Drug Treatment of Trigeminal Neuralgia: A Systematic Review of the Literature

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Purpose: This study undertook a systematic review of the literature on drug treatment of trigeminal neuralgia.

Methods: An electronic search was carried out for articles published between January 1960 to February 2005. Studies with high level of evidence were included. The levels of evidence of the articles were classified after the guidelines of the Oxford Centre for Evidence-Based Medicine.

Results: Of 770 publications, only 21 publications showed a high level of evidence (6 randomized controlled trials and 15 clinical trials/controlled clinical trials), with a total of 348 patients. A total of 749 publications were not included in the review as they showed a low level of evidence.

Conclusions: Anticonvulsants are effective in treating trigeminal neuralgia; however, few studies with high levels of evidence were found. It is quite difficult to compare or even combine their outcomes in a scientifically meaningful manner. Due to insufficient research data, there is a need for high-quality randomized controlled trials in this area of medicine.

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The first complete description of trigeminal neuralgia was given by the English philosopher John Locke.[1] The term "tic douloureux" (painful jerking) was coined by Nicolaus Andre in 1756.[1] In 1773, John Fothergil gave a full and accurate description of trigeminal neuralgia.[1] Trigeminal neuralgia is a disorder of the trigeminal nerve causing sudden, severe, electric shock-like, or stabbing pain typically felt on one side of the jaw or cheek. Pain distribution is unilateral and follows the sensory distribution of fifth cranial nerve, more commonly involving maxillary or mandibular division. Trigeminal neuralgia affects 1 in every 25,000 people. The cause of trigeminal neuralgia is unknown, but the disorder occurs most frequently in middle or old age (more common in women than in men).

There has been much debate over the exact etiology of trigeminal neuralgia. One of the main theories is vascular compression of the trigeminal nerve as it leaves the brainstem. Another theory suggests that intracranial tumors, particularly those located in the posterior fossa, may be the cause.[2] Trigeminal neuralgia is also associated with multiple sclerosis. Infrequently, adjacent dental fillings composed of dissimilar metals may trigger attacks.

Analgesics such as aspirin and ibuprofen are generally not effective against trigeminal neuralgia. Anticonvulsants, such as carbamazepine (CBZ), phenytoin, gabapentin, lamotrigine, oxcarbazepine, and topiramate are used commonly because they block firing of the nerve. These medications are initially effective for pain control in 90% of patients. These drugs can cause side effects (eg, drowsiness, unsteadiness, nausea, skin rash, blood dyscrasias). Therefore, patients are monitored routinely and undergo blood tests to ensure that the drug levels remain safe to minimize side effects. Medications are used as long as the pain is controlled and the side effects do not interfere with a patient's activities. When medication is no longer effective, surgical procedures may be considered. Muscle relaxants such as baclofen are sometimes effective in treating trigeminal neuralgia. Sometimes multiple drug therapy is necessary to control pain.

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The wide range of treatments used currently for trigeminal neuralgia is ample evidence that there is no simple answer to how it should be managed. An evidence-based practice aims to provide the best possible treatment based on sound evidence.

The aim of this article is to systematically identify the published literature on the role of anticonvulsants and other drugs in trigeminal neuralgia.

Methods

A literature search was conducted from January 1960 to February 2005. The following key words and Boolean operators were used, "Trigeminal neuralgia AND treatment," "Trigeminal neuralgia AND anticonvulsants," "Trigeminal neuralgia AND carbamazepine," "Trigeminal neuralgia AND oxcarbazepine," "Trigeminal neuralgia AND gabapentin," "Trigeminal neuralgia AND phenytoin," "Trigeminal neuralgia AND lamotrigen," "Trigeminal neuralgia AND clonazepam," "Trigeminal neuralgia AND antidepressants," "Trigeminal neuralgia AND amitriptylin," "Trigeminal neuralgia AND protriptyline," "Trigeminal neuralgia AND nortriptyline," "Trigeminal neuralgia AND fluoxetine," "Trigeminal neuralgia AND trazodone," "Trigeminal neuralgia AND baclofen," "Trigeminal neuralgia AND nonsteroidal anti-inflammatory drugs," "Trigeminal neuralgia AND opioids," "Trigeminal neuralgia AND cafergot," "Trigeminal neuralgia AND mexiletine," "Trigeminal neuralgia AND misoprostol," "Trigeminal neuralgia AND pimozide," "Trigeminal neuralgia AND sumatriptan," "Trigeminal neuralgia AND valproic acid."

The literature search was conducted in February 2005 using the following database:

- PubMed (National Library of Medicine; NLM). PubMed is NLM's online search interface for MEDLINE and PreMEDLINE (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi);
- lWebSPIRS (Silverplatter) MEDLINE: CD-ROM database (1990 to 2000);
- International Poster Journal of Dentistry and Oral Medicine: online database (http://ipj.quintessenz.de).

The primary focus of the search was on systematic reviews and meta-analysis of randomized controlled trials that used drug treatment for trigeminal neuralgia (evidence level Ia). Then randomized controlled trials (evidence level Ib), clinical trials without randomization (evidence levels IIa), and other experimental studies (evidence level IIb) were considered. Publications with evidence level III and IV were not included in the evaluation.

The levels of evidence of the articles were classified following the guidelines of the Oxford Centre for Evidence-Based Medicine (http://www.cebm.net/levels_of_evidence.asp).

Results

The MEDLINE searches in PubMed and WebSPIRS resulted in 727 and 42 citations respectively. The searches using IPJ did not result in any additional hits. Of 770 publications only 21 publications showed a high level of evidence (6 randomized controlled trials and 15 clinical trials/controlled clinical trials), with a total of 348 patients. A total of 749 publications were not included in the review as they showed a low level of evidence. Tables 1 and 2 show the summary of results of randomized controlled trials, controlled clinical trials, and clinical trials of medicinal treatment of trigeminal neuralgia.

Discussion

Anticonvulsants are usually the most effective drugs for treating classical trigeminal neuralgia pain. Tomson et al[3] studied diurnal pain distribution, its relation to carbamazepine dosing and plasma concen-

Table 1. SUMMARY OF RESULTS OF RANDOMIZED CONTROLLED TRIALS OF DRUG TREATMENT OF TRIGEMINAL NEURALGIA

Study	Drugs Used	Comparison	Design	Total No. of Patients	Total No. of Patients Benefited (%)	Adverse Effects
Fromm et al (1993)	Tizanidine	—	Crossover	10	80	—
Kramlinger et al (1994)	CBZ	—	—	113	—	Rash in 12% patients
Zakrzewska (1997)	Lamotrigine	Placebo	Crossover	13	84.61	Dose-dependent effects on CNS
Simpson (2000)	Lamotrigine	Placebo	—	42	—	Rash in 11.9% patients
Gilron et al (2001)	Topiramate	Placebo	Crossover	3	100	—

Abbreviations: CBZ, carbamazepine; CNS, central nervous system.

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Table 2. SUMMARY OF RESULTS OF CLINICAL TRAILS/CONTROLLED CLINICAL TRIALS OF DRUG TREATMENT OF TRIGEMINAL NEURALGIA

Study	Drugs Used	Total No. of Patients	Total No. of Patients Benefited (%)
Tomson (1981)	CBZ	8	100
Farago (1987)	CBZ analogues:		100
	(i) Dihydroketo	13	
	(ii) Dihydromono-hydroxy	11	
Liebel (2001)	Oxcarbazepine and CBZ	48	100 Benefited with oxcarbazepine 95 Benefited with CBZ
Zakrzewska et al (2002)	Oxcarbazepine	15	100 Benefited initially 80 Patients required surgery
Lindstrom (1987)	Tocainide and CBZ	12	—
Lechin et al (1989)	Pimozide and CBZ	48	100 Benefited with pimozide 56 Benefited with CBZ
Vilming (1986)	Tizanidine	6	Effects of tizanidine were inferior to
	CBZ	6	those of CBZ
Merren (1998)	Gabapentin	60	65
Delvaux et al (2001)	Lamotrigen	25	100
Steardo et al (1984)	Baclofen	25	All patients were improved by 68.61
Fromm (1984)	Baclofen	60	30
Parmar (1989)	Baclofen	20	65
From et al (1987)	L-Baclofen and racemic baclofen	9	66.6

Abbreviation: CBZ, carbamazepine.

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tration, and the effect of decreasing the dose. The diurnal pain distribution showed marked intraindividual similarities with pain-free nights and a significant drop in pain during mid-day hours. The latter coincided in time with the peak plasma concentration of CBZ, thus indicating an effect of plasma concentration fluctuations on pain relief. Shorter dosage intervals might therefore be beneficial in problem cases. MacQuay et al[4] stated that carbamazepine had a combined number needed to treat of 2.6 for effectiveness, 3.4 for adverse effects, and 24 for severe effects. Farago[5] tested the dihydroketo and dihydromonohydroxy analogues of carbamazepine (GP 47680, GP 47779) against carbamazepine for efficacy and tolerability in trigeminal neuralgia. Both derivatives brought about freedom from symptoms or a marked reduction in the pain in all patients. Onset of effect was observed within 48 hours in most cases. For both analogues the effective dose was between 10 and 20 mg/kg body weight in most patients. There was a linear relationship, with a correlation coefficient of 0.83 ($P < .001$), between the doses and the serum level. Doses almost twice as high as those of carbamazepine are needed to achieve freedom from symptoms with the carbamazepine analogues. Because unwanted effects, in the form of dizziness and ataxia, occur much less frequently than with carbamazepine, the analogues can be administered in higher doses. Koyama et al[6] in their study on 66 patients said that biochemical parameters such as levels of albumin and nonglycated albumin showed a significant relationship with carbamazepine-free fraction. Nonglycated albumin was more correlated strongly with carbamazepine-free fraction. Glycated albumin, nonglycated albumin, and carbamazepine-free fraction were strongly correlated with age, whereas albumin showed only a weak correlation with age. The major ligand of carbamazepine in the serum was nonglycated albumin, which decreased with age. Albumin and nonglycated albumin were much lower, and glycated albumin and carbamazepine-free fraction much higher in the elderly (65 to 83 years) than in patients less than 65 years of age. These observations suggested that in elderly patients, the elevation of free carbamazepine concentrations in the serum caused by reduced nonglycated albumin levels induces increases in the sensitivity of the pharmacologic effects of carbamazepine and the risk of drug interactions.

Merren[7] stated that gabapentin offers an effective, safe, alternative therapy or cotherapy for trigeminal neuralgia. The best responses occur in patients with peripherally mediated neuropathic pain. Gabapentin does not affect the metabolism of other medications and is well-tolerated. A novel anticonvulsant, lamotrigine, blocks voltage-sensitive sodium channels and inhibits the release of glutamate and aspartate.[8] Lamotrigine is a chemically novel antiepileptic drug that has not been assessed adequately for its antineuralgic properties. Zakrzewska et al[9] used lamotrigine in a double-blind placebo controlled crossover trial in 14 patients with refractory trigeminal neuralgia. Patients continued to take a steady dose of carbamaz-

epine or phenytoin throughout the trial over a 31-day period. Each arm of the trial lasted 2 weeks with an intervening 3-day washout period. The maintenance dose of lamotrigine was 400 mg. Lamotrigine was superior to placebo ($P = .011$) based on analysis of a composite efficacy index that compared the numbers of patients assigned greater efficacy on lamotrigine with those assigned greater efficacy on placebo. Efficacy for 1 treatment over another was determined according to a hierarchy of: *1*) use of escape medication; *2*) total pain scores; or *3*) global evaluations. Eleven of 13 patients eligible for inclusion in the composite efficacy index showed better efficacy on lamotrigine compared with placebo. Global evaluations further suggested that patients did better on lamotrigine than placebo ($P = .025$). The adverse reactions with both lamotrigine and placebo were predominantly dose-dependent effects on the central nervous system. A fourteenth patient withdrew from the study due to severe pain during the placebo arm of the trial. It would seem that lamotrigine has antineuralgic properties. Delvaux et al[10] showed that lamotrigine was most effective in trigeminal neuralgia, but was of little utility in the other head or facial pains. Simpson et al[8] showed that the frequency of rash was greater than in lamotrigine studies in epilepsy. Clonazepam seems to be an effective drug in idiopathic trigeminal neuralgia. Electrophysiologic investigations support the idea that this neuralgia is due to a loss of central inhibition. Caccia[11] showed that during the first 1 to 2 weeks of treatment marked drowsiness is observed in the majority of cases. In 1 case, presence of a synergism between clonazepam and L-dopa+ inhibitor was also observed.

Oxcarbazepine is a potent antineuralgic drug with very good acceptability and tolerability. Liebel[12] compared oxcarbazepine with carbamazepine as primary treatment of trigeminal neuralgia. The design used was a double-blind, multicenter trial with patients allocated randomly to either oxcarbazepine or carbamazepine. Trial duration for each patient was between 6 to 32 weeks. Starting dose was 300 mg 2 times a day for oxcarbazepine and 200 mg 2 times a day for carbamazepine. Dosage was increased gradually up to achieve the best therapeutic effect combined with satisfactory tolerability. Forty-eight patients aged 40 years and older with newly diagnosed untreated trigeminal neuralgia were included. All patients in the oxcarbazepine group experienced a 50% reduction in their number of attacks per week, compared with 95% of patients treated with carbamazepine. Ninety-six percent of oxcarbazepine treated patients had a reduction of 2 days or more in the number of days with pain per week compared with just 86% in the carbamazepine group. In the global assessment of efficacy, 96% of patients on oxcarbazepine had a "successful" rating compared with 91% on carbamazepine. No severe adverse effects were reported. Tiredness, dizziness, and vertigo were the most frequent adverse events of both treatments. Sixty-eight percent of patients on oxcarbazepine had a rating of "excellent" in the global assessment of tolerability compared with 52% on carbamazepine. Zakrzewska et al[13] in a study on 15 patients stated that its effectiveness was rather short term necessitating surgical intervention. The outcome measures used were: McGill Pain Questionnaire, Hospital Anxiety and Depression Scale, patient satisfaction questionnaire, and clinician's global evaluation. As surgery was associated with better outcome, patients may therefore benefit from having surgery earlier rather than later in the disease process to improve quality of life, freedom from medication, and the need for regular follow up.

Experiments in cats anesthetized with alpha-chloralose showed that tizanidine (TZD: 5-chloro-4-[2-imidazolin-2-yl-amino]-2,1,3-benzothiodiazole) partly resembled carbamazepine and baclofen in that it depressed excitatory transmission and facilitated segmental inhibition of neurons in the spinal trigeminal nucleus oralis that responded to tapping but did not affect the response of neurons that responded to light stroking of the skin or bending the whiskers. Vilming et al[14] showed that tizanidine was well tolerated, but the effects, if any, were inferior to those of carbamazepine. Fromm et al[15] described 6 patients who elected to continue taking tizanidine and experienced a recurrence of their attacks of trigeminal neuralgia within 1 to 3 months. The limited efficacy of tizanidine in the treatment of trigeminal neuralgia may be related to the fact that it has no effect on neuronal responses to low-threshold mechanoceptive stimuli, suggesting that low-threshold mechanoceptive neurons play an important role in the pathogenesis of trigeminal neuralgia.

Gilron et al[16] studied response of topiramate in 3 patients. All 3 patients responded to topiramate in this main study and entered a subsequent confirmatory study consisting of 3 topiramate-placebo crossovers. In the main study, topiramate reduced pain by 31%, 42%, and 64% in the 3 patients ($P = .04$). However, topiramate showed no effect in the confirmatory study. Lechin et al[17] compared pimozide with carbamazepine in a double-blind crossover trial in 48 patients with trigeminal neuralgia who were refractory to medical therapy. Pimozide treatment produced greater reduction in trigeminal neuralgia symptoms than carbamazepine treatment. All of the pimozide-treated patients improved, whereas only 56% of carbamazepine treated patients were relieved of their pain. Both drugs provoked some adverse effects.

Patients taking anticonvulsant drugs display a broad spectrum of side effects. Particularly, in the beginning of treatment and with increasing doses of carbamazepine, side effects such as dizziness, ataxia, drowsiness, and reduction of alertness occur. These side effects improve some days after the dose has reached a stable level. Delcker et al[18] quantified the effect of carbamazepine on postural stability by posturography. They carried out different neuropsychologic tests to study cognitive effects of carbamazepine. The composite equilibrium score showed a significant reduction of postural stability with increasing doses of carbamazepine. In sensory analysis the somatosensory ratio was significantly influenced by increased doses of carbamazepine during the study. Mean reaction time of tonic alertness and physical alertness varied significantly with different doses of carbamazepine. There was a significant influence in patients' attention during trail making tests and divided attention tests with increase in carbamazepine. They concluded that the rate of change of carbamazepine doses is an important determinant of cognitive and motor functions in the phase of increasing doses. Kramlinger et al[19] stated that carbamazepine is generally safe and well tolerated. Although serious adverse reactions such as hematologic toxicity may occur rarely, carbamazepine-induced rash is common. These benign rashes can occasionally progress to more fulminant and life-threatening eruptions.

Baclofen (β-4-chlorophenyl-γ-aminobutyric acid) is a new antineuralgic drug. Baclofen shows analgesic properties in rats and resembles carbamazepine and phenytoin in its effects on the spinal trigeminal nucleus of cats; however baclofen gives less undesirable side effects. In the study by Parmar et al[20] of 20 patients under treatment by this drug, 45% were relieved completely from pain whereas in 20% intensity or number of attacks of pain was reduced to half and in 35% effectiveness of baclofen could not be observed. Fromm et al[21] conducted a double-blind crossover study of the effects of baclofen on 10 patients with typical trigeminal neuralgia. Baclofen decreased significantly the number of painful paroxysms in 7 of 10 patients. An open trial in another 50 patients with trigeminal neuralgia refractory to or unable to tolerate carbamazepine showed that 37 (74%) were relieved of their attacks by baclofen, either alone (12 patients) or in combination with previously ineffective doses of carbamazepine or phenytoin (25). On long-term follow-up of 1 to 5 years (mean, 3 years), 18 of 60 patients (30%) continued pain-free while receiving baclofen; 10 (17%) went into remission after 3 to 6 months; 13 (22%) became refractory to baclofen after 1 to 18 months; and 2 (3%) elected operation despite a good response to baclofen. Steardo et al[22] conducted a clinical trial of baclofen in 25 subjects, 16 suffering from trigeminal neuralgia, of which 5 were refractory to or unable to tolerate carbamazepine. All groups, as a whole, were improved by 68.61%. These results substantiate that baclofen is useful in the treatment of trigeminal neuralgia and other painful conditions. Fromm et al[23] compared L-baclofen with racemic baclofen (Lioresal) in a double-blind crossover trial in 15 patients with typical trigeminal neuralgia. L-Baclofen was more effective than 5 times as much racemic baclofen in 9 patients. Six of these 9 patients have continued pain-free on L-baclofen for 4 to 17 months (mean, 10 months). L-Baclofen was much better tolerated than racemic baclofen. The results suggest that L-baclofen represents a significant improvement over racemic baclofen in the treatment of trigeminal neuralgia, and support our laboratory observations indicating that D-baclofen antagonizes the action of L-baclofen.

Antidepressants tend to be particularly effective for atypical forms of trigeminal neuralgia. Only 1 study on clomipramine and amitriptyline showed a high level of evidence. Clomipramine is the most potent 5-HT reuptake blockade agent among the antidepressants. Carasso et al[24] compared the effect of clomipramine and a less powerful 5-HT reuptake blockade agent (amitriptyline) to test the hypothesis that brain 5-HT is a mediator of pain sensation. The results after 3 months of treatment showed that clomipramine was better than amitriptyline in treating trigeminal neuralgia. Clomipramine was better tolerated. The results support the hypothesis that in certain pain situations, clomipramine exerts a beneficial effect, not only because of its effect on the depression and anxiety level of the patient, but also via its effects on the 5-HT brain system. Epstein et al[25] studied the efficacy of topical capsaicin in neuropathic and neuralgic pain and the effect of differing dosages and frequency of application. On the basis of the findings in this open-label clinical trial, controlled clinical study of capsaicin in neuropathic oral pain states seems warranted.

Anticonvulsants are effective in treating trigeminal neuralgia. Carbamazepine and its analogues were effective in trigeminal neuralgia in one study each. Phenytoin is considered the second drug of choice in trigeminal neuralgia after the failure of carbamazepine but our search did not show a single study with high level of evidence on phenytoin. Lamotrigine is effective in refractory trigeminal neuralgia; however, adverse effects may occur. Only 1 study showed the effectiveness of gabapentin, clonazepam, and topiramate each and further research is needed to prove their efficacy. The effects of tizanidine are inferior to that of carbamazepine and recurrence may occur. Oxcarbazepine, lamotrigine, and pimozide offer satisfactory treatment in refractory trigeminal neuralgia. Baclofen, a skeletal muscle relaxant, also provides

promising results mainly in refractory trigeminal neuralgia. Common side effects associated with these agents typically involve the central nervous system and include sedation, dizziness, ataxia, and nausea. In addition, hematologic toxicity and skin rash can be induced by the older anticonvulsants like carbamazepine. No drug has shown superiority over carbamazepine at acceptable toxicities. An antidepressant like clomipramine is better than amitriptyline in treating trigeminal neuralgia.

Due to insufficient research data, there is a need for high quality randomized controlled trials in this area of medicine. Scientific evidence alone does not dictate the selection of the treatment. When making health care decisions, clinicians also should consider a combination of values from patients and from professionals that determines if the intervention benefits are worth the cost. The application of evidence into clinical practice has to be related to professional expertise and the need of the patient.

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