



BOTULINUM TOXIN TYPE A VERSUS PREGABALIN IN THE TREATMENT OF REFRACTORY TRIGEMINAL NEURALGIA

A multicenter, triple blind, double dummy, randomized
controlled clinical trial

FINAL DEGREE PROJECT

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ABSTRACT

Background: Trigeminal neuralgia is a chronic disease characterised by recurrent attacks of brief episodes of intense electric shock-line pain in the distribution of one or more divisions of the trigeminal nerve. In most cases, these attacks are unleashed by stimulus like talking, brushing teeth or shaving. The pain is usually unilateral and lasts from few seconds to two minutes but patients may have until 50 attacks per day strongly affecting their quality of life. The only drug with strong evidence and with grade of recommendation A is Carbamazepine. However, in some patients this treatment is not useful or has high rate of adverse events. Second line options could be Oxcarbazepine, Lamotrigine or Baclofen. There is no evidence about which treatment should patients receive once these options have failed. Selected patients could undergo different surgical procedures but they are not exempt from risks and adverse effects. Recently, some randomized controlled trials compared the efficacy of Botulinum Toxin type A (BTX-A) versus placebo in refractory patients with good results. Pregabalin has also shown to be an effective option in some studies. However, there are no studies comparing both drugs.

Objectives: The main purpose of this study is to compare the efficacy of BTX-A versus Pregabalin in the treatment of patients diagnosed with trigeminal neuralgia that do not respond to, at least, two different pharmacologic treatments.

Design: Multicentric, triple blind, double dummy, randomized controlled clinical trial.

Methods: Patients enrolled in this study will be randomized in two groups (A and B). The group A (n=50) will receive injections of BTX-A in the affected area and will be provided with placebo pills while the group B (n=50) will receive injections of sterile isotonic saline (placebo) and Pregabalin pills in order to treat their refractory trigeminal neuralgia. Injections will be performed twice during the study, at the beginning and twelve weeks later. The other medication will be taken twice a day during the six month of the trial.

We define treatment efficacy when there is a reduction >50% in the mean of the Visual Analogue Scale (VAS) score from baseline to endpoint. The frequency of the attacks, an overall response to treatment and safety of these drugs will be evaluated and recorded. Patients will be followed-up every week during the first month and every two weeks during the next five months.

Participants: Adults diagnosed of trigeminal neuralgia with insufficient therapy response with at least 2 treatment attempts (one of them has to be Carbamazepine) or intolerable side effects.

Key words: trigeminal neuralgia, botulinum toxin type A, pregabalin, refractory patients, visual analogue scale.

ABREVIATIONS

TN: Trigeminal Neuralgia

ICDH-3: International Classification of Headache Disorders, 3rd edition

BTX-A: Botulinum Toxin Type A

MRI: Magnetic Resonance Imaging

CT: Computed Tomography

VAS: Visual Analogue Scale

EVA: Escalera Visual Analógica

CGI: Escala de Impresión Clínica Global

PGIC: Patient Global Impression of Change

SUNCT: Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

SUNA: Short-lasting unilateral neuralgiform headache attacks with autonomic symptoms

NSAIDs: Nonsteroidal Anti-Inflammatory Drugs

CBZ: Carbamazepine

OXC: Oxcarbazepine

NNT: Number Needed to Treat

RCT: Randomized Controlled Trial

CEIC: Clinical Research Ethics Comitee

1. INTRODUCTION

1.1. TRIGEMINAL NEURALGIA

1.1.A. Definition and anatomy

Neuralgia is defined as pain in the distribution of a nerve or nerves.

Trigeminal neuralgia (TN) is a chronic disorder characterized by recurrent brief episodes of unilateral electric shock-like pain, abrupt in onset and termination, in the distribution of one or more divisions of the fifth cranial nerve that typically are triggered by innocuous stimuli like talking, eating, brushing teeth or shaving. This neuropathic disorder has been shown to be profoundly distressing and to negatively impact the patient's well-being (1,2).

Regarding its anatomy, the trigeminal nerve is the fifth cranial nerve (V) and it is the largest one. It gives the sensibility to the greater part of the head (**Figure 1**) and has the motor control of several muscles, including the masticatory ones. It has 4 nucleus, the main sensory one lies in the posterior part of the pons, lateral to the motor nucleus (3,4).

The trigeminal nerve leaves the anterior pons as a small motor root and a large sensory root. The nerve passes forward out of the posterior cranial fossa and rests on the upper surface of the apex of the petrous part of the temporal bone, in the middle of the cranial fossa (5). The sensory root expands to form the trigeminal ganglion, also called Gasserian ganglion, from where, in its anterior border, the nerve leaves its three branches: ophthalmic (V1), maxillary (V2) and mandibular (V3) (4). The ophthalmic nerve leaves the skull through the superior orbital fissure. The maxillary nerve leaves from the foramen rotundum and the mandibular one from the foramen ovale. Each division will provide the sensibility to a specific part of the face (**Figure 1**), that will be important in order to know which branch is the affected in a TN patient (See **Annex 1**) (3,5).

1.1.B. History and epidemiology

The first description known is from II a.C. by Aretaeus of Cappadocia. However, the historical reference better established is from John Fothergill in 1775, who already observed the female predominance and the higher incidence of elderly people (2,6).

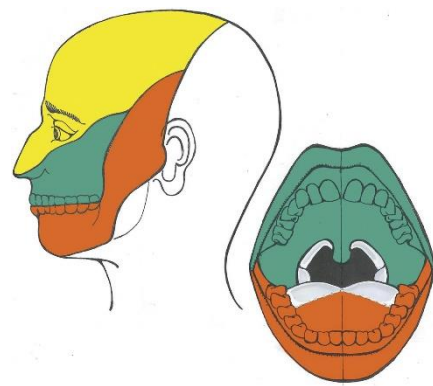


Figure 1: Innervation territories of the trigeminal nerve. From Cruccu et al. (18).

Yellow territory: ophthalmic branch (V1)
Green territory: maxillary branch (V2)
Orange territory: mandibular branch (V3)
White areas: innervated by cervical nerves
Light grey areas in the back of tongue and throat: innervated by glossopharyngeal

TN is one of the most frequently seen neuralgias in the older adult population despite its low incidence. There is not a clear consensus about its incidence. A epidemiological study developed in Minnesota during 1945-1984 found an annual incidence of 4.3/100.000 people (7). However, recent epidemiology surveys from UK (8) and the Netherlands (9) show higher incidences of 26.8 and 28.9 per 100.000 people, respectively. The incidence has been demonstrated to increase gradually with age, that is why most idiopathic cases begin after 40-50 years (2,6,10).

According to a work based on a UK community found a TN prevalence of 70 per 100.000 inhabitants (11). There is an evident female predominance, with a rate of 1:1,6 or more (2,10,12,13). This fact may be related to the increased longevity of women compared with men. (14). The vast majority of patients have sporadic disease since rare familial cases have been reported (15).

1.1.C. Etiology and pathogenesis

TN can be originated by multiple factors and its pathogenesis is not entirely known.

- The primary pathophysiologic mechanism thought is focal demyelination, which is supported by established neurophysiologic, neuroimaging and histological evidence. The affected part is the entry of the trigeminal root into the pons (16). That place is where myelin passes from being produced by Schwann cells to oligodendroglia, whose level of compression tolerance is lower (2,17)
- A second pathophysiologic theory is that these areas of focal demyelination may create ectopic impulse generation because of an ephaptic cross-talk between fibres (cross transmission impulse between parallel axons) which could precipitate the painful attacks by light tactile stimulation of facial trigger zones (13,15–17). This hypothesis could explain the effectiveness of some treatments like antiepileptic drugs that could act as a palliative form reducing the impulse transmission (2).

Remyelination is thought to occur during remission. In that point, some authors criticize the demyelination hypothesis because of an unexplainable fast curation of patients after some decompression surgical treatments without relation with the time needed to remyelinate. Moreover, demyelination cannot explain such a long refractory period between attacks (2,15).

- A third hypothesis is that stabbing pain could produce changes in the central pain mechanisms with a hyperexcitability state at the level of the brain stem. This hypothesis could explain the presence of refractory periods and the latency from the time of stimulation to the onset of pain (16,17).

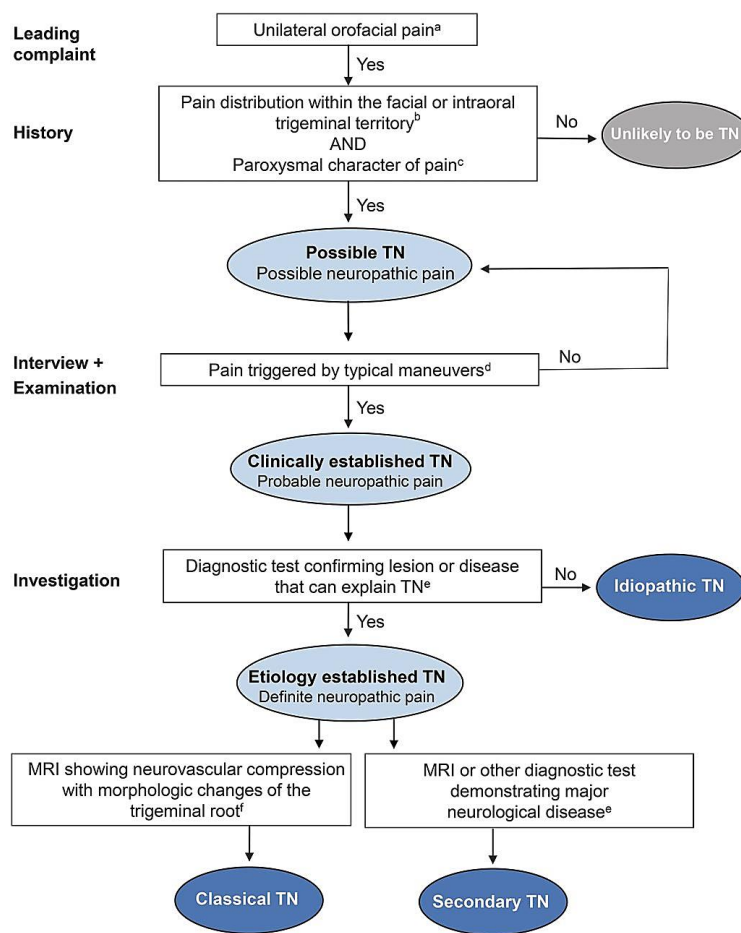
- Research done by Janneta inspired Dandy's theories about nerves compression because of surrounding blood vessels. These agrees with some surgical series (6). The place where is typical to find this compression is into the pons (the entry zone). Compression by an aberrant loop of an artery or vein is thought to account for 80 to 90% of cases (2,15). That compression can provoke alterations in the sensitive root, which extends electric stimulus inside the nerve creating axonal restimulations that could be the cause of repeated neural discharges (6).
- Only few authors defend other hypothesis about chronic inflammation due to a reactivation of Herpes virus after invasive procedures in the Gasser ganglion (2,10).

1.1.D. Classification

According to the International Classification of Headache Disorders 3rd edition (ICHD-3) (1), TN is divided into:

- **Classic TN (92-95%):** encompasses both idiopathic TN and those related to vascular compression.
- **Painful trigeminal neuropathy (secondary TN) (5-7%):** caused by structural brain lesions other than vascular compression, such as:
 - Acute herpes zoster
 - Postherpetic trigeminal neuropathy
 - Post-traumatic
 - Multiple sclerosis plaque (2-4%)
 - Space-occupying lesion (2-3%), especially vestibular schwannomas, meningiomas, epidermoid cysts.
 - Other disorders like syringobulbia, saccular aneurisms, carcinomatosis, brainstem infarcts (2)

Recently, Cruccu et al. developed a new classification for TN (**Figure 2**) (18). The main difference from the ICHD-3 is that in cases of unknown etiology for TN is classified as "Idiopathic TN" not as "Classic TN", as seen in the following algorithm.



^aTN is typically an unilateral condition
^bThe pain strictly follows the distribution of the trigeminal nerve branches.
^cParoxysmal pain is the main complaint but it may be accompanied by continuous pain.
^dTrigger maneuvers include innocuous mechanical stimuli, facial or complex activities such as shaving or applying make-up.
^eMRI readily identifies major neurologic diseases, such as tumors or multiple sclerosis. In cases of patients that cannot undergo MRI, recording of trigeminal reflexes and trigeminal evoked potentials may be useful.
^fAdvanced MRI techniques are capable of demonstrating neurovascular compression

Figure 2: New classification for TN. From Cruccu et al. (18).

1.1.E. Clinical features

The clinical features are the main point to diagnose TN. Its symptomatology includes paroxysmal, stereotyped attacks of unusually intense, sharp, superficial or stabbing pain in the distribution of at least one branch of the trigeminal nerve. The pain is described like an electric discharge, it mostly involves the V2 and/or V3 subdivisions of the fifth cranial nerve and is typically unilateral, with a right predominance (1,2,6,10). The ophthalmic division alone is involved in less than 5% of cases (12,13). Although tongue receives innervation from the mandibular branch of the nerve, the irradiation of the pain to it is unusual (6,10).

Regarding the attacks, they usually last from few seconds to two minutes and unlike some other facial pain syndromes, TN typically does not awaken patients at night. They are clinically characteristic because there is a refractory period of some minutes during which a paroxysm cannot be provoked (2,13,18). However, some patients with longstanding TN may have continuous dull pain that is present between paroxysms of pain (6,12,18). Frequency of the pain attacks may range from 1 to over 50 a day (18).

Trigger zones can be found in the distribution of the affected nerve especially in the central portion of the face and around the nose and mouth (18). On a physical examination, they can be demonstrated lightly touching these zones and observing if they trigger an attack (10). However, there are cases that do not occur or that facial exploration can be difficult because patients are reluctant since they are afraid of having new attacks. Moreover, abrupt interruptions of the speech can be seen during the medical interview when a pain attack appear (2). The physician must ascertain that the pain does not extend to the posterior third of the scalp, the back of the ear or the angle of the mandible as these territories are innervated by cervical nerves (18) (Figure 1).

Triggers can also appear when chewing, talking, brushing teeth, with cold air and smiling (6,10,14). So, a sensorial cutaneous stimulation of the mucosa or the teeth innervated by this nerve can trigger the pain which could create difficulties in order to eat and lead sometimes to malnutrition or important dehydration (2). However, there is no sensory or motor disturbance and there is not any focal neurologic deficit (6,13).

In cases of secondary TN, sensory loss in the distribution of the Vth nerve, atrophy and weakness of the masticatory muscles can be seen (18). If both trigeminal nerves are affected, multiple sclerosis should be considered (6). Moreover, in secondary TN the pain is more continuous than classical TN, it is not paroxysmal and there are not trigger zones. Alterations in the physical examination can be also found (10).

The pain resulting from TN creates a substantial burden on patients (19). Even between attacks, some patients feel an overwhelming fear that the pain could suddenly return at any time. It is said that TN impacted employment in 34% of patients (12). Consequently, quality of life of TN patients is profoundly worsened due to impairment of daily life activities, thus patients have more depression, anxiety and sleep disorders than not affected people (20,21). Moreover, patients with TN may be at risk for cognitive impairments because of pain, medicines used or advanced age which affects therapy adherence, personal relationships, capacity for work and leisure activities (21).

1.1.F. Diagnosis

The diagnostic criteria for TN according to the ICHD-3 (1), is as follows:

- A. At least three attacks of unilateral facial pain fulfilling criteria B and C
- B. Occurring in one or more divisions of the trigeminal nerve, with no radiation beyond the trigeminal distribution
- C. Pain has at least three of the following four characteristics:
 - Recurring in paroxysmal attacks lasting from a fraction of a second to two minutes
 - Severe intensity
 - Electric shock-like, shooting, stabbing, or sharp in quality

- At least three attacks precipitated by innocuous stimuli to the affected side of the face (some attacks may be, or appear to be, spontaneous)
- D. No clinically evident neurologic deficit
- E. Not better accounted for another ICHD-3 diagnosis

There are patients that fulfil these criteria for classic TN but have a persistent facial pain of moderate intensity in the affected area; these individuals are diagnosed of atypical TN or TN type 2 (1).

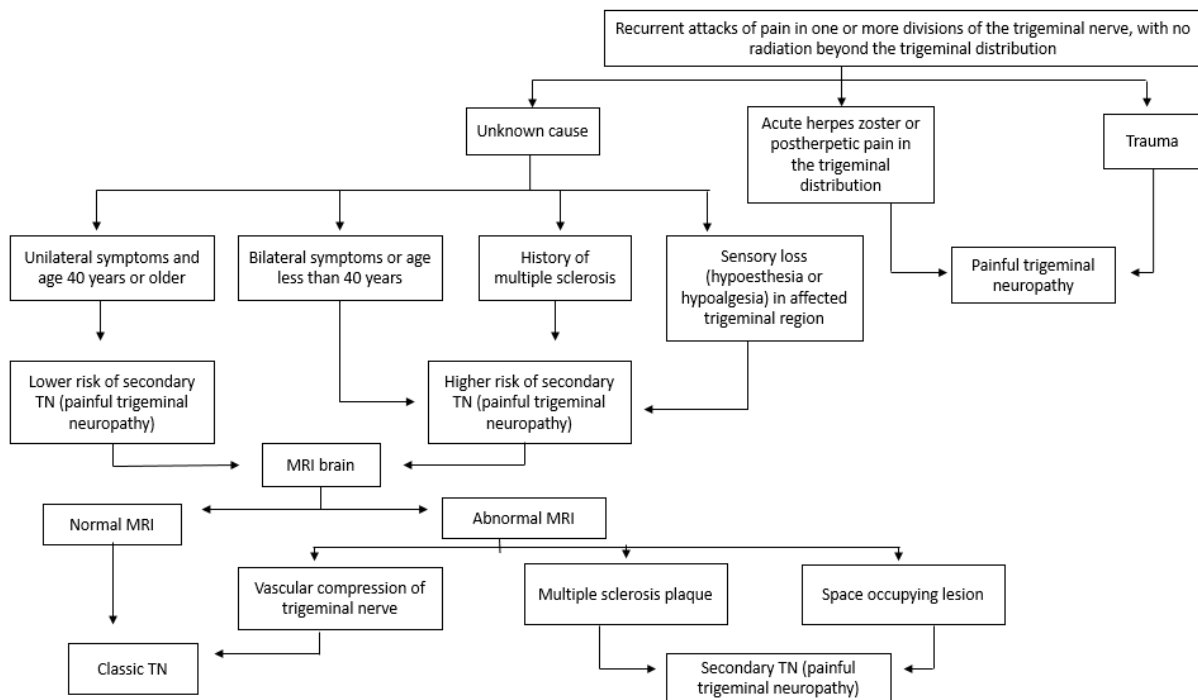


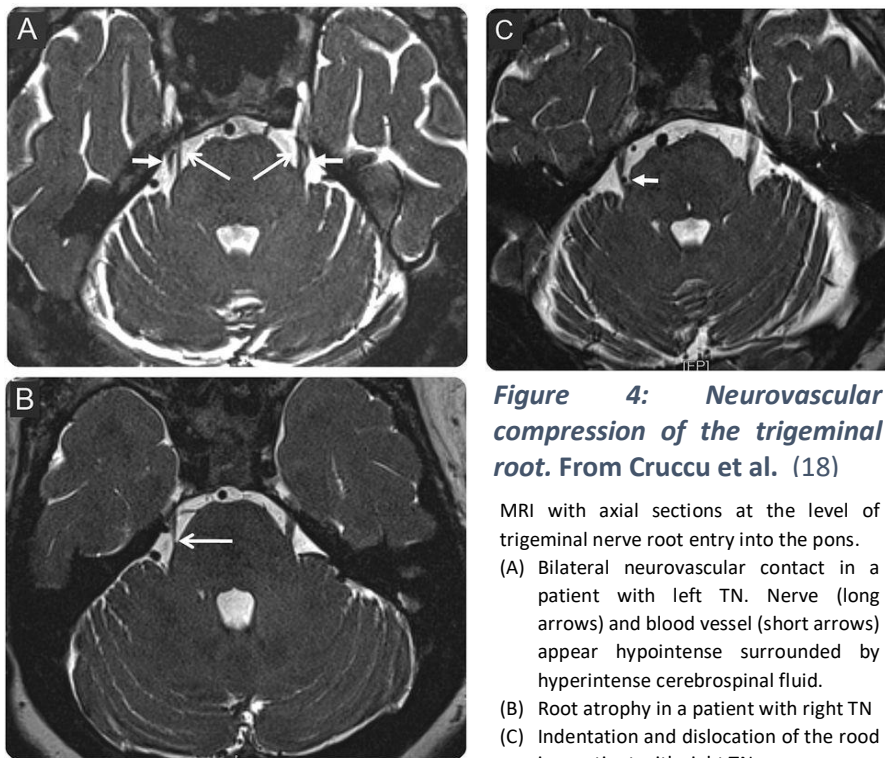
Figure 3: Management and diagnostic algorithm for TN. From Heras-Perez J. (2)

For all patients with suspected TN, a neuroimaging is recommended in order to exclude other diagnostic possibilities and to seek if there is an structural lesion that could distinguish classic TN from secondary TN (2,10,13). This could be done with a cerebral magnetic resonance imaging (MRI) or a cerebral computed tomography (TC). MRI with and without contrast is much preferred because its higher resolution enables imaging the trigeminal nerve, the presence of adjacent vessels in the Gasserian ganglion or other small adjacent lesions (2).

In general, it is accepted that all patients diagnosed with TN can apply for a cerebral MRI. However, some authors restrict this test for that patients with trigeminal sensory deficit and/or bilateral involvement of the trigeminal nerves because they may have a higher risk of secondary TN, especially in patients younger than 40 years who have more risk to have multiple sclerosis lesions (2,22).

The most commonly identified abnormalities are the neurovascular contacts, especially a vascular loop of the upper cerebellar artery above the trigeminal nerve (**Figure 3**). A tumour at the cerebellopontine angle or multiple sclerosis causes TN in 15% of patients (12,18,22). In an 11% of subjects, TN remains unclear (idiopathic) even after undergoing a MRI (18).

Nevertheless, in asymptomatic patients a vascular contact is seen in a 8% of the cases because MRI has a high sensitivity but poor specificity (2). Therefore, MRI is a valuable diagnostic tool only if preceded by symptoms and signs that may indicate TN (18).



Other diagnostic test like X-ray, evoked potentials, electromyography or stimulation of the nerve do not show alterations (2,6). However, electrophysiological examination can reliably distinguish classic TN from secondary TN since trigeminal reflex testing has a high specificity (94%) and sensitivity (87%) but is not routinely recommended (12,18,22). Blood test including blood count, erythrocyte sedimentation rate, biochemistry, tumour markers or autoimmunity can be useful in the differential diagnosis or in order to find an underlying cause but they are within normality in TN patients (2)

DIFFERENTIAL DIAGNOSIS

The main important differential diagnosis is with all the secondary causes of TN (12).

- Acute herpes zoster and postherpetic neuralgia can be distinguished from classic TN by a thorough history and examination (10). However, if there is an isolated involvement of the V1 subdivision (which occurs in <5% of patients with TN), postherpetic neuralgia must be discarded (2).
- Multiple sclerosis or mass lesion may be seen when neuroimaging is performed (10).
- Dental causes of pain can be confused with TN. However, dental pain is usually continuous, intraoral pain is dull or throbbing, whereas classic TN is typically intermittent pain and sharpening but sometimes can be triggered by oral manipulations such as chewing and brushing the teeth (2).
- Uncommon causes of headache and craniofacial pain such as short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with autonomic symptoms (SUNA). They are characterized by sudden brief attacks of severe unilateral head pain in orbital, peri-orbital or temporal regions, accompanied by ipsilateral cranial autonomic symptoms (2).
- Pathology of the temporomandibular articulation: the pain is commonly bilateral and may irradiate behind the ears. Opening of the mouth can be restricted (2).
- Trigeminal neuropathy: the pain is continuous and neuropathic and it is associated with a sensory deficit in the affected branch (2).
- Other neuralgias like occipital neuralgia (affects the posterior region of the scalp) or glossopharyngeal neuralgia (pain is set at the oropharynxes and is irradiated to the tongue or the tonsils) (2).

1.1.G. Treatment

Because of the high severity of pain, physicians should start the treatment as soon as possible in order to control the pain and improve the patient's conditions. Although the treatment available, there is a lot of variability between patients, for this reason individualized therapy is needed for all patients.

The general recommendation is to start with medical therapy and consider surgical procedures in patients who are refractory to medical treatment, as explained below (12).

Non placebo-controlled trials have evaluated the treatment of secondary TN. In those cases, treatment of the underlying condition, for example multiple sclerosis is recommended if feasible. In addition, it is important to treat the pain associated with secondary TN using the same medications that are employed in classic TN (2,12).

Commonly the treatment is initiated in monotherapy. In the case that there is no response or intolerance to it, changing the drug in a progressive way is accepted. Sometimes monotherapy is not useful and patients have to appeal to polytherapy even with 3 drugs to control pain. The treatment needs to be adjusted at a minimum effective dose and needs to be maintained at least until 1 or 2 months without attacks. Then, a gradual descent of the dose can be started until suspension, in the case of confirmed remission. If the pain reappears, the dose must be increased again repeating the same strategy again (2).

Broadly speaking about pharmacological treatment, common analgesics like nonsteroidal anti-inflammatory (NSAIDs) do not have effect in TN (2). The most commonly used drugs are antiepileptic, as explained below.

CARBAMAZEPINE

Carbamazepine (CBZ) is an antiepileptic drug and it is the best studied treatment for classic TN being established as effective (22) with a level of evidence I and a grade of recommendation A (13,17,23,24) (See [Annex 2](#)). That's why it is considered first-line therapy (2,6,10,12,13,17).

Dizziness, somnolence and ataxia are usual in elderly people or when doses are increased too fast (6,10,25). For that reason, the maximum initial dose is 100 to 200 mg daily. It can be increased gradually in increments of 50-100 mg every 3 or 4 days, as tolerated until sufficient pain relief. The typical maintenance dose ranges from 400 to 1200 mg daily (given in 2 divided doses for tables and extended release capsules, or 3 divided doses in the case of oral suspension) (2,13,25). When pain is controlled, the dose should be reduced progressively some weeks to find out if the patient is in remission (6,25).

The mechanism of analgesia is unknown. Its effect may be relate to the blockade of voltage-sensitive sodium channels resulting in the stabilization of hyperexcited neural membranes, inhibition of repetitive firing or reduction of propagation of synaptic impulses (12,25).

As reported by Gronseth et al. (22), who analysed 4 placebo-controlled studies with a total of 147 patients, concluded that CBZ reduced both the frequency and intensity of painful paroxysms with a number needed to treat (NNT) to attain important pain relief was less than 2 (2,17). However, CBZ was sometimes poorly tolerated with a number needed to harm (NNHs) of 3 for minor and 24 for severe adverse events. Although, we currently have other antiepileptics, neither of them has shown superiority to CBZ with enough evidence (2).

Common initial side effects include drowsiness, nausea, dizziness, diplopy, ataxia, elevation of transaminases and hyponatremia. Potentially serious but uncommon side effects are allergic rash, myelosuppression, hepatotoxicity, lymphadenopathy, systemic lupus erythematosus, Stevens-Johnson syndrome and aplastic anaemia (12,25). Complete blood count, serum sodium and liver function test should be performed within several weeks after initiation of treatment to detect complications in a timely manner. Moreover, the US Food and Drug Administration made recommendations about genetic testing for patients with Asian ancestry that are at highest risk for the development of Stevens-Johnson syndrome (12,25).

CBZ efficacy is approximately 70-85% initially (6,12,13). However, over time higher doses may be needed to maintain efficacy, which declines to approximately 50% of patients due to autoinduction of CBZ. (12).

OXCARBAZEPINE

Oxcarbazepine (OXC) is another antiepileptic drug that has a similar effect to CBZ, so it is usually used when there is an intolerance to CBZ. However, it is not recommended to prescribe OXC in cases of CBZ allergy because it has a 25% of cross reactions (2).

The recommended initial dose is 300-600 mg daily, given in two divided doses. It can be increased as tolerated in 300 mg increments every three days to a total dose of 1200 to 1800 mg daily (2). Usually the maintenance doses range between 300 and 600 mg twice daily (12,13). OXC level of recommendation is B (17,22,24).

According to Gronseth et al., that analysed several randomized controlled trials that compared OXC with CBZ reach the conclusion that both medications were equally effective, with a >50 percent reduction of attacks achieved by 88 percent of the patients (22). However, as CBZ, OXC losses its efficacy when it is used for a long time and then the therapeutic strategy must be changed (2).

OXC is rapidly metabolized into its pharmacologically active 10-monohydroxy metabolite and only weakly induces hepatic enzymes. This leads to a much better side effect profile than CBZ (12,13).

LAMOTRIGINE

Lamotrigine can be used with patients that have TN refractory to CBZ. So, it is used as a second-line treatment (12) with a grade of recommendation C (2,17,24).

Lamotrigine is an antiepileptic drug that acts at voltage-sensitive sodium channels, stabilizes neural membranes and inhibits the release of excitatory neurotransmitters (12).

Patients who are not taking other anticonvulsants, lamotrigine is typically started at 25 mg daily for the first 2 weeks and then increased to 50 mg daily for weeks 3 and 4. The target dose is 200-400mg/day divided between two doses. (12,22).

For patients who are taking an anticonvulsant drug that induces hepatic enzymes (e.g. CBZ or phenytoin), the initial dose is 50 mg once daily, titrating upward as needed to 100 mg once daily at week 3, 200mg once daily at week 5, 300 mg once daily at week 6, and 4000 mg once daily at week (10).

Potential side effects include dizziness, nausea, blurred vision and ataxia. Approximately a 7-10% of patients will report a skin rash during the first 4-8 weeks of therapy that most often resolve with continued therapy. Severe rash, desquamation, fever or lymphadenopathy indicative of Stevens-Johnson syndrome requires prompt discontinuation. The slower the titration, the less likely it is that these side effects will occur (12,16).

BACLOFEN

Baclofen is a muscle relaxer and it's also considered a second-line treatment, with a grade of recommendation C and level of evidence IV (2,13,17,22,24). It's a GABA_B receptor agonist and thus depresses excitatory neurotransmission (12).

The starting dose of baclofen is 15 mg daily given in 3 divided doses, with gradual titration to a maintenance dose of 30 to 80 mg per day (2,13).

The most common secondary effects include sedation, dizziness, and dyspepsia. Baclofen has to be discontinued slowly since seizures and hallucinations have been reported with upon withdrawal (2).

Figure 5 summarizes all the information explained before.

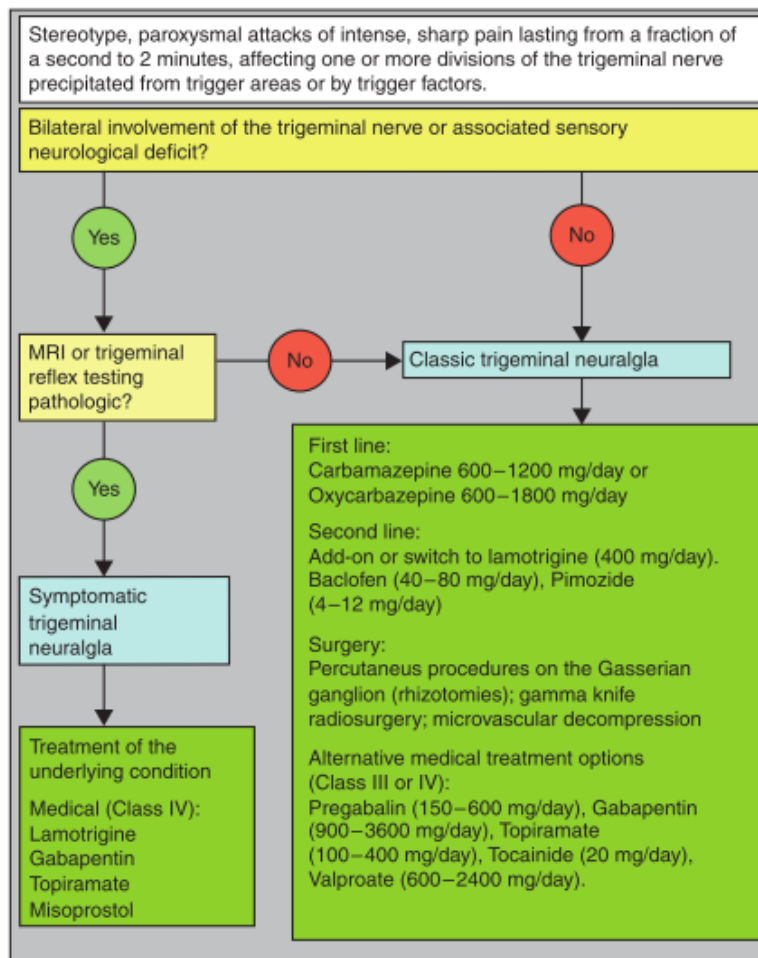


Figure 5: Workup and management of trigeminal neuralgia. From Obermann M. (12)

OTHER MEDICATIONS

About 25-50% of patients eventually stop responding or poorly response to drug therapy and require some form of alternative treatment (10,12,26). There is limited evidence to support treatment alternatives for patients with TN who are refractory to first-line medical therapy (6,10,12,17). Other antiepileptic drugs like topiramate, levetiracetam, gabapentin, pregabalin have been studied in small controlled or open-label studies (6,12).

- Gabapentin is initiated at 300mg daily and may be gradually increased by 300mg each 2-3 days until a maintenance dose of 900-2.400mg/day divided in three times (2). Probably because of its good results in clinical trials about neuropathic pain and its lack of interaction with other drugs with a relatively minor side effects like dizziness, somnolence, headache, diarrhoea, confusion or nausea it could be used in TN (2,12). It's level of evidence is IV and grade of recommendation C (13).
- Pregabalin is explained with more detail at [1.3. Pregabalin](#)

- Topiramate at a dose of 100-400mg/day suggested that was effective in a very small sample of only 8 patients (12).
- Levetiracetam was tested in 10 patients in an open-label design with a dose of 4000mg daily, and 4 reported some improvement (12)

So further randomized controlled trials will have to follow to confirm these preliminary findings (12).

Phenytoin, another antiepileptic drug, was used as an alternative of CBZ in the past. However, currently it could only be used when there are severe exacerbations, as fosphenytoin, since they may provide analgesia while oral medications are titrated because they have intravenous administration. Intranasal lidocaine could be also used in that patients (2,6,12).

SURGICAL THERAPY

Surgical treatments are reserved for those patients with TN that are refractory to at least three drugs including CBZ in sufficient dosage (12). There are different surgical methods, the main ones are explained below. However, only few of them have been studied in controlled trial and that is why most of the evidence comes from observational studies (12,13).

Broadly spoken, surgical therapies are well-tolerated but a feared complication is painful posttraumatic trigeminal neuropathy, also called painful anaesthesia. It's a condition characterized by persistent, painful anaesthesia or hyperesthesia in the denervated region (1).

- MICROVASCULAR DECOMPRESSION:

It is a major neurosurgical procedure, originally developed by Janneta. It involves a craniotomy of the posterior fossa and the removal or separation from the trigeminal nerve of some vascular structures (2,10).

In consonance with the review made by Gronseth et al., initial pain relief is attained in 90% of the patients, but that pain-free rates decline by one, three and five years to 80, 75 and 73 percent respectively (22). However, is the technique that has the most sustained pain relief, that's why it is considered the surgical gold standard (2,10,22).

The main advantage is the relief of pain without facial anaesthesia and that acts directly in the mechanism of action. Nevertheless, there is a risk of harming other cranial nerves specially IV, VII and VIII (6). The average mortality is 0,2-0.6% approximately though it may rise to 1% in some reports (2,10,22). The most common complication is aseptic meningitis which appears in 11% of patients, long term hearing loss in up to 10%, and

sensory loss in 7% of the cases. The major adverse events observed are cerebrospinal fluid leaks, infarction or hematoma in up to 4% of the patients (22).

- NEUROABLATIVE PROCEDURES

Consists in the interruption of the trigeminal axonal conduction before they reach the deeper structures in the encephalon with different percutaneous techniques (2,22).

- Radiofrequency thermocoagulation, which creates a lesion by application of heat (2). Its efficacy decreases to a 60% in 6-12months (10). The main complications are masticatory problems 10% and dysesthesias 5-24% (2).
- Mechanical balloon compression, which uses a Fogarty catheter through the foramen ovale to compress the Gasserian ganglion swelling a balloon. Up to 50% of patients suffer temporary masticatory problems (22). Other frequent reactions can be hypotension, bradycardia and facial paresis.
- Chemical rhizolysis, which involves the injection glycerol into the trigeminal cistern or the Meckel cavum producing dehydration of the Gasserian ganglion (2). This technique has recently been dropped out because of its high risk (10).

Since ablative procedures are less invasive, the recurrences may be more common. In general, pain relief is achieved in 90% of patients, but that pain-free rates declines by one year to 68-85% reaching to a 50% in five years (22). The most frequent long-term sequelae is sensory loss affecting nearly 50% of patients, postoperative dysesthesia 12%, painful anaesthesia and corneal numbness in 4% of the cases (6,12,22). However, the major complication of this procedure is meningitis, mainly aseptic, seen in 0.2% (22).

- RADIOSURGERY

Gamma knife radiosurgery produces lesions with focused gamma radiation at the proximal trigeminal root. Radiosurgery is found to have completed pain relief at one year in up to 69% of the patients and at three years in 52% (2,12,22). However, pain relief occurs after a lag time of about one month (2,12).

The main complication is a worsened facial sensory impairment, which occurs in 9 to 37%. However, painful anaesthesia is rare (22). The main disadvantage of gamma knife surgery is the cost, which limits their use only in patients that cannot undergo open surgery or have blood coagulation problems (12). Moreover, a specific control of the doses is needed and, sometimes, concomitant pharmacological treatment is required.

- PERIPHERAL NEURECTOMY

It may be performed on the branches of the trigeminal nerve, like the supraorbital, infraorbital, alveolar and lingual nerves or at the trigger points. However, according to Gronseth et al., the evidence of that technique is either negative or inconclusive (22).

1.1.H. Prognosis

The course of TN is variable with remission and exacerbation periods. Episodes may last weeks or months, followed by pain-free intervals (6). Recurrence is common and some patients have concomitant persistent background facial pain that creates a huge impact in their quality of life (2). It is typical that the intensity, duration and frequency of pain increases after several episodes of TN, which could explain the increased risk of psychiatric disorders (10,21).

1.2. BOTULINUM TOXIN TYPE A

BTX-A is a neurotoxin naturally produced during the *Clostridium botulinum* sporulation. There are seven antigenic subtypes (A-G), of which only the subtype A and B can be used in clinical practice, being the first one the most commonly used (27).

1.2.A. MECHANISM OF ACTION

BTX-A has been classically used because of its action during muscle contraction. Botulinum toxin can enter to the presynaptic terminals of the neuromuscular union, where can split an essential protein called SNAP-25, which is necessary for the correct fixation and release of acetylcholine, causing muscular relaxation (20,23,28). However, this mechanism does not explain the antinoceptive effect of BTX-A in TN or other neuropathic disorders.

BTX-A not only inhibits acetylcholine release, it also can inhibit other neurotransmissions that act in the discharge of muscle spindles or sympathetic transmission, which might play an important role in reducing the myofascial pain by inhibiting muscle spasms in cycle (26). Therefore, BTX-A has been related with the suppression of norepinephrine, epinephrine and ATP release, all implicated in chronic pain (29,30). Moreover, BTX-A has been implicated with the inhibition of substance P liberation, which an increase in spinal level can rise the central sensitivity to pain, being important in neurogenic inflammation (26,29). This last mechanism is the one implied in the analgesic effect of BTX-A in primary headache (23).

There are other neurotransmissions implicated in inflammatory mechanisms that can be inhibited with BTX-A, like the calcitonin gene-related peptide or glutamate (29–31), that are released in the Gasser ganglion through mechanisms that depend on calcium channels which are also implicated in migraine (26). An example of that was the research done by Cui et al. which demonstrated that subcutaneous BTX-A injection is associated with the inhibition of formalin-induced glutamate release (important mediator for the induction and maintenance of central sensitivity of pain) (30,32).

1.2.B. INDICATIONS

According to the technical data sheet (28), the indications of BTX-A are:

- Neurological disorders:
 - Focal spasticity associated with dynamic equine foot deformity
 - Focal spasticity of the wrist and hand secondary to a stroke
 - Blepharospasm, hemifacial spasm and associated focal dystonias
 - Cervical dystonia (spasmodic torticollis)
 - Chronic migraine, in patients that do not respond effectively or are intolerant to the prophylactic drugs of migraine.
- Bladder disorders:
 - Idiopathic overactive bladder in adult patients who have not responded adequately or are intolerant to anticholinergic medications
 - Urinary incontinence in adults with neurogenic detrusor overactivity
- Disorders of the skin
 - Severe or persistent primary hyperhidrosis of the axilla, resistant to topical treatment

1.2.C. CONTRAINDICATIONS

BTX is contraindicated in (28):

- Patients with known hypersensitivity to BTX-A or to any of the excipients
- Infection or skin problem at any of the injection sites

1.2.D. SIDE EFFECTS

BTX-A has a good safety profile because the vast majority of adverse effects are local.

Some studies have reported some local side effects such as mild and transient facial paresis (26,33–41), temporary dysesthesia (42), transient local oedema (39–41), local hematoma (34) and ptosis (43).

1.2.E. BTX-A AND TRIGEMINAL NEURALGIA

The therapeutic effect of BTX-A in TN was first mentioned after a serendipitous finding by Wang and Jankovic in 1998 (44). Jankovic described a patient who presented hemifacial spasm and TN, whose TN improved after treatment of the hemifacial spasm with BTX-A. Since then, case reports and open-label trials have been published in different medicine journals (**Table 1**)

There are only four randomized controlled trials (RCT) that compare BTX-A versus placebo in intractable TN. All evaluated efficacy and safety, and they found that BTX-A was safe and effective for the treatment of refractory TN (26,34,39,41).

There have been some systematic reviews and metaanalysis about the evidence of BTX-A (20,23,30,45). According to Morra et al. (20), who analysed the four RCT found a relative risk (RR) of 2.87 in terms of proportion of responders of BTX-A injections versus placebo. One of this reviews is made by Spanish investigators in the Hospital of San Pedro (Logroño), which also concluded that BTX-A could be an effective option (23).

In consonance with the review made by Kowacs P., who analysed all the available publications until 2015, demonstrated that most patients benefit from BTX-A injections, as 213 (89,9%) of the 237 patients described in the previous studies reported improvements (30).

Table 1: Reports of the efficacy of BTX-A in TN. Adapted from Castillo-Álvarez et al. (23) Kowacks et al. (30)

Author, year	Type of publication	Number of cases, response	BTX-A therapy	Type of measurement	Adverse effects
Michaeli et al. (46) 2002	Case report	1/1	2.5 MU in 5 sites (12,5 U), at 12wk intervals	Patient report	No
Allam et al. (35), 2005	Case report	1/1	2U in 8 points (16 U)	VAS	Facial paresis
Boscá-Blasco et al. (47), 2006	Case report	4/4	17,5 U at 6 mo intervals	VAS	No
Volcy et al. (48), 2006	Case report	1/1	6-7,5U at 4 mo intervals	Patient report	No
Uludz et al. (49), 2007	Case report	1/1	75 U at 3 mo intervals	Patient report	No
Carvalho Felicio et al. (50), 2007	Case report	1/1	100 U at 2 mo intervals	Patient report	No
Ngerow y Nair (37), 2010	Case report	1/1	100U divided into two sites	Patient report	Facial paresis
Yoon et al. (51), 2010	Case report	1/1	10 U	Patient report and current perception threshold	No
Borodic y Acquardo (36), 2002	Open-label trial	8/11	30-50U	Patient report	NR
Türk et al. (42), 2005	Open-label trial	8/8	50U in 2 sites	VAS and frequency at 1 st wk, 2 nd mo, 6 th mo)	No

Pioversan et al. (43), 2005	Open-label trial	13/13	6,45-9,11U per branch	VAS and pain area	Facial paresis 3/13
Zuñiga et al. (33), 2008	Open-label trial	10/12	20-50U	VAS and frequency	Facial paresis 1/12
Bohluli et al. (38), 2011	Open-label trial	15/15	50-100U at each trigger zone	VAS, frequency and global assessment	Facial paresis 3/15
Li et al. (40), 2014	Open-label trial	88/88 at 2mo 34/88 at 14 mo	25-170U (2,5-5U per point)	>50% reduction of VAS	Facial paresis 10/88
Xia et al. (52), 2016	Open-label trial	70/87	87U	>50% reduction of VAS	Facial paresis 7/87
Wu et al. (39), 2012	RCT 12 weeks	15/22 (22 other patients received placebo)	75U injected at 15 points	VAS, responders (>50% reduction), frequency, PGIC	Facial paresis 5/22 Oedema 2/22
Shehata et al. (26), 2013	RCT 12 weeks	20 patients (proportion NR)	40-60U (5U per point in a "follow the pain method"	VAS, frequency, QoL	Facial paresis 4/10 Problems at the injection point 3/10
Zuñiga et al. (34), 2013	RCT 3 months	36 patients (proportion NR)	50U (60U if involvement of V3)	VAS, frequency, functional impact	Facial paresis 2/20 Problems at the injection point 2/20
Zhang et al. (41), 2014	RCT 8 weeks	With 25U 19/27 With 75U 25/29	25U and 75U at 20 points	VAS, responders, PGIC	Facial paresis 3/56 Oedema 2/56

MU: mouse units, wk: week, VAS: visual analogue scale, mo: months, RCT: randomized controlled trial, PGIC: patient global impression of change, QoL: quality of life, V3: third branch of the trigeminal nerve, NR: not reported

1.3. PREGABALIN

The recommended initial dose for neuropathic pain is 150mg daily divided in 2 or 3 times. It can be increased to 300mg daily after 3-7 days and, if necessary, a maximum dose of 600mg daily can be administered after 7 more days (2,12,53).

1.3.A. MECHANISM OF ACTION

Pregabalin is an analogue of the gamma-aminobutyric acid acting as an antiepileptic drug. It joins to the alfa2-delta subunit of voltage-gated calcium channels in the central nervous system reducing the release of excitatory neurotransmitters from synaptic terminals and increasing the cerebral concentration and rate of synthesis of gamma-aminobutyric acid (GABA) (53–55).

In animal models, pregabalin shown that attenuate hyperactivity of nociceptive-specific neurones, which are the responsible of central sensitization mechanisms (54).

Pregabalin is completely absorbed, not bound to plasma proteins, not metabolized, and eliminated unchanged through the kidneys (53,54).

1.3.B. INDICATIONS

According to the technical data sheet (53), the indications of pregabalin are:

- Peripheral and central neuropathic pain
- Epilepsy: for partial crisis with or without secondary generalization
- Generalized anxiety disorder

1.3.C. CONTRAINDICATIONS

Pregabalin is contraindicated in patients with known hypersensitivity to pregabalin or to any of the excipients (53).

1.3.D. SIDE EFFECTS

According to the technical data sheet (53), the main side effects reported are dizziness and drowsiness (1/10 patients). Other frequent effects (between 1/100 and 1/10) are:

- Nasopharyngitis
- Increased appetite
- Euphoric mood, confusion, irritability, disorientation, insomnia and decreased libido
- Ataxia, abnormal coordination, tremor, dysarthria, amnesia, memory alteration, attention disturbance, paraesthesia, hypoesthesia, sedation, altered balance and lethargy
- Blurred vision, diplopia

- Vertigo
- Vomiting, nausea, constipation, diarrhoea, flatulence, bloating and dry mouth
- Muscle cramps, arthralgia, back pain, pain at the extremities and cervical spasm
- Erectile dysfunction
- Peripheral oedema, abnormal walk, falls, drunkenness, abnormal sensation and fatigue
- Weight gain

1.3.E. PREGABALIN AND TRIGEMINAL NEURALGIA

Pregabalin is recommended in the treatment of TN when patients do not respond to neither the first nor the second first line treatment (2,6,10,12).

Its efficacy has been demonstrated in the treatment of diverse neuropathies, especially postherpetic neuralgia and diabetic peripheral neuropathy (54,55). Specifically there are four articles that talk about its effect in TN (**Table 2**).

Table 2: Summary of previous reports on the efficacy of pregabalin for TN. Adapted from Hamasaki et al. (54)

Author, year	Patients	Dose of pregabalin (mg)	Type of therapy	Follow-up	Pain free
Obermann M. et al (55), 2008	53	150-600	Monotherapy	12 months	11 (20,8%)
Pérez C. et al (56), 2009	36	196±105	Monotherapy	12 weeks	13 (39,4%)
	29	234±107	Add-on	12 weeks	6 (21,4%)
Rustagi A. et al (57), 2014	11	150-300	Add-on	6 months	4 (36,3%)
Hamasaki et al. (54), 2017	33	167±74	Monotherapy or add-on	5,5 months	6 (18,2%)

2. JUSTIFICATION

Trigeminal neuralgia is one of the most frequently seen neuralgias in the older adult population. This neuropathic disorder has been shown to be profoundly distressing and produces a significant impact among those patients who suffer it. Because of the high severity of pain, patients with TN have a devastating impact in their lives having more risk of developing mental disorders (19–21).

The only procedure with strong evidence and consensus in TN treatment is the use of CBZ as the first line of TN treatment (2,6,10,12,13,17,22,24). However, a 25-35% of the patients do not respond to CBZ initially and its effectiveness decreases in up to 50% with long-time treatment. Moreover, CBZ sometimes is poorly tolerated with a 3-24% of people that suffer from adverse events (2,6,12,39). For this reason, patients will need and individualized therapy to improve their neuralgia and avoid adverse events.

TN treatment is a therapeutic challenge for physicians because of the intensity of pain, the refractory cases, the intolerability to some drugs and the lack of evidence to select a specific second line treatment (2,12). Some evidence supports add-on therapy with lamotrigine or a switch to baclofen (2,6,10,12,22). However, neither of them have its indication for TN treatment in the Spanish technical drug sheet.

Another possible option, in selected cases, could be to undergo a surgical treatment. There are different types of surgery but few have been studied in controlled trials because most of the evidence comes from observational studies (12). The overall mortality and complications rates of this procedures are low but as in any other kind of intervention there are risks, such as the painful posttraumatic trigeminal neuropathy (painful anaesthesia) that it can be more intolerable than the pain from classic TN itself (2,6,10,12,22). Moreover, initially there is a 90% of pain relief but that pain-free rates declined year by year during the follow-up, decreasing until a 70-50% in 3 years (22).

Furthermore, considering that TN usually starts after the age of 40, the disease poses therapeutic problems from a pharmacological and surgical standpoint because patients may develop side effects from centrally acting drugs and have contraindications for neurosurgical procedures (30). That is the main reason why other drugs, like BTX-A, are in currently in investigation for its treatment (26,34–43,46,47,49–52).

After analysing all the publications about BTX-A (**Table 1**) and bearing in mind that since some years ago BTX-A is indicated in the treatment of chronic migraine with very good results (58–60) we think that BTX-A could be a good option in the treatment of intractable TN. However, despite all information about the beneficial effects and safety of BTX-A, the use of it as a therapeutic option for TN has several drawbacks because there is a shortage of double-blind trials and there are no consensus guidelines.

We consider that the four RCT available until now are not evident enough for different reasons (26,34,39,41)

- All of them compared BTX-A versus placebo without unchanging the medication that they usually received. We consider that treating these patients with placebo is not ethically correct because we dispose from drugs that are useful for such a painful disease. Moreover, unchanging the medication that they received could create a confusion bias since they compare patients that take different drugs. For these reasons, we purpose a trial comparing BTX-A with another beneficial drug for refractory TN, like pregabalin, which will be equally distributed to all the subjects.
- These studies evaluated pain severity, frequency of the attacks and safety with the use of BTX-A. However, they do not analyse properly the duration of the effect since the follow-up of all of them was less than 12 weeks. There is only one study, Li et al. (40) that analysed their effects at long term. Specifically they followed-up 88 patients during 14 months. They showed that mainly the therapeutic effect decreased gradually after 3 months and only 38% of the patients showed complete control of pain at the fourteenth month. Consequently, we will design a longer study with 6 months follow up. Moreover, according to BTX-A mechanism of action and since its effect decreases at 3 months, our intention is to administer the injections twice during the follow up, once at the beginning of the trial and the other after 12 weeks.

With the objective to fill this important gap, we decided to develop a protocol of a RCT to compare the efficacy of BTX-A injections versus the administration of pregabalin in patients that have insufficient response to two different pharmacological treatments.

We believe that the results of this study could provide statistical significance to elaborate further studies to confirm the results and subsequently elaborate strong treatment recommendations, which could improve the management of TN, increasing the proportion of TN resolution and reducing the number of people that have to undergo surgery procedures, with the risks that this intervention supposes.

3. HYPOTESIS

3.1. MAIN HYPOTESIS

BTX-A is more effective in reducing pain than pregabalin in the treatment of patients diagnosed with TN that do not respond to, at least, two different pharmacologic treatments.

3.2. SECONDARY HYPOTHESIS

In the treatment of patients diagnosed with TN that do not respond to, at least, two different pharmacologic treatments.

1. Patients receiving BTX-A have less number of paroxysms per day than pregabalin ones.
2. Patients receiving BTX-A have a higher overall response to treatment than pregabalin ones.
3. Patients receiving BTX-A have a longer lasting effect in the reduction of pain severity than pregabalin ones
4. Patients receiving BTX-A is safer than pregabalin ones.

4. OBJECTIVES

4.1. MAIN OBJECTIVE

To compare the efficacy of BTX-A versus pregabalin in the treatment of patients diagnosed with TN that do not respond to, at least, two different pharmacologic treatments.

4.2. SECONDARY OBJECTIVES

To compare, in the treatment of patients diagnosed with TN that do not respond to, at least, two different pharmacological treatments:

1. The number of attacks (paroxysms) in patients that receive BTX-A versus pregabalin.
2. The overall response to treatment of BTX-A versus pregabalin.
3. The duration of the effect of BTX-A versus pregabalin.
4. The safety of BTX-A versus pregabalin.

5. METHODOLOGY

5.1. STUDY DESIGN

We will carry out a multicentric, triple blind, double dummy, randomized controlled clinical trial (RCT).

The duration of the study is estimated in 3 years although it is extensible to the time required to recruit all the patients needed.

5.2. STUDY SUBJECTS

The target population of this study are patients diagnosed with TN that do not respond to at least, two different pharmacological treatments in the health region of Catalonia.

Patients will be contacted by phone or at the consulting neurology room to be informed about the study.

5.2.A. Inclusion criteria

- Patients must be >18 years old, able to understand the information given relative to the trial and able to sign the informed consent
- Patients diagnosed of TN (according to the ICHD-3 established criteria)
- Patients with at least 2 treatment attempts, one of them has to be CBZ under a daily dosage of 600mg/day during 4 weeks minimum, with insufficient therapy response (pain intensity mean score ≥ 4 or mean attack frequency ≥ 4 per day) or intolerable side effects

5.2.B. Exclusion criteria

- Any disease that might put patients at increased risk if exposed to BTX-A (e.g. myasthenia gravis, motor neuron disease or Lamber-Eaton syndrome)
- Infection or skin problem at any of the injection sites
- Pregnancy, nursing, planning a pregnancy, or who were unable or unwilling to use a reliable form of contraception during the study
- Symptomatic painful trigeminopathies or symptomatic TN
- Significant unstable medical disease
- Creatinine clearance $<30\text{ml}/\text{min}$
- Current history of significant mental disorder or major depression
- Current history of alcoholism or substance abuse
- Previous treatment with pregabalin or BTX-A for the TN.
- Known hypersensitivity or intolerance to BTX-A, pregabalin or one of its excipients

5.2.C. Withdrawal criteria

- Any severe or life-threatening adverse event that could be related to the drug administrated
- Annulation of the informed consent
- Patients who do not follow the protocol of the study

The patients withdrawn from the study will not be replaced and they will be included in the statistical analysis.

5.3. SAMPLING AND SAMPLE SIZE

5.3.A. Sampling

Our sampling will be divided in two phases, so it will be a multi-staged (or conglomerate) sampling:

- **1st stage:** It will consist in choosing the hospitals that will participate in our study. It will be done by convenience, so it will be an intentional sampling. We choose this type of sampling for practical reasons. We assume that patients in the different Catalan hospitals have similar baseline characteristics, so we do not think that choosing the hospitals in that way could generate selection bias.
- **2nd stage:** It will consist in a non-probabilistic consecutive sampling in order to choose our patients in all these hospitals. This method consists on inviting all available subjects that are being visited in one of our hospitals and accomplishes the inclusion and exclusion criteria. Moreover, the informed consent must be accepted. It is the most convenient method taking into account that TN is a low-prevalence disease.

5.3.B. Sample size

In order to calculate the sample size we used the GRANMO software for our main dependent variable, efficacy, measured as the proportion of responders to each drug. Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral contrast, 50 patients are needed in the first group and 50 in the second group (100 patients in total) so as to recognize a statistically significant difference between our two independent proportions.

The group ratio will be 1:1 and an anticipated drop-out rate of 30% has been taken into account.

5.4. VARIABLES

5.4.A. Independent variables

The independent variables of this study will be the administration of the drugs. One group will receive injections of BTX-A (identified as the **drug A**) and placebo pills. The other group will receive pregabalin (identified as the **drug B**) and injections of sterile isotonic saline.

This is considered a dichotomous qualitative variable.

5.4.B. Dependent variables

The main dependent variable of this study is the efficacy. It will be measured as the proportion of responders for each drug received (drug A or drug B), according to the severity of pain in the last 24 hours calculated with the Visual Analogue Scale (VAS). VAS is a unidimensional measure of pain intensity that has been widely used in adults and it is validated for neuropathic pain.

VAS is a continuous scale constituted of 10 centimetres line, limited by 2 verbal descriptions of each symptom at the extremes: “no pain” (score of 0) and “pain as bad as it could be” (score of 10) (**Figure 6**). The numbers between them do not appear in order to avoid scores around a preferred numeric value. VAS is available in the public domain so it does not have any cost.

This scale will be provided to the patient in the screening and in all the follow-up visits, as it shows **Annex 5**. The patient must self-completed it every day before going to sleep, making a perpendicular line to the VAS line at the point that represents their pain intensity. The score will be measured by the doctor in the follow-up visits using a ruler and measuring the distance in millimetres between the “no pain” anchor and the patient’s mark, providing a range of scores from 0-10. A higher score indicates greater pain intensity. The results will be introduced in the database.

The advantages of VAS are that is simple, takes less than a minute to complete it and that no training is required.

Since this study is going to take place in Catalonia region, VAS will be used with the Spanish version: *Escala Visual Analógica (EVA)*, in order to facilitate the comprehension to the patients.

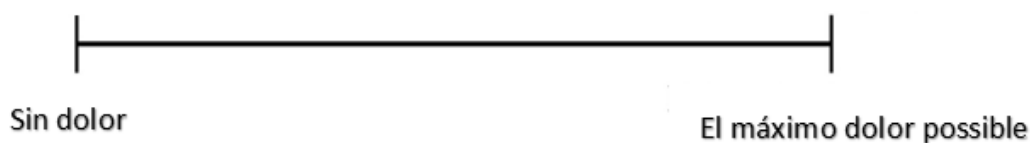


Figure 6: Example of visual analogue scale

We will define as a responder treatment patient those who will obtain a reduction >50% in the mean of VAS score from baseline to endpoint.

The secondary dependent variables of this study are:

- a. Mean paroxysms frequency per day: The patients will record the number of attacks per day before going to sleep each evening in the “patients recording sheet” (**Annex 5**).

Each neurologist will provide this sheet to the patients in the screening and in all the follow-up visits. Patients should bring this paper in all the follow-up visits in order to control and register them in the data base.

- b. Overall response to treatment: as assessed based on the *Escala de Impresión Clínica Global* (CGI). The CGI is a self-evaluation of the patient’s overall change since the start of the study according to a seven-point scale. Moreover, the impression of the neurologist is also required. (**Annex 6**).

It will be screened in every follow-up visit.

- c. Safety: It will be measured as the occurrence of adverse events defined as any change in the physiological or psychological state of the patient as compared to his/her situation before the start of the study. This is a dichotomous qualitative variable.

Patients must record the adverse effects in the “patients recording sheet” (**Annex 5**) and will be controlled in all the follow-up visits. They will be recorded and documented with information regarding the date of onset, severity, duration, frequency, relationship to study treatment, treatment required (if any) and outcome. According to severity, they will be divided in three groups: mild, moderate or severe as follows:

- Mild event: change in the patient’s condition, which does not affect his/her daily life activity.
- Moderate event: change that causes a slight alteration of his/her usual daily life activity.
- Severe event: causing significant change in his/her quality of life and normal daily life activity.

Adverse effects will be collected on the computer using MedDRA stile (Medical Dictionary for Regulatory Activities) in order to homogenize all the information recorded. If some severe adverse reaction appears, it will be urgently notified to the *Agencia Española de Medicamentos y Productos Sanitarios* (AEMPS).

5.4.C. Covariables

These variables will be collected in order to obtain epidemiological and clinical data.

- Age: expressed in years. It is a discrete quantitative variable.
- Gender: expressed as male or female. It is a dichotomous qualitative variable.
- Years since TN was diagnosed: expressed in years. It is a discrete quantitative variable.
- Branch of the trigeminal nerve affected: expressed as V1, V2 or V3. It's a qualitative variable.
- Previous treatment for TN:
 - Type of treatment: expressed with the active principle of the drug. It is a qualitative variable.
 - Dose of the treatment: expressed with milligrams per day. It is a continuous quantitative variable.
 - Duration of the treatment: expressed with months. It is a continuous quantitative variable.

5.5. STUDY INTERVENTIONS

5.5.A. Randomization and masking technique

The patients enrolled will be divided in two groups with a randomized electronic procedure, so investigators will not intervene in this process.

- **Group A**: they will receive injections of BTX-A and placebo pills that they should take daily.
- **Group B**: they will receive injections of sterile isotonic saline (placebo) and pregabalin pills that they should take daily.

This RCT will be tripled-blinded. It will not be possible for either researchers, doctors or patients to know at any time during the trial the drug assigned to any of the patients. It may only be disclosed in case of emergency if this is necessary for the patient's treatment.

The pharmacist of each center will be responsible for randomly dispersing the intervention according to the randomization list and he/she will also be responsible for masking the intervention since he/she will prepare these medicines. He/she will be trained to perform BTX-A preparation.

Pills will be re-encapsulated in order to guarantee the identical appearance (shape, consistency and colour). The administration form (volume and rate of injection) and the type of syringes and needles will be the same in both groups.

5.5.B. Concomitant treatment

Before the study intervention, in the screening visit (“week -2”) the neurologist should know which medication is the patient taking for TN.

CBZ will be maintained in both groups with a standard dose between 400-1200mg per day, which is the recommended maintenance dose (2,6,13,25).

Other medications that the patient could take will have to be removed in order to avoid a carry-over effect when the study intervention starts. In those cases, each neurologist will be the responsible of making a washout period according to pharmacodynamics and pharmacokinetic drug profile.

5.5.C. Study interventions

After the screening visit, at the second visit (week 0), patients will be randomly distributed in two groups (**Figure 7**)

Group A: this group will receive BTX-A injections. They will be applied between the epidermis and dermis where pain is experienced according to the patient’s descriptions. Ten subcutaneous injections will be performed 1 cm apart from one another at a dose of 5units/0.1mL of BTX-A (a total of 50U per patient will be needed). A syringe of 1mL with a 0.45x16mm needle will be used (26,33). A trained pharmacist will prepare this dosage, in that way neurologists which are the responsible of administrating the injections, will be blind.

BTX-A injections will be administrated at week 0 and at week 12.

Placebo pills will be given to this group which will be identical in appearance to the pregabalin ones that the group B will receive. Patients will have to take it twice a day.

Group B: this group will receive injections of a sterile isotonic saline, at a dose of 1mL of 0.9% NaCl (sodium chloride). They will be applied the same way and the same weeks as BTX-A in the group A and will be also prepared by a pharmacist.

Pregabalin pills will be given to this group. The starting dose will be 150mg (divided in 2 times) during 1 week. At the “week 1” this dose will be incremented to 300mg daily, also divided in 2 times (53,55,57). That dose will be maintained during all the study.

5.6. DATA COLLECTION

All the information that should be recorded appear in the “Data collection sheet” (**Annex 6**). In order to preserve anonymity and keep the blind during the study, every patient will be assigned with a specific identification number.

At the screening visit (“week -2”) those aspects will be done:

- Assess if the patient fulfills the inclusion and exclusion criteria
- Patients will receive the information sheet of our trial (**Annex 3**) and if they agree, they will sign the informed consent document (**Annex 4**)
- Recording of general information: gender, date of birth, address, telephone number, hospital and the date of enrolment to our RCT
- Recording of clinical information: allergies, other pathologies, concomitant treatment
- Examination of the nervous system by the neurologist
- Cerebral MRI in order to exclude patients with symptomatic TN. Those patients with previous cerebral MRI before the study will not repeat neuroimaging test.
- Completed blood count with liver and renal function
- Recording of study information: trigger areas, treatment previously received (drug, dose, duration, adverse drug reactions), branch of the trigeminal nerve affected, years since TN was diagnosed. Mean paroxysms per day and VAS with previous treatment (in order to have reliable information, a copy of the patient recording sheet (**Annex 5**) will be facilitated. Patients should complete and return it at the next visit (“week 0”).

To complete all these requisites, a period of 2 weeks between the screening visit (“week -2”) and the study intervention (“week 0”) will be guaranteed.

At the follow-up visits, those aspects will be recorded:

- Mean VAS score
- Mean number of paroxysms per day
- Adverse drug reactions (if any)
- Result of the *Escala de Impresión Clínica Global (CGI)*

Table 3: Visit schedule and methods during all the trial

	-2	0	1	2	3	4	6	8	10	12	14	16	18	20	22	24	Week	
Informed consent	x																	
Fulfil of the data collection sheet	x																	
Laboratory tests	x*																	
MRI	x*																	
BTX-A / placebo injections		x								x								
VAS		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Nº of paroxysms per day		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CGI		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse effects		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

X* = if it is not previously done

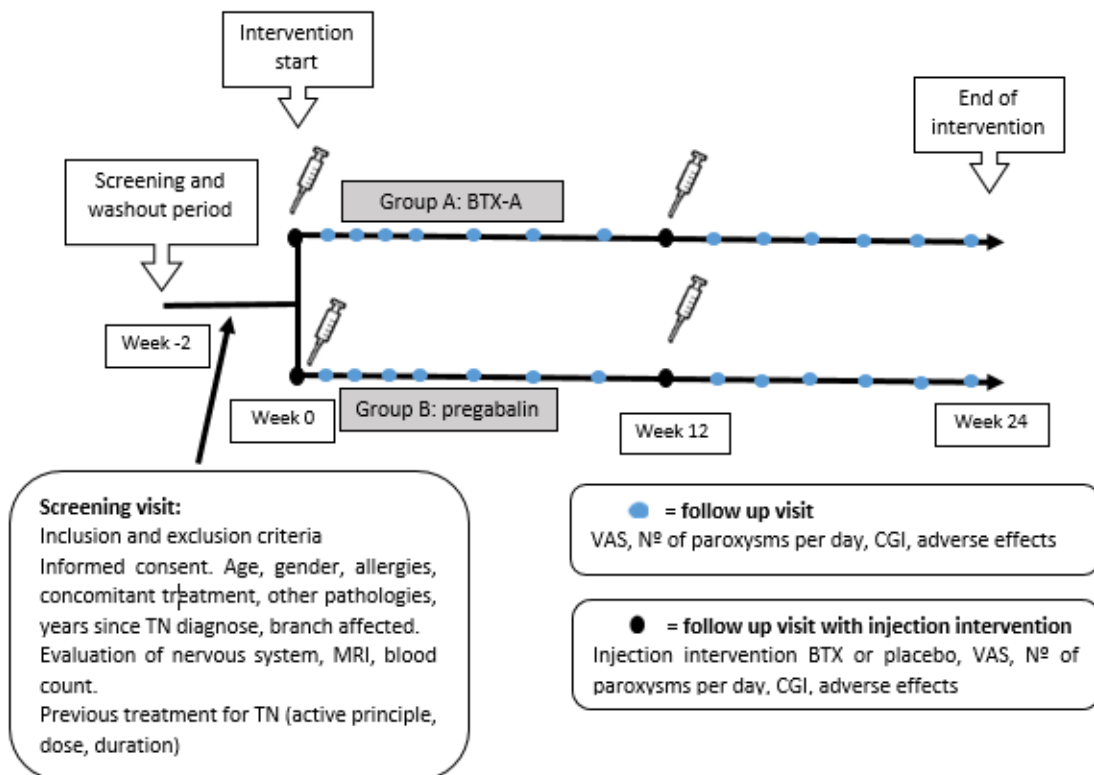


Figure 7: Patient flow chart

6. STATISTICAL ANALYSIS

The statistical analysis will be executed using Statistical Package for the Social Sciences (SPSS) version 25 (IBM, Armonk, NY, US). An intention-to-treat analysis will be performed. The imputation of missing values for endpoints variables will be accomplished using the latest observed values for each variable and subject.

6.1. UNIVARIATE ANALYSIS

The result of our qualitative variables will be expressed as proportions (percentage). A table of frequencies and a sector diagram will be used to represent these proportions.

For the quantitative variables, they will be expressed as a mean +/- standard deviation (SD) in case of Gaussian variables. For non-Gaussian variables, median and interquartile ranges will be used. To represent them, we will use a bar chart for the discrete variables and a histogram for the continuous ones.

6.2. BIVARIATE ANALYSIS

Different test will be used in order to find if there is association between the independent and the dependent variables. Since our independent variable is a dichotomous qualitative variable (BTX-A or pregabalin) the tests that will be used to analyse the association with the dependent variable will be:

- Relative risk (RR) to compare our two independent variables in order to know how many times one is better than the other is.
- Chi-square (χ^2) test if the dependent variable is qualitative.
- Student's t-test if the dependent variable is quantitative with a normal distribution. If it is not possible to assume a normal distribution, Mann-Whitney U test will be used.

The results will be considered statistically significant at a value of $p < 0.05$ with a confidence interval of 95%.

6.3. MULTIVARIATE ANALYSIS

A multivariate analysis will be performed in order to detect possible confusion produced by the covariables, which could interfere in the relationship between our independent, and dependent variables. Since our dependent variable is a dichotomous qualitative variable (BTX-A or pregabalin) a Logistic Regression Model will be used to perform the multivariate analysis.

7. WORK PLAN AND SCHEDULE OF EVENTS

This study will take place in the following hospitals:

- *Fundació Salut Empordà* (Figueres), which will be the reference center.
- *Hospital Universitari de Girona Doctor Josep Trueta* (Girona)
- *Hospital de Santa Creu i Sant Pau* (Barcelona)
- *Hospital Universitari Vall d'Hebron* (Barcelona)
- *Hospital del Mar* (Barcelona)
- *Hospital Clínic* (Barcelona)
- *Hospital Germans Trias i Pujol* (Badalona)
- *Hospital Universitari de Bellvitge* (Hospitalet de Llobregat)
- *Hospital Universitari Joan XXIII* (Tarragona)
- *Hospital Universitari Arnau de Vilanova* (Lleida)

A competitive recruitment in our selected hospitals will be performed and it will end when the 100 patients required will be included.

The time estimated is 3 years but it is extensible to the time required to recruit all the patients needed. The duration has been estimated taking into account that, according to non-published data, the *Fundació Salut Empordà* (Figueres) attends approximately 3 cases per year of patients with refractory TN. According to the attended population in the other 9 hospitals of this clinical trial, we estimate that they attend 50 patients per year that can be susceptible to participate in our study. So, according to our sampling size required and if we hypothesise that a 20% of patients that accomplish the inclusion and exclusion criteria may not accept to participate in the trial, 28 months will be needed to recruit all patients.

The principal investigators of our study will be neurologists of each hospital. They will coordinate and supervise the activity of their center and all of them will meet periodically.

This study will be multidisciplinary, so other professionals will be co-investigators: pharmacists, radiologists and nursing staff from each hospital.

Moreover, we will contact with one statistic in order to analyse the results.

7.1. STAGE 1: COORDINATION, REDACTION OF STUDY PROTOCOL AND TRAINING

- **Scientific research:** A research of information will be needed in order to know the topic of study and the lack of information about it that will justify the need to perform this clinical trial.
- **Protocol redaction and coordination meetings:** It will include the objectives, hypothesis, variables and the methodology. Then, there will be meetings to choose which hospitals will take part of it and who will be the principal investigators of each center. The schedule and the work plan will be also created.
- **Training:** All the neurologists who will participate in the study will have a training of 2 days to learn BTX-A infiltrations. Moreover, they will also receive information about the study protocol (collecting and registering data, transmitting study information to the patients, diagnosing and treating TN) and some possible problems will be discussed. These will ensure the homogeneity required to get representative conclusions.
- **Presentation to Clinical Research Ethics Comitee (CEIC):** It will be presented before recruiting the patients in order to be approved and ethically accepted.

The estimated duration of this phase is 4 months. Principal investigators and co-investigators will take part of it.

7.2. STAGE 2: SAMPLE COLLECTION, FOLLOW-UP VISITS AND DATA COLLECTION

- **Patient recruitment:** They will be recruited using a consecutive sampling if they meet the inclusion and exclusion criteria and if the informed consent is available.
- **Screening visit (“week -2”):** It will take place two weeks before receiving the treatment. The personal and baseline data will be collected (**Annex 5**).
- **Study intervention:** Patients will be randomly distributed in one of the groups of the study. After that, neurologists will administer the drugs (previously prepared by a pharmacist) according to the group assigned.
- **Follow-up visits:** It will be performed at the outpatient care during 6 months. The first month the follow-up visits will be every week, during the rest 5 months they will be every two weeks (twice a month).
- **Data collection:** Each neurologist will record all the information collected in every visit in our database (which will be frequently revised to guarantee its functioning).
- **Coordination meetings:** The principal investigators will meet four times during this phase in order to assess that the protocol is well executed and to determine if they

need to modify specific procedures. There will be a meeting every 6 months approximately.

The estimated duration of this stage is 28 months according to the time needed to recruit 100 patients. As in stage 1, principal investigators and co-investigators will take part of it.

7.3. STAGE 3: STATISTICAL ANALYSIS AND INTERPRETATION OF RESULTS

- **Statistical analysis:** It will be performed by the statistical who will analyse all the information recorded using different statistical test according to the variables of the trial.
- **Results interpretation:** It will be performed by principal investigators. Then, the pertinent conclusions will be obtained.

The duration of this phase is 3 months. Principal investigators and a statistician will be responsible of it.

7.4. STAGE 4: PUBLICATION OF RESULTS

The principal investigators will create a paper to show the study results and the conclusions. This document will be sent to the main neurologic journals and exposed in national and international conferences.

The duration of this stage is 2 months.

7.5. CHRONOGRAM

Time period		2017			2018			2019			2020				
		Set	Oct- Nov	Des	Jan- May	Jun	Jul- Nov	Des	Jan- May	Jun	Jul- Nov	Dec	Jan- Apr	May- Jun	Jul- Aug
STAFF															
STAGE 1: Coordination, redaction of study protocol and training															
Scientific research	Principal investigators														
Protocol redaction	Principal investigators														
Coordination meetings	Principal investigators and co-investigators														
CEIC, AEMPS approval															
Stage 2: Sample collection, follow-up visits and data collection															
Recruitment, data collection and intervention	Principal investigators and co-investigators														
Stage 3: Statistical analysis and interpretation of results															
Statistical analysis	Statistician														
Interpretation of results	Principal investigators														
Stage 4: Publication of results															
Publication of the results	Principal investigators														

8. LEGAL AND ETHICAL ASPECTS

This clinical trial follows the medical ethics requirements stated by the World Health Association in the *Declaration of Helsinki* (1964) about the Ethical Principles for Medical Research Involving Human Subjects.

Once this protocol will be finished, it will be sent to the Clinical Research Ethics Committee (CEIC) in order to be evaluated and approved. According to the “*Real Decreto 1090/2015, de 24 de diciembre, ensayos clínicos con medicamentos*” the approbation of the protocol by the CEIC is mandatory to start clinical research. Moreover, it will be also sent to the *Asociación Española de Medicamentos y Productos Sanitarios (AEMPS)* to receive its authorization. After its approval, an application for a registry number to the European Union Drug Regulating Authorities Clinical Trials (EudraCT) will be also sought.

CEIC will be the responsible to decide if our trial is considered an invasive procedure according to *Ley 14/2007 de 3 de Julio*.

According to the “*Real Decreto Legislativo 1/2015 de 24 Julio, artículo 2*” BTX-A is considered a research drug. For that reason, a specific assurance will be contract. Moreover, BTX-A will be used as an off-label drug.

Permission to perform this study will be asked to the direction of our hospitals.

Patients will only be enrolled in our study if the informed consent is available. In order to obtain it, patients will receive the information sheet of our clinical trial (**Annex 3**) and then if they agree, they will sign the informed consent document (**Annex 4**).

This clinical trial guarantees that all the information obtained will be confidential and anonymous according to the “*Ley Orgánica 15/1999 del 13 diciembre sobre Protección de Datos de Carácter Personal*”.

Regarding the ethics principles, a placebo treatment arm will not be used since it will not be ethical because patients suffer from a severe and disabling facial pain from which treatments are available.

9. LIMITATIONS

The main limitations of our study are:

- TN is a low prevalent disease, so the time estimated to recruit all patients will be long. We tried to minimize this point creating a multicentric trial in order to reach more population making the patients collection easier.
- Performing a multicentric study could create variability in the procedures done in each hospital. For that reason, we designed a standardized protocol, which includes formative courses because all the investigations can act similar to each other. Moreover, in order to avoid coordination problems, the principal investigators will perform periodic meetings.
- Our clinical trial has an expensive cost but we assume that a randomized clinical trial is the best design to respond to our objectives.
- To design a prospective study has the risk that patients can leave it due to adverse drug effects or to lack of compliance. However, this is not expected to create problems because it has been taken into account when the sample size was estimated.
- Despite being a triple blind clinical trial, there are some drug adverse effects that can be characteristic about one of the drugs of study (e.g. facial paresis with BTX-A) and interfere in the process creating a bias. For that reason, the person responsible of analysing the results will be also blind.
- The main objective (efficacy) will be measured using visual-analogue-score (VAS) which has been approved for the assessment neuropathic pain. However, their results can differ depending on the neurologist. In order to minimize this aspect, all the neurologists will be trained about how to use it and how do they have to teach the patients to fulfil the score.
- We assume that the results of the secondary variables could not be definitive because of lack of statistic power (due to reduced sample size or methodological procedures). New studies are recommended to confirm the results.
- Until now, BTX-A has only been evaluated for TN treatment compared with placebo (26,34,39,41). For ethical reasons, we have considered more appropriated to compare BTX-A versus pregabalin in patients with TN who have a worsening in their quality of life.
- According to our inclusions criteria, we decided to accept patients who have received any drug for TN treatment. We know that these medicines have different pharmacodynamics and pharmacokinetics mechanisms and these differences could affect our study. For this reason, a wash-out period will be done before the randomization in order to avoid a carry-over effect.

10. BUDGET

STUDY BUDGET	QUANTITY	COST	SUBTOTAL
1. Staff costs			
<ul style="list-style-type: none"> • Neurologists • Pharmacists • Nursing staff • Radiologists 		0€/hour	0€
2. Subcontracted professional services			
• Data management	450 hours	30€/hour	13.500€
• Statistician	100 hours	30€/hour	3.000€
3. Implementation costs			
<ul style="list-style-type: none"> • Drug purchase: <ul style="list-style-type: none"> - BTX-A - Pregabalin - Placebo pills - Placebo injections 	10 boxes 175 boxes 18.000 pills 100 injections	870,97€/box 48,75€/box 0.25€/pill 0.50€/injection	8.709,70€ 8.531,25€ 4.500€ 50€
• Laboratory test	100	30€/patient	3.000€
• MRI	100	160€/patient	16.000€
• Insurance policy	1	10.000€	10.000€
• Publication fees	1	2.500€	2.500€
• Software and bibliography	1	1.000€	1.000€
4. Travel			
Coordination meetings	7 meetings for 9 investigators	70€ per meeting per coordinator	4.410€
National conference	1	500€	500€
International conference	1	1.000€	1.000€
TOTAL COSTS:			76.700,95€

1. Staff costs

The investigators of our study will be workers of seven different hospitals, all of them included in the National Health System (NHS). The clinical trial will be performed during their working hours so no extra budget will be needed to hire them.

2. Subcontracted professional services

A data manager will be hired. He will be responsible for the data quality control. Every two months, during the 28 months of recruitment and data collection, he will go to each hospital in order to collect the fulfilled data recording sheet and the patient recording sheet. He will be responsible for verifying the information introduced in the database and he will make corrections if necessary. He will be contracted for 450 hours with a cost of 30€/hour, giving an amount of 13.500€.

A statistician will be also hired for the data analysis. We estimated that 100 hours will be required with a cost of 30€/hour.

3. Implementation costs

A box of BTX-A 50U that contains 10 vials has a cost of 870,97€. We assume that 10 boxes like this will be needed (because two vials will be used for each of the 50 patients, one at the week 0 and the other one at week 12, so 100 vials will be required) with a total cost of 8.709,70€.

A box of Pregabalin 150mg that contains 100 pills has a cost of 48,75€. Every one of our 50 patients, will take 2 pills daily during the 6 months. So, 175 boxes will be needed with a total cost of 8.531,25€.

Regarding the placebo a cost of 0.25€ per pill and 0.5€ per injection has been estimated.

In addition, in our study a blood test and a cerebral MRI will be required if the patient does not have done it before the inclusion to our trial. That is why we calculated the budget assuming the maximum number of tests required.

Moreover, since BTX-A is considered a research drug a specific insurance is required. Publication fees, software and bibliography have been taken into account too.

4. Travel

There will be 7 meetings during all the study in order to coordinate the seven different hospitals that will participate. The principal investigator of each hospital will be the responsible for attending to the meetings. An estimated cost of 70€ is assumed per person, in order to pay the displacement and diets.

Moreover, the assistance of two different conferences to show the results has been estimated.

11. IMPACT ON THE NATIONAL HEALTH SYSTEM

TN causes so insufferable pain that affects directly to patients quality of life. Some cases have been related with mental disorders, even attempt of suicide. A quickly control of pain is needed.

The information obtained from this study will provide valuable data to improve the treatment protocol when patients have refractory TN. The current management of these cases is not sustained by confirmed scientific evidence. Therefore, when the first-line drug (CBZ) for TN treatment fails, a big challenge appears for physicians because there are no standardized protocols and second line treatments have a lack of evidence.

Nowadays, there are some articles which exposes that BTX-A could be an effective option for those cases.

If our hypothesis is confirmed, BTX-A could be used in refractory TN patients. This will improve the management and the quality of life of those patients since nowadays some of them have to undergo to surgery procedures in order to try to reduce the disabling attacks and the severity of pain. The procedures are not exempt of complications, some of them severe, and have a high cost. Moreover, when they can not be performed, patients must have to take different drugs with low evidence of efficacy every day, having a risk to present side effects. For this reason, BTX-A injections would be beneficial for that patients since they do not need to be administered daily, the fast response, the safety and the low interactions with other treatments, being a good option for polypharmacy and elderly patients.

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13. ANNEXES

ANNEX 1: TRIGEMINAL DIVISIONS

Table 4: Trigeminal divisions. Adapted from Snell N. (3)

Components		Function	Opening in skull
Ophthalmic division (V1)	Sensory	Cornea, skin of forehead, scalp, eyelids and nose. Also mucous membrane of paranasal sinuses and nasal cavity	Superior orbital fissure
	Motor	Muscles of mastication, mylohyoid, anterior belly of digastric, tensor veli palatine, and tensor tympani	
Maxillary division (V2)	Sensory	Skin of face over maxilla, teeth of upper jaw, mucous membrane of nose, the maxillary sinus and palate	Foramen rotundum
Mandibular division (V3)	Motor	Muscles of mastication, mylohyoid, anterior belly of digastric, tensor veli palatine, and tensor tympani	Foramen ovale
	Sensory	Skin of cheek, skin over mandible and side of head, teeth of lower jaw and temporomandibular joint. Mucous membrane of mouth and anterior part of tongue	

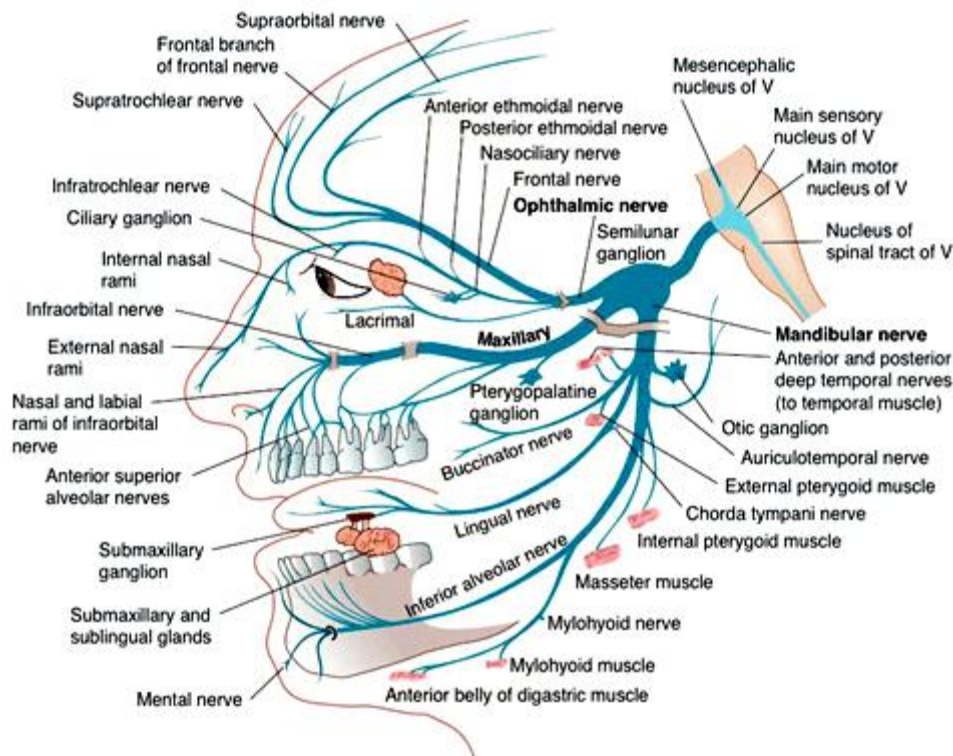


Figure 8: Representation of the trigeminal nerve. From Waxman SG (4)

ANNEX 2: GRADES OF RECOMMENDATION AND EVIDENCE LEVELS

Nivel I	Ensayos clínicos controlados, prospectivos y con evolución ciega realizados sobre población representativa. Revisiones sistemáticas de ensayos clínicos controlados en población representativa. En ambos se requieren las siguientes características: <ul style="list-style-type: none"> • Muestreo aleatorizado. • Objetivos claramente definidos. • Criterios de exclusión/inclusión claramente definidos. • Adecuado control de pérdidas de seguimiento. • Las características basales de los pacientes son explícitas en el texto y equivalentes entre los grupos o las diferencias han sido ajustadas estadísticamente.
Nivel II	Estudios de cohortes prospectivos en una población representativa con evolución ciega que reúne los criterios a-e. Ensayos clínicos controlados, prospectivos y con evolución ciega realizados sobre población representativa que no cumple alguno de los criterios a-e.
Nivel III	Todos los demás estudios controlados en una población representativa en los que la evolución es independiente del tratamiento del paciente.
Nivel IV	Estudios no controlados, series de casos, casos aislados u opiniones de expertos.
Grado A	Recomendación definitivamente efectiva, ineficaz o peligrosa. Requiere al menos un estudio concluyente de Nivel I o dos estudios convincentes de Nivel II.
Grado B	Recomendación probablemente efectiva, ineficaz o peligrosa. Requiere al menos un estudio concluyente de Nivel II o varios estudios de Nivel III.
Grado C	Recomendación posiblemente efectiva, ineficaz o peligrosa. Requiere al menos dos estudios concluyentes de Nivel III.

Figure 9: Grades of recommendation and evidence levels. From Pozo Rosich et al. (13)

ANNEX 3: INFORMATION SHEET

FULL D'INFORMACIÓ SOBRE L'ASSAIG CLÍNIC

Títol estudi: Toxina Botulínica tipus A versus Pregabalina en el tractament de la neuràlgia del trigemin refractària al tractament.

Investigador principal:

Centre:

Ens dirigim a vostè per informar-lo sobre la realització d'un estudi d'investigació en el que se'l convida a participar. El present estudi ha estat aprovat pel Comitè d'Ètica i Investigació Clínica (CEIC) i per l'Agència Espanyola del Medicamento y Productos Sanitarios (AEMPS), d'acord amb la legislació vigent, *Real Decret 1090/2015, del 24 de desembre*, sobre la realització d'assajos clínics amb medicaments.

La nostra intenció es que vostè rebi la informació de manera correcta i que aquesta sigui suficient per tal que pugui decidir si vol participar o no en aquest estudi. Per aquest motiu, li agrairíem que llegeixi atentament aquest full informatiu i posteriorment nosaltres li aclarirem els dubtes que li puguin sorgir.

Primerament ha de saber que la participació en aquest estudi es de forma completament voluntària. Si decideix participar en l'estudi ha de saber que podrà abandonar-lo en qualsevol moment sense que això suposi una alteració de la relació amb el seu metge/metgessa ni es produeixi cap perjudici en el seu tractament.

Què és la neuràlgia del trigemin?

La neuràlgia del trigemin és una malaltia crònica caracteritzada per atacs recurrents de dolor facial que es pot desencadenar per accions com menjar, beure, parlar o rentar-se les dents. El dolor acostuma a afectar només un costat de la cara i és molt intens. Els pacients el descriuen semblant a una descàrrega elèctrica. Aquests atacs tot i durar pocs segons o minuts, es van repetint al llarg del dia varis cops arribant a afectar a la qualitat de vida d'aquelles persones que ho pateixen. El medicament que més eficàcia ha demostrat de moment pel seu tractament és la carbamazepina. Tot i així, en alguns pacients no els hi redueix el dolor o els hi provoca molts efectes indesitjats, fent que s'hagin de prendre varis fàrmacs per eliminar el dolor o en alguns casos s'han de intervenir quirúrgicament.

Quina és la finalitat d'aquest estudi?

L'objectiu principal d'aquest estudi és comparar dos tractaments per la neuràlgia del trigemin en aquelles persones que han provat almenys dos tractaments mèdics diferents però no han estat eficaços.

Què se li farà?

Els pacients que es considerin candidats al nostre estudi se'ls hi realitzarà primer una entrevista amb un neuròleg on se'ls hi preguntaran dades com l'edat, al·lèrgies, altres

patologies que vostè pateixi, cada quan té atacs de neuràlgia del trigemin, com d'intensos són aquests, quina és la medicació que pren, amb quina dosi, des de quan etc. També, abans de iniciar el tractament se'ls farà una analítica i una ressonància magnètica cerebral (en el cas que ja es disposi d'alguna d'aquestes no se'ls tornaran a realitzar).

Posteriorment, tots els candidats seran distribuïts a l'atzar en dos grups:

La meitat rebrà 10 injeccions de Toxina Botulínica tipo A (5U/0.1mL) en la distribució del dolor, aquest procediment es realitzarà a la 2na visita, i al cap de 12 setmanes. També se'ls hi facilitaran varis comprimits que hauran de prendre 2 cops al dia durant els 6 mesos, que contindran només lactosa (sucre), anomenats comprimits placebo. Aquests comprimits substitueixen als de Pregabalina que rep l'altre grup.

L'altre meitat rebrà 10 injeccions de suero fisiològic (0.9%NaCl/0.1mL) en la distribució del dolor, en comptes de rebre Toxina Botulínica, aquestes injeccions actuaran com a placebo. Això se'ls hi farà a la 2na visita i al cap de 12 setmanes. També se'ls hi facilitaran varis comprimits de Pregabalina que hauran de prendre 2 cops al dia durant els 6 mesos.

Tots els pacients també seguiran rebran la dosi de Carbamazepina que prenen habitualment.

A cada visita de seguiment amb el neuròleg se li facilitarà un full i se li demanarà que l'ompli cada dia abans de anar a dormir. En el full haurà de fer una marca en una línia impresa d'acord amb la intensitat del dolor que vostè ha percebut. També se li preguntarà pel nombre d'atacs i per si ha experimentat algun altre efecte. És molt important que ompli diàriament aquest full i el porti a cada visita, ja que aquesta informació és essencial per complir la finalitat d'aquest estudi.

Quins són els beneficis i els riscos per participar en l'estudi?

La participació a l'estudi implica l'administració de medicaments de forma cega, és a dir, que ni el metge ni vostè sabran a quin grup, dels anteriorment explicats, pertanyen. Tot i això, tant la Toxina Botulínica com la Pregabalina són medicaments comercialitzats i que han demostrat que són útils en la reducció del dolor i del nombre d'atacs. Així doncs, en cap cas es quedarà sense rebre tractament, ja que l'objectiu d'aquest estudi es conèixer quin dels dos fàrmacs funciona millor.

No obstant, com tots els medicaments, poden haver-hi reaccions adverses. Les més freqüents que podria patir són dolor a les zones d'injecció, que es noti durant uns dies la zona de la cara més adormida o que se li infla lleugerament. També podria notar mareig o somnolència. Aquestes efectes es resolen espontàniament al cap de pocs dies. Tot i així, se li farà un seguiment periòdic on se li preguntarà si ha notat algun efecte indesitjat i en cas que sigui necessari es prendran les mesures pertinents per resoldre'l.

Hi ha alguna assegurança?

El promotor d'aquest assaig clínic disposa d'una pòlissa d'assegurança que s'ajusta a la legislació vigent i li proporcionarà compensació i indemnització en el cas de detriment de la seva salut que pugui produir-se al participar en l'estudi.

Com s'assegura la confidencialitat i protecció de dades?

Per la correcta realització de l'estudi necessitem saber algunes dades mèdiques sobre la seva malaltia. No obstant, li garantim que les seves dades seran tractades amb absoluta confidencialitat d'acord amb l'establert a la *Llei Orgànica 15/1999* del 13 de desembre sobre *Protecció de Dades de Caràcter Personal* que regula la confidencialitat de les dades informatitzades. Les seves dades seran utilitzades de forma exclusiva en aquesta investigació científica i en cap cas apareixerà el seu nom en la publicació dels resultats. Així com l'accés a la seva informació personal quedarà restringit als investigadors, al Comitè d'Ètica i Investigació Clínica (CEIC) i a les autoritats sanitàries sempre mantenint la confidencialitat d'acord amb la normativa vigent.

Rebré compensació econòmica?

Vostè no rebrà cap benefici econòmic per la participació en aquest assaig clínic, però tampoc li suposarà cap despesa. També és necessari que sàpiga que els investigadors que participen en aquest assaig tampoc rebran cap compensació econòmica.

Amb qui he de contactar per qualsevol dubte o problema?

Per contactar amb els responsables de l'estudi es pot dirigir a: *(espai per omplir amb les dades de l'hospital on se li realitzarà l'estudi)*

Per tal de dur a terme aquest projecte i d'acord amb les normatives legals vigent, li demanem la seva autorització. Pot realitzar les preguntes que cregui convenientes al personal sanitari responsable. Així com, quedar-se una còpia del present document.

Declaració del pacient:

Nom: _____

Data: ___ de _____ del 20__

Signatura:

Declaració de l'investigador:

Nom: _____

Data: ___ de _____ del 20__

Signatura:

HOJA DE INFORMACION SOBRE EL ENSAYO CLINICO

Título del estudio: Toxina Botulínica tipo A versus Pregabalina en el tratamiento de la neuralgia del trigémino refractaria al tratamiento.

Investigador principal:

Centro:

Nos dirigimos a usted para informarle sobre la realización de un estudio de investigación en el que se le invita a participar. El presente estudio ha estado aprobada por el Comité de Ética e Investigación Clínica (CEIC) del hospital y por la Agencia Española del Medicamento y Productos Sanitarios (AEMPS), de acuerdo con la legislación vigente, *Real Decreto 1090/2015, del 24 de diciembre*, sobre la realización de ensayos clínicos con medicamentos.

Nuestra intención es que usted reciba la información de forma correcta y que esta sea suficiente para que pueda decidir si quiere participar o no en este estudio. Por este motivo, le agradeceríamos que leyera atentamente esta hoja informativa y posteriormente nosotros le aclararemos las dudas que le puedan surgir.

Primeramente debe de saber que la participación en este estudio es de forma completamente voluntaria. Si decidir participar en el estudio debe saber que podrá abandonarlo en cualquier momento sin que esto suponga una alteración de la relación con su médico/medica ni que se produzca ningún perjuicio en su tratamiento.

¿Qué es la neuralgia del trigémino?

La neuralgia del trigémino es una enfermedad crónica caracterizada por ataques recurrentes de dolor facial que puede desencadenarse por acciones como comer, beber, hablar o lavar-se los dientes. El dolor suele afectar sólo un lado de la cara y es muy intenso. Los pacientes lo describen similar a una descarga eléctrica. Estos ataques aunque duran pocos segundos o minutos, se van repitiendo a lo largo del día varias veces llegando a afectar la cualidad de vida de las personas que la padecen. El medicamento que más eficacia ha demostrado en el momento para su tratamiento es la carbamazepina. Aun así, en algunos pacientes no se les reduce el dolor o les provoca muchos efectos indeseados, haciendo que tengan que tomar varios fármacos para eliminar el dolor o en algunos casos se tienen que intervenir quirúrgicamente.

¿Cuál es la finalidad de este estudio?

El objetivo principal de este estudio es comparar dos tratamientos por la neuralgia del trigémino en aquellas personas que han probado al menos dos tratamientos médicos diferentes pero que no han resultado efectivos.

¿Qué se le realizara?

Los pacientes que se consideren candidatos a nuestro estudio se les realizará primero una entrevista con un neurólogo donde se les preguntaran datos como la edad, alergias,

otras patologías que usted sufra, cada cuando tiene ataques de neuralgia del trigémino, cuanto de intensos son estos, cual es la medicación que toma, con que dosis i des de cuando etc. También, antes de iniciar el tratamiento se le realizará una analítica i una resonancia magnética cerebral (en el caso que ya disponga de alguna de estas pruebas no se les volverán a realizar).

Posteriormente, todos los candidatos serán distribuidos al azar en dos grupos:

La mitad recibirá 10 inyecciones de Toxina Botulínica tipo A (5U/0.1mL) en la distribución del dolor, este procedimiento se realizará en la 2nda visita i al cabo de 12 semanas. También se le facilitaran varios comprimidos que deberá de tomarse 2 veces al día durante los 6 meses, que contendrán solo lactosa (azúcar), denominados comprimidos placebo. Estos comprimidos substituyen los de Pregabalina que recibe el otro grupo.

La otra mitad recibirá 10 inyecciones de suero fisiológico (0.9%NaCl/0,1mL) en la distribución del dolor, en lugar de recibir Toxina Botulínica, estas inyecciones actuaran como placebo. Esto se realizará en la 2nda visita i al cabo de 12 semanas. También se le facilitaran varios comprimidos de Pregabalina que deberá de tomarse 2 veces al dia durante los 6 meses.

Todos los pacientes seguirán recibiendo la dosis de Carbamazepina que tomaban habitualmente.

En cada visita de seguimiento con el neurólogo se le facilitara un hoja y se le pedirá que la rellene cada día antes de irse a dormir. En la hoja deberá de hacer una marca en una línea impresa de acuerdo con la intensidad del dolor que usted haya percibido. También se le preguntara por el número de ataques i por si ha notado algún otro efecto. Es muy importante que rellene diariamente esta hoja y que la traiga en cada visita, ya que esta información es esencial para cumplir con la finalidad del estudio.

¿Cuáles son los beneficios y los riesgos de participar en el estudio?

La participación en el estudio implica la administración de los medicamentos de forma ciega, es decir, que ni el medico ni usted sabrán a que grupo, de los anteriormente explicados, pertenecen. A pesar de esto, tanto la Toxina Botulinica como la Pregabalina son medicamentos comercializados y que han demostrado que son útiles para reducir el dolor i el número de ataques. Así pues, en ningún caso se quedara sin recibir tratamiento, ya que el objetivo de este estudio es conocer cuál de los dos fármacos funciona mejor.

No obstante, como todos los medicamentos, puede haber reacciones adversas. Las más frecuentes que podría sufrir son dolor en el lugar de la inyección, que se note la cara adormecida unos días o que se le hinche ligeramente. También podría notar mareo o somnolencia. Estos efectos suelen resolverse por sí solos al cabo de pocos días. Aun así, se le hará un seguimiento periódico donde se le preguntara si ha notado algún efecto

indeseado y en el caso que sea necesario se tomaran las medidas pertinentes para resolverlo.

¿Hay algún seguro?

El promotor de este ensayo clínico dispone de una póliza de seguro que se adhiere a la legislación vigente y le proporcionara compensación y indemnización en el caso de detrimento de su salud que pueda producir-le participar en el estudio.

¿Cómo se garantiza la confidencialidad i la protección de datos?

Para la correcta realización de este estudio necesitamos saber algunos datos médicos sobre su enfermedad. No obstante, le garantizamos que sus datos serán tratados con absoluta confidencialidad de acuerdo con lo establecido en la *Llei Orgànica 15/1999* del 13 de diciembre sobre *Protecció de Dades de Caràcter Personal* que regula la confidencialidad de los datos informatizados. Sus datos serán utilizados de forma exclusiva para esta investigación científica y en ningún lugar aparecerá su nombre en la publicación de los resultados. Así como el acceso a su información personal quedara restringido a los investigadores, al Comité de Ética e Investigación Clínica (CEIC) y a las autoridades sanitaras siempre manteniendo la confidencialidad de acuerdo con la normativa vigente.

¿Recibiré compensación económica?

Usted no recibirá ningún beneficio económico para la participación de este ensayo clínico, pero tampoco le supondrá ningún gasto. También es necesario que sepa que los investigadores que participan en este ensayo tampoco recibirán ninguna compensación económica.

¿Con quién debo contactar en caso de duda o problema?

Para contactar con los responsables del estudio puede dirigir-se a: *(espacio para llenar con los datos del hospital dónde se le realizará el estudio)*

Para realizar este proyecto y de acuerdo con las normativas legales vigentes, le pedimos su autorización. Puede realizar las preguntas que considere oportunas al personal sanitario responsable. Así como, quedarse con una copia del documento presente.

Declaración del paciente:

Nombre: _____

Fecha: ____ de _____ del 20__

Firma:

Declaración del investigador:

Nombre: _____

Fecha: ____ de _____ del 20__

Firma:

ANNEX 4: INFORMED CONSENT DOCUMENT

FULL DE CONSENTIMENT INFORMAT PELS PACIENTS

Jo, _____, accepto participar en l'assaig clínic sobre l'ús de Toxina Botulínica tipus A o Pregabalina en el tractament de la Neuràlgia del Trigemín refractària al tractament, i confirmo que:

- He llegit tota la informació que se m'ha facilitat sobre el projecte
- He tingut l'oportunitat de preguntar els dubtes sobre el projecte
- He rebut respostes satisfactòries a les meves preguntes
- He rebut suficient informació sobre aquest projecte.
- He entès els possibles riscos associats a la participació en aquest projecte

Comprenc que la participació es voluntària i que puc revocar el consentiment prèviament signat en qualsevol moment, sense haver de donar explicacions i sense que aquest fet alteri la meva assistència sanitària posterior

Les dades obtingudes seran usades únicament per a investigació clínica i seran tractades amb confidencialitat.

L'investigador que m'ha parlat sobre aquest projecte és (nom i cognoms):

Signatura del pacient

Signatura de l'investigador

Lloc i data: _____, ____ de _____ del 20__

REVOCACIÓ DEL CONSENTIMENT INFORMAT

Jo, _____, revoco el consentiment prèviament signat per la participació en l'assaig clínic especificat a dalt.

Signatura del pacient

Signatura de l'investigador

Lloc i data: _____, ____ de _____ del 20__

HOJA DE CONSENTIMIENTO INFORMADO PARA PACIENTES

Yo, _____, acepto participar en el ensayo clínico sobre el uso de Toxina Botulínica Tipo A o Pregabalina en el tratamiento de la Neuralgia del Trigémino refractaria al tratamiento, y confirmo que:

- He leído toda la información que se me ha facilitado sobre el proyecto
- He tenido la oportunidad de preguntar sobre dudas de este proyecto
- He recibido respuestas satisfactorias a mis preguntas
- He recibido suficiente información sobre este proyecto
- He comprendido los posibles riesgos asociados a la participación de este proyecto

Comprendo que la participación es voluntaria y que puedo revocar el consentimiento previamente firmado en cualquier momento, sin tener que dar explicaciones y sin que esto altere mi asistencia sanitaria posterior.

Los datos obtenidos serán únicamente usados para la investigación clínica y serán tratados con confidencialidad.

El investigador que me ha hablado sobre este proyecto es (nombre y apellidos):

Signatura del paciente

Signatura del investigador

Lugar y fecha: _____, ____ de _____ del 20__

REVOCACION DEL CONSENTIMIENTO INFORMADO

Yo, _____, revoco el consentimiento previamente firmado para la participación del ensayo clínico especificado arriba.



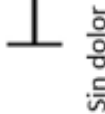

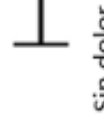

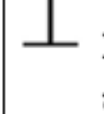

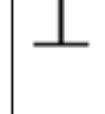

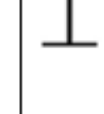

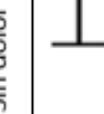

Signatura del paciente

Signatura del investigador







Lugar y fecha: _____, ____ de _____ del 20__

ANNEX 5: PATIENT RECORDING SHEET

FULL DE RECOLLIDA DE DADES DEL PACIENT: Si us plau, completa aquest full cada dia abans de anar a dormir **SETMANA NÚMERO** ___

Dia	Faci una ratlla perpendicular a la línia impresa, d'acord amb el dolor que ha notat al llarg del dia d'avui	Quants atacs ha tingut avui?	Ha notat algun altre efecte? Quin?
//_	 Sin dolor  El máximo dolor possible		
//_	 Sin dolor  El máximo dolor possible		
//_	 Sin dolor  El máximo dolor possible		
//_	 Sin dolor  El máximo dolor possible		
//_	 Sin dolor  El máximo dolor possible		
//_	 Sin dolor  El máximo dolor possible		
//_	 Sin dolor  El máximo dolor possible		

HOJA DE RECOGIDA DE DATOS PARA EL PACIENTE: Por favor, rellena esta hoja cada día antes de ir a dormir SEMANA NUMERO ____

Fecha	Haga una raya perpendicular a la línea impresa, de acuerdo con el dolor que haya notado a lo largo del día de hoy	¿Cuántos ataques ha tenido hoy?	¿Ha notado algún otro efecto? ¿Cuál?
//_-	 Sin dolor		
//_-	 Sin dolor	El máximo dolor posible	
//_-	 Sin dolor	El máximo dolor posible	
//_-	 Sin dolor	El máximo dolor posible	
//_-	 Sin dolor	El máximo dolor posible	
//_-	 Sin dolor	El máximo dolor posible	
//_-	 Sin dolor	El máximo dolor posible	

ANNEX 6: DATA COLLECTION SHEET

Botulinum Toxin Type A versus Pregabalin in the treatment of refractory trigeminal neuralgia

Date of the collection: __/__/__

Name of the investigator: _____

Information required in the screening visit (“week -2”):

GENERAL INFORMATION

Patient identification (number code)	
Gender	
Date of birth (age)	
Address	
Telephone number	
Date of enrolment to our RCT	
Hospital	

CLINICAL HISTORY

Allergies	
Other pathologies	
Concomitant treatment	
Evaluation of the nervous system examination	
MRI result*	
Completed blood count result*	
Liver function test*	
Renal function test*	

STUDY INFORMATION

Branch of the trigeminal nerve affected	
Years since TN was diagnosed	
Drugs and doses previously administered	
Duration of the administration	
Mean VAS score with previous treatment*	
Mean paroxysms per day with the previous treatment*	
Adverse drug reactions experienced	
Tigger areas	

* If the results are not available in the screening visit (week -2), they can be recorded in the next follow-up visit (week 0)

Information required in the follow-up visits:

FOLLOW UP VISIT NUMBER ____

Mean VAS score	
Mean number of the paroxysms per day	
Adverse drug reactions (if any) <ul style="list-style-type: none">• <i>Date of onset</i><ul style="list-style-type: none">• <i>Severity</i>• <i>Duration</i>• <i>Relationship to study treatment</i>• <i>Treatment required (if needed)</i><ul style="list-style-type: none">• <i>-Outcome</i>	
Escala de Impresión Clínica Global (CGI)	

**Escala de Impresión Clínica Global
(Clinical Global Impression, CGI)**

<p>Gravedad de la enfermedad (CGI-SI)</p> <p>Basándose en su experiencia clínica, ¿cuál es la gravedad de la enfermedad en el momento actual?</p> <ol style="list-style-type: none">0. No evaluado1. Normal, no enfermo2. Dudosamente enfermo3. Levemente enfermo4. Moderadamente enfermo5. Marcadamente enfermo6. Gravemente enfermo7. Entre los pacientes más extremadamente enfermos
<p>Mejoría global (CGI-GI)</p> <p>Comparado con el estado inicial, ¿cómo se encuentra el paciente en estos momentos? (Puntúe la mejoría total independientemente de que a su juicio se deba o no por completo al tratamiento)</p> <ol style="list-style-type: none">0. No evaluado1. Mucho mejor2. Moderadamente mejor3. Levemente mejor4. Sin cambios5. Levemente peor6. Moderadamente peor7. Mucho peor

Figure 10: Example of “Escala de Impresión Clínica Global (CGI)”