Chronic orofacial pain and pharmacological management: a clinical guide

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Orofacial pain is a widespread health concern that significantly hinders an individual's capacity to engage in daily activities. This type of pain can be classified into three main categories: nociceptive pain, neuropathic pain, and nociplastic pain. Each category involves different mechanisms and requires specific treatment approaches. For optimal treatment of orofacial pain disorders, a multidisciplinary pain management approach is essential. This approach should integrate both nonpharmacological and pharmacological modalities to address the diverse underlying causes and manifestations of pain. In this review, we focus on the current evidence and advancements in the pharmacological management of chronic orofacial pain. We explored the effectiveness of different medications, their mechanisms of action, and their role within a comprehensive pain management plan. (Oral Surg Oral Med Oral Pathol Oral Radiol 2025;140:e1–e21)

Orofacial pain could be defined as pain occurring mainly or exclusively the regions of the mouth and the region below the orbitomeatal line, in front of the ears, and above the neck.[1] In contrast, headache is characterized by pain occurring only or mainly above the orbitomeatal line and/or nuchal ridge.[2] Both the orofacial region and the head are innervated by the trigeminal nerve, though they are primarily served by different branches. Headaches are mainly mediated by the first division (ophthalmic division), while orofacial pain is typically mediated by the second (maxillary) and third (mandibular) divisions of the trigeminal nerve. However, referred pain to the orofacial region could also occur from other anatomical sites or systemic conditions, such as cervical spine disorders (e.g., cervicogenic orofacial pain and headache), cardiac conditions (e.g., angina and carotid, artery dissection), cerebral disorders (e.g., cerebral artery aneurysm) and neurovascular diseases (e.g., posterior reversible encephalopathy syndrome).[3-7] Additionally, headaches, including some autonomic cephalalgias (e.g., cluster headaches), may present with pain in the facial region due to the involvement of the trigeminal autonomic system.[8] The shared innervation and proximity of structures like the eyes, ears, nose, sinuses, and oral cavity add complexity to pain referral patterns, leading to overlapping and difficult-to-diagnose conditions. For example, temporomandibular disorders (TMD) and sinus infections may mimic each other's pain pathways, complicating differential diagnosis.[9,10]

Moreover, the trigeminal nerve provides primary innervation to the key structures such as the cavernous sinus, and peripheral divisions. From an anatomical perspective, this widespread and overlapping sensory network is incredibly complex. It encompasses a vast array of structures, each with its own complex vasculature and equally complicated innervation. The orofacial and head regions contain numerous critical components such as muscles, bones, glands, and sensory organs, all tightly packed within a relatively small area. This complicated network includes not only the trigeminal nerve and its three branches but also other cranial nerves, blood vessels, and connective tissues. The overlap of innervation across the trigeminal nerve branches and other structures creates potential convergence points for pain perception. This convergence suggests that the boundaries traditionally described between orofacial and headache pain may not be as distinct as previously thought. Pain originating from any branch of the trigeminal nerve, or even from neighbouring structures, may lead to overlapping or mislocalized pain. This phenomenon is further facilitated by peripheral sensitization, where nociceptive input from muscles or other peripheral structures activates previously silent neurons in the spinal cord, enhancing their responsiveness. As a result, pain is often perceived in regions distant

Statement of Clinical Relevance

Orofacial pain, a widespread health concern, hinders daily activities and requires a multidisciplinary management approach. Effective treatment involves tailored pharmacological and nonpharmacological strategies, considering individual patient needs, medication efficacy, safety, and cost-effectiveness.

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Received for publication Aug 9, 2024; returned for revision Dec 5, 2024; accepted for publication Feb 10, 2025.

2212-4403/$-see front matter
https://doi.org/10.1016/j.oooo.2025.02.005

from the original site of injury or irritation, reflecting the intricate referral patterns of the trigeminal network.[11-13] Referred pain may also arise due to central sensitization, a process in which the central nervous system becomes hyper-responsive to sensory stimuli after repeated or sustained nociceptive input.[14,15] In central sensitization, neurons within the spinal cord and brain undergo heightened sensitivity, resulting in an amplified perception of pain, even when the primary stimulus has diminished or is no longer present. This mechanism could lead to the mislocalization of pain, whereby pain is perceived in regions distant from the initial site of injury or inflammation. In orofacial and headache disorders, for example, prolonged nociceptive input from peripheral sources like the temporomandibular joint (TMJ) or cervical spine may lead to sensitization of the trigeminal nerve pathways. As a result, patients may experience referred pain in the face, head, or neck. Central sensitization is particularly significant in chronic pain conditions, where the persistence of heightened CNS sensitivity contributes to widespread and referred pain patterns.[14]

Chronic orofacial pain is common and often lacks a biological benefit, such as signalling tissue damage or aiding in wound healing.[16] In most cases, it is a non-protective and detrimental type of pain.[1] Defined as pain persisting for at least 50% of the days over three months and lasting at least 2 hours, it significantly impacts the quality of life of those affected.[17-19] The prevalence of the chronic orofacial pain varies from different studies from 7% to 33.2% and is higher in the female sex.[20-22] The aetiology of chronic orofacial pain varies significantly, ranging from organic to non-organic origin. Examples of chronic orofacial pain include chronic temporomandibular disorder (cTMD), trigeminal neuralgia, neurovascular orofacial pain, burning mouth syndrome, post-traumatic trigeminal neuropathic pain, persistent idiopathic facial pain, and persistent idiopathic dentoalveolar pain (atypical odontalgia). Among these, cTMD is the most common chronic orofacial pain condition.[23,24]

A broad classification for clinically determined orofacial pain can be categorized as nociceptive, neuropathic, and nociplastic (Figure 1).

NOCICEPTIVE PAIN

Nociceptive pain arises from neural pathways activated by actual or potentially damaging stimuli.[25] It is usually acute and acts as a protective mechanism, urging individuals to prevent further injury. This pain type is driven by nociceptors—sensory receptors sensitive to harmful stimuli.[26] However, nociceptive pain could transform into nociplastic pain due to various factors such as sustained nociceptive input, peripheral and central sensitization, changes in pain perception, and the perpetuation of nociplastic pain processes.[22,27-30]

NEUROPATHIC PAIN

The International Association for the Study of Pain (IASP) defines neuropathic pain as pain resulting from damage or disease affecting the somatosensory nervous system.[31] Compared to nociceptive pain, patients with neuropathic pain often experience shooting, stabbing, or burning sensations. This pain could be associated with sensory abnormalities or deficits such as numbness and allodynia, more pronounced pain paroxysms, and, depending on the affected nerve(s), specific neurological findings. Unlike many forms of nociceptive pain and acute nerve injury, chronic neuropathic pain is invariably maladaptive.[32] While the link between pain intensity and disability is generally weak, neuropathic pain tends to have a more profound impact on quality of life compared to similar levels of nociceptive pain. This greater detriment to quality of life may be due to the persistent and often severe nature of neuropathic pain, which could interfere more significantly with daily activities, emotional well-being, and overall functionality.[33,34]

NOCIPLASTIC PAIN

Nociplastic pain is mechanistically distinct from both nociceptive and neuropathic pain. It is characterized by pain arising from altered nociception without clear evidence of nociceptive or neuropathic origins. According to the IASP, it is defined as "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage activating peripheral nociceptors, or any disease or lesion of the somatosensory system causing the pain."[28,35] Central sensitization is the major underlying mechanism of nociplastic pain. The pathophysiological mechanisms underlying these disorders primarily involve changes in the ascending pain pathways and reduced efficacy of inhibitory pathways.[36] This leads to heightened sensitivity due to altered functioning of pain-related sensory pathways in both the peripheral and central nervous systems. Nociplastic pain is often characterized by psychological distress and widespread pain, framed within a biopsychosocial model.[37] Unlike other types of pain, it responds best to psychologically based interventions rather than opioids.[32]

Effective management typically involves a comprehensive approach that integrates patient education with various treatments, including pharmacological management, psychological therapy, physiotherapy, and lifestyle-based interventions. This paper aims to summarize the pharmacological management of chronic orofacial pain, including the management of nociplastic pain.

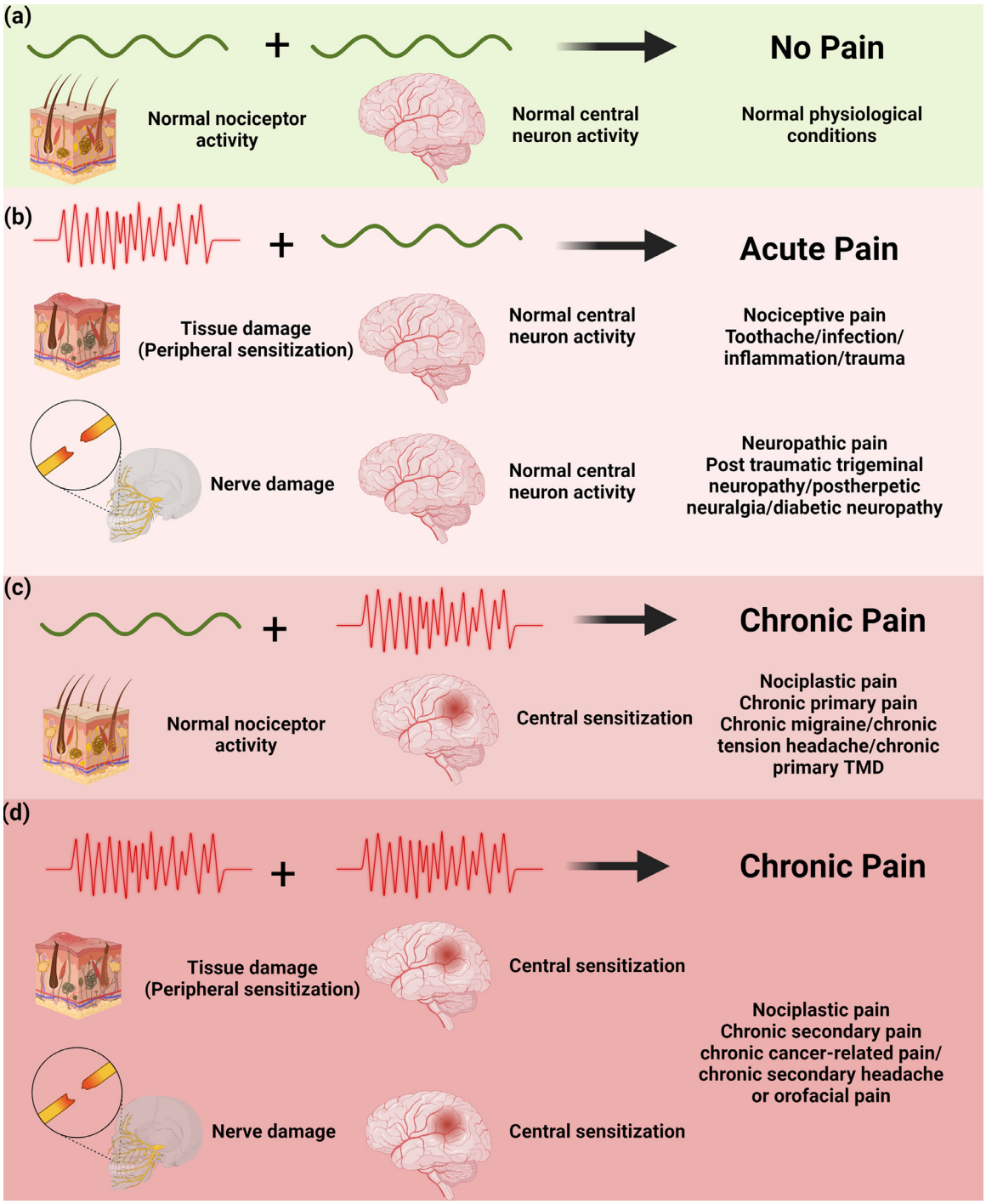

Fig. 1. General classification of orofacial pain. (**A**) Normal nociceptive and central neuron activity. In the absence of any sensitization or tissue damage, normal nociceptive (pain receptor) and central neuron activity typically do not induce pain. This represents the baseline state where pain pathways are not activated under normal physiological conditions. (**B**)Tissue damage and acute pain: peripheral sensitization: when tissue damage occurs, it leads to the release of inflammatory mediators that sensitize peripheral nociceptors. This sensitization lowers the threshold for activation, resulting in acute pain. Peripheral nerve damage: damage to peripheral nerves, such as from trauma or surgical procedures, also results in acute pain. (**C**) Chronic primary pain (central sensitization without peripheral sensitization): Central sensitization: in some cases, pain persists even without ongoing peripheral sensitization. This occurs due to changes in the central nervous system, where neurons become hyper-responsive. This heightened sensitivity leads to chronic primary pain, where the pain is maintained by central mechanisms. An example is fibromyalgia, where widespread pain occurs without direct tissue damage. (**D**) Chronic secondary pain (both peripheral and central sensitization): combined peripheral and central sensitization: chronic secondary pain arises when there is both peripheral and central sensitization. Ongoing tissue damage or inflammation keeps peripheral nociceptors sensitized, while central sensitization amplifies the pain signals. This dual sensitization results in persistent, often debilitating pain. (Created with BioRender.com).

PHARMACOLOGICAL MANAGEMENT

In the management of orofacial pain, a variety of pharmacological options are employed based on the underlying mechanisms of pain and the patient's specific condition. For example, antidepressants effectively modulate pain perception by influencing central mechanisms. Anticonvulsants, or antiepileptic drugs, are commonly used to stabilize neuronal hyperexcitabilityuscle relaxants modulate neuronal activity by enhancing gamma-aminobutyric acid (GABA)'s inhibitory effects in the central nervous system. Benzodiazepines, with both anticonvulsant and anxiolytic properties, act as positive allosteric modulators of GABA-A receptors, enhancing GABA activity. Antihypertensives, particularly calcium channel blockers, are incorporated for their vasodilatory and pain-modulating effects. Calcitonin gene-related peptide (CGRP) biologics are used to modulate orofacial pain, while opioid analgesics provide both opioid and nonopioid mechanisms to manage moderate to severe pain. Opioid receptor antagonists help modulate neuroinflammation, enhance opioid analgesic effects, and exhibit opioid-sparing properties. Triptans target migraine-related pain by focusing on specific headache pathways. Nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen, diclofenac, naproxen, and indomethacin are commonly used to treat orofacial pain, especially when caused by inflammation or vascular issues. Topical treatments, such as anesthetics and capsaicin, offer localized pain relief by acting on peripheral nociceptors. Botulinum toxin type A (BoNT-A) is utilized in chronic pain, particularly muscle-related disorders, by blocking nerve signaling and reducing muscle tension. Finally, cannabinoids are increasingly studied for their potential analgesic effects, particularly in cases of refractory orofacial pain. Notably, endocannabinoids are synthesized in postsynaptic terminals but exert their effects on presynaptic terminals. Tetrahydrocannabinol (THC) acts on both cannabinoid (CB)1 and CB2 receptors, while cannabidiol (CBD) primarily targets CB1 receptors. CB2 receptors are found in immune cells, suggesting a potential role in modulating inflammation (Table I). Medication selection should be personalized and targeted towards the underlying pathophysiological processes. However, many mechanisms involved in chronic orofacial pain, as well as the modes of action of the medications used, remain unclear. Most medications for chronic orofacial pain have adverse effects, some of which can impact quality of life (Table II). Combining medications is sometimes necessary, depending on the suspected pain mechanisms, the effectiveness of single medications, and other factors. However, polypharmacy often increases the risk of adverse effects and drug interactions, so the benefits of combination therapy must clearly outweigh these risks. Approaches to treating chronic orofacial pain can be either preventive or abortive, depending on factors such as pain frequency, associated disability, and patient preference.

ANTIDEPRESSANTS

Tricyclic antidepressants

The primary pharmacological action of tricyclic antidepressants (TCAs) is the inhibition of 5-hydroxytryptamine (5-HT) and noradrenaline reuptake. Given the critical role of 5-HT and noradrenaline pathways in pain modulation, TCAs are thought to enhance the descending pain modulation pathway.[38,39] Amitriptyline, a well-known TCA, is effective in managing various forms of chronic orofacial pain.[40] Its analgesic effect is independent of its antidepressant properties and could be achieved at much lower doses. A dose of 10 mg taken 1-2 hours before bedtime is recommended. The long elimination half-life of amitriptyline (10-26 hours) allows for a once-daily dosing schedule. If necessary, the dose may be increased by 10 mg per week, up to a maximum of 20-40 mg, depending on the condition being treated.[41,42] Long-term administration of 25 mg daily is not associated with significant reductions in a patient's cognitive processing or task-performing capacity.[43] Dry mouth, sedation, palpitations, nausea and sweating are the common adverse effects. Similar to amitriptyline, imipramine has been extensively utilized for neuropathic pain and may be considered an alternative if amitriptyline is not well tolerated.[44] The recommended starting dose is 12.5 mg daily, which can be gradually increased to a daily dose of 25-50 mg.[45,46] The number needed to treat (NNT) to achieve a significant improvement in neuropathic pain with amitriptyline is 4.6, meaning that on average, treating 4.6 patients with amitriptyline will result in one patient experiencing a meaningful reduction in pain.[47]

Nortriptyline, an antidepressant belonging to the same class as amitriptyline but with more potent reuptake activity for noradrenaline than 5-HT, is often considered for treating neuropathic pain. However, a Cochrane review found limited evidence supporting its effectiveness in this regard. Given its affordability and widespread availability, nortriptyline might be considered if other tricyclic antidepressants have been ineffective.[48] Nonetheless, there are alternative medications with stronger evidence supporting their efficacy and safety profiles. TCA are effective and have an overall NNT of 3.6 for the achievement of at least moderate pain relief.[40,47,49,50]

Serotonin-norepinephrine reuptake inhibitors

Venlafaxine is classified as a serotonin-noradrenaline reuptake inhibitor. It has been used in several orofacial pain conditions such as postherpetic neuralgia,

Table I. Pharmacological management of common chronic orofacial pain

Chronic orofacial pain	*First line*		*Second line*
	Topical	*Systemic*	*Systemic*
Myofascial orofacial pain		Amitriptyline/nortriptyline 10 mg once daily, increasing the dose at weekly intervals in 10 mg increments to a maximum dose of 25-50 mg once daily[230-232]	Gabapentin[233]
Burning mouth syndrome	Sucking on a 1 mg clonazepam tablet without swallowing, three times daily for 14 days[152]; 0.02% capsaicin rinse (15 mL) for 30 seconds three times daily[202]	Amitriptyline 10 mg once daily, increasing the dose at weekly intervals in 10 mg increments to a maximum dose of 25-40 mg once daily[42]	Gabapentin[104]
Persistent idiopathic dentoalveolar pain	Apply EMLA 5% cream on the affected area for 5 minutes follow by 0.025% capsaicin ointment for 3 minutes twice daily[206]	Amitriptyline at a dose of 5-25 mg/day[234,235]	Venlafaxine[52]; Duloxetine[236]
Persistent idiopathic facial pain		Amitriptyline/Nortriptyline 10 mg once daily, increasing the dose at weekly intervals in 10 mg increments to a maximum dose of 25-50 mg once daily	Venlafaxine[53]; topiramate[231]
Postherpetic neuralgia	Apply a pea-sized amount of 0.075% capsaicin cream to the affected area 3-4 times daily[237]; 5% lidocaine base (700 mg/patch)[238]	Gabapentin (300 mg on day 1, 300 mg twice daily on day 2, 300 mg three times daily on day 3; increase 300mg every three days up to 600 mg three times daily)[239] and pregabalin (75 mg twice daily for one week, then 150 mg twice daily for one to three weeks, then 300 mg twice daily)[240]; Amitriptyline/nortriptyline 10 mg once daily, increasing the dose at weekly intervals in 10 mg increments to a maximum dose of 25-50 mg once daily	Carbamazepine[241]; lamotrigine[242]
Trigeminal or glossopharyngeal neuralgia	8% lidocaine applied to the oral mucosa[243]	Take 100 mg of carbamazepine 1-2 times daily (some patients need a higher initial dose) gradually increase the dosage according to the patient's response, with a usual dose of 200 mg taken 3-4 times daily, and up to 1.6 g daily in some patients[244]; Start oxcarbazepine at 600 mg daily in two divided doses, increasing by 300 mg every three days as tolerated, up to 1200-1800 mg daily.	Gabapentin[245] and lamotrigine[246,247]
Post-traumatic trigeminal neuropathic pain	5% Lidocaine topical patches[193]	Acute stage: prednisone 30 mg for 7 days, 15 mg for 4 days, and 5 mg for 3 days[248,249]; Late stage: amitriptyline/nortriptyline 25-150 mg, once a day or in two divided doses[38,250]; gabapentin 900-3600 mg, in three divided doses[38,251]; carbamazepine 400-600 mg/day[250]	

(*continued*)

Table I. Continued

Chronic orofacial pain	*First line*		*Second line*
	Topical	*Systemic*	*Systemic*
Cluster headache	Lidocaine (1 mL with a concentration of 4%-10%, ipsilateral to the pain)[252]	Acute: Oxygen at 12 L/min via nonrebreather mask for 15 minutes[252]; sumatriptan 3-6 mg subcutaneous[253,254]	Verapamil,[255,256] topiramate,[257,258] prednisone[259]
Paroxysmal hemicrania		The starting dose of indomethacin for adults 25 mg three times a day. The typical maintenance dose is 25-100 mg daily.[260-262]	Verapamil,[263] topiramate[264] and prednisone[265,266]
Hemicrania continua		The starting dose of indomethacin for adults 25 mg three times a day, may require a dose increase from 75 mg-100 mg daily.[267]	Verapamil,[268] topiramate[269] and gabapentin[270]
SUNCT and SUNA*		Lamotrigine therapy may begin with a dosage of 25 mg daily for the first two weeks, followed by an increase to 50 mg daily for the subsequent two weeks. The standard maintenance dosage is 200 mg per day, administered in two divided doses[271]	Carbamazepine,[219,272,273] Oxcarbazepine[271] and topiramate[274]

*SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) and SUNA (short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms).

trigeminal neuralgia, persistent idiopathic dentoalveolar pain and persistent idiopathic facial pain.[51] To minimize the adverse effects, patient should start on 37.5mg daily for the first week before increasing to 75mg. Venlafaxine, at a dose of 112.5 mg per day, has been found effective in providing pain relief for persistent idiopathic dentoalveolar pain.[52] In a placebo-controlled, crossover study involving 30 participants with persistent idiopathic facial pain, venlafaxine (up to 75 mg/day) did not significantly reduce pain intensity. However, participants did report a significant improvement in pain relief on the verbal rating scale.[53] Dry mouth, constipation, nausea, anorexia, weight changes, and vomiting are possible adverse effects. The NNT to achieve a significant improvement in neuropathic pain with venlafaxine is 3.1.[49]

Duloxetine is a balanced selective serotonin-norepinephrine reuptake inhibitor that became the first medication approved in the United States for treating painful diabetic neuropathy in 2004.[54] The typical dose is 60 mg, and at this dosage, moderate-quality evidence suggests that duloxetine effectively reduces pain in both painful diabetic peripheral neuropathy and fibromyalgia.[55] Duloxetine has been reported to successfully manage burning mouth syndrome, both as a monotherapy and in combination with venlafaxine.[56-58] In addition to burning mouth syndrome, it is also effective in treating persistent idiopathic dentoalveolar pain.[59] The recommended dosage for pain management is 60 mg once daily.[46] The NNT to achieve a significant improvement in neuropathic pain with duloxetine is 6-8.[49,60]

Milnacipran is one of the selective serotonin-norepinephrine reuptake inhibitors. It is primarily used to treat fibromyalgia and major depressive disorder.[61] By inhibiting the reuptake of both serotonin and norepinephrine, milnacipran increases their concentrations in the synaptic cleft, thereby enhancing neurotransmission. This dual action helps regulate mood and pain perception, making it particularly effective in alleviating pain and improving mood in patients with fibromyalgia and depression.[62] Research has shown that milnacipran significantly improves chronic orofacial pain conditions, such as burning mouth syndrome (BMS) and persistent idiopathic dentoalveolar pain, regardless of concurrent depressive symptoms.[63] Clinical trials indicate that milnacipran, either alone or combined with ethyl loflazepate, can effectively reduce pain in BMS patients.[64,65] For those with BMS who do not respond to lower doses, escalating the dose of milnacipran to 30 mg daily—provided this dosage is well-tolerated—may be beneficial.[66] The relative benefit of milnacipran compared to placebo was 1.3, resulting in a NNT of 8.6 for achieving moderate pain relief in adults with fibromyalgia.[67,68]

Norepinephrine-dopamine reuptake inhibitor

Bupropion, a relatively weak inhibitor of norepinephrine and dopamine reuptake, operates through a

Table II. Summary of risk ratios, number needed to treat (NNT), and NNT to harm for various medications

Medication	*Condition*	*Risk ratio (95% CI)*	*NNT (95% CI)*	*NNT to harm (95% CI)*	*Adverse Events*
Overall TCAs[40]	Neuropathic pain	2.1 (1.8-2.5)	3.6 (3-4.5)	6 (4.2-10.7)-28 (17.6-68.9)	Dry mouth, sedation, palpitations, nausea and sweating
Amitriptyline[40,47]	Neuropathic pain and fibromyalgia	2.3 (1.8-3.1)	4.6 (3.6-6.6)	6 (4.2-10.7)-28 (17.6-68.9)	Dry mouth, vomiting, drowsiness and weakness
Venlafaxine[40]	Neuropathic pain	2.2 (1.5-3.1)	3.1 (2.2-5.1)	9.6 (3.5-13)-16.2 (8-436)	Dry mouth, constipation, nausea, anorexia, weight changes, and vomiting
Duloxetine[60]	PDPN*	1.65 (1.34-2.03)	6 (5-10)	17 (12-50)	Difficulty sleeping, Headaches, blurred vision, and dry mouth
	Fibromyalgia	1.57 (1.20-2.06)-1.58 (1.10-2.27)	8 (5-17)	N/A	
Milancipran[68]	Neuropathic pain and fibromyalgia	1.39 (1.23-1.58)	8.6 (6.3-14)	11 (8.2-16)-13 (9.3-22)	Nausea, headache, constipation, hot flush and dizziness
Carbamazepine[88]	TN*, PDPN and central post stroke pain	6.1 (3.9-9.7)	1.7 (1.5-2.0)	2.6 (2.1-3.5)	Giddiness, dizziness, unsteadiness, and somnolence
Oxcarbazepine[94]	Neuropathic pain	1.57 (1.01-2.44)-1.91 (1.08-3.39)	6 (3-114)-6 (3-41)	17 (11-42)	Dizziness, headache, nausea, somnolence, fatigue, vomiting, diarrhoea, tremor, and skin rash
Valproate[102]	Neuropathic Pain	Absolute risk difference:0.161	6.2	N/A	Dry mouth, stomach pain, diarrhoea and tremors
Gabapentin[115]	PN*	1.6 (1.3-1.9)	8.0 (6.0-12)	Adverse event withdrawals: 31 (20-60)	Dizziness, somnolence, peripheral oedema, and gait disturbance
	PDPN	1.9 (1.5-2.3)	5.9 (4.6-8.3)		
Pregabalin[109]	PN	2.1 (1.6-2.6)-2.7 (2.0-3.5)	2.7 (2.2-3.7)-5.3 (3.9-8.1)	4.8 (3.9-6.2)-11 (7.8-19) at 300mg; 3.8 (3.2-4.9)-7.1 (5.3-11.0) at 600mg	Dry mouth, somnolence, dizziness, oedema, and weight gain
	PDPN	1.1 (1.01-1.20)-1.4 (1.2-1.7)	7.8 (5.4-14)-22 (12-200)	10 (8.6-13)-35 (22-82) at 300mg; 5.6 (4.8-6.7)-12 (9.2-19) at 600mg	
	Post−traumatic neuropathic pain	1.2 (1.1-1.4)-1.5 (1.2-1.9)	7.2 (5.4-11.0)-8.2 (5.7-15.0)	N/A	
	Central neuropathic pain	1.6 (1.3-2.0)-1.7 (1.2-2.3)	5.9 (4.1-11.0)-9.8 (6.0-28.0)		
Topiramate[102,123]	Neuropathic pain and fibromyalgia	N/A	7.4	5.4 (4.3-7.1)-8.6 (4.9-35.0)	Dizziness, drowsiness, cognitive impairment, and weight loss
Lidocaine patch[198]	PNPS*	N/A	4.4 (2.5−17.5)	N/A	Skin irritations
Capsaicin[207]	Neuropathic pain and Musculoskeletal pain	1.4 (1.2−1.7)-1.5 (1.1-2.0)	5.7 (4.0-10.0)-8.1 (4.6-34)	2.5 (2.1-3.1)-9.8 (7.3-15)	Application site (burning, stinging, erythema)
Botulinum[221,275]	Chronic neuropathic pain	N/A	3.03 (1.64−21.6)-3.70 (2.04−23.2)	3.2 (1.9-5.6)-9.5 (4.7-18.9)	Blepharoptosis, muscle paralysis, neck pain, neck stiffness, paresthesias and skin numbness

**PDPN*, painful diabetic peripheral neuropathy; *TN*, trigeminal neuralgia; PN, postherpetic neuralgia; *PNPS*, peripheral neuropathic pain syndrome.

different mechanism compared to TCAs and offers a potential alternative for patients who do not respond to TCAs.[69,70] Clinical trials have demonstrated that bupropion (administered at 150-300 mg daily, starting with 150 mg once daily for one week followed by 150 mg twice daily for 5-7 weeks, with a maximum daily dose of 450 mg) is effective and well-tolerated for treating neuropathic pain.[70-72]

Serotonin modulator and stimulator

Vortioxetine is classified as a serotonin modulator and stimulator and is also known as a multimodal antidepressant. This classification reflects its unique mechanism of action, which involves not only selective blockade of serotonin reuptake (by inhibiting the serotonin transporter [SERT]), similar to selective serotonin reuptake inhibitors, but also direct modulation of 5-HT receptors activity (such as 5-HT_3, 5-HT_7, 5-HT_{1D} and 5-HT_{1B}).[73] Specifically, vortioxetine acts as an agonist at the 5-HT_{1A} receptor, and an antagonist at the 5-HT_3 and 5-HT_7 receptors. These combined actions contribute to its efficacy in treating major depressive disorder.[74]

In a case study, vortioxetine (10 mg/day) was introduced alongside duloxetine and clonazepam therapy. Within two weeks, duloxetine and clonazepam were gradually tapered, and the dosage of vortioxetine was increased to 20 mg/day. This adjustment led to a complete resolution of BMS and significant relief from glossodynia.[75] Further evaluation through a randomized open-label trial compared the efficacy and tolerability of vortioxetine (15 mg/day) against other antidepressants for treating BMS. The results indicated that vortioxetine was effective, with a shorter latency of action and fewer adverse events compared to medications such as paroxetine, sertraline, escitalopram, and duloxetine.[76] An open-label, flexible-dose pilot study supported these findings, demonstrating that vortioxetine is both effective and well-tolerated as a first-line treatment for BMS due to its favorable receptor pharmacological profile. It is also considered a viable second-line option for patients who have only partially responded or experienced adverse effects from previous treatments.[77] Additionally, a review of chronic orofacial pain found that vortioxetine, at doses of 10-20 mg/day, was effective for both short—and long-term treatment. It showed a higher rate of clinical response and remission, superior acceptability, safety, and tolerability, along with a shorter latency of action compared to other antidepressants.[78]

ANTICONVULSANTS OR ANTIEPILEPTIC MEDICATIONS

Anticonvulsants, or antiepileptic medications, are widely used in managing headaches and orofacial pain. Based on their mechanisms of action, these drugs can be categorized into three groups: those that enhance GABA neurotransmission, those that block neuronal ion channels, and those with mechanisms of action that remain unclear.[79]

Carbamazepine and oxcarbazepine

Carbamazepine is extensively utilized for managing chronic orofacial pain, particularly in conditions like trigeminal neuralgia and postherpetic neuralgia.[80] Both carbamazepine and its keto analogue, oxcarbazepine, are believed to alleviate pain by inhibiting voltage-gated sodium channels. This inhibition decreases the excitability of nerve cells, thereby reducing the transmission of pain signals.[81] Carbamazepine (200−1200 mg/day) has been reported to decrease pain severity, the frequency of spontaneous paroxysms, and the number of triggers.[82,83] Due to enzyme saturation, it exhibits zero-order kinetics, so caution is necessary regarding toxicity at higher doses.[84] In clinical practice, carbamazepine is typically started at 100 mg once or twice daily, although some patients may require a higher initial dose. The dosage is gradually increased based on the patient's response and tolerance to avoid intolerable adverse effects. The usual maintenance dose is 200 mg three to four times daily, with some patients requiring up to 1.6 g daily.[85] Common adverse effects of carbamazepine include dry mouth, nausea, vomiting, swelling, lack of coordination, dizziness, drowsiness, and fatigue. Severe skin reactions have been noted in some cases, especially among individuals positive for the HLA-A31:01 or HLA-B15:02 alleles. Carbamazepine induces hepatic enzymes, which can lead to transient enzyme fluctuations in 25-61% of patients.[86] Due to these potential effects, baseline and regular blood tests should encompass full blood count, liver function tests, renal function tests, iron studies, and folic acid levels. Caution should also be raised with women on oral contraceptive, due to enzyme induction and interfering with contraception.[87] The NNT for carbamazepine to achieve significant relief from neuropathic pain is 1.7.[88]

Oxcarbazepine is a derivative of carbamazepine. Oxcarbazepine therapy typically begins at 150 mg twice daily, with increases of 300 mg every three days as tolerated until pain relief is achieved.[89] Maintenance doses usually range from 300 mg to 600 mg twice daily, with a maximum recommended total daily dose of 1800 mg.[90-92] Due to a cross-reactivity risk of approximately 25% with carbamazepine allergy, oxcarbazepine should be avoided if there is a known sensitivity to carbamazepine.[93] However, the Cochrane review in 2017 found limited evidence supporting oxcarbazepine's effectiveness in treating painful diabetic neuropathy, radiculopathy-related neuropathic

pain, and mixed neuropathies.[94] The NNT for oxcarbazepine to achieve significant relief from painful diabetic neuropathy is 6.0.[94,95]

Valproate

Valproate encompasses sodium valproate, valproic acid and divalproex sodium, commonly prescribed for treating seizures, acute manic episodes, and as a prophylactic for migraines. The mechanism of action of valproate remains unclear, but several potential pathways have been proposed based on its effects on neuronal signal transduction and enhances GABA neurogenesis.[96] These include inhibiting Ca^{2+}-independent protein kinase C (PKC)-ε and α activation induced by kainate seizures, enhancing cytosolic and membranous PKC activity, increasing DNA-binding affinity of activator protein 1 in a time—and concentration-dependent manner, down-regulating myristoylated alanine-rich C kinase substrates, a major substrate for PKC-ε, up-regulating growth-associated protein 43, promoting neuronal differentiation, and stimulating novel neurite outgrowth.[97] A clinical trial has showed that sodium valproate (between 600 and 2000 mg per day in two divided doses) appears to be an effective drug in the treatment of cluster headache.[98] The recommended daily dose of valproic acid for prophylactic treatment of migraine is 500 to 600 mg, aiming for a target serum level below 50 micrograms/mL.[99] The Cochrane review indicates that sodium valproate might alleviate pain in diabetic neuropathy, and divalproex sodium in postherpetic neuralgia. However, there is not enough evidence to recommend valproic acid or sodium valproate as the initial treatment for neuropathic pain.[100] Valproate is associated with an increased risk of neural tube defects during pregnancy and should be discontinued if a woman becomes pregnant. Consider avoiding its use in women of childbearing age, or ensure they are fully educated on the risks if its use is necessary.[101] The NNT for valproate to achieve significant relief from pain is 6.2.[102]

Gabapentinoids

Gabapentin is commonly used to treat neuropathic pain. Gabapentin does not exert its effects through direct GABAergic action, nor does it inhibit GABA uptake or metabolism. Instead, it blocks the tonic phase of nociception triggered by formalin and carrageenanoreover, gabapentin demonstrates a robust inhibitory effect in models of neuropathic pain, effectively reducing mechanical hyperalgesia and both mechanical and thermal allodynia.[103] Research on burning mouth syndrome found the best outcomes with a study combining alpha lipoic acid and gabapentin 300 mg.[104] Another randomized controlled trial explored gabapentin combined with ropivacaine for managing trigeminal neuralgia.[105] Based on current evidence, initiating treatment at a dose of 900 mg/day (300 mg/day on day 1, 600 mg/day on day 2, and 900 mg/day thereafter) is recommended.[106] According to a Cochrane review, doses of gabapentin ranging from 1800 mg to 3600 mg daily (or 1200 mg to 3600 mg of gabapentin encarbil) can effectively alleviate pain in individuals with postherpetic neuralgia and peripheral diabetic neuropathy.[107]

Pregabalin has demonstrated effectiveness in treating postherpetic neuralgia, painful diabetic neuropathy, and mixed or unclassified post-traumatic neuropathic pain. However, study indicates that pregabalin is not effective for HIV-related neuropathy.[108] Evidence supporting its efficacy in central neuropathic pain remains insufficient.[109] The recommended dosage for pregabalin starts at 75 mg twice daily. If needed, this can be increased to 150 mg twice daily after 3-7 days. If further adjustment is required, the dosage can be increased to a maximum of 300 mg twice daily after an additional 7 days.[110] The common adverse effects of gabapentin and pregabalin are somnolence, dizziness, confusion and fatigue.[111] In high doses Gabapentin and pregabalin is suggested to cause cognitive and other neuropsychiatric effects.[112] Gabapentinoids, including medications like gabapentin and pregabalin, are widely recognized for their safety and efficacy when used according to prescribed guidelines. However, emerging evidence indicates a concerning trend: these medications may have potential for abuse, particularly among individuals with a history of substance abuse, including opioid use disorder.[113] Reports of misuse and addiction involving gabapentinoids are becoming more frequent, suggesting that their abuse potential should not be underestimated.[114] Healthcare providers must remain vigilant, especially when prescribing these drugs to high-risk populations, and should closely monitor patients for any signs of misuse or dependency. The NNT for a significant improvement in neuropathic pain is 1.6-1.9 for gabapentin[115] and 2.7-7.8 for pregabalin,[109] indicating that fewer patients need to be treated with pregabalin to achieve a meaningful reduction in pain compared to gabapentin.[49]

Topiramate

Topiramate is an antiepileptic drug with multiple possible mechanisms of action. The anticonvulsant effects of topiramate may primarily stem from its inhibition of GluR5 kainate receptors.[116] Additionally, topiramate reduces membrane depolarization through its action on AMPA/Kainate receptors and enhances the activity of GABA-A receptors, thereby increasing inhibitory effects.[117] Its effectiveness in treating migraines is thought to be from its inhibitory impact on AMPA and kainate subtypes of glutamate receptors and, to a lesser

degree, on voltage-gated calcium channels.[118,119] Furthermore, topiramate inhibits the release of CGRP and glutamate from trigeminal neurovascular nerve endings, which disrupts cortical spreading depression.[120,121] This dual action underscores its efficacy in managing both epilepsy and migraines. For individuals experiencing frequent episodic migraines, topiramate may help prevent the progression to chronic migraine[122] Topiramate doses can be increased up to 200 mg/day or 400 mg/day. However, there is no compelling evidence that topiramate at these doses is more effective than a placebo.[123] For migraine prophylaxis, the initial recommended dose is 25 mg once at night for 1 week. This can be increased in 25 mg increments daily at 1-week intervals. The usual dose is 50-100 mg daily, divided into two doses, with a maximum of 200 mg daily.[124] The first-line treatment for trigeminal neuralgia is carbamazepine, but switching to or adding topiramate at a dosage of 100-400 mg per day may also be an option.[89] The most commonly reported adverse effects of topiramate include dizziness, drowsiness, cognitive impairment, and weight loss.[89] The NNT for topiramate to achieve significant relief from pain is 7.4.[102]

Lamotrigine

Lamotrigine is prescribed for epilepsy and managing mood disorders such as bipolar disorder. While its exact mechanism of action is not fully understood, it is believed that lamotrigine selectively binds to and inhibits voltage-gated sodium or calcium channels.[125,126] This action stabilizes presynaptic neuronal membranes and reduces the release of presynaptic glutamate and aspartate.[127] Clinical trials indicated that lamotrigine, administered at doses of 300 to 400 mg daily, was inconsistently effective for managing pain associated with diabetic neuropathy.[128,129] For trigeminal neuralgia, the initial dosage is typically 25 mg twice daily, which can be gradually increased to a maintenance dose of 200 to 400 mg per day, divided into two doses.[90] However, there was no strong evidence supporting the efficacy of lamotrigine for treating neuropathic pain and fibromyalgia within this dosage range. Furthermore, nearly 10% of participants reported experiencing a skin rash as an adverse effect of lamotrigine.[130] Rapid titration of lamotrigine increases the risk of Stevens-Johnson Syndrome. The recommended titration rate is 25 mg twice daily for two weeks, followed by biweekly dose increases.

MUSCLE RELAXANTS

Baclofen

Baclofen is classified as a muscle relaxant and is specifically recognized as a gamma-aminobutyric acid (GABA) agonist.[131] It primarily functions as a GABA-B receptor agonist, which helps modulate neuronal activity by enhancing the inhibitory effects of GABA in the central nervous system.[132] Baclofen is widely utilized to manage spasticity associated with various neurological conditions, including multiple sclerosis, cerebral palsy, spinal cord injury, and other spinal cord pathologies.[133-135] Experiments conducted with cats revealed that baclofen, similar to carbamazepine and phenytoin sodium, effectively depresses excitatory synaptic transmission in the spinal trigeminal nucleus.[136] A double-blind crossover study was conducted to assess the effects of baclofen in ten patients with typical trigeminal neuralgia. The results demonstrated that baclofen significantly reduced the number of painful paroxysms in seven out of the ten patients.[137] These findings suggest that baclofen may be considered a secondary-line treatment option for managing trigeminal neuralgia.[138]

Cyclobenzaprine

Cyclobenzaprine is a centrally acting tricyclic dimethylpropanamine muscle relaxant widely used to alleviate muscle spasms, hypercontractility, and acute musculoskeletal pain, including conditions such as acute back or neck pain.[139,140] The exact mechanism of action remains unclear, but it is believed to reduce tonic somatic motor activity by modulating both gamma and alpha motor neurons in the brainstem. This modulation is thought to involve noradrenergic coeruleus−spinal or reticulospinal pathways, resulting in the relief of muscle spasms.[141] Cyclobenzaprine also acts as a 5-HT_2 receptor antagonist, with evidence suggesting that its muscle relaxant effects are primarily mediated through the inhibition of serotonergic rather than noradrenergic descending pathways in the spinal cord.[142] Structurally similar to tricyclic antidepressants, cyclobenzaprine may also exhibit mild anticholinergic and sedative effects.[143] Several case studies and clinical trials have demonstrated the efficacy of cyclobenzaprine in managing orofacial pain, including paroxysmal hemifacial pain and TMD.[144-146] However, a Cochrane review concluded that the evidence is insufficient to support its use in the treatment of myofascial pain.[147]

Benzodiazepines

Clonazepam, a benzodiazepines with anticonvulsant and anxiolytic properties, functions as a positive allosteric modulator of GABA-A receptors, enhancing the effects of the neurotransmitter GABA.[148] Despite these pharmacological actions, a Cochrane review found no high-quality evidence to support the use of clonazepam for chronic neuropathic pain.[149] Nonetheless, topical clonazepam is currently under investigation as a potential treatment for burning mouth syndrome.[150,151]

Sucking on a 1 mg clonazepam tablet without swallowing, three times daily for 14 days, alleviated pain symptoms of burning mouth.[152] Furthermore, a retrospective study has demonstrated that combining topical and systemic clonazepam administration can be an effective approach for managing BMS.[153] Adverse effects may include drowsiness, somnolence, hypersalivation, and dizziness. Clonazepam could be discontinued without significant withdrawal symptoms if the dose is gradually reduced.[154] While clonazepam is highly effective in treating BMS, it carries a risk of abuse due to its potential for dependence and addiction. As with other benzodiazepines, long-term use or misuse can lead to tolerance, physical dependence, and withdrawal symptoms upon cessation.[155] Its sedative properties may appeal to individuals self-medicating for anxiety or stress, increasing the risk of misuse.[156] Clinicians should monitor patients closely, prescribe the lowest effective dose, and explore nonbenzodiazepine alternatives when feasible to reduce these risks.

ANTIHYPERTENSIVES

Propranolol

Propranolol is a noncardio selective β-blocker that could be used in migraine prophylaxis (80-240 mg daily in divided doses). The exact mechanisms underlying propranolol's antimigraine effects remain unclear. However, it is known to exert its preventive action, at least partially, by inhibiting the central sensitization of descending pain control pathways that originate from the rostral ventromedial medulla and locus coeruleus. This inhibition helps prevent the prolonged facilitation of trigeminovascular transmission within the trigeminocervical complex, thereby reducing migraine occurrence and severity.[157] Currently, propranolol has been investigated as a novel drug for management of TMD—associated pain.[158,159] Propranolol was found to be more effective in alleviating TMD pain in individuals with migraines compared to those without. For TMD treatment, the initial dose was set at 60 mg daily, which was increased to 120 mg and maintained for eight weeks before tapering back down to 60 mg daily. This effect was largely due to the reduction in heart rate rather than the decrease in headache severity.[160] A recent study showed that a single dose of propranolol before extinction learning eliminated conditioned fear responses, prevented the return of fear, and decreased explicit memory of the fearful events without the drug. This effect involved brain regions such as the amygdala, midbrain, dorsomedial prefrontal cortex, ventromedial prefrontal cortex, hippocampus, and insula.[161] Common adverse effects may include gastro-intestinal disturbances, bradycardia, heart failure, hypotension, conduction disorders, coldness of the extremities, exacerbation of asthma, and peripheral vasoconstriction.

Verapamil

Verapamil functions as a calcium channel antagonist and has been utilized to treat both cluster headaches and migraines. The specific mechanisms through which verapamil impacts orofacial pain are not well understood. In the case of cluster headaches, verapamil is believed to exert its effects primarily within the hypothalamus.[162,163] Typically prescribed at doses ranging from 360 to 480 mg daily, verapamil effectively reduces the frequency of attacks during a cluster headache episode.[164] The dosages used for migraine prophylaxis typically range from 240 mg/day to 320 mg/day, with 320 mg/day proving more effective in reducing the frequency of migraines.[165,166] The most frequently reported noncardiac adverse effect is constipation.

CALCITONIN GENE-RELATED PEPTIDE BIOLOGICS

CGRP, a 37-amino-acid neuropeptide, plays a crucial role in modulating orofacial pain.[167] Recent research has expanded the potential therapeutic targets of CGRP to include chronic visceral pain, the enteric nervous system, ischemic cardiovascular events, opioid tolerance and withdrawal, and lung inflammation associated with COVID-19 infections.[168-170] In mice pretreated with MK-8825, a CGRP antagonist, there is a significant reduction in spontaneous orofacial pain behaviors. These findings suggest that CGRP may contribute to the pathophysiology of TMD, though not through inflammatory mechanisms during the acute phase.[171] Additionally, a meta-analysis indicates that CGRP antagonists are more effective than placebo for acute migraine.[172] Erenumab, a CGRP monoclonal antibody, shows promise as a treatment for patients with refractory trigeminal neuralgia.[173] However, additional research is needed to establish CGRP antagonists as a standard first-line treatment for orofacial pain.

OPIOID ANALGESICS

Tapentadol is a novel, centrally acting analgesic classified as an opioid analgesic. It combines mu-opioid receptor agonism with noradrenaline reuptake inhibition, offering both opioid and nonopioid mechanisms to manage moderate to severe pain.[174] This dual mechanism distinguishes it from traditional opioids like morphine or oxycodone, while also improving its side effect profile compared to opioids and nonsteroidal anti-inflammatory drugs. Tapentadol's unique action makes it particularly effective in treating acute, chronic, and neuropathic pain.[175]

A review of clinical studies demonstrated that tapentadol significantly reduced neuropathic pain in conditions such as chemotherapy-induced peripheral neuropathies, blood and solid cancers, as well as in the neuropathic component of neck pain and Parkinson's disease.[176] Clinical trials also highlighted its favorable safety profile, showing no evidence of acquired tolerance in long-term use. Overall, tapentadol is considered an effective and generally well-tolerated alternative to classical opioids.[177] Tapentadol has also shown antinociceptive effects in experimental models of orofacial pain, and case reports suggest it may be efficient and well-tolerated in managing trigeminal neuralgia.[178,179] However, further research is necessary to determine which individuals with chronic orofacial pain would benefit most from this promising new opioid.

OPIOID RECEPTOR ANTAGONIST

Naltrexone, a nonselective opioid receptor antagonist, is primarily used to treat opioid and alcohol dependence. In addition to its role in addiction management, low-dose naltrexone has been shown to modulate neuroinflammation, enhance the analgesic effects of opioids, and exhibit opioid-sparing properties. Notably, its antinociceptive effects have been observed in the management of postoperative orofacial pain, highlighting its potential in pain control beyond its traditional applications.[180] Research also indicates that low-dose naltrexone can reverse facial mechanical allodynia in a rat model of trigeminal neuralgia.[181] Case reports further suggest it may be a feasible and effective treatment for BMS, particularly in patients unresponsive to traditional therapies.[182,183] A systematic review has concluded that low-dose naltrexone may offer an additional option for managing orofacial pain conditions, which share characteristics with other chronic pain disorders.[184]

TRIPTANS

Triptans are selective agonists of 5-$HT_{1B/1D}$ receptors located at trigeminal vasculature. The mechanism of action in orofacial pain pathophysiology involving 5-HT1B/1D receptors includes vasoconstriction of dilated cerebral blood vessels, which contribute to pain, suppression of vasoactive neuropeptide release (calcitonin gene-related peptide and substance P) by trigeminal nerves, and inhibition of nociceptive neurotransmission.[185]

NSAID

NSAIDs such as ibuprofen, diclofenac, naproxen, and indomethacin are widely utilized in the management of orofacial pain, particularly for conditions with inflammatory or vascular origins.[186] Among these, indomethacin stands out for its exceptional efficacy in treating paroxysmal hemicrania and hemicrania continua, both classified as rare indomethacin-sensitive trigeminal autonomic cephalalgias. This unique responsiveness to indomethacin serves as a diagnostic criterion for these conditions, setting it apart from other NSAIDs.[187] Although the exact mechanism of action of indomethacin in these disorders is not entirely understood, it is believed to involve several pathways. These may include the inhibition of cyclooxygenase enzymes, which reduces prostaglandin synthesis, thereby mitigating pain and inflammation.[188] Additionally, indomethacin appears to inhibit nitric oxide-induced vasodilation and suppress trigeminal activity, effects that are notably absent in other NSAIDs like naproxen and ibuprofen.[189,190] Furthermore, indomethacin is thought to modulate vascular and neurogenic inflammation, which plays a central role in the pathophysiology of indomethacin-sensitive trigeminal autonomic cephalalgias.[191] The NNT for indomethacin in the indomethacin-sensitive trigeminal autonomic cephalalgias is not widely reported in clinical trials, likely due to the rarity of these disorders.

TOPICALS

Anaesthetics

Topical anesthetics are routinely used in dentistry. The 5% lidocaine patch is approved for treating specific neuropathic pain conditions, notably postherpetic neuralgia.[192] Case series indicate that using 5% lidocaine patches could be beneficial in managing chronic trigeminal pain.[193] These patches have been explored both as monotherapy and in combination with capsaicin for treating conditions like burning mouth syndrome and persistent idiopathic dentoalveolar pain.[194-197] The calculated NNT to achieve more than 50% pain relief with a 5% lidocaine patch is 4.4.[198]

Capsaicin

Capsaicin, the active component in chili peppers, induces intense burning pain in humans. Topical application of capsaicin results in sensations of heat, burning, stinging, or itching. The mechanisms behind capsaicin-induced desensitization are not fully understood. However, evidence suggests that this process involves the depletion of neuropeptides, such as substance P, in nerve fibers expressing the transient receptor potential cation channel subfamily V member 1 (TRPV1). Additionally, capsaicin increases intracellular calcium levels by inhibiting both high voltage-activated (HVA) and low voltage-activated (T-type) calcium channels.[199] Topical creams with capsaicin at either high (8%) or low (<1%) concentration are used to treat peripheral neuropathic pain. High-concentration topical capsaicin proved more effective in providing

moderate to substantial pain relief for individuals with postherpetic neuralgia, HIV neuropathy, and painful diabetic neuropathy compared to those using a lower concentration. In contrast, the data available for low-concentration capsaicin cream were inadequate to determine its effectiveness for treating neuropathic pain.[200,201] Clinical trials have demonstrated that topical capsaicin can be effective in alleviating the discomfort associated with burning mouth syndrome.[202] In particular, low doses of capsaicin (0.025%) applied to the painful areas three to four times a day provide rapid pain relief for those with this condition.[203,204] While systemic capsaicin (0.25%) has also shown short-term therapeutic benefits, its widespread and long-term use is limited by significant gastrointestinal adverse effects.[205] Topical capsaicin has been studied for treating persistent idiopathic dentoalveolar pain. EMLA cream achieved an average pain reduction of 60% in 38 patients (range 0%-100%), while 0.025% capsaicin ointment resulted in an average pain reduction of 50% in approximately 60% of patients, with follow-up assessments conducted at least three months later.[206] The relative benefit of topical capsaicin 0.025% or plaster compared to placebo was 1.5, with a NNT of 8.1.[207]

Topical compounded medications have emerged as a valuable option for managing neuropathic orofacial pain, particularly in patients using neurosensory stents. These compounds are custom formulated to address specific pain pathways and provide localized relief. For instance, formulations combining local anesthetics such as lidocaine or benzocaine with neuroleptics such as gabapentin or pregabalin could offer targeted pain management.[208] Clinical studies indicate that these compounded topicals could significantly reduce pain symptoms in conditions such as BMS and persistent idiopathic dentoalveolar pain. The integration of these medications into neurosensory stents could enhance their effectiveness by providing continuous, localized drug delivery, which may improve patient outcomes and reduce systemic side effects.

BOTULINUM TOXIN TYPE A (BONT-A)

Botulinum toxin is the most powerful of the neurotoxins, causing paralysis by temporarily blocking the release of acetylcholine at the neuromuscular junction. This leads to a reversible chemical denervation of the muscle fibers, resulting in partial paralysis and atrophy.[209,210] In dentistry, several studies have established the effectiveness of botulinum toxin in treating various conditions, including bruxism, hyperkinesis, synkinesis and facial imbalance due to facial palsy, TMD, neuropathic pain, sialorrhea with Parkinson's disease, and dystonia.[211-216] For example, a randomized, double-blind, placebo-controlled clinical trial evaluated the efficacy of BoNT-A in patients with refractory masticatory myofascial pain. The study concluded that a single session of BoNT-A injections significantly reduces pain and enhances psychosocial outcomes in these patients.[217] However, publications that explore the use of botulinum toxin for treating various orofacial neuropathic pain conditions, such as burning mouth syndrome, post-traumatic trigeminal neuropathic pain, persistent idiopathic facial pain, and dentoalveolar pain, are limited. Additionally, the evidence supporting botulinum toxin injections for conditions potentially linked to short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA), is of low quality.[218,219] There is a clear need for further research beyond case reports to generate high-quality evidence on the effectiveness of botulinum toxin for these conditions, as such evidence is currently lacking. The limited number of studies and participants may be attributed to the high cost of botulinum toxin and its "off-label" use for managing neuropathic disorders.[220] The NNT for 50% pain relief is 3.03 at 12 weeks.[221]

CANNABINOIDS

Cannabinoids are a class of chemical compounds found in the cannabis plant, Cannabis sativa, with over 100 different cannabinoids have been identified.[222,223] The two primary cannabinoids are THC and cannabidiol CBD. THC is known for its psychoactive effects and is responsible for the euphoric sensations often associated with cannabis use. In contrast, CBD has minimal to no psychoactive properties.[224] The CB1 and CB2 are part of the G-protein-coupled receptor superfamily. CB1 receptors are predominantly found in the frontal cortex, hippocampus, basal ganglia, hypothalamus, cerebellum, spinal cord, and peripheral nervous system, while CB2 receptors are mainly located in the peripheral immune system, hematopoietic cells, and within the central nervous system, specifically in the hippocampal CA2/3 pyramidal neurons and glial cells.[225] Endocannabinoids are synthesized in postsynaptic terminals but exert their effects on presynaptic terminals.[226] THC acts on both CB1 and CB2 receptors, while CBD primarily targets CB1 receptors. CB2 receptors, found in immune cells, suggest a potential role in modulating inflammation.[227] Several studies have examined the use of cannabinoid products for managing orofacial pain.[228] Among these, only one report indicated a positive effect in alleviating orofacial pain.[229] This suggests that while there is some potential for cannabinoids in pain management, the overall evidence remains limited and further research is necessary to

confirm their efficacy in treating orofacial pain conditions.

When evaluating the effectiveness of systemic and topical medications for orofacial pain, it is important to consider the placebo and nocebo effects, especially given the limited scientific evidence and high NNT for many of these therapies. The placebo effect occurs when patients experience symptom relief due to their belief in the efficacy of a treatment rather than the treatment itself. This could influence both systemic medications (such as antidepressants and anticonvulsants) and topical treatments (including compounded formulations) for orofacial pain, complicating the assessment of a medication's true effectiveness. Conversely, the nocebo effect involves worsened symptoms or adverse effects due to negative expectations about a treatment. This may also affect systemic and topical therapies, potentially skewing results and impacting perceived efficacy. To accurately evaluate treatment effectiveness, robust, double-blind, placebo-controlled studies are essential to differentiate genuine therapeutic benefits from psychological influences.

CONCLUSION

The management of orofacial pain requires a nuanced understanding of its complex pathophysiology, often compounded by psychological comorbidities. Given this complexity, a personalized and cautious approach to treatment is essential. Topical medications, due to their lower risk of systemic side effects, should be considered as a first-line option whenever feasible. However, clinicians must be aware that the evidence supporting the efficacy of certain medications remains limited. Additionally, the potential adverse effects, costs, and long-term implications of treatment must be carefully weighed against the anticipated therapeutic benefits. A comprehensive evaluation of these factors is vital to ensuring that the chosen treatment maximizes patient outcomes, prioritizing efficacy, safety, and cost-effectiveness.

DECLARATION OF INTERESTS

None.

DATA AVAILABILITY STATEMENT

All data have been presented in the article.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Guangzhao Guan: Writing – review & editing, Writing – original draft, Supervision, Software, Formal analysis, Data curation, Conceptualization. **Athula K. Polonowita:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Li Mei:** Writing – review & editing, Visualization, Validation, Software, Resources, Project administration. **Devinda A. Polonowita:** Writing – review & editing, Visualization, Resources, Project administration. **Ajith D. Polonowita:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Formal analysis, Conceptualization.

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