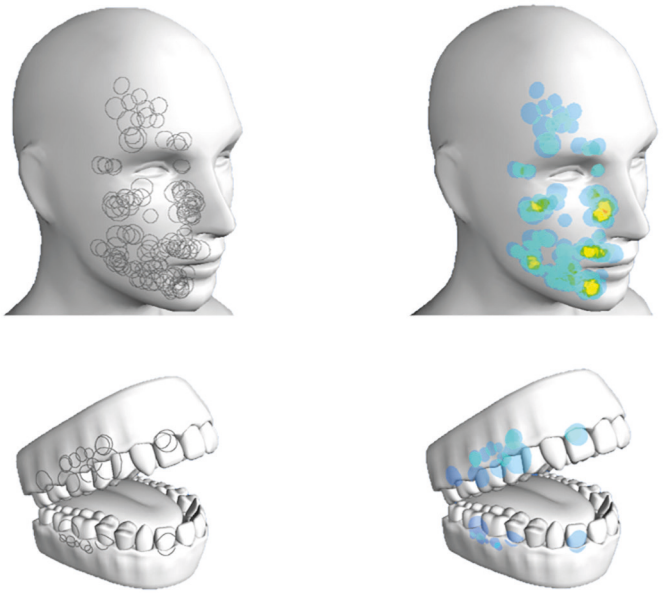
Studi e Ricerche

Medicina

# Trigeminal Neuralgia

## From clinical characteristics to pathophysiological mechanisms

Giulia Di Stefano



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# Medicina

# Trigeminal Neuralgia

## From clinical characteristics to pathophysiological mechanisms

*Giulia Di Stefano*

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# Table on Contents


Preface 7

Introduction 9

PART I

1. Triggering Trigeminal Neuralgia 19
   - 1.1. Introduction 19
   - 1.2. Methods 20
     - 1.2.1. Statistical analysis 22
   - 1.3. Results 22
     - 1.3.1. Trigger analysis 23
   - 1.4. Discussion 24
   - 1.5. Conclusions 26

PART II

2. Natural history and outcome of 200 outpatients with classical trigeminal neuralgia treated with carbamazepine or oxcarbazepine in a tertiary centre for neuropathic pain 37
   - 2.1. Introduction 37
   - 2.2. Methods 38
   - 2.3. Findings 39
   - 2.4. Discussion 40

PART III

3. Current and Innovative Pharmacological Options to Treat Typical and Atypical Trigeminal Neuralgia 47
   - 3.1. Introduction 47
   - 3.2. Search Process 49

3.3. Drugs in Classical or Idiopathic Trigeminal Neuralgia 49
3.3.1. First-line Treatments 49
3.3.2. Alternative Treatments 50
3.3.3. Drugs Under Development 54
3.3.4. Presurgical Procedures 55
3.4. Drugs in Secondary Trigeminal Neuralgia 56
3.5. Drugs in Trigeminal Neuralgia with Concomitant Continuous Pain 57
3.6. Expert Opinion 57
3.4. Supplementary Material 61

PART IV

4. General conclusions and future perspectrives 67

Bibliography 69

Acknowledgements 77

# Preface

This thesis is based on the work performed from 2014 to 2018 at the Department of Human Neuroscience, "Sapienza" University of Rome. Supervision was provided by Professor Giorgio Cruccu.
The research activity, in the field of neuropathic pain, especially focuses on Trigeminal Neuralgia. Below, the list of papers selected as the most relevant to the main research topic:

I. Triggering trigeminal neuralgia. Di Stefano G, Maarbjerg S, Nurmikko T, Truini A, Cruccu G. Cephalalgia. 2018 May;38(6):1049-1056.

II. Current and Innovative Pharmacological Options to Treat Typical and Atypical Trigeminal Neuralgia. Di Stefano G, Truini A, Cruccu G. Drugs. 2018 Sep;78(14):1433-1442.

III. Natural history and outcome of 200 outpatients with classical trigeminal neuralgia treated with carbamazepine or oxcarbazepine in a tertiary centre for neuropathic pain. Di Stefano G, La Cesa S, Truini A, Cruccu G. J Headache Pain. 2014 Jun 9;15:34.

*Giulia Di Stefano*

# Introduction

**Clinical characteristics and diagnostic criteria**

Trigeminal Neuralgia (TN) is a unique neuropathic facial pain condition, characterized by unilateral paroxysmal pain most often described as stabbing or electric shock-like, restricted to the distribution of one or more divisions of the trigeminal nerve territory and triggered by innocuous stimuli.[1] Some patients also suffer from persistent, dull, tingling pain between the paroxysms. The distribution of persistent pain coincides with that of the paroxysmal pain. TN with persistent pain between the paroxysms has been described with several definitions, including atypical TN and TN type 2; the International Headache Society Classification defined this relatively uncommon type of TN as TN with concomitant continuous facial pain.

TN has an annual incidence of three to five per 100.000. It is more common in women than men (age adjusted ratio: 1.74:1) and in people aged 50 to 69 years.[2]

According to the new classification and diagnostic grading of TN issued by the International Association for the Study of Pain, TN is distinguished in classical, caused by vascular compression producing anatomical changes in the trigeminal nerve root, secondary, due to an identifiable underlying neurologic disease, and idiopathic, when even after MRI or other investigation, the aetiology of TN remains unclear (Table 1).[3]

The starting points for a diagnosis of "possible TN" include unilateral facial pain, pain that cannot be felt outside the trigeminal territory, and pain that is paroxysmal. Bilateral TN is very rare, except for secondary TN in multiple sclerosis (MS) (Figure 1).

Stimulus dependence is one of the most striking features of TN, necessary for a diagnosis of "clinically established TN" (Figure 1). Although trigger factors constitute a hallmark sign of TN, very few studies to date have systematically investigated the role of triggers involved.

**Table 1**. Trigeminal Neuralgia diagnostic criteria

| IASP criteria | |
|---|---|
| Definition | TN is orofacial pain restricted to one or more divisions of the trigeminal nerve. With the exception of TN caused by multiple sclerosis, the pain affects one side of the face. It is abrupt in onset and typically lasts only a few seconds (2 minutes at maximum). Patients may report their pain as arising spontaneously, but these pain paroxysms can always be triggered by innocuous mechanical stimuli or movements. Patients usually do not experience pain between paroxysms. If they do report additional continuous pain, in the same distribution and in the same periods as the paroxysmal pain, they are considered to have TN with continuous pain. |
| Classification | Classical TN: caused by vascular compression of the trigeminal nerve root resulting in morphological changes of the root |
| | Secondary TN: caused by major neurological disease, e.g., a tumor of the cerebellopontine angle or multiple sclerosis |
| | Idiopathic TN: no apparent cause |
| ICHD criteria | |
| Criteria | At least three attacks of unilateral facial pain fulfilling criteria B and C |

| | |
|---|---|
| | Occurring in one or more divisions of the trigeminal nerve, with no radiation beyond the trigeminal distribution |
| | Pain has at least three of the following four characteristics: 1. recurring in paroxysmal attacks lasting from a fraction of a second to 2 minutes 2. severe intensity 3. electric shock-like, shooting, stabbing or sharp in quality 4. precipitated by innocuous stimuli to the affected side of the face |
| | No clinically evident neurological deficit |
| | Not better accounted for by another ICHD-3 diagnosis |
| Classification | 13.1.1.1 Classical TN (Classical TN, purely paroxysmal; Classical TN with concomitant continuous pain) |
| | 13.1.1.2 Secondary TN (TN attributed to multiple sclerosis; TN attributed to space-occupying lesion; TN attributed to other cause |
| | 13.1.1.3 Idiopathic TN (Idiopathic TN, purely paroxysmal; Idiopathic TN with concomitant continuous pain |

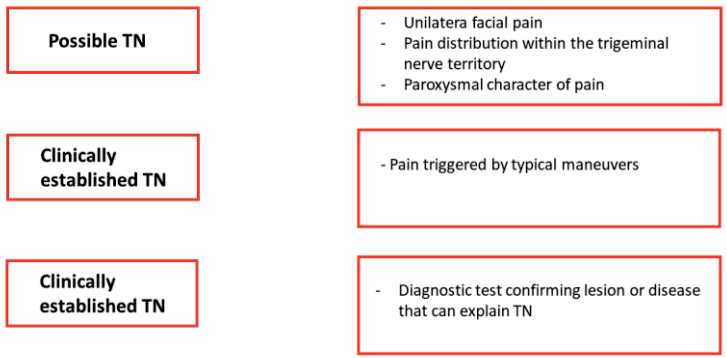


**Figure 1**. New classification for trigeminal neuralgia. Cruccu et al, Neurology 2016.

## Etiology

A diagnosis of "etiologically established TN" is based on identification of a cause for TN.

Classical TN is defined as a specific category of TN in which MRI demonstrates vascular compression with morphologic changes of the trigeminal nerve root. The degree of morphologic trigeminal root changes is therapeutically relevant. The long-term outcome after surgical correction of simple neurovascular contacts is poorer compared to the decompression of dislocated, distorted, or flattened nerve roots.[4]

Secondary TN is often related to MS or tumors, but other major neurologic diseases including aneurysms or rare trigeminal isolated sensory neuropathies should be considered. MS plaques are the most commonly identified abnormalities. Patients with MS have a 20-fold increased risk of developing TN; 1.9-4.9% of patients with MS suffer from this neuropathic pain condition.[5-7] MRI is routinely used for diagnosing MS and identifying TN secondary to MS. In patients with TN secondary to MS, T2-weighted MRI scans identify any linear plaques in the ventrolateral pons located between the trigeminal root entry zone and the trigeminal nuclei and involving the intrapontine part of primary afferents of the trigeminal nerve.[8] A prospective clinical and neuroimaging study in patients with MS revealed a significant association between neurovascular compression and TN secondary to MS, thus suggesting that a pontine plaque affecting the intra-axial primary afferents and neurovascular compression in concert might cause TN secondary to MS through a double-crush mechanism, involving inflammatory demyelination and mechanical demyelination, on the same first-order neurons[9].

## Pathophysiological mechanisms

Both in classic and secondary TN, the primary mechanism is focal demyelination of primary afferents near the entry (extraaxial or intraaxial) of the trigeminal root into the pons. This area represents a locus minoris resistentiae because it is the site where Schwann cells are substituted by oligodendroglia in providing the myelin sheath. Focal demyelination makes the axons hyperexcitable and increases the susceptibility to ectopic excitation, ephaptic transmission, and high-

frequency discharges. The consequences of the focal demyelination are not fully clarified, but it has been hypothesized that the focally demyelinated primary afferents become hyperexcitable when demyelination reaches such a level that ions can move in and out of the axon, also away from the Ranvier node zones, at which point the axons do not have enough energy to promptly re-establish the resting potential.[4] Hence the axons tend towards a depolarization level which makes them hyperexcitable. Ectopic impulses, which are generated either spontaneously along the sensory afferent or because of a local direct mechanical stimulus such as arterial pulsation, are probably also involved in the hyperexcitability. Moreover, supported by evidence in animal models of focal demyelination of the trigeminal root, ephaptic transmissjon, i.e. cross-talk from close, healthy nerve fibres, and the generation of high-frequency discharges are also suggested to contribute to the hvperexcitable nervous state in TN.[10,11] Finally, there is some evidence suggesting that the hyperactivity of primary afferents secondarily induces central sensitization of wide-dynamic-range neurons in the spinal trigeminal nucleus or even more central changes.[12]
The mechanisms underlying continuous as opposed to paroxysmal pain are not fully understood. Continuous pain may develop as a result of progressive root damage after prolonged compression[13] or reflect central mechanisms.[12]

**Treatment of trigeminal neuralgia**

Carbamazepine (CBZ) and oxcarbazepine (OXC) are the first-choice medical treatment in TN (Figure 2). They have the same mechanism of action, the blockade of voltage gated sodium channel in a frequency dependent manner, resulting in the stabilization of hyperexcited neural membranes and in the inhibition of repetitive firing. The AAN-EFNS guidelines recommended that patients unresponsive or that cannot reach the therapeutic dosage of the drug because of adverse events should be made aware of the availability of surgery.[14] Surgical procedures include Gasserian ganglion percutaneous techniques, microvascular decompression in the posterior fossa, and gamma knife radiosurgery. These procedures are extremely efficacious with relatively few complications. Microvascular decompression may be considered over other surgical techniques to provide the longest duration of pain

freedom.[4] According to the available evidence no oral treatment is better than CBZ or OXC, but in case of refractory trigeminal neuralgia, among the non-surgical option, lamotrigine and botulinum toxin injections should be considered.[4] Up to now, only few studies have focused on the drug efficacy and tolerability in time.

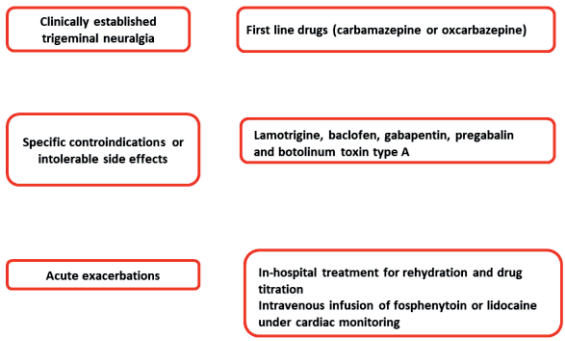


**Figure 2**. Pharmacological approach.

## Aims

The overall aim is to provide new insight into TN pathophysiological mechanisms and treatment. Specifically, the thesis aims to:

1. Describe the clinical characteristics of TN in a large consecutive cohort of patients focusing on trigger factors. Investigate how frequently triggers are present, which manoeuvres activate them and where cutaneous and mucosal trigger zones are located.
2. Analyse the natural history of TN in a large cohort of patients, by focusing on the drug responsiveness, the side effects related to the first-line pharmacological treatment, the changes in pain characteristics along with the duration of the disease, such as duration and intensity of paroxysms, and the possible onset of sensory disturbances.
3. Performing a systematic search of relevant literature, in order to provide current, evidence-based, knowledge about the pharmacological treatment of typical and atypical TN, with a specific focus on drugs in development.

# PART I

# 1. Triggering Trigeminal Neuralgia

*Work published on Cephalalgia. 2018 May;38(6):1049-1056. doi: 10.1177/0333102417721677*

## 1.1 Introduction

TN is a unique neuropathic pain condition characterized by unilateral paroxysmal pain, usually described as stabbing or electric shock-like, and restricted to the distribution of one or more divisions of the trigeminal nerve territory.[1,3] In ICHD-3, the most used classification of headache and facial pain disorders, the diagnostic criteria of classical TN, and those of MS-related TN (labelled painful trigeminal neuropathy) include provocation of paroxysmal pain from innocuous stimuli, but not as an essential condition (i.e., TN can be diagnosed without a trigger if three other pain characteristics are present). By contrast, the novel diagnostic grading system issued by the Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain makes the presence of a trigger an essential criterion, without which the clinical diagnosis of TN cannot be established. The view was taken on the basis of a literature review that suggested the presence of trigger zones in a high percentage of patients diagnosed with TN on clinical grounds.[3] In none of the quoted papers, however, was the frequency or characterization of trigger zones the main purpose. It is therefore imperative that given the dominance of triggers in the new classification their frequency and characteristics are defined as accurately as possible. Not only is this critical for the diagnosis of an individual patient, but also to support meaningful research on the pathophysiology and treatment of TN.

Provocation of paroxysmal facial pain by innocuous stimuli is very rare, except for TN. A very high percentage of triggers in patients who report all other pain qualities suggestive of TN (intense, short-lived pains of abrupt onset and cessation, coming in paroxysms) would strengthen the concept of TN as a unique pain, and an explanation for its pathophysiology would have to include generation of trigger zones. A low percentage would in turn suggest that TN can present with and without triggers and requiring separate pathophysiological explanations. In this study, we aimed to determine the frequency and nature of triggers as they pertain to patients with TN whose diagnosis is compatible with the ICDH-3 criteria.

## 1.2 Methods

We prospectively screened consecutive patients attending the Centre for Neuropathic Pain at Sapienza University from January 2015 to December 2016. Inclusion criteria were a diagnosis of TN according to the 3rd edition of the International Classification of Headache Disorders (ICHD-3, 2013), including 13.1. Classical trigeminal neuralgia, 13.1.2.4 Painful trigeminal neuropathy attributed to MS plaque and 13.1.2.5 Painful trigeminal neuropathy attributed to space-occupying lesion. In this classification, both latter diagnostic categories refer to patients who report facial pain with the characteristics of those in classical trigeminal neuralgia and are also called 'secondary TN'.[3] Exclusion criteria were cognitive disturbances and diagnosis of other orofacial pain condition. We also excluded four patients with secondary TN from the present series because they were shown to have a benign tumour at the cerebellopontine angle verified by MRI, and were promptly referred for surgery; therefore, they were not available for the present study. Two patients were excluded because, even though they presented with one-sided paroxysmal attacks and had normal MRI scans, the trigeminal reflex testing showed bilateral abnormalities in the mouth area that were typical of trigeminal neuropathy. The total number of the patients prospectively enrolled was 70.

Each patient underwent a precise sensory profiling using bedside tools as indicated by the European guidelines on neuropathic pain assessment.[15] Each patient also underwent both trigeminal reflex testing[14]

and 3T MRI, with specifications optimized for identification of the cause of TN.[9]

Three staff members were involved in the clinical examination and two in the neurophysiological testing. The diagnosis of TN was confirmed by two clinicians. Clinical characteristics were systematically collected using a dedicated questionnaire, focusing on triggers. Patients provided a thorough description of all trigger manoeuvres and drew both the trigger zones and the evoked paroxysmal pain distribution on a facial map. The overlap profiling of the trigger zones was carried out with dedicated software that provided representation and sum of the trigger areas on a standard 3D model of face and mouth. The frequency distribution of each trigger zone was computed at pixel level by counting the number of times each pixel of the model fell within each trigger area.

Besides the prospective patient enrolment, we also collected patients retrospectively. A staff nurse selected from our database the names and medical records of the most recent 70 outpatients with a diagnosis of TN (according to ICHD-3), who had attended our centre up to the point of commencement of the above prospective study (i.e., December 2014). A further staff member analysed the records and the diagnostic investigations, to confirm the diagnosis and classify the patients in classical or secondary TN.

The principal investigator subsequently examined the individual records for information on pain and triggers.

All patients included in the prospective or retrospective series suffered from paroxysmal attacks of pain affecting one or more divisions of the trigeminal nerve, regardless of the presence of concomitant continuous pain.[3,16]

For all patients included, we used as main outcome variables the side, distribution, and time course of pain, as well as manoeuvres triggering the paroxysms and distribution of trigger zones. For the prospective group we also collected information about the mean severity of paroxysms in the last month, as assessed with a numerical rating scale (NRS) ranging from 0 (no pain) to 10 (worst possible pain) and represented the trigger zones on the 3D-face model.

### 1.2.1 Statistical analysis

Descriptive statistics only was used for evaluation of the frequency of triggers. For comparisons between the prospective and retrospective groups we used Mann-Whitney Test, given that the main demographic and clinical data did not have a normal distribution. For comparisons of categorical data, we used Fisher exact test and Chi-squared tests.

## 1.3 Results

We included 140 patients in the analysis (54 M, 86 F, mean age 65.32 ± 12.01 years). Of these, 70 were collected retrospectively. Age and gender distribution did not differ between the prospective and retrospective groups (P> 0.3). Of the 140 included patients, 124 had a classical TN, and 16, all having trigeminal reflex testing abnormalities, had secondary TN. MRI showed that 14 out of these 16 patients had a multiple sclerosis-related TN, while two patients had TN due to an aneurysm and a megadolichobasilar artery. No difference was found between the two patient groups in the frequency of classical and secondary TN (P= 0.4), patient age at the time of onset of pain (P= 0.3) or frequency of affected trigeminal divisions (Table 2).

In all 140 patients combined, pain was more often located on the right (70%) than left side (29%), and the second (V2) and the third (V3) trigeminal divisions were more frequently affected than the first trigeminal division (V1) (Table 2). Patients described paroxysmal pain as a very abrupt, short-lasting pain, stabbing or similar to an electric shock in quality. Although most patients reported only daytime pain, 27 patients in the prospective group (39%) reported paroxysmal pain also during the night. The intensity of paroxysmal pain was 8.5 ± 1.6 on NRS (0-10). The duration of paroxysms was less than one second in four patients, from one to two minutes in nine patients and had a mean duration of 7 seconds in the remaining patients. The mean number of paroxysms was 11 a day. Fiftythree percent of patients experienced pain remission periods (mean duration of 10.52 ± 10.18 months) during which external stimuli failed to provoke any attacks.

Thirty-three patients (24%; 28 with classical and 5 with secondary TN) experienced concomitant continuous pain in the same division affected by paroxysms. Continuous pain was described as dull, burning

or tingling. Only in five patients this kind of pain was also evoked by trigger manoeuvres, including talking, eating, drinking, swallowing and gently touching the face. The mean pain intensity of continuous pain was 7.4 ± 2.5 in the prospective group. Concomitant pain was reported as being unrelenting day and night without pain-free intervals in 12 patients and lasting from five minutes to two hours in the remaining patients.

Whereas there was no difference in age at onset of TN between prospectively and retrospectively recruited patients, we found that patients with secondary TN had a lower age at onset compared to those with classical TN (median 51, 95% CI 46-57; median 61, 95% CI 57-62; P <0.02). On this point, however, there was a substantial overlap between the two populations as shown in Figure 3. The youngest age at onset was 31 and the oldest 89, both with classical TN.

### 1.3.1 Trigger analysis

Virtually all patients (136/140) reported trigger manoeuvres. The most frequent trigger manoeuvres were touching face (79%), talking (54%), chewing (44%), and brushing teeth (31%), with no difference between the prospective and retrospective groups. Unusual trigger manoeuvres included flexing the trunk (5%), contact with hot or cold food/water (4%), speaking loudly (2%) and turning the eyes to the right (1%) (Table 3). Of the 140 patients, 110 (78.6%) had extraoral and 117 (83.6%) intraoral trigger zones. The 3D face model showed that although the trigger zones were widely distributed within the whole trigeminal territory, they were more frequently located in the nasal wing (22%), upper lip (17%), cheek (13%), lower lip (12%), chin (11%), alveolar gingiva (11%) and cheekbone (10%) (Table 4, Figure 4). Most patients had more than one trigger zone/manoeuvre. All prospective patients drew their paroxysmal pain as a line rather than a circle and some explained that they felt the pain radiating from a point to another. Almost all patients, however, drew or reported that the pain paroxysms were restricted to the same trigeminal division of the trigger zone. Only in four patients the trigeminal division of the paroxysm and that of the trigger zone did not coincide: in one patient light touch of the nasal wing evoked pain in the supraorbital region, in the second patient pressing the first molar of the lower dental arch evoked pain in the upper lip, in the third

light touch of the chin evoked pain in the upper lip, and in the fourth light touch of the eyelid evoked pain in the mandibular region.
Of the four patients apparently without trigger manoeuvres (three in the prospective, one in the retrospective group), one suffered from multiple sclerosis-related TN. Of the three patients with classical TN, although being unaware of any specific trigger manoeuvre, one did report that to avoid the pain paroxysms she had to keep the face perfectly still, thus suggesting that a facial movement was the trigger.

## 1.4 Discussion

In this clinical study with a large sample of patients we show that in virtually all TN patients (97%) paroxysmal pain is associated with a trigger.
The frequency of triggers we found is higher (96% in the prospective study group) than that reported in a previous study (91%).[16] This difference probably reflects the dedicated questionnaire we used in our study for collecting information on triggers. We also hypothesize that in the few patients with no apparent trigger, the pain attacks are evoked by muscle movements they are unaware of, e.g. eye-blinking or facial mimicry. The observation that besides spontaneous paroxysmal pain, patients always invariably report triggered pain, further supports the use of triggers as a criterion for clinically established TN, and with that for probable neuropathic pain.[3]
As shown on our 3D face model, nearly all trigger zones were located within the central mask, most frequently in the perioral region. Although four of our patients felt the evoked paroxysmal pain in a trigeminal division different from that of the trigger zone, most often evoked paroxysms and trigger zones are located in the same trigeminal division. This finding, in line with previous studies,[17] is consistent with the mechanism of cross-excitation via ephaptic transmission from adjacent unaffected fibres within the trigeminal root.[10,11] The trigger zones were variable in size, and while some were no more than a pinpoint, most were much larger. Similar variability was mentioned in a previous study.[18] Our method of zone drawing has the advantage that it allows the patient to indicate the size directly on the facial map without relying on the estimate by an examiner. We hypothesize that the evoked paroxysmal pain might in some patients require a sequential

activation of mechanoreceptors, resulting in an enlarged trigger area. This hypothesis might also explain the "towel's sign", i.e. some patients soon learn to dry their face by slowly pressing, rather than brushing, the affected side to avoid the painful paroxysms.

Unexpectedly, we found that a few patients (4%) reported that consuming hot or cold food/water could provoke paroxysms. This finding goes against the common notion that only innocuous, mechanical stimuli can evoke the paroxysmal pain.[18,19] However, while the specific qualification of a thermal component was volunteered by the patients, the muscular activity in the lips, tongue and pharynx during eating or drinking is certainly sufficient to act as a trigger, precluding the argument that heat or cold alone could do so.

Unlike the common belief that TN does not awake patients from sleep, we found that many patients (38% of our sample in the prospective group) have nightly painful awakenings. This finding is however in line with the only other studies that used a dedicated questionnaire for patients and their partners about painful awakenings in TN.[20,16] Given that all our patients with nightly painful awakenings had extra-oral triggers, we suggest that an innocuous contact of the patient's skin with the sheet or the pillow acted as a triggering factor. We only found patients with nightly awakenings in the prospective group probably because we included a specific question about this in the questionnaire. It is worth pointing out that nightly attacks are less common than cluster headache where they are a prominent feature.

Besides the paroxysmal pain, several patients (24% of our sample) complained of concomitant continuous pain. All these patients, by definition, felt this type of pain in the same territory of paroxysmal pain. These findings, consistent with previous studies[21-23] support the idea that continuous pain is a relatively common symptom in TN. Central mechanisms[12,24] and progressive root damage due to compression[13] have been proposed as possible mechanisms underlying this type of pain.

We found that age at onset of pain in patients with secondary TN was significantly lower than that of patients with classical TN, confirming the current long-held view. However, there was substantial age overlap between the two populations preventing this aspect to be used as an indicator of secondary TN, in line with previous guidelines on trigeminal neuralgia.[14]

The demographic and clinical variables in our cohort of patients are similar to those reported in previous studies.[2,16] TN is more frequent in women and more frequently affects the right side of the face, in the V2 and V3 divisions, probably because of the somatotopic distribution of sensory fibres in the trigeminal root.[25]
The main limitation of the study is reliance on both retrospective and prospective data. However, as the demographics, clinical features, frequency of triggers and the nature of trigger manoeuvres were very similar between the two groups, we believe it was justified to use the combined data. The information extracted from the medical records was facilitated by a longstanding interest of the study centre in TN and the established clinical practice of detailed collection of all clinical data.

## 1.5 Conclusions

In nearly all patients with the diagnosis of TN based on ICHD-3 a trigger capable of provoking a paroxysm can be identified. Trigger zones are seen almost exclusively in the central mask, most commonly in the perioral area, and are variable in size. In all the trigger manoeuvres listed by the patients a mechanical component (touch or muscle movement) is present. These findings will be of assistance in future studies on the pathophysiological mechanisms of trigeminal neuralgia.

**Table 2**. Demographics, age at onset, duration of disease, side and anatomical localization of pain.

| | Prospective study | Retrospective study |
|---|---|---|
| Number of patients | 70 | 70 |
| Women | 46 | 40 |
| Men | 24 | 30 |
| Age in classical TN, mean (SD), years | 65,53 ± 12,38 | 66,75 ± 12,03 |
| Age in secondary TN, mean (SD), years | 61,90 ± 8,02 | 53,83 ± 9,10 |
| Disease duration, mean (SD), years | 8,18 ± 6,52 | 7,50 ± 8,00 |
| Age of onset in classical TN, mean (SD), years | 55,87 ± 14,40 | 53,83 ± 14,58 |
| Age of onset in secondary TN, mean (SD), years | 56,00 ± 9,70 | 43.50 ± 7.58 |
| Classical TN | 60 | 64 |
| Secondary TN | 10 | 6 |
| Right-sided | 49 (70%) | 49 (70%) |
| Left-sided | 20 (29%) | 20 (29%) |
| Bilateral | 1 (1%) | 1 (1%) |
| V1 | 23 (33%) | 20 (29%) |
| V2 | 51 (73%) | 54 (77%) |
| V3 | 42 (60%) | 39 (56%) |

**Table 3**. Frequency of trigger manoeuvres in trigeminal neuralgia.

| Trigger Manoeuvres | N(%) prospective study | N(%) retrospective study |
|---|---|---|
| Gently touching the face | 58 (83) | 52 (74) |
| Talking | 41 (59) | 35 (50) |
| Chewing | 29 (41) | 32 (46) |
| Tooth brushing | 25 (36) | 19 (27) |
| Washing one's face | 19 (27) | 20 (29) |
| Eating | 16 (23) | 19 (27) |
| Shaving | 7 (10) | 13 (19) |
| Drying one's face | 8 (11) | 10 (14) |
| Swallowing | 7 (10) | 9 (13) |
| Drinking | 6 (9) | 7 (10) |
| Jaw movement | 6 (9) | 5 (7) |
| Blowing one's nose | 5 (7) | 4 (6) |
| Flexing the trunk forward | 4 (6) | 3 (4) |
| Hot or cold food/water | 2 (3) | 4 (6) |
| Laughing | 1 (1) | 3 (4) |
| Raising own voice | 2 (3) | 1 (1) |
| Application of make-up | 2 (3) | 1 (1) |
| Yawning | 1 (1) | 2 (3) |

| | | |
|---|---|---|
| Pronouncing labial letters | 2 (3) | - |
| Combing | 1 (1) | 1 (1) |
| Eye movement | 1 (1) | 1 (1) |
| Washing one's hair | 1 (1) | 1 (1) |
| Head movements | 2 (3) | - |
| Tongue movement | - | 2 (3) |
| Sneezing | 1 (1) | 1 (1) |
| Cough | 1 (1) | - |

**Table 4**. Frequency of trigger zones in trigeminal neuralgia.

| Trigger Zones | N% Prospective study | N% Retrospective study |
|---|---|---|
| Nasal wing | 18 (26) | 13 (19) |
| Upper lip | 14 (20) | 10 (14) |
| Cheek | 8 (11) | 10 (14) |
| Lower lip | 7 (10) | 10 (14) |
| Chin | 10 (14) | 6 (9) |
| Alveolar gingiva | 7 (10) | 8 (11) |
| Nasolabial fold | 8 (11) | 6 (9) |
| Cheekbone | 9 (13) | 5 (7) |
| Jaw | 7 (10) | 5 (7) |
| Supraorbital region | 5 (7) | 5 (7) |
| Eyebrow | 5 (7) | 5 (7) |
| External eye side | 4 (6) | 2 (3) |
| Lower lateral incisor | 1 (1) | 3 (4) |
| Tongue | - | 3 (4) |
| Scalp | 3 (4) | - |
| Hard palate | - | 2 (3) |
| Conjunctival fornix | 2 (3) | - |

| | | |
|---|---|---|
| Upper lateral incisor | 2 (3) | - |
| Upper molars | 2 (3) | - |
| Lower eyelid | 1 (1) | 1 (1) |
| Lower molars | 1 (1) | - |
| Upper premolars | 1 (1) | - |
| Lower premolars | 1 (1) | 1 (1) |
| Orbital region | - | 1 (1) |

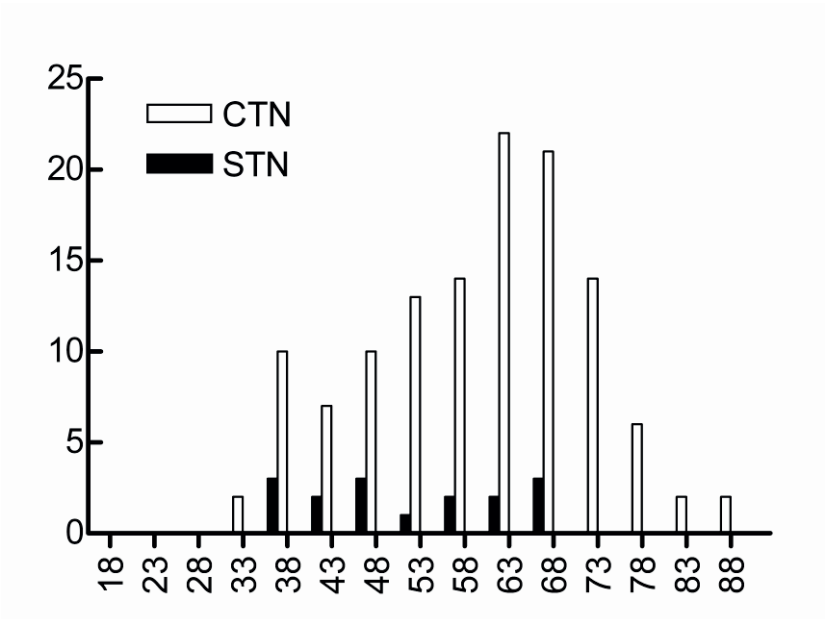


**Figure 3**. Histogram of age of onset. X-axis: age of onset. Y-axis: number of patients. CTN: classical trigeminal neuralgia. STN: secondary trigeminal neuralgia. Note that although STN patients are younger, their ages of onset are intermingled with those of CTN patients. Di Stefano et al, Cephalalgia 2018.

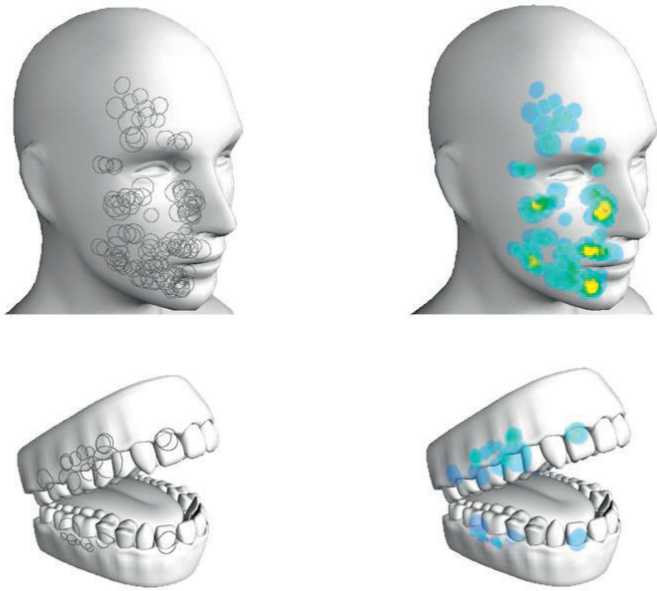

**Figure 4.** Trigger zone distribution. Data from 70 prospectively-enrolled patients with classical or secondary TN. Upper panel: extra-oral territories. Lower panel: intra-oral territories. Left column: trigger-zone contours. Right column: trigger-zone overlap profiling. The number of superimpositions ranges from 2 (cyan) to 15 (dark orange). The number of trigger zones in the intra-oral territory is smaller in comparison with the number of patients reporting talking or chewing as the main trigger manoeuvres, because of the patients' difficulty in identifying a circumscribed trigger zone region within the mouth. Di Stefano et al, Cephalalgia 2018.

# PART II

# 2. Natural history and outcome of 200 outpatients with classical trigeminal neuralgia treated with carbamazepine or oxcarbazepine in a tertiary centre for neuropathic pain

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## 2.1. Introduction

TN is a facial pain condition characterized by paroxysmal, usually unilateral, recurrent pain with a distribution consistent with one or more divisions of the trigeminal nerve. The paroxysmal attacks are stereotyped in the individual patient, last from a fraction of a second to 2 minutes and are usually evoked by stimulating cutaneous or mucous trigeminal territories, the so-called trigger zones. TN may be classified in classical, namely without a cause other than a neurovascular compression producing morphological changes on the trigeminal root, or secondary to a major neurological disease, including benign tumors of the cerebellopontine angle or multiple sclerosis. According to the symptom constellation, TN is categorized into typical and atypical form, the latter characterized by a constant and non-lancinating background pain. The annual age-adjusted incidence is 5.9% for women and 3.4% for men.[2] According to the American Academy of Neurology (AAN), the European Federation of Neurological Societies (EFNS), carbamazepine (CBZ) and oxcarbazepine (OXC) are the first-choice medical treatments for pain control in patients with TN.[14,26] They have the same mechanism of action, namely the blockade of voltage-gated sodium channels in a frequency-dependent manner. OXC may be preferred because of the minor risk for drug interactions and its better tolerability in comparison with CBZ.[26] The AAN-EFNS guidelines recommended that patients unresponsive or that cannot reach the

therapeutic dosage of the drug due to adverse events should be made aware of the availability of surgery. Surgical procedures include Gasserian ganglion percutaneous techniques, microvascular decompression in the posterior fossa, and gamma knife radiosurgery. These procedures are extremely efficacious with relatively few complications. Microvascular decompression may be considered over other surgical techniques to provide the longest duration of pain freedom.[14] In case of refractory TN, among the non-surgical option, lamotrigine and botulinum toxin injections should be considered.[27] Up to now, only few studies have focused on the development of the clinical picture and the drug efficacy and tolerability in time. The aim of this retrospective study was to analyse the natural history of TN in a large cohort of patients, by focusing on the drug responsiveness, the side effects related to the pharmacological treatment, the changes in pain characteristics along with the duration of the disease, such as duration and intensity of paroxysms, and the possible onset of sensory disturbances.

## 2.2 Methods

The staff nurse retrospectively selected the clinical notes of outpatients with a diagnosis of classical TN who had attended our centre for neuropathic pain from January 2000 to June 2013. One staff member analysed the clinical notes and selected the last consecutive 100 patients treated with CBZ and the last consecutive 100 treated with OXC. All patients included in the analysis suffered from paroxysmal attacks of pain, affecting one or more divisions of the trigeminal nerve. Pain was described as intense, sharp, or stabbing; paroxysms could be both spontaneous and precipitated by innocuous tactile stimulation of trigger zones. Paroxysmal attacks were stereotyped in the individual patient. The clinical examination did not show any clinical neurological abnormalities. All patients had undergone MRI scans of the brain and trigeminal reflex testing to identify with certainty even patients with typical presentation but a possibly secondary origin, including idiopathic sensory trigeminal neuropathy and nerve trauma[14]. Patients were seen at least monthly until the target dosage and/or a significant pain reduction was reached. Then, follow-up visits were scheduled every six months, unless side effects occurred. Two staff members were involved in the clinical examination and two in the

neurophysiological testing. The diagnosis of classical TN was confirmed by at least two clinicians. We analysed the average onset age of TN, the number of responders to CBZ or OXC, the possible CBZ/OXC lost efficacy, the side effects that caused interruption of treatment or a dosage reduction to an unsatisfactory level and the latency for the side effect onset. Patients were considered as responders on the bases of their global satisfaction and the willingness to continue the drug. We also analysed changes in pain characteristics during the course of disease, including paroxysms duration and intensity. By definition, classical TN is a pain syndrome that arises without a clinically manifest sensory deficit: anyway, we wanted to test the likelihood of the onset of sensory disturbances during the disease course.

## 2.3 Findings

We included 200 patients (68 M, 132 F, mean age 67.54 ± 12.11), with a mean follow-up period of 7.31 years. Among them, 22 patients with typical symptom constellation and a diagnosis of classical TN were excluded from the study because two of us considered the results of neurophysiological or neuroimaging investigations insufficient to exclude a secondary form with absolute certainty. The other 178 patients had a classical TN, without any evidence of a cause other than a neurovascular conflict at dedicated MRI scans. Ninety-five out of 178 patients were treated with CBZ and the remaining 83 with OXC. The average onset age of symptoms was 60 ± 11.6 years (range 35-80). The initial number of responders was 98% with CBZ at a median dosage of 600 mg (range 200–1200 mg), and of 94% with OXC at a median dosage of 1200 mg (range 600–1800 mg). Among responders to CBZ, 27% of patients incurred in adverse events that directly caused interruption of treatment or a dosage reduction to an unsatisfactory level, thus causing discontinuation, after a mean period of 8.6 months. In a mean period of 13 months, physician- or patient-decided discontinuations occurred in 18% of patients initially responders to OXC. The causes of these discontinuations are reported in Figure 5. The central nervous system disturbances were more frequent in patients treated with CBZ than those with OXC. In detail, these side effects included somnolence (10 patients treated with CBZ and 5 with OXC), postural unbalance (6 with CBZ and 4 with OXC) and dizziness (6 with CBZ and 1 with

OXC). Among patients under CBZ, three had an increase of transaminases, one anemia, one leucopenia, and one thrombocytopenia. Among those under OXC, 5 had hyponatremia, one patient had thrombocytopenia. Allergic reactions (cutaneous rash) affected two patients on CBZ and two on OXC. The onset of side effects on the central nervous system occurred with a mean dosage of 600 mg for CBZ and 1200 mg for OXC. With CBZ, anaemia, leucopenia, and thrombocytopenia occurred within the first three weeks of treatment, with dosages of 600 mg, 600 mg, and 1000 mg, respectively. With OXC, thrombocytopenia occurred within the first two weeks of treatment, with a dosage of 1200 mg. Hyponatremia was observed within the first month, with dosages of 900 mg in one patient, 1200 mg in three patients and 1800 mg in the fifth patient. Allergic reactions occurred at the beginning of treatment and required an immediate interruption of treatment. Among patients that had to interrupt CBZ because of adverse events, 16 were switched to OXC, and 5 to gabapentin. The new treatment was effective in 12 patients (10 with OXC and 2 with gabapentin), whereas in 7 patients (6 with OXC and 1 with gabapentin) the new treatment was unsuccessful. The remaining two patients were lost to follow up. Among patients that had to interrupt OXC because of adverse events, 3 were switched to CBZ, and 2 to gabapentin. The new treatment was effective in 4 patients (3 with CBZ and 1 with gabapentin), whereas in the remaining patient the new treatment was unsuccessful. Eight patients were lost to follow up. Eventually, 13 patients out of 178 were referred for surgery (5 patients treated with OXC and 8 with CBZ). Among patients who had a good initial response, three patients with CBZ and two with OXC developed late resistance after 24–76 months. The intensity of paroxysms worsened in six patients and their duration in four. Such a worsening occurred in a mean time of 55 months. Continuous pain developed in 5 patients, after an average duration of disease of 7 years. We did not observe the development of sensory disturbances with time in any patient suffering from classical TN.

## 2.4 Discussion

In this retrospective study involving a large cohort of patients, we investigated the natural history of classical TN, focusing our attention on the efficacy of CBZ or OXC, the possible onset of a late resistance

and the adverse events that eventually caused either interruption of treatment or a dosage reduction to an unsatisfactory level. The possible modifications in pain characteristics during the course of disease, including paroxysms duration and intensity, were also analysed. We found that the worsening of pain with time and the development of late resistance only occurred in a very small minority of patients. CBZ and OXC were confirmed to be efficacious in a large majority of patients, but the side effects caused the interruption of treatment in an important percentage of patients. Demographics matched those observed in previous studies,[2] with a higher frequency in women (65.17%) and an average onset age at 60 years. We found changes in pain characteristics only in an exiguous sub-set of patients. Such changes included the increase of both paroxysms duration and intensity. Unlike other reports,[19] no sensory deficit was observed since the beginning of the disease. It is generally agreed that the first-choice treatment of TN is pharmacological and based on the use of sodium channels blockers, CBZ and OXC. Four placebo-controlled trials demonstrated the efficacy of CBZ28-31 with a number needed to treat to obtain important pain relief of 1.7-1.8.[32] This efficacy is however compromised by the tolerability, with a numbers needed to harm of 3.4 for minor and of 24 for severe adverse events.[33,34] OXC has a comparable efficacy to that of CBZ but a greater tolerability and a lower potential for drug interaction.[35-37] This study confirmed that CBZ and OXC are efficacious in the majority of patients and that OXC is more tolerated in comparison with CBZ. If compared with other reports, the percentage of non responders was somewhat lower in our sample. Because CBZ 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 TN. 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 CBZ/ OXC may drop. Indeed, the diagnostic accuracy has always been a problem in studies in TN. Adverse events may cause withdrawal from treatment. This occurred in a significant percentage of patients, 27% of those with CBZ and 18% of those with OXC, who were initially responders. The most frequent adverse effects involved the central nervous system, and included somnolence, dizziness and postural unbalance. CBZ had a higher percentage of discontinuations

for all types of side effect, except for sodium depletion, which only occurred with OXC (Figure 5). Although in our centre we are well aware of the great efficacy of surgical interventions for TN and we always offer this chance to patients resistant to CBZ/OXC, only 7% of this large cohort of patients was eventually sent for surgery, a proportion decidedly low if compared to those reported by neurosurgical centres. To explain the low proportion of patients sent for surgery, we may think of this main explanation: the local population is not so keen on undergoing surgery unless they really cannot manage with medical treatment and the number of patients resistant to CBZ/OXC was very low. In conclusion, the failure of the treatment with CBZ/OXC, most of the times, is not due to the inefficacy of the drug, but rather to adverse effects to a level that causes interruption of treatment or a dosage reduction to an unsatisfactory level. These findings suggest the opportunity to develop better tolerated drugs.

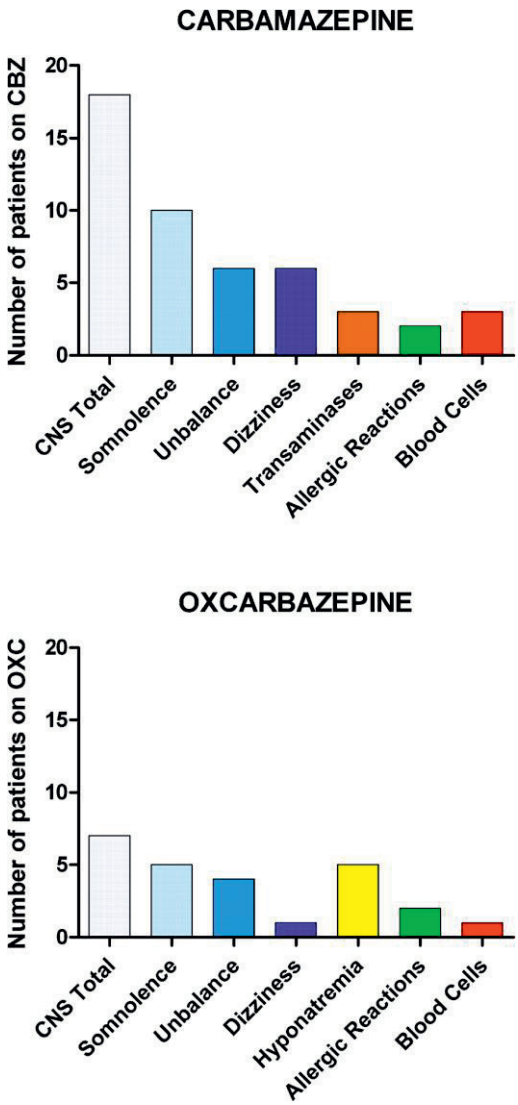


**Figure 5**. Tolerability of Carbamazepine (CBZ) and Oxcarbazepine (OXC). Y-axis: number of patients that discontinued first treatment because of adverse events. X-axis: causes of discontinuation. Note that CNS disturbances affected far more frequently the patients on CBZ, whereas hyponatremia only affected patients on OXC. The sum of patients reporting somnolence, postural unbalance, and dizziness is higher than the total CNS disturbances because many patients complained of more than one CNS disturbance. Di Stefano et al, J Headache Pain. 2014.

# PART III

# 3. Current and Innovative Pharmacological Options to Treat Typical and Atypical Trigeminal Neuralgia

*Work was published on Drugs. 2018 Sep;78(14):1433-1442. doi: 10.1007/s40265-018-0964-9*

## 3.1. Introduction

TN is a unique neuropathic facial pain condition, characterized by unilateral paroxysmal pain described as electric shock-like, in the distribution territory of one or more divisions of the trigeminal nerve and triggered by innocuous tactile stimulation of trigger zones.[1] According to the new classification and diagnostic grading of TN issued by the International Association for the Study of Pain (IASP), TN is distinguished in three diagnostic categories: classical, caused by neurovascular compression producing morphological changes on the trigeminal nerve root; secondary, due to an identifiable underlying major neurologic disease; idiopathic, of unknown aetiology (Table 1).[3] Regardless of the aetiology, the primary mechanism of paroxysmal pain is the focal demyelination of primary trigeminal afferents near the entry of the trigeminal root into the pons, making the axons hyper-excitable and increasing the susceptibility to ectopic excitation, ephaptic transmission, and high-frequency discharges.[10] TN has an annual incidence of three to five per 100,000. It is more common in women than men (age adjusted ratio: 1.74:1) and in people aged 50–69 years.[2] In virtually the totality of patients with TN, at least one trigger capable of provoking a paroxysm can be identified. In a recent study, provocation of paroxysmal pain by various trigger manoeuvres was reported by 136 of the 140 patients. The most frequent manoeuvres included gentle touching of the face and talking. Trigger zones were predominantly reported in the perioral and nasal region and were variable in size.

These data are coherent with the use of trigger factor as an essential diagnostic criterion for a clinically established diagnosis of TN.[3] Patients with TN may suffer from different types of pain, ranging from single attacks to a series of prolonged attacks, and it was suggested that these pain characteristics can vary over time.[38] Traditionally, autonomic symptoms such as tearing, and rhinorrhea have not been associated with TN. However, it is now known that a significant percentage of TN patients have autonomic symptoms.[16] A subgroup of patients with TN also suffer from concomitant continuous pain (CCP), described as dull, burning or aching.[23] This condition has been described with several definitions, including atypical TN and TN type 2; the International Headache Society Classification (ICHD) defined this relatively uncommon type of TN as TN with concomitant continuous facial pain. The presence of continuous pain is not related to aetiology and may occur in idiopathic, classic, or secondary TN. Background pain distribution coincides with that of the paroxysmal pain, and fluctuations of its intensity parallel in time those of the paroxysmal pain.[21,22] A prevalence three times higher in women than in men was reported.[23] In a cohort of 158 patients with TN, continuous pain developed within a mean period of 1.5 years since the disease onset, thus suggesting that this kind of pain is not related to a long duration of stabbing pain.[23] The mechanisms underlying continuous pain, as opposed to paroxysmal pain, are not fully understood, with implications for treatment. There is the evidence that continuous and paroxysmal pain may improve differently after microvascular decompression, thus supporting the hypothesis that the mechanisms responsible for the two pain components may be different.[4] Central mechanisms[12] and progressive root damage due to compression[13] have been proposed as possible factors. CBZ and OXC are the first-line medical treatment in TN. They have the same mechanism of action, the blockade of voltage gated sodium channel in a frequency dependent manner, resulting in the stabilization of hyperexcited neural membranes and in the inhibition of repetitive firing. In patients with purely paroxysmal pain, CBZ and OXC are effective in virtually the totality of patients. However, these drugs produce side effects to a level that cause interruption of treatment or a dosage reduction in 23% of patients, making necessary the development of new, more selective and better tolerated sodium channel blockers. Conversely in patients with CCP, the efficacy of CBZ

and OXC may drop, thus suggesting the opportunity to test the efficacy of different drug categories. A wide range of drugs has been investigated in TN, but the scientific literature highlighted the need of high-quality clinical trials in TN. The aim of this review, based on a systematic search of relevant literature, is to provide current, evidence-based, knowledge about the pharmacological treatment of typical and atypical TN, with a specific focus on drugs in development, such as botulinum toxin A and new, more selective sodium channel blockers.

## 3.2 Search Process

We searched for relevant papers within the PubMed, EMBASE and the Cochrane Database of Systematic Reviews, taking into account publications up to February 2018. All searches used the following synonyms for TN: trigeminal neuralgia and tic douloureux. The primary search was supplemented by a secondary search using the bibliographies of the retrieved articles. Only full-length, original communications including open-label studies were considered, and the search was limited to English language publications. Clinical trials database (ClinicalTrial.gov) has been checked in order to include in the analysis studies currently in progress. The review process was carried out independently by two reviewers and only publications independently approved by the two authors were taken into account (Figure 6). The authors independently assessed the quality of the individual trials during data extraction. Inclusion criteria were the following: trials including patients with a diagnosis of typical or atypical TN, including classical, idiopathic and secondary TN, and a minimum sample of 10 patients.

## 3.3 Drugs in Classical or Idiopathic Trigeminal Neuralgia

### 3.3.1 First-line Treatment

CBZ and OXC are the first-line treatment in TN. Their effect is related to the blockade of voltage-sensitive sodium channels in a

frequency dependent manner, resulting in the stabilization of hyperexcited neural membranes and inhibition of repetitive firing. Systematic reviews and randomised controlled trials, including 147 patients,[28-31] demonstrated the efficacy of CBZ compared to placebo, with a number-needed-to-treat (NNT) to obtain pain relief of 1.7–1.8.[32] However, CBZ showed a number-needed-to-harm (NNH) of 3.4 for minor and 24 for severe adverse events.[34] In the study of Killian and Fromm,[29] with a maximum daily dose of 1000 mg, 19 of 27 participants had a complete or very good response with CBZ compared with minimal or no response with placebo on a 5-day treatment. Nicol,[30] using a cross-over design and a maximum daily dose of 2400 mg, reported that 15 of 20 participants randomised to initial CBZ had a good or excellent response after 14 days' treatment, compared with 6 of 24 reporting good or excellent response who started on placebo. Superiority of CBZ was also reported by Rocklif and Davis[31] in a small sample of patients. In the study from Rasmussen and Riishede,[39] after 5 days' treatment, 46 of 55 patients with TN had good effect on CBZ, compared with 8 of 55 on placebo. Campbell and colleagues28 reported a mean fall in maximum pain intensity of 58% after 2 weeks treatment with CBZ 400–800 mg daily compared to 26% with placebo (Supplementary Material). Compared to CBZ, OXC showed a similar efficacy in reducing pain attacks but a greater tolerability and a lower potential for drug interaction.[37] However, data from full randomised controlled trials are not available, thus precluding the NNT and NNH calculation. A pilot study on OXC with extended-release formulation is currently in progress (ClinicalTrials.gov Identifer: NCT03374709).

### 3.3.2 Alternative Treatments

#### 3.3.2.1 Lamotrigine

Lamotrigine acts on voltage-sensitive sodium channels, stabilizes neural membranes and inhibits the release of excitatory neurotransmitters. Two systematic reviews[40,41] identified a small double-blind crossover randomised controlled trial comparing lamotrigine versus placebo in 14 patients treated with CBZ or phenytoin. Patients continued to take a steady dose of CBZ 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. This study showed that lamotrigine combined with CBZ or phenytoin was slightly more effective than placebo. The adverse effects with both lamotrigine and placebo were predominantly dose-dependent effects on the central nervous system. One patient withdrew from the study due to severe pain during the placebo arm of the trial. A crossover study involving 21 patients with TN compared lamotrigine (400 mg) with CBZ (1200 mg).42 CBZ reduced pain in 90.5% (19/21) and lamotrigine in 62% (13/21) of the patients using both visual analogue scale (VAS) and verbal rating scale. The reported adverse events were headache, dizziness and skin rash.

#### 3.3.2.2 Baclofen

Two studies analysed the efficacy of baclofen in patients with TN.[43,44] This drug is a GABAB receptor agonist and depresses excitatory neurotransmission. Baclofen was superior to placebo in reducing the number of paroxysms in a randomised controlled trial involving ten participants; baclofen significantly decreased the number of paroxysms in seven patients.[43] A double-blind crossover trial involving 15 patients showed that l-baclofen was more effective than five times as much racemic baclofen in nine patients. Six of these nine patients have continued pain-free on l-baclofen for 4–17 months (mean, 10 months). l-baclofen was much better tolerated than racemic baclofen.[44] However, these studies had several limitations, such as the small sample of patients and the short duration of treatment, so the findings must be interpreted with caution.

#### 3.3.2.3 Pimozide, Tizanidine and Tocainide

One systematic review[45] identified three randomised controlled trials comparing pimozide,[46] tizanidine[47] and tocainide[48] with CBZ. Pimozide was more effective than CBZ in a double-blind crossover 24-week trial including 48 patients suffering from refractory TN but significant side effects of this neuroleptic drug, including central nervous system disturbances, hand tremors and memory impairment were reported. The effect of tizanidine, a centrally acting alpha-adrenergic agonist, in comparison with CBZ was tested in a small sample of patients.

After individual titration of tizanidine and CBZ, the maximum daily doses were 18 mg and 900 mg, respectively, and the difference was not statistically significant. Tocainide, a sodium channel blocker with antiarrhythmic action, was tested in 12 patients in a double-blind crossover study for 2 weeks, but significant adverse events limited its use.

#### 3.3.2.4 Calcium Channel Blockers

The efficacy of calcium channel blockers, gabapentin and pregabalin, has been assessed in small controlled or open label studies. These drugs act by modulating voltage-gated calcium channels and thus reducing release of excitatory neurotransmitters. One systematic review and meta-analysis[49] identified 16 randomised controlled trials, published in Chinese, on the efficacy of gabapentin in comparison with CBZ in the treatment of patients with TN. 1331 patients were included and VAS score was used to assess the efficacy of treatment. The total effective rate of gabapentin therapy group was similar with CBZ therapy group and the adverse reaction rate of gabapentin therapy group was significantly lower than that of CBZ. However, the authors concluded that the trials are all poor in terms of methodological quality.[49] Pregabalin was not tested in randomised controlled trials. An open-label study involving 53 patients showed the efficacy of pregabalin in reducing TN by over 50% in 74% of patients.[50] Two observational studies, totalling 65 patients, proved the efficacy of pregabalin in monotherapy (n=36) or add-on (n=29) for 12 weeks. However, according to the inclusion criteria, patients with an atypical facial pain might also have been included.[51,52] In an open-label crossover trial in 22 patients with refractory TN using lamotrigine and pregabalin together with CBZ, pregabalin showed a comparable efficacy and a better tolerance than lamotrigine.[53]

#### 3.3.2.5 Levetiracetam

Among anticonvulsants, open label studies investigated the efficacy of levetiracetam. A pilot study investigated the efficacy and tolerability of this drug in 10 patients with TN over a period of 10 weeks. Patients were treated with up to 4000 mg daily and 40% reported an improvement of 50%–90%.[54] In an observational trial, including 23

patients with refractory TN, levetiracetam (3–4 g/day) for 16 weeks decreased the number of daily attacks by 62.4%.[55]

#### 3.3.2.6 Eslicarbazepine

Eslicarbazepine, a third-generation antiepileptic drug belonging to the dibenzazepine group, targets the voltage-gated sodium channels and is currently approved as adjunct therapy for focal seizures. A recent retrospective, open-label, multicentric, intention-to-treat study tested the efficacy and safety of this drug in patients with TN. Eighteen participants were included; the dose of eslicarbazepine ranged between 200 and 1200 mg/day. Responder rate was 88.9%; 71% of patients presented some adverse events and four patients discontinued the pharmacological treatment.[56]

#### 3.3.2.7 Local Anaesthetics

Two randomised controlled trials investigated the effect of local anesthesia injected into trigger area.[57,58] These studies, combining the peripheral analgesic block with ropivacaine and CBZ or gabapentin, showed improved outcome. In the randomised controlled trial combining the peripheral analgesic block with ropivacaine and CBZ in 45 patients, the association protocol resulted in a significant reduction in pain intensity, number of daily pain paroxysms and daily dose of CBZ intake, when compared with CBZ in monotherapy.[57] In the randomised controlled trial in 36 patients combining gabapentin with ropivacaine injection into trigger areas showed improved pain control and quality of life.[58] The association treatment was safe, without side effects and resulted in a significant benefit with an improvement of the functional health status of TN patients when compared with gabapentin alone. A reduction of VAS score after 7 and 28 days of treatment was reported, and this effect was still present 6 and 12 months later. The NNT (gabapentin + ropivacaine vs gabapentin protocols) to obtain 1 gabapentin + ropivacaine-treated patient with at least 50% pain relief was 1.71 (day 7) and 2.40 (day 28). Two randomised controlled trials tested the short-term effect of topical 8% lidocaine versus placebo in TN.[59,60] In the study of Kanai et al.,[59] including 25 patients with TN involving the second division, those given an 8% spray of lidocaine as

opposed to saline had a statistically significant decrease in pain. The effect of treatment persisted for a mean of 4 h without serious adverse reactions. In the study of Niki et al.,[60] including 24 patients with TN and severe intraoral pain, the application on the painful areas of 8% lidocaine significantly reduced the NRS score of paroxysmal pain for a mean of 3 h, without serious side effects. However, these studies showed several limitations and the results must be interpreted with caution.

#### 3.3.2.8 Sumatriptan

Recent studies tested the effect of 5-HT1A/1B/1D receptor agonist in patients with TN. These drugs may inhibit vasodilation and inflammation near the demyelinated trigeminal root. Two randomised controlled trials tested the effect of subcutaneous injection of sumatriptan 3 mg and the oral administration of 50 mg twice daily.[61,62] Fifteen minutes after injection of sumatriptan, the baseline VAS decreased from 8.3 to 2.4 cm. At the end of oral treatment, the VAS was significantly decreased, and this effect persisted after treatment discontinuation for a further week. However, the adverse events related to a long-term use, including a triptan overuse headache, prevent the use of sumatriptan in the long-term treatment of TN.

#### 3.3.2.9 Intravenous Drugs for Acute Exacerbations

In a randomised controlled trial including 20 patients with intractable TN, a single dose of intravenous lidocaine (5 mg/ kg over 60 min) was superior in reducing pain intensity compared to placebo during the first 24 h after the infusion.[63]

### 3.3.3 Drugs Under Development

#### 3.3.3.1 Vixotrigine

A new Nav1.7 selective state-dependent, sodium channel blocker (vixotrigine) is under development. Nav1.7, a major sodium receptor in the nociceptive system, is not located in the brain, thus preventing any side effects associated with depression of central nervous system excitability.[64] A Phase 1 study demonstrated the good tolerability of

vixotrigine, administered at therapeutic doses without lengthy titration. The new drug was tested in a double-blind, placebo-controlled, randomised withdrawal Phase 2a trial, involving 67 patients with a diagnosis of classical and idiopathic TN.[65] After a 7-day run-in phase, eligible patients received open-label, vixotrigine 150 mg 3 times per day, orally, for 21 days. Patients who met at least one response criteria were then randomly assigned (1:1) to vixotrigine or placebo for up to 28 days in a double-blind phase. Although the primary endpoint of treatment failure was not significantly lower in the vixotrigine group than in the placebo group, significant treatment differences versus placebo in secondary endpoints were reported, including time to treatment failure, number of paroxysms and average daily pain score. The new drug was well tolerated, and no severe or serious adverse events were reported. A Phase 3 placebo-controlled, double-blind randomised withdrawal study is currently in progress (ClinicalTrials.gov Identifier: NCT03070132).

### 3.3.4 Presurgical Procedures

#### 3.3.4. 1 Botulinum Toxin A

Botulinum toxin type A (BTX-A), an exotoxin released by the gram-positive bacterium Clostridium botulinum, is supposed to block the TRPV1 receptor of unmyelinated C fibre terminals and reduce the release of substance P, calcitonin gene-related peptide and glutamate from presynaptic terminals of the primary sensory neurons. A systematic review[66] identified 4 randomised controlled trials, involving 178 patients, testing the effect of BTX-A in patients with TN.[67-70] The total dosage administered varies from 25U to 75U and the number of injections from 8 to 20. The injections were administered intradermally and/or submucosally where pain was experienced according to the patient's description. The overall effect favoured BTX-A versus placebo in terms of proportion of responders; paroxysms frequency per day was significantly lower for BTX-A group. The duration of effect was relatively long (at least 3 months). Adverse effects included transient facial weakness, edema and hematoma at the site of injection. Future studies assessing the optimal dose, duration of the therapeutic efficacy, adverse events, the time and indications for repeat injection are

required. To our knowledge, no data are available about the effect of repeated BTX-A injections in TN. A clinical trial comparing intradermal/submucosal injection and intra-masseter injection of BTX-A is currently in progress (ClinicalTrials.gov Identifier: NCT03331913).

#### 3.3.4.2 Intranasal Non inhaled Carbon Dioxide

Recently, CO2 has been shown to be a modulator of activated nociceptive trigeminal neurons.[71] Based on animal model, an antinociceptive effect of intranasal CO2 by activation of mucosal primary trigeminal afferents through a decreased mucosal pH was postulated.[72] A controlled, randomised, parallel-group study investigated the effects of intranasal CO2 on TRPV1-mediated trigeminal pain in healthy volunteers. Only mild modulatory effect of intranasal insufflation of CO2 at flow rates of 1 L/min was found, and the clinical utility seemed limited since changes in pain ratings were therapeutically irrelevant.[73] A Phase 2 placebo-controlled, single-blind study to evaluate the safety and efficacy of nasal CO2 has been conducted in patients with classical TN. All subjects received 3 doses of active and 3 doses of placebo. A single dose consisted of a 60-second delivery of CO2 or placebo. The primary outcome was pain relief assessed on VAS. Recruitment phase is completed; however, the study findings have not yet been published (ClinicalTrials.gov Identifier: NCT02473016).

## 3.4 Drugs in Secondary Trigeminal Neuralgia

No randomised controlled trials were found in patients with TN secondary to a major neurological disease. The existing studies based on CBZ, OXC, eslicarbazepine, lamotrigine, gabapentin, pregabalin, topiramate and misoprostol have an open label design and include small sample of patients with multiple sclerosis (MS).[74-88] Only few studies provided details about the type of MS and the TN diagnostic criteria.88 One study used a VAS and recorded both intensity and number of attacks.[85,88] These case series reported the potential efficacy of lamotrigine as monotherapy or in association with gabapentin or CBZ, topiramate and gabapentin. Three studies reported the efficacy of misoprostol (a prostaglandin-E1-analogue) in a total of 27 patients

with TN secondary to MS.[84-86] According to the international guidelines,14 there is insufficient evidence to support or refute the effectiveness of any medication in TN secondary to MS.

## 3.5 Drugs in Trigeminal Neuralgia with Concomitant Continuous Pain

No clinical trials assessing pharmacological treatment of CCP in TN have been conducted. Different studies clearly demonstrated that concomitant continuous pain is associated with poor medical and surgical outcome.[4,23,52] Recently, in a prospective study involving 158 patients with TN the prevalence of responders to sodium channel blockers was lower in the group with also CCP.[16] On the basis of these data, constant pain is considered a predictor of poor treatment response. No study has assessed the drug effect in reducing constant and paroxysmal pain intensity separately. Because CBZ and OXC are extremely efficacious in increasing the refractory period of action potentials, they act on the high frequency discharges that characterize the paroxysms of TN. Usually, in patients with also continuous pain mediated by other pathophysiological mechanisms, a monotherapy with sodium channel blocker is not sufficient to control pain and other drugs are usually needed. As far as we know, calcium channel blockers and antidepressants, whose efficacy has already been proven in the treatment of neuropathic continuous pain due to several aetiologies, have never been systematically tested in TN patients with CCP. Future randomised controlled trials assessing these drugs as add-on treatment in TN with CCP are required.

## 3.6 Expert Opinion

Based on evidence,[14] CBZ (400–1200 mg/day) and OXC (900–1800 mg/day) are the first-line medical treatment in patients with TN. OXC should be preferred for better tolerability and the decreased potential for drugs interactions. These drugs are effective in most patients and the development of late resistance only occurred in a very small minority of patients. However, the side effects cause withdrawal from

treatment in a significant percentage of patients. Common initial side effects include drowsiness, nausea, dizziness, diplopia, ataxia and elevation of transaminases. Hyponatremia occurs in 6–8% of patients; sodium levels are dose related and should be monitored during the treatment, especially when high dosage is used. Patients treated with diuretics may be more susceptible to developing sodium depletion.[4] The addition of sodium chloride capsules can be helpful in patients with persistent hyponatremia. Serious but uncommon side effects include allergic rash, hepatotoxicity, lymphadenopathy, systemic lupus erythematosus, Stevens–Johnson syndrome and aplastic anemia. Specific contraindications are cardiac conduction problems or severe arrhythmias. In a prospective, observational, exploratory survey of 161 patients with idiopathic TN, females treated with CBZ or OXC reported significantly more side effects than males.[89] Pharmacokinetic and pharmacodynamic differences are likely to be the reason for gender differences in reporting side effects. The consumers' views on treatments used for TN was investigated by using a self-administered questionnaire distributed to 133 patients and 21 clinicians attending national support group meetings in the USA and UK.[90] All patients reported at least one side effect. The clinicians underestimated the number of side effects, but both groups agreed that drowsiness and cognitive impairment were the most disliked side effects. A prospective study investigated the risk and genetic association of OXC-induced cutaneous adverse reactions, including Stevens–Johnson syndrome/toxic epidermal necrolysis, in Asian populations. The authors found that HLA-B*15:02 was significantly associated with OXC-Stevens-Johnson syndrome in Chinese and Thai populations.[91] CBZ is a potent inducer of CYP3A4 and other oxidative enzyme systems in the liver, and it may also increase glucuronyl transferase activity, leading to a number of clinically relevant drug interactions. OXC, a keto-analogue of CBZ, rapidly converted into its pharmacologically active metabolite, should be preferred for the better tolerability and the decreased potential for drugs interactions. A recent meta-analysis investigating the teratogenic effects of different antiepileptic drugs showed that children exposed to CBZ were at a higher risk of malformation than children born to women without, and women with untreated epilepsy.[92] Vixotrigine, a new sodium channel blocker that is selective for the Nav1.7 receptor is under development and has promise of efficacy without inducing

side effects related to CNS depression. Lamotrigine is considered a second-line treatment in patients with TN. Potential side effects of lamotrigine include dizziness, nausea, blurred vision and ataxia. Approximately 7–10% of patients will report a skin rash during the first 48 weeks of therapy. The dose of lamotrigine must be increased slowly in order to avoid skin rash. In patients with refractory TN, or in the event of withdrawal due to side effects, surgery should at least be proposed and discussed with the patient. In refractory TN, BTX-A is a promising alternative treatment option that might spare the need for surgical interventions.[27] Although it is reasonable that BTX-A primarily acts on constant pain, to our knowledge, no study has reported the effects of injections in a subgroup of patients with continuous pain until now. During acute exacerbation, in-hospital treatment may be necessary for rehydration, management of hyponatraemia, titration of drugs, and, in selected case, lidocaine or fosphenytoin intravenous infusion, under specialist supervision and cardiac monitoring. Intravenous loading of fosphenytoin was reported in case series but no randomised controlled trials have been conducted until now.[93-95] The first-line therapy in secondary TN is based on sodium channel blockers. In patients with MS-related TN, gabapentin, lamotrigine and topiramate represent other therapeutic options, but the quality of evidence is poor. In this patient category pharmacological treatment may potentiate some of the MS symptoms with a high percentage of dropout. Expert consensus suggests that baclofen may be useful in patients with MS who develop TN. Such patients are often taking baclofen already to reduce spasticity and may achieve control of symptoms without having to add CBZ. The main side effects of baclofen are transient sedation and loss of muscle tone. Abrupt discontinuation may cause seizures and hallucinations. In patients with TN, CCP is associated with poor medical and surgical outcome. In this condition, both calcium channel blockers (gabapentin and pregabalin) and antidepressants may be efficacious and should be tried as an add-on to OXC or CBZ. However, randomised, controlled, double-blinded trials are still lacking.

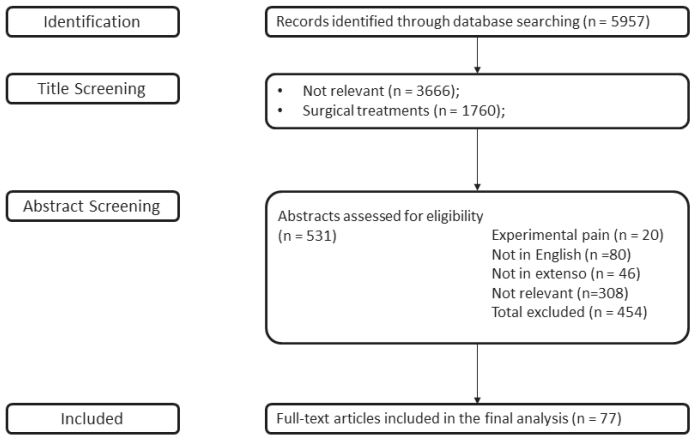


**Figure 6**. Flowchart of the search process

## 3.7 Supplementary material

Placebo controlled trials in Trigeminal Neuralgia

| Author/year | N° patients | Intervention | Design | Measure | Outcome |
|---|---|---|---|---|---|
| **Campbell et al. 1966 [25]** | 70 | CBZ 300-800 mg per day | R, D-B, C-O | Pain severity | Improved on active at week 4: 58%<br>Improved on placebo: 26% |
| **Killian and From 1968 [26]** | 24 | CBZ 400-1000 mg per day | R, D-B, C-O | Global pain response | Improved on active at week 2: 24/24 Improved on placebo: 0/24 |
| **Nicol 1969 [27]** | 44 | CBZ 100-2400 mg per day | R, D-B, C-O | Global pain response | Improved on active at week 2: 15/20 Improved on placebo: 6/7 |
| **Fromm et al. 1984 [35]** | 10 | Baclofen 40-80 mg per day | Randomization unclear, D-B, C-O | N° paroxysms | Improved on active at week 1: 7/10 reduction<br>Improved on placebo: 1/7 |
| **Zakrzewska et al. 1997 [33]** | 14 | Lamotrigine 400 mg per day | R, D-B, C-O | Composite index, global response | Improved on active at week 2: 7/13<br>Improved on placebo: 1/14 |

| | | | | | |
|---|---|---|---|---|---|
| **Kanai et al. 2006 [50]** | 25 | Intranasal lidocaine 8% spray | R, D-B, C-O | Pain severity (VAS) | Active: baseline: 8.0 (2.0) cm, 15 min postspray: 1.5 (1.9) cm, mean (SD)<br>Placebo: 7.9 (2.0) cm, 7.6 (2.0) cm |
| **Niki et al. 2014 [51]** | 24 | Intraoral lidocaine 8% application | R, D-B, C-O | Pain severity (NRS) | Active decreased the NRS from 5 (4, 8) (median [25, 75 percentiles]) to 1 (0, 4) at 15 minutes post-application<br>Placebo: from 5 [4, 8] points, to 5 [4, 8] points) |
| **Kanai et al. 2006 [53]** | 24 | 3 mg (1 mL) of sumatriptan subcutaneously | R, D-B, C-O | Pain severity (VAS) | Active: baseline: 8.3 (2.1) cm, 15 min post application: 2.4 (3.0) cm<br>Placebo: 8.5 (2.1) cm, 8.1 (2.6) cm |
| **Wu et al. 2012 [57]** | 40 | Intradermal and/or submucosal injection of BTX-A (75 U) | R, D-B | Pain severity (VAS-pain frequency-PGIC) | Improved on Active (>50% reduction) at week 12: 68.2%<br>Improved on placebo: 15.0% |
| **Zhang et al. 2014 [58]** | 84 | BTX-A (25U or 75U) subcutaneously | R, D-B | Pain severity (VAS) | Improved on active (>50% reduction) at week 8: 25U group 70.4%, 75U group 86.2%<br>Improved on placebo: 32.1% |
| **Zúñiga et al. 2013 [59]** | 36 | BTX-A (50 U) subcutaneously | R, D-B | Pain severity (VAS-pain frequency) | Mean VAS reduction from 8.9 to 4.8 in BTX group, mean attacks frequency |

| | | | | | |
|---|---|---|---|---|---|
| **Shehata et al. 2013 [60]** | 20 | BTX-A (5U) subcutaneously | R, S-B | Pain severity (VAS) | reduction from 29.1 to 7.1 attacks at week 8<br>Mean VAS scores in BTX group showed a decrease of 6.5<br>compared with a decrease of 0.3 for placebo at week 12 |
| **Zakrzewska et al. 2017 [21]** | 67 | BIIB074 150 mg three times per day orally | R-D-B | Difference between groups<br>in the number of treatment failure<br>during the double-blind phase | 33.0% of patients<br>receiving BIIB074 were classified as treatment failures<br>versus 64.0% of patients receiving placebo |

# PART IV

# 4. General Conclusions and Future Perspectives

The findings in this thesis offer new insights into the clinical characteristics of TN with a specific focus on trigger factors, the natural history of this unique facial pain condition, the drug responsiveness and the changes in pain characteristics.

Findings support that in virtually the totality of patients with TN trigger factors can be observed; this confirms the key role of triggers for a clinically established diagnosis of TN. For the first time an overlap profiling of the trigger zones in a large cohort of patients with TN was carried out with a dedicated software, providing a graphical representation of the sum of the trigger areas on a standard 3D model of face and mouth. Trigger zones were located almost exclusively in the central mask, most commonly in the perioral area, and were variable in size. In all the trigger manoeuvres listed by patients a mechanical component (touch or muscle movement) was present. These findings will be of assistance in future studies on the pathophysiological mechanisms TN.

Findings on the natural history and outcome of 200 outpatients with classical TN suggested that worsening of pain with time and the development of late resistance only occurred in a very small minority of patients. First line drugs (CBZ and OXC) are effective in virtually the totality of patients. The failure of the treatment with CBZ or OXC, most of the times, is not due to the inefficacy of the drug, but rather to undesired effects to a level that causes interruption of treatment or a dosage reduction to an insufficient level. These results suggest the opportunity to develop better tolerated drugs. Vixotrigine, a new sodium

channel blocker that is selective for the Nav1.7 receptor, is under development and has promise of efficacy without inducing side effects related to CNS depression.

In patients with TN, CCP is associated with poor medical and surgical outcome. In this condition, both calcium channel blockers (gabapentin and pregabalin) and antidepressants may be efficacious and should be tried as an add-on to OXC or CBZ. There is a need for randomised, controlled, double-blinded trials assessing these drugs as add-on treatment in atypical TN.

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Trigeminal Neuralgia is a unique neuropathic facial pain condition, characterized by unilateral paroxysmal pain most often described as stabbing or electric shock-like, restricted to the distribution of one or more divisions of the trigeminal nerve territory and triggered by innocuous stimuli. Trigger zones are reported in virtually the totality of patients and represent the hallmark sign of Trigeminal Neuralgia. The development and application of a dedicated software allowed trigger zone overlap profiling of the extraoral and intraoral territories. The analysis of the natural history of Trigeminal Neuralgia showed that the failure of the treatment with first-line drugs (carbamazepine and oxcarbazepine), most of the times, is not due to the inefficacy of the drug, but rather to undesired effects to a level that causes interruption of treatment or a dosage reduction to an insufficient level. These results suggest the opportunity to develop a better tolerated drug.

**Giulia Di Stefano**, MD, PhD, is a researcher of Sapienza University of Rome, at the Department of Human Neuroscience. In the last 10 years, her research projects focused on the development of new, neurophysiological techniques to test the nociceptive afferents, on the application of neurophysiological and morphometric techniques in the study of the pathophysiological mechanisms of pain and on the investigation of possible biomarkers to predict drug response in patients with neuropathic pain. In 2013, in the framework of a fellowship at the Department of Neuroscience, Physiology and Pharmacology, University College of London, she focused on the trigeminal function, and on the brainstem circuitry of defensive responses in humans. One of the main research themes is the study of the pathophysiological mechanisms of facial pain, with a specific focus on trigeminal neuralgia.

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