Refractory Orofacial pain: Is it the patient or the pain?

Tara Renton BDS, MDSC, PhD

Professor Oral Surgery Kings College London

Fax 02032991210

Email Tara.renton@kcl.ac.uk

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Abstract

Aims To highlight and discuss the term 'refractory' when used to describe pain conditions and its application to orofacial pain and to highlight the factors that must be considered in a 'refractory'patient

Methods A scoping review of recent publications (2010-2021) applying the term 'Refractory' to orofacial pain and presentation of limitations and definitions.

Results The use of the term 'refractory' is often used instead of persistent or non-responsive pain. There are clear definitions in the use of the term 'refractory' in Migraine, Cluster headaches and other non-headaches disorders. Currently the term refractory is applied to pain conditions to alter the patient pathway of treatment. Sometimes to escalate a patient from one care sector to another or to escalate treatment to more costly surgical interventional techniques.

Conclusion There is a need for clear definitions for the 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 the term refractory in assessing and managing our patients.

Key Words Refractory, pain, orofacial, persistent, non-responsive

Introduction

Chronic pain in the orofacial region is extremely challenging for both patient and clinician. The psychosocial and functional impact of chronic pain in the trigeminal region is likely to have an increased limbic component when compared with other regional pain.[1] The trigeminal system also has several complexes adding to divergence and convergence of neural systemsconnecting with sympathetic, parasympathetic and cervical nerve systems.[2] Just to add the considerable diagnostic challenges we have several head and neck specialities involved with their own siloed training adding to the frustration of many patients often resulting in delayed diagnosis and repeated unsuccessful interventions.[3]

One of the foremost issues in managing patients with chronic pain is around the language that we use. Consistency and agreed terminology underpin what and how we diagnose the pain condition and how we decide to manage the patient most effectively, whilst expediating and validating research. Semantics is the branch of linguistics and logic concerned with meaning, and we need to be responsible and aware of the explicit meaning and reference of the words used for patient care.

There are attempts in ‘unifying’ our 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 or response is predicated on whether the patient encounters a general physician or specialist along their journey in seeking a clear diagnosis and treatment plan. A recent 'leap' in progress in defining agreed diagnostic criteria, with acknowledgement of limitations is The International Classification of orofacial pain has for the first time collaboratively addressed both acute and chronic orofacial pain diagnoses in the region aligned to the ICHD3 (https://ichd-3.org/), with the intention of all concerned talking the same 'language' when diagnosing orofacial pain. [4]

One of more confusing categories in labelling chronic pain is when a clinician uses the term 'refractory', how this differs from persistent, chronic or intractable. Definitions for non-responsive pain are summarised in Table 1.

Refractory pain When a patient has seen multiple specialists and undergone exhaustive investigations and still does not respond to treatment, many of us are significantly challenged about the next step. Thus, when this pain does not respond, the term 'refractory' is often used in pain conditions to describe intractable or persistent pain that cannot be adequately controlled. However, more specifically, refractory can be used as a criteria for escalation of managing patients with poor responses to conventional pain management techniques to more complex expensive treatments. A recent guest editorial provided a definition of refractory pain to assist in decisions making with regard insertion of implantable devices for back pain.[13]

A tool to assess refractory lower back pain indicating the need for neurostimulation has been developed.[13] The questionnaire developed with a modified decision algorithm, new prototypes were generated with range of high sensitivity (80–100%) and specificity (89–97%) values. The authors recommended RCPST tool to identify patients that should be referred for consideration for neurostimulation. However, the final implant decision requires appropriate neurological diagnostic workup, psychological assessment, and trial stimulation. [13] Baron [13] also states that

‘Ideally, 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 evidence of long-term effectiveness and safety is still limited, which strengthens the need for larger randomized controlled trials before final recommendations can be made.[14]

Refractory Orofacial Pain If we define orofacial pain according to MacFarlane et al (MacFarlane et al 2002) then there are criteria for defining refractory orofacial pain in migraine, cluster headache, SUNCT and SUNHA however, not for all the other orofacial pain conditions.

Refractory Migraine Migraine can be categorised as episodic (less than 14 days per month), chronic (equal to or more than 15 days a month) and refractory migraine in 5% of cases (Table 2) which requires neuromodulation rather than preventative or abortive treatments.[15] A recent consensus for the criteria for refractory or resistant Migraine have been published.[16] Patients with migraine with or without aura or with chronic migraine can be defined as having resistant migraine and refractory migraine according to previous preventative failures. Table 2. Resistant migraine is defined by having failed at least 3 classes of migraine preventatives and suffer from at least 8 debilitating headache days per month for at least 3 consecutive months without improvement; definition can be based on review of medical charts. Refractory migraine is defined by having failed all of the available preventatives and suffer 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 conduct activities of daily living despite the use of

pain-relief drugs with established efficacy at the recommended dose and taken early during the attack; failure of at least two different triptans is required.

Why do we need criteria for refractory Migraine? The main drive to establish criteria for refractory migraine is to escalate treatment to neuromodulation but also has other implications (Table 3).

The authors also highlighted the need for criteria to define refractory chronic Cluster Headache are stated as available, but treatments are not always efficient leaving patients without pain remission.[18]

Refractory Sudden Onset Unilateral Neuralgiform Conjunctival injection and tearing (SUNCT) and Sudden Onset Unilateral Neuralgiform headache (SUNHA) have been published by ICHD3 (Table 4) .[19] The authors summarised their findings as that SUNHA is more refractory than SUNCT to medical intervention, Lamotrigine should be considered the drug of choice for the management of SUNCT and SUNA. Oxcarbazepine, duloxetine and topiramate can be useful options for patients who fail to respond to lamotrigine or as add-on options. Intravenous lidocaine is an extremely effective treatment for patients with frequent, severe attacks, but it may not be available in every hospital. Conversely, GONB may only be effective in a small proportion of patients. The efficacy of sodium channels blockers raises the possibility that one of the biological hallmarks of SUNHA may be sodium channel dysfunction. [19]

Refractory Trigeminal Neuralgia (TN) The American Academy of Neurology (AAN) and the European Federation of Neurological Societies (EFNS) recommend that patients suffering from TN unresponsive to carbamazepine or oxcarbazepine be offered the surgical option.. [20,21,22] A recent metanalysis of PRCTs in TN[23] evaluated two different interventions were analyzed: 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 standalone 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 thermo-coagulation have the highest probability of being the best treatments in the respective group of interventions. No inconsistency was observed between direct and indirect comparisons. They concluded that drug-related interventions that include sumatriptan, intranasal lidocaine, intravenous lidocaine, and 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 assumed definition of refractory TN is recommended in patients unresponsive to carbamazepine or oxcarbazepine should be offered the surgical option was refuted by Cruccu et al[24], who highlighted that many patients non-responsive to medical management may benefit from non-surgical interventions for example Ona Botulinum Toxin . The highlighted that because some patients may not be willing to resort to surgery, they searched the literature for alternative treatment in refractory trigeminal neuralgia. They reported that 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 suggest 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.

‘Refractory’ Burning Mouth Syndrome (BMS) There is a single publication on BMS and BMD even though there are no agreed definition of refractory BMS.[25] BMS with or without

sensory changes is placed in the ICOP idiopathic pain group which be definition is refractory mainly due to unknown cause and inability to manage or treat the condition.

'Refractory Temporomandibular Joint Disorders (TMD)' Without clear definition for refractory TMD 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'. [26] Importantly INFORM does not provide a definition of refractory TMDs.

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

Factors for the patient's pain not responding Factors may relate to;

- Incorrect diagnosis: We encounter many patients seemingly non-responsive to treatment due to their underlying diagnosis being incorrect.[27,28,29]
- Rare diagnosis: Auriculotemporal neuralgia occurs at a frequency of 0.4 % at a tertiary headache outpatient clinic.[30] However, this frequency may be even higher in outpatient orofacial pain due to the possible involvement of lateral pterygoid muscle in the aetiology of auriculotemporal nerve entrapment. Idiopathic diagnoses, by definition, are conditions for which we do not understand the pathophysiology and as a result are persistent and 'refractory' to interventions.
- Confounding impact of previous interventions: Often patients have had multiple medical and often surgical interventions that may alter the pain phenotype making a core diagnosis increasingly unreachable.[31]
- Medication overuse 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 potentially any painkiller can be the trigger.[32,33] MOH is common in those patients who are at risk of overusing acute medications.[34]

Factors increasing the 'refractoriness' of the patient There are many reasons why a patient may be 'refractory', Factors impacting on response to treatment for pain are all encompassing and include; Demographic, social, comorbid medical disorders, psychological factors (mood and personality disorders), behavioural (sleep disorders) diet, exercise, medical non-compliance) and physiological factors (medicine sensitivity, allergy, endogenous pain modulation). Overlooking patient refractoriness is likely due to the lack of holistic approach in endotyping the patient.[35]

Demographic factors It is well recognised that there are gender and age implications in the development and persistence of chronic pain.[36,37]

Social factors A recent report highlighted the significance of social and demographic factors in pain research.[38]

Resilience defined as the ability to restore and living a fulfilling life in the presence of pain which may be based upon Psychological flexibility and self-determination models.[39.40]

Psychological factors It is often questioned as to whether the psychological 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.[41,42,43] However, there are recognised psychological drivers for chronic pain as chronic pain and mental health disorders are common in the general population, and epidemiological studies suggest that a bidirectional relationship exists between these 2 conditions.[44,45] The observations from functional imaging studies suggest that this bidirectional relationship is due

in part to shared neural mechanisms.[46] 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 pharmacological 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.[47] Comorbid pain is a significant contributor and fibromyalgia and chronic widespread pain are associated with non response to treatment.[48] Obesity, lack of exercise, diabetes, sickle cell, connective tissue disorders are all implicated in the development and maintenance of chronic pain.[49]

Prior significant life events The severity and development of chronic pain experience are affected by early life factors: people who experience adversity or emotional trauma (e.g. death of parent and being raised in the care system) or physical trauma (e.g. substantial hospitalisation 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 9-19 years with chronic pain found that the most common ACE in children with chronic pain was having family members with mental health illnesses; 55% of children with multiple ACEs experience chronic pain. The more ACEs, the

greater the level of chronic widespread pain and psychological 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 more likely to experience subsequent chronic pain.[50,51,52]

Sleep disorders The link between poor quality or quantity of sleep and precipitation and or perpetuation of chronic pain is heavily evidenced.[53] In addition, a recent Machine learning approach supports that sleep disorders are a core factor in chronic pain.[54] A recent review, discusses the direction between sleep–pain in adult and pediatric populations will be discussed. Moreover, the possible mechanisms contributing to this relationship as endogenous pain modulation, inflammation, affect, mood and other states, the role of different endogenous substances (dopamine, orexin, melatonin, vitamin D) as well as other lesser known such as cyclic alternating pattern among others, will be explored. Finally, directions for future studies on this area will be discussed, opening up to the addition of tools such as brain imaging (e.g., fMRI), electrophysiology and non-invasive brain stimulation techniques. Such resources paired with artificial intelligence are key to personalized medicine management for patients facing pain and sleep interacting conditions.[55] A recent paper highlighted that by establishing a phenotypic profile and clustering pragmatically identifies diagnostically and mechanistically informative subgroups of chronic pain patients in relation to sleep.[56]

Nutrition - and prevention of chronic pain is unclear. However, Vit D Omega 3, Magnesium, CoEnzyme Q10 and Vitamin B3 are evidenced in prevention of migraines.[57] A recent systematic review and metaanalysis 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 included in the meta-analysis, were of low quality, and there is insufficient evidence to make specific dietary recommendations. [58,59]

Sunshine and vitamin D Colder climates and lack of sunshine correlate with chronic pain; a study 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 anatomic, endocrine, neurological, and immunological changes, which predispose to onset and perpetuation of chronic pain. However, the 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.[60,61]

Endogenous pain modulation (EPM) is likely predicated on genetic, gender, ethnic, social and psychological factors. Paraaqueductal Grey and Insula cortex are the brain structures activated during the process. GABA and Serotonin 5HT are likely mediators for downward pain modulation.[62,63]

Drug intolerance/Dru sensitivity/Drug non-compliance 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 greater than 3 or more unrelated drug intolerances or allergies. Based on medical record data, about 2 to 5% of the population in North America and Europe, with higher rates seen in hospitalized patients. Multiple drug intolerance syndrome is more likely to occur with increasing age, in females and in individuals being treated for higher numbers of different specific health conditions. One study reported over 20% of the general population reported being very sensitive to the effects of medication those with more symptoms. 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.[64-66] Multiple drug intolerance is an emerging condition that is likely overlooked by many pain clinicians, and possibly due to psychological factors for which there is scale developed.[67-68]

Microbiome Gastrointestinal microbiota can directly or indirectly modulate peripheral sensitisation underlying chronic pain through multiple gut microbiota-derived mediators, including microbial by-products (e.g. PAMPs), metabolites (e.g. SCFAs, BAs), and neurotransmitters or neuromodulators release (e.g.GABA). [69] Some microbiota-derived mediators (e.g. TLRs agonists and FPR1 agonists) can directly activate or sensitise primary nociceptive neurones in dorsal root ganglia (DRG) to enhance pain, as other microbiota-derived mediators (e.g. KYNA and proteases) can directly decrease the excitability of DRG neurones 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.[70]

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). Heart rate variability (HRV) can be measured simply to assess autonomic tone. Within that minute there may be 0.9 seconds between two beats, for example, 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 heart rate variability, 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.[71] Several studies have reported that compromised

Autonomic tone may contribute to orofacial pain.[72,73] Koszewicz, et al reported on investigation of 33 BMS, 20 PD patients demnstrating prolonged SSR curves compared with 30 controls highlighting a significant impairment of sypathetic and parasympathetic activity in patients with BMS. [74]

Genetics The patients' genetic and epigenetic make up may have several influences on their pain response. Firstly, are they more susceptible? Several candidate genes and gene polymorphisms have been recognised as potential contributors to chronic pain susceptibility,[75,76] and more specifically several neuropathic pain conditions have had specific alleles identified.[77] Secondly, do they have enzymic deficiency or change which alters their analgesic drug metabolism? A genetic basis for inability to metabolise certain analgesics has been identified for opiates[78] and Tegretol.[79] Thirdly, do they have a specific pain condition that is related to a polymorphism that would optimally responds to one type of medication? For example Erthromyaligia and response to carbamazepine therapy due to a NaV 1.7 mutation.[80] And lastly, is there a polymorphism diminishing the patients endogenous pain mechanism and or more at risk of opioid addiction?[10] Lederman[81] 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 pain and how it is applied to orofacial pain. This report highlights that the pain may be refractory but that there are significant factors that contribute to the patient being non-responsive to treatment, which may easily be overlooked. The importance of clear phenotyping of the pain to gain a diagnosis that reflects current ICOP/ICHD3 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. The repercussion of the label ‘refractory’ is usually to consider upward referral between care settings or more commonly consideration of pain management interventions, specifically neuromodulation or Microvascular decompression.

Select a heading based on the research area: • Clinical implications & Public health relevance

Key findings Without clear definitions for Refractory in man orofacial pain conditions, the term should be only applied where it has clear criteria with the intent to improve treatment for the patient.

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