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Carbamazepine for acute and chronic pain in adults

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Abstract

Background—Carbamazepine is used to treat chronic neuropathic pain.

Objectives—Evaluation of analgesic efficacy and adverse effects of carbamazepine for acute and chronic pain management (except headaches).

Search methods—Randomised controlled trials (RCTs) of carbamazepine in acute, chronic or cancer pain were identified, searching MEDLINE, EMBASE, SIGLE and Cochrane CENTRAL to June 2010, reference lists of retrieved papers, and reviews.

Selection criteria—RCTs reporting the analgesic effects of carbamazepine.

Data collection and analysis—Two authors independently extracted results and scored for quality. Numbers needed to treat to benefit (NNT) or harm (NNH) with 95% confidence intervals (CI) were calculated from dichotomous data for effectiveness, adverse effects and adverse event withdrawal. Issues of study quality, size, duration, and outcomes were examined.

Main results—Fifteen included studies (12 cross-over design; three parallel-group) with 629 participants.

Carbamazepine was less effective than prednisolone in preventing postherpetic neuralgia following acute herpes zoster (1 study, 40 participants). No studies examined acute postoperative pain.

Fourteen studies investigated chronic neuropathic pain: two lasted eight weeks, others were four weeks or less (mean 3 weeks, median 2 weeks). Five had low reporting quality. Ten involved

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NOTES This review has been substantially amended following a search for new trials up to June 2010.

fewer than 50 participants; mean and median maximum treatment group sizes were 34 and 29. Outcome reporting was inconsistent.

Most placebo controlled studies indicated that carbamazepine was better than placebo. Five studies with 298 participants provided dichotomous results; 70% improved with carbamazepine and 12% with placebo. Carbamazepine at any dose, using any definition of improvement was significantly better than placebo (70% versus 12% improved; 5 studies, 298 participants); relative benefit 6.1 (3.9 to 9.7), NNT 1.7 (1.5 to 2.0). Four studies (188 participants) reporting outcomes equivalent to 50% pain reduction or more over baseline had a similar NNT.

With carbamazepine, 66% of participants experienced at least one adverse event, and 27% with placebo; relative risk 2.4 (1.9 to 3.1), NNH 2.6 (2.1 to 3.5). Adverse event withdrawals occurred in 12 of 323 participants (4%) with carbamazepine and 0 of 310 with placebo. Serious adverse events were not reported consistently; rashes were associated with carbamazepine. Five deaths occurred in patients on carbamazepine, with no obvious drug association.

Authors' conclusions—Carbamazepine is effective in chronic neuropathic pain, with caveats. No trial was longer than four weeks, of good reporting quality, using outcomes equivalent to at least moderate clinical benefit. In these circumstances, caution is needed in interpretation, and meaningful comparison with other interventions is not possible.

Medical Subject Headings (MeSH)

Acute Disease; Analgesics, Non-Narcotic [adverse effects; *therapeutic use]; Anticonvulsants [adverse effects; therapeutic use]; Carbamazepine [adverse effects; *therapeutic use]; Chronic Disease; Neuralgia [drug therapy]; Neuralgia, Postherpetic [drug therapy]; Pain [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans

BACKGROUND

This updated review was originally published in *The Cochrane Library* as 'Anticonvulsant drugs for acute and chronic pain' (2000, issue 2). At the third update in 2003, 12 new included studies were identified mainly of the newer anticonvulsants gabapentin and lamotrigine. In total the included studies provided data on six different medicines used in at least six identified neuropathic pain conditions. Issues of dose response and trial design added to the complexity. A decision was therefore taken to split that review into a number of smaller reviews each covering one medicine (chemical entity). This review looks at the evidence for carbamazepine. Reviews of gabapentin (Wiffen 2005) and pregabalin (Moore 2009a) have also been completed.

Anticonvulsant drugs currently used for neuropathic pain are: carbamazepine, clonazepam, gabapentin, lamotrigine, oxcarbazepine, phenytoin, topiramate, and valproate; licensed status may vary between regions. Pregabalin is also licensed in some countries for neuropathic pain and the evidence for this has been reviewed (Moore 2009a).

Anticonvulsant drugs have been used in pain management since the 1960s (Blom 1962), very soon after they were first used in medicine and revolutionised the medical management of epilepsy. The clinical impression is that they are useful for neuropathic pain, especially when the pain is lancinating or burning (Jacox 1994). Primary care incidences per 100,000 person years observation of 28 (95% CI 27 to 30) for post-herpetic neuralgia, 27 (26 to 29) for trigeminal neuralgia, 0.8 (0.6 to 1.1) for phantom limb pain and 21 (20 to 22) for painful diabetic neuropathy have been reported in the UK (Hall 2008). Incidence varies between studies, often because of small numbers of cases, and a study of facial pain in The Netherlands found incidences per 100,000 person years of 12.6 for trigeminal neuralgia and 3.9 for postherpetic neuralgia (Koopman 2009). A systematic review of chronic pain incidence demonstrated that some neuropathic pain conditions, like painful diabetic neuropathy, can be more common, with prevalence rates up to 400 per 100,000 person years (McQuay 2007). Some forms of neuropathic pain, like diabetic neuropathy and post surgical chronic pain, which is often neuropathic in origin, are increasing (Hall 2008).

Although these disorders are not common, they can be very disabling. Chronic pain is also associated with substantial changes to the brain, to the extent that chronic pain is argued to be a disease in its own right (Tracey 2009). Effective pain relief is associated with large improvements in associated symptoms like depression, fatigue, sleep problems, quality of life, and work (Hoffman 2010; Moore 2010a).

In addition to use in epilepsy, carbamazepine is licensed in the UK for paroxysmal pain of trigeminal neuralgia (up to 1600 mg daily). The precise mechanisms of action of anticonvulsant drugs in relation to relief of neuropathic pain remain uncertain, but they reduce the ability of the neuron to fire at high frequency (Chong 2000). The two standard explanations are enhanced gamma-aminobutyric acid inhibition (valproate, clonazepam) or a stabilising effect on neuronal cell membranes. A third possibility is action via N-methyl-D-aspartate (NMDA) receptor sites. pain that manifests in different diseases may operate through common mechanisms however the same symptom in two patients may be caused by different mechanisms. It is therefore impossible to predict the mechanisms responsible for an individual's pain based on the aetiology of the neuropathy or on the distribution or nature of symptoms (Woolf 1999). Carbamazepine is thought to work by blocking voltage sensitive sodium channels, meaning that fewer of these channels are available to open, making brain cells less excitable (less likely to fire).

Anticonvulsant drug use is not without risk: serious adverse effects have been reported, including deaths from haematological reactions (blood dyscrasias; Sweetman 2005) and life-threatening cutaneous problems (Chung 2010). The commonest adverse effects are impaired mental and motor function, which may limit clinical use, particularly in older people (Grahame-Smith 1992; Rall 1992; Sweetman 2005).

OBJECTIVES

The purpose of this review was to evaluate the analgesic effectiveness of carbamazepine in acute and chronic pain and to evaluate adverse effects reported in the studies.

METHODS

Criteria for considering studies for this review

Types of studies—Studies were included in this review if they were RCTs investigating the analgesic effects of carbamazepine in patients, with pain assessment as either the primary or a secondary outcome. We excluded studies which were: non-randomised, of experimental pain, case reports, clinical observations or studies of carbamazepine used to treat pain produced by other drugs.

Migraine and headache studies previously included in an earlier version of this review were excluded. This subject is being dealt with in greater depth by the Cochrane Pain, Palliative Care and Supportive Care Review Group.

Types of participants—Adult participants. A wide range of neuropathic pains were considered including: trigeminal neuralgia, post-herpetic neuralgia, diabetic neuropathy, HIV related neuropathy, central pain after stroke, irritable bowel, and temporomandibular joint dysfunction pain. Other types of acute or chronic pain would be accepted if found, but the known use of carbamazepine is in neuropathic pain.

Types of interventions—Administration of carbamazepine, any dose, by any route to provide relief of pain.

Types of outcome measures—Information about the pain condition and number of patients studied, anticonvulsant drug and dosing regimen, study design (placebo or active control, parallel or cross-over), study duration and follow-up, analgesic outcome measures and results, withdrawals and adverse effects (minor and major) was taken from each report using a data extraction sheet.

A variety of outcome measures were used in the studies, the majority using standard subjective scales for pain intensity and/or pain relief.

A hierarchy of outcome measures was agreed as follows:

1. Patient reported pain relief of 50% or greater
2. Patient reported global impression of clinical change
3. pain on movement
4. pain on rest or spontaneous pain
5. Any other pain related outcomes
6. Adverse events

In addition, pain outcomes equivalent to at least moderate benefit (at least 30% pain reduction over baseline) and substantial benefit (at least 50% pain reduction over baseline) recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group were sought (Dworkin 2008). During the updating process consensus was being discussed concerning a common core data set for pain reviews, and to

reflect that we also used a working set of seven outcomes that might form a core data set, and this overlapped to some extent to outcomes already identified:

- At least 50% pain reduction
- Proportion below 30/100 mm (no worse than mild pain)
- Patient global impression
- Functioning
- Adverse event withdrawal
- Serious AE
- Death

Search methods for identification of studies

Studies were identified by several methods. RCTs of anticonvulsants in acute, chronic or cancer pain were identified by MED-LINE (Silver Platter 3.0, 3.1 and 3.11) from 1966 to June 2010, EMBASE 1994 to Dec 2009, SIGLE 1980 to July 1999, and CENTRAL (Issue 4, 2010). This search strategy was narrowed to include carbamazepine only. Additional studies were identified from the reference list of the retrieved papers, and by contacting investigators. Appendix 1 has the MEDLINE and EMBASE search strategies.

For the first version of this review, 41 medical journals were hand searched, chosen from the 50 with the highest number of reports in MEDLINE, and nine specialist journals which were either not on that list or were not indexed (Jadad 1994). The search process included volumes published between 1950 and 1990. No further hand searching has been undertaken as the key journals are now being searched by the Cochrane Collaboration.

Data collection and analysis

Eligibility was determined by reading each study identified by the search. All studies were read by two review authors and agreement was reached by discussion. Only RCTs were included. The studies were not anonymised in any way prior to assessment. Intention-to-treat analysis was not carried out and patients who dropped out of studies were not included in the analysis.

In the first version, a letter was sent to the first author of a report for further information on their published report (method of randomisation, double blinding, outcome measures and dropouts) and to ask if they knew of any other studies which met our inclusion criteria, either undertaken by them or by other investigators. Dichotomous data were used to calculate relative risk or benefit with 95% CIs using a fixed-effect model, together with numbers-needed-to-treat-to-benefit (NNTs) (Cook 1995). This was done for effectiveness, for adverse effects and for drug-related study withdrawal. Meta-analysis was also undertaken when appropriate data were available. NNTs were calculated as the reciprocal of the absolute risk reduction (McQuay 1998). For unwanted effects, the NNT becomes the NNH (number-needed-to-treat-to-harm), and is calculated in the same way.

Assessment of risk of bias in included studies—Each report was scored independently for quality by three of the authors using a three-item scale (Jadad 1996b). They then met to agree a ‘consensus’ score for each report. Quality scores were not used to weight the results in any way.

The three item scale is as follows:

Is the study randomised ? If ‘yes’ , then 1 point.

If described, is the randomisation appropriate? If ‘yes’ add 1 point, if not deduct 1 point.

Is the study double blind ? If ‘yes’, then 1 point.

Is the double blind method appropriate ? If ‘yes’ add 1 point, if not deduct 1 point.

Are withdrawals and dropouts described? (i.e., the number and reason for drop-outs for each of the treatment groups)

If ‘yes’, add 1 point.

Scores of two and below have been associated with greater estimates of efficacy than studies of higher quality (Khan 1996). In this update, a ‘Risk of bias’ table was completed for randomisation, allocation concealment, blinding, size, duration, incomplete outcome assessment, and outcome.

In the process of completing the review, a more extensive list of potential biases was published (Moore 2010b). This added duration (less than 2 weeks, 2-6 weeks, 8-12 weeks), outcome (typically pain reduction less than 30% of baseline, pain intensity reduction 30% from baseline, pain intensity reduction 50% from baseline, though with other definitions), incomplete outcome assessment (how pain measures are dealt with on withdrawal), and treatment arm size (50, 50-199, and 200 patients per treatment arm) as potential sources of bias, with definitions that could be used in risk of bias tables in Cochrane reviews. This updated procedure has been used in this review.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

In this update, 23 potentially relevant studies (24 publications) were identified, of which 15 studies (16 publications) are included (629 participants, 447 receiving carbamazepine). One study is awaiting assessment Liebel 2001. Two studies awaiting assessment in the previous version have now been processed (Harke 2001; Wilton 1974); however, two further studies have been identified but are not available for inclusion (Badran 1975; Liebel 2001). Details of included studies are given in the ‘Characteristics of included studies’. In an earlier version of this review data were requested from 19 authors but only one (Leijon 1989) was able to

supply information relevant to this review. In this update, no further attempt was made to contact authors.

A wide range of carbamazepine doses, ranging from 100 mg to 2400 mg daily, were used for in these studies (Nicol 1969). Crossover studies predominated; only three had a parallel group design (Gerson 1977; Jia 2006; Vilming 1986). A single study in acute herpes zoster examined whether carbamazepine reduced later development of postherpetic neuralgia (Keczkes 1980). Chronic pain conditions studies included trigeminal neuralgia, painful diabetic neuropathy, postherpetic neuralgia, and post stroke pain.

Many of the studies were relatively old, with five published in the 1960's. Only one study (Jia 2006) has been published in the last ten years. A consequence of the age of the studies is that outcomes - pain, adverse event, and discontinuation - were reported inconsistently. Pooling of trial data in meta-analyses was therefore problematical, because few studies reported the same outcomes in the same way in the same condition.

Risk of bias in included studies

Out of a maximum of five points, one study scored 5 points, five scored 4 points, three scored 3 points, and five scored 2 points on the Oxford Quality Scale. Points were lost due to studies not being double blind (Gerson 1977; Keczkes 1980; Rasmussen 1970) or failure to adequately report withdrawals or details of the randomisation and blinding processes. Scores for individual trials are reported in the notes section of 'Characteristics of Included Studies' table.

A risk of bias table was completed for randomisation, allocation concealment and blinding. Three studies were potentially at high risk of bias due to issues around blinding (Gerson 1977; Keczkes 1980; Rasmussen 1970) and allocation concealment (Rasmussen 1970) (Figure 1).

There are three other potential sources of bias in the included studies, relating to size, duration, and outcome.

Numbers of participants were small ranging from 9 to 132 in chronic pain studies (mean 40, median 30 participants). Studies were small because 12 of the 15 studies were cross-over and only three were three parallel-group studies (Gerson 1977; Jia 2006; Vilming 1986); mean and median maximum treatment group sizes were 34 and 29 participants. Small studies can be associated with larger treatment effects than bigger studies (Counsell 1994; Moore 1998a; Moore 1998b).

Chronic pain studies were short, and while duration of the intervention ranged from two three-day crossover comparisons (Rockliff 1966) to 42 months (Nicol 1969), studies were generally four weeks or shorter (mean three weeks, median two weeks). Only two eight-week studies lasted more than four weeks (Gerson 1977; Lechin 1989). Chronic pain studies of six weeks or less have been shown to manifest greater treatment effects than those of eight weeks or more (Moore 2009b).

A variety of different pain outcomes was reported, including average pain scores, raw individual pain scores (though not always complete), dichotomous outcomes like the proportion with any improvement or benefit, including scores (like global impression of change) equivalent to IMMPACT outcomes of moderate or substantial benefit (Dworkin 2008); some studies gave little or no indication of how many patients benefited from treatment. Higher levels of benefit (e.g. 50% pain relief rather than any pain relief) result in higher NNTs (Moore 2009b).

The question of whether cross-over trials exaggerate treatment effects in comparison with parallel group designs, as has been seen in some circumstances (Khan 1996), is a general effect is unclear (Elbourne 2002). The predominance of cross-over trials in this review has to be considered as a possible source of additional bias. In these circumstances, caution is needed in interpreting the data as far as efficacy is concerned. In particular, meaningful comparison of efficacy with other interventions is not possible.

Effects of interventions

Fifteen studies were suitable for inclusion. Three additional studies were included in this updated review. Details of results in individual studies are presented in Appendix 2.

Acute pain—Comparing carbamazepine 400 mg daily with prednisolone (40 mg daily for 10 days reducing to zero over three subsequent weeks) in the management of acute herpes zoster, participants treated with prednisolone reported less pain and faster skin healing on average (3.7 weeks compared to 5.3 weeks) than those treated with carbamazepine. At two months 13 of 20 carbamazepine participants developed postherpetic neuralgia compared with 3 of 20 treated with prednisolone (Keczkes 1980).

No studies were found that investigated carbamazepine for the treatment of established acute pain after surgery, including third molar extraction.

Chronic pain—Studies in chronic pain all involved neuropathic pain. We could find no randomised studies that tested carbamazepine in musculoskeletal conditions like arthritis or back pain, or other chronic painful conditions.

Trigeminal neuralgia—Eight studies of carbamazepine in trigeminal neuralgia were identified. Two of these (Killian 1968; Rasmussen 1970) also recruited some participants with other neuralgias; one reported results on trigeminal neuralgia separately (Rasmussen 1970), while in the other 30 of 42 participants had trigeminal neuralgia (Killian 1968).

Five were placebo-controlled (Campbell 1966; Killian 1968; Nicol 1969; Rasmussen 1970, Rockliff 1966). Using dose titration to a maximum daily dose of 1000 mg, 19 of 27 participants had a complete or very good response with carbamazepine compared with minimal or no response with placebo on five days' treatment in a subset of patients with trigeminal neuralgia (Killian 1968). Again using dose titration and a cross-over design, but to a maximum daily dose of 2400 mg, 15 of 20 participants randomised to initial carbamazepine had a good or excellent response after 14 days' treatment, compared with 6 of 24 reporting good or excellent response who started on placebo (Nicol 1969). Superiority

of carbamazepine was also claimed by Rockliff (Rockliff 1966) in a small study of nine participants with three days' treatment with carbamazepine, but no evaluable data were presented. The study from Rasmussen 1970 contained a mixture of typical trigeminal neuralgia, atypical neuralgia and a 'non neuralgiform' group. The study was not blinded, and appears to have been conducted without patient consent (states 'patients not informed'). The outcomes used were 'good effect' (after five days, 46 of 55 with trigeminal neuralgia had good effect on carbamazepine, compared with 8 of 55 on placebo), though it is not clear what this means in terms of pain relief.

A study by Campbell 1966 reported results by the number of changes in the pain score; this study has been removed from the analyses in this version as the numbers presented in the paper are events rather than patient data. It had claimed a mean fall in maximum pain intensity of 58% after two weeks with carbamazepine 400 to 800 mg daily compared to 26% with placebo.

Combining the short-term results for any measure of benefit from the studies with dichotomous pain relief outcomes (Killian 1968; Nicol 1969; Rasmussen 1970) produced, in 208 participants, a relative benefit for carbamazepine compared to placebo of 5.9 (3.6 to 9.6), and a NNT of 1.5 (1.3 to 1.8). Restricting the analysis to randomised and double blind studies (Killian 1968; Nicol 1969) produced, in 98 participants, a relative benefit for carbamazepine compared to placebo of 6.0 (2.8 to 13), and a NNT of 1.7 (1.3 to 2.2).

Three active controlled studies were identified. Carbamazepine was compared with tizanidine (an alpha-2 adrenergic agonist for spasticity associated with multiple sclerosis or spinal cord injury) (Vilming 1986), tocainide (an antiarrhythmic drug) (Lindstrom 1987) and pimozide (an antipsychotic drug) (Lechin 1989). Carbamazepine produced better results than tizanidine over three weeks in a total of 12 participants; there was no significant difference in the tocainide study in 12 participants over two weeks; pimozide produced better results than carbamazepine in 59 participants over eight weeks.

Diabetic neuropathy—Four studies evaluated carbamazepine in diabetic neuropathy (Gomez-Perez 1996; Jia 2006; Rull 1969; Wilton 1974).

Two were placebo controlled (Rull 1969; Wilton 1974). In a complicated three-way cross-over, Rull 1969 found that, using the top two levels of pain improvement (3 points or better out of 5), in the first two of three cross-over periods for each group, 17 of 30 improved with carbamazepine and 2 of 30 for placebo. The other study (Wilton 1974) reported only on preferences after one week of treatment with carbamazepine and placebo; 24 of 40 preferred carbamazepine, 14 of 40 preferred placebo, and 2 of 40 had no preference.

Two active controlled studies met the inclusion criteria. One compared carbamazepine 200 mg to a nortriptyline 10 mg plus fluphenazine 0.5 mg combination over four weeks (Gomez-Perez 1996). No significant difference was found between carbamazepine and the nortriptyline combination; both treatments improved paraesthesia and pain. Jia 2006 compared venlafaxine with carbamazepine over two weeks in 132 participants, with both

drugs given at fixed and relatively low dose. Both drugs demonstrated effect with venlafaxine showing a somewhat larger mean effect.

Post-herpetic neuralgia—An active-controlled study (Gerson 1977) compared a combination of carbamazepine (up to 1000 mg daily) plus clomipramine (up to 75 mg daily) with transcutaneous electronic nerve stimulation (TENS) in 29 participants over eight weeks. The study authors report that the drug combination was superior to TENS in terms of pain relief: 50% pain intensity reduction or more was achieved by 7 of 16 and 0 of 13 with drug combination and TENS respectively, and 30% pain intensity reduction or more was achieved by 8 of 16 and 0 of 13 respectively.

Post stroke pain—A cross-over study compared carbamazepine, amitriptyline, and placebo, with a treatment duration of four weeks for each (Leijon 1989). Global report of any improvement occurred in 10 of 15 on amitriptyline, 5 of 15 on carbamazepine, and 1 of 15 on placebo.

Overall estimation of efficacy—Five studies with 298 participants contributed dichotomous outcomes of the highest available definition of improvement for carbamazepine and placebo (Killian 1968; Leijon 1989; Nicol 1969; Rasmussen 1970; Rull 1969), though over relatively short treatment duration (Analysis 1.1). The results were consistent (Figure 2), and overall 70% of patients improved on carbamazepine compared with 12% on placebo. Carbamazepine at any dose, and using any definition of improvement, was significantly better than placebo (Figure 3), with a relative benefit of 6.1 (3.9 to 9.7) and NNT of 1.7 (1.5 to 2.0) (Summary of results A). Results did not change in any major way by restriction to randomised and double blind trials (Summary of results A).

Using data from 188 participants in four studies (Killian 1968; Leijon 1989; Nicol 1969; Rull 1969) with an outcome equivalent to the IMMPACT outcome of substantial improvement gave a 60% response rate with carbamazepine and 10% with placebo, with an NNT of 1.9 (1.6 to 2.5). Using the lowest level of benefit in the five studies gave an 80% response rate with carbamazepine and 23% with placebo, with an NNT of 1.7 (1.5 to 2.1).

Summary of results A: Efficacy outcomes with carbamazepine in postherpetic neuralgia Withdrawals—

Outcome	Number of		Percent with outcome			
	Studies	Participants	Carbamazepine	Placebo	Relative benefit (95% CI)	NNT (95% CI)
Pain relief						
Highest level available	5	298	70	12	6.1 (3.9 to 9.7)	1.7 (1.5 to 2.0)
IMMPACT substantial	4	188	61	10	6.5 (3.4 to 12)	1.9 (1.6 to 2.5)
Lowest level available	5	298	81	23	3.5 (2.6 to 4.8)	1.7 (1.5 to 2.1)

Outcome	Number of		Percent with outcome			
	Studies	Participants	Carbamazepine	Placebo	Relative benefit (95% CI)	NNT (95% CI)
Highest level available (restricted to randomised and double blind)	4	188	61	10	6.5 (3.4 to 12)	1.9 (1.6 to 2.5)
Other outcomes						
Adverse event withdrawal	9	573	4	0	not calculated	
At least one AE	4	346	66	27	2.4 (1.9 to 3.1)	2.6 (2.1 to 3.5)

Withdrawals—Nine studies provided information on adverse event withdrawals with carbamazepine (Campbell 1966; Gomez-Perez 1996; Killian 1968; Lechin 1989; Leijon 1989; Lindstrom 1987; Nicol 1969; Rasmussen 1970; Wilton 1974). In these studies, 12 of 323 participants (4%) withdrew because of adverse events with carbamazepine, compared with 0 of 310 with placebo. There were a further three adverse event withdrawals from 16 participants on a combination of carbamazepine and clomipramine (Gerson 1977).

At least one adverse event—Four studies provided information on participants experiencing at least one adverse event (Campbell 1966; Lechin 1989; Leijon 1989; Wilton 1974). Adverse event experience was more common with carbamazepine (66% of participants) than placebo (27%), relative risk 2.4 (1.9 to 3.2), NNH 2.6 (2.1 to 3.5) (Summary of results A).

Serious adverse events—Serious adverse events were not reported consistently, and that included the absence of negative statements that there were no serious adverse events. Only one study (Gomez-Perez 1996) reported an adverse event as serious, a case of upper gastrointestinal bleeding thought to be associated with alcohol rather than carbamazepine. Rashes associated with carbamazepine were reported by Rasmussen 1970 (3) and Rull 1969 (2); these may be considered serious because of association with Stevens-Johnson syndrome.

Deaths—Five deaths occurred on carbamazepine. Nicol 1969 reported four deaths; Two participants died suddenly, presumably of cardiovascular disease, one had a brain tumour, and one died of progressive debilitating disease. Rasmussen 1970 reported one death associated with cardiovascular disease.

Specific adverse effects—Specific adverse events reported at high incidence (>10%) included giddiness, dizziness, unsteadiness, and somnolence. These were not reported in sufficient detail to be combined, but the incidence of somnolence and dizziness was as high as 40-60% on carbamazepine.

DISCUSSION

Much has been written about how to justify the use of our long-established medical interventions. While the randomised controlled trial (RCT) is the gold standard for the assessment of health care technologies and interventions (DOH 1992), buttressed by double blinding when the outcome measures are subjective (Colditz 1989; Schulz 1994; Turner 1994), the fact remains that many interventions are time-honoured rather than RCT-honoured. On whom then does the burden of proof fall? (Eddy 1993). The aim of this systematic review was to review the effectiveness and safety of the anticonvulsant drug carbamazepine in the management of pain. Since the first version of this review, gabapentin has become established as a treatment for neuropathic pain, and is now licensed for this indication in a number of countries. More recently both lamotrigine and pregabalin have been assessed in chronic pain studies. These agents are considered in other Cochrane reviews (Moore 2009a; Wiffen 2005; Wiffen 2007).

Summary of main results

Carbamazepine generally provided better pain relief than placebo in a comparison that included several different chronic neuropathic pain conditions (trigeminal neuralgia, painful diabetic neuropathy, postherpetic neuralgia, and central post stroke pain). Five placebo-controlled studies provided some indication of pain improvement over the short term, with 70% improving on carbamazepine compared with 12% with placebo, leading to an NNT of 2. However, these were short term studies, with poorly defined outcomes, in only 298 participants (only a tenth of the number of participants available for one dose of pregabalin, for instance; (Moore 2009a). The NNH for minor harm was 4, though again reporting was neither consistent nor complete.

There is no evidence for carbamazepine being effective in established acute pain, and very limited evidence for any efficacy in acute herpes zoster.

What we have is a good indication that carbamazepine can produce good levels of pain relief for some patients with distressing chronic painful conditions.

Overall completeness and applicability of evidence

The problems are:

- Limited size, with all but two studies involving fewer than 60 participants.
- Short duration, with all but two studies being four weeks or less in treatment duration.
- Inadequate outcomes, with inconsistent reporting not allowing outcomes equivalent to IMMPACT outcomes of at least moderate benefit to be assumed.

Despite this, carbamazepine has been used with good effect in many patients suffering chronic neuropathic pain, and the results that we do have support this.

Poor quality reporting limited the ability to combine data, because many studies reported insufficient information, used a variety of different outcome measures, and several studies

used variable dosing. Although the authors of the original reports were originally contacted by letter, not all of them replied, and of those who did, only Leijon 1989 was able to provide additional data.

Doses of carbamazepine used in some of the studies were small; Gomez Perez, for example, used 200 mg daily, which while effective in some is not effective in all (Taylor 1981). Dose escalation was rapid in some studies, potentially resulting in adverse effects. Although carbamazepine takes 2-4 days to achieve its maximum effect, autoinduction of enzymes that metabolise the drug, which is complete at three weeks, often means that late dose increases are needed. These factors are largely ignored, and this limits the applicability of the available evidence.

These studies do not provide adequate information about adverse events, and in particular serious adverse events. This is of particular importance for serious cutaneous adverse events in particular parts of the world. A strong genetic association between HLAB*1502 and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis has been shown in Han Chinese (Chung 2010), Indian (Mehta 2009), and Thai (Tassaneeyakul 2010) populations, and Asian populations generally may be more susceptible. While the frequency of this allele is low in Europe, its frequency in Asian populations is 5-10% (Chung 2010). Carbamazepine is the most common causative agent for Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe (8% of total), rising to 26% in Taiwan, 36% in Malaysia and 28% in Singapore (Chung 2010).

There is also an interaction between carbamazepine and warfarin metabolism which can be of major clinical importance (Herman 2006). If treatment with carbamazepine cannot be avoided, patients taking warfarin should be frequently monitored, especially when initiating or stopping carbamazepine therapy

Quality of the evidence

Several possibilities exist for bias: 5 of 14 chronic pain studies had quality scores of 2 of 5 on the Oxford Quality Scale, studies were small, short, and with inadequate definition of benefit. For each of these there is some evidence that they could be the source of systematic bias, and this significantly reduces the weight we can give the evidence we have. In particular, it limits comparability of carbamazepine results with results for other interventions obtained from larger, longer, and better studies and meta-analyses.

In order to be sure that carbamazepine works in chronic painful conditions and to be confident of the magnitude of the effect, the ideal would be several large randomised double blind studies comparing carbamazepine at sensible doses with placebo, over 8-12 weeks, and using IMMPACT outcomes (perhaps at least moderate improvement or benefit) or their equivalent in each of several clinical conditions, as we have for pregabalin, for example (Moore 2009a). We actually have only two studies of sufficient duration; one using a combination of carbamazepine and clomipramine (Gerson 1977) with 29 participants in postherpetic neuralgia had a quality score of 2 of 5 and reported an IMMPACT equivalent outcome, while the other (Lechin 1989), with 59 participants in trigeminal neuralgia, had a quality score of 4 of 5 but reported only an undefined improvement.

Potential biases in the review process

Criteria for assessing potential biases in chronic pain are becoming more stringent as new biases are being discovered (Moore 2010b). Potential biases in the review process derive from including studies with the potential for bias, though the review has sought to highlight the potential for bias when it occurs.

Using only criteria of sufficient stringency to avoid all these potential biases would reduce the pool of included studies to nil, which, given that carbamazepine is used to treat neuropathic pain, is less than helpful.

Agreements and disagreements with other studies or reviews

The results of this review are generally in agreement with the previous version. We are not aware of any other systematic reviews specifically concerning carbamazepine, but a broad overview of interventions for neuropathic pain (Finnerup 2005) had a combined NNT for efficacy of 2.0 (1.6-2.5), very similar to our estimate of 1.7 (1.5 to 2.0). The source of the small difference cannot be ascertained from details provided.

AUTHORS' CONCLUSIONS

Implications for practice

Acute pain—Carbamazepine was ineffective in acute herpes zoster (Keczkes 1980). There is no logic in using anticonvulsants to manage acute nociceptive pain when there are effective pain relieving drugs. Carbamazepine has no obvious place in the treatment of acute pain.

Chronic pain—The use of carbamazepine in neuropathic pain has stood the test of time and is likely to be chosen in situations where treatment cost is of prime importance. These studies indicate that for every two patients with neuropathic pain treated with carbamazepine at least one will achieve at least moderate pain relief in the short term who would not have done with placebo; overall about 70% achieve some level of pain relief. However, the numbers of participants in trials is generally small and study duration short.

Medical students are often taught that a positive response to carbamazepine is 'diagnostic' for trigeminal neuralgia. While about 70% of patients respond with carbamazepine, 30% do not, and 12% respond with placebo. If only one patient responds out of two treated this statement needs to be qualified. One caveat is that the study populations may include patients who have had other interventions, such as nerve blocks, and the NNT for effectiveness may be more impressive in trigeminal neuralgia treated with carbamazepine in the initial stages. Clinically it appears that trigeminal neuralgia can become refractory to carbamazepine.

The usual clinical decision for chronic neuropathic pain is a choice between antidepressant and anticonvulsant as first-line treatment, and there is insufficient evidence to support the use of carbamazepine as first line. In addition the need for laboratory monitoring and significant drug interactions with the use of carbamazepine have discouraged the use of carbamazepine with the emergence of newer compounds like gabapentin and pregabalin.

Implications for research

This review shows that there is still a need for large, high quality, long duration studies using sensible outcomes to establish relative effectiveness of different anticonvulsants in chronic pain syndromes, and for comparisons of other treatments such as antidepressants with anticonvulsants; appropriate trial designs have been suggested for this (Moore 2009c). The usefulness of such studies would be increased greatly by improvements in the quality of reporting, and particularly with use of clinically important end points rather than undefined improvement. Investigators presenting data as means for treatment and control should also consider the (simple) presentation of categorical and binary data. It is unlikely that the pharmaceutical industry will conduct further studies of carbamazepine but national funding agencies might be willing to investigate this drug further. Enriched enrolment randomised withdrawal studies have real potential (McQuay 2008).

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Campbell 1966

Methods	Multicentre, randomised, double blind, placebo controlled, cross-over. Not enriched. Duration 8 weeks (4 two-week periods)
Participants	Trigeminal neuralgia N = 77 (but 7 excluded, 6 for logistic problems, one for a rash) 36 started on carbamazepine, 34 (report says 35 in one place) started on placebo Age range 20 to 84 (mean 59) years. Male 34%
Interventions	CBZ 100 mg 4 × daily to 200 mg 3 × daily (1 centre), or 200 mg 4 × daily (2 centres) Placebo Order of treatment CBZ, P, CBZ, P or P, CBZ, P, CBZ
Outcomes	Pain intensity: 4 point scale to determine "upgrading" Frequency of paroxysms and triggers Adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1, Total = 5 Geigy supplied tablets
<i>Risk of bias</i>	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'random number lists'
Allocation concealment (selection bias)	Unclear risk	'neither patient nor doctor knowing the order of therapy given'
Blinding (performance bias and detection bias) Active and controlled appeared similar	Low risk	'placebo indistinguishable in appearance from active drugs'
Duration	High risk	two week treatment period
Outcome	High risk	upgrading not level of change
Incomplete outcome assessment	Unclear risk	not stated
Size	High risk	group size below 50

Gerson 1977

Methods	Randomised, open, active control, parallel group. Not obviously enriched. Duration 8-10 weeks No follow-up
Participants	Postherpetic neuralgia N = 29 Age and sex not reported
Interventions	CBZ 150 mg to 1000 mg daily plus clomipramine 10 to 75 mg daily; N = 16. (Note potentially high dose of CBZ) TENS 15 mins per week for 4 weeks; N = 13 Four participants who did not benefit from drug treatment were allowed to cross over to TENS. Eight who did not benefit on TENS crossed to drug treatment
Outcomes	Pain intensity: VAS, categorical? (responder = >50% reduction in pain, >30% reduction in pain) Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 0, W = 1, Total = 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'patients randomly allocated'
Allocation concealment (selection bias)	Unclear risk	No statement
Blinding (performance bias and detection bias) Active and controlled appeared similar	High risk	Open-label study
Duration	Low risk	8-10 weeks
Outcome	Low risk	50% responder
Incomplete outcome assessment	Unclear risk	Not stated
Size	High risk	group size below 50

Gomez-Perez 1996

Methods	Randomised, double blind, double dummy, active controlled, cross-over (washout and phase 2 only). Duration two 30 day treatment periods plus washout. Not obviously enriched	
Participants	Adult patients with diabetic neuropathy - severe pain N=16 Age and sex not stated	
Interventions	CBZ 300 mg to 600 mg daily Nortriptyline 10 mg plus fluphenazine 0.5 mg combination (3 to 6 tablets daily) Dose increment over 3 days then stable to day 15 then double dose for next 15 days 2 to 4 weeks washout then cross-over	
Outcomes	Symptom intensity for pain and paraesthesia: Vertical VAS 0-100% Withdrawals Adverse events	
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1, Total = 4 Geigy supplied the drugs	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	‘randomly assigned’
Allocation concealment (selection bias)	Unclear risk	No statement
Blinding (performance bias and detection bias) Active and controlled appeared similar	Low risk	‘an identical placebo tablet of the comparing drug was given simultaneously with the active drug’ Double dummy design
Duration	Unclear risk	4 week treatment periods
Outcome	Low risk	At least 50% decrease of pain
Incomplete outcome assessment	Unclear risk	not stated
Size	High risk	group srze below 50

Jia 2006

Methods	Randomised, double blind, double dummy, active control, parallel group. Not obviously enriched Duration 14 days	
Participants	Painful peripheral diabetic neuropathy N = 132 (66 in each treatment group) Age and sex not reported	
Interventions	CBZ 100 mg twice daily Venlafaxine 25 mg twice daily	
Outcomes	Numerical pain intensity scores using 11 point Likert scale Assessment of ADL, sleep and mood Withdrawals Adverse events	
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1, Total = 5	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'random sequence generated by computer'

Allocation concealment (selection bias)	Low risk	'sealed opaque envelopes'
Blinding (performance bias and detection bias) Active and controlled appeared similar	Low risk	Double dummy design. 'each patient took venlafaxine 25mg plus one dummy carbamazepine' or vice versa
Duration	High risk	14 days
Outcome	High risk	Mean data only, no responder analysis
Incomplete outcome assessment	Unclear risk	Not stated
Size	Unclear risk	66 in each treatment group

Keczkes 1980

Methods	Randomised, probably not blind, active control, parallel group. Duration 4 weeks. Clinic follow-up until no pain (maximum > 1 year)
Participants	Acute herpes zoster N = 40 participants All over 50 years old. Sex not reported
Interventions	CBZ 100 mg 4 × daily Prednisolone 40 mg daily for 10 days then reduced to nought over next 3 weeks Topical antibiotics on the lesions. Carbamazepine was regarded as a placebo by the investigators Free access to analgesics in the post-herpetic neuralgic phase but not in the acute phase
Outcomes	Pain, skin healing, incidence of postherpetic neuralgia (> 2 months)
Notes	Oxford Quality Score R = 1, DB = 0, W = 0, Total = 1

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'allocated randomly'
Allocation concealment (selection bias)	Unclear risk	No statement
Blinding (performance bias and detection bias) Active and controlled appeared similar	High risk	No statement
Duration	Unclear risk	duration 4 weeks
Outcome	Unclear risk	No applicable outcomes
Incomplete outcome assessment	Unclear risk	Not applicable
Size	High risk	group size below 50

Killian 1968

Methods	Randomised, double blind, placebo controlled, partial cross-over. Duration 10 days (2 5-day periods). Not obviously enriched Open follow-up, range 2 weeks to 36 months
Participants	Trigeminal neuralgia N = 30. PHN, n = 6, other chronic neuralgia, n = 6.

	36 of 42 participants studied double blind (24 of 32 with TN) Age range 36 to 83 (mean 52) years, Female 66%	
Interventions	Carbamazepine dose titration 400 mg to 1g daily Placebo	
Outcomes	Complete or very good pain response Withdrawals Adverse events	
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1, Total = 4 Geigy sponsored	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	‘which were randomised’
Allocation concealment (selection bias)	Unclear risk	No statement
Blinding (performance bias and detection bias) Active and controlled appeared similar	Low risk	‘a double blind technique ...consisted of identical tablets’
Duration	High risk	5 day treatment period
Outcome	Low risk	Complete or very good pain response is equivalent to 50% pain relief
Incomplete outcome assessment	Unclear risk	Not stated
Size	High risk	groups size below 50

Lechin 1989

Methods	Multicentre (4), randomised, double blind, active control, cross-over. Duration 24 weeks (4 week run-in, then two 8-week periods with 4-week washout). Not enriched Open follow up on pimoizide.	
Participants	Trigeminal neuralgia. Duration of illness 8-17 (median 13.2) years N = 59 randomised. Only 48 evaluated due to protocol violation and dropout Age 48 to 64 (mean 59.3) years. Male 24, Female 24	
Interventions	CBZ 300 to 1200 mg daily in 2 divided doses Pimoizide 4 to 12 mg daily in 2 divided doses Step titration with daily doses as follows: CBZ and pimoizide, days 1 to 4 300 mg and 4 mg respectively; days 5 to 9 600 mg and 6 mg respectively; days 10 to 14, 900 mg and 8 mg respectively; day 15 to end of treatment, 1200 mg and 12 mg respectively	
Outcomes	TN symptom score Adverse events	
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1, Total = 4 Grant from Foundation of the institute for Experimental Medicine	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'patients were randomly distributed in two groups'
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias)	Low risk	'all medications were administered in identical dark capsules'

Active and controlled appeared similar

Duration	Low risk	8 weeks treatment
Outcome	High risk	Average pain score
Incomplete outcome assessment	Unclear risk	Not stated
Size	High risk	group size below 50

Leijon 1989

Methods	Randomised, double blind, double dummy, active control, cross-over. Duration 14 weeks (three 4-week periods with two one-week washouts). No follow up. Partially enriched
Participants	Central post stroke pain N=15 Age not reported, Male 12, Female 3
Interventions	Stepped increase to final dose of CBZ 800 mg daily starting at 100 mg 2 × daily on day 1 then increasing on days 2, 6, 15, 18 Stepped increase to final daily dose of amitriptyline of 25 mg in the morning and 50 mg at night, starting at 12.5 mg 2x daily on day 1 then increasing on days 2, 6, 15, 18
Outcomes	Daily pain intensity (10 step verbal scale), post treatment global rating Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1, Total = 4 Sponsorship - Swedish public funds

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'treatment given in randomised order'
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Active and controlled appeared similar	Low risk	'identical capsules containing active drug or lactulose(!) were given in double dummy technique'
Duration	Unclear risk	4 week treatment periods
Outcome	Low risk	Individual pain response levels shown
Incomplete outcome assessment	Unclear risk	Not stated
Size	High risk	group size below 50

Lindstrom 1987

Methods	Randomised, double blind, active control, cross-over (two 2 week periods - washout?). No follow up. Not enriched
Participants	Trigeminal neuralgia. N = 12 Age 41-78 years. Male 5, Female 7.
Interventions	CBZ to maximum tolerated dose Tocainide 20 mg/kg in 3 divided daily doses. Actual doses not reported

Outcomes	TN score consisted of severity, frequency and duration of attacks	
Notes	Oxford Quality Score: R = 1, DB = 1, W = 0, Total = 2 Sponsored by Folsam Research Foundaton, Vivian L Smith Foundation	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'randomised double blind technique'
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Active and controlled appeared similar	Unclear risk	Stated as double blind but no further information
Duration	High risk	2 week treatment
Outcome	Low risk	Individual start and end pain scores given
Incomple outcome assessment	Unclear risk	Not stated
Size	High risk	group size below 50

Nicol 1969

Methods	Randomised, double blind, placebo controlled, partial crossover (successful first treatment period stayed on same treatment). Duration of treatment 2-42 months. Not obviously enriched Follow up 46 months.		
Participants	Facial pain N = 64, 54 with trigeminal neuralgia. Results presented on 44 TN only, due to insufficient follow up Age not given. Male 21, Female 23		
Interventions	CBZ dose titration 100 mg to 2.4 g daily Placebo Participants started on one treatment and increased dose to 8 tablets daily. At two weeks, if no satisfactory results, the second treatment was substituted 20 had carbamazepine only, 7 had placebo only. 17 had placebo then carbamazepine		
Outcomes	Withdrawals		
Notes	Oxford Quality Score: R = 1, DB = 1, W = 1, Total = 3 Geighy supplied the tablets		
<i>Risk of bias</i>			
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Unclear risk	'randomised investigation'	
Allocation concealment (selection bias)	Unclear risk	Not stated	
Blinding (performance bias and detection bias) Active and controlled appeared similar	Unclear risk	Stated as double blind but no further information	
Duration	Low risk	long duration	12 weeks
Outcome	Unclear risk	Probable that response was equivalent to 30% pain relief	

Incomplete outcome assessment	Unclear risk	Not stated
Size	High risk	Partial crossover means that groups size was below 50

Rasmussen 1970

Methods	Single blind, placebo controlled, cross-over study based on drawn lots (three 5-day periods as either active-placebo-active or placebo-active-placebo). Partial enrichment, participants who had previously received carbamazepine were excluded
Participants	Facial pain divided into 3 groups: typical trigeminal neuralgia, n = 40, atypical trigeminal neuralgia, n = 16, non neuralgiform, n = 15 Total N = 71 80% aged over 60 years. Sex not reported
Interventions	CBZ 1 tablet 2 or 3x daily. Actual dose not stated. Assumed to be 200 mg tablets Placebo
Outcomes	'Good effect' not clearly defined. Withdrawals Adverse events
Notes	Oxford Quality Score: R = 1, DB = 0, W = 1, Total = 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Lots were drawn'
Allocation concealment (selection bias)	High risk	Statement that authors were aware of the code
Blinding (performance bias and detection bias) Active and controlled appeared similar	High risk	Statement that authors were aware of the code
Duration	High risk	5 day treatment period
Outcome	High risk	no definition
Incomplete outcome assessment	Unclear risk	Not stated
Size	Unclear risk	group size over 50 in crossover study

Rockliff 1966

Methods	Randomised, double blind, placebo controlled, cross-over. Duration two 3-day periods. No washout. Not obviously enriched
Participants	Trigeminal neuralgia. Duration of illness 2 weeks to 30 years N = 9 Mean age 65 (37-81) years. Male 1 Female 8
Interventions	Carbamazepine 200 mg or placebo 3x daily for 3 days, then crossover
Outcomes	
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1, Total = 1 Geigy supplied the tablets

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'the sequence as pre-randomised'
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Active and controlled appeared similar	Low risk	'similar appearing tablets were given'
Duration	High risk	3 days treatment
Outcome	High risk	Preference rather than level of pain relief
Incomplete outcome assessment	Unclear risk	Not stated
Size	High risk	group size below 50

Rull 1969

Methods	Randomised, double blind, placebo-controlled, cross-over. Duration 6 weeks (three 2-week periods), no follow-up. Not obviously enriched
Participants	Diabetic neuropathy N = 30 Mean age 54 (21-81) years. Male 21, Female 30
Interventions	CBZ 200 mg to 600 mg daily Placebo Sequence CBZ, P, CBZ or P, CBZ, P
Outcomes	Adverse events
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1, Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'on a random basis, individuals were assigned'
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Active and controlled appeared similar	Low risk	'both drug and placebo were identical'
Duration	High risk	2 week treatment period
Outcome	Low risk	individual patient level results available
Incomplete outcome assessment	Unclear risk	Not stated
Size	High risk	Group size below 50

Vilming 1986

Methods	Randomised, double blind, active control, parallel group. 3 weeks, no follow up. Not obviously enriched
Participants	Trigeminal neuralgia. N = 12. Age range 47-72 years

Interventions	CBZ titrated to maximum of 300 mg 3 × daily Tizanidine 6 mg 3 × daily Dose titrated over 12 days and continued for a further 9 days	
Outcomes	Pain intensity, pain relief, global assessment	
Notes	Oxford Quality Score: R = 1, DB = 1, W = 1, Total = 3	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'randomly allocated'
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Active and controlled appeared similar	Unclear risk	Stated as double blind but no further information
Duration	Unclear risk	3 week treatment period
Outcome	Low risk	Number with various grades of pain relief, including very good by patient
Incomplete outcome assessment	Unclear risk	Not stated
Size	High risk	Group size below 50

Wilton 1974

Methods	Randomised, double blind, placebo controlled, cross-over. Duration 4 weeks: 2-week washout then 7 days on each treatment period. No washout between treatments	
Participants	Diabetic neuropathy of at least 3 months. N = 40 Mean age 56 (range 28-70) years. Female 75%	
Interventions	Carbamazepine 200 mg 3 × daily Placebo	
Outcomes	Patient reported pain: 10 cm VAS scale. Reported numbness, agitation, ability to sleep, depression and anxiety	
Notes	Oxford Quality Score: R = 1, DB = 1, W = 0, Total = 2 Geighy gave assistance	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'according to a pre-randomised balanced sequence'
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Active and controlled appeared similar	Low risk	'tegretol and an identical placebo dosage'
Duration	High risk	7 days treatment period
Outcome	High risk	Mean pain scores
Incomplete outcome assessment	Unclear risk	Not stated
Size	High risk	Group size below 50

ADL - activities of daily living
 ADR - adverse drug reactions
 AE - adverse effects
 CBZ- carbamazepine
 TN - Trigeminal neuralgia
 DN - diabetic neuropathy
 NSAIDs - non steroidal anti-inflammatory drugs
 vs - versus
 SE - side effect
 ADR - adverse drug reaction
 QS - quality score

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Crill 1973	Review
Erzurumlu 1995	Not RCT
Harke 2001	RCT but required pretreatment with spinal cord stimulation. 8 days treatment
Kudoh 1998	Not RCT
Lloyd-Smith 1969	Not randomised. Some patients crossed to placebo without consent
Swerdlow 1981	Case series
Swerdlow 1984	Review

Characteristics of studies awaiting assessment *[ordered by study ID]*

Badran 1975

Methods	
Participants	
Interventions	
Outcomes	
Notes	Unable to locate paper

Liebel 2001

Methods	
Participants	
Interventions	
Outcomes	
Notes	Unable to locate paper

DATA AND ANALYSES

Comparison 1

Carbamazepine in neuropathic pain

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any pain improvement	5	298	Risk Ratio (M-H, Fixed, 95% CI)	6.13 [3.89, 9.65]
1.1 Trigeminal neuralgia	3	208	Risk Ratio (M-H, Fixed, 95% CI)	5.87 [3.58, 9.61]
1.2 Painful diabetic neuropathy	1	60	Risk Ratio (M-H, Fixed, 95% CI)	8.5 [2.15, 33.62]
1.3 Central post stroke pain	1	30	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.66, 37.85]
2 At least 1 adverse event	4	346	Risk Ratio (M-H, Fixed, 95% CI)	2.40 [1.85, 3.12]

Analysis 1.1. Comparison 1 Carbamazepine in neuropathic pain, Outcome 1 Any pain improvement

Review: Carbamazepine for acute and chronic pain in adults

Comparison: 1 Carbamazepine in neuropathic pain

Outcome: 1 Any pain improvement

Analysis 1.2. Comparison 1 Carbamazepine in neuropathic pain, Outcome 2 At least 1 adverse event

Review: Carbamazepine for acute and chronic pain in adults

Comparison: 1 Carbamazepine in neuropathic pain

Outcome: 2 At least 1 adverse event

Appendix 1. 1Search strategies for this update

Database: Ovid MEDLINE(R) <1950 to 2009>

1. (pain* or analgesi* or neuralgi* or headache* or toothache* or earache* or sciatica or causalgi* or arthralgi* or colic* or dysmenorrhoea or dysmenorrhea).mp.
[mp=title, original title, abstract, name of substance word, subject heading word]
(490213)
2. (carbamazepin* or neurotol or tegretol or amizepine or epitol).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (11734)
3. exp carbamazepine/ (8329)
4. 3 or 2 (11734)
5. 4 and 1 (1435)

6. (2004**** or 2005**** or 2006**** or 2007**** or 2008**** or 2009****).ed. (4042683)
7. 6 and 5 (401)
8. randomized controlled trial.pt. (277669)
9. controlled clinical trial.pt. (80174)
10. randomized.ab. (186996)
11. placebo.ab. (114494)
12. drug therapy.fs. (1336724)
13. randomly.ab. (135505)
14. trial.ab. (193866)
15. groups.ab. (927296)
16. or/8-15 (2446949)
17. (animals not (humans and animals)).sh. (3333937)
18. 16 not 17 (2074319)
19. 18 and 7 (259)

Database: EMBASE <1980 to 2009 >

1. (pain* or analgesi* or neuralgi* or headache* or toothache* or earache* or sciatica or causalgi* or arthralgi* or colic* or dysmenorrhoea or dysmenorrhea).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (511178)
2. (carbamazepin* or neurotol or tegretol or amizepine or epitol).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (36636)
3. exp carbamazepine/ (36104)
4. 3 or 2 (36636)
5. 4 and 1 (7006)
6. (2004** or 2005** or 2006** or 2007** or 2008** or 2009**).em. (3307567)
7. 6 and 5 (3493)
8. random*.ti,ab. (405268)
9. factorial*.ti,ab. (8500)
10. (crossover* or cross over* or cross-over*).ti,ab. (40175)
11. placebo*.ti,ab. (112349)
12. (doubl* adj blind*).ti,ab. (86312)

13. (singl* adj blind*).ti,ab. (7630)
14. assign*.ti,ab. (111498)
15. allocat*.ti,ab. (35309)
16. volunteer*.ti,ab. (100932)
17. CROSSOVER PROCEDURE.sh. (21622)
18. DOUBLE-BLIND PROCEDURE.sh. (73566)
19. RANDOMIZED CONTROLLED TRIAL.sh. (172175)
20. SINGLE BLIND PROCEDURE.sh. (8418)
21. or/8-20 (676735)
22. ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/ (3500786)
23. HUMAN/ (6578853)
24. 22 and 23 (552965)
25. 22 not 24 (2947821)
26. 21 not 25 (589330)
27. 7 and 26 (487)

Appendix 2. Results in individual studies

Study Particular issues	Maximum daily dose of carbamazepine Titration/fixd	Comparator Numbers in trial	Withdrawals	Efficacy	Adverse events (general)	Adverse events (specific)
Trigeminal neuralgia						
Cambell 1966	Carbamazepine 100 mg 4x daily to 200 mg 3x daily (1 centre) or 200 mg 4x daily (2 centres) in order C,P,C,P where C= carbamazepine, P= placebo. Placebo order P,C,P,C	Placebo n=70 total	7 withdrawals (1 rash, other logistic) AE withdrawal Carbamazepine 1/70 Placebo 0/70	58% of maximum pain relief carbamazepine 26% maximum placebo	At least 1 Adverse event Carbamazepine 35/70 Placebo 17/70	Giddiness (30%) and unsteadiness (15%) most commonly reported
Killian 1968	Carbamazepine dose titration 400 mg to 1g /day	Placebo n=42 total but 26 studies by double blind technique, and 24/30 with trigeminal neuralgia studied by double blind technique	AE withdrawal Carbamazepine 3/30 Placebo 0/30	19/27 TN complete or very good response after 5 days. Placebo responses 'minimal or absent in all cases'	At least 1 AE in 23/36 patients on carbamazepine	With carbamazepine 47% had dizziness and some drowsiness
Lechin 1989	Step titration carbamazepine 300 to 1200 mg daily Pimozide 4-12 mg daily in 2 divided doses. days 1-4 300 mg/d and 4 mg/d respectively; days 5-9 600 mg/d and 6mg/d days 10-14, 900 mg/d and 8 mg/d days 14 to end of treatment, 1200 mg/d and 12 mg/d	Pimozide n=59/68 recruited, 59 randomised, 11 excluded from analysis - 10 protocol violation, one did not return	No AE withdrawals noted on either drug	TN symptom score. Pimozide lowered symptom score by 78% from baseline compared with 50% on carbamazepine. All patients 'improved' on pimozide; 14/24 (58%) 'improved' on carbamazepine	At least 1 AE Carbamazepine 40/48 Pimozide 21/48	
Lindström & Lindblom 1987	Maximum tolerated dose for carbamazepine, 20 mg/kg in 3 divided daily doses for tocainide. Actual doses not reported	Tocainide n=12	No AE withdrawals noted on either drug	TN score consisted of severity, frequency and duration of attacks. Tocainide and carbamazepine produced similar improvement compared with 'no treatment'. No significant difference between the active treatments		
Nicol 1969	Carbamazepine dose titration 100 mg to 2.4 g/day. Placebo patients started on one treatment and increased dose until 8 tablets a day. At two weeks if no satisfactory results the second treatment was substituted	Placebo n=variable	AE withdrawal Carbamazepine 2/37 Placebo 0/24	15/20 starting on carbamazepine had good or excellent response (four point pain relief scale). 12/17 switched from placebo to carbamazepine and 6/7 who continued on placebo had good or excellent response (6/24 who started on placebo)	Not concisely described	Death 4 deaths on carbamazepine, 2 with presumed cardiovascular problems, one frontal lobe glioblastoma, and one of progressive generalised debilitating disease
Rasmussen 1970	Carbamazepine (CBZ) vs placebo, 1 tablet twice daily or three times daily. Actual dose not stated. Assumed to be 200mg tablets	Placebo n=55 (trigeminal neuralgia only)	AE withdrawal Carbamazepine 4/55 Placebo 0/55	Undefined good effect Carbamazepine 46/55 Placebo 8/55	High rates of CNS and balance disturbance initially	1 death in carbamazepine group associated with cardiovascular condition 3 rashes with carbamazepine
Rockliff & Davis 1966	Carbamazepine 200 mg or placebo 3x a day for 3 days, then crossover. No washout	Placebo n=9		Patient preference. 8/9 patients expressed preference for carbamazepine. 1/9 found both treatments equally effective. No evaluable data		
Vilming 1986	Carbamazepine titrated to maximum of 300mg 3 times per day or tizanidine 6mg three times per day. Dose titrated over 12 days and continued for a further 9 days	Tizanazide n=12				
Painful diabetic neuropathy						
Gomez-Perez 1996	Carbamazepine (300mg to 600mg) vs nortriptyline 10mg/fluphenazine 0.5 mg combination (3 to 6 tablets daily). Dose increment over 3 days then stable to day 15	Nortriptyline plus fluphenazine n=16	AE withdrawals 2/16 Carbamazepine 0/16 Nortriptyline	About 50% average pain relief on both treatments		1 serious AE with carbamazepine - upper gastrointestinal bleeding, thought to be alcohol induced

Study Particular issues	Maximum daily dose of carbamazepine Titration/fixd	Comparator Numbers in trial	Withdrawals	Efficacy	Adverse events (general)	Adverse events (specific)
then double dose for next 15 days. 2-4 weeks washout then crossover then double dose for next 15 days. 2-4 weeks washout then crossover						
Jia 2006	Venlafaxine 25mg twice a day or CBZ 100mg twice a day for 14 days	Venlafaxine n=132	AE withdrawals Carbamazepine 2/66 Venlafaxine 4/66	mean pain intensity significantly reduced in both groups but greater in venlafaxine. Mean pain score preintervention: 7 Mean pain score at 14 days: venlafaxine 2; carbamazepine 3.5 (from graph)	Severe AE Carbamazepine 1/66 Venlafaxine	Dizziness and somnolence (10%, 13%) with carbamazepine, GI discomfort, dizziness and somnolence (18%, 14%, 12%) with venlafaxine
Rull 1969	Carbamazepine 200 mg to 600 mg daily	Placebo n=30	None mentioned	Pain intensity improved (any level) Carbamazepine 28/30 Placebo 19/30 0/30 worsened on carbamazepine versus 11/30 on placebo Improvement equivalent to 50% pain relief in first period Carbamazepine 17/30 Placebo 2/30		2 cutaneous rashes with carbamazepine. Somnolence (53%) dizziness (40%) and gait change (13%) most common AEs
Wilton 1974	Carbamazepine 200 mg three times a day	Placebo n=40	No withdrawals noted	Preference for carbamazepine 24/40, placebo 14/40, no preference 2/40	At least 1 AE Carbamazepine 25/40 Placebo 2/40	Dizziness most common AE (21/40)
Postherpetic neuralgia						
Gerson 1977	Carbamazepine 150 mg - 1 g /day plus clonipramine 10 - 75 mg/day; or TENS 15 mins/week	TENS N=29	7 withdrawals on drug treatment, 4 (no effect) crossed (successfully) to TENS. 10 withdrawals on TENS and 8 crossed to drug treatment, (3 successfully)	7/16 achieved > 50% reduction in pain on drug combination 0/13 achieved >30% reduction in pain on TENS 8/16 achieved >30% reduction in pain on drug combination 0/13 achieved >30% reduction in pain on TENS		
Post stroke pain						
Leijon & Boivie 1989	Stepped increase to final dose of carbamazepine 800 mg daily starting at 100 mg 2x daily on day 1 then increasing on days 2, 6, 15, 18; amitriptyline started at 12.5 mg 2x daily on day one and increasing on the days above to 25 mg in the morning and 50 mg at night	Placebo Amitriptyline n=15	No AE withdrawals reported Carbamazepine 0/15 Amitriptyline 0/15 Placebo 0/15	Much improved or pain free Carbamazepine 5/15 Amitriptyline 2/15 Placebo 1/15 Improved, much improved or pain free Carbamazepine 10/15 Amitriptyline 5/15 Placebo 1/15	At least 1 AE Carbamazepine 13/14 Amitriptyline 14/15 Placebo 7/15 Moderate or severe AE Carbamazepine 5/14 Amitriptyline 2/15 Placebo 1/15	

HISTORY

Review first published: Issue 3, 2005

Date	Event	Description
8 February 2011	Amended	Contact details updated.
8 December 2010	New citation required but conclusions have not changed	This review update has been recorded for publication again as it was incorrectly published previously in July 2010. By republishing this review as a new citation we would like to draw the readers' attention to the fact that this review has been substantively updated with new current methods up to June 2010. The conclusions on the whole remain the same, however, the conclusions are now based on stronger methodology which were used to analyse all results. The review byline has also changed since the original publication in 2000 The review was updated as follows: Review updated at first to December 2009 with searches re-run in June 2010 prior to publication. There are three new included studies and new parameters are considered for the chronic pain studies. Results have also been reanalysed
8 December 2010	Amended	This review has been republished to draw attention to its revised methodology and more firm conclusions
24 September 2010	Amended	Contact details updated.
1 June 2010	New search has been performed	Review updated Dec 2009 with searches re-run in June 2010. Three new included studies. New parameters considered for chronic pain studies. Re-analysis
27 October 2008	Amended	Further minor Cochrane style changes made to this review as part of RevMan 5 conversion process
7 July 2008	Amended	Converted to new review format.
19 May 2005	Amended	This updated review on Carbamazepine was originally published as Anticonvulsant drugs for acute and chronic pain. At the third update in 2003, 12 new included studies were identified mainly of the newer anticonvulsants gabapentin and lamotrigine. In total the included studies provided data on six different medicines used in at least six identified neuropathic pain conditions. Issues of dose response and trial design added to the complexity. A decision was therefore taken to split this review into a number of smaller reviews each covering one medicine (chemical entity)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The major difference between the original protocol and this update is the concentration on issues of methodological validity and bias that have emerged subsequently - namely on size, on duration, on outcome, and potentially on a dependence on crossover designs. These are commented on and referenced in the updated review.

WHAT'S NEW

Last assessed as up-to-date: 15 September 2011.

Date	Event	Description
27 June 2012	Amended	Contact details updated.
15 September 2011	Review declared as stable	The authors scanned the literature during August 2011 and were confident that this review would not need updating for at least five years

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* Indicates the major publication for the study

PLAIN LANGUAGE SUMMARY

Carbamazepine (an anticonvulsant medicine) for acute and chronic pain

Carbamazepine is effective for relieving chronic pain caused by damage to nerves, either from injury or disease, although the data available to support this is limited.

Anticonvulsants (also known as antiepileptics) are a group of medicines commonly used for treating 'fits' or epilepsy, but which are also effective for treating pain. The type of pain which responds well is neuropathic pain, e.g., postherpetic neuralgia (persistent pain experienced in an area previously affected by shingles), trigeminal neuralgia, and painful complications of diabetes. About two-thirds of patients who take carbamazepine for neuropathic pain can expect to achieve good pain relief in the short term, and two thirds can expect to experience at least one adverse event.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Duration	Outcome	Incomplete outcome assessment	Size
Campbell 1966	+	?	+	-	-	?	-
Gerson 1977	?	?	-	+	+	?	-
Gomez-Perez 1996	?	?	+	?	+	?	-
Jia 2006	+	+	+	-	-	?	?
Keczkes 1980	?	?	-	?	?	?	-
Killian 1968	?	?	+	-	+	?	-
Lechin 1989	?	?	+	+	-	?	-
Leijon 1989	?	?	+	?	+	?	-
Lindstrom 1987	?	?	?	-	+	?	-
Nicol 1969	?	?	?	+	?	?	-
Rasmussen 1970	?	-	-	-	-	?	?
Rockliff 1966	?	?	+	-	-	?	-
Rull 1969	?	?	+	-	+	?	-
Vilming 1986	?	?	?	?	+	?	-
Wilton 1974	?	?	+	-	-	?	-

Figure 1.

Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

Figure 2.

Five studies showing percentage improvement (any definition) with carbamazepine (any dose) and placebo. Size of the study is proportional to the size of the symbol (inset scale). Yellow symbols = trigeminal neuralgia, blue = painful diabetic neuropathy, red = post stroke pain

Figure 3.

Forest plot of comparison: 1 Carbamazepine in neuropathic pain, outcome: 1.1 Any pain improvement.