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GUEST EDITORIAL

Novel ways of approaching the pharmacologic treatment of trigeminal neuralgia

Trigeminal neuralgia (TN) is an exemplary neuropathic facial pain condition in adults, characterized by unilateral recurrent paroxysmal pain in the distribution of one or more branches of the trigeminal nerve.[1,2] TN can be divided into classical (solely due to neurovascular compression, producing morphological changes on the trigeminal root), secondary (related to a major neurological disease), and idiopathic. Regardless of the etiology, the key mechanism underlying paroxysmal pain is the focal demyelination of primary trigeminal afferents near the entry of the trigeminal root into the pons, causing myelinated axons to become hyperexcitable and increasing their susceptibility to ectopic excitation, ephaptic transmission, and high-frequency discharge.[3] Patients may also experience concomitant continuous pain, described as dull or burning. A characteristic feature of TN is that paroxysmal pain can be precipitated by innocuous tactile stimuli (e.g., brushing teeth).[2,4]

Despite these paroxysmal attacks last seconds to 2 min, the pain is severe and can negatively affect quality of life,[5,6] prompting the need for effective treatment. First-line pharmacologic treatment for TN, no matter the subtype, is based on voltage-gated sodium-channel blockers carbamazepine or oxcarbazepine,[7] whose efficacy is thought to be secondary to stabilizing neuronal hyperexcitability and inhibition of high-frequency repetitive nerve firing.[8] However, treatment efficacy can be offset by significant side effects. Oxcarbazepine is often used initially given its relatively better drug tolerability and a decreased potential for drug interaction compared to carbamazepine.[9] A recent study showed a higher frequency of treatment refractoriness in patients with idiopathic and secondary TN than in patients with classical TN.[10] Other drugs, such as lamotrigine, gabapentin, and phenytoin, can be considered in patients with a suboptimal response or toxicity to first-line pharmacologic treatment. Oftentimes, these medications are given as an add-on to first-line treatment despite there not being comparative studies between first-line monotherapy and combination therapy.[11] Although there is limited clinical experience in refractory TN, onabotulinumtoxinA is a promising add-on therapy.[7,12] Emerging drugs and new pharmacological options are under development.

Triptans are migraine-specific acute treatments that are thought to produce their therapeutic effect via their agonism on $5HT_{1B}$ and $_{1D}$ receptors.[13,14] Agonism of these receptors ultimately leads to selective vasoconstriction of intracranial arteries, inhibition of vasoactive neuropeptide release, and reduced trigeminal sensory nerve firing.[15] In addition to triptans' efficacy in the acute management of migraine, they are thought to be useful in the treatment of acute exacerbation of TN.

In this issue of *Headache*, Munoz et al. published a narrative review of the management of TN with triptans. Four studies were eligible to be included in their review and suggested that there was facial pain improvement with triptans. The included studies had oral, subcutaneous, and intranasal triptan formulations.

Triptans' therapeutic effects on TN may be caused by the inhibition of vasodilation and inflammation near the demyelinated trigeminal root.[16] A possible mechanism of symptomatic relief is triptans' effects on reducing the release of calcitonin gene-related peptide (CGRP) and substance P, which is involved in trigeminovascular pain transmission and intracranial vessel vasodilation. However, the side effects related to long-term use, including a triptan overuse headache, prevent the use of sumatriptan in the long-term treatment of TN.

Erenumab is a humanized monoclonal antibody against CGRP receptors and it is approved for preventive treatment in migraine. Given CGRP's possible role in pain perception in TN, one can hypothesize that erenumab would be beneficial in this patient population. Parascandolo and colleagues published a retrospective case series of 10 patients with medically refractory TN. Nine reported a significant reduction in pain and an increased global improvement with erenumab treatment over 6 months.[17] Despite this being a small open-label study with no placebo group, its promising results may open a new avenue of pharmacologic treatment with a favorable side-effect profile compared to first-line pharmacologic treatment. There is currently a clinical trial underway assessing the effect of rimegepant, an oral CGRP receptor antagonist, in treatment-refractory TN (ClinicalTrials.gov Identifier: NCT03941834).

As mentioned previously, carbamazepine and oxcarbazepine are a nonselective sodium channel blocker, which may need drug titration to achieve a therapeutic effect. Vixotrigine (BIIB074) is a Nav1.7 selective state-dependent sodium channel blocker that may be useful in the treatment of TN. Nav1.7 has a relatively specific expression in the peripheral nervous system, thus suggesting that selective Nav1.7 sodium channel blockers may have fewer side effects than currently available agents. A phase IIa, double-blind, placebo-controlled randomized trial tested the effect of vixotrigine (BIIB074) versus placebo in TN. Although the primary end point was not reached, there was a significant difference in the time to treatment failure, the number of paroxysmal attacks, the average daily pain scores, and patient and clinical global impression of

change, which favored vixotrigine.[18] The medication was generally well-tolerated.[18] A phase III trial for it is underway (ClinicalTrials.gov Identifier: NCT03637387).

Eslicarbazepine is a third-generation antiseizure drug, targeting the voltage-gated sodium channels and used as an adjunct therapy in the management of focal seizures. Eslicarbazepine has a higher selectivity for voltage-gated sodium channels during the slow inactivation phase, has a longer half-life allowing for daily dosing, and has little if any effect on cytochrome P450 activity.[19] Sanchez-Larson and colleagues presented a retrospective, open-label, multicentric, intention-to-treat study on the effectiveness and safety of eslicarbazepine in the treatment of TN, which demonstrated an improvement in pain intensity and paroxysms with most patients having subjectively good drug tolerance.[20] However, randomized clinical trials are needed.

Carbon dioxide may play a role in neuronal pain modulation. Vause and colleagues demonstrated that this treatment under isohydric conditions reduced the intracellular pH of rat trigeminal ganglia, which ultimately led to a reduction in the secretion of CGRP.[21] There is a placebo-controlled, single-blind study currently underway evaluating the safety and efficacy of carbon dioxide in the treatment of classical TN (ClinicalTrials.gov Identifier: NCT02473016).

Patients with acute exacerbations of TN may benefit from intravenous fosphenytoin or lidocaine, under specialist supervision and cardiac monitoring. Noro and colleagues published a single-center, retrospective, observational study of 20 patients treated with intravenous fosphenytoin as rescue treatment for acute TN crisis and found that there was a significant reduction in pain 24 h following treatment.[22] There is currently an observational prospective cohort study underway on the management of acute exacerbations of TN with fosphenytoin (ClinicalTrials.gov Identifier: NCT03712254). Stavropoulou and colleagues published their randomized, controlled trial on the treatment of TN with intravenous lidocaine. They found that intravenous lidocaine led to significant pain reduction compared to placebo and the effect was maintained for the first 24 h following treatment.[23] In patients with concomitant continuous pain, the efficacy of first-line drugs may drop, and both calcium channel blockers (gabapentin and pregabalin) and antidepressants should be tried as an add-on to first-line drugs.

Treatment of TN can pose a great challenge for the clinician and can be frustrating for patients. Despite there being effective pharmacologic treatment there are still patients who do not respond and still experience this debilitating facial pain disorder. Novel pharmacologic treatments are fortunately on the rise and results appear favorable, although more rigorous studies are needed to provide patients with tolerable and effective pharmacologic treatment, obviating the need for surgical treatment, which poses risks in and of itself.

KEYWORDS

calcitonin gene-related peptide, carbon dioxide, facial pain disorder, sodium-channel blockers, trigeminal neuralgia

CONFLICT OF INTEREST

Dr. Dominguez and Dr. Di Stefano do not have any conflicts of interest.

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