Refractory Orofacial Pain: Is It the Patient or the Pain?

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This paper is based on part of a presentation titled "Refractory Orofacial Pain" at the 45th American Academy of Orofacial Pain annual meeting, May 7, 2021.

Aims: To highlight and discuss the term "refractory" when used to describe pain conditions and its application to orofacial pain, as well as to highlight the factors that must be considered in a refractory patient. **Methods:** A scoping review of recent publications (2010 to 2021) applying the term "refractory" to orofacial pain was conducted, and this paper presents their limitations and definitions. **Results:** The term "refractory" is often used to describe pain instead of "persistent" or "nonresponsive." There are clear definitions in the use of refractory for migraine, cluster headaches, and other nonheadache disorders. Currently, the term is applied to pain conditions in order to alter the patient pathway of treatment, sometimes to escalate a patient from one care sector to another and sometimes to escalate treatment to more costly surgical interventional techniques. **Conclusion:** There is a need for a clear definition for use of the term "refractory" in orofacial pain conditions, excluding migraine and cluster headaches. In addition, there is a requirement for a consensus on the implications of the use of refractory when assessing and managing patients. *J Oral Facial Pain Headache 2021;35:317–325. doi: 10.11607/ofph.3009*

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Chronic pain in the orofacial region is extremely challenging for both the patient and the clinician and is likely to have an increased limbic component when compared to other regional pain.[1] The trigeminal system also has several complexes adding to the divergence and convergence of neural systems connecting with sympathetic, parasympathetic, and cervical nerve systems.[2] As a further diagnostic challenge, there are several head and neck specialities involved with their own siloed training, adding to the frustrations of many patients and often resulting in delayed diagnosis and repeated unsuccessful interventions.[3]

One of the foremost issues of managing patients with chronic pain is the language used. Consistency and agreed terminology underpin what and how pain conditions are diagnosed and how patients are managed most effectively while expediating and validating research. "Semantics," the branch of linguistics and logic concerned with meaning, are extremely important for these considerations, as there is a need to be responsible and aware of the explicit meaning and reference of the words used for patient care.

There have been attempts at unifying the language for chronic pain with definitions, diagnostic criteria, and specific assessment or treatment guidelines. National and international guidelines for managing patients with various types of chronic pain are emerging; however, due to remaining lack of consensus, treatment and response are predicated on whether the patient encounters a general physician or a specialist along their journey in seeking a clear diagnosis and treatment plan. Although its limitations are acknowledged, a recent leap in progress in defining agreed diagnostic criteria is the International Classification of Orofacial Pain (ICOP),[4] which has for the first time collaboratively addressed both acute and chronic orofacial pain diagnoses aligned with the International Classification of Headache Disorders third edition (ICHD-3; https://ichd-3.org/), with the intention of all concerned talking the same language when diagnosing orofacial pain.[5]

One of the more confusing categories in labeling chronic pain is when a clinician uses the term "refractory," and how this pain differs from persistent, chronic, or intractable pain. Definitions for nonresponsive pain are summarized in Table 1.[6–12]

Refractory Pain

When a patient has seen multiple specialists and undergone exhaustive investigations and still does not respond to treatment, there are significant challenges regarding the next step. The term "refractory" is often used in pain conditions to describe intractable or persistent pain that cannot be adequately controlled; however, more specifically, it can be used as a criterion for escalation of managing patients with poor responses to conventional pain management techniques to more complex and/or expensive treatments. A recent guest editorial provided a definition of refractory pain to assist in decision-making with regard to insertion of implantable devices for back pain,[13] and a tool to assess refractory lower back pain indicating the need for neurostimulation has been developed.[14] The questionnaire was developed with a modified decision algorithm, and new prototypes were generated with a range of high sensitivity (80% to 100%) and specificity (89% to 97%) values. The authors recommended the Refractory Chronic Pain Screening Tool (RCPST) to identify patients who should be referred for consideration for neurostimulation. However, the final implant decision requires an appropriate neurologic diagnostic workup, psychologic assessment, and trial stimulation.[14] Baron et al[14] also state that treatment should be individualized using a mechanism-based approach; however, current treatments are usually dispensed without precision, and calcium-channel–acting modulators (pregabalin, gabapentin), tricyclic antidepressants, and serotonin-noradrenalin reuptake inhibitors (duloxetine, venlafaxine) represent first-line treatment options for neuropathic pain. Although neurostimulation techniques for the treatment of refractory chronic pain have become more important, most of the evidence for long-term effectiveness and safety is still limited, which strengthens the need for larger randomized controlled trials before final recommendations can be made.[15]

Refractory Orofacial Pain

If orofacial pain is defined according to MacFarlane et al (2002), then there are criteria for defining refractory orofacial pain in migraine, cluster headache, sudden onset unilateral neuralgiform conjunctival injection and tearing (SUNCT), and sudden onset unilateral neuralgiform headache (SUNHA), but not for all the other orofacial pain conditions.

Refractory Migraine

Migraine can be categorized as episodic migraine (less than 15 days) or chronic migraine (at least 15 days), and as refractory migraine in 5% of chronic cases. If medication resistant, refractory migraine may require consideration of neuromodulation techniques rather than persisting with ineffective preventive or abortive treatments.[16] A recent consensus for the criteria for refractory or resistant migraine has been published.[17] Patients with migraine with or without aura or with chronic migraine can be defined as having resistant migraine and refractory migraine according to previous preventive failures (Table 2).[18] Resistant migraine is defined by having failed at least 3 classes of migraine preventives and suffered from at least 8 debilitating headache days per month for at least 3 consecutive months without improvement; its definition can be based on review of medical charts. Refractory migraine is defined by having failed all of the available preventives and suffered from at least 8 debilitating headache days per month for at least 6 consecutive months. Drug failure may include lack of efficacy or lack of tolerability. Debilitating headache is defined as headache causing serious impairment to conducting activities of daily living despite the use of pain-relief drugs with established efficacy at the recommended dose and taken early during the attack, and failure of at least 2 different triptans is required.

Criteria are needed for refractory migraine in order to escalate treatment to neuromodulation, but also have other implications (Table 3). Although the criteria to define refractory chronic cluster headache are stated as available, treatments are not always efficient, leaving patients without pain remission.[19]

Criteria for refractory SUNCT and SUNHA have been published by the ICHD-3 (Table 4).[20] The authors found that SUNHA is more refractory than SUNCT to medical intervention, and lamotrigine should be considered the drug of choice for the management of both SUNCT and SUNA. Oxcarbazepine, duloxetine, and topiramate can be useful add-on options or alternatives for patients who fail to respond to lamotrigine. Intravenous lidocaine is an extremely effective treatment for patients with frequent severe attacks, but it may not be available in every hospital. Conversely, greater occipital nerve block may only be effective in a small proportion of patients. The efficacy of sodium channel blockers raises the possibility that one of the biologic hallmarks of SUNHA may be sodium channel dysfunction.[20]

Refractory Trigeminal Neuralgia

The American Academy of Neurology (AAN) and the European Federation of Neurological Societies (EFNS) recommend that patients suffering from trigeminal neuralgia (TN) who are unresponsive to carbamazepine or oxcarbazepine be offered a sur-

Table 1 Definitions for Nonresponsive Pain
"Refractory pain" has no medical dictionary definition, unlike the others below. It is often used by oncologists to describe intractable pain that cannot be adequately controlled using conventional treatments,[6] and a recent review could not come to a consensus for definition.[7]
Intractable pain has varied definitions, but the commonly used definition is: ". . .a state of pain for which (A) the cause of the pain cannot be removed or otherwise treated; and (B) in the generally accepted course of medical practice, relief or cure of the cause of the pain (i) is not possible or (ii) has not been found after reasonable efforts."[8]
Persistent pain is any pain that goes on for longer than would be expected after an injury or illness.[9]
Chronic pain is classified as pain that lasts longer than 3 to 6 months.[10]
"Unresponsive pain patient" is usually a term used specifically for nonresponse to opioids due to lack of enzyme CYP-2D6, which is involved in the metabolism of opioids.[11]
Idiopathic disease is any disease with an unknown cause or mechanism of apparent spontaneous origin.[12]

Table 2 Definition of Refractory and Resistant Migraine[18]
Definitions are based on fulfilling the ICHD-3 criteria for migraine with or without aura or for chronic migraine and having at least 8 debilitating headache days per month plus failure of previous preventive treatments.
Resistant migraine is defined by having failed at least 3 classes of migraine preventives and having suffered from at least 8 debilitating headache days per month for at least 3 consecutive months without improvement; its definition can be based on a review of medical charts.
Refractory migraine is defined by having failed all of the available preventives and having suffered from at least 8 debilitating headache days per month for at least 6 consecutive months. For refractory migraine, a chart review alone is not sufficient, and a minimum period of observation of 6 months is required together with completed diaries. The drug classes considered for meeting the definitions include antidepressants, antiepileptics, beta-blockers, calcium channel blockers, drugs acting on the calcitonin gene related peptide pathway, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and onabotulinum toxin A, as well as any new developed drug with established efficacy in migraine prevention. Drug failure may include lack of efficacy or lack of tolerability.

Table 3 Why Do We Need Criteria for Refractory Migraine and What are the Implications?
To provide a reason for referral to a specialist headache clinic by a general practitioner
To provide a reason for referral for neurostimulation by a neurologist
For the purpose of clinical trials
Issues with the International Headache Society definitions of episodic and chronic migraine.
To determine: Is the cut-off of 2 to 3 or > 3 failed treatments reasonable?
To determine: Can episodic migraine be refractory?
In the UK, according to NICE (National Institute for Health and Care Excellence) guidance, botulinum toxin type A is indicated if ≥ 3 preventive treatments have failed.

Table 4 Definition of Refractory Cluster Headache Diagnostic Criteria (ICHD-3)
Diagnostic criteria:
A. Headache attacks fulfilling the ICHD-3 beta criteria for chronic cluster headache (CCH) or probable cluster headache (CH) and criteria B–E .
B. At least 3 severe CH attacks per week that impact patients' quality of life despite preventive or symptomatic treatment.
C. Failed consecutive prophylactic treatment trials with at least three agents that showed efficacy over placebo in randomized controlled studies, used at the maximum tolerated dose over a sufficient period of time.
D. Symptomatic CCH ruled out by negative investigation with brain MRI and MRA, eventually supplemented with carotid CT angiograms or triplex carotid ultrasound.
E. Not better accounted for by another ICHD-3 beta diagnosis.
Notes:
1. Treatments with a good clinical experience for the prevention of CCH and/or that showed efficacy over placebo in RCTs include verapamil, lithium, oral or intravenous steroids, greater occipital nerve infiltration, topiramate, methysergide, ergots, civamide, and long-acting triptans. Among these, verapamil has better documentation. Some agents may be not available across all European countries.
2. Combinations of suggested preventive treatments are recommended, especially when one preventive treatment decreased the attack frequency but did not control the situation satisfactorily upon the physician's decision.
3. Several preventive treatments require special monitoring (eg, verapamil, lithium, methysergide) or appropriate clinical experience (eg, greater occipital nerve infiltration).

gical treatment option.[21–23] A recent meta-analysis of prospective RCTs in TN[24] evaluated drug-related and radiofrequency-related interventions. In the former group, sumatriptan, intranasal lidocaine, botulinum toxin, and intravenous lidocaine were observed to perform better than ophthalmic proparacaine and placebo based on pooled estimates in a forest plot. In the latter group, conventional radiofrequency (both stand-alone and in combination with pulsed radiofrequency) was found to be better than pulsed radiofrequency alone. Rankogram plots revealed sumatriptan and combined continuous and pulsed radiofrequency thermocoagulation to have the highest probability of being the best treatments in the respective group of interventions. No inconsistency was observed between the direct and indirect comparisons. The authors concluded that drug-related interventions that include sumatriptan, intranasal lidocaine, intravenous lidocaine, or botulinum toxin and combined continuous and pulsed radiofrequency thermocoagulation had significant effects in reducing pain in patients with refractory TN. However, the quality of evidence was graded as very low for all except botulinum toxin.

The assumption that refractory TN patients who are unresponsive to carbamazepine or oxcarbazepine should be offered the surgical option was refuted by Cruccu and Truini,[25] who suggested that many patients who are nonresponsive to medical management may benefit from nonsurgical interventions; for example, onabotulinum toxin. Because some patients may not be willing to resort to surgery, Cruccu and Truini[25] searched the literature for alternative treatment for refractory TN and reported on other oral treatments, intranasal spray, subcutaneous injections, various kinds of peripheral nerve blocks, and injections of botulinum toxin. On the basis of the available evidence, they suggested that no oral treatment other than carbamazepine or oxcarbazepine is useful, and there is increasingly strong evidence that botulinum toxin injections are efficacious and may be offered before surgery or to those unwilling to undergo surgery. However, Bendsten et al reported that lamotrigine would be a suitable alternative medical intervention before considering interventional treatment for patients with TN.[21]

Refractory Burning Mouth Syndrome

There is a single publication on refractory burning mouth syndrome (BMS), even though there are no agreed definitions of refractory BMS.[26] BMS with or without sensory changes is placed in the ICOP idiopathic pain group, which by definition is refractory mainly due to unknown cause and inability to manage or treat the condition.

Refractory Temporomandibular Disorders

Without clear definition for refractory temporomandibular disorders (TMDs), there are several case reports and case series related to articular recurrent or persistent disc displacement without reduction or recurrent persistent dislocation. The authors appear to be using refractory to describe patients with TMDs unresponsive to routine care.[27] Importantly, InFORM does not provide a definition of refractory TMDs.

One of the most important assumptions when using refractory terminology is that the pain phenotype is refractory, thus ignoring the significant contribution of the refractory patient. So why does a patient with chronic pain not respond to treatment?

Factors for Nonresponse to Treatment

Factors may relate to:

- Incorrect diagnosis: Many patients who are seemingly nonresponsive to treatment are nonresponsive because their underlying diagnosis is incorrect.[28–30]
- Rare diagnosis: Auriculotemporal neuralgia occurred at a frequency of 0.4% at a tertiary headache outpatient clinic[31]; however, this frequency may be even higher in outpatient orofacial pain due to the possible involvement of the lateral pterygoid muscle in the etiology of auriculotemporal nerve entrapment. Idiopathic diagnoses, by definition, are conditions for which the pathophysiology is unclear, and as a result are persistent and refractory to interventions.
- Confounding impact of previous interventions: Often patients have had multiple medical and sometimes surgical interventions that may alter the pain phenotype, making a core diagnosis increasingly unreachable.[32]
- Medication overuse headache (MOH): MOH is defined by ICHD-3b criteria as a headache occurring 15 or more days per month resulting from overuse of acute headache medication for more than 3 months. MOH tends to resolve when the offending medication is limited. Causal agents include both simple and combination analgesics, such as NSAIDs, triptans, ergot derivatives, and opioids, but any painkiller can potentially be the trigger.[33,34] MOH is common in patients who are at risk of overusing acute medications.[35]

Factors Increasing Refractoriness

There are many reasons why a patient may be refractory. Factors impacting response to treatment are all-encompassing and include demographic, social, psychologic (mood and personality disorders), behavioral (sleep disorders), and physiologic (medi-

cine sensitivity, allergy, endogenous pain modulation) factors, as well as comorbid medical disorders, diet, exercise, and medical noncompliance. Overlooking patient refractoriness is likely due to the lack of a holistic approach when endotyping the patient.[36]

Demographic factors. It is well recognized that there are gender and age implications in the development and persistence of chronic pain.[37,38]

Social factors. A recent report highlighted the significance of social and demographic factors in pain research.[39] Resilience, defined as the ability to restore and live a fulfilling life in the presence of pain, may be based on psychologic flexibility and self-determination models.[40,41]

Psychologic factors. It is often questioned whether psychologic morbidity is a precipitating factor in chronic pain or a result of chronic pain. There is no doubt that chronic orofacial pain has a significant mental health morbidity, unsurprisingly due to the functional impact.[42–44] However, there are recognized psychologic drivers for chronic pain, as chronic pain and mental health disorders are common in the general population, and epidemiologic studies suggest that a bidirectional relationship exists between these two conditions.[45,46] The observations from functional imaging studies suggest that this bidirectional relationship is due in part to shared neural mechanisms.[47] In addition to depression, anxiety, and substance use disorders, individuals with chronic pain are at risk of other mental health problems, including suicide and cigarette smoking, and many have sustained sexual violence. Within the broader biopsychosocial model of pain, the fear-avoidance model explains how behavioral factors affect the temporal course of chronic pain and provides the framework for an array of efficacious behavioral interventions, including cognitive-behavioral therapy, acceptance-based therapies, and multidisciplinary pain rehabilitation. Concomitant pain and mental health disorders often complicate pharmacologic management, but several drug classes, including serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and anticonvulsants, have efficacy for both conditions and should be considered first-line treatment agents.

Medical comorbidities. Comorbid pain and other medical disorders are associated with the onset and maintenance of chronic pain.[48] Comorbid pain is a significant contributor, and fibromyalgia and chronic widespread pain are associated with nonresponsiveness to treatment.[49] Obesity, lack of exercise, diabetes mellitus, and sickle cell and connective tissue disorders are all implicated in the development and maintenance of chronic pain.[50]

Prior significant life events. The severity and development of chronic pain experience are affected by early life factors: individuals who experience adversity or emotional trauma (eg, the death of a parent and being raised in the care system) or physical trauma (eg, substantial hospitalization and preterm birth) in childhood have a higher risk of chronic pain in their adult lives. Early stress in life can alter the function of the hypothalamic pituitary adrenal axis, affecting the stress response. Young people who have experienced traumatic adverse childhood experiences (ACEs) have a greater chance of developing chronic pain than those who have not. A study of children and teenagers aged 9 to 19 years with chronic pain found that the most common ACE in children with chronic pain was having family members with mental health illnesses, and 55% of children with multiple ACEs experience chronic pain.[51] The more ACEs, the greater the level of chronic widespread pain and psychologic distress, such as anxiety and depression (which have been noted previously to be related to the development and severity of chronic pain). People who have experienced personal violence or abusive relationships are also more likely to experience subsequent chronic pain.[51–53]

Sleep disorders. There is strong evidence for the link between poor quality or quantity of sleep and the precipitation and/or perpetuation of chronic pain.[54] In addition, a recent machine-learning approach supports that sleep disorders are a core factor in chronic pain.[55] A recent review[56] discussed the direction between sleep and pain in adult and pediatric populations, as well as the possible mechanisms contributing to this relationship, such as endogenous pain modulation; inflammation; affect, mood, and other states; the roles of different endogenous substances (dopamine, orexin, melatonin, vitamin D); and lesser known potential mechanisms, such as cyclic alternating pattern. Directions for future studies in this area are also discussed, including the addition of tools such as brain imaging (eg, fMRI), electrophysiology, and noninvasive brain stimulation techniques. Such resources paired with artificial intelligence are key to personalized medicine management for patients facing pain and sleep-interacting conditions.[56] A recent paper highlighted that establishing a phenotypic profile and clustering pragmatically identifies diagnostically and mechanistically informative subgroups of chronic pain patients in relation to sleep.[57]

Nutrition. The relationship between nutrition and prevention of chronic pain is unclear. However, there is some supporting evidence for vitamin D, Omega 3, magnesium, Coenzyme Q10, and vitamin B3 for the prevention of migraines.[58] A recent systematic review and meta-analysis of 23 papers found that interventions based on nutrition, particularly those testing an altered overall diet or a single nutrient, had a significant effect on reducing participants' reported pain severity and intensity. However, the studies in

the field of nutrition and chronic pain, including those that were included in the meta-analysis, were of low quality, and there is insufficient evidence to make specific dietary recommendations.[59,60]

Sunshine and vitamin D. Colder climates and lack of sunshine are correlated with chronic pain; one study[61] showed less pain was experienced on longer, sunnier days. A relationship between high levels of reported pain and low levels of vitamin D has been demonstrated, with the suggestion that low vitamin D levels cause anatomical, endocrine, neurologic, and immunologic changes, which predispose to the onset and perpetuation of chronic pain. However, this effect is not replicated across all studies, with only 25% of studies concluding that there is a correlation between low levels of vitamin D and chronic pain.[61,62]

Endogenous pain modulation (EPM) is likely predicated on genetic, gender-related, ethnic, social, and psychologic factors. The periaqueductal gray and insula cortex are the brain structures activated during this process. GABA and serotonin 5HT are likely mediators for downward pain modulation.[63,64]

Drug intolerance / sensitivity / noncompliance. Drug intolerance or drug sensitivity refers to an inability to tolerate the adverse effects of a medication, generally at therapeutic or subtherapeutic doses. Conversely, a patient is said to be tolerating a drug when they can tolerate its adverse effects. Multiple drug intolerance syndrome is defined as having three or more unrelated drug intolerances or allergies. Based on medical record data, about 2% to 5% of the population in North America and Europe have multiple drug intolerance syndrome, with higher rates seen in hospitalized patients. Multiple drug intolerance syndrome is more likely to occur with increasing age, in women, and in individuals being treated for a higher number of different specific health conditions. One study found that over 20% of the general population, those with more symptoms, reported being very sensitive to the effects of medication. Those with high perceived sensitivity also reported having more conditions, being more likely to seek information about medicines, and had significantly more general practitioner visits.[65–67] Multiple drug intolerance is an emerging condition that is likely overlooked by many pain clinicians, possibly due to psychologic factors, and for which a scale has been developed.[68,69]

Microbiome. Gastrointestinal microbiota can directly or indirectly modulate peripheral sensitization underlying chronic pain through multiple gut microbiota–derived mediators, including microbial byproducts (eg, pathogen-associated molecular pattern molecules [PAMPs]), metabolites (eg, short chain fatty acids [SCFAs], butyric acid [BA]), and neurotransmitters or neuromodulators (eg, GABA).[70] Some microbiota-derived mediators (eg, toll-like receptor [TLR] agonists and formyl peptide receptor 1 [FPR1] agonists) can directly activate or sensitize primary nociceptive neurones in the dorsal root ganglia (DRG) to enhance pain, as other microbiota-derived mediators (eg, kynurenic acid [KYNA] and proteases) can directly decrease the excitability of DRG neurons to inhibit pain. Microglia, the resident macrophages of the central nervous system (CNS), are critically involved in the initiation and persistence of chronic pain. Microglia respond to local signals from the CNS but are also modulated by signals from the gastrointestinal tract. Emerging data from preclinical and clinical studies suggest that communication between the gut microbiome—the community of bacteria residing within the gut—and microglia is involved in producing chronic pain. Targeted strategies that manipulate or restore the gut microbiome have been shown to reduce microglial activation and alleviate symptoms associated with inflammation.[71]

Autonomic dysfunction and chronic pain. Vagal nerve activity, indexed by heart-rate variability (HRV), has been linked to altered pain processing and inflammation, both of which may underpin headache disorders and lead to cardiovascular disease (CVD). HRV can be measured simply to assess autonomic tone; for example, within 1 minute, there may be 0.9 seconds between two beats and 1.15 seconds between two others. The greater this variability is, the more "ready" your body is to execute at a high level. When you have high HRV, it means that your body is responsive to both sets of inputs (parasympathetic and sympathetic). This is a sign that your nervous system is balanced and healthy. Lorduy et al found that central sensitization symptoms are associated with stronger emotional suffering in TMD patients,[72] and several studies have reported that compromised autonomic tone may contribute to orofacial pain.[73,74] Koszewicz et al reported an investigation of 33 BMS patients and 20 Parkinson's disease patients demonstrating prolonged sympathetic skin response (SSR) curves compared to 30 controls, highlighting a significant impairment of sympathetic and parasympathetic activity in patients with BMS.[75]

Genetics. Genetic and epigenetic make-up may have several influences on pain response. First, they may influence susceptibility: Several candidate genes and gene polymorphisms have been recognized as potential contributors to chronic pain susceptibility,[76,77] and, more specifically, several neuropathic pain conditions have had specific alleles identified.[78] Second, enzymic deficiency or change may alter analgesic drug metabolism, as a genetic basis for the inability to metabolize certain analgesics has been identified for opiates[79] and tegretol.[80] Third, specific pain conditions related to a polymorphism that would optimally respond to one type of medication may influence response to

treatment; for example, erythromelalgia and response to carbamazepine therapy due to a NaV 1.7 mutation.[81] And last, polymorphisms diminishing the patient's endogenous pain mechanisms and/or more at risk of opioid addiction should be considered.[11] Lederman[82] et al studied a polymorphism in the serotonergic receptor HTR3A gene that is differently associated with striatal dopamine D2/D3 receptor availability in the right putamen in fibromyalgia patients and healthy controls.

Conclusions

This review provides a succinct summary of the use of the term "refractory" to describe pain and how it is applied to orofacial pain. This report highlights that the pain may be refractory, but there are significant factors that contribute to a patient being nonresponsive to treatment that may be overlooked. The importance of clear phenotyping of the pain to gain a diagnosis that reflects current ICOP/ICHD-3 diagnostic guidance is as important as careful endotyping of the patient, which requires a holistic approach and multidisciplinary input. The term "refractory" should be applied correctly where the criteria stipulate its use in specific diagnoses, and its use is usually to consider upward referral between care settings, or more commonly consideration of pain management interventions (specifically neuromodulation or microvascular decompression).

Key Findings

Without clear definitions for "refractory" in many orofacial pain conditions, this term should only be applied where it has clear criteria with the intent to improve treatment for the patient.

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