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 last from a few seconds to 2 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. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of treatments in people with trigeminal neuralgia? We searched: Medline, Embase, The Cochrane Library, and other important databases up to September 2007 (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 14 systematic reviews, RCTs, or observational 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: ablative neurosurgical techniques to the Gasserian ganglion; baclofen; carbamazepine; clonazepam; cryotherapy of peripheral nerves; gabapentin; lamotrigine; microvascular decompression; nerve block; oxcarbazepine; peripheral acupuncture; phenytoin; proparacaine eye drops; sodium valproate; stereotactic radiosurgery; tizanidine; and topiramate.

QUESTIONS

INTERVENTIONS

TREATMENTS

To be covered in future updates

Lidocaine

Streptomycin

Sumatriptan

Footnote

*Categorisation based on 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 last from a few seconds to 2 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 annual incidence in the UK is 26.8/100,000.

- Carbamazepine is considered the gold standard in treatment for symptoms of trigeminal neuralgia.

  Carbamazepine has been shown to increase pain relief compared with placebo, but also increases adverse effects, such as drowsiness, dizziness, constipation, and ataxia.

  There is consensus that oxcarbazepine is an effective treatment in people with trigeminal neuralgia, although there is a lack of RCT-based data to confirm this.

- We found no sufficient evidence to judge the effectiveness of tizanidine, 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 don't know the effectiveness of other antiepileptic drugs, such as phenytoin, clonazepam, sodium valproate, gabapentin, or topiramate, in people with trigeminal neuralgia.
- Despite a lack of RCT data, observational evidence supports the use of microvascular decompression to relieve symptoms of trigeminal neuralgia.
- Proparacaine eye drops (single application) do not relieve pain in people with trigeminal neuralgia, despite initial open-label use that suggested they were helpful.
- We don't know whether peripheral nerve treatments such as acupuncture, cryotherapy, laser surgery, or nerve block are effective in people with trigeminal neuralgia.
- We found no RCT evidence assessing stereotactic radiosurgery or ablative neurosurgery to the Gasserian ganglion. However, 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. Typically, pain relief with radiosurgery is not immediate.

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 2 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. In any individual, the pain has the same character in different attacks. It is triggered by light touch in a specific area or by eating, talking, washing the face, or cleaning the teeth. Other causes of facial pain may need to be excluded. [1] [2] [3] In trigeminal neuralgia, the neurological examination is usually normal. [1] [2] [3]

INCIDENCE/ PREVALENCE

Most evidence about the incidence and prevalence of trigeminal neuralgia is from the USA. [4] The annual incidence (age adjusted to the 1980 age distribution of the USA) 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. [5] One questionnaire survey of neurological disease in a single French village found one person with trigeminal neuralgia among 993 people. [6] 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. [7]

AETIOLOGY/ RISK FACTORS

The cause of trigeminal neuralgia remains unclear. [8] [9] It is more common in people with multiple sclerosis (RR 20.0, 95% CI 4.1 to 59.0). [5] 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). [5] One case control study in the USA found that people with trigeminal neuralgia smoked less, consumed less alcohol, had fewer tonsillectomies, and were less likely than matched controls to be Jewish or an immigrant. [10]

PROGNOSIS

One retrospective cohort study found no reduction in 10-year survival in people with trigeminal neuralgia. [11] We found no evidence about the natural history of trigeminal neuralgia. The illness is characterised by recurrences and remissions. Many people have periods of remission with no pain for months or years. [9] Anecdotal reports suggest that in many people it becomes more severe and less responsive to treatment with time. [12] Most people with trigeminal neuralgia are initially managed medically, and a proportion eventually have a surgical procedure. [9] 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. [9] [12]

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

Clinical Evidence search and appraisal September 2007. The following databases were used to identify studies for this review: Medline 1966 to September 2006, Embase 1980 to September 2007, and The Cochrane Database of Systematic Reviews 2007, Issue 3. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE clinical guidelines. Abstracts of the studies retrieved were assessed independently by an information specialist using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, 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 required to include studies. We excluded all RCTs described as "open"', "open label", or not blinded. 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 contributor also included results from a 2005 search conducted whilst writing a guideline on the surgical management of trigeminal neuralgia. The search strategy for this guideline was designed to find RCTs and CCTs related to surgical options in trigeminal neuralgia in Medline, Embase, and Cochrane 1966 to 2005. Additionally, the contributors have used results from their own database collated from 1990 to September 2007, which includes case series reports. 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 the interventions in this review. As trigeminal neuralgia is a rare disease, and patents on many of the drugs have expired, it is highly unlikely that further trials comparing carbamazepine versus local anaesthetics (such as tizanidine or proparacaine) will be conducted. 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 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. Different trial designs are needed. 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 21). 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).

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

OPTION CARBAMAZEPINE

- For GRADE evaluation of interventions for Trigeminal neuralgia, see table, p 21 .
- Carbamazepine is considered the gold standard in treatment for symptoms of trigeminal neuralgia.
- Carbamazepine has been shown to increase pain relief compared with placebo, but also increases adverse effects, such as drowsiness, dizziness, constipation, and ataxia.

Benefits and harms

Carbamazepine versus placebo:

We found one systematic review (search date 2004, 3 crossover RCTs). [13] Another systematic review (search date 1994) examined the number of people who withdrew from RCTs of carbamazepine versus placebo because of adverse effects. [14]

Pain relief

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Patient-reported response					
[13] Systematic review **Crossover design**	161 people with trigeminal neuralgia 3 RCTs in this analysis	**Proportion of people reporting a "good" or "excellent" response , 5 days to 2 weeks** 57% with carbamazepine 18% with placebo Absolute numbers not reported	OR 4.8 95% CI 3.4 to 6.9 NNT 3 95% CI 2 to 4	●●○	carbamazepine

Psychological distress

No data from the following reference on this outcome. [13]

Ability to perform normal activities

No data from the following reference on this outcome. [13]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[13] Systematic review **Crossover design**	161 people with trigeminal neuralgia 3 RCTs in this analysis	**Adverse effects** with carbamazepine with placebo Carbamazepine significantly increased adverse effects (drowsiness, dizziness, constipation, and ataxia) compared with placebo	NNH 3 95% CI 2 to 7	○○○	placebo
[14] 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

Long-term carbamazepine treatment versus stopping carbamazepine earlier:
We found one retrospective cohort study on the long-term benefits of carbamazepine. [15]

Pain relief

Long-term carbamazepine treatment compared with stopping earlier We don't know whether carbamazepine treatment is effective in the long term (5–16 years) in people with trigeminal neuralgia (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[15] Cohort study	143 people with trigeminal neuralgia followed up for up to 16 years	**Treatment success** with carbamazepine over time Initially, carbamazepine was successful in 99 (69%) people, but beyond 5 years, only 31 (22%) people were still finding carbamazepine effective, and 63 (44%) required additional or alternative treatment			

Psychological distress

No data from the following reference on this outcome. [15]

Ability to perform normal activities

No data from the following reference on this outcome. [15]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[15] Cohort study	143 people with trigeminal neuralgia followed up for up to 16 years	**Adverse effects** with carbamazepine over time Eight people developed adverse effects necessitating cessation of carbamazepine. Adverse effects included rash (6 people), nausea and thirst (1 person), and water intoxication (1 person)			

Carbamazepine versus oxcarbazepine:
See option on oxcarbazepine, p 6 .

Carbamazepine versus tizanidine:
See option on tizanidine, p 10 .

Carbamazepine versus baclofen:
See option on baclofen, p 9 .

Further information on studies

[13] 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.

Other adverse effects described in observational studies include rashes, leucopenia, and abnormal liver function tests. [16]

Clinical guide:
Most clinicians believe that carbamazepine is the first-line treatment for trigeminal neuralgia. It has been widely advocated for use in primary care. [17] 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.

OPTION OXCARBAZEPINE

- For GRADE evaluation of interventions for Trigeminal neuralgia, see table, p 21 .
- There is consensus that oxcarbazepine, p 6 is an effective treatment in people with trigeminal neuralgia, although there is a lack of RCT-based data to confirm this.
- It is the first-line treatment for trigeminal neuralgia in Scandinavian countries and second-line treatment after carbamazepine in North America.

Benefits and harms

Oxcarbazepine versus carbamazepine:

We found no systematic review, but found one RCT. [18]

Pain relief

Oxcarbazepine compared with carbamazepine We don't know how oxcarbazepine and carbamazepine compare for relieving pain (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[18] RCT	48 people with primary trigeminal neuralgia	**Number of pain attacks per week , 4 to 6 weeks** with oxcarbazepine with carbamazepine Oxcarbazepine and carbamazepine both reduced the number of pain attacks per week by at least 50% from baseline after 4 to 6 weeks' treatment	Results were not directly compared between groups. No significance data reported		

Psychological distress

No data from the following reference on this outcome. [18]

Ability to perform normal activities

No data from the following reference on this outcome. [18]

Adverse effects

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

Further information on studies

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, [12] most clinicians regard oxcarbazepine as effective. It is the first-line treatment for trigeminal neuralgia in Scandinavian countries and second-line treatment after carbamazepine in North America. One non-systematic review (3 RCTs, 130 people) [19] found that oxcarbazepine and carbamazepine were associated with similar reductions in attacks (pain, global symptoms) of trigeminal neuralgia.

OPTION LAMOTRIGINE

- For GRADE evaluation of interventions for Trigeminal neuralgia, see table, p 21 .
- 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 1999), [20] which identified one small double-blind crossover RCT comparing lamotrigine versus placebo in people receiving carbamazepine or phenytoin. [21]

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					
[21] RCT **Crossover design**	14 people with refractory trigeminal neuralgia using either carbamazepine or phenytoin In review [20]	**Proportion of people improved, 2 weeks of treatment** 10/13 (77%) with addition of lamotrigine 8/14 (57%) with addition of placebo	Significance assessment not performed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Results after crossover			

Psychological distress

No data from the following reference on this outcome. [21] [20]

Ability to perform normal activities

No data from the following reference on this outcome. [21] [20]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] RCT **Crossover design**	14 people with refractory trigeminal neuralgia using either carbamazepine or phenytoin In review [20]	**Total number of people reporting adverse effects** 7/14 (50%) 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			

Further information on studies

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.

OPTION OTHER ANTIEPILEPTICS (PHENYTOIN, CLONAZEPAM, SODIUM VALPROATE, GABAPENTIN, TOPIRAMATE)

- For GRADE evaluation of interventions for Trigeminal neuralgia, see table, p 21 .

- We don't know the effectiveness of other antiepileptic drugs, such as phenytoin, clonazepam, sodium valproate, gabapentin, or topiramate, in people with trigeminal neuralgia.

Benefits and harms

Other antiepileptics:

We found no systematic review or good-quality RCTs on the effects of antiepileptic drugs, such as phenytoin, clonazepam, sodium valproate, gabapentin, or topiramate, in people with trigeminal neuralgia. For further information on harms of phenytoin, sodium valproate, gabapentin, oxcarbazepine, and topiramate, see harms of antiepileptic drugs under epilepsy.

Further information on studies

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 neuropathic pain, [22] there is currently insufficient evidence for its use in trigeminal neuralgia. One RCT of gabapentin published after the search date for this review will be evaluated for possible inclusion at the next update. [23]

OPTION BACLOFEN

- For GRADE evaluation of interventions for Trigeminal neuralgia, see table, p 21 .
- 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 2005), which identified one controlled trial (double-blind crossover, 10 people, 4 using carbamazepine or phenytoin, not clearly randomised). [24]

Racemic versus L-baclofen:

We found one systematic review (search date 2005), which identified one trial (double-blind crossover, 15 people, not clearly randomised), which compared racemic (standard) baclofen versus L-baclofen over 2 weeks. [24]

Baclofen versus carbamazepine:

We found one systematic review (search date 2005), which identified one randomised, double-blind, parallel-group trial comparing carbamazepine, baclofen, and combinations of both. [24]

Pain relief

Baclofen compared with carbamazepine We don't know how baclofen and carbamazepine compare for relieving pain (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain relief					
[24] Systematic review	30 people resistant to carbamazepine	**Proportion of people with pain relief** 5/7 (71%) with baclofen 3/10 (30%) with carbamazepine	RR 2.38 95% CI 0.83 to 6.85 See further information on studies regarding assessment of this result	⟷	Not significant

Psychological distress

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

Ability to perform normal activities

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

Adverse effects

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

Further information on studies

[24] Over 30% of people withdrew from the study comparing baclofen with carbamazepine, and analysis was not by intention to treat, so the results should be treated with caution.

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

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.

OPTION TIZANIDINE

- For GRADE evaluation of interventions for Trigeminal neuralgia, see table, p 21 .
- We found no sufficient evidence to judge the effectiveness of tizanidine.

Benefits and harms

Tizanidine versus placebo:

We found one systematic review (search date 2005), [24] which found no RCTs but one small, double-blind crossover study (10 people).

Pain relief

Tizanidine compared with placebo Tizanidine may be more effective at increasing pain relief at 3 to 7 days (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain relief					
[24] **Crossover design**	10 people	**Proportion of people with pain relief , 3 to 7 days** 8/10 (80%) with tizanidine 1/10 (10%) with placebo Only three people became pain-free, and symptoms recurred after 1 to 3 months in all participants	RR 8.00 95% CI 1.21 to 52.69 P = 0.03	●●●	tizanidine

Psychological distress

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

Ability to perform normal activities

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

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[24] **Crossover design**	10 people	**Adverse effects** with tizanidine with placebo Absolute results not reported One person withdrew from the study owing to influenza-like symptoms (no further details reported)			

Tizanidine versus carbamazepine:

We found two systematic reviews (search dates 2004 [14] and 2006) [24] which identified the same small RCT.

Pain relief

Tizanidine compared with carbamazepine We don't know how tizanidine and carbamazepine compare for increasing the proportion of people who rated the treatment as having "very good" efficacy (not further defined) in people with trigeminal neuralgia (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Patient-reported efficacy					
[24] Systematic review	12 people Data from 1 RCT	**Proportion of people who rated the treatment as having "very good" efficacy** 1/5 (20%) with tizanidine (18 mg/day or less) 4/6 (67%) with carbamazepine (900 mg/day or less)	RR 0.30 95% CI 0.05 to 1.89 P = 0.20 Analysis not by intention to treat The RCT was too small to detect clinically important effects	⟷	Not significant

Psychological distress

No data from the following reference on this outcome. [14] [24]

Ability to perform normal activities

No data from the following reference on this outcome. [14] [24]

Adverse effects

No data from the following reference on this outcome. [14] [24]

Further information on studies

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:
There is little satisfactory evidence for the benefit of tizanidine in the treatment of people with trigeminal neuralgia.

OPTION PROPARACAINE HYDROCHLORIDE EYE DROPS

- For GRADE evaluation of interventions for Trigeminal neuralgia, see table, p 21 .
- Proparacaine eye drops (single application) do not relieve pain in people with trigeminal neuralgia, despite initial open-label use that suggested they were helpful.

Benefits and harms

Proparacaine hydrochloride versus placebo:

We found one systematic review (search date 2005), [24] which found one double-blind RCT comparing single-application proparacaine hydrochloride eye drops versus placebo eye drops instilled for 20 minutes on the same side as the trigeminal neuralgia. [25]

Pain relief

Proparacaine hydrochloride compared with placebo A single application of proparacaine hydrochloride eye drops to the eye on the same side as the trigeminal neuralgia pain is no more effective at reducing pain at 30 days (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain relief					
[25] RCT	47 people with trigeminal neuralgia In review [24]	**Reduction of pain , 30 days** 6/25 (24%) with proparacaine eye drops 5/22 (23%) with placebo eye drops	ARI +1.3% 95% CI –23% to +26%	⟷	Not significant

Psychological distress

No data from the following reference on this outcome. [25]

Ability to perform normal activities

No data from the following reference on this outcome. [25]

Adverse effects

No data from the following reference on this outcome. [25]

Further information on studies

[25] No significant reduction of pain after 3 or 10 days.

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:
Proparacaine eye drops have not been shown to be effective in RCTs to date despite initial open-label use that suggested they were helpful.

OPTION PERIPHERAL NERVE TREATMENTS (ACUPUNCTURE, CRYOTHERAPY, LASER SURGERY, NERVE BLOCK)

- For GRADE evaluation of interventions for Trigeminal neuralgia, see table, p 21 .
- We don't know whether peripheral nerve treatments such as acupuncture, cryotherapy, laser surgery, or nerve block are effective in people with trigeminal neuralgia.

Benefits and harms

Nerve block versus placebo or no treatment:

We found no systematic review or RCTs.

Streptomycin plus local anaesthetic versus local anaesthetic alone:

We found two RCTs comparing injections of streptomycin (1 g) plus lidocaine (2 mL of 2% solution) versus lidocaine injections alone (1 injection weekly for 5 weeks). [26] [22]

Pain relief

Streptomycin plus local anaesthetic compared with local anaesthetic alone We don't know whether combined streptomycin plus local anaesthetic is more effective (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[26] RCT	18 people with trigeminal neuralgia who had previously responded poorly to lidocaine injection alone (24 hours' or less pain relief from lidocaine alone) One person who had no pain relief from allocated treatment was excluded (see further information on studies)	**Chance of being pain free , 1 week after the final injection** 89% with streptomycin plus lidocaine 38% with lidocaine alone Absolute numbers not reported	ARR 51% CI not reported P = 0.04	○○○	streptomycin plus lidocaine
[26] RCT	18 people with trigeminal neuralgia who had previously responded poorly to lidocaine injection alone (24 hours' or less pain relief from lidocaine alone) One person who had no pain relief from allocated treatment was excluded (see further information on studies)	**Chance of being pain free , 30 months** 33% with streptomycin plus lidocaine 25% with lidocaine alone Absolute numbers not reported	ARR 8% CI not reported P = 0.38	⟷	Not significant
[22] RCT **Crossover design**	20 people with idiopathic or traumatic trigeminal neuralgia	**Severity or frequency of pain , 5 weeks** with streptomycin (1 g) plus lidocaine (3 mL of 2% solution) with lidocaine alone for 5 weeks No significant short-term differences between groups in severity		⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		or frequency of pain, as assessed after crossover by a variety of clinical tests, such as a visual analogue scale and from pain diaries			

Psychological distress

No data from the following reference on this outcome. [26] [22]

Ability to perform normal activities

No data from the following reference on this outcome. [26] [22]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[22] RCT **Crossover design**	20 people with idiopathic or traumatic trigeminal neuralgia	**Adverse effects** with streptomycin (1 g) plus lidocaine (3 mL of 2% solution) with lidocaine alone for 5 weeks 2/20 (10%) of people found the injections painful and some refused to have further injections. No sensory changes or other adverse effects were reported			

No data from the following reference on this outcome. [26]

Further information on studies

[26] The RCT did not report the method of randomisation. Reliability of results may have been limited by selection bias. Streptomycin was used on the assumption that it causes a long-term peripheral nerve block.

[22] The RCT did not report the method of randomisation. It had short-term follow-up. Streptomycin was used on the assumption that it causes a long-term peripheral nerve block.

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:
RCTs of treatments that target the peripheral nerve have not been undertaken and are unlikely to be in future because of ethical considerations. There is now sufficient observational evidence to

show that these techniques provide only a few months of pain relief, and that ablative neurosurgical techniques at the level of the Gasserian ganglion are more effective. [27] [9]

OPTION MICROVASCULAR DECOMPRESSION

- For GRADE evaluation of interventions for Trigeminal neuralgia, see table, p 21 .
- Despite a lack of RCT data, observational evidence supports the use of microvascular decompression to relieve symptoms of trigeminal neuralgia.
- Consensus suggests that microvascular surgery is effective at reducing symptoms in the long term, although it can lead to ipsilateral hearing loss.

Benefits and harms

Microvascular decompression:

We found no systematic review or RCTs of microvascular decompression in people with trigeminal neuralgia.

Further information on studies

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 not yet evaluated in RCTs, there is some evidence to support the use of microvascular decompression to reduce painful attacks of trigeminal neuralgia, with well-conducted observational studies [28] [29] that used independent assessors to evaluate outcomes, and found 70% to 80% of people being pain-free at 5 years. The main adverse effect is ipsilateral hearing loss, which can occur in up to 10% of cases, and can sometimes be permanent. [30] [31] Other adverse effects include aseptic meningitis, infarcts, haematomas, and cerebrospinal fluid leaks. [30] We found one cohort study (80 people) comparing microvascular decompression versus stereotactic radiosurgery. It 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% microvascular decompression *v* 80% with stereotactic radiosurgery, P = 0.01; at 5 years: 77% microvascular decompression *v* 45% stereotactic radiosurgery, P = 0.002). [32]

OPTION STEREOTACTIC RADIOSURGERY

- For GRADE evaluation of interventions for Trigeminal neuralgia, see table, p 21 .
- We found no RCT evidence assessing stereotactic radiosurgery. However, 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. Typically, pain relief with radiosurgery is not immediate.

Benefits and harms

Stereotactic radiosurgery versus placebo or versus other treatments:

Three systematic reviews (search dates 2003) [33] [34] [35] identified no RCTs comparing stereotactic radiosurgery versus placebo or versus other treatments.

Stereotactic radiosurgery using one versus two isocentres:

One weak RCT compared radiosurgery using either one or two isocentres, the latter regimen to treat a longer length of the trigeminal nerve. [36]

Pain relief

Stereotactic radiosurgery using one isocentre compared with two isocentres Stereotactic radiosurgery using one isocentre may be as effective at 26 months at relieving pain (with or without additional pain-relieving drugs) (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain relief					
[36] RCT	87 people with trigeminal neuralgia People in the RCT took additional pain medication, which was not specified	**Rates of maximal pain control (no pain with or without drugs) , median 26 months (range 1–36 months)** 29/44 (66%) with 1 isocentre 28/43 (65%) with 2 isocentres			
[36] RCT	87 people with trigeminal neuralgia People in the RCT took additional pain medication, which was not specified	**Rates of pain control (no pain with or without drugs) at final follow-up , median 26 months (range 1–36 months)** 20/44 (45%) with 1 isocentre 23/43 (53%) with 2 isocentres			

Psychological distress

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

Ability to perform normal activities

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

Adverse effects

Stereotactic radiosurgery using one isocentre compared with using two isocentres Stereotactic radiosurgery using both one and two isocentres was associated with numbness and paraesthesia, with a tendency towards increased numbness with higher irradiation volume (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[36] RCT	87 people with trigeminal neuralgia People in the RCT took additional pain medication, which was not specified	**Numbness** 3/44 (7%) with 1 isocentre 8/43 (19%) with 2 isocentres			
[36] RCT	87 people with trigeminal neuralgia People in the RCT took additional pain medication,	**Mild paraesthesia** 4/44 (9%) with 1 isocentre 5/43 (12%) with 2 isocentres			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	which was not specified				
[36] RCT	87 people with trigeminal neuralgia People in the RCT took additional pain medication, which was not specified	**Severe paraesthesia** 0/44 (0%) with 1 isocentre 1/43 (2%) with 2 isocentres			

Further information on studies

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) [33] identified nine observational studies (mainly case series, 2077 people) comparing stereotactic radiosurgery versus ablative neurosurgical techniques. It suggested that radiofrequency thermocoagulation may offer higher rates of complete pain relief than glycerol rhizolysis and stereotactic radiosurgery, although it is also associated with the highest rate of complications. We found stronger RCT evidence about stereotactic radiosurgery than we did regarding ablative techniques, but the RCT comparing different regimens does not allow conclusions to be drawn about the effects of radiosurgery compared with no treatment. RCTs comparing the effects of radiosurgery with no treatment have not been undertaken and are unlikely to be in future because of ethical considerations. Typically, pain relief with radiosurgery is not immediate. [37] We found one cohort study comparing stereotactic radiosurgery versus microvascular decompression (see clinical guide for microvascular decompression, p 16).

OPTION ABLATIVE NEUROSURGICAL TECHNIQUES TO THE GASSERIAN GANGLION (RETROGASSERIAN PERCUTANEOUS RADIOFREQUENCY THERMOCOAGULATION, GLYCEROL RHIZOLYSIS, OR BALLOON COMPRESSION) New

- For GRADE evaluation of interventions for Trigeminal neuralgia, see table, p 21 .
- We found no RCT evidence assessing ablative neurosurgery to the Gasserian ganglion. However, there is some observational data suggesting that radiofrequency thermocoagulation may offer higher rates of complete pain relief than glycerol rhizolysis, but is associated with the highest rate of complications.

Benefits and harms

Ablative neurosurgical techniques to the Gasserian ganglion (retrogasserian percutaneous radiofrequency thermocoagulation, glycerol rhizolysis, or balloon compression):

Three systematic reviews (search dates 2003) [33] [34] [35] identified no RCTs comparing ablative neurosurgical techniques to the Gasserian ganglion (retrogasserian percutaneous radiofrequency thermocoagulation, glycerol rhizolysis, or balloon compression) versus placebo or versus other treatments. [33]

Further information on studies

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:
See clinical guide for stereotactic radiosurgery, p 16 .

GLOSSARY

Microvascular decompression Major neurosurgical procedure that involves access through the posterior fossa to 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.

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

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.

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

SUBSTANTIVE CHANGES

Ablative neurosurgical techniques to the Gasserian ganglion (retrogasserian percutaneous radiofrequency thermocoagulation, glycerol rhizolysis, or balloon compression): New option for which we found no RCTs. Categorised as Unknown effectiveness, although there is some observational evidence suggesting that radiofrequency thermocoagulation may offer higher rates of complete pain relief than glycerol rhizolysis and stereotactic radiosurgery, although it is also associated with the highest rate of complications. [33]

Microvascular decompression New observational data [32] and awareness of consensus that microvascular surgery is effective at reducing symptoms in the long term, although it can lead to ipsilateral hearing loss, led to change of categorisation to Trade-off between benefits and harms (based on consensus).

REFERENCES

1. Classification Subcommittee of the International Headache Society. The international classification of headache disorders. *Cephalalgia* 2004;24(suppl 1):1–160.[PubMed]
2. Katusic S, Williams DB, Beard CM, et al. Epidemiology and clinical features of idiopathic trigeminal neuralgia and glossopharyngeal neuralgia: similarities and differences, Rochester, Minnesota, 1945–1984. *Neuroepidemiology* 1991;10:276–281.[PubMed]
3. Zakrzewska JM. Diagnosis and differential diagnosis of trigeminal neuralgia. *Clin J Pain* 2002;18:14–21.[PubMed]
4. Zakrzewska JM, Hamlyn PJ. Facial pain. In: Crombie IK, Croft PR, Linton SJ, et al, eds. *Epidemiology of pain.* Seattle: IAS Press, 1999:171–202.
5. Katusic S, Beard CM, Bergstralh E, et al. Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945–1984. *Ann Neurol* 1990;27:89–95.[PubMed]
6. Munoz M, Dumas M, Boutros-Toni F, et al. A neuro-epidemiologic survey in a Limousin town. *Rev Neurol (Paris)* 1988;144:266–271.[PubMed]
7. Hall GC, Carroll D, Parry D, et al. Epidemiology and treatment of neuropathic pain: the UK primary care perspective. *Pain* 2006;122:156–162.[PubMed]
8. Devor M, Amir R, Rappaport ZH. Pathophysiology of trigeminal neuralgia: the ignition hypothesis. *Clin J Pain* 2002;18:4–13.[PubMed]
9. Zakrzewska JM. Trigeminal neuralgia. In: Zakrzewska JM, Harrison SD, eds. *Assessment and management of orofacial pain*, 1st ed. Amsterdam: Elsevier Sciences; 2002:267–370.
10. Rothman KJ, Monson RR. Epidemiology of trigeminal neuralgia. *J Chronic Dis* 1973;26:3–12.[PubMed]
11. Rothman KJ, Monson RR. Survival in trigeminal neuralgia. *J Chronic Dis* 1973;26:303–309.[PubMed]
12. Zakrzewska JM, Patsalos PN. Long-term cohort study comparing medical (oxcarbazepine) and surgical management of intractable trigeminal neuralgia. *Pain* 2002;95:259–266.[PubMed]
13. Wiffen PJ, McQuay HJ, Moore RA. Carbamazepine for acute and chronic pain. In: The Cochrane Library, Issue 3, 2005. Chichester, UK: John Wiley & Sons, Ltd. Search date 2004; primary sources Medline (1966–2004), Embase (1994–2004), Sigle (1980–2004), and the Cochrane Controlled Trials Register (Central/CCTR) (The Cochrane Library Issue 3, 2003). In addition, 41 medical journals were hand searched for a previous version of this review. Additional reports were identified from the reference list of the retrieved papers, and by contacting investigators.[PubMed]
14. McQuay H, Carroll D, Jadad AR, et al. Anticonvulsant drugs for management of pain: a systematic review. *BMJ* 1995;311:1047–1052. [PubMed]
15. Taylor JC, Brauer S, Espir MLE. Long-term treatment of trigeminal neuralgia with carbamazepine. *Postgrad Med J* 1981;57:16–18.[PubMed]
16. Sweetman SC, ed. *Martindale: the complete drug reference.* 33rd ed. London: Pharmaceutical Press, 2002.
17. Trigeminal neuralgia. Available online at: http://cks.library.nhs.uk/clinical_knowledge/clinical_topics/previous_version/trigeminal_neuralgia.pdf (last accessed 4 September 2007).
18. Liebel JT, Menger N, Langohr H. Oxcarbazepine in the treatment of trigeminal neuralgia. *Nervenheilkunde* 2001;20:461–465. [In German]
19. Beydoun A. Safety and efficacy of oxcarbazepine: results of randomized, double-blind trials. *Pharmacotherapy* 2000;20:152S–158S.[PubMed]
20. Wiffen P, Collins S, McQuay H, et al. Anticonvulsant drugs for acute and chronic pain. In: The Cochrane Library, Issue 3, 2005. Chichester, UK: John Wiley & Sons Ltd. Search date 1999; primary sources Medline (1966–1999), Embase (1994–1999), Sigle (1980–1999), and the Cochrane Controlled Trials Register (Central/CCTR) (The Cochrane Library Issue 3, 1999). In addition, 41 medical journals were hand searched. Additional reports were identified from the reference list of the retrieved papers, and by contacting investigators.
21. Zakrzewska JM, Chaudhry Z, Nurmikko TJ, et al. Lamotrigine (lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled crossover study. *Pain* 1997;73:223–230.[PubMed]
22. Bittar GT, Graff-Radford SB. The effects of streptomycin/lidocaine block on trigeminal neuralgia: a double blind crossover placebo controlled study. *Headache* 1993;33:155–160.[PubMed]
23. Lemos L, Flores S, Oliveira P, et al. 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.[PubMed]
24. He L, Wu B, Zhou M. Non-antiepileptic drugs for trigeminal neuralgia. In: The Cochrane Library, Issue 4, 2006. Chichester, UK: John Wiley & Sons Ltd. Search date 2005; primary sources Cochrane Neuromuscular Disease Group Register, Medline, Embase, and Lilacs (all to August 2005) and the Chinese Biomedical Retrieval System, the database of the Chinese Cochrane Center (The Cochrane Library, Issue 1, 2005), conference paper databases, bibliographies, and hand searches of 10 Chinese journals. [PubMed]
25. Kondziolka D, Lemley T, Kestle JR, et al. The effect of single-application topical ophthalmic anesthesia in patients with trigeminal neuralgia. A randomized double-blind placebo-controlled trial. *J Neurosurg* 1994;80:993–997.[PubMed]
26. Stajcic Z, Juniper RP, Todorovic L. Peripheral streptomycin/lidocaine injections versus lidocaine alone in the treatment of idiopathic trigeminal neuralgia. A double blind controlled trial. *J Craniomaxillofac Surg* 1990;18:243–246.[PubMed]
27. Lopez BC, Hamlyn PJ, Zakrzewska JM. Systematic review of ablative neurosurgical techniques for the treatment of trigeminal neuralgia. Neurosurgery 2004;54:973–982. Search date 2003; primary sources Medline, Embase, Bids, The Cochrane Library, and references of reported studies.
28. Barker FG 2nd, Jannetta PJ, Bissonette DJ, et al. The long-term outcome of microvascular decompression for trigeminal neuralgia. *N Engl J Med* 1996;334:1077–1083.[PubMed]
29. Zakrzewska JM, Lopez BC, Kim SE, et al. Patient reports of satisfaction after microvascular decompression and partial sensory rhizotomy for trigeminal neuralgia. *Neurosurgery* 2005;56:1304–1311.[PubMed]

30. Piatt JH Jr, Wilkins RH. Microvascular decompression for tic douloureux. *Neurosurgery* 1984;15:456.[PubMed]
31. Zakrzewska JM, Thomas DG. Patient's assessment of outcome after three surgical procedures for the management of trigeminal neuralgia. *Acta Neurochir (Wien)* 1993;122:225–230.[PubMed]
32. Linskey ME, Ratanatharathorne V, Penagaricano J. A prospective cohort study of microvascular decompression and Gamma Knife surgery in patients with trigeminal neuralgia. *J Neurosurg* 2008;109:160–172.[PubMed]
33. Lopez BC, Hamlyn PJ, Zakrzewska JM. Systematic review of ablative neurosurgical techniques for the treatment of trigeminal neuralgia. *Neurosurgery* 2004;54:973–982.[PubMed]
34. Lim JNW, Ayiku L. The clinical efficacy and safety of stereotactic radiosurgery (gamma knife) in the treatment of trigeminal neuralgia. 2004. Available online at: http://www.nice.org.uk/nicemedia/pdf/ip/173systematicreview.pdf (last accessed 4 September2007). Search date 2004; primary sources Biosis, Cochrane Controlled Trials Register (CCTR), The Cochrane Library, CRD Databases (DARE, NHS EED, HTA), Current Controlled Trials, Embase, Medical Research Council (MRC) Clinical Trials Register, Medline, National Research Register, PreMedline, Science Citation Index, and TRIP Database.
35. Lopez BC, Hamlyn PJ, Zakrzewska JM, et al. Stereotactic radiosurgery for primary trigeminal neuralgia: state of the evidence and recommendations for future reports. *J Neurol Neurosurg Psych* 2004;75:1019–1024.[PubMed]
36. Flickinger JC, Pollock BE, Kondziolka D, et al. Does increased nerve length within the treatment volume improve trigeminal neuralgia radiosurgery? A prospective double-blind, randomized study. *Int J Radiat Oncol Biol Phys* 2001;51:449–454.[PubMed]
37. Régis J, Metellus P, Hayashi M, et al. Prospective controlled trial of gamma knife surgery for essential trigeminal neuralgia. *J Neurosurg* 2006;104:913–924.[PubMed]

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Competing interests: JMZ is the author of two systematic reviews, one cohort study, one RCT, and three support data studies. ML declares that he has no competing interests.

Disclaimer

GRADE **Evaluation of interventions for Trigeminal neuralgia.**

Important outcomes	Ability to perform normal activities, Adverse effects, Pain relief, Psychological distress								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of treatments in people with trigeminal neuralgia?									
3 (161) [13]	Pain relief	Carbamazepine versus placebo	4	–2	0	–1	+1	Low	Quality points deducted for sparse data and short follow-up. Directness points deducted for inclusion of different pain severities and uncertainties about diagnostic criteria and outcomes measured. Effect-size point added for OR 2 to 5
1 (143) [15]	Pain relief	Long-term carbamazepine treatment versus stopping carbamazepine earlier	2	–1	–1	0	0	Very low	Quality point deducted for sparse data. Consistency point deducted for different results at different time points
1 (48) [18]	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) [21]	Pain relief	Lamotrigine versus placebo	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, crossover design with no pre-crossover results, and short period of treatment. Directness point deleted for concurrent use of other medication
1 (17) [24]	Pain relief	Baclofen versus carbamazepine	4	–3	0	0	0	Very low	Quality points deducted for sparse data, no intention-to-treat analysis, and poor follow-up
1 (10) [24]	Pain relief	Tizanidine versus placebo	4	–3	0	–1	+2	Low	Quality points deducted for sparse data, short follow-up, and crossover design. Directness point deducted for different results at different time frames (pain relief not sustained). Effect-size points added for RR over 5
1 (12) [24]	**Pain relief**	Tizanidine versus carbamazepine	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and lack of intention-to-treat analysis. Directness point deducted for unclear measurement of outcome
1 (47) [25]	**Pain relief**	Proparacaine hydrochloride versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (37) [26] [22]	Pain relief	Streptomycin plus local anaesthetic versus local anaesthetic alone	4	–2	–2	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency points deducted for conflicting results between RCTs and different results at different time points. Directness point deducted for selection bias in one RCT
1 (87) [36]	Pain relief	Stereotactic radiosurgery using one versus two isocentres	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for inclusion of other interventions
1 (87) [36] [25]	Adverse effects	Stereotactic radiosurgery using one versus two isocentres	4	–2	0	0	0	Low	Quality points deleted for sparse data and incomplete reporting

Important outcomes	Ability to perform normal activities, Adverse effects, Pain relief, Psychological distress								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
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.								