

# Considerations When Using Gabapentinoids to Treat Trigeminal Neuralgia: A Review

Gianfranco De Stefano <sup>\*</sup>, Giuseppe Di Pietro <sup>\*</sup>, Andrea Truini, Giorgio Cruccu, Giulia Di Stefano

Department of Human Neuroscience, Sapienza University, Rome, Italy

<sup>\*</sup>These authors contributed equally to this work

Correspondence: Giulia Di Stefano, Department of Human Neuroscience, Sapienza University, Rome, Viale Università 30, Rome, 00185, Italy, Tel +39 06 49694209, Email [giulia.distefano@uniroma1.it](mailto:giulia.distefano@uniroma1.it)

**Abstract:** Despite the exemplary efficacy of voltage-gated sodium channel blockers as a first-line treatment of trigeminal neuralgia, the pharmacological management of this excruciating facial pain condition remains a major issue, as these first-line drugs produce intolerable side effects in a significant portion of patients. In addition, in patients with concomitant continuous pain, the efficacy of these drugs may drop, thus suggesting the opportunity to test the efficacy of different drug categories. The aim of this review is to provide current, evidence-based, knowledge about the use of gabapentin and other  $\alpha 2\delta$  ligands in patients with trigeminal neuralgia. We searched for relevant papers within PubMed, EMBASE, the Cochrane Database of Systematic Reviews and the Clinical Trials database (ClinicalTrials.gov), considering publications up to April 2023. Two authors independently selected studies for inclusion and data extraction. The efficacy of  $\alpha 2\delta$  ligands, gabapentin and pregabalin, has been assessed in seven controlled or open-label studies. Despite the low quality of evidence, the favorable tolerability profile and the possible action on concomitant continuous pain make this drug category of interest for future trials in trigeminal neuralgia.

**Plain Language Summary:** Trigeminal neuralgia is a really excruciating neuropathic pain condition. Although sodium channel blockers are efficacious in most of the patients, the poor tolerability profile and the limited efficacy in patients with concomitant continuous pain represent a major issue over the long-term treatment.

Gabapentin and other  $\alpha 2\delta$  ligands, which have been shown to be effective in the treatment of other neuropathic conditions characterized by continuous pain, may be tried as additional agents along with sodium channel blockers.

In this review, based on a systematic search of relevant literature, we aim to provide current, evidence-based, knowledge about the use of gabapentin and other  $\alpha 2\delta$  ligands in patients with trigeminal neuralgia. The favourable tolerability profile and the possible action on concomitant continuous pain make this drug category of interest for future trials in trigeminal neuralgia.

**Keywords:** gabapentin, pregabalin, trigeminal neuralgia

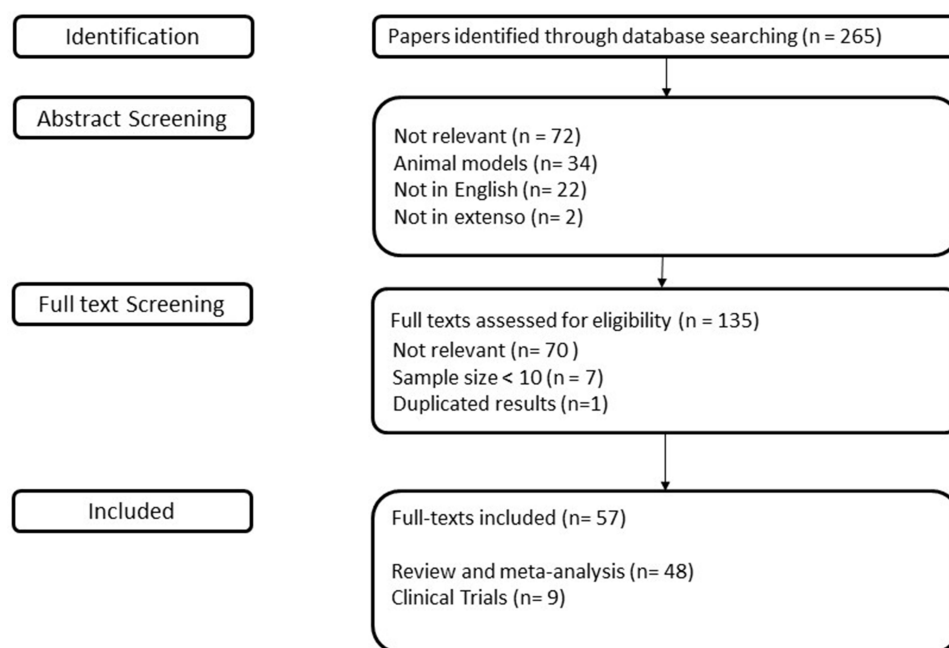
## Introduction

Trigeminal neuralgia (TN) is a peculiar neuropathic facial pain condition characterized by paroxysmal pain in the distribution territory of one or more divisions of trigeminal nerve, evoked by tactile, innocuous stimulation of trigger zones.<sup>1</sup> Trigger zones and paroxysmal pain sensation may be dissociated, probably due to a phenomenon of cross-excitation between somatosensory afferents and a refractory period of several seconds or minutes usually occur between paroxysms. According to the etiology, TN is classified as Classical TN, related to a neurovascular compression producing morphological changes on the trigeminal root, Secondary TN, related to a major neurological disease, and Idiopathic, of unknown etiology.<sup>1</sup> Regardless of the etiology, the pathophysiological mechanism triggering paroxysmal pain is the focal demyelination of primary trigeminal afferents near the entry of the trigeminal root into the pons, making the axons hyperexcitable and increasing their susceptibility to ectopic excitation, ephaptic transmission, and high-frequency discharges.<sup>2</sup> This peculiar mechanism explains the remarkable efficacy

of sodium channel blockers (carbamazepine and oxcarbazepine) as first-choice medical treatments.<sup>3</sup> However, in a significant portion of patients, the efficacy of these drugs may drop due to undesired effects causing interruption of treatment or a dosage reduction to an unsatisfactory level.<sup>4</sup> Another issue is the pharmacological treatment of patients with concomitant continuous pain, a background pain associated with poor medical outcome, affecting 24 to 49% of patients.<sup>5</sup> This continuous pain, with a distribution coherent with that of the paroxysmal pain, is usually described as burning, throbbing, or aching and is probably mediated by different pathophysiological mechanisms, requiring tailored pharmacological management. Progressive damage to the nerve root, unmyelinated axonal loss and central sensitization mechanisms have been hypothesized to explain the development of this pain quality. Among the therapeutic options,  $\alpha 2\delta$  ligands could be considered in monotherapy or as an add-on treatment for a synergistic approach. These drugs exert their pharmacodynamic effect by modulating voltage-gated calcium channels and thus reducing the release of excitatory neurotransmitters. The aim of this review, based on a systematic search of relevant literature, is to provide current, evidence-based, knowledge about the use of gabapentin and similar  $\alpha 2\delta$  ligands in the treatment of TN.

## Search Process

We searched for relevant papers within the PubMed, EMBASE and the Cochrane Database of Systematic Reviews, taking into account studies published in peer-reviewed journals up to April 2023. The search terms included gabapentin and  $\alpha 2\delta$  ligands OR calcium channel blockers. All searches used the following synonyms for TN: trigeminal neuralgia and tic douloureux. Inclusion criteria were the following: trials including patients with a definite diagnosis of TN, including classical, idiopathic and secondary TN. Other trigeminal pain conditions (eg, isolated trigeminal neuropathy, postherpetic neuralgia) and conditions such as atypical facial pain and atypical odontalgia were not included in the analysis. Only full-length, original communications including open-label studies were selected, and the search was limited to English language publications. In the absence of top-level articles, case series were also considered. Clinical trials database (ClinicalTrials.gov) has been checked in order to include studies currently in progress. The primary search was supplemented by a secondary search using the bibliographies of the retrieved articles. The review process was carried out independently by two reviewers (Figure 1). Two independent authors assessed the studies in terms of methodological quality using the five-point Oxford Quality Scale.<sup>6</sup>



**Figure 1** Flowchart of the search process.

## Results

We initially identified 265 studies on the topic and, after abstract screening, 135 full texts were assessed for eligibility (Figure 1). We excluded 70 studies as not relevant, seven studies involving a small number of patients (less than 10), and one paper for duplicated results. Forty-eight reviews and meta-analysis and nine clinical trials, testing the effect of  $\alpha 2\delta$  ligands in patients with TN, were identified (Figure 1, Table 1).

### Gabapentin

One systematic review and meta-analysis<sup>17</sup> identified 16 randomised controlled trials, all published in Chinese, comparing the efficacy of gabapentin with that of carbamazepine in 1331 patients with TN. The efficacy of the two drugs, evaluated through the VAS score, was comparable and the adverse event rate was lower with gabapentin than with carbamazepine. However, the inclusion criteria, endpoints and dosages were often not clearly detailed and the quality of the studies was poor. A recent systematic review and meta-analysis, including 18 randomized controlled trials, most of them published in Chinese, confirmed the efficacy and the better tolerability of gabapentin in comparison with carbamazepine. However, the quality of the study was globally poor.<sup>18</sup> In the study of Lemos et al,<sup>7</sup> the authors assessed the efficacy of gabapentin associated with ropivacain analgesic block of facial trigger points in 36 patients with TN. The association of gabapentin and ropivacain improved the functional health status of patients when compared with gabapentin alone, without side effects.

In the prospective study conducted by Kaur et al,<sup>8</sup> medical treatment with gabapentin was compared to carbamazepine. In this study, carried out in a relatively small sample size (42 patients), gabapentin treatment resulted in similar efficacy as carbamazepine, with a non-significant trend to lower side effects. A similar study was performed by Agarwal et al.<sup>9</sup> In this study, involving 46 patients, gabapentin treatment resulted in a better management of TN as compared to carbamazepine. A retrospective study reported the efficacy of gabapentin, with a mean dosage of 930 mg, in 43 out of 92 patients with TN.<sup>10</sup> Gabapentin was also reported as an effective option in patients with TN related to multiple sclerosis, to lower the dose of carbamazepine or lamotrigine when these drugs produce intolerable side effects.<sup>11</sup>

### Pregabalin

No randomized-controlled trials tested the efficacy of pregabalin for the treatment of TN. In an open-label, crossover trial in 22 patients with a diagnosis of refractory TN, using lamotrigine and pregabalin together with carbamazepine, pregabalin showed a comparable efficacy but a better tolerability in comparison with lamotrigine.<sup>12</sup> An open-label study involving 53 patients showed a significant pain reduction in 74% of patients treated with pregabalin.<sup>13</sup> An observational study, involving 65 patients, reported that pregabalin was effective in monotherapy and as an add-on treatment. However, the inclusion of patients with atypical facial pain cannot be excluded.<sup>14,15</sup> In a retrospective study involving 33 patients with refractory TN waiting for a surgical procedure, pregabalin was effective in 48.5% of patients.<sup>16</sup>

No studies tested the efficacy of mirogabalin in the treatment of TN. The efficacy of this drug was only reported in an 89-year-old female patient with trigeminal trophic syndrome secondary to herpes zoster.<sup>19</sup>

No ongoing trials on the use of  $\alpha 2\delta$  ligands in TN have been identified.

### Expert Opinion

Based on evidence, the first-line pharmacological treatment in TN is carbamazepine (400–1200 mg/day) or oxcarbazepine (900–1800 mg/day). These frequency-dependent sodium-channel blockers are the most effective drugs to relieve the paroxysmal pain of TN and are efficacious in almost 90% of patients.<sup>20</sup> The remarkable efficacy of these drugs depends on the stabilization of hyperexcited neuronal membranes and in the inhibition of repetitive firing. The problem is that both drugs may induce intolerable side effects with interruption of treatment or a dosage reduction to an unsatisfactory level in a significant percentage of patients.<sup>4,20</sup> The poor tolerability of first-line drugs makes necessary the development of alternative treatment options. Despite the high quality of evidence on the efficacy of  $\alpha 2\delta$  ligands in different neuropathic pain conditions, the quality of evidence in trigeminal neuralgia is low.<sup>3</sup> Most of the trials are small controlled

**Table 1** Studies Testing the Effect of  $\alpha\delta$  Ligands in the Treatment of Trigeminal Neuralgia

Study	Study Design	Sample Size	Trigeminal Neuralgia etiology	Treatment	Control	Outcome Measure	Pain Outcome	AE with $\alpha\delta$ Ligands
Lemos et al, 2008 <sup>7</sup>	Parallel-group randomized trial	36	iTN	GBP (300–900 mg/die) plus ropivacain	GBP ropivacain	0–100 VAS	Combination therapy results in a faster reduction of VAS score	No adverse events
Kaur et al 2018 <sup>8</sup>	Parallel-group randomized trial	42	iTN	GBP (600–1800 mg/die)	CBZ (400–1200 mg/die)	Good response: no attacks; Average response: 2–3 attacks/day; nonresponsive: no decrease in frequency	No attacks in 52.38% of patients	Side effects reported in 9.5% of patients (drowsiness, vertigo, nausea, and vomiting)
Agarwal et al 2020 <sup>9</sup>	Parallel-group randomized trial	46	cTN iTN	GBP (600–1800 mg/die)	CBZ (400–1200 mg/die)	0–10 VAS	Efficacy in 58.4% of patients	Not reported
Cheshire, 2002 <sup>10</sup>	Retrospective, open-label study	92	19 sTN 4 cluster-tic	GBP (100–2400mg/die)	–	Grade of pain relief	Pain relief (complete to partial) in 47% of patients	Not reported
Solaro et al, 2000 <sup>11</sup>	Case series	11	sTN	GBP (300–1200 mg/die) in combination with CBZ or LMT	–	3-point scale	Pain control in 10 patients	No adverse events
Rustagi et al, 2014 <sup>12</sup>	Randomized open-label crossover study	22	Not reported	PGB (150–300 mg/die) plus CBZ	LMT (200–400 mg/die) plus CBZ	Pain diary score	Pain control with both treatment	PGB most associated with dizziness, nausea, peripheral edema, muscle aches, weight gain and somnolence
Obermann et al, 2008 <sup>13</sup>	Prospective, open-label study	53	47 iTN 6 sTN	PGB (150–600 mg/die)	–	Reduction of pain intensity and attack frequency by > 50%	49% of responders	Side effects reported in 42% of patients (dizziness, somnolence, headache, peripheral oedema and dry mouth)
Perez et al, 2009 <sup>14,15</sup>	Prospective, open-label study	65	Not reported	PGB in monotherapy (196±105 mg/day) or add-on (234±107 mg/day)	–	Reduction of pain by > 50%	59.4% of responders	Not reported
Hamasaki et al, 2018 <sup>16</sup>	Retrospective, open-label study	33	25 cTN 4 iTN 4 sTN	PGB (166.7 mg at the mean follow-up period)	–	Effective: pain-free or manageable pain; ineffective: unmanageable pain	PGB was effective in 48.5% of patients	Side effects reported in 21.2% of patients (slight dizziness)

**Abbreviations:** GBP, gabapentin; PGB, pregabalin; VAS, visual analogue scale; CBZ, carbamazepine; LMT, lamotrigine; cTN, classic Trigeminal Neuralgia; iTN, idiopathic Trigeminal Neuralgia; sTN, secondary Trigeminal Neuralgia; AE, Adverse events.

or open-label studies and the diagnostic criteria used are often not clarified, with the possible inclusion of patients with atypical facial pain or other orofacial pain condition.

Despite the low quality of evidence on the use of  $\alpha 2\delta$  ligands in the treatment of TN (Suppl. Table), clinical experience shows that gabapentin and pregabalin have lower effect but better tolerability than carbamazepine and oxcarbazepine.<sup>3</sup> These drugs can be used in patients who cannot tolerate first-line drugs, in monotherapy or as an add-on treatment to reduce the dosage of sodium channel blockers. These anticonvulsants have been consistently shown to induce analgesia by targeting the  $\alpha 2\delta$  auxiliary subunit of voltage-gated calcium channels, resulting in impaired trafficking of these channels to the plasma membrane and reduction of neurotransmitter release and neuronal excitability.<sup>21–23</sup> As an additional mechanism, these drugs have been shown to suppress subthreshold oscillations and peripheral ectopia, probably due to a selective effect on the slow component of sodium channel conductance. However, it is still unclear whether this is a direct effect on sodium channels or an indirect effect via  $\alpha 2\delta$  binding.<sup>24</sup>

Although better tolerated in comparison with sodium channel blockers, gabapentin and pregabalin may produce side effects like dizziness, somnolence, headache, diarrhoea, confusion, nausea and ankle swelling.

In addition to the poor tolerability of first-line drugs, another issue in the management of TN is the treatment of concomitant continuous pain. Different studies suggested that continuous pain is associated with poor medical and surgical outcome.<sup>5,25</sup> Recent neurophysiological and neuroimaging studies supported the hypothesis that small fibre axonal loss, a direct consequence of neurovascular compression, may underly the pathophysiological mechanism of concomitant continuous pain.<sup>26,27</sup> When the unmyelinated axonal loss reaches a threshold level, continuous pain can be triggered through a central mechanism of denervation supersensitivity.<sup>28–30</sup> Concomitant continuous pain could therefore arise from an abnormal spontaneous activity of denervated second-order trigeminal neurons. Accordingly,  $\alpha 2\delta$  ligands, whose efficacy has already been proven in the treatment of neuropathic continuous pain due to several aetiologies,<sup>31</sup> could be considered as possible candidates for treating concomitant continuous pain. Future randomized controlled trials assessing these drugs as an add-on treatment in TN with concomitant continuous pain are required. In addition, trials focusing on the differential impact of pharmacological treatment on paroxysmal and continuous pain are also needed.

## Conclusions

Although first-line treatment with voltage-gated sodium channel blockers is highly effective in TN, some issues including the poor tolerability profile and the possible loss of efficacy in patients with concomitant continuous pain suggest the opportunity to test additional class of drugs.  $\alpha 2\delta$  ligands, despite the lower efficacy for treatment of paroxysmal pain in comparison with carbamazepine and oxcarbazepine, offers a favorable tolerability profile and may specifically act on continuous pain component.

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