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Neuropathic orofacial pain – diagnostic and therapeutic challenges

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Abbreviations:

CNS	– Central nervous system
DN4	– Neuropathic Pain Diagnostic Questionnaire
EFIC	– The European Pain Federation
IHS	– The International Headache Society
IASP	– The International Association for the Study of Pain
ICHD-3	– 3rd International Classification of Headache Disorders
LANSS	– The Leeds Assessment of Neuropathic Symptoms and Signs
NPQ	– Neuropathic Pain Questionnaire
NSAIDs	– non-steroidal anti-inflammatory drugs
OFP	– Chronic neuropathic orofacial pain
PHN	– postherpetic neuralgia
SSNRIs	– selective serotonin norepinephrine reuptake inhibitors
SSRIs	– selective serotonin reuptake inhibitors
TAD	– tricyclic antidepressants
TN	– trigeminal neuralgia

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Abstract

Chronic neuropathic orofacial pain (OFP) is the leading symptom for a wide range of conditions. It can exist independently of any addition signs, symptoms and radiological or laboratory abnormalities. In addition to physical suffering, OFP causes emotional, psychological and social disturbances and thus significantly influences the quality of life of those affected. Several key factors make OFP a complex diagnostic and therapeutic challenge. These include a lack of diagnostic criteria that are both validated and readily applicable in clinical settings and a lack of sufficient education about pain in undergraduate medical training programs. There is also a need to develop more analgesic therapies offering improved efficacy and side effect profiles. Finally, the provision of analgesic therapies by health insurance programs need to be harmonized with the most current evidence-based treatment protocols. In addition to offering recommendations in these areas, this paper provides an overview of the most common clinical forms of nonodontogenic OFP, epidemiological data, and current diagnostic and therapeutic options.

INTRODUCTION

Pain is one of the most unpleasant aspects of many diseases. To underscore the importance of pain as a global health problem, the International Association for the Study of Pain (IASP) launched its first "Global Year Against Pain," in 2004 with the slogan; *Pain management should be a human right*. Each IASP annual campaign is dedicated to the study of pain arising from particular conditions or etiologies. For example, 2013 marked the year against chronic pain, whereas orofacial pain was the focus in 2014, which was followed by a year against neuropathic pain in 2015 *(1)*. Such campaigns help raise awareness for the many ways in which various types of pain effect health, ranging from a vital warning sign to a debilitating condition. Acute pain, which signals the occurrence of injury or disease, provides an important protective function. Conversely, chronic pain provides no real or potential benefits, resulting only in unnecessary suffering. This is particularly true of neuropathic pain, an important component of numerous medical conditions *(2)*. Whatever its origin, pain is recognized globally as one of the primary reasons for seeking medical attention. The pain suffered by individuals creates not only personal but also societal costs. Communities are burdened with both the direct costs of healthcare utilization and the indirect costs of reduced worker productivity and increased absenteeism due to pain.

One of the most significant sources of pain in the human body is the orofacial region, a highly sensitive area with abundant pain receptors (3).

The orofacial region also has great psychological significance as the center for chewing, swallowing, speech production, communication and personal expression *(4)*. Therefore, chronic pain is associated with additional emotional, psychological and social disturbances when located in the orofacial region. These changes significantly affect the quality of life of those living with chronic orofacial pain (OFP) *(5)*. The global prevalence of orofacial pain is estimated at 17–26%, with 7–11% of patients experiencing chronic OFP *(6)*. It is not known what share of this percentage is attributable to neuropathic pain, an important causative factor in many OFP conditions. The prevalence of orofacial and chronic pain can reasonably be expected to increase as demographics shift toward longer life expectancies. An aging population includes an increased number of patients living with chronic and painful conditions such as diabetes and cancer. Aging also results in increased exposure to therapeutic methods for these and other conditions that can result in neuropathic pain. Such an increasing potential for chronic and orofacial pain creates the need to consider a range of likely consequences, not least of which is the impact on quality of life *(6, 7)*.

The causes and mechanisms of chronic pain are not entirely clear, although risk and precipitating factors have been identified for the majority of conditions. A large body of evidence shows that pain is often inadequately treated. Over time, continuous pain symptoms alter neuroplasticity and may cause hyperexcitability, changes that lead to the development of chronic pain *(5)*. Thus, unabated neuropathic pain can become a neurological disorder or dysfunction of the central nervous system (CNS), in much the same way as epilepsy or Parkinson's disease. These changes to the CNS pain signaling pathways hinder the effectiveness of therapies aimed at alleviating the symptoms of chronic pain.

Nonodontogenic neuropathic orofacial pain

A diagnosis of nonodontogenic neuropathic orofacial pain can only be made after eliminating the teeth as the potential source of pain. Odontogenic OFP arises from tooth damage or decay and is often localized to the oral cavity. It can also occur in the region of the face that is above the neck, in front of the ears, and below the orbitomeatal line. If dental caries, poor fillings, trauma, and dental fractures have all been eliminated as the source of pain, OFP is considered unrelated to teeth and is therefore referred to as nonodontogenic. Additional findings related to the distribution and timing of pain may help confirm its origin. Nonodontogenic pain is often treatment resistant, even with the use of local anesthetics and is prone to developing into a chronic condition *(8)*. Additionally, pain that is bilateral or simultaneously encompasses multiple teeth is likely to be of a nonodontogenic origin *(9)*.

Nonodontogenic neuropathic OFP shares many of the characteristic features recognized in other forms of neuropathy. Neuropathic pain arises from peripheral and central changes in neuronal function that are perceived as persistent pain and sensory abnormalities. Permanent loss or injury of primary afferent fibers, a process referred to as deafferentation, results in peripheral neuropathic pain. Central neuropathic pain, however, arises from direct damage to the structure of the central nervous system *(10)*. The timing and duration of symptoms are characteristic of neuropathic pain, which can be both episodic (or *paroxysmal*) and continuous. While some patients experience complete relief from pain symptoms between episodes, others can experience paroxysms of pain as an acute exacerbation of an otherwise continuous pain syndrome (4). While some causes of OFP may be difficult to discern, a careful history including the duration and nature of symptoms can pinpoint a likely etiology. For example, pain described as continuous and burning is typical of neuritis and post-traumatic neuropathy. Neuropathy most often manifests as repeated, episodic attacks of short stabbing or shooting pain. The onset of these episodes can be either spontaneous (or *stimulus independent*) or provoked by stimuli. Pain is intensified by the stimulation of trigger-points or individual muscles. Pain can also be increased by emotional stress, physical activity, changes in the position of the head and so on. Neuropathic pain is often accompanied by additional sensory signs and symptoms such as allodynia, pain provoked by a stimulus (as a light touch of the skin) which would not normally provoke pain. Thermal and mechanical stimuli are the types most often associated with provoking allodynia. Hyperalgesia, an increased sensitivity to painful stimuli, is another characteristic positive sign. Negative signs, such as hypoalgesia and hypoesthesia, can also indicate a neuropathic etiology. While many of these signs can be elucidated from patient history, the full range of sensory changes experience by an individual patient is best assessed using quantitative sensory testing. This non-invasive method relies on the selective response of specific types of nerve fibers to particular stimuli. Given that A-beta fibers are selectively stimulated by electricity, A-delta fibers respond to cold or punctate mechanical stimuli and C-fibers are stimulated by heat, these types of stimuli are applied externally to selectively stimulate and record a response from each type of nerve fiber. The area from which neuropathic pain and sensory changes are elicited represents the receptive field of a particular nerve, allowing identification of the involved nerve or nerve root. Pain in the head and neck is mediated by the upper cervical spinal roots, the intermediate, glossopharingeal and vagus nerves, along with sensory fibers from the trigeminal nerve *(11)*.

Trigeminal neuralgia

The most common orofacial clinical entity involving underlying neuropathic pain is trigeminal neuralgia (TN). Trigeminal neuralgia; also known as *tic douloureux, Fothergill disease and suicide disease*; is estimated to

affect 4–13 people per 100,000 population *(11–13).* It occurs at a rate of about 15,000 new cases per year in the US (14). TN can occur at any age, including childhood, but the incidence generally increases with age. Idiopathic cases are the most common after the age of 50 *(15).* Considered a natural consequence of their longer life expectancies, women are about 1.5 times more likely to experience TN *(14).* Although the disease is more common in some families, 80–90% of TN is sporadic *(16)* and attributable to aberrant loop arteries or veins compressing the trigeminal root *(17–19).* This frequent etiology makes trigeminal neuralgia due to vascular compression *(10)* considered "classical" idiopathic trigeminal neuralgia. Secondary TN arises from compression by other structures, such as an acoustic neuroma, meningioma, epidermoid cyst, aneurysm or AV malformation *(10, 20–26).* Although all three branches of the trigeminal nerve may be involved, TN is usually limited to one or two branches. The second and third trigeminal branches are those most commonly affected by TN. The first branch of the trigeminal nerve is affected in only about 5% of TN cases, usually due to herpes zoster infection. The pain of trigeminal neuralgia is usually unilateral, sudden, severe, and sometimes described as lightning–like. Pain may be bilateral, but both sides are not usually affected at the same time *(14*). TN is often accompanied by paresthesias, such as burning and shock-like sensations. Pain and paresthesia symptoms can be provoked by chewing, talking, brushing teeth, cold air, laughing, light touch, smiling or any other stimulation of trigger-points around the nose and mouth. As is typical of allodynia, the pain induced by trigger-points is usually disproportionate to the stimulus, such that a mild stimulus causes severe pain. Notably, injection of local anesthetic at trigger-points is usually effective in providing pain relief. The pain of trigeminal neuralgia typically occurs as episodic attacks ranging in duration from a few seconds to several minutes. Whereas the pain typically subsides completely between episodes, some patients with long-standing TN experience pain continuously between paroxysms. Although the course of the disease is unpredictable, symptomatic periods of frequent TN paroxysms generally occur over the course of weeks or months, followed by periods of remission. The course of the disease for some patients tends toward unremitting pain while others experience a decrease in frequency and intensity of TN symptoms. Patients with trigeminal neuralgia are generally able to sleep through the night without suffering paroxysms of pain.

The diagnostic criteria for classical trigeminal neuralgia described in the Third International Classification of Headache Disorders (ICHD-3) of the International Headache Society (IHS) *(10)* are based on the timing, characteristics and distribution of OFP. Classic TN presents as paroxysmal pain that is intense, sharp, superficial, stabbing, or was precipitated from stimuli at trigger-points and lasts up to two minutes. The pain involves one or more branches of the trigeminal nerve and is not associated with any other disease. In addition, attacks are stereotyped in individual patients who have no clinically evident neurological deficit.

The ICHD-3 diagnostic criteria for secondary (or *symptomatic*) trigeminal neuralgia require that anything other than vascular compression causes the spectrum of symptoms associated with TN. One distinctive clinical feature of the secondary form is that it lacks a refractory period after paroxysms *(10).* Potential causes of secondary TN include acute herpes zoster, postherpetic neuralgia, trauma, multiple sclerosis plaques, and other non-vascular compressive lesions. Post-traumatic trigeminal neuropathy, or *anesthesia dolorosa*, is an important cause of secondary TN that is defined by the ICHD-3 *(10)* as one-sided pain of the face or oral cavity in a patient with a history of verified mechanical, chemical, thermal or radiation-induced trauma in the same area of the trigeminal nerve associate with symptoms. The pain must appear within three to six months after the traumatic event, and is not better characterized by another ICHD-3 diagnosis. The pain of post-traumatic TN must also be associated with clinically apparent positive or negative signs of trigeminal nerve dysfunction. Positive signs such as hyperalgesia and allodynia may coincide with negative signs such as hypoesthesia and hypoalgesia. The clinical finding of pain in a facial area where the sensation is either missing or impaired is characteristic of anesthesia dolorosa. Patients can find this mix of positive and negative symptoms difficult to explain, making a careful clinical history especially important in identifying causes of central pain such as post-traumatic TN.

While the precise mechanism remains to be fully elucidated, the symptoms associated with trigeminal neuralgia are likely due to demyelination in the area of compression or damage *(27, 28).* Demyelination also occurs in multiple sclerosis and other structural lesions of the brain stem, making these an important part of the differential diagnosis *(29–32).* Demyelinated areas can generate ectopic impulses that contribute to abnormal nerve conduction *(17).* Such alteration of afferent inputs can disinhibit pain pathways in the spinal trigeminal core. Evidence supporting involvement of central pain mechanisms includes the occurrence of a refractory period after triggered episodes of pain *(29).* During the refractory period, which usually lasts a few minutes, a paroxysm of pain is not possible. The complex mechanisms involved in the development and presentation of trigeminal neuralgia require a range of specialists including dentists and neurologists be included in a multidisciplinary approach to its diagnosis and treatment.

Herpes zoster and postherpetic neuralgia

Herpes zoster may cause pain with neuropathic characteristics in the area innervated by one of the facial

nerves. Systemic and topical analgesics may help but are usually insufficient for providing complete pain relief. The onset of pain from herpes zoster often precedes the occurrence of the vesicular rash and can persist even months after the lesions are no longer visible. The diagnosis of OFP due to herpes zoster is often difficult, particularly before the appearance of the characteristic rash. The primary factor confounding a clear diagnosis is that herpes zoster can mimic dental pain. Reliable laboratory tests for the unambiguous diagnosis of herpes zoster OFP have not yet been developed. Early diagnosis and treatment may help prevent the development of postherpetic neuralgia (PHN), a condition in which pain endures at least one month after the herpes zoster rash has healed. The pain is usually a continuation of that experienced before and during the acute herpes zoster skin eruption. While it usually lasts up to six months, PHN can continue for years after the rash has healed.

Atypical odontalgia

Atypical odontalgia is characterized by constant pain after removal of a tooth, tooth apex, or dental pulp. Also known as idiopathic, or *phantom*, toothache, this condition can also be caused by facial trauma. Studies have shown that atypical odontalgia appears in 3–6% of patients after endodontic treatment. In atypical odontalgia, a throbbing ache is experienced in the area of a tooth or alveolar process over prolonged periods. The sensation may be intermittent or constant, and persists despite a lack of clinical and radiographic evidence that would indicate a disorder related to the teeth. Patients may have difficulty localizing the pain, which is usually more intense on the side where the trauma or dental procedure occurred. The pain may spread into adjacent areas unilaterally and bilaterally, with the teeth most frequently affected being the upper premolars and molars. Local anesthesia can, but does not necessarily, alleviate the pain. Unfortunately, the symptoms of atypical odontalgia are often untreated as they are mistaken for a normal response to the treatment or trauma that precipitated this OFP condition.

Glossopharyngeal neuralgia

Glossopharyngeal neuralgia is an infrequent disorder that is likely due to compression of the glossopharyngeal or upper portions of the vagus nerve. Damage to these nerves is suggested by asymmetry in the movement of the soft palate and uvula or the absence of the emetic reflex *(33).* Glossopharyngeal neuralgia manifests as paroxysmal pain in the area innervated by the 9th and 10th cranial nerves and is most often experienced as pain in the throat, particularly when chewing and swallowing *(10, 34).* The pain, which is usually unilateral, can encompass the pharynx, base of the tongue, and the area inferior to the angle of the mandible and ear. The pain may encompass the receptive field of the auricular and pharyngeal branches of the vagus nerve. Bilateral involvement is possible and occurs in about 12% of patients *(35).* The carotid arteries should be examined for pathological changes such as arterial dissection, before considering other potential sources of pain in this region. If the teeth, ears and carotid arteries have been eliminated as the source of pain, glossopharyngeal neuralgia should be considered in the differential diagnosis. Trigeminal neuralgia, which is 70 to 100 times more common than glossopharyngeal neuralgia, can occur as a comorbid condition .

The pain of glossopharingeal neuralgia is usually projected from the oropharynx to the ear. It is usually paroxysmal and intense, but can be superimposed on a constant, less severe pain. Attacks may occur several times per day and may even arouse the patient from sleep. The ICHD-3 diagnostic criteria for glossopharyngeal neuralgia requires at least three attacks of unilateral pain, in the base of the tongue, tonsillar fossa, pharynx, below the angle of the mandible or ear in patients without evident neurological deficit *(10).* Glossopharyngeal neuralgia occurs in paroxysmal attacks of strong, sharp, stabbing, or throbbing pain that lasts up to two minutes. Movements such as swallowing, coughing, talking or yawning can induce paroxysms of pain. Such findings, if not better characterized another ICHD-3 diagnosis, confirm a diagnosis of glossopharyngeal neuralgia. As with trigeminal neuralgia, glossopharyngeal neuralgia exists as either a primary or a secondary OFP condition. Secondary glossopharyngeal neuralgia can be caused by demyelinating lesions, tumors in the cerebellopontine angle, peritonsillar abscess, aneurysm of the carotid artery, Eagle's syndrome, *(36–39)* and vascular compression of the vertebral artery or rear lower cerebellar artery. Similar to trigeminal neuralgia, episodes of glossopharyngeal neuralgia can last for weeks or months, punctuating long periods of remission. A key diagnostic feature, glossopharyngeal neuralgia is the only cranial neuralgia in which painful afferent impulses can precipitate a cardioinhibitory reflex causing vagal bradycardia, asystole and syncope *(34, 40).* This symptom must be distinguished from cardiac pain that radiates to the orofacial area, such as may occur with sickle cell anemia and some neoplasms. It should be noted that pain resembling that of glossopharyngeal neuralgia can also be of traumatic, postoperative, and psychogenic origin. Also included in the differential diagnosis of glossopharyngeal neuralgia are several rare disorders such as neuralgia of the intermediate nerve, occipital neuralgia, optic neuritis, headache due to ipsilateral ischemic lesions of the oculomotor nerves (III, IV and VI), Tolosa Hunt syndrome, Raeder's syndrome, recurrent painful ophthalmoplegic neuropathy, neuralgia of the superior laryngeal nerve, burning mouth syndrome, persistent facial pain, temporal arteritis and carotidynia. Although uncommon, glossopharyngeal neuralgia is an important consideration in the differential diagnosis of OFP.

Diagnostic approach to OFP

Multiple factors contribute to the diagnostic and therapeutic challenges related to orofacial pain, making a multidisciplinary approach essential to the treatment of this disorder. OFP may arise from a variety of tissues in the face and head, including the meninges, cornea, dental pulp, oral mucosa, nasal mucosa and temporomandibular joint. So, the many pathophysiological mechanisms giving rise to orofacial pain is reflective of the diverse tissue types in which it originates. A lack of validated diagnostic criteria is one of several obstacles to improving care for patients, but also in translational research. Although efforts have been made in the classification of patients with temporomandibular joint disorder *(41),* headache *(42)* and orofacial pain *(43),* clinical trials indicate that the results of pharmacological, electrophysiological and imaging studies have not yet provided sufficient means for the comprehensive diagnosis of orofacial pain *(44, 45).* Screening questionnaires, such as the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Neuropathic Pain Diagnostic Questionnaire (DN4), Neuropathic Pain Questionnaire (NPQ) and others, can help in the identification of neuropathic pain, but conclusive results require assessment of questionnaire findings in light of the clinical examination and other diagnostic methods. Despite its format, the optimal diagnostic tool should distinguish neuropathy from other OFP etiologies. Another factor potentially contributing to diagnostic and therapeutic failure is insufficient education about pain in medical education programs. Anecdotal evidence of such a shortcoming was recently confirmed in a study of 242 medical schools from 15 European countries. The authors found that 82% of medical programs do not include a separate, compulsory course on pain in the curriculum. In schools that do dedicate coursework specifically to the study of pain, students only receive an average of 12 elective or mandatory educational hours on pain management, equating to only 0.2% of the overall educational program *(46).* A similar proportion of medical education in the United States and Canada is dedicated to the management of pain conditions *(5).*

The development and management of analgesic therapies presents another area of future improvement. While there has been significant progress in the identification of pathophysiological mechanisms underlying acute and chronic pain, this knowledge has not led to the development of new analgesic or coanalgesics which are more efficient, safer or have fewer side effects. In the treatment of most chronic neuropathic pain conditions, opioid and non-steroidal anti-inflammatory drugs (NSAIDs) remain the therapies most frequently prescribed in clinical practice *(47).* The use of these drugs is very often limited because of the risk for abuse of opioids and the gastrointestinal, renal and cardiovascular side effects associated with NSAIDs *(48, 49).* Other therapies more specifically targeting neuropathic pain are included as the accepted standard of care in algorithms published by professional organizations. These include tricyclic antidepressants, serotonin reuptake inhibitors (SSRIs), selective serotonin norepinephrine reuptake inhibitors (SSNRI), anticonvulsants, topical lidocaine, topical capsaicin, intrathecal opioids, corticosteroids and ziconotide. This variety of therapies offers clinicians the potential to utilize drugs whose mechanisms of action more specifically targets the particular pathophysiological processes underlying a given pain condition. Most of these therapies act on specific neurotransmitters involved in pain pathways, providing a sound theoretical basis for their use in the treatment of neuropathic and nociceptive pain. Tramadol, for example, provides opioid-like activity and also modulates serotonergic and noradrenergic systems. Antidepressants also provide pain relief through the modulation of select neurotransmitters while also helping to alleviate symptoms of depression, a frequent comorbid condition for those suffering from chronic pain. Among the oldest drugs in this therapeutic group, tricyclic antidepressants (TCAs) appear to modulate pain by potentiating the antinociceptive roles of serotonin and norepinephrine. The activity of both of these neurotransmitters has been shown to be enhanced by the TCA amitriptyline, the drug most commonly used when an antidepressant is included in the treatment of chronic pain. The efficacy of newer antidepressants varies according to class. While SSRIs have been shown to be less effective than TCAs in treating neuropathic pain, SSNRIs are more effective being recommended as the drug of choice in some guidelines *(50).* If medication management fails, then surgical procedures may be considered, such as a microvascular decompression to remove pressure from the trigeminal or glossopharyngeal nerve, radiofrequency thermocoagulation, gamma knife radiosurgery, or rhizotomy *(51, 52).*

Potential barriers to proper pain treatment were underscored by the results of a recent study in Croatia. The cross-sectional controlled study was conducted on 100 patients with chronic neuropathic orofacial pain of non-odontogenic origin. The results confirmed previous findings that pain imparts a significant effect on quality of life as measured by standardized parameters *(53).* The study also revealed that the treatment of chronic neuropathic pain is not in accordance with recommendations from IASP, European Pain Federation EFIC or The Croatian Pain Society. The study found that 61% of patients used NSAIDs and another 34% of patients used the weak opioid tramadol alone or in a fixed combination with paracetamol. Only 20% of the study participants were receiving an anticonvulsant. Medicines from the group of strong opioids, tricyclic antidepressants, corticosteroids and spasmolytics were not used by any respondent. An insignificant number of patients reported using some other treatment, such as acupuncture or biofeedback. Some respondents were not receiving any ongoing therapies.

It can be concluded from this study that the majority of neuropathic pain treatments administered in Croatia are not in accordance with current guidelines. This may be largely explained by administrative restrictions on drug prescriptions. Physicians nationwide are largely guided in their choice of drug therapy by the extent to which specific medications are fully covered by the Croatian Health Insurance Fund.

CONCLUSION

The future of orofacial pain treatment depends on the development of several key areas. Firstly, further research is required to firmly establish a comprehensive, sensitive and specific diagnostic classification scheme for all types of orofacial pain. This tool should integrate quality of life indicators such that they provide additional data on clinical outcomes *(54).* Additionally, the curriculum of study for doctors of both medicine and dentistry should include an increased number of educational hours devoted specifically to the treatment of pain. Finally, health policy should be harmonized such that the guidelines for prescribing medications established by insurance providers match the most recent evidence-based recommendations for the treatment of neuropathic pain.

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