ORAL SURGERY

Oral Surgery ISSN 1752-2471

INVITED REVIEW

Trigeminal neuralgia and its variants. Management and diagnosis

E. Besi[1] & J.M. Zakrzewska[2,3]

[1]Edinburgh Dental Institute, Edinburgh, UK
[2]Royal National ENT & Eastman Dental Hospitals, London, UK
[3]Pain Management Centre, National Hospital for Neurology & Neurosurgery, UCLH NHS Foundation Trust, London, UK

Key words:
diagnosis, facial pain, headache, MRI, trigeminal neuralgia

Correspondence to:
E Besi
Edinburgh Dental Institute
Lauriston Place
Edinburgh EH3 9HA
UK
Tel.: +44 074 115 56567
Fax: +44 013 128 19374
email: eleni.besi@nhs.net

Accepted: 15 November 2019

doi:10.1111/ors.12464

Abstract

Trigeminal neuralgia (TN) and trigeminal autonomic cephalalgias (TACs) can cause severe facial pain. The differential diagnosis can be very challenging as both present with a sudden, usually unilateral, severe, recurrent pain in the distribution of one or more branches of the trigeminal nerve; with TACs including one or more autonomic symptom. A light touch can trigger the pain and it will stop patients from their daily activities creating a significant impact on their quality of life. Patients will present with pain to the dentist or doctor even to accident and emergency and they could receive incorrect and sometimes irreversible treatment. Clinical and radiographic examination, including a magnetic-resonance imaging, are essential to establish diagnosis and a referral to a specialist should be considered. The long-term treatment for TN could be pharmacological or surgical and patients should be informed their options, benefits as well as their side effects.

Introduction

Trigeminal neuralgia (TN) is defined as a: 'unilateral brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve and triggered by innocuous stimuli. It may develop without apparent cause or be a result of another diagnosed disorder. Additionally, there may be concomitant continuous pain of moderate intensity within the distribution(s) of the affected nerve division(s)'[1].

Early studies in the USA estimated prevalence of 4.1/100 000 thus defining it as a rare disease[2]. More recent studies in Europe using data from primary care records suggests a higher incidence of 8–12.6 per 100 000 per annum[3,4]. Another study in Germany where the diagnosis was validated by specialists a lifetime prevalence of 0.3% (95% CI 0.1–0.5%) was estimated[5]. The peak incidence is between the ages of 60–70 but TN can also rarely occur in young people and children estimated incidence per 100 000 person years at 0.4 based on GP records[2]. There is a slight predominance in women, and about 4–7% of patients with multiple sclerosis will have TN and there is a tendency for the patients to be younger 40 to 50-year old[6]. Tumours on the other hand account for a smaller number of cases and an association with hypertension and stroke and TN has been shown[7,8]. A population-based study in Taiwan suggests that after diagnosis of TN patients are at increased risk of depression, anxiety and sleep disorder[9].

Trigeminal autonomic cephalalgias (TAC) (Table 1)[10] on the other hand also characterised by the clinical features of unilateral headache and, usually, prominent cranial parasympathetic autonomic features, which are lateralised and ipsilateral to the headache. Experimental and human functional imaging suggests these syndromes activate a normal human trigeminal-parasympathetic reflex, with the clinical signs of cranial sympathetic dysfunction being secondary[1].

There are four subcategories for TACs: cluster headache (CH), paroxysmal hemicranias (PH),

hemicrania continua (HC) and short-lasting unilateral neuralgiform headache attacks (SUNHA). SUNHA for some is further subdivided into short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with autonomic symptoms (SUNA)[11]. It is important to make the distinction as management is radically different. Acute treatment for CH is inhalation of high flow oxygen or sumatriptan injection and verapamil is used for prophylaxis. PH and HC respond dramatically to indometacin which is also a diagnostic criteria[10]. SUNHA are most like TN but current data suggest that response is better with lamotrigine although a recent trial randomised controlled trial suggests topiramate may also be useful[11].

Aetiology and pathophysiology

Trigeminal neuralgia is considered a neuropathic pain the cause of which is still not fully understood. There is a wide range of terminologies being used which has resulted in some confusion. The most recent classification from the Neuropathic Pain Special Interest group of the International Association for the Study of Pain (IASP) and the European Academy of Neurology (EAN) suggests three main aetiological categories: (1) classical with neurovascular contact (NVC); (2) idiopathic no cause identified; (3) secondary caused by pathology other than NVC e.g. cerebellopontine angle tumours, multiple sclerosis or A-V malformations. The term primary TN is also used for group 1 and 2. The International Headache Classification of Headache Disorders puts forward two phenotypes: (1) purely paroxysmal TN (paroxysmal pain only) and (2) TN with concomitant continuous pain. This has been described by neurosurgeons as type 1 and 2 TN[1,12].

Empirical evidence indicates that in a high number of patients, up to 95%, a major arterial blood vessel is pressing on the trigeminal nerve at a point where the cells producing myelin change from the peripheral to central type[13]. This demyelination can initiate a cross-circuit between those nerve fibres which relay light touch sensations and those which relay pain signals, the so called ignition hypothesis[14]. The nerve can become atrophic and deformed and that will lead to an intermittent but excruciating and debilitating pain. Numerous abnormalities regarding nerve functions have been found in patients with TN including abnormal sodium channels, nociceptive inhibitory pathways and possible inflammatory changes which can account for the idiopathic cases; though more research needs to be carried out establish the cause[15,16]. In TN secondary to MS the double-crush mechanism has been suggested; which includes the inflammatory demyelination as described above along with mechanical demyelination through plaque compression of the trigeminal root[17].

Table 1 Trigeminal autonomic cephalalgias (TACs), demographics and pain characteristics

	Cluster headache	Paroxysmal hemicranias	Hemicrania continua	Short-lasting unilateral neuralgiform headache
Demographics				
Age	27–31	34–41	30–40	40–70
Gender ratio (M: F)	4:1	1:1.6	1:2.8	1.5:1
Pain characteristics	Stabbing boring	Stabbing throbbing	Stabbing throbbing	Sharp stabbing
Location	Unilateral	Unilateral	Unilateral	Unilateral
	V1 predominates	V1	V1	V1-V2
	Maxillary areas	Some V2	Some V2	Fewer V3
Duration	15–180 min	2–30 min	Continuous	Seconds
				Minutes
Frequency	Alternate days up to max 8 per day	Five times or more per day		Single or series of episodes per day with no refractory period hundreds
Intensity	Severe	Moderate to severe	Moderate	Severe
Triggers	Alcohol	Sometimes alcohol		Light touch especially cold
	No cutaneous trigger			
Other features	Ptosis or miosis periorbital oedema facial sweating or redness conjunctival injection rhinorrhoea pacing or agitation	Ptosis or miosis, periorbital oedema facial sweating or redness conjunctival injection rhinorrhoea	Ptosis or miosis, periorbital oedema, facial sweating or redness, conjunctival injection, rhinorrhoea	Ptosis or miosis periorbital oedema facial sweating or redness conjunctival injection fullness of the ear keep still
Not all may be present, varying severity				

V1, ophthalmic division; V2, maxillary division; V3, mandibular division.

Regarding the TACs, the hypothalamus plays a key role in TACs by mediating nociceptive and autonomic responses; which is been supported by functional imaging studies[18–20] as well as animal studies[21].

Presentation and diagnosis

It might seem that the diagnostic criteria of TN as published in classification systems such as IASP make it easy to diagnose but there is increasing recognition that there are many variants and high-quality evidence-based studies are missing. Cruccu *et al*. have published a consensus on the diagnostic criteria and these are in line with the more detailed characteristics published by Maarbjerg *et al*[1,22,23]. Table 2 describes the main clinical features as well as patient description of the pain. The pain is triggered by innocuous sensory stimuli which includes light touch triggers such as washing the face, eating and wind[24].

Patients with TN will often first visit their dentist, because the pain commonly presents intra-orally and the patient is convinced that the cause is dental. TN occurs suddenly and often with great severity at its first presentation so many patients remember exactly what they were doing during their first attack, termed a memorable onset. Care needs to be taken to establish the exact timing of this episodic pain and drawing diagrams as shown in Figure 1 can be discussed with the patients and prove to be very helpful.

Patients with classical TN will opt for diagram one in Figure 1 but when severe it can be like number 2 where patients describe a series of stabs lasting seconds but in such quick succession that they can last for hours. Clinicians report that patients have a refractory period when pain cannot be triggered but this can be difficult to elicit. Patients will report that the start of eating is very difficult but there comes a moment when they can bolt down their food. It does not occur on the rebound as in cracked tooth. However, there can be an afterpain that is less severe and more burning as shown in Figure 1 number 3. This more prolonged pain has variously been termed TN with concomitant pain or type 2 TN, it often disappears completly[23]. Remission periods can last for months before the next relapse and are more likely at the start of the condition. However, these periods are

Table 2 Features of classical trigeminal neuralgia as described by clinicians and patients

Feature	Clinical feature	Patient description
Onset	Sudden and memorable	'Put a tomato in my mouth, and I might as well have sunk my teeth into bubbling electric acid. I did not know what was happening, except that an ongoing electric current was somehow switched on inside my mouth, left side of my gum area only, upper and lower'
Timing	Each attack lasts seconds to minutes	'The pain would last only for seconds.. but felt like an eternity'
Periodicity	Number per day can vary from 4–50, can get series of stabs Remission periods of weeks or years	'Within 30 min I had three jolts of pain each lasting 30–45 s' 'It would be with me for 3 months and then be gone for 3 months'
Site	Trigeminal nerve distribution, most common lower part of the face and intraoral	'One side of my face along my jaw around my ear or teeth'
Character	Shooting, sharp, electric	'shooting jolts of electricity directly into the raw nerves', 'sometimes just a twitch'
Severity	Severe	'the level 10 pain doubled me over the ground and I did not have control of my faculties. Imagine toothache, only 10 times worse'
Provoking factors	Light touch	'The wind caused me pain, even just touching my moustache gave me pain', 'when I ate or brushed my teeth'
Relieving factors	Keeping still medications	'It helped not to move my face at all'
Associated factors	May be some background dull aching pain Occasionally autonomic features Weight loss	'There would be a dull sensation after the pain subsided'
Impact	Depression, anxiety, decreased quality of life, fear	'Wanted to take my own life, but I looked at my husband who was desperately trying to help me fight this, yet feeling so useless and I had to hold on' 'I cannot carry as much responsibility as I used to because of how exhausting the pain is' 'I feel very isolated' 'The pain causes great fear of being out of control, and of course fear of the terrible pain'

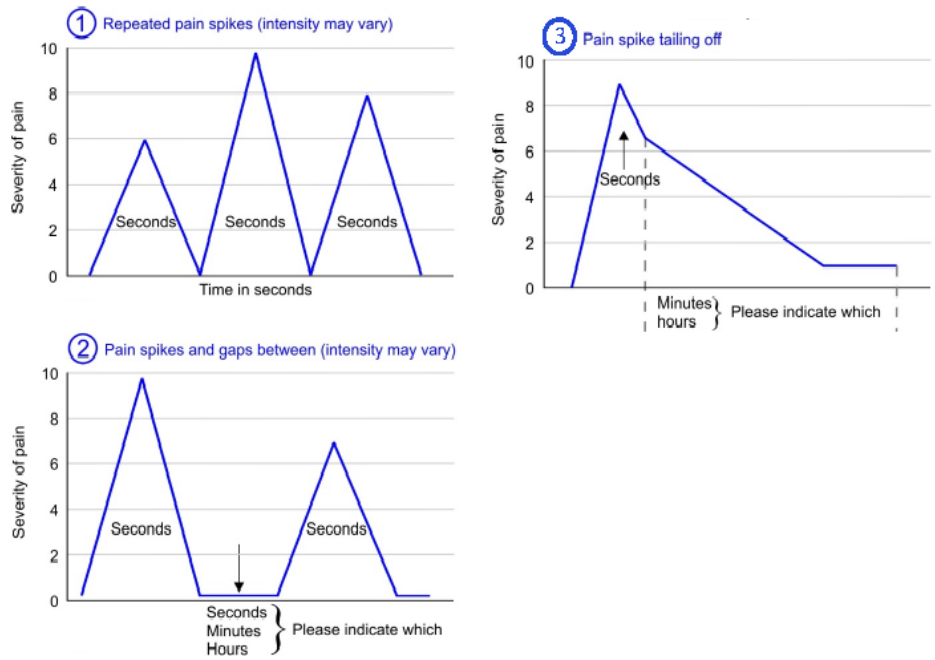

Figure 1 Timing of attacks, severity across time.

totally unpredictable and vary from patient to patient.

Pain severity is variable but during severe flare ups patients cannot eat even swallowing saliva can be difficult. This can lead to dehydration and significant weight loss.

Patients answer to the question 'How does it feel?' should elicit descriptions such as shooting, electrical, sharp, stabbing. Metaphors can be very helpful as illustrated in Table 2. Patients will report that sleep brings welcome relief except when going through a very severe bout. Autonomic symptoms such as described by patients with one of the TACs may be reported but are not present during each attack, more likely during longer lasting ones. Few patients with TN report other types of chronic pain. Some of the background aching pain may be due to unequal use of the muscles of mastication.

Witnessing an attack of pain during a consultation or when touching a trigger point can be diagnostic. Some patients may have an altered response to light touch and pin prick. Marked differences can sometimes be noted in oral hygiene on the affected side as well as a hesitancy to move the face or open the mouth.

As shown in Table 2 the impact on quality of life is significant and particularly notable with activities that involve the face (e.g. brushing teeth, eating, talking, touching the face, going out in cold windy weather). As many social activities involve eating patients become reluctant to attend these events and so this leads to isolation. The unpredictability of the condition leads to fear which is a major driver for more pain. As noted from epidemiological surveys and recent work in the UK patients score high on anxiety (>50%) and depression (>40%) on the Hospital Anxiety and Depression Scale and catastrophising as elicited on the Pain Catastrophising Scale is high (75%)[25]. Eight patients have committed suicide since 1996 as a result of TN, information from Trigeminal Neuralgia Association (TNA UK) and the national press. Patients take time off work during flare up periods.

Based on low evidence the EAN guidelines on TN suggest that there are no clinical characteristics to distinguish primary from secondary TN and magnetic resonance imaging (MRI) of the brain and brain stem is strongly recommended as part of the examination in TN patients[26]. Trigeminal reflex testing and evoked potentials will help to identify patients with different neuropathic pain[26].

Differential diagnosis

The initial diagnosis can be very challenging due to the short history of pain and the absence of remission periods; especially in patients with heavily restored dentition, where a dental cause of the pain

in much more common. A detailed history of the pain along with a thorough clinical and radiographic examination can help to establish the diagnosis. For example trigeminal neuropathic pain will be linked to a traumatic event be it dental or facial trauma and post-herpetic neuralgia will be associated with a history of previous herpes zoster and the pain is continuous.

Carbamazepine can be used as a diagnostic tool in the initial phases of the condition and it might result in complete pain relief. As we have mentioned above there is a strong link between multiple sclerosis (MS) and TN and although often the pain from MS is bilateral distinguishing between primary and secondary TN is challenging. Often MS presents first but it can be the other way round. TN is difficult to differentiate from glossopharyngeal neuralgia. Location and duration of pain are key factor for the diagnosis; for example: in glossopharyngeal neuralgia the pain is located either in the throat on swallowing or in the ear.

Temporal arteritis needs to be ruled out if the pain is centred over the temple region, is of longer duration and the patient is over 50 years old. An ESR and C reactive protein must be done as temporal arteritis can lead to blindness very rapidly.

It can take up to 4 years for a correct management plan to be adopted as patients go from one specialist to another as shown in Figure 2. Over 80% of patients would have been seen by at least one other specialist and around 30% by two or more specialists[25]. Patients perceive their pain to be dental and 70% will consult a dentist and unfortunately 8% can undergo unnecessary and irreversible dental treatment. Thus, the primary health care provider will often dictate which specialist centre is chosen. Even within the secondary care service patients may not be correctly allocated.

Investigations

Ruling out a dental cause of the pain is essential and radiographic examination might help with that. According to the 2019 guidelines from EAN MRI should be included in work-up for TN patients as there are no clinical elements that can determine the diagnosis of secondary TN. EAN guidelines also advise the use of combination of three high resolution sequences – 3D T2-weighted, 3D TOF-MRA and T1-Gad. In cases where an MRI is contraindicated for medical reasons or it is not available then trigeminal reflexes, which involves electrical stimulation of the divisions of the trigeminal nerve and measurement of the response with standard electromyography apparatus[1,27] or a CT can be used as an alternative to differentiate secondary from the primary TN. Further to that it is also suggested that the neuroradiologist should be blinded regarding the side

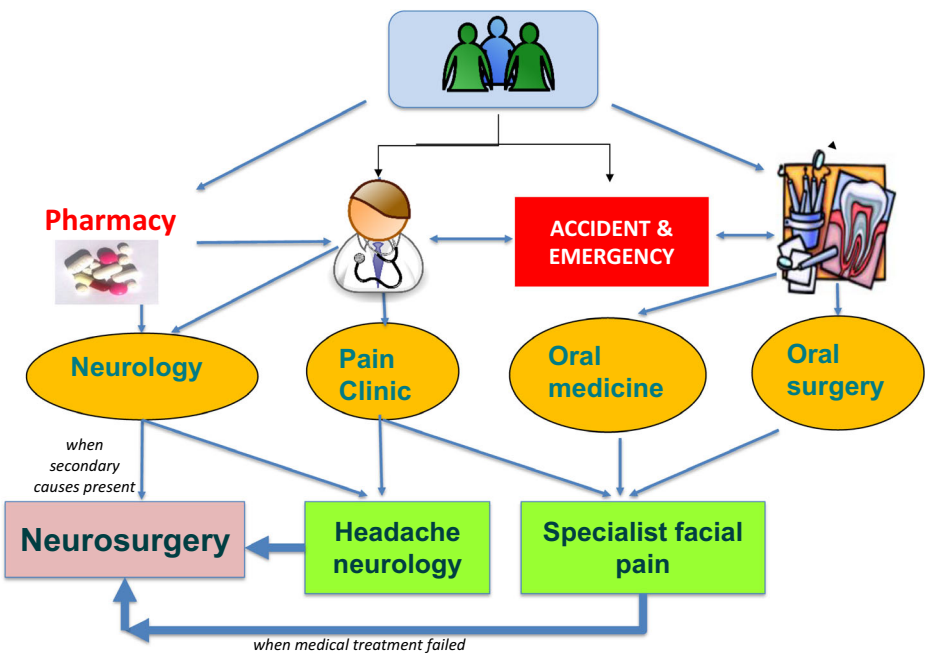

Figure 2 Pathways of referral for patients with trigeminal neuralgia.

of the pain and the report should describe not only the contact between vessel and nerve but also any possible morphological changes to the nerve[26].

Management

Due to lack of high-quality studies and the wide range of medical and surgical treatment options available it can be difficult to determine the most effective pathway[28]. The lack of standardise methods to evaluate treatment outcomes makes it impossible to compare treatments[29]. Another factor which should be taken into consideration is the difference level of pain reduction which is considered successful, for example a 50% reduction for medical management and a 100% pain relief from surgical procedures. Figure 3 illustrates the care pathway as used at UCLH NHS Foundation Trust which is based on a multidisciplinary approach and it is similar to that used by the neurologists in Denmark[30].

Pharmacological management (long term)

The analgesics including the opioids cannot provide sufficient pain relief and the drugs of choice for the long-term management of TN are the anti-epileptic drugs.

Carbamazepine (CBZ)

NICE guidelines recommend that CBZ should be the first line drug[31]. RCT's and systematic reviews have shown pain reduction is better when compared with placebo. However, side effects such as drowsiness, dizziness, rash, liver damage, cognitive impairment and ataxia as well as drug interactions make it a difficult drug to use. There is a 50% chance of treatment failure in the long-term (5-10 years) pain management with CBZ[26,32,33].

Oxcarbazepine

Oxcarbazepine (OXC) is effective for TN although there are no fully reported RCTs[34]. OXC is associated with adverse effects such as dizziness, cognitive impairment and sleepiness but fewer drug interactions due to lack of impact on the liver cytochrome system[34]. Clinical experience (EAN) strongly recommends the use of OXC for long-term treatment of TN[26].

Lamotrigine

Lamotrigine may result in fewer adverse effects than OXC and CBZ and it can be used as an alternative for patients who cannot tolerate OXC or CBZ or as

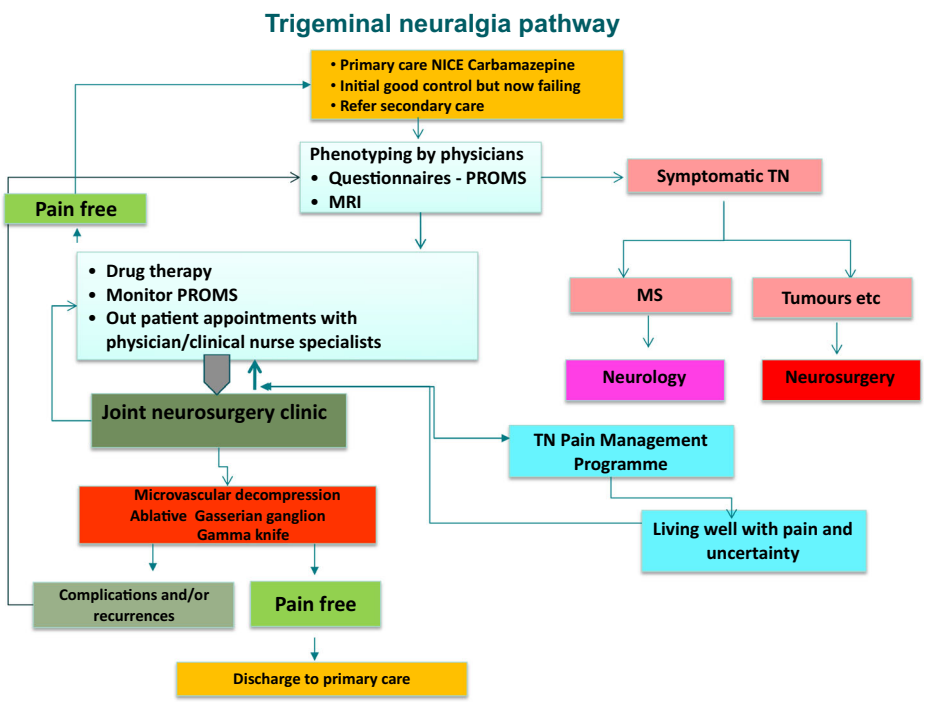

Figure 3 Care pathway for trigeminal neuralgia used at UCLH NHS Foundation Trust UK.

add-on therapy (EAN guidelines). In order to avoid side effects such as a rash the dose of lamotrigine should be increased very slowly which makes it less useful for the acute management of TN[35]. The risk of a Steven Johnson syndrome is increased if valproic acid is used concomitantly and it occurs within 1–3 weeks of use[35].

Gabapentin (GABA)

A systematic review[36] suggests that GABA has fewer side effects than CBZ but clinical experience suggests that GABA is less effective than CBZ in pain control. GABA can be used as an alternative for patients who cannot tolerate OXC or CBZ or as add-on treatment (EAN guidelines). It is now a controlled drug in the UK due to its potential for misuse and addiction.

Botulinum toxin type A (Botox)

There is limited evidence as well as lack of clinical experience with the use of Botox for TN therapy. There is only a weak recommendation for the use of Botox with TN patients according to EAN guidelines[26].

Other drugs

Other drugs are used such as pregabalin, baclofen, phenytoin and ropivacaine injections but there are no RCTs. A phase 2 study of a sodium 1.7 channel blocker is showing promise both in terms of efficacy and tolerability[25].

Surgical management

There are a variety of neurosurgical procedures that can be offered to patients who are finding difficulty with drug management, for example efficacy or tolerability. All the procedures except microvascular decompression (MVD) are destructive which means that they result in sensory changes and do not offer as long a period of pain relief. The destructive procedures are partial sensory rhizotomy (PSR) and internal neurolysis (both posterior fossa surgical procedures), stereotactic radiosurgery SRS (often Gamma Knife surgery), radiofrequency thermocoagulation (RFT), balloon compression (BC) and glycerol rhizolysis (GR). More peripheral procedures include cryotherapy, alcohol injections and peripheral neurectomy, there are now not recommended.

Comparisons between the techniques is difficult as the outcome measures are so variable and there are very few RCTs. It is expected that surgical techniques should result in 100% pain relief.

There are no RCTs comparing MVD with SRS but prospective and retrospective non-randomised studies showed better results for MVD versus SRS both in the medium- and long-term regarding pain-free status. Up to 70% of patients undergoing an MVD can expect to be pain free at 10 years[26].

All the other destructive procedures can be done as day cases or short overnight stays and can result in variable sensory loss. On average pain relief is for 4 years but the procedures can be repeated)[26].

Surgical complications

Microvascular decompression has the highest risk of mortality but this is low, 0.13–1.16[37]. Immediate complications include CSF leak, wound infections and hearing loss but there is no loss of sensation as the procedure is non-destructive. Long-term complications are most commonly reduced hearing and mild headaches. PSR and internal neurolysis result in similar complications to MVD but numbness and even anaesthesia dolorosa occurs as these are destructive procedure. All the other procedures result in varying sensory changes (Table 3).

Table 3 Surgical interventions and most common complications

Intervention	Mortality	Cerebral	Hearing loss	Corneal Hypaesth	V motor weakness	AD	Keratitis	CN palsy	CSF leak	Meningitis	HS	Sensory changes
MVD	X	X	X					X	X	X	X	
SRS				x		x	x	x				x
RFT				x		x	x	x				x
BC				x	x	x	x	x				x
GR				x		x	x	x				x
IN	x	x	x			x	x	x	x	x	x	x

AD, anaesthesia dolorosa; BC, balloon compression; CN, cranial nerve; CSF, cerebrospinal fluid; SRS, stereotactic radiosurgery surgery; GR, glycerol rhizolysis; HS, herpes simplex; IN, internal neurolysis; MVD, microvascular decompression; RFT, radiofrequency thermocoagulation; V, fifth cranial nerve; cerebral: oedema, haemorrhage, stroke.

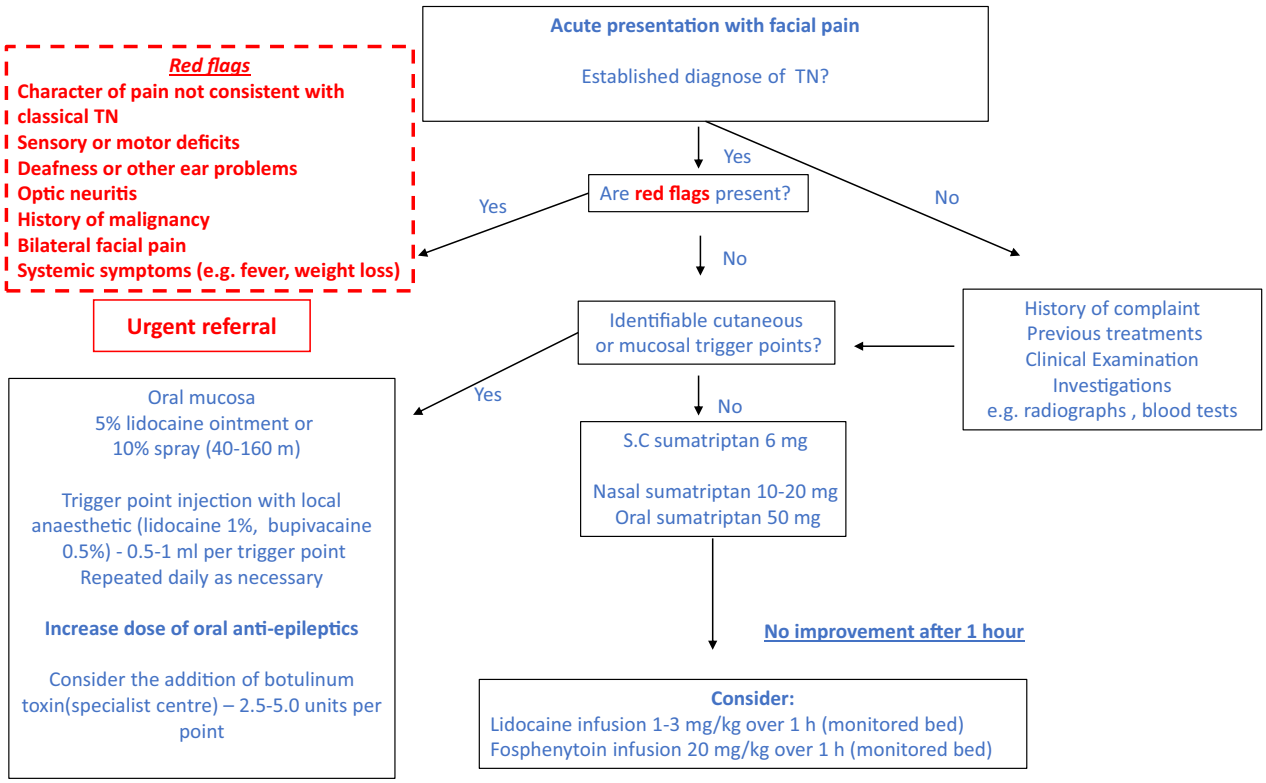

Figure 4 Algorithm for the acute management of trigeminal neuralgia.

The impact of the complications on patients' quality of life for all surgical treatments has been poorly assessed and the most significant impact is from anaesthesia dolorosa.

Patients need to be provided with better evidence-based information so they can make more effective decisions. Support groups for patients with TN provide a forum for both patients and health care professionals to exchange views and help to increase awareness among both the public and healthcare professionals[28]. Trigeminal Neuralgia Association UK is an example of such an organisation www.tna.org.uk. The Brain and Spine Foundation publish a useful booklet on facial pain which can be accessed from the internet. A preliminary pilot study has shown that providing support from clinical nurse specialists, psychologists and physiotherapists can improve outcomes and reduce fear and isolation.

Acute management

TN is a painful condition and although medical and surgical treatments are available for the long-term control; it is still often associated with flare-ups that can be very disruptive for patients' personal and professional life. Flare-up can lead to sick leave from work even to hospital admissions.

Unfortunately, there is low evidence regarding the effectiveness and the superiority of the acute treatments for TN. Although Moore *et al*. in their recent paper published an algorithm which could be used for the acute management[38] some of the medications used are not available in the UK. Figure 4 has been adapted to reflect availability of medications in the UK.

Lidocaine has been tried through local application (orally or nasally). Although it has a short duration it is the preferred anaesthetic agent due to less side effects regarding cardiac and neurological toxicity. It is believed to be effective for TN due to the fact that is a voltage-gated sodium channel blocker but it could also be due to its anti-inflammatory properties[39,40].

Injections of lidocaine, Marcaine into the different trigger points e.g. infraorbital, mental can be easily be performed by dentally trained staff and can be repeated daily till drug therapy becomes effective. This is a more useful option than opioids often given by emergency services. Lidocaine has been used IV as it can provide a neuromodulatory effect by

decreasing C-fibre transduction of pain signals and inhibition of ectopic discharges from damaging neurons, with no impact to the normal sensory function[41–43].

Apart from lidocaine, proparacain 0.5% eye drops has been used with promising results[38,41]. Other anaesthetics that have been injected to the trigger point or distal nerve branch are bupivacaine[44], ropivacaine with or without the use of GABA[45], tetracaine with or without lidocaine[46,47].

Other agents that have been used include MgSO4, Ketamine and dextromethorphan, but more evidence is required for their use. Botox has been reported in several RCTs but these are difficult to compare due to variation in methodology and use of outcome measures. Sumatriptan orally, intranasal, subcutaneous and rectally have also been proposed as they reduce neuroinflammation which may play a role in TN and are better tolerated in patients without cardia problems[48–52].

Case reports suggest success with phenytoin and its progdrug-fosphenytoin given as I.V under cardiac supervision.

Future directions

The pathophysiology as well as the prognosis of TN is still an enigma. The diagnostic criteria and the potential variants of TN need to be characterised better. More uniform agreed outcome measures are needed which include quality of life in order to improve comparisons between medical and surgical treatments. Newer drugs or re-purposed drugs are needed which would be equally effective but more tolerable. There is a need for prospective RCTs to compare different surgical treatments. Evidence-based care pathways which involve multidisciplinary teams are needed to ensure that personalised care can be provided for all patients.

Conclusions

Updated classifications have proposed that TN is divided into three categories: idiopathic, classical and secondary and two phenotypes: paroxysmal pain and concomitant continuous pain. The use of MRI is now recommended for the work up of TN patients. Medical treatment of TN should start with CBZ or OXC and if they fail due to side effects or poor pain control then surgical treatment should be considered as they are very effective. Patients need to be referred to specialist services as soon as the first-line drug CBZ fails (NICE guidelines)[31].

Acknowledgements

This work was undertaken by JZ at UCL/UCLHT who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centre funding scheme.

References

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalagia 2018;38:1–211.
2. Katusic S, Beard CM, Bergstralh E, Kurland LT. Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945–1984. Ann Neurol 1990;27:89–95.
3. Hall GC, Carroll D, Parry D, McQuay HJ. Epidemiology and treatment of neuropathic pain: the UK primary care perspective. Pain 2006;122:156–62.
4. Koopman JS, Dieleman JP, Huygen FJ, de Mos M, Martin CGM, Sturkenboom MCJM. Incidence of facial pain in the general population. Pain 2009;147:122–7.
5. Mueller D, Obermann M, Yoon MS, Poitz F, Hansen N, Slomke MA *et al*. Prevalence of trigeminal neuralgia and persistent idiopathic facial pain: a population-based study. Cephalalgia 2011;31:1542–8.
6. Wu J, Brathwaite TS. A systematic review of the management of trigeminal neuralgia in patients with multiple sclerosis. World Neurosurg 2018;111:291–306.
7. Pan SL, Chen LS, Yen MF, Chiu YH, Chen HH. Increased risk of stroke after trigeminal neuralgia–a population-based follow-up study. Cephalalgia 2011;31:937–42.
8. Pan SL, Yen MF, Chiu YH, Chen LS, Chen HH. Increased risk of trigeminal neuralgia after hypertension: a population-based study. Neurology 2011;77:1605–10.
9. Wu TH, Hu LY, Lu T, Chen PM, Chen HJ, Shen CC *et al*. Risk of psychiatric disorders following trigeminal neuralgia: a nationwide population-based retrospective cohort study. J Headache Pain 2015;16: https://doi.org/10.1186/s10194-015-0548-y.
10. Khawaja S, Scrivani S. Trigeminal autonomic cephalalgia and facial pain: a review and case presentation. J Oral Facial Pain Headache 2019;33:e1–e7. https://doi.org/10.11607/ofph.2143.
11. Karrisa NA, Halker RB. SUNCT and SUNA: an update and review. Curr Pain Headache Rep 2018;22:56.
12. Cruccu G, Finnerup NB, Jensen TS, Scholz J, Sindou M, Svensson P *et al*. Trigeminal neuralgia: new

classification and diagnostic grading for practice and research. Neurology 2016;87:220–8.
13. Maarbjerg S, Wolfram F, Gozalov A, Olesen J, Bendtsen L. Association between neurovascular contact and clinical characteristics in classical trigeminal neuralgia: a prospective clinical study using 3.0 Tesla MRI. Cephalalgia 2015;35:1077–84.
14. Devor M, Amir R, Rappaport ZH. Pathophysiology of trigeminal neuralgia: the ignition hypothesis. Clin J Pain 2002;18:4–13.
15. Moisset X, Villain N, Ducreux D, Serrie A, Cunin G, Valade D *et al*. Functional brain imaging of trigeminal neuralgia. Eur J Pain 2011;15:124–31.
16. Hung PS, Chen DQ, Davis KD, Zhong J, Hodaie M. Predicting pain relief: use of pre-surgical trigeminal nerve diffusion metrics in trigeminal neuralgia. Neuroimage Clin 2017;15:710–8.
17. Di Stefano G, Maarbjerg S, Truini A. Trigeminal neuralgia secondary to multiple sclerosis: from the clinical picture to the treatment options. J Headache Pain 2019;20:20.
18. May A, Bahra A, Buechel C, Frackowiak R, Goadsby P. Hypothalamic activation in cluster headache attacks. Lancet 1998;352:275–8.
19. Matharu Cohen A, McGonigle D, Ward N, Frackwoak R, Goadsby P. Posterior hypothalamic and brainstem activation in hemicrania continua. Headache 2004;44:747–61.
20. Matharu M, Cohen A, Frackowiak R, Goadsby P. Posterior hypothalamic activation in paroxysmal hemicrania. Ann Neurol 2006;59:535–45.
21. Cohen A. SUN: short-lasting unilateral neuralgiform headache attacks. Headache 2017;56:1010–20.
22. Maarbjerg S, Gozalov A, Olesen J, Bendtsen L. Trigeminal neuralgia–a prospective systematic study of clinical characteristics in 158 patients. Headache 2014;54:1574–82.
23. Maarbjerg S, Gozalov A, Olesen J, Bendtsen L. Concomitant persistent pain in classical trigeminal neuralgia–evidence for different subtypes. Headache 2014;54:1173–83.
24. Maarbjerg S, Di Stefano G, Bendtsen L, Cruccu G. Trigeminal neuralgia - diagnosis and treatment. Cephalalgia 2017;37:648–57.
25. Zakrzewska JM, Wu J, Mon-Williams M, Phillips N, Pavitt SH. Evaluating the impact of trigeminal neuralgia. Pain 2017;158:1166–74.
26. Bendtsen JM, Zakrzewska JA, Braschinsky M, Di Stefano G, Donnet A, Eide PK *et al*. European Academy of Neurology guideline on trigeminal neuralgia. Eur J Neurol 2019;1–19.
27. Cruccu G, Biasiotta A, Galeotti F, Iannetti GD, Truini A, Gronseth G. Diagnostic accuracy of trigeminal reflex testing in trigeminal neuralgia. Neurology 2006;66:139–41.
28. Zakrzewska JM, Linskey ME. Trigeminal neuralgia. BMJ 2014;348:g474.
29. Cruccu G, Gronseth G, Alksne J, Argoff C, Brainin M, Burchiel K *et al*. AAN-EFNS guidelines on trigeminal neuralgia management. Eur J Neurol 2008;15:1013–28.
30. Heinskou T, Maarbjerg S, Rochat P, Wolfram F, Jensen RH, Bendtsen L. Trigeminal neuralgia–a coherent cross-specialty management program. J Headache Pain 2015;16:66.
31. NICE. Neuropathic Pain: The Pharmacological Management of Neuropathic Pain in Adults in Non-specialist Settings Guideline. London: NICE. 2013;173:1–41.
32. Rasmussen P, Riishede J. Facial pain treated with carbamazepine in trigeminal neuralgia. Arch Neurol Sacand 1970;46:385–408.
33. Taylor JC, Brauer S, Espir ML. Long-term treatment of trigeminal neuralgia with carbamazepine. Postgrad Med J 1981;57:16–8.
34. Besi E, Boniface DR, Cregg R, Zakrzewska JM. Comparison of tolerability and adverse symptoms in oxcarbazapine and carbamazepine in the treatment of trigeminal neuralgia and neuralgiform headches using the Liverpool Adverse Events Profile (AEP). J Headache Pain 2015;16:563.
35. Wang XQ, Lv B, Wang HF, Zhang X, Yu SY, Huang XS *et al*. Lamotrigine-induced cutaneous adverse reaction: update data from 1999–2014. J Clin Neurosci 2015;22:1005–11.
36. Yuan M, Zhou HY, Xiao ZL, Wang W, Li X-L, Chen S-J *et al*. Efficacy and safety of gabapentin vs carbamazepine in the treatment of trigeminal neuralgia: a meta-analysis. Pain Pract 2016;16:1083–91.
37. Zakrzewska JM, Coakham HB. Microvascular decompression for trigeminal neuralgia: update. Curr Opin Neurol 2012;25:296–301.
38. Moore D, Chong MS, Shetty A, Zakrzewska JM. A systematic review of rescue analgesic strategies in acute exacerbations of primary trigeminal neuralgia. Br J Anaesth 2019;123:e385–96.
39. Niki Y, Kanai A, Hoshi K, Okamoto H. Immediate analgesic effect of 8% lidocaine applied to the oral mucosa in patients with trigeminal neuralgia. Pain Med 2014;15:826–31.
40. Kanai A, Suzuki A, Kobayashi M, Hoka S. Intranasal lidocaine *% spray for second-division trigeminal neuralgia. Br J Anaesth 2006;97:559–63.
41. Galer BS, Miller KV, Rowbotham MC. Response to intravenous lidocaine infusion differs based on clinical diagnosis and site of nervous system injury. Neurology 1993;43:1233–5.
42. Chaudhry P, Froedman DI. Intravenous lidocaine treatment in classical trigeminal neuralgia with

concomitant persistent facial pain. Headache 2014;54:1376–9.
43. Stavropoulou E, Argyra E, Zis P, Vadalouca A, Siafaka I. The effect of intravenous lidocaine on trigeminal neuralgia: a randomized double blind placebo controlled trial. ISRN Pain 2014;2014:853826.
44. Dergin G, Gorcmen G, Sener BC. Treatment of trigeminal neuralgia with bupivacaine HCL using a temporary epidural catheter and pain pump: preliminary study. J Craniomaxillofac Surg 2012;40:124–8.
45. Lemos L, Flores S, Oliveira P, Almeida A. Gabapentin supplemented with ropivacain block of trigger points improves pain control and quality of life in trigeminal neuralgia patients when compared with gabapentin alone. Clin J Pain 2008;24:64–75.
46. Goto F, Ishizaki K, Yoshikawa D, Obata H, Arii H, Terada M. The long lasting effects of perioheral nerve blocks for trigeminal neuralgia using high concentration of tetracaine dissolved in bupivacaine. Pain 1999;79:101–3.
47. Radwan IA, Saito S, Goto F. High- concentration tetracaine for the management of trigeminal neuralgia: quantitative assessment of sensory function after peripheral nerve block. Clin J Pain 2001;17:323–6.
48. Yousef AA, Al-deeb AE. A double-blinded randomised controlled study of the value of sequential intravenous and oral magnesium therapy in patients with chronic low back pain with a neuropathic component. Anaesthesia 2013;68:260–6.
49. Mathisen LC, Skjebred P, Skoglund LA, Øye I. Effect of ketamine an NMDA receptor inhibitor, in acute and chronic orofacial pain. Pain 1995;61:215–20.
50. Gilron I, Booher SL, Rowan MS, Smoller MS, Max MB. A randomized, controlled trial of high-dose dextromethorphan in facial neuralgias. Neurology 2000;55:964–71.
51. Shimohata K, Shimohata T, Motegi R, Miyashita K. Nasal sumatriptan as adjunctive therapy for idiopathic trigeminal neuralgia: report of three cases. Headache 2009;49:768–70.
52. Kanai A, Suzuki A, Osawa S, Hoka S. Sumatriptan alleviates pain in patients with trigeminal neuralgia. Clin J Pain 2006;22:677–80.