

Orofacial neuropathic pain: a pharmacological approach

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Abstract

Orofacial neuropathic pain is a medical condition that arises due to somatosensory nervous system injury or disease in the orofacial region. Multiple types of orofacial neuropathic pain have been identified, such as nonodontogenic neuropathic orofacial pain, trigeminal neuralgia, postherpetic neuralgia, atypical odontalgia and glossopharyngeal neuralgia. To date, pharmacological intervention is considered the cornerstone in the management of neuropathic pain. Drugs from different classes including anticonvulsants, antidepressants, opioids, nonsteroidal anti-inflammatory drugs and others are commonly used in the treatment of neuropathy. Nevertheless, the majority of these drugs are yet to be approved by the food and drug administration for neuropathy. This review will explore recent clinical findings and pieces of evidence regarding medical agents used in the management of orofacial neuropathic pain and will discuss their efficacy and mode of action, at the same time highlighting a number of promising therapeutic options.

Keywords: orofacial neuropathic pain, neuropathy, facial pain, pharmacological management

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Introduction

Neuropathic pain can be defined as pain caused by a disease or injury of the somatosensory nervous system.¹ Orofacial neuropathic pain is a term used to describe a number of clinical conditions that may be either spontaneous or initiated by local damage or systemic disorders, thereby complicating its differential diagnosis.² Generally, orofacial pain can be classified, by its major underlying cause, into three main classes: somatic, neuropathic and psychological.³ Various identified disorders can trigger orofacial pain including: pulpal diseases, periodontal diseases, burning mouth syndrome, mouth ulcers, headaches, Eagle's syndrome, temporomandibular joint dysfunction, oral tumours and neuropathy.^{4,6} Post-stroke pain, trigeminal neuralgia, postherpetic neuralgia and painful polyneuropathy, are all examples of neuropathic pain.⁷ Orofacial neuropathic pain can be either persistent or episodic and other characteristic symptoms may vary considerably according to the underlying cause.⁸ Therefore, differential diagnosis and early identification of orofacial neuropathic pain are vital in order to avoid unnecessary dental procedures since dentists rarely address neuropathic pain as a potential cause of orofacial pain.⁹ While the pathophysiological mechanisms underpinning orofacial neuropathic pain are not fully understood, it is believed to share a number of features with other peripheral neuropathies.⁹ Nerve conduction test (NCS) and electromyography (EMG) are used by neurologists to confirm neuropathy; moreover, magnetic resonance imaging (MRI), positron emission tomography (PET) and computed tomography

(CT) scan are other techniques used to identify/exclude any potential underlying causes.¹⁰ A number of orofacial neuropathic pain disorders in relation to the nerves affected and the underlying causes have been identified; nonodontogenic neuropathic orofacial pain, trigeminal neuralgia, herpes zoster and postherpetic neuralgia, atypical odontalgia and glossopharyngeal neuralgia.¹¹ The management of orofacial pain requires a multidisciplinary approach which involves pharmacological, physiological and psychological therapy.¹² Pharmacological treatment is considered the central player in the control of orofacial neuropathic pain. Clinical guidelines have recommended the use of certain medical agents; however, only a few of them are approved by the food and drug administration (FDA) for the management of neuropathic pain. Pharmacological options available for the treatment of orofacial neuropathic pain are quite similar to the drugs used to treat neuropathic pain associated with other medical conditions, for instance, neuropathy developed in patients with diabetes, multiple sclerosis and cancer.^{13,14} This review will discuss the latest clinical findings and scientific evidence regarding the use of a number of medical agents from various pharmacological classes in the management of orofacial neuropathic pain.

Anticonvulsants

Clinical investigations have shown that the use of a number of anticonvulsants is beneficial in controlling neuropathic pain. Anticonvulsants' mechanism of action in reducing neuronal hyperexcitation may explain their role in the management of

neuropathic pain.¹⁵ Carbamazepine and oxcarbazepine use is well-recommended in the treatment of neuropathic pain; their mode of action is suggested to be via the blockade of sodium ion channels.¹⁶ According to evidence-based trials, medical guidelines have recommended the administration of (200–1200 mg/day) and (600–1800 mg/day) of carbamazepine and oxcarbazepine respectively for the management of neuropathic orofacial pain of trigeminal neuralgia.¹⁷ Pregabalin and gabapentin are also found to be effective in relieving pain associated with neuropathy via the inhibition of voltage-gated calcium channels.¹⁸ At present, pregabalin is the only anticonvulsant agent approved by the FDA for the treatment of neuropathic pain, which was approved in June 2012, as clinical trials have generated sufficient evidence to support its use.¹⁹ In an open-label study on patients suffering from trigeminal neuralgia, pregabalin dosage of (150–600 mg/day) over a period of eight weeks has produced long-lasting pain relief and reduced pain severity in the majority of cases.²⁰ Furthermore, in postherpetic neuralgia, pregabalin (300–600 mg/day) was found to be effective in reducing associated neuropathic pain.²¹ Pregabalin and gabapentin are also suggested to be effective in atypical odontalgia and cancer neuropathic pain.^{22,23} Lamotrigine is another anticonvulsant used in neuropathic pain, with a mode of action similar to carbamazepine (i.e. inhibits sodium ion channels). Lamotrigine is usually considered as a second-line option in the management of neuropathic pain.²⁴ Its indications include glossopharyngeal neuralgia and trigeminal neuralgia.²⁵ Lamotrigine administration starts with an initial dose of 25 mg/day, further increased to 200–400 mg/day.²⁶ Topiramate plays a role in neuropathic pain through inhibiting sodium ion channels, augmenting gamma-aminobutyric acid (GABA) activity, reducing glutamate transmission and inhibiting carbonic anhydrase enzyme.²⁷ Topiramate is found to be effective in the management of trigeminal neuralgia secondary to multiple sclerosis.²⁸ Presently, recent clinical research findings and medical guidelines suggest the use of a combination of multiple anticonvulsants or with other pharmacological classes rather than monotherapy, which might be insufficient in pain control.²⁹

Antidepressants

Antidepressants have been observed to exert an analgesic-like effect with established efficacy in the relief of chronic pain, especially with the use of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors.³⁰ Pain is frequently found as a symptom of depression and vice versa, as patients with chronic pain have a high risk of developing depression. These findings support the claims that depression and pain may share a number of pathophysiological and biochemical mechanisms.³¹ The exact mechanism of pain and the role of antidepressants are not clear; however, a theory suggests that pain and depression occur as a result of negative neuroplastic alterations in the central nervous system; thus, antidepressants' positive mechanism in modulating such negative molecular changes may explain their role in symptomatic amelioration of chronic pain.³² In orofacial neuropathic pain cases of trigeminal neuralgia, geniculate neuralgia (also known as

intermediate nerve neuralgia), persistent idiopathic facial pain and burning mouth syndrome, the use of antidepressants is recommended.³³ TCAs are considered first-line pharmacological therapies for neuropathic pain and are frequently administered in combination with other classes, such as anticonvulsants.³⁴ The mechanism of action of TCAs is through inhibiting the activity of serotonin and norepinephrine transporters, which in turn elevates their concentration in the synaptic cleft and potentiates their effects.³⁵ A recent experimental study in a rat model suggests that TCAs' modulation of neuropathic pain may be mediated, not only by serotonin and norepinephrine, but also via affecting dopamine levels.³⁶ Examples of TCAs used in the management of neuropathic pain include amitriptyline, nortriptyline, imipramine, clomipramine and desipramine.³⁷ Nonetheless, poor patient tolerability to TCAs is due to their unpleasant side-effects that are mainly related to their anti-muscarinic activity; for instance, dry mouth, blurred vision, constipation, urinary retention, weight gain, impaired cognitive functions, confusion, dizziness and many other adverse events.³⁸ Therefore, it is recommended to consider other alternative treatment options when TCAs are intolerable. Serotonin-norepinephrine reuptake inhibitors (SNRIs), the mechanism of which is quite similar to TCAs, have also been observed to be efficacious in the management of neuropathic pain. Clinical trials on patients with neuropathic pain support the use of venlafaxine and duloxetine in the treatment of neuropathic pain. In a randomised double-blind clinical trial, the administration of venlafaxine (150–255 mg/day) was able to achieve over 50% reduction in pain intensity.³⁹ Moreover, duloxetine (60–120 mg/day) was found to be effective in treating both neuropathic and chronic pain with minimal side-effects reported at lower doses i.e. 60 mg/day.⁴⁰ However, newer pharmacological investigations have revealed that the mode of action of SNRIs regarding their analgesic properties is mainly related to the norepinephrine reuptake inhibition, while serotonin only plays a minimal role.⁴¹ Therefore, these findings may provide a reasonable theory behind the low efficacy of selective serotonin reuptake inhibitors in the management of neuropathic pain.⁴²

Nonsteroidal anti-inflammatory drugs

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) in the management of neuropathic pain is controversial and their efficacy is debatable. A vast number of views state that the use of NSAIDs in neuropathic pain is unnecessary and insinuate that NSAIDs are ineffective in pain relief. In addition, various medical guidelines have even neglected NSAIDs in the proposed management protocols of neuropathic pain.⁴³ In clinical trials, different results and conclusions are observed regarding the use of NSAIDs, as many are backing their use and many others are against it.^{44,45} Other opinions took a stand in between, suggesting that NSAIDs can be effective only in certain types of neuropathic pain (e.g. diabetic neuropathy) and point out that their use is associated with many undesirable side-effects.⁴⁶ However, all these claims cannot deny the fact that NSAIDs are widely prescribed for patients with neuropathic pain.⁴⁷ The rationale behind the use

of NSAIDs in the management of neuropathic pain is still vague due to the lack of sufficient knowledge about their mechanisms on the molecular level in order to find a sensible link between NSAIDs mode of action and neuropathic pain pathophysiology. Nevertheless, a study was conducted to investigate the potential role of prostaglandin- E_2 , a known pro-inflammatory mediator, in the activation of spinal microglia in relation to neuropathic pain. The study has suggested that *in vivo* prostaglandin- E_2 plays a role in the maintenance of neuropathic pain by activating spinal neurons and retaining microglia in the central terminals of primary afferent fibres.⁴⁸ Furthermore, some clinical findings suggest that targeting cyclooxygenase-2/prostaglandin- E_2 /EP signalling pathway via local administration of NSAIDs seems a promising approach in the treatment of neuropathic pain caused by nerve injury.⁴⁹ Prostaglandin- I_2 (prostacyclin) has also been linked to the development of neuropathic pain in post-traumatic nerve injury, in which early synthesis of prostacyclin has been observed to elevate the accumulation of interleukin 1β -expressing resident macrophages at the site of injury.⁵⁰ Early and continuous administration of meloxicam was observed to lower pain and reduce macrophages count.⁵⁰ While these findings may, to some extent, illustrate the potential of NSAIDs in the management of neuropathic pain in post-traumatic cases, it can still be argued that patients with mixed type pain (i.e. nociceptive and neuropathic) may only partially benefit from the use of NSAIDs; nonetheless, in solely neuropathic pain cases the use of NSAIDs is still questionable. Ultimately, further clinical investigations should be undertaken in order to confirm these claims and explain why there is a significant variation among the efficacy of different NSAIDs in the management of neuropathic pain and if the pathophysiological mechanisms of neuropathic pain differ according to the underlying cause or injured nerves.

Opioids

Opioids illustrated some clinical efficacy in the management of chronic orofacial pain and other forms of long-term neuropathic pain.⁵¹ Examples of opioids used for long-term treatment of neuropathic pain include morphine, methadone, oxycodone, levorphanol, fentanyl patches and oxymorphone.⁵¹ Clinical studies have reported the common occurrence of minor side-effects with the short/intermediate use of opioids, for instance, nausea, vomiting, constipation, drowsiness and dizziness.⁵² In contrast, long-term use of opioids may raise a number of serious issues, such as major adverse events (e.g. respiratory depression) and elevated risk of addiction.^{53,54} Tramadol, another opiate derivative, has been widely prescribed for neuropathy; nonetheless, its long-term effects in neuropathic pain are still poorly studied.⁵⁵ Adverse events associated with opioid use are mainly contributed to their agnostic activity on the μ -opioid receptor; in addition, opioids with higher risk of addiction and abuse are found to possess elevated affinity to μ -receptor.⁵⁶ However, newer approaches are emerging in developing novel agents that may have the efficacy of the classical opioid therapies with lesser side-effects. Biased μ -receptor ligands are suggested to have a potential in pain

management with a much lower risk of developing unpleasant side-effects, as they have the ability to activate and modulate differentially specific downstream signalling pathways.⁵⁷ Other examples include developing novel medical agents that target the delta-opioid receptors, as experimental investigations have revealed that delta-opioid receptors activity is superior to other subtypes of opioid receptors in modulating neuropathic pain.⁵⁸ In addition, novel agents targeting the delta-opioid receptors are suggested to have a finer safety profile with a lower incidence of major side-effects.⁵⁹

Topical therapies

Topical treatments for orofacial neuropathic pain may have the advantage of lesser adverse events compared to systemic drugs. Topical treatments are also observed to have a rapid onset of action and the ability to exert pain relief in orofacial neuropathy, especially in superficial pain.⁶⁰ Capsaicin, a pungent compound derived from capsicum, has been widely used as a topical agent for analgesia. Its mode of action in pain management is achieved through the activation of the transient receptor potential cation channel subfamily V member 1 (TrpV1) via pH changes, heat and alterations in endogenous lipids, which will eventually lead to neuronal depolarisation.⁶¹ In 2009, Capsaicin 8% transdermal patches were approved by the FDA for postherpetic neuralgia.⁶² In placebo-controlled trials, capsaicin has been observed to be efficacious in the management of diabetic and post-surgical neuropathy.⁶³ Side-effects of capsaicin include burning/stinging sensation, erythema, respiratory irritation (i.e. if inhaled) and transient elevation in blood pressure.⁶⁴ Moreover, a study using a mouse model found that frequent application of capsaicin may evoke skin carcinogenesis in the presence of tumour promoters (e.g. sunlight).⁶⁵ Lidocaine, a sodium channel blocker, has also been used as a topical agent for the treatment of neuropathic pain.⁶⁶ Lidocaine is available as a 5% transdermal patch, which has been approved for the management of postherpetic neuralgia.⁶⁷ Clove oil extract, derived from *Syzygium aromaticum*, has been used for centuries in the management of various types of pain, such as dental and joint pain, yet sufficient evidence to support its use in orofacial neuropathic pain is lacking. Nevertheless, the phenylpropanoid compound eugenol is thought to be responsible for the antinociceptive activity of clove oil. However, eugenol's mechanism of action is not fully understood, but it is suggested to exert an activity similar to capsaicin; however, further clinical investigations are needed to confirm its potential in neuropathy.⁶⁸ Lastly, a combination of topical agents with systemic drugs can achieve a higher degree of pain relief.⁶⁹

Endocannabinoids

Another proposed strategy for treating neuropathic pain is through targeting the endocannabinoid system.⁷⁰ A number of CB_1 and CB_2 agonists have been used for multiple indications, such as treating nausea and vomiting associated with chemotherapy, increasing appetite and controlling cancer-induced pain and/

or neuropathic pain.⁷⁰ Since it was first identified, the naturally derived palmitoylethanolamide has established some evidence of effectiveness in the management of neuropathic pain.⁷¹ Palmitoylethanolamide is suggested to exert its action via the putative activation of cannabinoid receptors and its entourage effects on TrpV1 channels.^{71,72} Palmitoylethanolamide is usually well-tolerated with low adverse events and it is frequently administered at a dose of 600 mg twice daily for neuropathic pain management.⁷³ Nabiximols (Sativex[®] developed by GW Pharmaceuticals, UK) is a medical agent composed of Δ 9-tetrahydrocannabinol, cannabidiol and several terpenoids derived from *Cannabis sativa*.⁷⁴ Nabiximols is available as a buccal spray intended to be absorbed through oral mucosa, since buccal administration of tetrahydrocannabinol exhibits better and more predictable pharmacokinetics, namely bioavailability, compared to oral tetrahydrocannabinol.⁷⁴ Nabiximols is licensed in 21 European countries for the management of spasticity in multiple sclerosis patients, and results of early clinical trials have shown promising outcomes in the management of neuropathy. However, targeting the endocannabinoid system is associated with a number of unwanted side-effects, for instance, sedation, motor and cognitive impairments.⁷⁵ Moreover, the cannabinoids therapeutic index has not been thoroughly examined yet; therefore, it is still undetermined if cannabinoids will be beneficial in neuropathy management at low doses with no adverse events.⁷⁵

Miscellaneous agents

Certain medical agents have been suggested to have a potential in the management of orofacial neuropathic pain. The muscle relaxant drug baclofen is observed to have a potential in neuropathy.⁷⁶ A combination of baclofen and carbamazepine can aid in improving pain relief in patients with orofacial neuropathic pain.⁷⁷ Sumatriptan, a selective agonist of serotonin type-1 like receptors used in migraine treatment, was found in clinical trials to be effective in trigeminal neuralgia when administered subcutaneously at a dose of 3 mg.⁷⁸ Botulinum toxin intraoral injection in trigeminal neuralgia has shown a significant improvement in patients that adds up to the piece of evidence which supports botulinum toxin use; however, further studies are required to confirm its relative safety and efficacy.⁷⁹ In a preliminary open-labeled study, a novel approach was used which involved local injection of mesenchymal stem cells in the pain field in patients with neuropathic trigeminal pain. The study results showed a significant amelioration in four out of nine subjects and pain diminished over a period of six months after stem cell administration with no signs of local or systemic side-effects.⁸⁰ These findings may possibly indicate a potential of stem cell therapy for neuropathic pain.

Conclusion

Orofacial neuropathic pain is a serious debilitating disorder that needs proper diagnosis and careful management. A wide range of pharmacological treatment options for orofacial neuropathic pain is available. Currently, TCAs (amitriptyline), SNRIs (duloxetine)

and the anticonvulsants pregabalin and gabapentin, are recommended as first-line options for neuropathy according to various available medical guidelines.⁸¹ A combination of different pharmacological treatments (systemic/systemic or systemic/topical) is more effective in pain relief than monotherapy. Biased-mu receptor ligands, targeting delta-opioid receptors and mesenchymal stem cells injection, are all novel approaches in the management of neuropathic pain that may have a potential in the future. Eventually, further clinical investigations should be undertaken to increase the understanding of neuropathic pain behaviour and pathogenesis in order to introduce more efficacious treatment protocols.

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