



# Recommendations for the Management of Idiopathic Trigeminal Neuralgia

The Multidisciplinary Panel on Neuropathic Pain\*

## Hierarchy (Level) of Evidence<sup>1</sup>

- Ia Evidence from meta-analysis of randomized, controlled trials.
- Ib Evidence from at least 1 randomized, controlled trial.
- IIa Evidence from at least 1 controlled study without randomization.
- IIb Evidence from at least 1 other type of quasi-experimental study.
- III Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies.
- IV Evidence from expert committee reports or opinions, and/or clinical experiences of respected authorities.

## I. Pathophysiology and Prevalence

**T**rigeminal neuralgia (TN) is a severely painful, easily diagnosed condition, which can be managed medically in most patients. The incidence of TN is approximately 70 cases per 100,000 population.<sup>2-5</sup> Of unknown aetiology, TN typically arises in otherwise healthy people older than 50 years and affects females twice as often as males. TN is rarely seen in patients younger than 30 years; however, if it does occur in younger

### \* Panel members:

**Chen Phoon Ping**, MBBS, FANZCA, FFPANZCA, FHKCA, FHKAM, DipPainMgt  
Consultant, Department of Anaesthesiology, Intensive Care and Operating Services, Alice Ho Miu Ling Nethersole Hospital, and Adjunct Associate Professor, The Chinese University of Hong Kong, Hong Kong SAR.

**Josephine WY Ip**, MBBS, MS, FRCS(Ed), FHKAM(Ortho), DipHandSurg(FESSH)  
Chief, Division of Hand and Foot Surgery, Department of Orthopaedic Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong SAR.

**Joseph MK Lam**, MBChB, FRCS(Edin), FCSHK, FHKAM(Surg)  
Consultant Neurosurgeon and Adjunct Associate Professor, Division of Neurosurgery, Department of Surgery, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong SAR.

**Lee Tsun Woon**, MBBS, FANZCA, FHKCA, FHKAM(Anaesthesiology), DipPainMgt  
Chief of Service, Department of Anaesthesia and Intensive Care, Tuen Mun Hospital, Hong Kong SAR.

**Tsoi Tak Hong**, MBBS, MRCP, FRCP(Edin), FRCP(Glas), FHKCP, FHKAM(Med)  
Specialist in Neurology and Consultant Physician, Department of Medicine, Pamela Youde Nethersole Eastern Hospital, Hong Kong SAR.

**Wong Chun Por**, MBBS, FHKAM(Med), FRCP(Lond), FRCP(Glas)  
Chief of Service, Integrated Medicine Service, Consultant Geriatrician, and Head, Department of Geriatrics, Ruttonjee Hospital, Hong Kong SAR.

**Lawrence KS Wong**, MBBS, MD, MRCP, FHKAM(Med), FRCP  
Associate Professor, Division of Neurology, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong SAR.

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Figure 1. Distribution of the trigeminal nerve.



patients, it is usually associated with multiple sclerosis (MS). The pain is unilateral in 97% of cases, but, if it is 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 less 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. 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.<sup>6,7</sup> When microvascular decompression is performed, a blood vessel is often found to have compressed or caused a groove in the trigeminal root.<sup>8</sup> Since immediate relief is obtained by decompression, this indicates that pain is due to electrical activity with focal demyelination and microneuromas.<sup>6,7,9</sup>

Acoustic neuromas, cholesteatomas, aneurysms, arteriovenous malformation, meningioma and bony abnormalities may also lead to the compression of nerve roots. About 2 to 3% of patients with TN also have MS. Therefore, coexistent MS should be considered in any patient younger than 50 years who presents with TN. 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.

### Major Characteristics

Idiopathic TN has 5 major characteristics:

1. A history of shooting, stabbing, jabbing, electric-shock pain in the distribution of the trigeminal nerve, which occurs in paroxysms;
2. Unilateral pain attacks that start abruptly and last from several seconds to 2 minutes;
3. Pain triggered by talking, chewing, kissing, drinking and brushing the teeth;
4. A normal neurological examination; and
5. Relatively pain-free periods between attacks.

### Main Differential Diagnoses

1. Temporal tendinitis;
2. Ernest syndrome (associated with temporomandibular joint [TMJ] disorders);
3. Occipital neuralgia;
4. Glossopharyngeal neuralgia;
5. Postherpetic TN;
6. Atypical facial pain (a group of

pain conditions characterized by an intense, deep, constant pain that does not follow anatomical pathways of peripheral nerves);<sup>10</sup> and

7. The SUNCT syndrome (Short-lasting, Unilateral, Neuralgiform pain with Conjunctival injection and Tearing).

### Exclusion of Pathological Causes of TN

Other causes of TN include:

1. Tumour compressing on the trigeminal nerve; and
2. MS

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 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. 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, a number of other agents can be used as second-line treatment. This includes other anticonvulsant agents, such as gabapentin, lamotrigine, phenytoin and baclofen, although the latter two drugs tend to be used less frequently since newer anticonvulsants became available. Antidepressants, such as

amitriptyline, are also effective in the treatment of neuropathic pain.

Although most evidence for gabapentin is in painful diabetic neuropathy and postherpetic neuralgia, gabapentin may be effective in other neuropathic pain conditions.<sup>11</sup> Gabapentin should be commenced at 300 mg at bedtime and increased by 300 mg every 3 days up to a dose of 1,800 mg daily after 1 week (given in 3 divided doses). 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

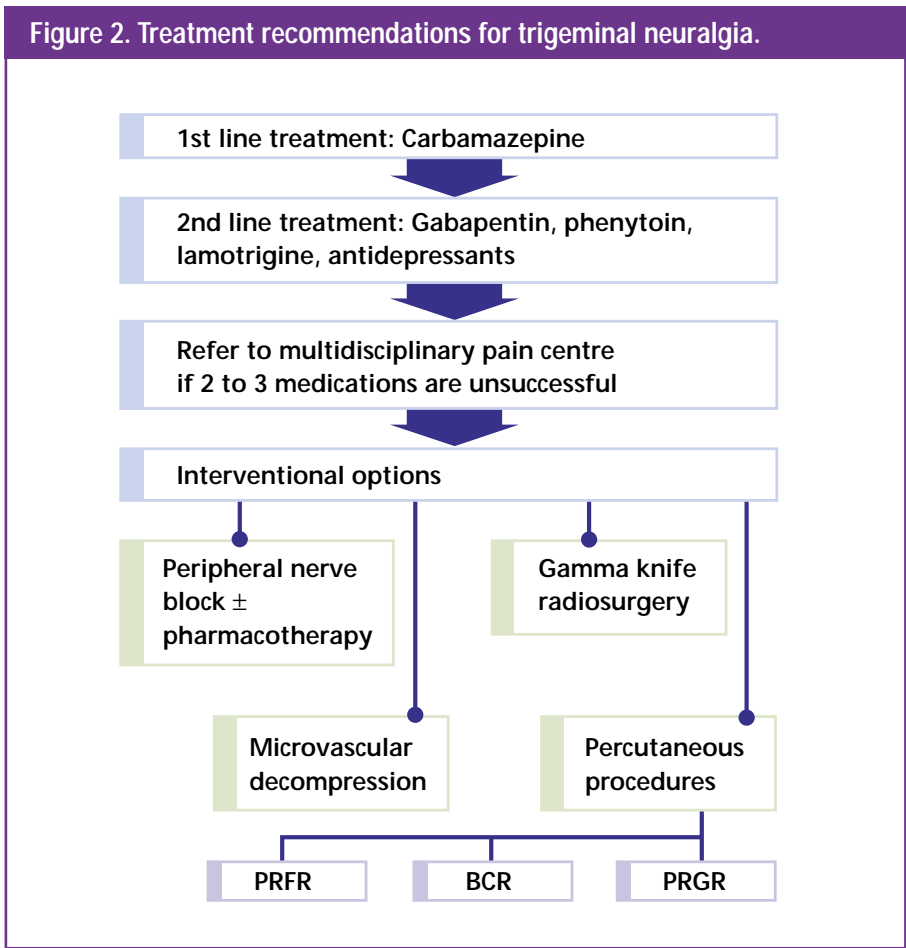
side effects, it is recommended to increase gabapentin dosage by 300 mg every week, or to commence with a lower dose (eg, 100 mg). Doses as high as 3,600 mg per day have been used in clinical trials.

*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). For minor harm, the number-needed-to-harm (NNH) 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 (Level Ia evidence).<sup>12</sup>

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) (Level Ib evidence).<sup>13</sup> For those patients not responding to other drugs, baclofen may be used as a single agent or in combination with other agents (Level IV evidence). 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 has an additional effect in patients with insufficient pain relief from carbamazepine or phenytoin (NNT = 2.1) (Level Ib evidence).<sup>14</sup>

**Other drugs:** Uncontrolled observations and clinical practice indicate that gabapentin,<sup>15-19</sup> phenytoin (usual dose 300 mg daily),<sup>20,21</sup> clonazepam,<sup>22,23</sup> sodium valproate,<sup>24,25</sup> and lidocaine can also relieve TN. When a single drug is ineffective, combining two or more drugs may provide greater pain relief.<sup>14</sup>

### Summary

Considering efficacy and cost, it is suggested that carbamazepine should be the first-line treatment. For second-line treatment, gabapentin, 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 2 to 3 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, streptomycin/lidocaine,<sup>26</sup> 0.5% bupivacaine,<sup>27</sup> 1% mepivacaine,<sup>27</sup> 4% tetracaine or 0.5% dibucaine. The treatment is safe and provides immediate symptom 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<sup>28-30</sup> compared with 7 months with glycerol.<sup>31</sup> Local anaesthetic agents have an even shorter duration of action.<sup>27,32</sup> The major side effect is reduced facial sensation, which can last from weeks to months.<sup>32</sup>

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 adequate 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.<sup>33-50</sup> The operation involves identifying the trigeminal root close to the brain stem, isolating the offending, compressing blood vessel 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.<sup>37,40,42,44,48,51-</sup>

<sup>57</sup> 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 a 2-year 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 dysesthesia, 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 less 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.

**“Operations on the trigeminal nerve have higher risks and should not be preformed before adequate pharmacotherapy has been tried”**

*Balloon compression rhizotomy (BCR):* Percutaneous microcompression of the ganglion is performed by introducing and inflating a balloon in Meckel's cavity.<sup>58,59</sup> 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 less common TN involving 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.<sup>60-67</sup> 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% 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, including cardiac arrest, fatal intracranial haemorrhage, meningitis, abscess and cranial nerve injuries. Corneal anaesthesia may also occur. Anaesthesia dolorosa is an extremely unpleasant and painful complication of destructive procedures.

*Gamma knife radiosurgery (GKR):* GKR is a relatively new intervention for TN, and more than 700 cases of primary and secondary

TN treated with GKR have been reported.<sup>68-83</sup> The median follow-up period was usually less than 2 years. The procedure involves focal irradiation (70-90 Gy) of the proximal trigeminal nerve near the pons via a 4-mm collimator. Histological examination shows focal degeneration of all the nerve fibres targeted by irradiation. The duration between treatment and onset of effect is between 1 day and 8 months. The delay in onset of effect is a disadvantage over other modalities of treatment. Studies show most patients have initial success following this procedure. At a median follow-up of 18 months, 10% had recurrent neuralgia, 10 to 34% experienced an increase in sensory loss in the trigeminal nerve distribution and up to 8% developed corneal numbness. Two years after GKR, 40 to 75% of patients were pain-free, with or without medications. GKR may be repeated once if the first attempt is not successful. However, the effect of scattered irradiation on the cornea may induce the development of cataracts. The major advantage of GKR is the avoidance of mortality or other serious complications.

### III. Summary

The primary-care physician should try carbamazepine first and, if the response is not satisfactory or the patient cannot tolerate treatment, 1 or 2 second-line drugs may be tried. (Figure 2) The second-line drugs include gabapentin, 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 3 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.

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