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Trigeminal neuralgia

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ABSTRACT

INTRODUCTION: Trigeminal neuralgia is a sudden, unilateral, brief, stabbing, recurrent pain in the distribution of one or more branches of the fifth cranial nerve. Pain occurs in paroxysms, which can last from a few seconds to several minutes. The frequency of the paroxysms ranges from a few to hundreds of attacks a day. Periods of remission can last for months to years, but tend to shorten over time. The condition can impair activities of daily living and lead to depression. **METHODS AND OUTCOMES:** We conducted a systematic review and aimed to answer the following clinical question: What are the effects of ongoing treatments in people with trigeminal neuralgia? We searched: Medline, Embase, The Cochrane Library, and other important databases up to September 2013 (BMJ Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). **RESULTS:** We found seven studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. **CONCLUSIONS:** In this systematic review, we present information relating to the effectiveness and safety of the following interventions: baclofen; carbamazepine; gabapentin; lamotrigine; oxcarbazepine; microvascular decompression; and destructive neurosurgical techniques (radiofrequency thermocoagulation, glycerol rhizolysis, balloon compression, and stereotactic radiosurgery).

QUESTIONS

What are the effects of ongoing treatments in people with trigeminal neuralgia? 4

INTERVENTIONS

TREATMENTS

Likely to be beneficial

Carbamazepine 4

Oxcarbazepine* 7

Baclofen (in people with multiple sclerosis who develop trigeminal neuralgia)* 10

Trade off between benefits and harms

Microvascular decompression* 11

Non-percutaneous destructive neurosurgical techniques (stereotactic radiosurgery)* 12

Percutaneous destructive neurosurgical techniques (radiofrequency thermocoagulation, glycerol rhizolysis, or balloon compression)* 13

Unknown effectiveness

Lamotrigine 8

Gabapentin 10

Footnote

*Categorisation based on observational studies and/or consensus.

Key points

- Trigeminal neuralgia is a sudden, unilateral, brief, stabbing, recurrent pain in the distribution of one or more branches of the fifth cranial nerve. The diagnosis is made on the history alone, based on characteristic features of the pain.
 - Pain occurs in paroxysms, which can last from a few seconds to several minutes. The frequency of the paroxysms ranges from a few to hundreds of attacks a day.
 - Periods of remission can last for months to years, but tend to get shorter over time.
 - The condition can impair activities of daily living and lead to depression.
 - The annual incidence in the UK (based on GP practice lists and rather liberal diagnostic criteria) has been reported to be 26.8 per 100,000. However, studies in other countries such as the US and the Netherlands, with stricter definitions, have reported much lower incidence rates ranging between 5.9 and 12.6 per 100,000.
 - Experts find that symptoms worsen over time and become less responsive to medication despite dose increases and adding further agents.
- Treatment success is defined differently in studies of medical and surgical therapies for trigeminal neuralgia.
 - Treatment success in medical studies is usually defined as at least 50% pain relief from baseline. However, complete pain relief is the measure of treatment success in surgical studies.
- **Carbamazepine** is considered the gold-standard for the initial medical treatment of trigeminal neuralgia symptoms.
 - Carbamazepine has been shown to increase pain relief compared with placebo, but also increases adverse effects, such as drowsiness, dizziness, rash, liver damage, and ataxia.
 - Studies evaluating durability of response with carbamazepine are lacking, but consensus expert opinion suggests that it may have a greater than 50% failure rate for long-term (5-10 year) pain control.
 - Based on the strength of published evidence, carbamazepine remains the best supported standard medical treatment for trigeminal neuralgia.

- There is consensus that [oxcarbazepine](#) is an effective treatment in people with trigeminal neuralgia and may have fewer adverse effects than carbamazepine, although there is a lack of RCT-based data to confirm this.

Oxcarbazepine rarely provides complete or long-term pain relief, although studies evaluating durability of response with this drug are lacking.
- We found no sufficient evidence to judge the effectiveness of [baclofen](#) or [lamotrigine](#).

Lamotrigine is often used in people who cannot tolerate carbamazepine, but the dose must be increased slowly to avoid rashes, thus making it unsuitable for acute use.

There is consensus that baclofen may be useful for people with multiple sclerosis who develop trigeminal neuralgia.
- We found no evidence comparing [gabapentin](#) versus placebo/no treatment or other treatments covered in this review in people with trigeminal neuralgia.

Gabapentin does have support for use in treating other neuropathic pain conditions, particularly multiple sclerosis.
- Despite a lack of RCT data, observational evidence supports the use of [microvascular decompression](#) to relieve symptoms of trigeminal neuralgia.

[Microvascular decompression](#) has been shown in at least two prospective comparative cohort trials to have superiority over [stereotactic radiosurgery](#) for complete pain relief, durability of response (up to 5 years), and preservation of trigeminal sensation.

However, microvascular decompression requires general anaesthesia and can, albeit rarely, be associated with surgical complications, of which a less than 5% risk of ipsilateral hearing loss appears to be the most common.

Well-conducted observational studies have demonstrated that microvascular decompression has a greater magnitude of therapeutic effect than any medical and surgical therapy for trigeminal neuralgia. As such, this procedure is unlikely to be compared against best medical therapy in an RCT.
- We found no RCT evidence comparing [percutaneous destructive neurosurgical techniques](#) (radiofrequency thermocoagulation, [glycerol rhizolysis](#), [balloon compression](#)) or [non-percutaneous destructive neurosurgical techniques](#) (stereotactic radiosurgery) versus placebo/no treatment or other treatments covered in this review in people with trigeminal neuralgia.

Observational data suggest that [radiofrequency thermocoagulation](#) may offer higher rates of complete pain relief than glycerol rhizolysis and stereotactic radiosurgery, but may also be associated with higher rates of complications (e.g., facial numbness and corneal insensitivity).

In contrast to stereotactic radiosurgery, pain relief with microvascular decompression and percutaneous destructive neurosurgical techniques is immediate, but they require sedation and/or anaesthesia to perform, which are not required for stereotactic radiosurgery.

Clinical context

GENERAL BACKGROUND

Trigeminal neuralgia is a rare condition that causes excruciating intermittent, short-lasting facial pain that is usually unilateral, is typically provoked by light touch, and is often mistaken initially as a tooth pain. First-line treatment involves anticonvulsant drugs, generally carbamazepine or oxcarbazepine, but other agents are also used. These drugs can provide significant initial pain relief, but with time response becomes poorer despite escalating doses. Side effects also increase significantly. Patients may then be referred for surgery or treated with second-line medications, although there is little or no evidence to guide these choices.

FOCUS OF THE REVIEW

Trigeminal neuralgia can be managed both medically and surgically with varying outcomes. This review identifies the clinical trial evidence supporting the use of the first-line medical options and the surgical treatments for classical idiopathic trigeminal neuralgia. There are RCTs supporting use of anticonvulsants such as carbamazepine and oxcarbazepine, which provide 50% pain relief in 70% of patients. Surgery can provide 100% pain relief with no further need for medication but there are no RCTs of microvascular decompression, potentially the most effective management, and other surgical procedures have been evaluated only in RCTs comparing techniques, and as such are very limited.

COMMENTS ON EVIDENCE

The most effective drugs are anticonvulsants, but design of drug trials is complicated because the gold-standard drug, carbamazepine, takes up to 3 weeks to be fully eliminated, and the disease is so severe that it is unethical to use a placebo. New designs are, therefore, needed and are being attempted. There are no randomised controlled trials comparing surgical options, and very few comparing technical variations of single techniques. The best surgical data are from prospective comparative cohort trials. Moreover, the disease can suddenly become extremely severe with longer-lasting bouts of pain, and there are no studies on how this should be managed. Given the difficulties in-

herent in conducting trials for both medical and surgical treatments, the evidence remains sparse, especially for the surgical therapies.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this review was carried out from the date of the last search, September 2007, to September 2013. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the review, please see the Methods section. Searching of electronic databases retrieved 170 studies. After deduplication and removal of conference abstracts, 75 records were screened for inclusion in the review. Appraisal of titles and abstracts led to the exclusion of 54 studies and the further review of 21 full publications. Of the 21 full articles evaluated, two systematic reviews were added at this update. Based upon their own search, the contributors added two additional observational studies to the Comment section.

ADDITIONAL INFORMATION

Ideally, patients benefit from surgical evaluation and counselling early in the disease process, so that appropriate contingency plans among varying surgical alternatives can be considered and decided upon before high-dose drug therapy interferes with cognition and memory, and before severe pain leads to time-urgent desperation. Acute severe attacks should be managed with lidocaine injections or infusions rather than opioids, which are ineffective.

DEFINITION

Trigeminal neuralgia is a characteristic pain in the distribution of one or more branches of the fifth cranial nerve. The diagnosis is made on the history alone, based on characteristic features of the pain.^{[1] [2] [3]} It occurs in paroxysms, with each pain lasting from a few seconds to several minutes. The frequency of paroxysms is highly variable, ranging from hundreds of attacks a day to long periods of remission that can last years. Between paroxysms, the person is asymptomatic. The pain is severe and described as intense, sharp, superficial, stabbing, or shooting — often like an electric shock. It can be triggered by light touch in any area innervated by the trigeminal nerve, including eating, talking, washing the face, or cleaning the teeth. The condition can impair activities of daily living and lead to depression.^{[4] [5]} In some people there remains a background pain of lower intensity for 50% of the time. This has been termed atypical trigeminal neuralgia or type 2 trigeminal neuralgia. The International Classification for Headache Disorders (ICHD) refers to this condition as trigeminal neuralgia with concomitant pain.^[1] Other causes of facial pain may need to be excluded.^{[1] [2] [3]} In trigeminal neuralgia, the neurological examination is usually normal but sensory and autonomic symptoms may be reported,^{[1] [2] [3]} and people with longer histories may demonstrate subtle sensory loss on careful examination.

INCIDENCE/ PREVALENCE

Most evidence about the incidence and prevalence of trigeminal neuralgia is from the US.^[6] The annual incidence (age adjusted to the 1980 age distribution of the US) is 5.9/100,000 women and 3.4/100,000 men. The incidence tends to be slightly higher in women at all ages, and increases with age. In men aged over 80 years, the incidence is 45.2/100,000.^[7] One questionnaire survey of neurological disease in one French village found one person with trigeminal neuralgia among 993 people.^[8] A retrospective cohort study in UK primary care, which examined the histories of 6.8 million people, found that 8268 people had trigeminal neuralgia, giving it an incidence of 26.8/100,000 person-years.^[9] A similar primary care study carried out in the Netherlands reported an incidence of 12.6/100,000 person-years when trained neurologists reviewed the data.^[10] A population-based study in Germany reported a lifetime prevalence of 0.3%.^[11]

AETIOLOGY/ RISK FACTORS

The cause of trigeminal neuralgia remains unclear but the most common hypothesis is that of the ignition theory.^{[12] [13]} More peripheral and central mechanisms may be involved,^[14] and trigeminal nerve microstructure may be altered.^[15] It is more common in people with multiple sclerosis (RR 20.0, 95% CI 4.1 to 59.0) and stroke.^[7] Hypertension is a risk factor in women (RR 2.1, 95% CI 1.2 to 3.4), but the evidence is less clear for men (RR 1.53, 95% CI 0.30 to 4.50).^{[7] [16] [17]}

PROGNOSIS

One retrospective cohort study found no reduction in 10-year survival in people with trigeminal neuralgia.^[18] We found no evidence about the natural history of trigeminal neuralgia. However, the TNA Facial Pain Association continues to periodically receive individual isolated reports of people with trigeminal neuralgia who either die from overdose of medications, take their own life, or both. The illness is characterised by recurrences and remissions. Many people have periods of remission with no pain lasting months or years.^[13] At least 50% of people with trigeminal neuralgia will have remissions lasting at least 6 months in duration.^[19] Collective expert experience suggest that, in many people, trigeminal neuralgia becomes more severe and less responsive to treatment over time, despite increasing medication doses and adding additional agents.^[20] Most people with trigeminal neuralgia are initially managed medically, and a proportion eventually have a surgical procedure.^[13] We found no good evidence about the proportion of people who require surgical treatment for pain control. Anecdotal evidence indicates that pain relief is better after surgery than

with medical treatment.^[13] ^[20] Furthermore, responses from a questionnaire taken by people who had surgery for trigeminal neuralgia indicated that the majority of respondents wished they had surgery earlier.^[21]

AIMS OF INTERVENTION	To relieve pain, with minimal adverse effects.
OUTCOMES	Pain relief: pain frequency and severity scores; psychological distress; ability to perform normal activities; adverse effects.
METHODS	<p><i>Clinical Evidence</i> search and appraisal September 2013. The following databases were used to identify studies for this systematic review: Medline 1966 to September 2013, Embase 1980 to September 2013, and The Cochrane Database of Systematic Reviews 2013, issue 8 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. An information specialist identified the titles and abstracts in an initial search, which an evidence scanner then assessed against predefined criteria. An evidence analyst then assessed full texts for potentially relevant studies against predefined criteria. An expert contributor was consulted on studies selected for inclusion. An evidence analyst then extracted all data relevant to the review. Study design criteria for inclusion in this review were: published systematic reviews and RCTs, at least single-blinded and containing more than 10 individuals, of whom more than 80% were followed up. There was no minimum length of follow-up. We included systematic reviews and RCTs where harms on an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are continually added to the review as required. The contributors have also used results from their own database, collated from 1990 to September 2007, which includes case series reports; further studies after this date have been added to the Comment sections. As <i>Clinical Evidence</i> was unable to perform a second appraisal of results retrieved by the contributor's search, we may have missed studies that could affect our overall assessment of the interventions in this review. As <i>Clinical Evidence</i> reports only systematic reviews and RCTs, studies from the additional searches that did not meet this criteria (e.g., case series reports) are reported in the Comment sections, and not the Benefits and Harms tables of this review. Trigeminal neuralgia is a very painful condition and, therefore, placebo-controlled trials are considered unethical. Trials using active controls have important limitations. The gold-standard drug for treating trigeminal neuralgia is carbamazepine, but it is difficult to be sure that its effects have been totally eliminated before crossover when compared with other drug treatments in trials with crossover designs. This is because carbamazepine alters liver enzymes, and reversal of this takes about 3 weeks. The choice of active control is limited because few drugs have been subjected to high-quality trials. An enhanced, enriched, randomised control trial has been suggested as a method of overcoming these obstacles.^[22] Another limitation of trigeminal neuralgia trials is that outcomes for treatment success differ for medical (drug) therapies and surgical interventions. For example, treatment success in medical studies is usually defined as at least 50% pain relief from baseline. However, complete pain relief is the measure of treatment success in surgical studies. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as RRs and ORs. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 18). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).</p>

QUESTION What are the effects of ongoing treatments in people with trigeminal neuralgia?

OPTION CARBAMAZEPINE

- For GRADE evaluation of interventions for Trigeminal neuralgia, see table, p 18 .
- Carbamazepine is considered the gold-standard for the initial medical treatment of trigeminal neuralgia symptoms.
- Carbamazepine has been shown to increase pain relief compared with placebo, but also increases adverse effects, such as drowsiness, dizziness, rash, liver damage, and ataxia.

- Although studies evaluating durability of response with carbamazepine are lacking, consensus expert opinion suggests that it may have a greater than 50% failure rate for long-term (5-10 years) pain control.
- Based on the strength of published evidence, carbamazepine remains the best supported standard medical treatment for trigeminal neuralgia.

Benefits and harms

Carbamazepine versus placebo:

We found one systematic review (search date 2010), which identified three crossover RCTs.^[23] We found another systematic review (search date 1994), which examined the number of people who withdrew from RCTs of carbamazepine versus placebo because of adverse effects.^[24]

Pain relief

Carbamazepine compared with placebo Carbamazepine for 5 to 14 days seems to be more effective at relieving pain compared with placebo (*moderate-quality evidence*).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain improvement					
^[23] Systematic review	208 people with trigeminal neuralgia 3 RCTs in this analysis RCTs were crossover design	Any pain improvement , 5–14 days 80/102 (78%) with carbamazepine 14/106 (13%) with placebo	RR 5.87 95% CI 3.58 to 9.61 P <0.00001 NNT 2 95% CI 1 to 2		carbamazepine

No data from the following reference on this outcome.^[24]

Psychological distress

No data from the following reference on this outcome.^[23] ^[24]

Ability to perform normal activities

No data from the following reference on this outcome.^[23] ^[24]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
^[23] Systematic review	154 people with trigeminal neuralgia 2 RCTs in this analysis RCTs were crossover design	Death with carbamazepine with placebo 1 RCT reported 4 deaths in those taking carbamazepine (2 with presumed cardiovascular problems, 1 frontal lobe glioblastoma, and 1 of progressive generalised debilitating disease), another RCT reported 1 death with carba-	Significance not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		mazepine, which was associated with a cardiovascular condition; the review did not report whether any deaths occurred in the placebo group			
[23] Systematic review	164 people with trigeminal neuralgia 2 RCTs in this analysis RCTs were crossover design	Adverse effects with carbamazepine with placebo 1 RCT reported dizziness and some drowsiness in 47% of those taking carbamazepine (absolute numbers not reported), Another RCT reported rash in 3 people taking carbamazepine; the review did not report whether any adverse effects occurred in the placebo group	Significance not reported		
[24] Systematic review	People with trigeminal neuralgia	Adverse effects with carbamazepine with placebo Significantly more people taking carbamazepine than placebo withdrew from the RCTs because of adverse effects	NNH for withdrawal 24 95% CI 14 to 112	○ ○ ○	placebo

Carbamazepine versus oxcarbazepine:

See option on Oxcarbazepine, p 7 .

Carbamazepine versus baclofen:

See option on Baclofen, p 10 .

Further information on studies

[23] All the RCTs were small and short-term, used simple measures for pain outcomes, and reported no quality-of-life outcomes. In addition, diagnostic criteria were not clearly stated, and previous treatment and duration of pain varied considerably.

Comment:

As *Clinical Evidence* was unable to perform a second appraisal of results retrieved by the contributor's search, we may have missed studies that could affect our overall assessment of this intervention.

Clinical guide:

We found one retrospective cohort study comparing long-term carbamazepine treatment versus stopping carbamazepine earlier. [25] The study did not show carbamazepine treatment to be beneficial in the long term (5–16 years) in people with trigeminal neuralgia. In another retrospective study of 178 people with classical trigeminal neuralgia receiving either carbamazepine or oxcarbazepine, with a mean follow-up of only 13 months, 2% of people taking carbamazepine failed to initially respond, and 27% of responders had adverse effects which either led to treatment interruption or dose reduction and subsequent discontinuation. After a mean follow-up of 13 months, 6% of

people taking oxcarbazepine failed to initially respond, and 18% of responders discontinued owing to adverse effects. [26] While durability of response with carbamazepine has been poorly studied, consensus expert opinion suggests that it may have a greater than 50% long-term (5-10 years) failure rate for pain control. [25]

Adverse effects associated with carbamazepine treatment that are not mentioned in the Benefits and Harms table but have been described in observational studies include constipation, leucopenia, and abnormal liver function tests. [26] [27]

Most clinicians believe that carbamazepine is the first-line medical treatment for trigeminal neuralgia. It has been widely advocated for use in primary care. [28] The National Institute for Health and Care Excellence (NICE) has published recommendations that state that carbamazepine should be offered as the initial pharmacological treatment for trigeminal neuralgia. [29] Clinicians should start or stop treatment by changing the dose in increments over several days to reduce common adverse effects. After starting treatment, a dose adjustment is often necessary at about 3 weeks owing to induction of liver enzymes. As carbamazepine is an enzyme inducer, NICE recommends a full blood count, measurements of electrolytes, liver enzymes, and vitamin D levels, and other tests of bone metabolism (e.g., serum calcium and alkaline phosphatase) every 2 to 5 years in those taking this drug. [30]

Drug safety alert:

(2008, carbamazepine) — Carbamazepine is associated with a risk of potentially life-threatening skin reactions, including Stevens-Johnson syndrome. The risk of carbamazepine-induced Stevens-Johnson syndrome is greater in people with the allele *HLA-B*1502*. The frequency of this allele varies worldwide and is highest in some Asian populations. Individuals of Han Chinese, Hong Kong Chinese, or Thai origin should be screened for *HLA-B*1502* before starting treatment with carbamazepine. [31] Those who test positive for *HLA-B*1502* should not start carbamazepine treatment unless the benefits clearly outweigh the risk of Stevens-Johnson syndrome. [32]

OPTION OXCARBAZEPINE

- For GRADE evaluation of interventions for Trigeminal neuralgia, see table, p 18 .
- There is consensus that oxcarbazepine is an effective treatment in people with trigeminal neuralgia and may have fewer side effects than carbamazepine, although there is a lack of RCT-based data to confirm this.
- Oxcarbazepine rarely provides complete or long-term pain relief, although studies evaluating durability of response with this drug are lacking.
- It is the first-line medical treatment for trigeminal neuralgia in Scandinavian countries and it is regularly used as a second-line medical treatment after carbamazepine in the UK and North America.

Benefits and harms

Oxcarbazepine versus carbamazepine:

We found one small RCT comparing oxcarbazepine with carbamazepine in people with classical trigeminal neuralgia. [33]

Pain relief

Oxcarbazepine compared with carbamazepine We don't know how oxcarbazepine and carbamazepine compare at relieving pain after 4 to 6 weeks of treatment in people with classical trigeminal neuralgia (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[33] RCT	48 people with classical trigeminal neuralgia	<p>Number of pain attacks per week , 4–6 weeks</p> <p>with oxcarbazepine</p> <p>with carbamazepine</p> <p>Oxcarbazepine and carbamazepine both reduced the number of pain attacks per week by at least 50% from baseline after 4–6 weeks' treatment</p>	<p>Results were not directly compared between groups</p> <p>Significance not reported</p>		

Psychological distress

No data from the following reference on this outcome. ^[33]

Ability to perform normal activities

No data from the following reference on this outcome. ^[33]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
^[33] RCT	48 people with classical trigeminal neuralgia	<p>Adverse effects</p> <p>with oxcarbazepine</p> <p>with carbamazepine</p> <p>Absolute results not reported</p> <p>The most common adverse effects with both oxcarbazepine and carbamazepine were fatigue and dizziness</p>	No direct comparison of adverse effects between oxcarbazepine and carbamazepine was performed		

Comment: As *Clinical Evidence* was unable to perform a second appraisal of results retrieved by the contributor's search, we may have missed studies that could affect our overall assessment of this intervention.

Clinical guide:

On the basis of observational studies, including a 15-year prospective cohort study,^[20] most clinicians regard oxcarbazepine as effective. Furthermore, there is consensus among clinicians that oxcarbazepine is associated with fewer adverse effects than carbamazepine. Although studies assessing the durability of response with oxcarbazepine are lacking, this drug rarely provides complete or long-term pain relief. It is the first-line medical treatment for trigeminal neuralgia in Scandinavian countries and second-line medical treatment after carbamazepine in the UK and North America. One non-systematic review (3 RCTs, 130 people)^[34] found that oxcarbazepine and carbamazepine were associated with similar reductions in attacks (pain, global symptoms) of trigeminal neuralgia. Although oxcarbazepine has not demonstrated superiority over carbamazepine for pain control, and is more expensive in countries where it is still under patent, many clinicians favour it for its lower toxicity profile.

OPTION LAMOTRIGINE

- For GRADE evaluation of interventions for Trigeminal neuralgia, see table, p 18 .
- We found insufficient evidence to judge the effectiveness of lamotrigine in people with trigeminal neuralgia.
- Lamotrigine is often used in people who cannot tolerate carbamazepine, but the dose must be increased slowly to avoid rashes, thus making it unsuitable for acute use.

Benefits and harms

Lamotrigine versus placebo:

We found one systematic review (search date 2011), ^[35] which identified one small double-blind crossover RCT comparing lamotrigine versus placebo in people receiving carbamazepine or phenytoin. ^[36]

Pain relief

Lamotrigine compared with placebo We don't know whether adding lamotrigine is more effective than adding placebo to current treatment at increasing the proportion of people improved (improvement not further defined) after 2 weeks of treatment (*very low-quality evidence*).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
^[36] RCT Crossover design	14 people with refractory trigeminal neuralgia using either carbamazepine or phenytoin In review ^[35]	Proportion of people improved, 2 weeks of treatment 10/13 (77%) with addition of lamotrigine 8/14 (57%) with addition of placebo Results after crossover	Significance not assessed		

Psychological distress

No data from the following reference on this outcome. ^[36] ^[35]

Ability to perform normal activities

No data from the following reference on this outcome. ^[36] ^[35]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
^[36] RCT Crossover design	14 people with refractory trigeminal neuralgia using either carbamazepine or phenytoin In review ^[35]	Total number of people reporting adverse effects 7/13 (54%) with addition of lamotrigine 7/14 (50%) with addition of placebo Adverse effects with lamotrigine included dizziness, constipation, nausea, and drowsiness. Lamotrigine may also cause serious skin rash and allergic reactions, particularly if the dose is escalated rapidly; there were no reports of skin rash in the study			

Comment: As *Clinical Evidence* was unable to perform a second appraisal of results retrieved by the contributor's search, we may have missed studies that could affect our overall assessment of this intervention.

Clinical guide:

We found no good evidence assessing the benefits of lamotrigine. However, clinicians often use lamotrigine in people who cannot tolerate carbamazepine (e.g., because of allergy), or in addition to carbamazepine when the latter becomes less effective. The dose of lamotrigine must be escalated slowly in order to avoid rashes, and it is therefore not appropriate for acute management of trigeminal neuralgia. It is most effective when used for long-term control of moderate pain, such as in people with multiple sclerosis.^[37]

OPTION GABAPENTIN

- For GRADE evaluation of interventions for Trigeminal neuralgia, [see table, p 18](#) .
- We found no evidence comparing gabapentin versus placebo/no treatment or other treatments covered in this review in people with trigeminal neuralgia.
- Gabapentin does have support for use in treating other neuropathic pain conditions, particularly multiple sclerosis.

Benefits and harms

Gabapentin:

We found no systematic review or good-quality RCTs on the effects of gabapentin compared with placebo/no treatment or other listed interventions in the review in people with trigeminal neuralgia. For further information on harms of gabapentin, see harms of anti-epileptic drugs under Epilepsy.

Comment: As *Clinical Evidence* was unable to perform a second appraisal of results retrieved by the contributor's search, we may have missed studies that could affect our overall assessment of this intervention.

Clinical guide:

Although gabapentin has been shown to be effective in treating some neuropathic pain conditions,^[38] particularly multiple sclerosis,^[39] evidence for its use in trigeminal neuralgia is lacking. We did find one RCT that showed that gabapentin plus ropivacain (injected into trigger points) compared with gabapentin alone can improve pain and functional health status in trigeminal neuralgia with little or no side effects.^[40]

OPTION BACLOFEN

- For GRADE evaluation of interventions for Trigeminal neuralgia, [see table, p 18](#) .
- We found no sufficient evidence to judge the effectiveness of baclofen.
- There is consensus that baclofen may be useful for people with multiple sclerosis who develop trigeminal neuralgia.

Benefits and harms

Baclofen versus placebo:

We found one systematic review (search date 2011), which identified one controlled trial (double-blind crossover, 10 people, 4 using carbamazepine or phenytoin, not clearly randomised).^[41] The review excluded the study owing to its crossover design and insufficient washout period (7 days before crossover).

Baclofen versus carbamazepine:

We found one systematic review (search date 2011), which identified one randomised, double-blind, parallel-group trial comparing carbamazepine, baclofen, and combinations of both. ^[41] The review excluded the study as it lasted only 10 days and the washout period was insufficient.

Comment: As *Clinical Evidence* was unable to perform a second appraisal of results retrieved by the contributor's search, we may have missed studies that could affect our overall assessment of this intervention.

Clinical guide:

We found no good evidence of benefit for baclofen from any RCTs. Consensus has suggested that it may be useful in people with multiple sclerosis who develop trigeminal neuralgia. This group of people are often taking baclofen already, and may achieve control of symptoms without having to add carbamazepine. Only one research group to date has carried out trials on L-baclofen and has now ceased to do so.

Baclofen is associated with transient sedation and loss of muscle tone. Abrupt discontinuation may cause seizures and hallucinations.

OPTION MICROVASCULAR DECOMPRESSION

- For GRADE evaluation of interventions for Trigeminal neuralgia, [see table, p 18](#) .
- Despite a lack of RCT data, observational evidence supports the use of [microvascular decompression](#) to relieve symptoms of trigeminal neuralgia.
- Microvascular decompression has been shown in at least two prospective comparative cohort trials to have superiority over stereotactic radiosurgery for initial complete pain relief, durability of response (up to 5 years), and preservation of trigeminal sensation.
- Multiple well-conducted observational studies have concordantly demonstrated that microvascular decompression has a greater magnitude of therapeutic effect than any medical or surgical intervention for trigeminal neuralgia. As such, this procedure is unlikely to be compared against best medical therapy in an RCT.
- Microvascular decompression requires general anaesthesia and can, albeit rarely, be associated with surgical complications, of which a less than 5% risk of ipsilateral hearing loss appears to be the most common.

Benefits and harms**Microvascular decompression:**

We found no systematic review or RCTs of [microvascular decompression](#) in people with trigeminal neuralgia.

Comment: As *Clinical Evidence* was unable to perform a second appraisal of results retrieved by the contributor's search, we may have missed studies that could affect our overall assessment of this intervention.

Clinical guide:

Although unlikely to be evaluated in RCTs, there is some observational evidence to support the use of microvascular decompression to reduce painful attacks of trigeminal neuralgia. ^[42] Many of these studies are of poor quality. However, a number of 'highly' rated observational studies (based on the Surgical Trigeminal Neuralgia Score ^[43]) are discussed here.

Two well-conducted observational studies ^[21] ^[44] that used independent assessors to evaluate outcomes found 70% to 80% of people being pain-free at 5 years. The main adverse effect with microvascular decompression is ipsilateral hearing loss, which usually occurs in less than 5% of cases, and is usually permanent. ^[45] ^[46] Hearing loss rates can be kept even lower by routine use of intra-operative monitoring with auditory brainstem evoked responses (ABR). ^[47] The risk of

hearing loss associated with microvascular decompression is small, but it may be a prohibitive consideration for people with pre-existing contralateral hearing impairment, or for those rare individuals whom, from a professional career stand-point, would prefer to remain incapacitated by trigeminal neuralgia pain than face the small risk of ipsilateral hearing loss. Other rare adverse effects associated with microvascular decompression include aseptic meningitis, infarcts, haematomas, and cerebrospinal fluid leaks.^[45]

Two concordant prospective comparative cohort studies have compared microvascular decompression versus stereotactic radiosurgery.^{[48] [49]} The first study (80 people) found that microvascular decompression significantly increased the proportion of people with pain relief immediately after treatment, at 2 years, and at 5 years compared with stereotactic radiosurgery (immediately after treatment: 100% with microvascular decompression v 78% with stereotactic radiosurgery, reported as significant, P value not reported; at 2 years: 88% with microvascular decompression v 80% with stereotactic radiosurgery, P = 0.01; at 5 years: 77% with microvascular decompression v 45% with stereotactic radiosurgery, P = 0.002).^[48] The second study (140 people) found that microvascular decompression significantly increased the proportion of people with complete pain relief at 1 year and 4 years after treatment compared with stereotactic radiosurgery (at 1 year: 84% with microvascular decompression v 66% with stereotactic radiosurgery; at 4 years: 77% with microvascular decompression v 56% with stereotactic radiosurgery; HR 2.5 with 95% CI 1.4 to 4.6, P = 0.003).^[49] In addition, people who had stereotactic radiosurgery had significantly higher numbness rates (35% with stereotactic radiosurgery v 18% with microvascular decompression, P = 0.04).

Pain relief with microvascular decompression is usually immediate, therefore, it can be considered for the emergency management of people with trigeminal neuralgia in acute extremis. However, this procedure does require the use of general anaesthesia.

The large therapeutic effect size with microvascular decompression of up to 70% to 80% of people achieving immediate complete pain relief (note: 50% pain relief from baseline is generally used as an endpoint in drug trials) and up to 60% to 70% remaining pain-free at 10–20 years following surgery^{[21] [44] [48] [49] [50]} means there are ethical concerns with using RCTs to compare microvascular decompression with medical therapies. It also suggests that it is reasonable to consider microvascular decompression as a first-line therapy in certain circumstances (e.g., in younger patients, those with major side effects from anticonvulsant drug use, and those unable and/or unwilling to tolerate the potential side effects of antiepileptic drugs).

Microvascular decompression has a lower treatment success rate for those with multiple sclerosis-related trigeminal neuralgia, as they may be experiencing pain caused by a different mechanism to idiopathic trigeminal neuralgia.^{[51] [52] [53]} It is, therefore, generally not considered a first-line surgical therapy for people with multiple sclerosis-related trigeminal neuralgia.

OPTION

NON-PERCUTANEOUS DESTRUCTIVE NEUROSURGICAL TECHNIQUES (STEREOTACTIC RADIOSURGERY)

- For GRADE evaluation of interventions for Trigeminal neuralgia, [see table, p 18](#).
- We found no RCT evidence comparing [non-percutaneous destructive neurosurgical techniques \(stereotactic radiosurgery\)](#) versus placebo/no treatment or other treatments covered in this review in people with trigeminal neuralgia.
- There is some observational data suggesting that [radiofrequency thermocoagulation](#) may offer higher rates of complete pain relief than [glycerol rhizolysis](#) and stereotactic radiosurgery, but is associated with the highest rate of complications.
- Stereotactic radiosurgery does not require sedation or general anaesthesia but, typically, pain relief with this procedure is not immediate.

Benefits and harms

Non-percutaneous destructive neurosurgical techniques (stereotactic radiosurgery):

We found three systematic reviews (search dates 2003),^{[54] [55] [56]} which identified no RCTs comparing stereotactic radiosurgery versus placebo/no treatment or other treatments covered in this review.

Comment: As *Clinical Evidence* was unable to perform a second appraisal of results retrieved by the contributor's search, we may have missed studies that could affect our overall assessment of this intervention.

Clinical guide:

One of the systematic reviews ^[54] identified nine observational studies (mainly case series, 2077 people) comparing stereotactic radiosurgery versus percutaneous destructive neurosurgical techniques to the [Gasserian ganglion](#) and/or pre-ganglionic nerve route. It suggested that radiofrequency thermocoagulation may offer higher rates of complete pain relief than stereotactic radiosurgery and glycerol rhizolysis (a percutaneous destructive neurosurgical technique), but it is associated with the highest rate of complications. We found stronger RCT evidence for stereotactic radiosurgery than for other destructive neurosurgical techniques, but the RCT comparing different regimens does not allow conclusions to be drawn about the effects of stereotactic radiosurgery compared with no treatment. RCTs comparing the effects of stereotactic radiosurgery with no treatment have not been undertaken and are unlikely to be in future because of ethical considerations. We found two prospective comparative cohort studies comparing stereotactic radiosurgery versus microvascular decompression (see [Comment section for Microvascular decompression, p 11](#)). ^[48] ^[49] The studies showed superiority of microvascular decompression over stereotactic radiosurgery for initial complete pain relief, durability of response (up to 5 years), and preservation of trigeminal sensation.

We also found one systematic review ^[57] that identified one RCT that compared stereotactic radiosurgery using either one or two isocentres, the latter regimen to treat a longer length of the trigeminal nerve. ^[58] The study found that stereotactic radiosurgery using one isocentre was as effective as stereotactic radiosurgery using two isocentres at relieving pain at 26 months (with or without additional pain-relieving drugs).

Stereotactic radiosurgery is performed using technologies such as the [Gamma Knife®](#), [CyberKnife®](#), and linear accelerators with multileaf collimator capabilities ([LINAC-MLC](#)). Unlike other surgical interventions for trigeminal neuralgia, stereotactic radiosurgery does not require general anaesthesia (or any form of sedation) to perform. However, the pain-relieving effects of this procedure are not immediate, ^[59] therefore, it is not considered an option for the emergency management of people with trigeminal neuralgia in acute extremis.

As with percutaneous destructive neurosurgical techniques, stereotactic radiosurgery can be used to treat people with multiple sclerosis-related trigeminal neuralgia, albeit with somewhat lower anticipated success rates. ^[60] ^[61] ^[62]

If stereotactic radiosurgery is repeated for pain recurrence, a significantly lower dose of radiation must be used, otherwise significantly higher rates of numbness will be encountered. De-afferentation pain, in addition to trigeminal neuralgia pain, could then become a problem. ^[63] ^[64] ^[65] ^[66]

OPTION

PERCUTANEOUS DESTRUCTIVE NEUROSURGICAL TECHNIQUES (RADIOFREQUENCY THERMOCOAGULATION, GLYCEROL RHIZOLYSIS, OR BALLOON COMPRESSION)

- For GRADE evaluation of interventions for Trigeminal neuralgia, see [table, p 18](#) .
- We found no RCT evidence assessing [percutaneous destructive neurosurgical techniques](#) (radiofrequency thermocoagulation, [glycerol rhizolysis](#), or [balloon compression](#)) versus placebo/no treatment or other treatments covered in this review in people with trigeminal neuralgia.
- There is some observational data suggesting that [radiofrequency thermocoagulation](#) may offer higher rates of complete pain relief than glycerol rhizolysis and [stereotactic radiosurgery](#), but is associated with the highest rate of complications (e.g., facial numbness and corneal insensitivity).
- Percutaneous destructive neurosurgical techniques require sedation and, sometimes, general anaesthesia before they are performed.

Benefits and harms

Percutaneous destructive neurosurgical techniques (radiofrequency thermocoagulation, glycerol rhizolysis, or balloon compression):

We found four systematic reviews (search date 2003; ^[54] ^[55] ^[56] search date 2010 ^[57]), which identified no RCTs comparing percutaneous destructive neurosurgical techniques (radiofrequency thermocoagulation, glycerol rhizolysis, or balloon compression) versus placebo/no treatment or versus other treatments covered in this review.

Comment: As *Clinical Evidence* was unable to perform a second appraisal of results retrieved by the contributor's search, we may have missed studies that could affect our overall assessment of this intervention.

Clinical guide:

One of the systematic reviews (search date 2003)^[54] identified nine observational studies (mainly case series, 2077 people) comparing percutaneous destructive neurosurgical techniques to the [Gasserian ganglion](#) and/or pre-ganglionic nerve route versus stereotactic radiosurgery. It suggested that radiofrequency thermocoagulation may offer higher rates of complete pain relief than glycerol rhizolysis and stereotactic radiosurgery (a non-percutaneous destructive neurosurgical technique), but it is also associated with the highest rate of complications. RCTs comparing the effects of percutaneous destructive neurosurgical techniques with no treatment have not been undertaken and are unlikely to be in future because of ethical considerations.

We did identify one small prospective comparative cohort observational study comparing radiofrequency thermocoagulation with glycerol rhizolysis.^[67] This low-quality evidence study of 79 people with relatively short median follow-ups of 24 to 36 months for each technique showed better pain control results for radiofrequency thermocoagulation compared with glycerol rhizolysis (85% v 59%, $P < 0.05$) based on raw data, but this difference lost significance when life-table analysis was applied ($P = 0.51$).

One of the systematic reviews (search date 2010)^[57] identified a small RCT comparing pulsed radiofrequency thermocoagulation versus conventional radiofrequency thermocoagulation.^[68] Everyone in the pulsed radiofrequency thermocoagulation treatment group dropped out and needed conventional radiofrequency thermocoagulation. Furthermore, everyone in the pulsed radiofrequency thermocoagulation group required additional carbamazepine and/or gabapentin, compared with one person in the conventional radiofrequency thermocoagulation group. We found a similar study assessing combined pulsed radiofrequency and continuous radiofrequency.^[69] The benefits of pulsed radiofrequency thermocoagulation in treating trigeminal neuralgia appear to be limited.

The main complications associated with radiofrequency thermocoagulation are facial numbness and corneal insensitivity. Although radiofrequency thermocoagulation runs the risk of adding to the problem of de-afferentation and trigeminal neuralgia pain, sensory loss in the area of facial pain appear to correlate with the best chance of pain relief and durability of response when used as a first percutaneous destructive neurosurgical technique.^[54]

Similar to microvascular decompression, but unlike stereotactic radiosurgery, percutaneous destructive neurosurgical techniques can achieve immediate pain relief.^{[70] [71] [72] [73] [74] [75] [76] [77] [78] [79] [80] [81]} These procedures can therefore be considered along with microvascular decompression for the emergency management of people with trigeminal neuralgia in acute extremis. However, the duration of response with percutaneous destructive neurosurgical techniques is shorter than that of microvascular decompression.^{[50] [44] [54]} Furthermore, these procedures require a brief pulse of heavy sedation and, sometimes, general anaesthesia before they are performed.

Percutaneous destructive neurosurgical techniques can be repeated for trigeminal neuralgia pain recurrence, but the damage to the nerve is cumulative. Each re-treatment is, therefore, associated with a cumulative higher risk of trigeminal de-afferentation.^{[82] [83]} De-afferentation pain, in addition to trigeminal neuralgia pain, could then become a problem.

As with stereotactic radiosurgery, percutaneous destructive neurosurgical techniques can be used to treat multiple sclerosis-associated trigeminal neuralgia, albeit with somewhat lower anticipated success rates.^{[84] [85]}

GLOSSARY

Balloon compression A percutaneous (requiring a needle inserted through the skin of the cheek) neurosurgical procedure carried out at the Gasserian ganglion and/or pre-ganglionic nerve route. The procedure involves using a balloon to press the nerve against bony tissue which causes mechanical nerve destruction (partial nerve damage), and is designed to stop the transmission of pain signals to the brain by selectively damaging the small unmyelinated and small myelinated pain fibres of the trigeminal nerve while ideally sparing the rest of the nerve fibres. This minimally invasive procedure is also known as microcompression.

CyberKnife® radiosurgery A non-invasive stereotactic radiosurgery procedure that utilises a robotic arm technology that directs individual doses of radiation onto multiple points on the trigeminal nerve root. The procedure is usually performed with CT scan guidance, without the use of a stereotactic reference frame.

Gamma Knife® radiosurgery A minimally invasive stereotactic radiosurgery procedure that utilises a technology that focuses beams of radiation onto a very small spot (isocenter) within the trigeminal nerve root. The procedure is performed with a stereotactic reference frame that is temporarily attached to the head of the person undergoing the procedure, therefore, local anaesthesia is required. The dominant number of studies and volume of clinical outcomes data for stereotactic radiosurgery for trigeminal neuralgia utilises this technique.

Gasserian ganglion Cluster of nerve cells in which the three main branches of the trigeminal nerve meet. Also known as trigeminal ganglion or semilunar ganglion.

Glycerol rhizolysis A percutaneous (requiring a needle inserted through the skin of the cheek) neurosurgical procedure that involves using a viscous alcohol called glycerol to damage the Gasserian ganglion and/or pre-ganglionic nerve route. The procedure stops the transmission of pain signals to the brain by causing selective chemical damage to the small unmyelinated and small myelinated pain fibres of the trigeminal nerve while ideally sparing the rest of the nerve fibres. This minimally invasive procedure is also known as percutaneous retrogasserian glycerol rhizolysis.

LINAC-MLC-based radiosurgery Non-invasive stereotactic radiosurgery procedures that utilises technologies that focus small high-dose radiation beams onto specific points (focus spot) within the trigeminal nerve root (isocentric treatment). The technologies use a large high-energy linear accelerator (LINAC) x-ray source and have multileaf collimator (MLC) capability. Machines that utilise this technology include Novalis®, Trilogy®, and Truebeam®. The procedures are usually performed with CT scan guidance, without the use of a stereotactic reference frame.

Microvascular decompression A neurosurgical (microsurgical) procedure that involves accessing via the posterior fossa the trigeminal nerve just at its point of entry into the brain. Any vessels distorting or in close contact with the nerve are moved out of the way with the aim of avoiding nerve damage and hence preserving function. This procedure requires general anaesthetic. It is the only neurosurgical procedure designed to spare the trigeminal nerve from damage, and to directly address the cause of trigeminal neuralgia in most cases, rather than just relieve the symptom of pain. Results of this procedure vary the most from surgeon to surgeon.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Non-percutaneous destructive neurosurgical techniques Neurosurgical procedures that cause destruction (ablation) of specific nerves, but do not require needle insertion through the skin of the cheek (e.g., stereotactic radiosurgery [performed with technologies such as the Gamma Knife®]). Also known as non-percutaneous ablative surgical procedures.

Percutaneous destructive neurosurgical techniques Neurosurgical procedures that require needle insertion through the skin of the cheek, and that cause partial destruction (ablation) of the trigeminal nerve by selectively targeting damage to the small unmyelinated and small myelinated pain fibres of the trigeminal nerve, while ideally sparing the rest of the nerve fibres (e.g., radiofrequency thermocoagulation, glycerol rhizolysis, and balloon compression). Also known as percutaneous ablative surgical procedures.

Radiofrequency thermocoagulation A percutaneous (requiring a needle inserted through the skin of the cheek) neurosurgical procedure that uses an electrode to damage the Gasserian ganglion and/or pre-ganglionic nerve route. The procedure stops the transmission of pain signals to the brain by selectively damaging the small unmyelinated and small myelinated pain fibres of the trigeminal nerve while ideally sparing the rest of the nerve fibres. This minimally invasive procedure is also known as percutaneous retrogasserian radiofrequency thermocoagulation.

Stereotactic radiosurgery A non-percutaneous (does not require needle insertion through the skin of the cheek) neurosurgical procedure that involves using a focused beam of ionising radiation to selectively damage the small unmyelinated and small myelinated pain fibres of the trigeminal nerve, while ideally sparing the rest of the nerve fibres. While several technologies purport similar results (CyberKnife® radiosurgery and other LINAC-MLC-based radiosurgery technologies), the predominant and proven technology for this non-invasive neurosurgical technique is the Gamma Knife®.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Carbamazepine One systematic review added, ^[23] which replaces an older systematic review. One retrospective cohort study was moved into the Comment section, as it no longer met our inclusion criteria. Categorisation unchanged (likely to be beneficial).

Lamotrigine One systematic review added, ^[35] which replaces an older systematic review. Categorisation unchanged (unknown effectiveness).

Microvascular decompression New observational data ^[49] added to Comment section. Categorisation unchanged (trade-off between benefits and harms [based on observational studies and/or consensus]).

Non-percutaneous destructive neurosurgical techniques (stereotactic radiosurgery) New observational data [49] and systematic review [57] added to the Comment section. Categorisation changed (from unknown effectiveness to trade off between benefits and harms [based on observational studies and/or consensus]).

Percutaneous destructive neurosurgical techniques (radiofrequency thermocoagulation, glycerol rhizolysis, or balloon compression) New observational data, [67] systematic review, [57] and RCTs [68] [69] added to Comment section. Categorisation changed (from unknown effectiveness to trade-off between benefits and harms [based on observational studies and/or consensus]).

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GRADE Evaluation of interventions for Trigeminal neuralgia.

Important outcomes	Ability to perform normal activities, Pain relief, Psychological distress								GRADE	Comment
	Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size		
<i>What are the effects of ongoing treatments in people with trigeminal neuralgia?</i>										
3 (208) ^[23]	Pain relief	Carbamazepine versus placebo	4	-2	0	-1	+2	Moderate	Quality points deducted for crossover design and short follow-up; directness point deducted for inclusion of different pain severities and uncertainties about diagnostic criteria and outcomes measured; effect-size points added for RR = 5 or higher	
1 (48) ^[33]	Pain relief	Oxcarbazepine versus carbamazepine	4	-3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and no direct comparison between groups	
1 (14) ^[36]	Pain relief	Lamotrigine versus placebo	4	-2	0	-1	0	Very low	Quality points deducted for sparse data and crossover design with no pre-crossover results; directness point deducted for concurrent use of other medication	

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.