



Recommendations for the Management of Idiopathic Trigeminal Neuralgia

Multidisciplinary Panel on Neuropathic Pain*

The Multidisciplinary Panel on Neuropathic Pain has prepared recommendations for the management of idiopathic trigeminal neuralgia (TN) to provide healthcare professionals in Hong Kong with current, accurate and useful information concerning disease management. Where possible, evidence-based reviews and comparisons were used to develop these recommendations. The recommendations were first published in 2003.¹ The current update includes new clinical data for pharmacotherapy and surgical interventions in TN.

The Recommendations for the Management of Idiopathic Trigeminal Neuralgia are the product of review and appraisal of current evidence in the medical literature. The recommendations serve to assist healthcare professionals in evaluating a patient's condition and deciding on a suitable treatment modality. They are not intended to replace professional judgment in determining the appropriate management of individual patients. While we have taken due care in preparing the recommendations, we cannot warrant the accuracy of the

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Figure 1. Distribution of the trigeminal nerve



original publications. In selecting good-quality references, a certain degree of judgment based on our professional knowledge in the subject was needed. Such biases are minimized by multidisciplinary discussion and review.

I. Pathophysiology and Prevalence

TN is an extremely painful, easily diagnosed condition, which can be managed medically in most patients. The prevalence of TN is around 0.1-0.2 per 1,000 population, and the annual incidence is about 4-5 per 100,000 population per year.^{2,3} TN occurs more frequently in older people, and is more likely to affect females than males.^{2,3} The pain is unilateral in the majority of cases, but if bilateral, it occurs in the same division of the nerve. The second or third division of the nerve is affected in most patients, with the first division being affected in fewer than 5% of cases. (Figure 1) The pain is characterized by paroxysms of electric shock-like pain lasting from

several seconds up to 2 minutes. Many daily activities, such as brushing the teeth, eating, shaving, or washing the face, may provoke attacks and cause spasms of the facial muscles.^{2,4,5} Hence, TN is also referred to as *tic douloureux*.

Although the pathophysiology of the pain is obscure, vascular compression of the trigeminal root is an important contributing factor.^{2,4-7} When microvascular decompression is performed, a blood vessel is often found to have compressed or caused a groove in the trigeminal root.⁴ Since immediate relief is obtained by decompression, this indicates that pain is due to electrical activity with focal demyelination and micro-neuromas.⁵⁻⁸

Acoustic neuromas, cholesteatomas, aneurysms, arteriovenous malformations, meningiomas and bony abnormalities may also lead to the compression of nerve roots. TN is a complication of multiple sclerosis (MS); about 2% to 4% of patients with TN also have MS.^{2,5} Therefore, coexistent MS should be considered in younger patients presenting with TN.⁵ The diagnosis is made by taking a careful history and conducting a physical examination. Tumours of the head and neck must also be ruled out.

II. Diagnosis

The diagnosis of idiopathic TN should be based on the clinical symptomatology and exclusion of pathological causes of TN.

Five Major Characteristics of Idiopathic TN

- A history of paroxysmal shooting, stabbing, jabbing, electric-shock pain in the distribution of the trigeminal nerve;

- Unilateral pain attacks that start abruptly and last from several seconds to 2 minutes;
- Pain triggered by talking, chewing, kissing, drinking and brushing the teeth;
- A normal neurological examination; and
- Relatively pain-free periods between attacks.

Main Differential Diagnoses⁵

- Temporal tendinitis;
- Ernest syndrome (associated with temporomandibular joint [TMJ] disorders);
- Occipital neuralgia;
- Glossopharyngeal neuralgia;
- Postherpetic TN;
- Atypical facial pain (a group of pain conditions characterized by an intense, deep, constant pain that does not follow anatomical pathways of peripheral nerves);⁹ and
- The SUNCT syndrome (short-lasting, unilateral, neuralgiform pain with conjunctival injection and tearing).

Exclusion of Pathological Causes of TN

Other causes of TN include:

- Tumour compressing the trigeminal nerve; and
- Multiple sclerosis.

Although imaging of the brain seldom reveals the precise reason for nerve irritation, a high-quality magnetic resonance image (MRI) of the brain can usually detect whether TN is caused by a tumour, or by MS.

III. Treatment

Pharmacotherapy

Pharmacotherapy is the mainstay of treatment for TN and may be initiated by general practitioners.

Full product information should be consulted before prescribing pharmacotherapy. If a patient remains refractory to two or three agents, they should be referred to a multidisciplinary pain management centre.

First-line Treatment

Carbamazepine is an anticonvulsant that is also indicated for use in TN and diabetic neuropathy. Carbamazepine is usually the first-line treatment for TN and has been proven effective for TN in randomized, controlled clinical trials.¹⁰ The usual dose of carbamazepine in TN is up to 1,200 mg daily in divided doses. Unfortunately, side effects of carbamazepine are common and limit its use in some patients. Some very common side effects of carbamazepine include dizziness, ataxia, allergic skin reactions, leucopenia and vomiting. Laboratory parameters should be monitored throughout treatment.

Other Pharmacotherapy Options

When carbamazepine is contraindicated or is not well tolerated, there are several alternatives for second-line treatment. These include other anticonvulsants, such as gabapentin,¹¹ pregabalin,¹²⁻¹⁴ lamotrigine,¹⁵ phenytoin,^{1,5} and baclofen.¹⁶ The latter two drugs tend to be used less frequently, since newer anticonvulsants are now available. Antidepressants, such as amitriptyline, are also effective in the treatment of neuropathic pain.¹⁷

Although most evidence for gabapentin is in painful diabetic neuropathy and postherpetic neuralgia, gabapentin is effective in other neuropathic pain conditions.¹⁰ Gabapentin should be commenced as a single 300 mg dose on Day 1, 600 mg/day on Day 2 (divided BID),

and 900 mg/day on Day 3 (divided TID). The dose can subsequently be titrated up as needed for pain relief, to a daily dose of 1,800 mg (divided TID).¹⁸ If higher daily doses are required for maintenance, the maximum recommended dose is 3,600 mg daily (a lower dose is recommended in patients with renal impairment). For elderly patients, or patients susceptible to side effects, care should be taken in dose selection, and dose should be adjusted based on creatinine clearance values in these patients.¹⁸

Pregabalin, a new anticonvulsant, is also emerging as an effective and safe treatment for various neuropathic pain syndromes,¹²⁻¹⁴ and may have a role in TN. Pregabalin is initiated at 150 mg/day in two divided doses, and then increased to 300 mg/day after 1 week. Pregabalin may be up-titrated to a maximum dose of 600 mg/day, depending on patient response.

Pharmacological Agents for TN

Some of the clinical evidence supporting the use of pharmacological agents in the treatment of TN is described below.

Carbamazepine: Three placebo-controlled studies of carbamazepine in TN had a combined number-needed-to-treat (NNT) of 2.5 (95% confidence interval [CI] 2.0-3.4).¹⁰ The same review, combining all results for carbamazepine in different neuropathic pain syndromes, revealed that the number-needed-to-harm (NNH) for minor harm was 3.7 (95% CI 2.4-7.8). NNHs for major harm were not statistically significantly different for carbamazepine compared with placebo. Therefore, carbamazepine has been shown to be effective in the treatment of TN.¹⁰

However, minor side effects are common, limiting its use to patients who can tolerate them. Before commencing therapy, the patient should be informed of possible side effects, which include dizziness, sedation, confusion and rash. The starting dosage should be 100 to 200 mg at night for 2 nights. The dosage should be gradually increased over 2 days as side effects allow, until pain relief is obtained or a total daily dose of 1,200 mg in equally divided doses is reached. When pain relief is obtained, the patient should be maintained on that dosage for at least 6 months before tapering. Careful monitoring of laboratory parameters is mandatory to avoid the rare possibility of life-threatening blood dyscrasias. Hepatotoxic and haematological side effects include agranulocytosis, aplastic anaemia, leucopenia or pancytopenia. At the first sign of a blood abnormality or rash, carbamazepine should be discontinued.

Baclofen: Small, single-centre, controlled trials have shown that baclofen alone provides pain relief (NNT=1.4).¹⁶ For those patients not responding to other drugs, baclofen may be used as a single agent or in combination with other agents. However, its use is limited by side effects. Baclofen has significant hepatic and central nervous system adverse effects, including weakness and sedation, and is poorly tolerated by many patients.

Lamotrigine: Lamotrigine may be of benefit in patients with insufficient pain relief from carbamazepine or phenytoin.¹⁵

Other Drugs: Uncontrolled observations and clinical experience indicate that gabapentin,¹⁷⁻²¹ phenytoin (usual dose 300-600 mg daily),¹⁵ clonazepam,^{22,23} valproic

acid,^{15,24} and lidocaine²⁵ can also relieve TN. Randomized clinical trials showed pregabalin significantly reduced mean pain scores compared with placebo in patients with postherpetic neuralgia and diabetic peripheral neuropathy.¹²⁻¹⁴ However, trials have not been performed to evaluate pregabalin in TN. When a single drug is ineffective, combining two or more drugs may provide greater pain relief.^{13,26}

Summary

Considering efficacy and cost, it is suggested that carbamazepine should be the first-line treatment. For second-line treatment, gabapentin, pregabalin, phenytoin, sodium valproate, clonazepam or baclofen may be tried if the patient cannot tolerate carbamazepine. Lamotrigine may be added to normal or reduced doses of carbamazepine or phenytoin. Antidepressants, such as amitriptyline, may also be useful in some patients.

As TN can be transient, the length of therapy should be adequate to establish drug efficacy (ie, 3 to 6 months). In general, if a patient has not achieved a satisfactory response after a trial of two to three pharmacological agents, the primary-care physician should consider referring the patient to a multidisciplinary pain service for further assessment and management, which may include surgical intervention.

Peripheral Trigeminal Nerve Block

Peripheral trigeminal nerve block at the trigger zone has been used to treat TN. A number of agents can be used, including 60% alcohol, 10% phenol, glycerol, 2% lidocaine,^{27,28} streptomycin/lidocaine,^{27,28} 0.5% bupivacaine,²⁹ 4% tetracaine or 0.5% dibucaine. The treatment is safe and provides immediate symp-

tom relief in most cases. However, the effect is only temporary and the duration of relief depends on the agent used. Using alcohol or phenol, the median duration of effect was 9 to 19 months,³⁰⁻³² compared with 7 months with glycerol.³³ Local anaesthetic agents have an even shorter duration of action.^{29,34} The major side effect is reduced facial sensation, which can last for several weeks.³⁴

Peripheral trigeminal nerve block may be used as an adjunct to pharmacotherapy to achieve immediate and intermediate-term pain relief. Elderly patients who are refractory to pharmacotherapy but refuse trigeminal nerve intervention may undergo repeated peripheral nerve block for symptomatic relief.

Interventions/Operations on the Trigeminal Nerve

In general, interventions/operations on the trigeminal nerve are much more effective than pharmacotherapy, but have higher risks. These procedures should not be performed before pharmacotherapy has been tried for a reasonable period (ie, 3 to 6 months). However, these procedures are performed infrequently in Hong Kong. If surgery is indicated, the short- and long-term risks of different treatments and their overall effect on quality of life and comorbidities should be assessed. To compare the efficacy of various interventions or operations, the focus should be on results from patients who have not had a previous intervention or operation. The major criteria for comparison are percentage of pain- and medication-free patients, recurrence rate and rate of serious complications.

Microvascular Decompression

Microvascular decompression (MVD)

of the trigeminal root is the major neurosurgical procedure of choice for intractable TN. Results from more than 5,000 cases with MVD have been published.³⁵⁻⁵² The operation involves identifying the trigeminal root close to the brain stem, isolating the blood vessel that is causing the compression, and interposing a sponge between the vessel and the nerve. This relieves the compression and, thus, the pain. Immediate pain relief occurs in 85% to 99% of patients. Patients with prolonged TN are less likely to experience pain relief with MVD than those with symptoms of shorter duration. This is probably secondary to morphological changes in the nerve that do not revert to normal after relieving the pulsatile vascular compression. Five to 10 years after a single MVD, the likelihood of being pain-free without medication, or with low-dose medication, is around 70% and 80% respectively. The subsequent rate of recurrence is 1% to 2% per year.

In over 85% of cases, the normal function of the trigeminal nerve is preserved. This is in contrast to other procedures that aim to create a lesion on the trigeminal nerve. This may be an important consideration for younger patients. There is a small risk (<5%) of complications, such as facial numbness or weakness, double vision, infection, or deficiencies in hearing or balance. The major disadvantage of this procedure is the need for craniotomy and its associated risks. The risk of mortality or severe morbidity is around 1%. Experienced surgeons with a good track record in performing operations in the posterior fossa and cerebellopontine angle should perform this procedure.

In general, this treatment should

be recommended for relatively young patients who want to avoid the risk of permanent facial numbness and corneal sensation loss. Patients older than 70 years and those with substantial atherosclerosis should be advised to use alternative therapeutic modalities.

Percutaneous Procedures

Percutaneous radiofrequency rhizotomy (PRFR): The destruction of the Gasserian ganglion by radiofrequency (RF) is used for patients who have failed medical treatment and suffer from intractable TN. It is assumed that selective destruction of A-delta and C fibres occurs by graded heating. This is the most commonly used and most studied percutaneous technique for the treatment of TN, and results from over 5,000 cases have been published.^{39,42,45-47,50,53-58} Initial pain relief occurs in 88% to 99% of patients, but the recurrence rate is high (25% to 50% of patients have recurrent pain after 3 years). With repeated procedures, the overall success rate at the end of 2 years' follow-up was 91.7%.

There is a direct relationship between the rate of complete pain relief and the complication of trigeminal nerve dysfunction. A variable degree of facial numbness is usual. Serious complications, such as anaesthesia dolorosa, severe facial dysaesthesia, diminished corneal reflex and keratitis, could be more distressing and more difficult to treat than TN. These serious trigeminal nerve complications occur in about 1% to 4% of cases. Masseter muscle weakness may occur in fewer than 5% of cases. Life-threatening complications, such as cerebrospinal fluid leakage, carotid-cavernous fistula, aseptic meningitis, intracranial

haemorrhage and optic nerve damage, have been reported rarely.

Balloon compression rhizotomy (BCR): Percutaneous microcompression of the ganglion is performed by introducing and inflating a balloon in Meckel's cavity.^{59,60} The degree and duration of inflation determine the extent of damage to the ganglion, which relates to the degree of sensory loss. Although BCR is technically less demanding than other percutaneous procedures, the number of cases reported is relatively small. Compared with other percutaneous techniques, BCR has a much lower risk for affecting corneal sensation. Hence, in patients with TN that involves the ophthalmic branch, or all three branches of the trigeminal nerve, BCR may be preferred to PRFR or percutaneous retro-Gasserian glycerol rhizotomy (PRGR).

Percutaneous retro-Gasserian glycerol rhizotomy (PRGR): Glycerol injection into the Gasserian ganglion is thought to destroy large myelinated fibres that conduct triggering impulses.⁶¹⁻⁶⁸ Over 1,200 cases have been reported in the literature. It is technically less demanding than PRFR. This procedure has a high initial success rate (75% to 95%), but also a high recurrence rate. After a single treatment, 30% to 50% of cases will recur within 3 to 5 years. With repeated procedures, over 70% of cases will be pain-free, with or without medications.

A variable degree of trigeminal dysfunction is common. Serious complications related to trigeminal nerve dysfunction may occur in 10% to 20% of cases. Mortality is extremely unlikely. Hence, PRGR is often used for patients who are unsuitable for operations, and accept a higher risk of local complications.

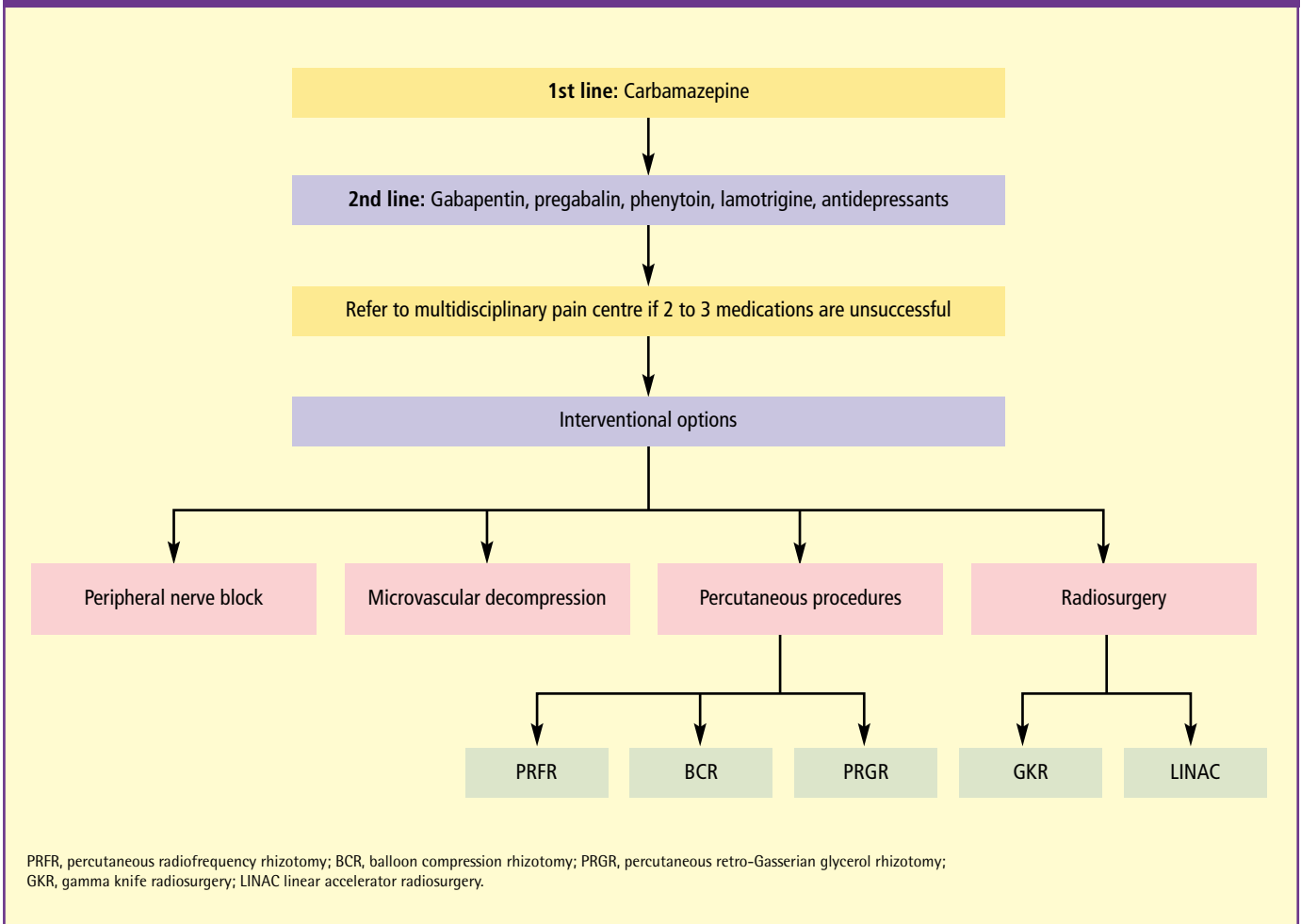
Rare, but serious, complications are common to all percutaneous procedures. These include cardiac arrest, fatal intracranial haemorrhage, meningitis, abscess formation and cranial nerve injuries. Corneal anaesthesia may also occur. Anaesthesia dolorosa is an extremely unpleasant and painful complication of destructive procedures.

Radiosurgery

Gamma knife radiosurgery (GKR) is a relatively new intervention for TN, and more than 700 cases of primary and secondary TN treated with GKR have been reported.⁶⁹⁻⁸⁵ A review of 151 TN cases treated with GKR targeted 2 to 4 mm anterior to the entry of the trigeminal nerve into the pons using maximal radiation doses ranging from 50 to 90 Gy showed 47%, 45% and 34% of patients were pain free without medication after 1, 2 and 3 years of follow-up, respectively.⁸⁵ However, 27% of patients with initial improvement subsequently experienced pain recurrence after a median of 12 months post-GKR. Furthermore, the effect of scattered irradiation on the cornea may induce the development of cataracts. The major advantage of GKR is that it is rarely associated with mortality or other serious complications.

Linear accelerator (LINAC) radiosurgery is another noninvasive procedure for treating TN. Retrospective studies evaluating LINAC surgery as primary treatment for essential TN showed focusing 90 Gy on the nerve root entry zone provided good to excellent pain relief in 87.8% to 100% of patients on long-term follow-up (of up to 70 months).⁸⁶⁻⁸⁸ Median times to relief in these studies ranged from 2 to 2.7 months. Post-procedural numbness was experienced by 25% to 32% of

Figure 2. Treatment recommendations for trigeminal neuralgia



patients. The relapse rate was 32%, with relapse tending to occur 4 to 13 months after treatment.

IV. Summary

The primary-care physician should try carbamazepine first. If the response is not satisfactory or the patient cannot tolerate treatment, one or two second-line drugs may be tried. (Figure 2) The second-line drugs include gabapentin, pregabalin, phenytoin, sodium valproate, clonazepam, baclofen, lamotrigine

and antidepressant agents. For chronic, intractable pain, a patient should be referred to a multidisciplinary pain management centre.

Peripheral trigeminal nerve block is a useful adjunctive therapy, and may be used while pharmacotherapy is being optimized. If treatment is not successful following a trial of two or three medications for an adequate period (3 to 6 months), an operation or interventional treatment should be considered.

Selecting a procedure to treat TN is both difficult and controversial.

Patients should be given the opportunity to consider all of the available options. In general, for patients younger than 70 years who have a low surgical risk and prefer to preserve trigeminal nerve function, MVD should be recommended. PRFR is considered the best non-operative choice of treatment. In cases where TN involves the ophthalmic division or all three divisions, BCR should be considered over PRFR. The reported success rate for GKR in the treatment of TN is much lower than for the other

operations or interventions. GKR should be reserved for patients who have failed both surgical and percutaneous procedures. LINAC radiosurgery, which has higher response rates and provides more rapid relief than GKR, may be a better option, depending on the availability of the necessary technology. However, recurrence and post-treatment facial numbness is common.

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