

Efficacy of drugs for classical trigeminal neuralgia; statistical study comparative to gold-standard carbamazepine

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Abstract

Background: Trigeminal neuralgia (TN) is a painful symptom that impact the trigeminal nerve, whose primary function is to provide sensory and motor innervation to the face. The standard therapy is with carbamazepine (CMZ). **Aims:** The aim of the present study is to compare published data for studies comparing newly introduced antiepileptic or non-antiepileptic agents versus CMZ. **Results:** Short-term use confirms that gabapentin is significantly more effective than CMZ, however, long-term use showed a non-significant difference between compared studies. Present clinical trials showed therapeutic effectiveness of topiramate not to differ from CMZ in the management of TN. However, a large-scale data analysis showed a favourable effect of topiramate compared with CMZ after a treatment of 8 weeks period. CMZ was useful for 90.5% of the patients with pain relief ($p < 0.05$), in comparison to 62% of patients using lamotrigine. Three studies have compared CMZ to tizanidine, tocainide and pimozide, and only pimozide was superior to CMZ. These studies have shown that CMZ is still the drug of choice for TN. Lamotrigine and pimozide are recommended as second line drugs indicated for refractory cases. Topiramate and tocainide had no sufficient analgesic effects. **Conclusions:** There is low-quality evidence that the effect of anti-epileptics or tizanidine is not significantly different than that of CMZ in treating TN. Pimozide is more effective than CMZ, although the evidence is insufficient, and the data did not allow comparison of adverse event rates.

Introduction

Trigeminal Neuralgia (TN) is described as a unilateral paroxysmal severe pain described as stabbing or electric shock-like, limited to the distribution of one or more divisions of the trigeminal nerve area and aggravated by innocent stimuli (Stefano *et al.*, 2017). Some patients experienced continuing, unexciting, prickly pain between the attacks. The distribution of continuing pain overlaps with that of the paroxysmal pain. TN with continuous pain between the attacks has been defined as TN with recurrent continuous facial pain (Stefano *et al.*, 2017). The incidence of TN is three to five *per* 100.000 per year. The incidence is higher in women than men (ratio: 1.74:1) and in people aged 50-69 years (Neuralgia *et al.*, 1990 & Maarbjerger *et al.*, 2017). The new diagnostic classification of TN approved by the International Association for the Study of Pain, TN is classically described as a pain caused by vascular pressure

inducing anatomical deformity in the trigeminal nerve root, secondary, due to a particular underlying neurologic disease, and idiopathic (when even after MRI or other diagnosis) the aetiology of TN remains uncertain (Finnerup and Svensson, 2016). The aim of the present study is to compare published data for studies comparing newly introduced antiepileptic or non-antiepileptic agents versus CMZ (US Food and Drug Administration approved therapy for TN); in order to identify the best therapeutic agent(s) for treatment of TN.

The underlying cause of TN is unknown; however, evidence indicate that demyelination at the entry site of trigeminal nerve which is associated with cross-talk between axons; these complex processing could be associated with triggering of a sequence of events resulting in symptom of TN (Devor *et al.*, 2002). At molecular level, the demyelinated trigeminal nerve might be associated with modulated expression of voltage-gated sodium channels which might associated with reduction in pain threshold (Siqueira *et al.*, 2009). Although there is a new drug available for treatment of TN; Carbamazepine (CMZ) is still the drug of choice for treatment of trigeminal neuralgia due to availability of great evidence of it is effectiveness in randomized controlled trials in the treatment of patients with TN (Rockliff, Davis and Angeles, 2015 & James, 2015). The mechanism of action might be linked to the blocking of voltage-gated sodium channels resulting in inhibition of hyperpolarised trigeminal neural membranes (George, 2011).

We searched Iraq Virtual Science Library (IVSL), PubMed, Cochrane Library MEDLINE, EMBASE, and the Chinese Biomedical Database (CBM), for the 3 target words '*Trigeminal Neuralgia Carbamazepine*' and target English papers published in the year 2000 and thereafter. To be included, papers should be original work and full text articles. All published manuscripts were screened by reading the title and abstract for potential relevance to this research topic; whenever the title and abstract did not obviously state the degree of relevance, the manuscript itself was reviewed. To overcome search bias, another researcher conducted the review procedure independently; only studies jointly accepted by the two independent reviewers were taken into considerations. To simplify tracking the results in the present study, the results were categorised into drug versus CMZ.

The literature search revealed 755 articles, among which 731 studies were excluded as duplicates, unrelated or not clinical trials or compared drugs with placebo. The 24 relevant articles were selected and reviewed by two independent authors. We further excluded another 18 unrelated articles. Ultimately, 6 trials met our inclusion criteria (Figure 1), and the summarised data listed in Table 1 and 2. Only six trials included patients diagnosed of TN by the criterion of the International Classification of Headache Disorders, while other ten studies used other local and foreign standards. Sixteen eligible randomized controlled trials were identified, but definitive randomization was found only in six studies, among which four studies used the method of random number table for random distribution, and the remaining two were randomly assigned according to the date of treatment and the visiting sequence. The other ten studies were found to be lacking definitive randomization, with only one article describing blinding method. The allocation concealment was not reported in any of the trials, and the number of dropouts or withdrawals was clearly reported in three trials. Only ten studies mentioned the follow-up time.

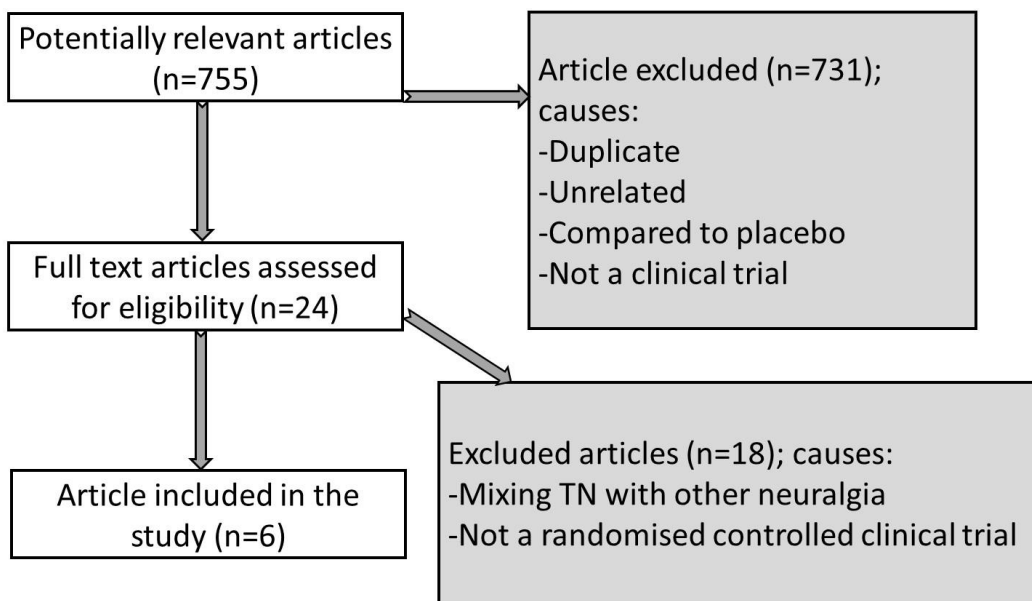


Figure 1: Flowchart describing the rules that were followed to choose the included articles.

Results and discussion

The designing of trigeminal neuralgia clinical trial is limited by the low incidence of this disease condition, by hard diagnosis, by the high remissions rate, by the requests of active disease patients and by the failure of using a placebo control group due to pain severity. Additionally, the choice of findings to be assessed is also impaired because available methods to measure pain severity and pain improvement may have their application limited due to the paroxysmic and episodic manner of trigeminal neuralgia. Therefore, in this review article we have collected published paper and analysed the results to give an evidence-based idea about the role of drugs in TN.

I. Comparisons between carbamazepine and other anti-epileptic drugs:

1. Comparison between CMZ and OXC

Stefano *et al.*, 2014; have randomly selected 178 patients (68 M, 132 F, mean age 67.54 ± 12.11), with a duration of therapy and follow-up of approximately 7.31 years. All patients had diagnosed with classical TN. Ninety-five out of 178 patients were placed on CMZ and 83 placed on OXC. The age onset of symptoms was 60 ± 11.6 years (35-80 range). The rate of responders was 98% with CMZ at a dose of 600 mg (200–1200mg range), and of 94% with OXC at a dose of 1200 mg (600–1800mg range). Besi *et al.*, 2015 have randomly selected 160 patients, with a duration of therapy and follow-up of approximately 2 years. All patients had diagnosed with classical TN. Eighty patients were placed on either CMZ or OXC. The rate of responders was 80% with CMZ at a dose range of (200–300mg), and of 68% with OXC at a dose range of (300–600mg) (Table 1).

It is generally agreed that the first line therapy of TN is pharmacological and based on the use of sodium channels blockers, CMZ and OXC. Four placebo-controlled trials demonstrated the efficacy of CMZ (Campbell, Graham and Zilkha, 1966 & Nicol, no date) with a number needed to treat to obtain important pain relief of . This study confirmed that CMZ and OXC are efficacious in a great majority of patients and that OXC is more tolerated in comparison with CMZ. If compared with other reports, the percentage of non-responders was somewhat lower in this study. Because CMZ and OXC are extremely efficacious in increasing the refractory period of action potentials, they are bound to be most active on the high frequency

discharges that characterize the paroxysms of trigeminal neuralgia. Naturally, if the patient selection is not very strict, and concedes the recruitment of a few patients that also have some ongoing pain, then the efficacy of CMZ/OXC may drop. Indeed, the diagnostic accuracy has always been a problem in studies in trigeminal neuralgia. (Sindrup and Jensen, 2002).

2. Comparison of CMZ and LTG:

Pain assessments showed that, out of the total of 21 patients, 13 patients (62%) attained pain relief from LTG in contrast to 19 (90.5%) attaining pain relief from CMZ. Eight patients (38%) failed to achieve any benefit of pain relief from LTG, whereas 2 patients (10%) failed to achieve any benefit of pain relief from either drug. Under CMZ, the p value of the test was 0.001 (<0.05) indicating a large proportion of patients benefited in pain relief from CMZ (Table 1).

In the present study, it was confirmed that LTG is an effective agent for the treatment of TN, despite of high responder rate of patients achieved pain relief from CMZ, however, the responder rate in terms of score of pain relief a higher proportion of patients obtained a complete score of pain relief from TN with LTG compared with CMZ. The positive effective role of LTG shown in the present study is in agreement with the result achieved by Zakrzewska *et al.*, 1997 who has piloted to study the effects of LTG in 14 patients with TN. In this study, regarding patient's responder rate, the efficacy of CMZ was greater compared with that of LTG. This result was in agreement with another two clinical studies; Sato *et al.*, 2004 confirmed that the responder rate of 90.5 for CMZ, in a confirmative study to assess the significance of CMZ in 50 TN patients. Silver *et al.*, 2007 investigated a low response rate of LTG (<50%), in a clinical trial to assess the effect of LTG in 112 patients with neuropathic pain.

3. Comparison of CMZ and GBP:

Comparing CMZ with GBP, the results indicated that both are effective, but GBP has slightly showed a higher responder rate than CMZ. In the present study, we outlined a data-analysis of all published randomized controlled trials on the comparison of the response rate of gabapentin (GBP) treatment versus CMZ treatment. The results confirm that the effectiveness of GBP treatment was similar for the treatment of trigeminal neuralgia (TN). However, in 1 month, GBP efficacy was significantly higher than CMZ. Some studies confirm that GBP has effective role in TN, however, the effect was similar to CMZ (Yuan *et al.*, 2016). Whether the effectiveness of GBP for the management of TN is similar with that of CMZ and the onset of response is earlier or whether the target studies may be insufficiently addressed the effects of GBP might be underwhelming the results. More studies are required to shape these conclusions. The potential mechanism that underlie the pathophysiology of TN remain elusive. The central hypothesis suggests that TN is resulted from same seizure action in the central pathway of the trigeminal nerve, which described the continued strikes and dissemination of TN. Some investigators suggested that TN was sensory convulsion, and its originated in the hypothalamic cortical or trigeminal nucleus (Yuan *et al.*, 2016). Several studies confirmed that anticonvulsant drugs had been indicated in neuropathic pain since the 1960s, and the newly introduced anticonvulsant drugs, such as GBP, hold a great promise in the treatment of TN in last few years (Prisco *et al.*, 2011 & Lemos *et al.*, 2008), and there is suggestions that GBP can be as effective as first or second line therapy of TN, even in cases resistant to classical CMZ treatment (Cheshire, 2002). Earlier studies have shown that GBP's primary pain resistant mechanism is as follows:

(1) It is bind with NMDA receptors, thus suppressing the action of NMDA receptors, and then acts against pain signalling mechanisms (Chen & Eisenach, 2000).

(2) Increase the concentrations of GABA receptors in the brain, elevating the production of GABA, inhibiting the breakdown of GABA. GBP share structural similarities to the neurotransmitter (GABA); thus, crossing the blood-brain barrier to initiate an inhibitory action on GABA, leading to sedative and analgesic action (Zavoreo, Dubrovnik and Govori, 2009).

(3) With the build-up of GBP concentrations in the brain, it binds with voltage-dependent calcium channel receptor and then control calcium channels and neurotransmitter (Jensen, 2002). Further studies regarding GBP role in TN is required to address the underlying pathology more clearly on the superiority GBP versus CMZ for treatment of TN. Based on the available data, it is impossible to draw a clear conclusion regarding the effects and adverse effects of GBP compared to CMZ (Table 1).

4. Comparison of CMZ and topiramate:

A total of 354 patients were enrolled in different clinical trials. All patients were middle aged, and the duration of disease ranged (from approximately 1-4 years) to 42 months. Topiramate-treated groups were given starting dose (25 mg twice per day), and the dose increased gradually according to clinical response. The dose range (200-600 mg/day) among trials. Duration of treatment in three of the trials was 1 month, and it was 2 months in the other trials.

Three controlled clinical trials have compared CMZ to tizanidine 43, tocainide 44 and pimozone 45. CMZ was more effective as compared to tizanidine. A positive effect reported confirming tocainide analgesic activity in all patients. Pimozone has offered better results as compared to CMZ, with pain reduction rate of $78,4\% \pm 3,1\%$ from baseline rate as compared to $49,7\% \pm 19,3\%$ with CMZ. All patients placed on pimozone have shown improvement, while CMZ has improved only 14 patients (58%)(Table 1).

II. Comparisons between carbamazepine and non anti-epileptic drugs:

Three trials compared one of the oral non-antiepileptic drugs tizanidine, tocainide or pimozone with CMZ. The quality of results for all outcomes for which data were available was low. In a trial of tizanidine involving 12 participants (one dropped out due to unrelated disease), one of five participants treated with tizanidine and four of six treated with CMZ improved. For pimozone, there was evidence of higher response rate than CMZ at six weeks. Limited data meant that we could not assess the effects of tocainide (Table 2).

There is low-quality evidence that the effect of tizanidine showing a non-significant difference than that of CMZ in treating trigeminal neuralgia. Pimozone is more effective than CMZ, although the evidence is of low quality and the data did not allow comparison of adverse event rates. Insufficient data for tocainide limit any conclusions being drawn. There is limited evidence from randomised controlled trials to prove significant result from non-antiepileptic drugs in trigeminal neuralgia. More research is required.

Conclusion

Although trigeminal neuralgia is a rare disorder with a high degree of morbidity a myriad of medical and surgical options do exist to alleviate the patient's symptoms. Carbamazepine and oxcarbazepine have clearly surpassed other drugs in terms of strength of evidence and experience in this condition. Surgical options may be considered for patients who do not respond to medical management.

Considerable debate exists as to which should be the alternative drug in patients who fail to respond to carbamazepine/oxcarbazepine. Baclofen, antiepileptic drugs such as lamotrigine, gabapentin, topiramate, levetiracetam and botulinum toxin appear to be promising second line options though well designed double blinded RCTs are still lacking. The need of the hour is to generate more evidence using well designed double blind controlled trials to substantiate their efficacy and safety in these patients. This may be feasible, only if the trial is done as multicentric study owing to the uncommon occurrence of trigeminal neuralgia in dental and neurologic practice.

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Table 1: data collected from studies comparing carbamazepine with other anti-epileptic drugs

Study/year	drugs	Dose (mg)	No. of patients	Response rate	Outcome comments
Stefano et al., 2014	Carbamazepine	200-1200	95	98%	-Both are effective
	Oxcarbazepine	600-1800	83	94%	-CMZ slightly higher responder rate than OXC
Besi et al., 2015	Carbamazepine	200-800	79	80%	-CMZ moderately higher responder rate than OXC
	Oxcarbazepine	300-600	79	68%	-Approximately 30% of patients showed no response to OXC
Shaikh et al., 2011	Carbamazepine	100-400mg/day	19	90.5%	-CMZ moderately higher responder rate than LTG
	Lamotrigine	300-1200mg/day	13	62%	-LTG, an effective treatment for TN, but has lower responder rate than CMZ.
Yuan et al., 2016*	Carbamazepine	100-2400mg/day	568	77%	-Both are effective
	Gabapentin	300-3600mg/day	588	84%	-GBP slightly higher responder rate than CMZ
Wang and Bai, 2011	Carbamazepine	300-3000mg/day	177	68%	The results of the data analysis showed that topiramate was more effective than CMZ after a treatment duration of 2 months
	Topiramate	50-600mg/day	177	91%	

*secondary reference (primary references unavailable)

Table 2: data collected from studies comparing carbamazepine with non anti-epileptic drugs

Study/year	drugs	Dose (mg)	No. of patients	Response rate	Outcome comments
Sistemática, 2004 TA et al*	Carbamazepine	200-900	6	60%	-Tizanidine slightly higher responder rate than CMZ -Approximately 10% of patients showed more response to tizanidine.
	Tizanidine	18mg/day	6	49%	
Sistemática, 2004 TA et al*	Carbamazepine	400-800	12	75%	50% pain reduction 12 weeks after the start of treatment
	Tocainide	20mg/kg/day	12	100%	
Sistemática, 2004 TA et al*	Carbamazepine	300-1200	24	49%	-Pimozide moderately higher responder rate than CMZ -Approximately 30% of patients showed more response to pimozide.
	Pimozide	4-12mg/day	24	78%	

*secondary reference (primary references unavailable)