



The Open Pain Journal

Content list available at: <https://openpainjournal.com>



REVIEW ARTICLE

A Historical Note on the Treatment of Trigeminal Neuralgia

Silvana Bara¹, Gentian Vyshka^{2,*} and Eris Ranxha³

¹Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, University of Medicine in Tirana, Tirana, Albania

²Biomedical and Experimental Department, Faculty of Medicine, University of Medicine in Tirana, Tirana, Albania

³Stroke Unit, University Hospital Centre "Mother Teresa" Tirana, Tirana, Albania

Abstract:

Trigeminal neuralgia, otherwise known under the French denomination of *tic douloureux*, is a chronic painful condition of a particular severity. Its descriptions are numerous and date back to centuries before. Although the anatomy of the trigeminal nerve has been well known, the pathophysiology and hence the treatment of this disease has been largely fortuitous. Disparate pharmacological and surgical approaches have been tried, some of them heralding a much-required therapeutic success. The authors make a brief description of the first sources that have systematized the disease, along with all therapies documented in a written form, especially from indexed journals of the two last centuries. Very few remnants of the previous therapies, actually considered obsolete, have survived to the proof of time; one of them relies on the possible role of the autonomic nervous system and anticholinergic therapies, later replaced from modern conservative and interventional approaches. Anticonvulsants have been, since 1940, the mainstay of the therapy, however, progressions in neurosurgery and mini-invasive procedures have substantially improved the quality of life and the prognosis of an otherwise very painful and chronic condition.

Keywords: Trigeminal neuralgia, Facial pain, Tic douloureux, Microvascular decompression, Anticonvulsants, Chronic condition.

Article History

Received: April 5, 2021

Revised: June 3, 2021

Accepted: June 24, 2021

1. INTRODUCTION

Trigeminal Neuralgia (TN) has been a major challenge to family doctors, neurologists, and dental specialists long before its systematized approach as a diagnostic notion. Actually, the prevailing position is to consider it as a true neuropathy, albeit this has hardly been reflected in the classification of peripheral neuropathies as of to date. Even authoritative sources make a vague distinction between TN and trigeminal neuropathy, based on the fact that TN has a clear and constant painful component, whereas neuropathy as a concept not necessarily is equivalent to pain itself but may present with other symptoms such as numbness, paresthesia, hypoalgesia and so on [1].

The first PubMed/Medline indexed papers referring to *tic douloureux*, the French disambiguation of TN, dates from 1806 and are all case reports of particular interest, curiosity, and meticulousness as it comes to the narratives, published from *Edinburgh Medical and Surgical Journal* [2, 3]. Carbonate of iron, cinchona, arsenic, calomel, and opium were some of the conservative options suggested as efficacious and safe [4, 5]. It is worth mentioning that the first systematized reports, as well as the most important bulk of studies come from medical

sources and not from dental specialists. This fact, which might seem trivial in its importance, has a lot of say even in the actual envisioning and understanding of the problem itself [6]. Misinterpreting TN as tooth pain remains, unfortunately, a common error. This will lead to the unnecessary extraction of the presumed 'offending tooth'. Such extractions have even been multiple, with some patients losing several teeth without any proper relief or benefit.

Several factors contribute to this diagnostic error:

(1) Dental anesthesia with or without any tooth extraction will alleviate symptoms immediately, and sometimes, for a period long enough to believe that dental structures were responsible for the ailing; when otherwise the patient suffers from TN [7].

(2) Iatrogenic trigeminal nerve injury happens [8, 9]. Following a problematic dental procedure, patients will turn back to the same doctor, entering a vicious circle of local treatments and re-treatments that will only hypersensitize further the affected area.

(3) Paroxysms of pain elicited while masticating or during tooth percussion are possible, reinforcing the suspicion that one or more teeth are responsible for the condition [10]. This will justify further dental procedures that are destined to fail when the pain is due to TN [11].

* Address correspondence to this author at the Biomedical and Experimental Department, Faculty of Medicine, University of Medicine in Tirana, Tirana, Albania;
E-mail: gvyshka@gmail.com

Detailed descriptions of non-odontogenic toothache and atypical odontalgia are available [9, 12]. Nevertheless, the condition remains seriously challenging, even with a therapeutic armamentarium that is becoming richer year after year.

There is a long list of potential noxious factors and differential diagnoses highly resembling TN: from primary dental diseases to migraine and all the spectrum of facial pain and all forms of atypical headache. Although TN in its typical form is very particular and therefore easily detectable, however, the classical and clinical picture might be surreptitious and atypical in the early phase, hence the need for detailed diagnostic criteria (Table 1).

Table 1. Diagnostic criteria of TN.

Diagnostic criteria of the classical TN [13]	
A	Paroxysmal attacks of pain lasting from a fraction of a second to 2 minutes, affecting one or more divisions of the trigeminal nerve and fulfilling criteria B and C
B	Pain has at least one of the following characteristics: 1. Intense, sharp, superficial, or stabbing 2. Precipitated from trigger areas or by trigger factors
C	Attacks are stereotyped in the individual patient
D	There is no clinically evident neurological deficit
E	Not attributed to another disorder

2. OBSOLETE TREATMENTS: ANY RATIONALE?

Geo Nesse Hill, a surgeon from Chester, has published an extraordinary narrative on the several years' natural course of *tic douloureux* [14]. The patient, a female aged in her fifties, respects the epidemiology of TN as a rule: she is a middle-aged woman, typical for this disorder. Paroxysms of severe pain in the forehead considered rheumatic in nature were causing emaciation and requests for continuing medical visits and assistance.

The first set of medical treatments comprised:

- (a) Blisters
- (b) A stimulating cold lotion for the face and head
- (c) An acrid sternutatory
- (d) Cathartics

The wide usage of cathartics, senseless and obsolete from the actual medical point of view, is worth mentioning since it targeted an extremely wide range of diseases, serving mainly and purely as a placebo in the majority of cases. As the initial mixture served little, the suffering woman had another composite treatment:

- (a) Leeches to the temples
- (b) Blisters
- (c) Active purges
- (d) Surgery

The surgical procedure involved cutting both jaws of the right side all the way down to the bone, followed by a division of the infra-orbital nerve. Obviously, the woman needed further interventions, some weeks later that included:

- (a) Incision completely across the palatine arch
- (b) Active cathartics
- (c) A mercurial course
- (d) Warm baths
- (e) Laudanum

The use of laudanum (opium) obviously is of help, but since the improvement was unstable and not lasting, the patient received treatment with blisters, leeching, and even *arsenic*. The ensuing treatment was composed of repeated incisions as well as plenty of other preparations:

- (1) Belladonna
- (2) Conium (internally & externally) [poison hemlock]
- (3) Soap liniments with opium
- (4) Opium combined with digitalis
- (5) Iron preparations
- (6) Arsenic
- (7) Epsom salts [magnesium sulphate]

To close up, the woman ended up in being 'in good health and spirits' [14].

3. EXCURSUS: SOME CHOLINERGIC INFLUENCES

Of course, the variety of treatments as described above do reflect the developments of pharmacology and medicine of the time. However, we would like to shed light on a particular perspective of all previous (and weighed as obsolete) treatments, some of which have a strong autonomous/cholinergic component.

The effect of purges/cathartics on the vagal system is apparent, however, some authors highlight the vagal effects throughout their therapeutics. Here below, some sentences from the clinical lecture of Dr. Pearson – dating 1807:

'...calomel was directed to be swallowed, and mercurial ointment to be rubbed into the skin, till a very sore mouth was produced at first and next a copious ptyalism...' [15].

The acrobatic play between the cholinergic stimulation and inhibition (a strong vagolytic such as *belladonna* was part of the armamentarium) seems to have been playing some role in occasionally controlling the symptomatology of the patients. Maybe, and due to the fact that we are dealing with strong, active principles, all these interventions had some placebo effect. Calomel (mercurous chloride working as a purgative) was not the only preparation applied from the last source. Hemlock, hyoscyamus (here again an anticholinergic!), Peruvian bark (*cinchona*), etc., are mentioned, albeit eventually of 'no service' [15].

It's not surprising, therefore, that many of these (and other) treatments may still be found in publications and websites promoting homeopathic treatments. [16, 17]. Not only the 'alternative' medicine has suggested an (anti) cholinergic pathway of treating TN: several studies have underscored the importance of the autonomic nervous system in triggering painful occurrences [18, 19]. The bulk of studies focusing on

parasympathetic activity and drugs influencing this field might be deferred to some decennia before; however, one should not forget the fact that antiepileptic drugs are widely used and accepted as efficacious for TN and possess a highly intrinsic anticholinergic activity [20]. Carbamazepine, which has a mild anticholinergic profile, is clearly one of the most active antiepileptic medications in the treatment of TN [21].

Since 1940, authors have reported diphenylhydantoin as beneficial [22]. The era of anticonvulsants brought significant improvements in the quality of life of patients, alleviating the unbearable pain of TN. However, the new anticonvulsant patented as Geigy 32883 and later marketed as carbamazepine overshadowed previous drugs. The mechanisms of action of anticonvulsants (including carbamazepine and oxcarbazepine) are multiple: the decrease in neuronal activity through modulation of voltage-gated sodium channels has a strong experimental confirmation [23].

The pharmacological similarity with imipramine, a tricyclic antidepressant is noteworthy: reports of therapeutic success with tricyclics in neuropathic pain are also available, but not for trigeminal neuralgia [24, 25]. Tricyclic antidepressants have an intrinsic and clinically important anticholinergic activity, but their use in the trigeminal neuralgia is of little practical interest [26].

4. HISTORIA MAGISTRA VITAE

...the age-old scriptures-controlled thought, but they were flexible, and their control allowed wide variety in interpretation... [27]. This opinion will be as true when discussing reported results from different authors that dealt with controversial medical occurrences such as TN: sources accept to interpret methods, but at the end, everyone defend their own approach reluctantly and is convinced that the outcome of their patients were the best.

Thus, interpreting the past approaches is not an easy duty. Surgeons, for example, historically have believed that the more current intervention was (thus, bloody or painful), the more probability it had to succeed. Kitson so describes his intervention (1806):

"...I determined to divide the frontal nerve, and made an incision about half an inch in length directly above the eyebrow down to the bone... The operation gave him great pain, and brought on a violent attack of spasm..." [2].

This might be a story of two centuries before, but ever since; surgeons have tried and tested a diversity of surgical procedures. It is clear that the 'vitreous ether' applied from Kitson to his patient could not control the pain; yet the pre-anesthetic age would soon be replaced from other drugs [28].

Exhaustive reviews on the history of surgical interventions for TN are available, but such an approach was synonym to pain, probably until 1853 when Patruban in Germany used a combination of ether, nitrous oxide and chloroform [29]. Iatrogenic injuries were a common occurrence, since for the majority of operating physicians the only efficacious option was to cut somewhere the offending nervous fibers of the trigeminal nerve: localizing the ailing portion of the nerve was approximate and based only on clinical data.

Updated classification of headaches and other pains of a similar nature is available, but all algorithms will hardly replace the intuition of an experienced clinician. Even more, evaluation errors can occur even in the age of the magnetic resonance imaging, a procedure actually considered as of irreplaceable value, when in fact other simpler examinations, can be also of a great diagnostic help [30].

Of course, such a controversial disorder will have even differences in the way that authors describe the history: even the laurels are granted on one side to Fothergill (1773) from English sources, and to André (1756) from French sources, as being the first authors to offer a systematized description to the disorder [31, 32]. Zealous authors have even uncovered in the remote antiquity medical reports of situations similar to TN, eventually described from Aretaeus of Cappadocia already in the second century [33]. Numerous further descriptions and cases followed such as to render impossible an exhaustive list.

5. THERAPY: NOW AND THEN

The anticonvulsants are obviously the first drug of choice (carbamazepine above all) when discussing the modern and non-invasive options. Very few elements remain from therapies of previous centuries that focused on autonomous / parasympathetic influences on the TN. As noted above, carbamazepine has some anticholinergic effects; its discovery in 1962 probably changed substantially the natural history of the disease [34]. Only four years after its discovery and the marketing under the trade name of *Tegretol*, sources were already reporting their enthusiastic results [35].

Even surgery, of course, has had notable advances: Janetta with his microvascular decompression opened a new era, once again probably just re-discovering seventy years later Walter Dandy's findings [36]. The focus was righteously directed onto the Gasser's ganglion, from demyelination hypotheses into the 'ignition' of models due to injured and hyperexcitable axons [37].

Historically, TN treatment has seen the use of almost every anticonvulsant drug. This class of drugs actually represents the most used, from old-fashioned principles like phenytoin, to the brand-new synthesized molecules such as levetiracetam, topiramate, and others [23, 38, 39]. Tricyclic antidepressants, benzodiazepines, baclofen and other pharmacological therapies are also of some interest, especially as add-on therapies when the first drug of choice (carbamazepine) fails to control satisfactorily the paroxysms of pain. The surgical / interventional options are different, from the microvascular decompression, tractotomies, and ethanol infiltration of Gasser's ganglion, just to mention a few of them [40, 41].

CONCLUSION

Trigeminal neuralgia is a painful condition of a particular severity, challenging to the treating clinician and seriously hampering the quality of life of the suffering patient. Although it is technically a neuropathic pain, most sources classify it differently, including it among the wide range of atypical headaches and facial pains. Not infrequently, patients wander from one specialist to the other (even dental practitioners) and sometimes undergo unnecessary and inefficient teeth

extractions, adding more to their everyday ailment.

In fact, the earliest clinical description from Drs. Johannes Michael Fehr and Elias Schmidt in 1688 requires no explanation: *a sharp, shooting pain in the maxilla, which prevented eating solid food, varying in time – the person died of malnutrition...* [42].

The history of TN treatment reflects largely the suffering of the patients as well as the demands of the practicing clinicians for an alleviating therapy that strived to be instantaneous, efficacious, and long-acting, during a course of centuries when little was known, with regard to the pathophysiology of a serious and debilitating medical condition.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no other conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

- Neff BA, Carlson ML, O'Byrne MM, Van Gompel JJ, Driscoll CLW, Link MJ. Trigeminal neuralgia and neuropathy in large sporadic vestibular schwannomas. *J Neurosurg* 2017; 127(5): 992-9. [http://dx.doi.org/10.3171/2016.9.JNS16515] [PMID: 28084915]
- Kitson G. Case of tic douloureux. *Edinb Med Surg J* 1806; 2(7): 319-20. [PMID: 30329996]
- Corkindale J. Case of tic douloureux cured by calomel and opium. *Edinb Med Surg J* 1808; 4(15): 306-9. [PMID: 30331323]
- Beale JE. Case of tic douloureux, successfully treated by carbonate of iron. *Lond Med Phys J* 1823; 50(295): 201-2. [PMID: 30494549]
- Robinson DR. Case of tic douloureux cured by cinchona. *Edinb Med Surg J* 1821; 17(67): 229-32. [PMID: 30330109]
- Truelove E. Management issues of neuropathic trigeminal pain from a dental perspective. *J Orofac Pain* 2004; 18(4): 374-80. [PMID: 15636023]
- Moore D, Chong MS, Shetty A, Zakrzewska JM. A systematic review of rescue analgesic strategies in acute exacerbations of primary trigeminal neuralgia. *Br J Anaesth* 2019; 123(2): e385-96. [http://dx.doi.org/10.1016/j.bja.2019.05.026] [PMID: 31208761]
- Renton T, Yilmaz Z. Profiling of patients presenting with posttraumatic neuropathy of the trigeminal nerve. *J Orofac Pain* 2011; 25(4): 333-44. [PMID: 22247929]
- Renton T, Adey-Viscuso D, Meechan JG, Yilmaz Z. Trigeminal nerve injuries in relation to the local anaesthesia in mandibular injections. *Br Dent J* 2010; 209(9): E15. [http://dx.doi.org/10.1038/sj.bdj.2010.978] [PMID: 21072069]
- Matwychuk MJ. Diagnostic challenges of neuropathic tooth pain. *J Can Dent Assoc* 2004; 70(8): 542-6. [PMID: 15363215]
- Renton T. Tooth-related pain or not? *Headache* 2020; 60(1): 235-46. [http://dx.doi.org/10.1111/head.13689] [PMID: 31675112]
- Okeson JP, Falace DA. Nonodontogenic toothache. *Dent Clin North Am* 1997; 41(2): 367-83. [PMID: 9142490]
- International Classification of Headache Disorders. Headache classification subcommittee of the international headache society. *Cephalalgia* 2004; 24(1): 9-160. [http://dx.doi.org/10.1111/j.1468-2982.2004.00653.x]
- Hill GN. Narrative of a case of tic douloureux. *Edinb Med Surg J* 1822; 18(71): 241-5. [PMID: 30332012]
- Observations on the Treatment of Tic-Douloureux, Illustrated by Cases. *Edinburgh medical and surgical journal* 1834; 41(118): 132. [PMID: 30329299]
- Neepa S. Homeopathic treatment of trigeminal neuralgia (facial pain) <https://azkurs.org/homeopathic-treatment-of-trigeminal-neuralgia-facial-pain.html> [Last accessed March 8th, 2021]
- Lennihan B. Homeopathy for pain management. *Altern Complement Ther* 2017; 23(5): 176-83. [http://dx.doi.org/10.1089/act.2017.29129.ble]
- Kränzl B, Kränzl C. The role of the autonomic nervous system in trigeminal neuralgia. *J Neural Transm (Vienna)* 1976; 38(1): 77-82. [http://dx.doi.org/10.1007/BF01254142] [PMID: 1262865]
- af BJORKESTEN. Effect of parasympatholytic drugs in trigeminal neuralgia. *Acta Psychiatr Scand* 1960; 35(2): 140-4. [http://dx.doi.org/10.1111/j.1600-0447.1960.tb09473.x] [PMID: 13801103]
- Imran I, Koch K, Schöfer H, Lau H, Klein J. Effects of three anti-seizure drugs on cholinergic and metabolic activity in experimental status epilepticus. *J Pharm Pharm Sci* 2019; 22(1): 340-51. [http://dx.doi.org/10.18433/jpps30439] [PMID: 31356760]
- Kaur U, Chauhan I, Gambhir IS, Chakrabarti SS. Antiepileptic drug therapy in the elderly: A clinical pharmacological review. *Acta Neurol Belg* 2019; 119(2): 163-73. [http://dx.doi.org/10.1007/s13760-019-01132-4] [PMID: 30953298]
- Blom S. Trigeminal neuralgia: Its treatment with a new anticonvulsant drug (G-32883). *Lancet* 1962; 1(7234): 839-40. [http://dx.doi.org/10.1016/S0140-6736(62)91847-0] [PMID: 13870089]
- Gambeta E, Chichorro JG, Zamponi GW. Trigeminal neuralgia: An overview from pathophysiology to pharmacological treatments. *Mol Pain* 2020; 161744806920901890 [http://dx.doi.org/10.1177/1744806920901890] [PMID: 31908187]
- Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain in adults. *Cochrane Database Syst Rev* 2015; (7): CD008242 [PMID: 26146793]
- Derry S, Wiffen PJ, Aldington D, Moore RA. Nortriptyline for neuropathic pain in adults. *Cochrane Database Syst Rev* 2015; 1(1): CD011209 [PMID: 25569864]
- Al-Quliti KW. Update on neuropathic pain treatment for trigeminal neuralgia. The pharmacological and surgical options. *Neurosciences (Riyadh)* 2015; 20(2): 107-14. [http://dx.doi.org/10.17712/nsj.2015.2.20140501] [PMID: 25864062]
- Rogers AD. *Historia magistra vitae*. Theology 2000; 103(816): 426-32. [http://dx.doi.org/10.1177/0040571X0010300604]
- Duncum BM. Ether anaesthesia, 1842-1900. *Postgrad Med J* 1946; 22(252): 280-90. [http://dx.doi.org/10.1136/pgmj.22.252.280] [PMID: 20276652]
- Harris W. A history of the treatment of trigeminal neuralgia. *Postgrad Med J* 1951; 27(303): 18-21. [http://dx.doi.org/10.1136/pgmj.27.303.18] [PMID: 14807868]
- Kubitz PK, Wijdicks EF, Bolton CF. Tic douloureux or "tic dentaire". *Neurology* 2004; 62(2): 333. [http://dx.doi.org/10.1212/01.WNL.0000096165.17801.46] [PMID: 14745085]
- Straus DC, Ko AL, Sekhar LN. Trigeminal neuralgia principles of neurological surgery. Elsevier 2018; pp. 745-52. [http://dx.doi.org/10.1016/B978-0-323-43140-8.00053-6]
- Sindou M, Kéravel Y, Laurent B. Aspects cliniques et thérapeutiques des névralgies essentielles du trijumeau et du glossopharyngien. *EMC—Neurologie* 2014; 11(2): 1-21.
- Cole CD, Liu JK, Apfelbaum RI. Historical perspectives on the diagnosis and treatment of trigeminal neuralgia. *Neurosurg Focus* 2005; 18(5): E4 [http://dx.doi.org/10.3171/foc.2005.18.5.5] [PMID: 15913280]
- Bialer M. How did phenobarbital's chemical structure affect the development of subsequent antiepileptic drugs (AEDs)? *Epilepsia*

- 2012; 53(Suppl. 8): 3-11.
[<http://dx.doi.org/10.1111/epi.12024>] [PMID: 23205958]
- [35] Spillane JD. The treatment of trigeminal neuralgia: Preliminary experience with 'Tegretol'. *Practitioner* 1964; 192: 71-7. [PMID: 14106649]
- [36] Patel SK, Markosian C, Choudhry OJ, Keller JT, Liu JK. The historical evolution of microvascular decompression for trigeminal neuralgia: From Dandy's discovery to Jannetta's legacy. *Acta Neurochir (Wien)* 2020; 162(11): 2773-82. [<http://dx.doi.org/10.1007/s00701-020-04405-7>] [PMID: 32519161]
- [37] Devor M, Amir R, Rappaport ZH. Pathophysiology of trigeminal neuralgia: The ignition hypothesis. *Clin J Pain* 2002; 18(1): 4-13. [<http://dx.doi.org/10.1097/00002508-200201000-00002>] [PMID: 11803297]
- [38] Sindrup SH, Jensen TS. Pharmacotherapy of trigeminal neuralgia. *Clin J Pain* 2002; 18(1): 22-7. [<http://dx.doi.org/10.1097/00002508-200201000-00004>] [PMID: 11803299]
- [39] Gay-Escoda C, Mayor-Subirana G, Camps-Font O, Berini-Aytés L. Suncet syndrome. Report of a case and treatment update. *J Clin Exp Dent* 2015; 7(2): e342-7. [<http://dx.doi.org/10.4317/jced.51854>] [PMID: 26155359]
- [40] Jannetta PJ. Arterial compression of the trigeminal nerve at the pons in patients with trigeminal neuralgia. 1967. *J Neurosurg* 2007; 107(1): 216-9. [<http://dx.doi.org/10.3171/JNS-07/07/0216>] [PMID: 17639898]
- [41] Shah SA, Khan MN, Shah SF, Ghafoor A, Khattak A. Is peripheral alcohol injection of value in the treatment of trigeminal neuralgia? An analysis of 100 cases. *Int J Oral Maxillofac Implants* 2011; 40(4): 388-92. [<http://dx.doi.org/10.1016/j.ijom.2010.11.010>] [PMID: 21168309]
- [42] Dewhurst K. A symposium on trigeminal neuralgia; with contributions by Locke, Sydenham, and other eminent seventeenth century physicians. *J Hist Med Allied Sci* 1957; 12(1): 21-36. [<http://dx.doi.org/10.1093/jhmas/XII.1.21>] [PMID: 13406256]

© 2021 Bara *et al.*

This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 International Public License (CC-BY 4.0), a copy of which is available at: (<https://creativecommons.org/licenses/by/4.0/legalcode>). This license permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.