, Bluestone Center for Clinical Research
NYU College of Dentistry
New York, New York

Thuan Dao, DMD, MSc, PhD, FRCD(c)
Associate Professor
Faculty of Dentistry
University of Toronto
Toronto, Ontario, Canada

Jean-Paul Goulet, DDS, MSc, FRCD
Professor and Dean
Faculty of Dentistry
Université Laval
Québec City, Québec, Canada

Correspondence to:
Dr Gilles Lavigne
Faculté de Médecine Dentaire
Université de Montréal
C.P. 6128, Succursale centre-ville
Montréal, Québec H3C 3J7
Canada
Fax: +514 343 2233
E-mail: gilles.lavigne@umontreal.ca

This article presents an overview of possible mechanisms associated with pain perception, with a specific focus on understanding unusual manifestations of orofacial pain associated with nerve insult. It includes recent evidence concerning neurobiological changes that occur in the periphery at tissue and nerve sites, or within the central nervous system, and that may involve chemical and inflammatory responses, sensitization, or alterations of cellular function. Moreover, the contribution of the autonomic nervous system, changes in emotional reactivity and vigilance, the roles of high brain centers such as the basal ganglia (nigro-striatal) system, and the influence of aging and gender, are briefly described. J OROFAC PAIN 2005;19:9–21

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Orofacial pain, whether perceived as coming from inside or outside the oral cavity, refers to any type of pain occurring below the orbitomeatal line, above the neck, and anterior to the ear.[1] The term "unusual orofacial pain" is used to refer to any pain condition that has an unexpected clinical presentation, whether it is uncommon or not. The concept of "heterotopic pain" best describes most cases of unusual pain. Heterotopic pain is broadly defined as a sensation that, relative to its source, is felt in some other part of the body. To better understand this concept, it is important to remember that pain can *(1)* be felt at the site of origin or referred through branches of the same nerve (eg, toothaches and earaches from the mandibular and auriculo-temporal branches of the trigeminal nerve, respectively); *(2)* be perceived at a site adjacent to the site of origin due to the convergence of afferent inputs (eg, concomitant head and neck pain through trigeminal and cervical afferent convergence in the central nervous system); *(3)* be felt distant from the site of origin, ie, at a site lacking any direct link to the site where the pain originated (eg, pain associated with angina pectoris that is referred to the lower left jaw); and *(4)* be associated with a widespread distribution of sensations (eg, fibromyalgia). Unusual orofacial pain also refers to puzzling clinical pain entities, where, in the absence of clear clinical findings, the predominant feature is the pain itself. Atypical

MEDICATIONS

Topical/in situ action

- Anesthetics also acting on nerves: lidocaine, Emla, antihistamine
- Other substances also acting on nerve: topical capsaicin (Zostrix), injected botulinum toxin (Botox), topical clonazepam (Klonapin, Rivotril), mixture of gabapentin + capsaicin + Orabase

Systemic

- Anxiolytic-sedative (short-term): clonazepam (Klonapin, Rivotril), lorazepam (Ativan)
- Hypnotic (short-term): clonazepam, temazepam (Restoril), triazolam (Halcion)
- Nerve/neuron action (administration for long period):
  - Anticonvulsive: carbamazepine (Tegretol), baclofen (Lioresal), pimozide (Orap), lamotrizine (Lamictal), oxcarbazepine (Trileptal), clonazepam
  - Ionic channel action: tricyclic antidepressant such as amitriptyline and nortriptyline
  - Others: gabapentin (Neurontin), lidocaine patches
- Cardioactive action: propranolol (Inderal), clonidine (Catapress patches or pills)
- Antiinflammatory: ibuprofen, Cox-2 inhibitors (eg, Celebrex)

Others

- Opioids (oxycodone, morphine); NMDA antagonists (eg, methadone, dextromethorphan and conotoxin for ionic channels), phentolamine (Rogitine), and guanethidine (Ismelin) for cardioactive actions, etc.

The efficacy and safety of most medications have not been specifically tested for trigeminal pain management.

TECHNIQUES

- Low-level laser therapy, skin-nerve electrical stimulation, acupuncture
- Surgical (eg, sensory root decompression)
- Surgical nerve graft, without or with entubation

Fig 1 Some of the medications and techniques used to manage pain associated with nerve damage including neuropathic pain, atypical pain, and postsurgical pain.[2,4,6–19]

odontalgia and burning mouth syndrome are just 2 examples of unusual orofacial pain. The management of such conditions is not an objective of this review, and readers interested in this aspect can refer to specific publications[2–7] and Fig 1.

The pain experience is an integrated process that includes the following: *(1)* perception of a given sensory input as being potentially noxious, *(2)* rapid assessment of that noxious input as being unpleasant and as a threat to bodily integrity or functioning, *(3)* the elaboration of a biological response (eg, an increase in heart rate or a withdrawal reflex from the noxious source), and *(4)* the construction of an attitude toward pain (eg, anxiety, fear, catastrophizing, or even distress, depression, or insomnia).[8]

The pain experience may be brief; it is then labeled acute. Common dental procedures, postsurgery pain, or pain following trauma are examples of acute pain experiences. It may be long-lasting and/or be intermittent or recurrent (ie, it may come and go); it is then called chronic. Most temporomandibular disorder pain and trigeminal neuralgia, for example, would be considered chronic. The chronic pain patient becomes a "pain victim" as pain "crises" interfere with functions (eg, chewing, talking, or sleeping) and with social or familial activities. The authors have adapted information from various sources to create an up-to-date glossary of orofacial pain (Table 1). Both acute and chronic pain sometimes are strongly influenced by the patient's beliefs, past experiences, socio-familial background, and genetic makeup.[25] It is essential to recognize the importance of emotional-behavioral reactions to pain, but this topic is beyond the scope of this paper and has been extensively covered in recent publications.[8,9,26,27]

Peripheral Sensory Mechanisms and Pain Pathways

The transformation of a mechanical, thermal, or chemical sensory experience into a biological signal and a conscious pain event involves a sequence of processes (see summary in Fig 2). Insults to peripheral tissues (eg, in the tooth pulp, periapical area, oral mucosa) induce subtle changes in the milieu such as a reduction in pH and the release of chemical substances, eg, potassium (K+), serotonin (5-HT), bradykinin (BK), histamine (H), prostaglandins (PG), leukotrienes (LT), interleukin (IL), substance P (SP), and calcitonin gene-related peptide (CGRP). Some of these substances directly activate sensory nerves, while others increase the excitability of nerve terminals. This last process is termed *peripheral sensitization*. Both activation and peripheral sensitization occur at free nerve

Table 1 Pain Glossary

Term	Definition
Algesia	Any pain experience following a stimulus
Allodynia	Pain due to a stimulus which does not normally provoke pain or which is innocuous (eg, skin touch after a sunburn)
Causalgia	Pain after trauma to a nerve that may be associated with vasomotor dysfunction
Habituation	A decrease or loss of response in nerve terminals or neurons following repeated stimulation
Hyperalgesia	An increased pain response to a noxious stimulus in an affected area versus a control area
Hypoalgesia	A diminished pain response to a noxious stimulus in an affected area versus a control area
Hypoesthesia	A decreased sensitivity to stimulation that feels similar to the effect of local anesthesia
Neuroma	The mass of peripheral neurons formed by a healing scar at a damaged nerve. Can cause hyperexcitability of neurons or spontaneous discharge (also termed ectopic discharge)
Neuropathic pain	The aberrant pain induced by an injury to a sensory nerve or neuron. May be evoked by a thermal, mechanical, or chemical stimuli, or may be secondary to a disease (eg, diabetes, postherpetic neuralgia); may also be central in origin. May occur spontaneously
Nociception	The reception and transmission of nociceptive messages
Pain	An unpleasant sensory, emotional, and motivational experience associated with actual or potential tissue damage that requires consciousness
Pain threshold	The lowest level of stimulation perceived as painful by a subject (> 50% of the time)
Pain tolerance	The highest level of pain which a subject is prepared (able) to tolerate
Paresthesia/dysesthesia	An abnormal sensation that is termed dysesthesia when it becomes unpleasant
Sensitization	The increased excitability of nerve terminals or neurons produced by trauma or inflammation of peripheral tissues. Can be peripheral or central or both
Sprouting	The extensive spread of regenerated nerve endings into surrounding tissues following a nerve damage

Adapted from several publications.[9,20–24]

endings, where action potentials are formed to transmit the nociceptive "signal" to the spinal cord or trigeminal brainstem complex.

Innocuous stimulation that results in a sensation of touch mostly activates Aβ sensory fibers. Noxious stimuli activate thin myelinated Aδ and unmyelinated C fibers. The C fibers are of prime importance in nociception, but they also have an important role in the control of the local microcirculation and inflammatory-humoral response.[28–31]

The A and C fibers have their cell bodies in the trigeminal or spinal ganglia. The A and C fibers that innervate the orofacial area end in the trigeminal brainstem sensory nuclear complex, while those innervating the rest of the body terminate in the dorsal horn of the spinal cord. The trigeminal sensory complex is divided into a main sensory nucleus devoted to the sensation of touch and the spinal trigeminal nucleus. The latter is divided into subnuclei oralis, interpolaris, and caudalis.[32–34] The subnucleus caudalis has many similarities with spinal cord dorsal horn; for example, many caudalis neurons mainly receive nociceptive inputs from the small-diameter Aδ and C fibers, as in the spinal dorsal horn lamina 1. The presynaptic release of glutamate, aspartate, and SP dominates nociceptive transmission; postsynaptic channels (eg, alpha amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid [AMPA], kainate, and *N*-methyl-D-aspartate [NMDA] for glutamate) and G protein-coupled receptors (eg, neurokinin [NK_1] for SP) contribute to the cascade of events that trigger action potentials in the second-order projection neurons.[32,33,35] In addition to the activation of ascending nociceptive pathways to higher brain structures, descending influences from several sites in the brainstem have been shown to reduce the nociceptive transmission through the release of neurochemicals such as 5-HT from the raphe magnus and noradrenaline (NA) from the locus coeruleus, which then activate opioid-containing (eg, enkephalin-containing) interneurons, eg, in the subnucleus caudalis.[32,33,36]

The main ascending pathways from the spinal cord to higher brain structures are the spino-thalamic, spino-reticular, and spino-mesencephalic or

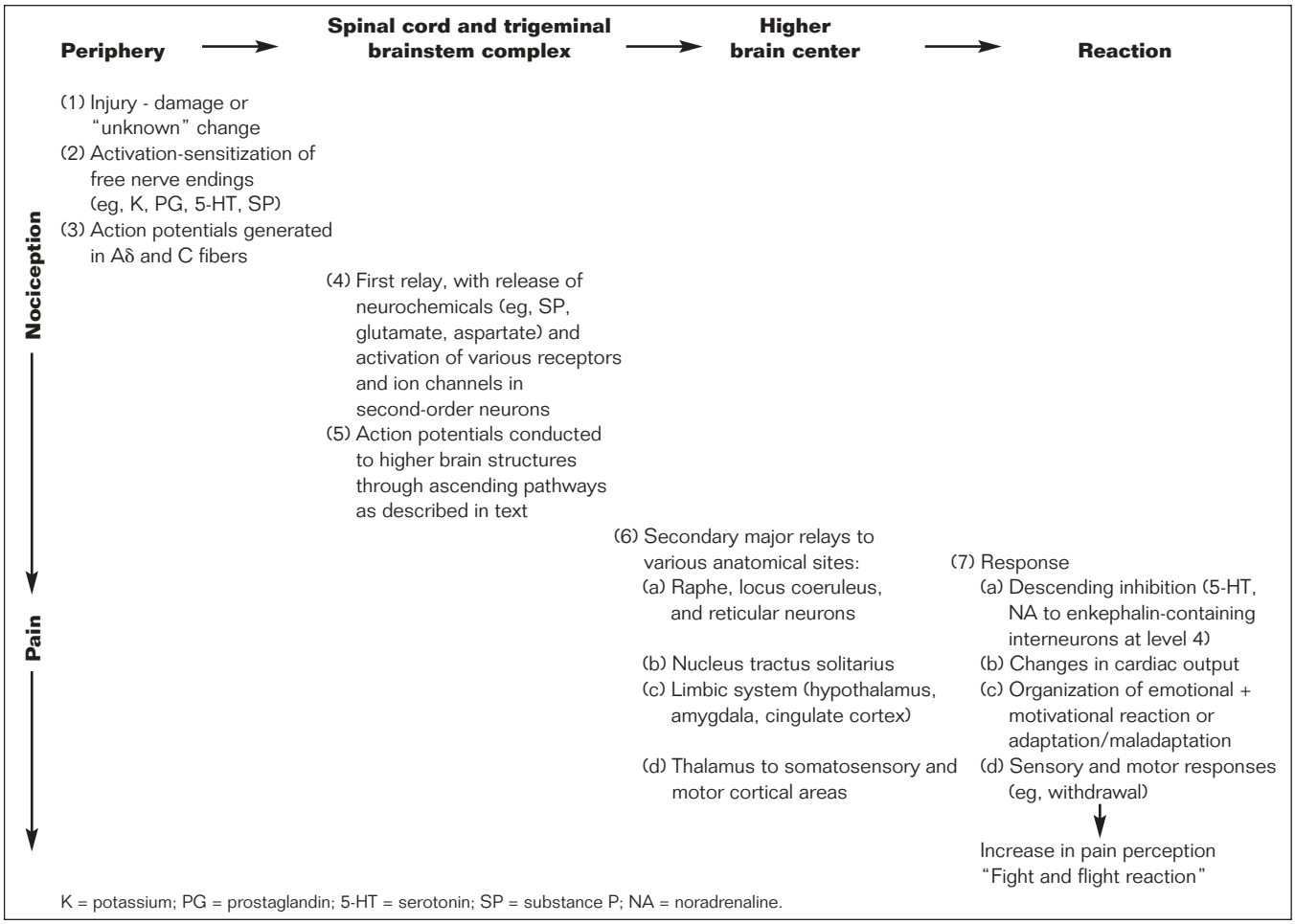

Fig 2 Sequence of events involved in pain perception.

parabrachial tracts.[32–36] The spino-thalamic neurons project to the ventroposterolateral (VPL) nucleus of the thalamus, and the targeted thalamic neurons further project to the primary somatosensory and motor cortical areas. The spino-reticular tract targets neurons of the reticular formation that project to the medial thalamus. The spino-mesencephalic tract projects to parabrachial areas and to limbic structures such as the hypothalamus, amygdala, and anterior cingulate and frontal cortical areas.[9,36] The spino-thalamic VPL-cortical pathway is especially involved in the discriminative component of pain sensation. The spino-reticular and mesencephalic pathways have more of a role in emotional-motivational and motor aspects of pain sensation and reactions. The spino-parabrachial pathway is involved primarily in visceral pain-related reactions.

Similar ascending pathways have been described for the integration of nociceptive information from the trigeminal area. The nociceptive neurons convey information to rostral components of the trigeminal brainstem sensory nuclear complex, to the spinal cord, periaqueductal gray, reticular formation, motor nuclei and autonomic centers, or to higher brain areas such as the thalamus and cortex. Most information from the face and mouth relays in the ventroposteromedial nucleus of the thalamus, which plays a role in detection and discrimination of noxious stimuli. Some trigeminal information instead relays in the medial thalamic nuclei (submedius, parafascicular, and intralaminar nuclei), which play a role in affective, attentional, and motivational aspects of pain perception and responses. The thalamic neurons project to the somatosensory and motor cortical areas or to limbic structures such as the hypothalamus and anterior cingulate cortex.[32,33,37]

Modulatory Mechanisms that Inhibit Nociceptive Transmission

In the spinal cord and in the trigeminal brainstem complex, several modulatory mechanisms are responsible for inhibiting the transmission of a nociceptive message.[38] One mechanism has been proposed within the framework of a gate control theory of pain. This theoretical model proposes the attenuation of nociceptive information relaying through the spinal cord to the upper brain centers.[39] The model suggests that a reduction of inputs from Aδ and C fibers is produced by a touch-evoked activation of Aβ fibers, the net result being that less nociceptive information is sent to upper brain structures. This model has clinical relevance since it provides an explanation of pain relief based on manipulations that activate large A fibers.

The gate control theory also postulates another mechanism involving descending inhibitory controls that may influence the transmission of nociceptive messages. These controls have subsequently been shown to arise from several structures in the brainstem that send descending axons to the dorsal horn of the spinal cord and to the trigeminal brainstem complex.[32,33,36] These include the brainstem raphe and locus coeruleus, which release, respectively, 5-HT and NA, and may activate enkephalin-containing interneurons (see previous section) that further reduce nociceptive transmission. This effect may also be elicited by activation of specific brain structures (eg, periaqueductal gray matter) and is one of the mechanisms by which opioid analgesics such as codeine or morphine act to reduce pain perception.

Diffuse noxious inhibitory controls (DNIC) are another pain inhibitory mechanism, which may be known by clinicians as counterirritation. In this mechanism, the perception of pain at a given body site can be attenuated by the production of a second pain at a distant site, or by an intense nonnoxious stimulation (eg, vibration).[40] This phenomenon may explain the efficacy of clinical pain management strategies such as electro-acupuncture. Interestingly, DNIC has been shown to act, at least in part, through endogenous opioids (eg, enkephalins) since the observed analgesia is partially reversed by naloxone, an opioid antagonist.[41–43]

Changes Related to Neuropathic Inflammatory Pain and Trauma

The previously described nociceptive mechanisms occur for brief periods and are usually reversible events. However, pain sometimes extends beyond the healing time, when tissue damage or inflammation is no longer visible. Examples include the many clinical conditions that are induced by peripheral nerve injury following surgical (including endodontic) procedures, infections, or idiopathic insult. Although the literature on dental deafferentation is limited, interesting information can be extracted from changes that occur in peripheral nerves and/or in central neurons following nerve damage.[31,33] When the noxious insult is prolonged or too intense, it can trigger persistent modifications of neurochemicals and their corresponding receptors that are expressed at the level of primary afferent nerve endings, nerve fibers, and the primary afferent's cell body. For example, nerve injury is associated with decreases in CGRP, vanilloid receptor subtype 1, VR1 (now termed TRPV1), SP, and mμ opioid receptors in the primary afferent neurons, and increases in the expression of brain-derived neurotrophic factor (BDNF) and its receptor tyrosine kinase (trk), and/or the upregulation of sodium channels.[31,36,44–46] It has also been reported that Aδ fibers may lose their myelin sheath, which causes them to conduct impulses more slowly.[47] The C fibers may also degenerate and disappear. Moreover, an aberrant sprouting of Aβ fibers, which normally conduct tactile signals, may occur and make connections with nociceptive neurons in the dorsal horn. Inhibitory interneurons of the dorsal horn may also be lost. All these mechanisms could be responsible for an unusual painful experience that could be triggered by low-intensity stimulations (eg, touch), a condition referred to as allodynia (see Table 1). Furthermore, after regeneration, sensory C fibers may also be associated with an abnormal rise in the expression of catecholamine and/or adrenergic receptors. As a result, sprouting of autonomic sympathetic nerve terminals may influence the activity in these C fibers and may, consequently, contribute to the activation of pain pathways together with abnormal reactions such as edema, vascular redness or vasodilation at the pain site.[48] In addition, following a nerve injury, dorsal horn nociceptive neurons may become hyperexcitable (as in central sensitization) because of the decreased expression of inhibitory substances, receptors, and related genes that normally reduce nociceptive transmission (eg, endogenous opioid, γ-aminobutyric acid [GABA], or glycine).[31,36,47]

Conversely, chronic pain can also trigger the activation of "endogenous analgesia" to prevent further increases in pain perception. The activation of the DNIC system, as already described, may

also contribute to some of the changes associated with persistent pain conditions. This finding is based upon a recent study using experimental neuropathic rats, where sciatic nerve constriction was found to induce sensitization and nerve sprouting, with a concomitant activation of the DNIC "analgesic" mechanism.[49]

Recent studies have suggested that some animals are genetically resistant to nerve injury, while others seem to have a dysfunctional opioid/morphine analgesia response as a result of specific gene/receptor differentiation.[50] It is therefore possible that some patients with persistent pain or paresthesia following nerve insults could be genetically "less protected" or have a less efficient nerve healing system.[25] However, such a hypothesis remains to be proven.

Dental Nerve Damage

Following damage to a branch of the trigeminal nerve, changes similar to those already described may also occur in trigeminal afferents and in the cervical spinal cord and trigeminal brainstem complex.[28,32-34,51–53]

At the periphery, nerve injury triggers an inflammatory response and *(1)* the release of neurochemicals such as SP and nerve growth factor (NGF), *(2)* autonomic activation, and *(3)* neuronal activation in the trigeminal ganglion and brainstem complex.[28,32,33,51] When the healing associated with nerve injury is retarded or disturbed, persistent nerve damage is likely to occur. There is no simple explanation for any ongoing disturbance associated with peripheral trigeminal nerve healing, although several mechanisms have been suggested. These could include: *(1)* nerve constriction or transection[53]; *(2)* sympathetic nerve sprouting within the trigeminal ganglion following inferior alveolar nerve constriction (although this now appears unlikely), and an increase in SP expression in rat skin and ectopic re-innervation of the lip by parasympathetic cholinergic fiber invasion of the lip following mental nerve injury[48,53,54]; *(3)* overexpression of the pro-oncogene C-fos and increased excitability of cervical and trigeminal brainstem neurons, for example, following temporomandibular joint (TMJ) injury (eg, with mustard oil).[33,55–57]

Other changes can be observed in the CNS. Since most trigeminal neuropathic pain and idiopathic pain conditions, whether associated with nerve injury or not, are similar to neuropathic pain reported elsewhere in the body, the same mechanisms acting at the spinal cord level (described previously) are also likely to be found at the trigeminal level.[58,59] As recently reviewed,[32,33] pulp removal, for example, induces morphological (eg, cell degeneration) and neurochemical (eg, GABA, NMDA) changes, and an increase in excitability and spontaneous firing of mainly low-threshold mechanoreceptive neurons (ie, neurons coding for touch). The mechanosensitive afferent fibers (Aβ) also could sprout and make excitatory connections with nociceptive neurons, but this has not been found following pulp removal.[33] As described, over-regeneration of C fibers with aberrant connections to sympathetic and parasympathetic efferent fibers might also take place at the trigeminal level and may be associated with an unusual pain response.

As previously mentioned, although peripheral nerves seem to be able to regenerate following an injury, their potential to reconnect to CNS neurons is low; in fact, this may be nearly impossible.[60] Several factors could promote CNS axon growth and guidance (eg, semaphorins, trk, NGF, acetylcholine, inflammatory cytokines), while 3 myelin-associated proteins have been recently identified that limit or inhibit CNS axonal regeneration (myelin-associated glycoprotein [MAG], Nogo, oligodendrocyte-myelin glycoprotein).[61,62] Moreover, the role of glia, for so long seen as not being important in pain, has been revisited and reported to be important in mechanisms associated with pain amplification (eg, expression of neuroreceptors such as purinergic P2X receptors or immune factors).[63–65] These discoveries may represent new avenues for drug development, since recent studies have described the role of P2X and TRP channel ANKTMI after mustard oil application to tooth pulp or trigeminal ganglia in rats.[63,64,66,67]

Clinically, injury to the trigeminal nerve may induce sensory disturbances, ie, changes in somatic perception. Unusual chronic pain following a technically "acceptable" endodontic treatment is occasionally observed. A common tooth avulsion may also trigger such long-term pain. Depending on the severity of the injury, sensory disturbances may be transient or permanent, and may vary from partial (paresthesia) to complete loss of sensation (anesthesia), or exaggerated pain responses to either innocuous (allodynia) or painful stimuli (hyperalgesia) (see Table 1 for definitions). These complications have been widely reported following trigeminal nerve injuries, including various oral and maxillofacial surgical procedures. For instance, the reported incidence of altered sensation due to inferior alveolar nerve injury ranges from 0.4% to

Table 2 Neurosensory Testing or Analysis Following Nerve Injury and its Prognosis Assessment

Modality	Stimulation (threshold)	Outcome	Note
Sensory			
Thermal [24,58,80–84]	•Warm	•Possible allodynia	Assessment needed with at least a distant site (eg, hand or arm) as control or baseline values. Validation needed (specificity and sensitivity), and reliability unknown.
	•Cold	•Possible allodynia	
	•Heat pain	•Hyperalgesia	
	•Cold pain	•Hyperalgesia	
Tactile[10,58,80,82–85]	•von Frey hair/touch	•Hyperalgesia/allodynia	Assessment needed with at least a distant site (eg,hand or arm) as control or baseline values. Validation needed (specificity and sensitivity), and reliability unknown.
	•Pin prick	•Hyperalgesia/allodynia	
	•2-point discrimination	•Hyperalgesia/allodynia	
	•Brush stroke	•Hyperalgesia/allodynia	
Vibration[10,58]	•Tuning fork	•Unknown	Validation needed (specificity and sensitivity), and reliability unknown.
	•Electrical tooth brush (30 sec)	•Hyperalgesia	
Electric shock[24,80]	20 μA to 3.5 mA	Initial deficit in perception but no relation with recovery	Aversive, and unknown validity for trigeminal nerve injury. Validation needed (specificity and sensitivity), and reliability unknown.
Blink and jaw reflexes[86,87]	7 to 23.5 mA	Increase threshold for blink reflex	
Taste[88–90]	•Bitter/metallic	•Modified perception in BMS	Validation needed (specificity and sensitivity), and reliability unknown.
	•Sour	•Modified perception in BMS	
	•Sweet	•Unknown	
	•Salt	•Unknown	
	•Umani	•Unknown	

Other tests: self-report on Visual Analog Scale (VAS) or category scale; use of verbal descriptors/pain words; body map showing site of sensation or pain radiation[80,84]; imaging (eg, magnetic resonance imaging [MRI])[86,91,92]; biopsy (no relation between ultra-structural changes and dysesthesia[24]).
There is not yet any standardized procedure in regard to testing following nerve injury.

7.5% with third molar removal,[53,68–71] up to 85% with mandibular osteotomies,[72,73] and from 38% to 69% with preprosthetic surgeries (eg, vestibuloplasty and ridge augmentation procedures).[74–76] For lingual nerve injury following third molar extractions, the incidence ranges from 0.06% to 11.5%.[52,53,73–77]

According to a recently published study, the incidence rate of chronic neuropathic pain (assessed in 1,458 patients) following surgical removal of third molars is low, 0% to 0.4%.[78] Among the risk factors, patient age, the removal of bone distal to the third molar, molar roots in close proximity to the inferior alveolar nerve, and deflection of the mandibular canal were reported to be the best predictors of permanent injuries. In another prospective study, of 1,117 surgical extractions performed in 946 patients, 13% had a temporary complaint, and resolution occurred in 75% of them within 18 months.[79] The various techniques (eg, thermal, mechanical, electrical, and reflex tests) that have been used to assess trigeminal nerve damage and its prognosis are listed in Table 2 to inform readers of their existence and to stimulate research on their use. Much more validation is needed before these can be used clinically for positive, prospective, and reproducible assessment of trigeminal nerve damage.

Since sensory disturbances may remain permanent and persistent, pain can have an emotional influence on the patient (eg, depression, hypervigilance), so patient referral to a physician, psychologist, or psychiatrist may be necessary. Figure 1 summarizes current medications and some techniques used to manage nerve-related pain; most still need to be tested in controlled study designs to assess their efficacy and safety.

Examples of the Pathophysiology of Other Persistent and Unusual Pain Conditions

In a review paper it is impossible to cover in detail the pathophysiology of several unusual pain conditions. The authors have therefore elected to pres-

ent 2 conditions, burning mouth syndrome (BMS) and fibromyalgia, since they are not uncommon in clinical practice. Both are more prevalent in women, both are associated with mood alteration, and the pathophysiologies of both include hormonal imbalance, autonomic reactivity, and sleep disturbance. However, they differ in other respects: BMS is localized to the oral cavity, whereas fibromyalgia is a more generalized condition, although it includes some orofacial pain-related complaints. The mechanisms underlying these 2 conditions are also unclear. BMS, also named stomatodynia, is reported mainly in peri- or postmenopausal women. It is characterized by a burning sensation of the tongue, palate, or other oral mucosal region. This pain cannot be explained by an isolated local or systemic cause. Several risk factors, such as psychogenic or hormonal factors, local irritation, or trauma are probably involved.[93] It has also been suggested that BMS patients may present with alexithymia (a personality dysfunction characterized by difficulty in verbal expression of emotions associated with an enhanced sensitivity to pain and unpleasant stimuli and frequent reports of poor sleep quality).[94–96] The influence of such psychological conditions on reports of pain needs to be further assessed by comparing patients with unusual orofacial pain to others presenting with more usual painful conditions. It has also been suggested that BMS may be induced, at least in part, by a peripheral neuropathy.[29,88] A reduction in mucosal blood flow in BMS patients, primarily in the palate, was recently demonstrated, which suggests a dysfunction in local vasoreactivity and the involvement of the autonomic nervous system.[97] Interestingly, reduction of central inhibitory influences to trigeminal, chorda tympani, and/or glossopharyngeal-related neurons has also been proposed.[98] It is obvious that the pathophysiology of BMS is not explained by a simple "cause and effect relationship."

Fibromyalgia is a specific generalized chronic pain condition that is different from BMS but is thought to be associated with some neuropathic pain mechanisms. The majority of these patients are women who present with muscle pain in several sites, including the orofacial area, as well as poor sleep, headache, depressive syndrome, fatigue, muscle stiffness, reduction in pain threshold, and behavioral/cognitive hypervigilance.[99] Fibromyalgia and orofacial myofascial pain are often found as concomitant conditions and may be influenced by hormonal dysregulation.[100] Furthermore, it has been suggested that fibromyalgia could be associated with a dysfunction of the DNIC system.[101,102] The widespread pain of fibromyalgia patients may also result from nociceptive hyperexcitability and central sensitization.[103]

Patients with fibromyalgia also show some abnormalities in the regulation of the autonomic nervous system. Following an orthostatic stressor (eg, postural change), men with fibromyalgia demonstrate a hyperactive sympathetic-cardiac response.[104] Similarly, during the sleep of fibromyalgic patients, the level of sympathetic-cardiac activity remains high.[105] Under normal circumstances, during wakefulness, the heart rate variability is high and under the influence of a dominant sympathetic-autonomic nervous system. During sleep, the sympathetic dominance normally decreases and parasympathetic/vagal influences (ie, influences that slow cardiac activity) that are necessary for non-REM sleep consolidation become dominant. It remains possible that complaints of poor sleep in patients with fibromyalgia and the so-called electroencephalographic (EEG) α-wave intrusions may result from the absence of parasympathetic dominance during restorative sleep (stages 3 and 4).[106–108]

Potential Role of Basal Ganglia/ Nigro-striatal System in Persistent Pain

The lack of dopamine, an active brain neurotransmitter at the basal ganglia level, is associated with a neurodegenerative disorder, Parkinson's Disease (PD). Patients with PD have difficulty initiating voluntary movements (eg, walking), develop limb rigidity and lack of facial expression, frequently experience pain, and have difficulty in chewing.[109–111] The roles that dopamine and the basal ganglia play in pain have recently been investigated. The basal ganglia is a network comprising the caudate-putamen, globus pallidus, and substantia nigra and is connected to the thalamus and cortex. In animals, its neurons have been observed to respond to noxious stimulation and to participate in persistent nociception.[112–114] The relevance of these findings to pain in humans is supported by the observation that BMS patients present a decrease in putamen dopaminergic function (an observation made using fluorodopa imaging), while women with fibromyalgia show lower cerebral blood flow in the caudate nucleus.[91,92,115] Moreover, in atypical facial pain patients, there is a slight increase in dopamine type 2 (D2) receptors in the putamen of one side and a significant decrease in the D1/D2 ratio bilaterally in the putamen.[92] While it is unclear what is cause and what

is effect, the understanding of these topics becomes increasingly important since, with the aging of the population, dental practitioners are more frequently called upon to manage orofacial pain in patients with dopamine/basal ganglia-related disorders (eg, PD or oral tardive dyskinesia).

Influences of Aging and Gender on Persistent Pain

Aging is an important covariable in reports of pain such as in fibromyalgia. For instance, the prevalence of fibromyalgia doubles in populations aged over 50 years old.[116] Also, BMS is rarely found in young people. Although it has not been proven that aging is a risk factor for neuropathic pain or causalgia in humans, recent animal studies have shown that, with aging, the functional recovery and axonal regeneration of injured peripheral nerves is delayed, and the descending pain inhibitory system is less active.[60,117] This last finding is supported by 1 human study showing that, in older adults (67 to 87 years), the analgesia resulting from DNIC is weaker than in younger adults (22 to 27 years).[118] Medication use, the presence of concomitant disease, and changes in sleep quality and architecture may also influence pain perception during the aging process.[119] Another age-related observation is that elderly patients appear to be better able to cope with chronic or persistent pain than middle-aged patients.[119,120] Moreover, it was found that females under the age of 65 years reported more orofacial pain (eg, TMJ pain, face pain, toothache, oral mucosa pain or discomfort, pain when chewing) than older women. These findings are directly relevant to how dental practitioners plan and assess the efficacy of pain management.[120–127]

Gender is another important variable that may influence the clinical presentation of persistent pain.[29,122,128–130] Women are more often diagnosed with fibromyalgia, rheumatoid arthritis, temporomandibular disorder pain, and BMS. In males, cluster headaches and duodenal ulcer pain are more frequent. The use of steroid hormones to prevent pregnancy or as a replacement therapy for menopause has been associated with higher reports of experimental pain and a higher prevalence of temporomandibular disorder pain, although there are conflicting reports.[128,131,132] The potential cause-and-effect relationship between hormones and chronic pain is a topic that requires further exploration in prospective studies. Recently, it was suggested that the typical DNIC pain inhibitory mechanism is not as active in females as in males and that genetic differences in the expression of the melanocortin-I receptor gene in relation to kappa-opioid analgesia may partially explain pain-related differences between males and females.[102,133]

Variable Responses to Pain Management Strategies

Pain is a multifaceted and complex human experience. Accordingly, the assessment of pain must go beyond the amount of related tissue damage and the intensity of the painful sensation. The patient's response to management strategies depends on a mixture of psychological factors (eg, fear, anxiety, personal belief, coping capacities, motivation, vigilance, expectation, catastrophizing attitudes) and physiological factors (eg, difference in medication absorption and distribution). One potential source of therapy that has recently been examined is the placebo effect, which involves both psychological factors (eg, expectation) and the activation of endogenous opioid systems.[134,135] A human brain imaging study, for example, has demonstrated that the high variation in the placebo effect and opioid analgesic activity between subjects could be due to interindividual variability in opioid receptor binding.[136] Finally, the relationship between genetic factors (heredity or current "dysfunctional" gene expression with insult), social variables, and the past experience of pain is another emerging area of interest.[25,50,131,137–139] The presence of concomitant oral habits, parafunctional activities, or movement disorders could also contribute to and exacerbate some of the common as well as unusual orofacial pain conditions.[130,140–142] Since the etiology and pathophysiology of idiopathic orofacial pain is not exclusive to the trigeminal system and to dentistry,[34] the recent challenging review on the "complex regional pain syndrome,"[143] is most relevant. The similarities of this syndrome to unusual orofacial pain conditions are striking.

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