

Management Issues of Neuropathic Trigeminal Pain from a Medical Perspective

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The purpose of this article is to review the pharmacological treatment of neuropathic trigeminal pain by means of a systematic review. A number of randomized controlled trials and important historical and uncontrolled studies in trigeminal neuralgia and postherpetic neuralgia were identified. Trigeminal neuralgia is a unique neuropathic pain disorder with a specific therapy. It does not respond to the usual drugs used for other neuropathic pains. The drug therapy of trigeminal postherpetic neuralgia is similar to that of other neuropathic trigeminal pain conditions.

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“ Nous avons ... l'essayer (a diphenyl-hydantoine) dans ... la névralgie épileptiforme de Trousseau. ; ce terme lui-même indique assez notre hypothèse de départ.”

Bergouignan, 1942¹

With the above logic (that trigeminal neuralgia resembles epilepsy with its paroxysms of pain, as described by Trousseau²) Bergouignan¹ studied phenytoin and took the initial steps which led to the later 1960s reports by Blom of carbamazepine.^{3,4} Carbamazepine has been the most effective treatment for trigeminal neuralgia (TN). This article will outline and contrast the pharmacotherapy of TN (tic douloureux) and postherpetic neuralgia (PHN) in particular.

Trigeminal neuralgia is a condition unique to the trigeminal system and has its own specific therapy, consisting of both medical and surgical components, which does not apply to most other head and orofacial pain conditions (except for glossopharyngeal neuralgia). Aside from some randomized controlled trials (RCTs) in TN, there is little scientific evidence bearing on management for any other chronic neuropathic trigeminal pain condition, except for PHN; however, the evidence regarding PHN is lumped with non-trigeminal PHN. There is some data that the facial form of PHN is more intractable. The drug therapy of PHN is more akin to the treatment of other neuropathic facial pains such as anesthesia dolorosa, causalgia, and neuropathic pain below the neck. The author will argue that this data (from PHN) can be extrapolated to neuropathic facial pain conditions other than TN. In order to review and assess the literature on this subject, a systematic review

Table 1 NNT Data in Some Neuropathic Pain Conditions (Excludes Trigeminal Neuralgia)

Drug/study	Condition				Comments
	Postherpetic neuralgia	Diabetic neuropathy	Painful neuropathy	Central pain	
Antidepressants					
McQuay et al ⁵	2.3	3.0		1.7	Systematic review
Sindrup and Jensen ⁶	2.3	2.4		1.7	Review
Collins et al ⁷	2.1	3.4			Systematic review
Venlafaxine and Imipramine					
Sindrup et al ⁸			5.2 (venlafaxine)		RCT
			2.7 (imipramine)		RCT
Gabapentin					
Sindrup and Jensen ⁶	3.2	3.7			Systematic review
Rice and Maton ⁹	5.0				RCT
Pregabalin					
Dworkin et al ¹⁰	3.4				RCT
Oxycodone					
Watson and Babul ¹¹	2.5				RCT
Watson et al ¹²		2.6			RCT
Tramadol					
Sindrup and Jensen ⁶			3.4		Review
Lidocaine patch					
Meier et al ¹³			4.4		RCT
Capsaicin					
Sindrup and Jensen ⁶			5.3		Review

Caution should be used in interpreting these figures as they involve studies of differing experimental designs, including selection (inclusion criteria), numbers of patients, and data analyses. Because of differing selection in RCTs, NNT data may not be generalizable to clinical practice.

was carried out using the terms “trigeminal neuralgia,” “postherpetic neuralgia,” and “treatment” to search Medline, Embase, Cinahl, PubMed, and the Cochrane Library. RCTs and important historical and uncontrolled data were sought. Number-needed-to-treat (NNT) figures were sought from reviews and single articles in order to give to the reader an idea of the clinical meaningfulness of the results of RCTs (Tables 1 and 2). NNT expresses the number of patients in an RCT required to be treated in order to obtain 50% or greater improvement over placebo. Number-needed-to-harm (NNH) figures are calculated in the same way, but represent the patients in a clinical trial suffering minor or major harm. These data need to be interpreted with some caution, taking into consideration the differing methodologies, data analyses, and numbers of patients, and as well as the selection (inclusion criteria) involved in these studies.

TN

Historical Overview of Treatment

In the 1850s, Trousseau² thought that painful attacks of TN resembled epilepsy. Based on this idea, in 1942 Bergouignan¹ described the successful

Table 2 NNT Data for TN (adapted from Sindrup and Jensen⁶ and McQuay et al¹⁴)

Drug	NNT
Carbamazepine ^{15,16}	2.6 (2.2 to 3.3)
Lamotrigine ¹⁷	2.1 (as add-on)
Baclofen ¹⁸	1.4 (1.0 to 2.6 as add-on)

use of phenytoin in this condition very soon after the drug was first approved for use in epilepsy. In the early 1960s, Blom reported that carbamazepine was more effective than phenytoin in preventing the attacks.^{3,4}

Carbamazepine. A number of RCTs of carbamazepine followed the reports of Blom.^{15,16,19–21} A systematic review⁵ considered 3 trials of carbamazepine eligible for inclusion.^{15,19,21} One crossover study reported at least a very good response in 19 of 20 patients with up to 1,000 mg per day (versus no response with placebo). A second crossover design found 15 of 20 (75%) with at least a good response (versus 6% with placebo). A third trial reported a mean fall in pain of 58% with carbamazepine (versus 26% with placebo).²¹ According to the systematic review of McQuay et al,¹⁴ the NNT with carbamazepine for effectiveness versus placebo was 2.6 (Table 2). The NNH for minor side effects was 3.4, and for drug-related withdrawal the NNH was 24.

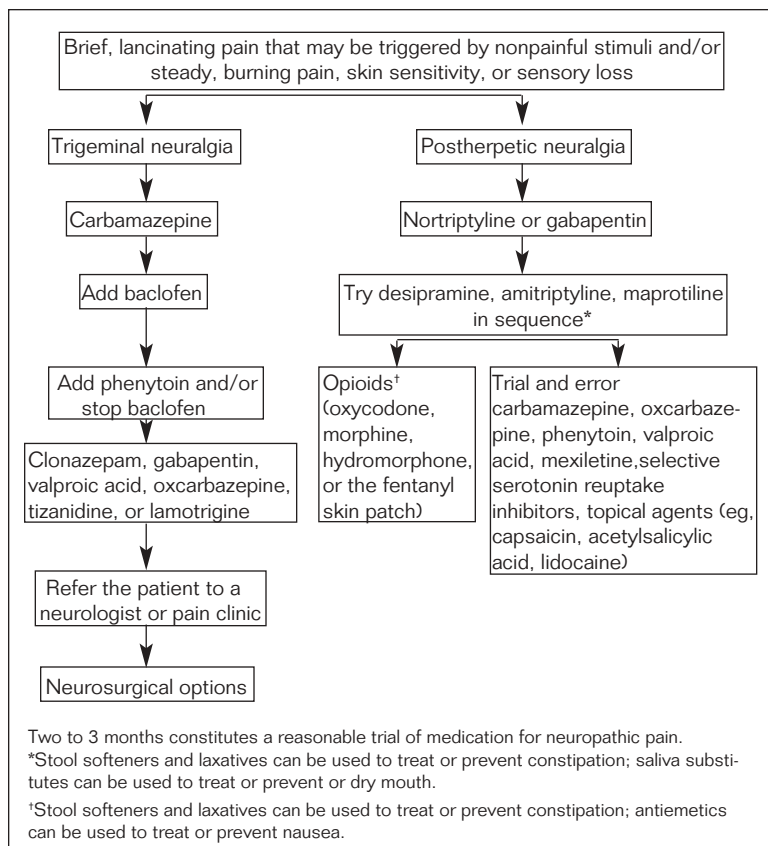


Fig 1 Pharmacologic management of neuropathic orofacial pain.

McQuay et al went on to discuss 3 RCTs using other agents, with carbamazepine as the control. Carbamazepine was found to be more effective than tizanidine²² (an antispasticity drug) and no more or less effective than tocainide²³ (an antiarrhythmic). Pimozide (an antipsychotic) was found to be superior to carbamazepine.²⁴ Unfortunately, tocainide has been found to have serious hematologic side effects, including death, and frequent adverse reactions have been found with pimozide. Sindrup and Jensen^{6,25} concluded from several RCTs in TN that the NNT was 1.7 for carbamazepine.

Baclofen. Baclofen potentiates gamma-aminobutyric acid (GABA) and is frequently used for spinal spasticity. It acts to facilitate segmental inhibition and depresses excitatory transmission in the trigeminal brainstem subnucleus oralis in cats.²⁶ Successful open label trials and an RCT using placebo¹⁸ have demonstrated its efficacy. Baclofen has a synergistic action with carbamazepine. Baclofen is a racemic mixture, and the L isomer is 5 times as potent in TN.²⁶ In a recent review, the NNT of baclofen was found to be 1.4 (Table 2).⁶

Lamotrigine. In an RCT, lamotrigine was effective when used as an add-on to carbamazepine or phenytoin.¹⁷ An NNT of 2.1 was calculated for this drug when used in this fashion (Table 2).⁶

Other Drugs. Phenytoin was the first drug to be reported effective in TN. Uncontrolled data suggest the utility of the benzodiazepine clonazepam and the anticonvulsant valproate. Other drugs that may be useful but are unproven include gabapentin and oxcarbazepine. The latter is related to carbamazepine and is thought to have fewer adverse effects; it lacks enzyme induction and therefore should have fewer drug interactions. No NNT data are available for phenytoin, clonazepam, valproate, gabapentin, or oxcarbazepine in TN.

Suggested Treatment of TN

The following recommendations are based on the scientific evidence as well as the author's clinical experience as a neurologist treating chronic pain patients for 30 years (Fig 1).

First-line Approach. The most successful treatment of TN occurs with carbamazepine, which initially relieves the majority of sufferers when used appropriately. The dose of this drug is variable and can range from 200 mg to 2,000 mg per day (bid or qid). A start-low-and-go-slow approach is best. The author usually begins with a controlled-release preparation of 100 to 200 mg every 8 to 12

hours po, with prn rescue doses of the shorter-acting preparation of 100 to 200 mg every 4 hours.

Rescue medication may be timed to anticipate attacks that occur with eating, speaking, washing the face, or brushing the teeth. Dose escalation with the longer-acting preparation may then occur as needed. Blood levels can be used as a guide to compliance and dosage. If higher doses are accompanied by lower blood levels, symptoms are uncontrolled, and there are no significant side effects, the dose may be escalated. There is no therapeutic range for TN, as has been suggested for epilepsy. The author does not use an arbitrary ceiling for dosing but increases the dose until satisfactory relief occurs or unacceptable side effects (eg, drowsiness, ataxia, or nausea) are experienced. The most serious potential side effects of carbamazepine are aplastic anemia and hepatitis. Monitoring of hematologic and hepatic parameters rarely results in withdrawal of the drug but is prudent every 2 weeks for the first 3 months of therapy and less frequently thereafter. Dermatologic reactions, such as Stevens-Johnson syndrome and lupus, may be serious and require that therapy be stopped. Many patients will have good control of their pain with carbamazepine, and after an appropriate period, it may be gradually reduced or withdrawn, as a remission may occur. Future attacks may be more readily treated with the knowledge about dosage that is gained from the first therapeutic experience.

Second-line Approach. Some patients are only partially relieved by carbamazepine, and about 40% of patients experience side effects. Although the side effects often subside with time, about 10% require discontinuation of the drug. Long-term studies also indicate that only about 50% are helped by carbamazepine after 6 to 16 years of treatment, perhaps because of the progression of the disorder. It is the author's practice to add baclofen if the response to carbamazepine is incomplete, or to use baclofen as a monotherapy if carbamazepine has to be discontinued. The dose of baclofen can be slowly increased from 5 mg to 80 mg per day, depending on the response and side effects. Often the drug needs to be taken every 4 hours because of its short half-life. Baclofen does not have carbamazepine's potential for life-threatening side effects; it most commonly causes drowsiness, dizziness, and gastrointestinal reactions. About 10% of patients cease treatment on monotherapy because of side effects. One should never stop baclofen suddenly, since hallucinations or seizures may occur.

Phenytoin may also be used as monotherapy, but it is much less effective than carbamazepine,

and the author finds it most useful as an add-on to carbamazepine or to a combination of carbamazepine and baclofen. With add-on therapy, it is reasonable to use 100 mg in a single dose at bedtime to start and to increase the dose slowly every 7 to 10 days, keeping to evening single dosing and using blood levels as a guide to compliance and dose increases. With this approach, one should be mindful that there is no proven therapeutic range; the end points are pain relief or intolerable side effects. Phenytoin has the advantage of being available intravenously for very severe pain that makes oral intake difficult. A loading dose of 15 mg/kg may be used as for epilepsy and given slowly at a rate of 25 mg/min or less. The most common side effects of phenytoin are drowsiness, dizziness, diplopia, and ataxia. These are dose related, but may occur at low doses with combined therapy. Other less common potential difficulties are gingival hyperplasia, low folic acid levels, and idiosyncratic reactions such as hepatitis, lupus, bone marrow depression, Stevens-Johnson syndrome, and lymphadenopathy.

Lamotrigine is a possibility as an add-on treatment, but common side effects are a rash in 1 in 1,000 and Stevens-Johnson syndrome in 3 in 1,000. Close monitoring is required. If it is used as an add-on, the initial dose could be 25 mg/d for 2 weeks, then 25 mg bid for 2 weeks, with a maximum of 50 to 100 mg bid.

Third-line Approaches. Other drugs of potential use in refractory cases are the anticonvulsants clonazepam (3 to 8 mg/d), valproic acid (250 to 500 mg qid), gabapentin (300 mg/d to 1,200 mg tid), and the antispasticity agent tizanidine or oxcarbazepine. The author has seldom had good success with these agents with patients who did not respond to carbamazepine, and refractory patients may have to be referred for surgery, which has a high success rate. Conventional analgesics, including opioids, do not satisfactorily relieve this pain. Interestingly, amitriptyline, a drug that relieves the shocklike pains of PHN, is not effective for TN (Table 3).

Neuropathic Facial Pains Other Than TN

There is little scientific evidence in the form of RCTs of therapeutic approaches for this group other than in PHN. Sharav et al²⁷ found that amitriptyline was effective in an RCT of chronic facial pain but thought most subjects had evidence of musculoskeletal pain.

Table 3 Comparison of TN and PHN

Clinical data	TN	PHN
Seriousness of injury	Minor injury	Major injury
Branch of trigeminal nerve affected	V2, V3	V1
Trigger	Localized tactile trigger areas within or outside of the affected area	Non-noxious tactile trigger in the affected area
Pain qualities	Shocklike pain	Shocklike pain, steady pain (allodynia), skin sensitivity (hyperesthesia, dysesthesia)
Sensory loss	Little or no	Yes
Pain-free intervals	Yes	No
Pathology	Demyelination at nerve root	Damage to dorsal horn, nerve root, nerve, and spinal cord
Treatment		
Surgery	Relief in 80% of patients with (1) Decompression of vessel loops; (2) radiofrequency/glycerol; (3) gamma knife	Some relief in up to 50% of patients with dorsal root entry zone lesions
First-line drug(s)	carbamazepine	Amitriptyline, nortriptyline, gabapentin

RCTs in PHN

Antidepressants. A large number of studies support the utility of antidepressants in a variety of chronic pain problems. An important part of this literature concerns favorable, well-designed trials of the use of these agents in neuropathic pain, particularly PHN.²⁸⁻³² PHN is a good model of neuropathic pain for drug trials because, if patients are chosen carefully, the pain is fairly stable over time and sufficient numbers of cases for trials can be readily obtained. Most studies include trigeminal PHN (about 20% of PHN cases are trigeminal PHN). Antidepressant therapy, as opposed to many other putative therapies of this difficult problem, has come to have a sound scientific basis.

The earliest RCT of amitriptyline as a placebo control found good results in 16 of 22 patients (67%).²⁸ Most patients were not depressed, and pain relief occurred without a change in depression ratings in most patients, indicating that the drug appeared to result in pain relief independently of its antidepressant effect. This analgesia occurred at lower doses than those usually used to treat depression (median 75 mg). Median follow-up was 12 months. Two patients were lost to follow-up; a good result was maintained in 12 of 22 (55%). A subsequent trial has corroborated these results.²⁹ Amitriptyline has limitations in the long term

because of side effects and the fact that relief is rarely complete and occurs in only about two thirds of patients.

One of the effects of this drug is to potentiate both serotonin and noradrenaline in the central nervous system. Subsequent studies have explored whether selective serotonergic or noradrenergic antidepressants might be more effective and have fewer untoward effects.³⁰⁻³² Experience with serotonergic agents (clomipramine, trazodone, nefazodone, fluoxetine, and zimelidine) in PHN has been disappointing.³³ The evidence supporting the use of noradrenergic agents is more compelling. Desipramine, a selective norepinephrine reuptake inhibitor, has been shown to be more effective than placebo in PHN,³⁰ and pain relief with this drug was found not to be mediated by mood elevation. An RCT comparing maprotiline (a noradrenergic agent) with amitriptyline found that both were effective; amitriptyline was the more effective of the 2.³¹ Nine patients responded equally well to both drugs, 7 responded only to maprotiline and 8 required amitriptyline for good relief. All 3 aspects of PHN pain (ie, steady pain, brief jabbing pain, and pain on tactile skin contact) responded to treatment in this study. Side effects were troublesome with both agents, limiting their effectiveness. Most patients were not depressed, and pain relief occurred in most without a change in depression rating scales. A com-

parison of amitriptyline with nortriptyline (which is more noradrenergic than amitriptyline) showed about equal efficacy for both drugs, with less severe side effects with nortriptyline.³²

Anticonvulsants. RCTs support the use of gabapentin in PHN.^{9,34} These studies found 20% to 30% of patients to have at least moderate improvement (ie, 50% improvement) over placebo with few serious side effects. Many patients in 1 study achieved the target dose of 3,600 mg per day.

Opioids. For a long time, there has been a bias against the use of opioids for noncancer pain. There is now increasing support for the view that these drugs are helpful and justifiable for use with noncancer pain, including neuropathic pain. Survey data in PHN have indicated that opioids are useful for some patients.³³ Twenty-five of 90 patients with otherwise intractable pain achieved good to excellent results, and 50 others had 25% to 50% relief. In an RCT¹¹ of 50 patients treated with sustained release oxycodone, 58% of patients had at least moderate improvement versus 18% with placebo; the NNT was 2.5.

Topical Agents. A variety of topical agents (capsaicin, acetylsalicylic acid, and local anesthetics) have been studied in PHN.³⁵ Capsaicin, the active ingredient in red peppers and other plants, acts by depleting the neurotransmitter substance P in small primary afferent fibers. Capsaicin has a modest effect according to RCTs and may best be used as an adjunct to other treatments.³⁵ The burning sensation induced by capsaicin is often unpleasant or unbearable and limits therapy. A recent RCT of the lidocaine patch (Lidoderm) has indicated efficacy in PHN.³⁶ The patch itself has been found to offer protection, but a significant drug effect was also present with this simple topical approach.

NNT data for different drugs used for the neuropathic pain disorders of PHN, painful diabetic neuropathy, and other neuropathies are given in Table 1. These data should be interpreted with caution because they compare different trial designs, numbers of patients, and data analyses. Unfortunately, few head-to-head trials exist that allow direct comparisons of analgesic drugs of differing classes. Also, because of patient selection in RCTs, NNT data may not be generalizable to clinical practice.

Suggested Treatment of PHN and Neuropathic Orofacial Pains Other Than TN

In conclusion, a reasonable first-line approach for facial neuropathic pain other than TN is either an

older generation antidepressant or gabapentin (Fig 1). These data indicate that pain may be reduced from moderate or severe to mild in about 50% to 60% of patients by commencing with amitriptyline or nortriptyline at a dose of 10 mg qhs in those over 65 years old and 25 mg in those younger than 65. The dose is increased by similar increments in a single hs dose every 7 to 10 days until relief is obtained or intolerable side effects interfere with the treatment. If these agents fail, desipramine or maprotiline can be tried in similar doses. Occasional patients failing these may benefit from a serotonergic drug such as trazodone, clomipramine, or fluoxetine, but these do not appear useful for the majority of patients. Gabapentin has a modest effect with few severe side effects; divided doses up to 3,600 mg may be required. A trial-and-error approach in refractory patients may also include the anticonvulsants carbamazepine, phenytoin, clonazepam and valproic acid. For resistant cases, opioids may be safely prescribed on an as-needed or round-the-clock basis. Long-acting oral forms of oxycodone, morphine, and hydromorphone and the fentanyl skin patch may be helpful. Trials of different opioids may reveal one that is preferred.

The use of topical agents, such as capsaicin, acetylsalicylic acid, and local anesthetic agents is attractive as it is simple and free of systemic effects. The most useful of these appears to be the lidocaine patch, but this may be difficult or impossible to use, as it may be considered cosmetically unacceptable on the head and face. For most patients, topical agents do not appear useful as sole therapy, but they may be a useful adjunct to other therapies in some individuals.

Transcutaneous electrical nerve stimulation, although unproven by RCT, may be worth trying. Electrode placement, frequency, intensity, and duration of stimulation are a matter of trial and error. There are no good favorable data for acupuncture in PHN. Some patients may benefit from nerve blocks which, if efficacious, may be repeated at appropriate intervals. These have not been subjected to an RCT.

In at least 40% of patients, pain remains totally refractory or unsatisfactorily relieved. These patients should be seen regularly. Different opioids, along with any approaches that seem reasonable and safe, should be tried for the limited relief they give, with the hope that improvement will occur with time. Approximately 50% of patients, even those with pain of long duration, will improve over the years, half of these with no treatment.³⁷

Differences Between TN and Trigeminal PHN

The clinical features and pharmacologic treatment of TN and PHN are very different (Table 3). Amitriptyline or nortriptyline and gabapentin are the first-line drugs for PHN, while carbamazepine is the first-line drug for TN. At least 80% of TN patients find relief with carbamazepine, whereas opioids and amitriptyline have been found to have no effect on TN. About 50% to 60% of PHN patients respond to amitriptyline, nortriptyline, gabapentin, or opioids. These pharmacologic differences suggest different pathophysiological mechanisms.³⁸

Other Trigeminal Neuropathies

Many other conditions may cause trigeminal neuropathy, with and without pain in the nerve and nerve root.^{38,39} A large group of conditions are difficult to categorize as to cause and have been grouped together as atypical facial pain. In the author's view, a substantial proportion of these are neuropathic because they occur after situations which can cause nerve injury such as root canal therapy and dental extractions. Trauma to facial structures and the skull may damage branches of the fifth nerve such as the supraorbital and infraorbital nerves. Mental nerve neuropathy may be the first sign of cancer. Neurotoxins such as trichloroethylene and stilbamidine are known to affect the fifth nerve. Inflammatory conditions of the ear and petrous apex may spread to the nerve root or ganglion and also involve the sixth nerve. Individuals with multiple sclerosis may present with TN or develop it or other neuropathic orofacial pain in the course of the disease. Primary or secondary extracranial tumors may cause progressive trigeminal nerve sensory loss and pain. Intracranial tumors, including cholesteatomas, acoustic neuromas, and meningiomas, may also affect the fifth root. A benign sensory neuropathy may occur acutely and then resolve slowly. A slowly progressive unilateral or bilateral trigeminal sensory neuropathy has been reported to be associated with numbness and sometimes pain. Some of these cases are associated with collagen diseases such as lupus and scleroderma. One approach to pain therapy in these usually difficult problems is to treat them like PHN if the pain is mainly steady and burning. If there is a major shocklike component with a suggestion of triggered pain, even with a steady burning component, then an approach

similar to the therapy of TN may be best, with carbamazepine as the first approach (although amitriptyline and nortriptyline also relieve shocklike pain). Chronic opioid therapy may be necessary to provide at least some relief if the pain is constant, severe, and intractable to all other measures. Generally it is wise to avoid ablative neurosurgical procedures for neuropathic facial pain that is not clearly TN.

Conclusions

Trigeminal neuralgia and PHN may occupy opposite ends of the spectrum of neuropathic facial pain and these disorders may depend upon the different location and severity of the insult to the nerve. Probably both disorders result in reduced inhibition and excess excitation of hyperactive, damaged central neurons in the nucleus of the trigeminal nerve. Clinical and pharmacological differences point to different pain mechanisms and require further elucidation. First-line therapy for TN is carbamazepine whereas amitriptyline, nortriptyline, and gabapentin are first choices for PHN and other neuropathic facial pain. In refractory cases opioids are reasonable but they do not relieve TN. The drug therapy of PHN may be extrapolated to other neuropathic trigeminal pain conditions. There continues to be a need for RCTs of new drugs in TN and especially in neuropathic facial pain other than TN.

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