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THERAPY IN PRACTICE

Refractory Trigeminal Neuralgia

Non-Surgical Treatment Options

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Abstract The guidelines on trigeminal neuralgia management published by the American Academy of Neurology (AAN) and the European Federation of Neurological Societies (EFNS) recommended that patients unresponsive to carbamazepine or oxcarbazepine be offered the surgical option. However, because some patients may not be willing to resort to surgery, we searched the literature for treatment in refractory trigeminal neuralgia. We found other oral treatments, intranasal spray, subcutaneous injections, various kinds of peripheral nerve blocks and injections of botulinum toxin. On the basis of the available evidence we suggest that no oral treatment other than carbamazepine or oxcarbazepine is useful. Among the other options, there is increasingly strong evidence that botulinum toxin injections are efficacious and may be offered before surgery or to those unwilling to undergo surgery.

1 Introduction

First of all, we must explain what is meant by trigeminal neuralgia (TN) and then by refractory TN. TN is characterized by sudden, usually unilateral, severe, brief, stabbing recurrent episodes of pain in the distribution of one or more branches of the trigeminal nerve [1]. A distinction should be made between classical TN (no cause other than a neurovascular compression can be found) and symptomatic TN (secondary to major neurological disease, such as multiple sclerosis or benign tumours of the cerebellopontine angle). It should be noted that categorization of TN into typical and atypical forms is based on symptom constellation and not aetiology [2, 3].

The guidelines on TN management that have been agreed upon and jointly published by the American Academy of Neurology (AAN) and the European Federation of Neurological Societies (EFNS) were very clear as to the medical treatment. On the basis of evidence, the treatment should begin either with carbamazepine 400–1200 mg/day or with oxcarbazepine 900–1800 mg/day. If the patient reaches the therapeutic dosage without achieving the desired pain relief, surgery should be proposed, which is extremely efficacious in TN [2, 3].

Hence, the definition of 'refractory trigeminal neuralgia' is easy: a patient with TN that is a non-responder to either of these two drugs, or a patient that cannot take them because of specific counter indications or who cannot reach the therapeutic dosage because of excessive adverse effects.

Many patients, however, may not accept surgery that easily. In this case, the AAN-EFNS guidelines suggest trying other medical options, as monotherapy or add-on. In particular, their analysis of the evidence-based trials led to the following suggestions: baclofen, lamotrigine and pimozide may be considered to control pain in patients with classical TN (grade C recommendation). In other words, very weak evidence was available for anything besides carbamazepine/oxcarbazepine.

We decided to find out if other treatment options to control refractory TN are available, taking into account oral treatments and also treatments that could be considered minimally invasive. To do so, we searched the material published since 2006, i.e. the last year analysed by the above-mentioned guidelines.

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2 Search Strategy

We searched PubMed from 2006 to August 2012, using the string 'trigeminal neuralgia treatment' and the limits 'Clinical trial', 'Humans' and 'English'. We excluded studies dealing with surgical treatments, peripheral and central neurostimulation therapy, conditions other than classical TN and mixed studies without a clear indication of how many patients were affected by TN. The findings are summarized in Fig. 1.

3 Results of the Literature Search

We found 68 items. Of these, 12 were completely not pertinent, 32 dealt with surgical treatments and 7 assessed peripheral or central neurostimulation procedures. Seventeen studies were eligible and were thus attentively read. One study was a duplicate [4, 5]. One study, dealing with trigeminal neuropathic pain, did not include any patient with TN [6]. One study was a review on TN management [7]. One study was an experimental pain study by capsaicin injection [8]. Finally, one study was a trial of oxcarbazepine, which only reasserted the efficacy of this drug and was therefore outside the scope of this review [9]. These five articles were excluded and the remaining 12 selected for final analysis (Fig. 1).

3.1 Oral Treatments

A first consideration is that neither baclofen nor pimozide were studied in the 2006–2012 period, thus the weak level of recommendation that the AAN-EFNS guidelines attributed to these two drugs remains unchanged [2, 3].

In contrast, the third drug that had reached a grade C recommendation, i.e. lamotrigine, was studied in two recent trials. The first trial was a double-blind placebo-controlled trial of lamotrigine in combination with other medications for neuropathic pain [10]. The result was that lamotrigine did not show any superiority over placebo in any of the endpoints. There were only 11 patients with TN. The second trial was a crossover, head-to-head trial against carbamazepine in 21 TN patients [11]. Patients were titrated to lamotrigine 400 mg and carbamazepine 1,200 mg. Efficacy of the medications was determined by a visual analogue scale (VAS) and a verbal rating scale (VRS). On both VAS and VRS assessments, carbamazepine was beneficial to 90.5 % (19/21) and lamotrigine to 62 % (13/21) of the patients. Hence, lamotrigine does not appear a good option in patients resistant to carbamazepine/oxcarbazepine if used in monotherapy. It is worth noting that lamotrigine had been found effective as add-on therapy [12], thus, if the patient must be kept to a relatively low dosage of carbamazepine/oxcarbazepine because of adverse effects, then it is worth trying to add lamotrigine. In this case, we recommend a very slow titration of lamotrigine (25 mg daily for 2 weeks, then add 25 mg every 2 weeks till reaching the therapeutic dosage, i.e. 200–400 mg) to minimize the risk of skin rash, a major problem with lamotrigine [13].

Two other studies have been dealing with oral therapy alone. In a primary-care setting, observational study, 65 patients refractory to previous 'analgesic therapy' (NSAIDs, paracetamol [acetaminophen], opioids, tricyclic

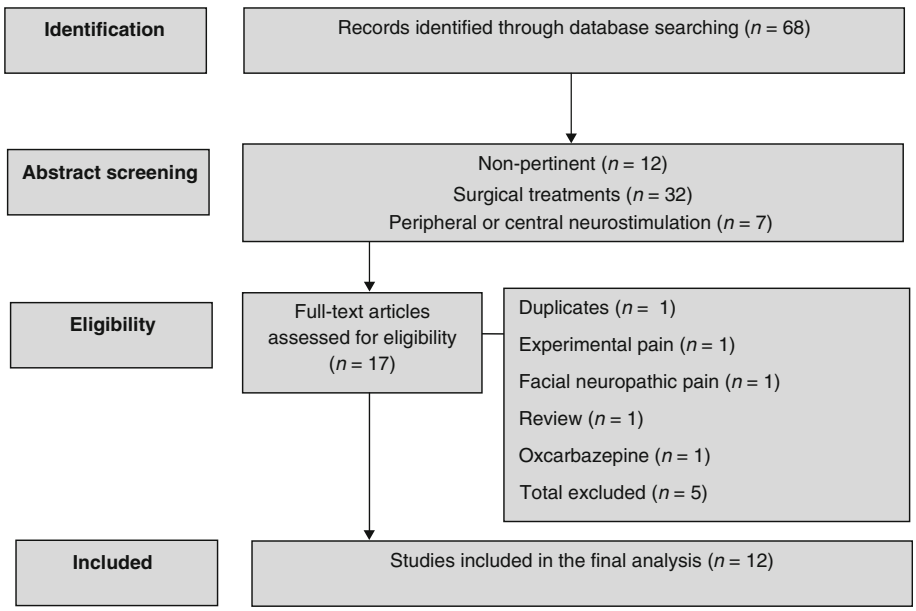

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) chart

antidepressants or other anticonvulsants) were treated with pregabalin in monotherapy ($n = 36$) or add-on ($n = 29$) for 12 weeks [4, 5]. The success of pregabalin, titrated to a rather low mean level (around 200 mg), was undeniable: after 12 weeks, pregabalin reduced the baseline pain intensity by 55 %, with 59 % of responders (pain relief ≥50 %). Furthermore, pregabalin improved anxiety, depression, sleep, physical function and health state. We, however, are strongly doubtful about the diagnosis: all enrolled patients had to be 'positive' at the 0–10 DN4 neuropathic pain questionnaire [14]. This questionnaire is excellent in disclosing neuropathic pain, when the patients score 4 or more. But in classical TN, a peculiar type of neuropathic pain because by definition there must be no sensory deficit, the patients usually score 1 (does your pain have the quality of electric shocks?), whereas the patients in this study scored an average of 6 and 7 in the two monotherapy and add-on groups. In short, we believe that many patients had, rather than classical TN, an atypical facial pain. This would also explain why many patients had some degree of benefit from NSAIDs, paracetamol, opioids and antidepressants. In another open-label trial, ten patients with TN received levetiracetam for 10 weeks [15]. All of the patients had to be good responders to 'standard treatment' (carbamazepine, oxcarbazepine or lamotrigine), thus, this is not a study in refractory patients. Nevertheless, when switched from their usual drug to levetiracetam at high dosages (3,000–5,000 mg daily), 5/10 patients used escape medication (their previous drug) at some point during the trial. At the end of the 10 weeks, four patients were considered 'responders', three 'non-responders', two dropped out because of insufficient benefit and one dropped out because of social reasons. In short, in this pilot study, levetiravetam did not even approach the frequency of responders to carbamazepine/oxcarbazepine (equally about 88 %).

No orally administered drug, therefore, seems promising for patients resistant to carbamazepine/oxcarbazepine.

3.2 Spray and Subcutaneous Injections

Positive news came from a crossover, randomized controlled trial on intranasal lidocaine (lignocaine) [16]. Twenty-five patients with second-division TN were randomized to receive two sprays (0.2 mL) of either lidocaine 8 % or saline placebo in the affected-side nostril using a metered-dose spray. After a 7-day period, patients were crossed over to receive the alternative treatment. The results were impressive: after 15 min the VAS decreased from 8.0 to 1.5 cm with lidocaine and remained unchanged (7.9 pre- and 7.6 cm post-treatment) with placebo. The patients remained pain free for an average time of 4.3 h. The authors explained that the local anaesthetic was expected to block the sphenopalatine ganglion and that the patients could carry the spray bottle and use it whenever pain appeared. A further advantage, despite 15 patients reporting stinging or burning sensation on the nasal mucosa, would be the absence of serious adverse events. The method has two main limitations: it is restricted to patients with pain in the second trigeminal division and the study only examined the response to triggering manoeuvres. Unfortunately, spontaneous pain was not tested and this peripheral block would probably be ineffective on it.

A Japanese group published two trials on sumatriptan [17, 18]. Because mechanical compression of the trigeminal root by an artery is thought to cause classical TN in the great majority of patients, sumatriptan, i.e. a serotonin 5-$HT_{1B/1D}$ receptor agonist, may be useful by inhibiting neurogenic inflammation and vasodilation near the irritated trigeminal root. In a randomized controlled trial, 24 patients with classical TN refractory to previous treatment received subcutaneously either 3 mg of sumatriptan or saline. After 7 days, patients crossed over to receive the alternative treatment. Fifteen min after injection of sumatriptan, but not of placebo, the baseline VAS decreased from 8.3 to 2.4 cm. The number of patients who benefited from sumatriptan was 20 whereas only one patient reported improvement after placebo. The mean duration of pain relief was 7.9 h. Encouraged by this first trial, the authors did another, in 15 patients, whom they treated first with the subcutaneous injection of sumatriptan 3 mg, then (having verified efficacy of the drug) with 1-week oral administration (50 mg twice daily). At the end of oral treatment, the VAS was significantly decreased and this beneficial reduction persisted a further week after treatment discontinuation. The adverse effects associated with oral administration were fatigue in two patients, nausea in one and chest discomfort in one. The problem with sumatriptan is that patients with TN should take 100 mg of sumatriptan daily for months, at least, and the consequences of its long-term use are not known, but a triptan overuse headache would certainly be unavoidable.

3.3 Blocks

A study assessed the efficacy of blocking the trigger points with ropivacaine alone or in combination with gabapentin [19]. Thirty-six TN patients were assigned either to gabapentin alone or to an anaesthetic block once a week alone, or to the combination of the two. The anaesthetic block alone gave poor results, with 7 out of 12 patients discontinuing because of insufficient pain relief. However, the repeated blocks together with oral gabapentin were far better than gabapentin alone at 7 and 28 days after treatment. It was possible to reduce the dosage of gabapentin and also obtain an improvement of functional well-being.

One open-label study reported the efficacy of bupivacaine injected into the infraorbital, mental or mandibular nerves [20] in 14 patients diagnosed with classical TN in the second or third division, and who were resistant to carbamazepine at high dosages. Once the target foramen was reached with an epidural catheter, a pump injected 60 mL of 0.5 % bupivacaine hydrogen chloride at a rate of 1 mL/h. After 60 h the catheter was removed. None of the patients complained about sensory disturbances such as paraesthesia or any sensory disturbance after this procedure. Five days after the procedure, at 2 weeks and at 1, 3, 6 and 9 months, the effects were evaluated. The pain score decreased from a mean of almost 70 to about 20 and this change remained highly significant till the last evaluation, 9 months after the procedure ($p < 0.001$). Another study [21] examined the effect of high concentration (10 %) lidocaine injected into the supraorbital, infraorbital, maxillary or mandibular nerves, or the Gasserian ganglion, in 35 patients with classical TN, many of them unresponsive to carbamazepine. Only 12 patients were found to respond and these remained pain free for 3–172 weeks.

We report these three studies together because (regardless of the different level of invasiveness and efficacy) they can be commented on with the conclusions of the AAN-EFNS guidelines: "The evidence about peripheral techniques (including all sorts of blocks with anaesthetics distal to the Gasserian ganglion) either is negative (two Class I studies on streptomycin/lidocaine) or is insufficient (Class IV studies for all the other peripheral techniques)".

3.4 Botulinum Toxin

Two studies dealt with subcutaneous infiltration of botulinum toxin A [1, 2]. Because botulinum toxin was not examined in the AAN-EFNS guidelines on TN management, neither in the section on medical treatment nor in the one on surgical treatment, thus provoking a complaint [24], we decided to search for all trials with botulinum toxin in patients with TN, with no time limit. We found six trials [22, 23, 25–28], plus many case reports that are not examined here.

In general, the results were excellent: 81 patients underwent the injections, with a responder rate of 85 %, i.e. similar to that of carbamazepine/oxcarbazepine, and the pain relief lasted on average 105 days (Table 1). Complications were mostly represented by transient facial weakness (38 patients), sometimes with obvious facial asymmetry. Nevertheless, the motor deficit disappeared in a few weeks. Some patients showed focal oedema at the sites of injection, lasting about 1 week. In short, according to these reports the efficacy was comparable to that of carbamazepine/oxcarbazepine and the adverse effects were very minor.

Table 1 Evidence table of trials that assessed botulinum toxin injections

Study, year	Diagnosis/soundness	Blindness	Randomized	Site of injection	R/T	Duration of effect
Borodic and Acquadro [28], 2002	CTN/no clear definition	Open	No	Painful dermatome	8/11	5–12 weeks
Türk et al. [27], 2005	Refractory CTN/clear description but 3 patients had bilateral TN[a]	Open	Yes	Above and below the zygomatic arch	8/8	6 months
Piovesan et al. [26], 2005	CTN/clear definition but 3 patients had previous surgery	Open	No	Painful site	13/13	60 days
Zúñiga et al. [25], 2008	Refractory CTN/no clear definition	Open	No	Trigger zones	10/12	60 days
Bohluli et al. [22], 2011	Refractory CTN/clear definition	Open	No	Trigger zones	15/15	6 months
Wu et al .[23], 2012	Refractory CTN/clear definition	Double-blind	Yes	Trigger zones	15/22	12 weeks
Total					69/81 (85 %)	105 days

CTN classical trigeminal neuralgia, *R/T* responders/total number of patients that were injected with botulinum toxin, *TN* trigeminal neuralgia

[a] That 3 out of 8 patients were diagnosed as bilateral CTN casts some doubts on the soundness of diagnosis, the frequency of bilateral CTN in controlled studies being zero [2, 3]

Most studies were open label with no control, but the most recent one [23] was a randomized, double-blind, placebo-controlled trial in 42 patients with classical TN.

Hence, when compared with the other options that we examined here, botulinum toxin injections seem very promising.

Our main concern with botulinum toxin is the difficulty in explaining the mechanism of action. Botulinum toxin is supposed to block the TRPV1 receptor of unmyelinated C fibre terminals and to counteract peripheral sensitization of C nociceptors. This, in turn, would limit the release of substance P, calcitonin gene-related peptide and glutamate from presynaptic terminals of the primary sensory neurons, thus counteracting central sensitization [8, 29, 30]. Indeed, botulinum toxin proved efficacious in several experimental pain models of neuropathic pain, as well as in some neuropathic pain conditions. But in classical TN this mechanism would not work. Blocking C nociceptors of the trigger zones should not block the trigger mechanism. According to an established notion [31, 32], innocuous stimuli excite large-myelinated Aβ fibres that ephaptically excite trigeminal root fibres near the entry zone into the pons, which have become hyperexcitable because of mechanical (neurovascular compression, benign tumours) or inflammatory (multiple sclerosis) demyelination [33].

Naturally, however, what really matters is efficacy in the patients. Botulinum toxin may also have other mechanisms.

4 Conclusion: Practical Guide

We suggest to follow the AAN/EFNS guidelines on TN management, i.e. if a patient reaches the therapeutic dosage either with carbamazepine or oxcarbazepine and does not have satisfactory pain relief then the patient should be referred for surgery. If a patient has too many adverse effects either with carbamazepine or oxcarbazepine, then the other drug should be tried. If a patient cannot reach the therapeutic dosage with both drugs, then the patient should be referred for surgery.

For patients who do not want to undergo surgery, lamotrigine as add-on or botulinum toxin injections should be tried.

One may speculate that botulinum toxin injections may straightforwardly be regarded as an alternative to surgery, but the evidence is not yet strong enough.

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References

1. Merskey H, Bogduk N. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. Seattle: IASP Press; 1994. p. 59–71.
2. Cruccu G, Gronseth G, Alksne J, et al. AAN-EFNS guidelines on trigeminal neuralgia management. Eur J Neurol. 2008;15(10):1013–28.
3. Gronseth G, Cruccu G, Alksne J, et al. Practice parameter: the diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies. Neurology. 2008;71(15):1183–90.
4. Pérez C, Navarro A, Saldaña MT, et al. Patient-reported outcomes in subjects with painful trigeminal neuralgia receiving pregabalin: evidence from medical practice in primary care settings. Cephalalgia. 2009;29(7):781–90.
5. Pérez C, Saldaña MT, Navarro A, et al. Trigeminal neuralgia treated with pregabalin in family medicine settings: its effect on pain alleviation and cost reduction. J Clin Pharmacol. 2009;49(5):582–90.
6. Scrivani S, Wallin D, Moulton EA, et al. A fMRI evaluation of lamotrigine for the treatment of trigeminal neuropathic pain: pilot study. Pain Med. 2010;11(6):920–41.
7. van Kleef M, van Genderen WE, Narouze S, et al. World institute of medicine: 1. Trigeminal neuralgia. Pain Pract. 2009;4:252–9.
8. Gazerani P, Pedersen NS, Staahl C, et al. Subcutaneous botulinum toxin type A reduces capsaicin-induced trigeminal pain and vasomotor reactions in human skin. Pain. 2009;141(1–2):60–9.
9. Gomez-Arguelles JM, Dorado R, Sepulveda JM, et al. Oxcarbazepine monotherapy in carbamazepine-unresponsive trigeminal neuralgia. J Clin Neurosci. 2008;15(5):516–9.
10. Silver M, Blum D, Grainger J, et al. Double-blind, placebo-controlled trial of lamotrigine in combination with other medications for neuropathic pain. J Pain Symptom Manage. 2007;34(4):446–54.
11. Shaikh S, Yaacob HB, Abd Rahman RB. Lamotrigine for trigeminal neuralgia: efficacy and safety in comparison with carbamazepine. J Chin Med Assoc. 2011;74(6):243–9.
12. Zakrzewska JM, Chaudhry Z, Nurmikko TJ, et al. Lamotrigine (lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled crossover trial. Pain. 1997;73(2):223–30.
13. Wiffen P, Rees J. Lamotrigine for acute and chronic pain. Cochrane Database Syst Rev 2007;(2):CD006044.
14. Bouhassira D, Attal N, Alchaar H, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005;114(1–2):29–36.
15. Jorns TP, Johnston A, Zakrzewska JM. Pilot study to evaluate the efficacy and tolerability of levetiracetam (Keppra) in treatment of patients with trigeminal neuralgia. Eur J Neurol. 2009;16(6):740–4.
16. Kanai A, Suzuki A, Kobayashi M, et al. Intranasal lidocaine 8% spray for second-division trigeminal neuralgia. Br J Anaesth. 2006;97(4):559–63.
17. Kanai A, Saito M, Hoka S. Subcutaneous sumatriptan for refractory trigeminal neuralgia. Headache. 2006;46(4):577–82. (discussion 583–4).
18. Kanai A, Suzuki A, Osawa S, et al. Sumatriptan alleviates pain in patients with trigeminal neuralgia. Clin J Pain. 2006;22(8):677–80.
19. Lemos L, Flores S, Oliveira P, et al. Gabapentin supplemented with ropivacain block of trigger points improves pain control and

quality of life in trigeminal neuralgia patients when compared with gabapentin alone. Clin J Pain. 2008;24(1):64–75.
20. Dergin G, Gocmen G, Sener BC. Treatment of trigeminal neuralgia with bupivacaine HCL using a temporary epidural catheter and pain pump: preliminary study. J Craniomaxillofac Surg. 2012;40(2):124–8.
21. Han KR, Kim C, Chae YJ, et al. Efficacy and safety of high concentration lidocaine for trigeminal nerve block in patients with trigeminal neuralgia. Int J Clin Pract. 2008;62(2):248–54.
22. Bohluli B, Motamedi MH, Bagheri SC, et al. Use of botulinum toxin A for drug-refractory trigeminal neuralgia: preliminary report. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011;111(1):47–50.
23. Wu CJ, Lian YJ, Zheng YK, et al. Botulinum toxin type A for the treatment of trigeminal neuralgia: results from a randomized, double-blind, placebo-controlled trial. Cephalalgia. 2012;32(6):443–50.
24. Teive HA, Piovesan EJ, Kowacs PA, et al. Comment on AAN-EFNS guidelines on trigeminal neuralgia management. Eur J Neurol. 2009;16(5):e105.
25. Zúñiga C, Díaz S, Piedimonte F, et al. Beneficial effects of botulinum toxin type A in trigeminal neuralgia. Arq Neuropsiquiatr. 2008;66(3A):500–3.
26. Piovesan EJ, Teive HG, Kowacs PA, et al. An open study of botulinum-A toxin treatment of trigeminal neuralgia. Neurology. 2005;65(8):1306–8.
27. Türk U, Ilhan S, Alp R, et al. Botulinum toxin and intractable trigeminal neuralgia. Clin Neuropharmacol. 2005;28(4):161–2.
28. Borodic GE, Acquadro MA. The use of botulinum toxin for the treatment of chronic facial pain. J Pain. 2002;3(1):21–7.
29. Aoki KR. Review of a proposed mechanism for the antinociceptive action of botulinum toxin type A. Neurotoxicology. 2005;26(5):785–93.
30. Aoki KR, Francis J. Updates on the antinociceptive mechanism hypothesis of botulinum toxin A. Parkinsonism Relat Disord. 2011;17(Suppl. 1):S28–33.
31. Kugelberg E, Lindblom U. The mechanism of the pain in trigeminal neuralgia. J Neurol Neurosurg Psychiatry. 1959;22(1):36–43.
32. Cruccu G, Bonamico LH, Zakrzewska JM. Cranial neuralgias. Handb Clin Neurol. 2010;97:663–78.
33. Cruccu G, Biasiotta A, Di Rezze S, et al. Trigeminal neuralgia and pain related to multiple sclerosis. Pain. 2009;143(3):186–91.