Rev Estomatol. 2023; 31(1):e12854. DOI: 10.25100/re.v31i1. 12854

NARRATIVE REVIEW

Trigeminal Neuralgia: Anticonvulsants and antidepressants

Andrés Felipe Aguirre Osorio [1]

OPEN ACCESS

Institutional Affiliation

[1] University of Sydney, Department of Prosthodontic, Sydney, New South Wales, Australia.

Citation:
Aguirre Osorio AF. Trigeminal neuralgia: Anticonvulsants and antidepressants. *Rev Estomatol.* 2023; 31(1):e12854. DOI: 10.25100/re.v31i1.12854

Received: June 27th 2023
Evaluated: August 18th 2023
Accepted: October 20th 2023
Published: December 30th 2023

Corresponding author: Andrés Felipe Aguirre. Contact: +61 408 747 976. Email: andresaguirredds@outlook.com

KEYWORDS
Orofacial pain, drug therapy, Trigeminal neuralgia, Neuropathic Pain.

ABSTRACT

Orofacial neuropathic pain happens due to somatosensory nervous system injury or disease in the orofacial region. Multiple types of orofacial neuropathic pain have been identified, including nonodontogenic neuropathic orofacial pain, postherpetic neuralgia, atypical odontalgia, glossopharyngeal neuralgia and trigeminal neuralgia. Currently, pharmacological intervention is well known as the foundation for managing neuropathic pain. Drugs from different classifications, including anticonvulsants, antidepressants, opioids, and nonsteroidal anti-inflammatory drugs, are generally used to treat these events. However, these drugs are not yet broadly accepted for these treatments. This review will explore recent clinical findings and fragments of evidence regarding anticonvulsants and antidepressants in the management of trigeminal neuralgia.

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INTRODUCTION

Oral neuropathic pain is challenging to the clinician because the orofacial region is complicated, and pain can arise from many sources. The practitioner requires substantial knowledge of the pain conditions from these structures for a proper diagnosis. A multidisciplinary approach to managing these conditions is the recommended course of care.[2,3] Trigeminal neuralgia (tic douloureux) is neuropathic in origin and is an infrequent condition (prevalence estimated in 5/100000) that produces excruciating and short-lasting.

Pain over one side of the face and the trigeminal nerve distribution (usually 2d or 3rd division of the nerve) is characterised by sudden, sporadic, and debilitating burning or shock-like pain, typically produced by light touch provocation, which affects more women than men. It is more common in an older population. The most common cause is nerve compression by vessels that wears down the myeline coverage with every heartbeat. It is essential to have a proper work-up when presented in younger patients as it can also be related to multiple sclerosis and brain tumours **(Table 1)**.[4-7]

It is supposedly an easy diagnostic to make, but as you get into the patient's medical history, more and more layers of complex reasons can be unveiled for this type of pain. The pain is initially sudden and with a memorable onset; this painful condition can often mimic a toothache, and therefore these patients end up with the dentist and sometimes receive unnecessary dental treatments.

The patient can pinpoint the day the pain started even years after the first attack. With time the pain becomes more severe and more frequent. Usually, the pain presents periods of remission and disappears; the patient and clinician might think that everything has been solved. It is unknown how long these remission periods will last and how long they will stay.

In some patients, the relapses are very quick and lead to prompt surgical interventions, but for other patients seem to progress intermittently and can be managed medically. It is not easy to identify to which group a patient will belong.[7-9]

Table 1. Multiple sclerosis and brain tumours related with nerve compression.

Character/ severity	**Timing/ periodicity**	**Provoking Associated factors**	**Site**
Sharp, shooting	Paroxysmal	Light touch evoked	Unilateral 97%
Electric, lightning	Acute onset	Spontaneous	Trigeminal area
Terrifying	< 2-minute attacks	May be trigger spots	Rare first division
Unbearable	Periods complete remission		
Moderate to severe			

Although there have been attempts to create a classification of the different presentations of trigeminal neuralgia, there is still some debate; the American Academy of Neurology divided it into three aetiological categories:

Idiopathic TN (no neurovascular contact), classical TN (due to a neurovascular compression) and secondary TN (due to major neurological diseases such as cerebellopontine angle tumours or multiple sclerosis).

On the other hand, The International Headache Society (IHS) divides trigeminal neuralgia into classical and symptomatic. The typical or classic form of the disorder (TN1) causes intermittent pain characterised as severe burning facial pain, with each episode lasting for up to two minutes. The onset of pain may occur in clusters that persist for several hours. In contrast, the atypical form of trigeminal neuralgia (TN2) is described as constant, characteristically burning and stabbing, though of lesser severity than TN1.[6] They also classified two phenotypes: purely paroxysmal TN (with paroxysmal pain only) and TN with concomitant continuous pain.[10,11]
Treatment options for trigeminal neuralgia include medications, surgery, and complementary approaches. Indifferent of its classification, The European Academy of Neurology guideline on trigeminal neuralgia 2019 recommends starting pharmacological treatment in patients with classic TN. Surgical procedures should be reserved for patients who are refractory to medical therapy or if medical treatment is poorly tolerated due to unacceptable adverse effects.[12]

Since the studies with phenytoin by Bergouignan in 1942 and with carbamazepine by Blom in 1962, medical pharmacotherapy has been the initial management of choice for trigeminal neuralgia.[11-15] Medications such as anticonvulsants and tricyclic antidepressants (TCAs) are the core of the treatment. Carbamazepine is the first-line therapy for Trigeminal neuralgia; however, other drugs include Oxcarbazepine, *phenytoin*, baclofen, clonazepam, valproate, Lamotrigine, Gabapentin, lidocaine, misoprostol, Botulinum toxin type A (Botox). have demonstrated efficacy in trigeminal neuralgia cases.[11.12.14-17] Depending on the author of the entity, the first-line medication may switch to TCAs.

Most patients respond at least momentarily to treatment with anticonvulsant medications. Patients who do not bear or fail medical management may benefit from neurosurgical intervention. The major procedures are microvascular decompression of the trigeminal nerve root, neuro-ablation via rhizotomy with radiofrequency thermocoagulation, mechanical balloon compression, and chemical neurectomy.

Some evidence suggests that botulinum toxin injections may benefit medically refractory cases. Neuromodulation and peripheral nerve field stimulation are promising alternative techniques for pain refractory to traditional methods and merit further exploration.[3,5-7,18,19]

How anticonvulsants improve pain events is much discussed and often oversimplified. Most anticonvulsants may affect pain indirectly through their effect on mood and sleep.[20] The following elaborates on the usage of anticonvulsants and antidepressants in managing pain from trigeminal neuralgia.

PATHOPHYSIOLOGY

The pathophysiology of pain caused by trigeminal neuralgia can be explained as a complex interaction of neuromodulators and neurotransmitters leading to a convergence of nociceptive transmission onto the trigeminal neurons. The principal rationale for the pathophysiology of trigeminal neuralgia involves compression of the nerve root at the entry zone by cerebral vessels. Still, the pathophysiology of the mechanisms underlying Trigeminal Neuralgia is poorly understood.[21] Neurovascular compression (NVC) can be primary or secondary to another pathology. Primary compression is visual compression of the nerve without a secondary cause. Secondary compression causes include brain tumours such as meningiomas and vestibular schwannomas, aneurysms, arteriovenous malformations, and cysts.[4,22,23]

This compression usually results in the demyelination of nerve fibres, which then start firing in an abnormal condition; the NVC hypothesis is supported by evidence that most patients achieve continuous pain relief after microvascular decompression surgery. Nonetheless, this evidence, NVC, can also be seen in asymptomatic patients.[24] Several changes have been described resulting from vascular compression, including localised demyelination at the entry zone of the trigeminal nerve, atrophy or hypertrophy of peripheral axons, and damage to Schwann cells well as to peripheral myelin. In the “ignition hypothesis”,[25] aims to correlate the physical changes with paroxysmal pain events, representing the condition. It claims that after trigeminal root damage, partially damaged neurons trigger a stimulus-induced burst of activity, making them hyperexcitable and susceptible to cross excitation due to the physical proximity of the neurons to the root compression site.

Consequently, the severe increase in post-trigger neuronal activity recruits extra neighbouring neurons, leading to a rapid build-up of electrical activity, which can be amplified by ephaptic interaction among neurons since the myelin sheath is damaged and nerve fibres maintain close contact among them.

There is evidence that voltage-gated sodium channels (VGSCs) play a crucial role in generating ectopic activity in trigeminal afferents.[17,23,26]
Neuroimaging studies have shown that patients with Trigeminal neuralgia have altered brain structure, function, and connectivity.[4]

PHARMACOLOGICAL TREATMENT

Trigeminal neuralgia is a chronic condition that can be approached with different surgical procedures in case an offending vessel is easily identified; nevertheless, pharmacological management is the first option due to the risk of the processes involved. Nevertheless, managing this pain type is challenging and best accomplished using a multidisciplinary team.

Pain is a subjective experience, and it is essential to understand a patient’s pain, address psychosocial comorbidities, and set realistic treatment goals since obtaining effective long-term relief is notoriously difficult.[19]

Evidence-based guidelines are available to guide treatment but high-quality, evidence-based recommendations are often lacking.[22,27]

According to different authors, not all trials of treatment for trigeminal neuralgia state the diagnostic criteria used, do not have strong outcome measures, and may not account for the variations in results. There are, on average, few large-high-quality randomised controlled trials of medical management in trigeminal neuralgia, and their design is so variable that meta-analysis is almost impossible.[20,28]

The first-line medication for managing trigeminal neuralgia has been long-time anticonvulsants. Still, some articles and guidelines show a shift to antidepressants, apparently due to the complexity of the disorder's presentation. Other components such as the potential for side effects; treatment of other comorbidities (e.g., depression, difficulty sleeping); risk of drug interactions, overdose, or abuse; and cost add to the decision of which medication is considered a first-line medication.[14,22,27,29-31]

Classically, Carbamazepine has been the first treatment option for Trigeminal Neuralgia and is the gold standard.[6,20,32] Its history dates from the early 1960's when anticonvulsants were first used for the treatment of Neuropathic pain due to the characteristics of temporal profiles and abrupt nature of the pain attacks of this disease, which have similar characteristics to those seen in epileptic seizures.

The mechanisms by which they exert their analgesic effect have been studied, but it is in some regards uncertain. However, it is probably related to a reduction in the high-frequency firing of neurones and may work by increasing the effectiveness of the other major inhibitory network involving GABA.[17,33]

Anticonvulsants.

Carbamazepine and phenytoin were the first anticonvulsants used in a controlled trial, and some studies have shown the efficacy of these drugs at relieving paroxysm in trigeminal neuralgia. Nevertheless, adherence to the treatment is affected by the high development of side effects (every patient reports any side effects, particularly in the cognitive spectrum, such as inability to find words, memory loss, tiredness, and sleepiness).[20] Some of the classical clinical trials done on Carbamazepine reported poor pain outcome indicators with no quality of life measures, no description of diagnosis parameters, and little information regarding how the allocation of patients was achieved.[10,34] Currently, when Carbamazepine's (dose starting at 100 to 200 mg twice daily) side effects are not barred by the patient, this is replaced by Oxcarbamazepine (dose starting at 150 mg twice daily).[11] However, there is limited evidence for the usage of this drug.

Other studies have reported that gabapentin (dose starting at 300mg daily) and pregabalin (dose began at 150 mg per day) with their analgesic, anticonvulsant and anxiolytic effects are effective for the treatment of Trigeminal Neuralgia. These newer anticonvulsants also present unwanted effects such as Sedation which may be helpful in patients with sleep problems; gabapentin shows faster titration, no known idiosyncratic skin reactions and a favourable side effect profile; hyperlipidaemia is a significant side effect to watch.[11,33]

Lamotrigine is another anticonvulsant used in the management of Trigeminal neuralgia (dose starting at 25 mg twice daily) thanks to its effect of reducing ectopic discharges in the affected nerve endings and neurones in the dorsal root ganglia by blocking sodium channels, it presents common side effects like sleepiness, dizziness, headache, vertigo, ataxia and skin rash.[11,20] In Australia, pregabalin is the only antiepileptic medication that has been approved and therefore subsidised by the government for the management of neuropathic pain.[17]

Antidepressants

Tricyclic Antidepressants (TCA) are widely used in treating neuropathic pain; evidence gathered over several decades has indicated their effectiveness.[30] The precise mechanism by which the tricycling anti-depressants relieve neuropathic pain is still debatable; it appears that it is independent of its antidepressant effect, although some authors attribute the success to the impact on common comorbidities (anxiety, depression and insomnia), which helps modulate the perception of pain.[35]

The evidence suggests that TCAs are more effective in some types of neuropathic pain than others. They are generally effective in treating painful diabetic neuropathy and postherpetic neuralgia. (Amitriptyline, Clomipramine, and Imipramine). Apparently, they act, increasing the availability of central noradrenaline and serotonin; more recently, Cardoso et al. 2022 supported the notion that the blockade of neuronal calcium ion channels by TCAs is at least partially responsible for their analgesic effect.[36] Some other actions had been granted to their analgesic effect. Their most frequent adverse events are nausea, somnolence, dry mouth, constipation, diarrhoea, blur vision, hyperhidrosis, dizziness, and weight gain, which may limit its use. Nevertheless, they seem to be more effective than selective serotonin reuptake inhibitors.[17,34]

TCAs must be used cautiously in the elderly and patients with heart disease, narrow-angle glaucoma, prostatism and seizure disorders. Although TCAs have no addictive side effects, their incorrect discontinuation may produce distressing cholinergic rebound symptoms, including gastrointestinal distress, sleep disorders and motor restlessness. Overdose can increase the chance of life-threatening cardiac arrhythmias. Significant potential drug-drug interactions with TCAs include additive sedative effects (as with alcohol) and competitive inhibition of TCA metabolism with selective serotonin reuptake inhibitors.[17,34] An optimal analgesic effect can be achieved with a dose lower than the primary indicated. (does starting at 10mgrs twice daily). These medications are the first-line option in some guidelines and for specific neuropathic pain disorders.

CONCLUSIONS

There is limited availability of high-quality clinical trials of sufficient duration to manage chronic neuropathic pain. The lack of proper clinical trials means many recommendations are based on indirect comparisons and anecdotic experiences.[16]
Current guidance recommends that a tricyclic antidepressant or antiepileptic drug, gabapentin or pregabalin, should be the first-line choice for the pharmacological treatment of neuropathic pain of most causes.[14,29]

In the absence of solid evidence of the predominance of one drug over another, it would seem practical to use the lowest-cost medicines first. Carbamazepine remains an option for first-line treatment of trigeminal neuralgia.[11]

Although Some new drugs show promise in managing Trigeminal Neuralgia (Pimozide, Tizanidine, Levetiracetam, Lacosamide, Eslicarbazepine, vixotrigine),[6,24] more studies are needed.
The treatment of TN is still challenging, and individual responses to different medical options vary considerably. The treatments' efficacy cannot be guaranteed, and the patient must be informed about the treatment goals.[37,38]

Although it has been a significant advance since the publication of the first attempts to treat neuropathic pain, there is still a gap in understanding the physiopathology of Neuropathic pain and the effect of the medication used to control it.[4]

Cases of refractory NP may benefit from several procedures, including microvascular decompression, gamma knife therapy, and percutaneous treatments.[2,12,17,39]
The prevalence of TN is likely underestimated as studying this condition is challenging, and the general population is aging. The TN prognosis is poor because half of the patients report no improvement, less than one-third experience some progress, and only 10%–20% experience significant improvement.[38,40]
Pain relief therapies that do not block peripheral or central neurotransmissions are essential since most orofacial pain patients present complex psychological and psychosocial history that is better treated with a multimodal approach.[41,42]

Conflict of interest statement

The author declare that there is no conflict of interest related to the companies mentioned on this editorial.

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