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Milnacipran for neuropathic pain in adults (Review)

Derry S, Phillips T, Moore RA, Wiffen PJ

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[Intervention Review]

Milnacipran for neuropathic pain in adults

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ABSTRACT

Background

Milnacipran is a serotonin–norepinephrine reuptake inhibitor (SNRI) that is sometimes used to treat chronic neuropathic pain and fibromyalgia. This is an update of an earlier review of milnacipran for neuropathic pain and fibromyalgia in adults originally published in *The Cochrane Library* Issue 3, 2012. We split that review so that this one looked only at neuropathic pain, and a separate review looks at fibromyalgia.

Objectives

To assess the analgesic efficacy and associated adverse events of milnacipran for chronic neuropathic pain in adults.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE to 23 February 2015, together with reference lists of retrieved papers and reviews.

Selection criteria

We included randomised, double-blind studies of eight weeks' duration or longer, comparing milnacipran with placebo or another active treatment in chronic neuropathic pain.

Data collection and analysis

Two review authors independently searched for studies, extracted efficacy and adverse event data, and examined issues of study quality. We did not carry out any analysis.

Main results

We included a single study of 40 participants with chronic low back pain with a neuropathic component. It found no difference in pain scores between milnacipran 100 mg to 200 mg daily or placebo after six weeks (very low quality evidence). Adverse event rates were similar between treatments, with too few data to draw conclusions (very low quality evidence).

Authors' conclusions

There was no evidence to support the use of milnacipran to treat neuropathic pain conditions.

PLAIN LANGUAGE SUMMARY

Milnacipran for neuropathic pain in adults

Neuropathic pain is pain coming from damaged nerves. It is different from pain messages that are carried along healthy nerves from damaged tissue (for example, a fall, or cut, or arthritic knee). Neuropathic pain is treated by different medicines to those used for pain from damaged tissue. Medicines such as paracetamol or ibuprofen are not usually effective in neuropathic pain, while medicines that are sometimes used to treat depression or epilepsy can be very effective in some people with neuropathic pain.

Milnacipran is an antidepressant, and antidepressants are widely recommended for treating neuropathic pain; milnacipran may also be useful in these painful conditions.

This is an update of a review of milnacipran for neuropathic pain and fibromyalgia, first published in 2012. That review has been split so that this one looked only at neuropathic pain, and a separate review looks at fibromyalgia.

In February 2015 we performed searches to look for clinical trials where milnacipran was used to treat neuropathic pain in adults.

We found only a single, small study of 40 participants who had chronic low back pain with a neuropathic component. Milnacipran was no different from placebo in terms of pain or adverse events (very low quality evidence).

There was no evidence to support use of milnacipran to treat neuropathic pain conditions.

BACKGROUND

This is an update of an earlier review of milnacipran for neuropathic pain and fibromyalgia in adults originally published in *The Cochrane Library* Issue 3, 2012 (Derry 2012a). The efficacy of milnacipran for fibromyalgia is now dealt with in a separate review (Cording 2015).

In the update we have used a template for reviews of drugs used to relieve neuropathic pain. The aim is for all reviews to use the same methods, based on current criteria for what constitutes reliable evidence in chronic pain (Moore 2010a; Appendix 1).

Description of the condition

The 2011 International Association for the Study of Pain definition of neuropathic pain is "pain caused by a lesion or disease of the somatosensory system" (Jensen 2011), and based on a definition agreed at an earlier consensus meeting (Treede 2008). Neuropathic pain is cause by injury to the nervous tissue, either peripheral or central and it can be followed by plastic changes in the central nervous system (CNS) (Moisset 2007). The origin of neuropathic pain is complex (Baron 2010; Baron 2012; Tracey 2011; von Hehn 2012), and neuropathic pain features can be found in people with joint pain (Soni 2013).

Many people with neuropathic pain conditions are significantly disabled with moderate or severe pain for many years. Chronic pain conditions comprised five of the 11 top-ranking conditions for years lived with disability in 2010 (Vos 2012), and are responsible for considerable loss of quality of life, employment, and increased healthcare costs (Moore 2014a).

Neuropathic pain is usually divided according to the cause of nerve injury. There may be many causes, but some common causes of neuropathic pain include diabetes (painful diabetic neuropathy, PDN), shingles (postherpetic neuralgia, PHN), amputation (stump and phantom limb pain), neuropathic pain after surgery or trauma, stroke or spinal cord injury, trigeminal neuralgia (TGN), and human immunodeficiency virus (HIV) infection. Sometimes the cause is not known.

In systematic reviews, the overall prevalence of neuropathic pain in the general population is reported to be between 7% and 10% (van Hecke 2014), and about 7% in a systematic review of studies published since 2000 (Moore 2014a). In individual countries, prevalence rates have been reported as 3.3% in Austria (Gustorff 2008), 6.9% in France (Bouhassira 2008), and up to 8% in the UK (Torrance 2006). Some forms of neuropathic pain, such as PDN and post-surgical chronic pain (which is often neuropathic in origin), are increasing (Hall 2008). The incidence of PHN may decrease where vaccination programmes are introduced; vaccination for herpes zoster is ongoing in the UK, for example.

Estimates of incidence vary between individual studies for particular origins of neuropathic pain, often because of small numbers of cases. In primary care in the UK, between 2002 and 2005, the incidences (per 100,000 person-years' observation) were 28 (95% confidence interval (CI) 27 to 30) for PHN, 27 (26 to 29) for TGN, 0.8 (0.6 to 1.1) for phantom limb pain, and 21 (20 to 22) for PDN (Hall 2008). Others have estimated an incidence of 4 in 100,000 per year for trigeminal neuralgia (Katusic 1991; Rappaport 1994), and 12.6 per 100,000 person-years for TGN and 3.9 per 100,000 person-years for PHN in a study of facial pain in the Netherlands (Koopman 2009). One systematic review of chronic pain demonstrated that some neuropathic pain conditions, such as PDN, can be more common than other neuropathic pain conditions, with prevalence rates up to 400 per 100,000 person-years (McQuay 2007).

Neuropathic pain is difficult to treat effectively, with only a minority of people experiencing a clinically relevant benefit from any one intervention. A multidisciplinary approach is now advocated, combining pharmacological interventions with physical or cognitive (or both) interventions. Conventional analgesics like paracetamol and nonsteroidal antiinflammatory drugs are not thought to be effective, but are frequently used (Di Franco 2010; Hall 2013; Vo 2009). Some people may derive some benefit from a topical lidocaine patch or low-concentration topical capsaicin, though evidence about benefits is uncertain (Derry 2012b; Derry 2014). High-concentration topical capsaicin may benefit some people with PHN (Derry 2013). Treatment is often by so-called 'unconventional analgesics', such as antidepressants (duloxetine and amitriptyline; Lunn 2014; Moore 2012a; Sultan 2008), or antiepileptics (gabapentin or pregabalin; Moore 2009; Moore 2014b; Wiffen 2013).

The proportion of people who achieve worthwhile pain relief (typically at least 50% pain intensity reduction; Moore 2013a) is small, generally only 10% to 25% more than with placebo, with numbers needed to treat for an additional beneficial outcome (NNT) usually between 4 and 10 (Kalso 2013; Moore 2013b). Neuropathic pain is not particularly different from other chronic pain conditions in that only a small proportion of trial participants have a good response to treatment (Moore 2013b).

One overview of treatment guidelines pointed out some general similarities between recommendations, but guidelines are not always consistent with one another (O'Connor 2009), nor followed (Hall 2013). The current National Institute for Health and Care Excellence (NICE) guidance in the UK suggests offering a choice of amitriptyline, duloxetine, gabapentin, or pregabalin as initial treatment for neuropathic pain (with the exception of trigeminal neuralgia), with switching if first, second, or third drugs tried are not effective or not tolerated (NICE 2013). Antidepressant drugs are also suggested as first line agents in the latest Canadian guidelines (Moulin 2014), and in updated guidance from the Neuropathic pain Special Interest Group of the International Association for the Study of Pain (Finnerup 2015).

Description of the intervention

Milnacipran (trade names Ixel, Savella) is a serotonin–norepinephrine reuptake inhibitor (SNRI), used to treat depression and chronic pain. It is licensed for different indications in different countries and is a relatively new therapy.

How the intervention might work

5-hydroxytryptamine (5HT or serotonin) and norepinephrine (NE) are involved in the modulation of endogenous analgesic mechanisms via descending inhibitory pain pathways in the brain and spinal cord (Suzuki 2004). Disinhibition and imbalance of 5HT and NE in endogenous pain inhibitory pathways could contribute to persistent pain. An increase in 5HT and NE may increase inhibition of painful signals, improving pain relief, but the exact mechanism of action is not fully understood. Milnacipran has equipotent 5HT

and NE reuptake inhibition and a linear dose-concentration trend at therapeutic doses (Pae 2009).

Why it is important to do this review

Milnacipran is a recent addition to the pharmacological interventions available to treat chronic neuropathic pain and fibromyalgia. A previous Cochrane review found no evidence for efficacy in neuropathic pain, and an update is needed to investigate whether any new evidence has emerged that might change this result. It is important to establish its efficacy compared with placebo or other active interventions to understand its place amongst the available treatment options.

The standards used to assess evidence in chronic pain trials have changed substantially, with particular attention being paid to trial duration, withdrawals, and statistical imputation following withdrawal, all of which can substantially alter estimates of efficacy (Appendix 1). The most important change is the move from using average pain scores, or average change in pain scores, to the number of participants who have a large decrease in pain (by at least 50%); this level of pain relief has been shown to correlate with improvements in comorbid symptoms, function, and quality of life. These standards are set out in the *PaPaS Author and Referee Guidance* for pain studies of the Cochrane Pain, Palliative and Supportive Care Group (PaPaS 2012).

This Cochrane review will assess evidence in ways that make both statistical and clinical sense, and will use developing criteria for what constitutes reliable evidence in chronic pain (Moore 2010a). Trials included and analysed will need to meet a minimum of reporting quality (blinding, randomisation), validity (duration, dose and timing, diagnosis, outcomes, etc) and size (ideally at least 500 participants in a comparison in which the NNT is 4 or above; Moore 1998). This approach sets high standards and marks a departure from how reviews were conducted previously.

OBJECTIVES

To assess the analgesic efficacy and associated adverse events of milnacipran for chronic neuropathic pain in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies if they were randomised controlled trials (RCTs) with double-blind assessment of outcomes, reported after eight weeks of treatment or longer. Full journal publication was required, with the exception of extended abstracts of otherwise unpublished clinical trials. Short abstracts (usually meeting reports) were not included. We excluded non-randomised studies, studies of experimental pain, case reports, and clinical observations.

Types of participants

Studies enrolled adults aged 18 years and above with one or more of a wide range of chronic neuropathic pain conditions including (but not limited to):

1. cancer-related neuropathy;
2. central neuropathic pain;
3. complex regional pain syndrome (CRPS) Type II;
4. human immunodeficiency virus (HIV) neuropathy;
5. painful diabetic neuropathy (PDN);
6. phantom limb pain;
7. postherpetic neuralgia (PHN);
8. postoperative or traumatic neuropathic pain;
9. spinal cord injury;
10. trigeminal neuralgia;
11. and CRPS Type 1.

We included studies of participants with more than one type of neuropathic pain; in such cases, we analysed results according to the primary condition.

Types of interventions

Milnacipran in any dose, by any route, administered for the relief of neuropathic pain, and compared to placebo, no intervention or any other active comparator. We excluded studies using milnacipran to treat pain resulting from the use of other drugs.

Types of outcome measures

We anticipated that studies would use a variety of outcome measures, with most of them using standard subjective scales (numerical rating scale (NRS) or visual analogue scale (VAS)) for pain intensity or pain relief, or both. We were particularly interested in Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) definitions for moderate and substantial benefit in chronic pain studies (Dworkin 2008). These are defined as:

1. at least 30% pain relief over baseline (moderate);
2. at least 50% pain relief over baseline (substantial);
3. much or very much improved on Patient Global Impression of Change (PGIC; moderate);
4. very much improved on PGIC (substantial).

These outcomes are different from those used in most earlier reviews, and concentrate on dichotomous outcomes in circumstances where pain responses do not follow a normal (Gaussian) distribution. People with chronic pain desire high levels of pain relief, ideally more than 50%, and having no worse than mild pain (Moore 2013a; O'Brien 2010).

We have not included a 'Summary of findings' table because there was no useful information to include.

Primary outcomes

1. Patient reported pain relief of 30% or greater.
2. Patient reported pain relief of 50% or greater.
3. Patient reported global impression of clinical change (PGIC) much or very much improved.
4. Patient reported global impression of clinical change (PGIC) very much improved.

Secondary outcomes

1. Any pain-related outcome indicating some improvement.
2. Withdrawals due to lack of efficacy, adverse events, and for any cause.

3. Participants experiencing any adverse event.
4. Participants experiencing any serious adverse event. Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an 'important medical event' that may jeopardise the patient, or may require an intervention to prevent one of the above characteristics or consequences.
5. Specific adverse events, particularly CNS effects such as somnolence and dizziness.

Search methods for identification of studies

Electronic searches

We searched the following databases.

1. the Cochrane Central Register of Controlled Trials (CENTRAL) (via CRSO) to 23 February 2015.
2. MEDLINE (via Ovid) 1946 to 23 February 2015.
3. EMBASE (via Ovid) 1976 to 23 February 2015.

See Appendix 2 for the MEDLINE search strategy, Appendix 3 for the EMBASE search strategy, and Appendix 4 for the CENTRAL search strategy.

There was no language restriction.

Searching other resources

We reviewed the bibliographies of all identified RCTs and review articles, and searched clinical trial databases (ClinicalTrials.gov (ClinicalTrials.gov) and World Health Organization (WHO) ICTRP (apps.who.int/trialsearch/)) to identify additional published or unpublished data. We did not contact investigators (except to clarify the status of ongoing studies) or study sponsors.

Data collection and analysis

The intention was to perform separate analyses according to particular neuropathic pain conditions. We would have performed analyses combining different neuropathic pain conditions for exploratory purposes only. In the event, there were insufficient data for any pooled analyses.

Selection of studies

Two review authors independently determined eligibility by first reading the title and abstract of each study identified by the search. We eliminated studies that clearly did not satisfy the inclusion criteria, and obtained full copies of the remaining studies. Two review authors then independently read these studies to determine inclusion and reached agreement by discussion. We did not anonymise the studies before assessment.

Data extraction and management

Two review authors independently extracted data using a standard form and checked for agreement before entry into Review Manager 5 (RevMan 2014) and other analysis tools. We included information about the pain condition and number of participants treated, drug and dosing regimen, study design (for example, parallel-group or cross-over, placebo or active control, titration schedule), study duration and follow-up, analgesic outcome measures and results, withdrawals and adverse events (participants experiencing any adverse event, or serious adverse event).

Assessment of risk of bias in included studies

We used the Oxford Quality Score as the basis for inclusion, limiting inclusion to studies that were randomised and double-blind as a minimum (Jadad 1996).

Two review authors independently assessed the risk of bias for each study, using the criteria outlined in the 'Risk of bias' tool in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and adapted from those used by the Cochrane Pregnancy and Childbirth Group. We resolved any disagreements by discussion. We assessed the following for each study.

1. Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process such as random number table or computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process (odd or even date of birth; hospital or clinic record number).
2. Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation (open list).
3. Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, such as identical tablets matched in appearance and smell); unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how it was achieved). We excluded studies that were not double-blind.
4. Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk (less than 10% of participants did not complete the study or used 'baseline observation carried forward' (BOCF) analysis, or both); unclear risk of bias (used 'last observation carried forward' (LOCF) analysis); high risk of bias (used 'completer' analysis).
5. Size (checking for possible biases confounded by small size). Small studies have been shown to overestimate treatment effects, probably because the conduct of small studies is more likely to be less rigorous, allowing critical criteria to be compromised (Dechartres 2013; Kjaergard 2001; Nüesch 2010). Studies were considered to be at low risk of bias if they had 200 participants or more, at unclear risk if they had 50 to 200 participants, and at high risk if they had fewer than 50 participants.

Measures of treatment effect

We planned to pool dichotomous data to calculate risk ratio (RR) with 95% CIs using a fixed-effect model unless we found significant statistical heterogeneity (see Assessment of heterogeneity), and to calculate NNTs as the reciprocal of the absolute risk reduction (ARR) (McQuay 1998). For unwanted effects, the NNT becomes the number needed to treat to treat for an additional harmful outcome (NNH) and is calculated in the same manner. We did not plan to use continuous data in analyses. In the event, there were insufficient data and we were able only to present results descriptively.

Unit of analysis issues

The unit of analysis was the individual participant. For cross-over studies we planned to use the first period data only, but we did not include any cross-over studies.

Dealing with missing data

We planned to use intention-to-treat (ITT) analysis where the ITT population consisted of participants who were randomised, took at least one dose of the assigned study medication, and provided at least one post-baseline assessment. We assigned missing participants zero improvement wherever possible.

Assessment of heterogeneity

We planned to deal with clinical heterogeneity by combining studies that examined similar conditions, and to assess statistical heterogeneity visually (L'Abbé 1987) and using the I^2 statistic, but pooling of data was not possible.

Assessment of reporting biases

The aim of this review was to use dichotomous data of known utility and of value to people with neuropathic pain (Moore 2010b; Moore 2013a). The review did not depend on what authors of the original studies chose to report or not, although clearly difficulties arose in studies that did not report any dichotomous results. We planned to extract and use continuous data, which probably poorly reflect efficacy and utility, only where useful for illustrative purposes.

We planned to assess publication bias using a method designed to detect the amount of unpublished data with a null effect required to make any result clinically irrelevant (usually taken to mean an NNT of 10 or higher) (Moore 2008). We were unable to do this because of a lack of data.

Data synthesis

We planned to use a fixed-effect model for meta-analysis unless there was significant clinical heterogeneity and it was still considered appropriate to combine studies, in which case we would have used a random-effects model. However, there were insufficient data for any pooled analysis.

We assessed data for each painful condition in three tiers, according to outcome and freedom from known sources of bias.

1. The first tier used data meeting current best standards, where studies reported the outcome of at least 50% pain intensity reduction over baseline (or its equivalent), without the use of LOCF or other imputation method other than BOCF for dropouts, reported an ITT analysis, lasted eight or more weeks, had a parallel-group design, and had at least 200 participants (preferably at least 400) in the comparison (Moore 2010a; Moore 2012b). We planned to report these first-tier results first.
2. The second tier used data from at least 200 participants, but where one or more of the above conditions was not met (reporting at least 30% pain intensity reduction, using LOCF or a completer analysis, or lasting four to eight weeks).
3. The third tier of evidence used data from fewer than 200 participants, or where there were expected to be significant problems because, for example, of very short duration studies of less than four weeks, where there was major heterogeneity between studies, or where there were shortcomings in allocation concealment, attrition, or incomplete outcome data. For this third tier of evidence, no data synthesis is reasonable, and may be misleading, but an indication of beneficial effects might be possible.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analysis for:

1. dose of milnacipran;
2. different painful conditions.

Sensitivity analysis

We planned no sensitivity analyses, because the evidence base was known to be too small to allow reliable analysis.

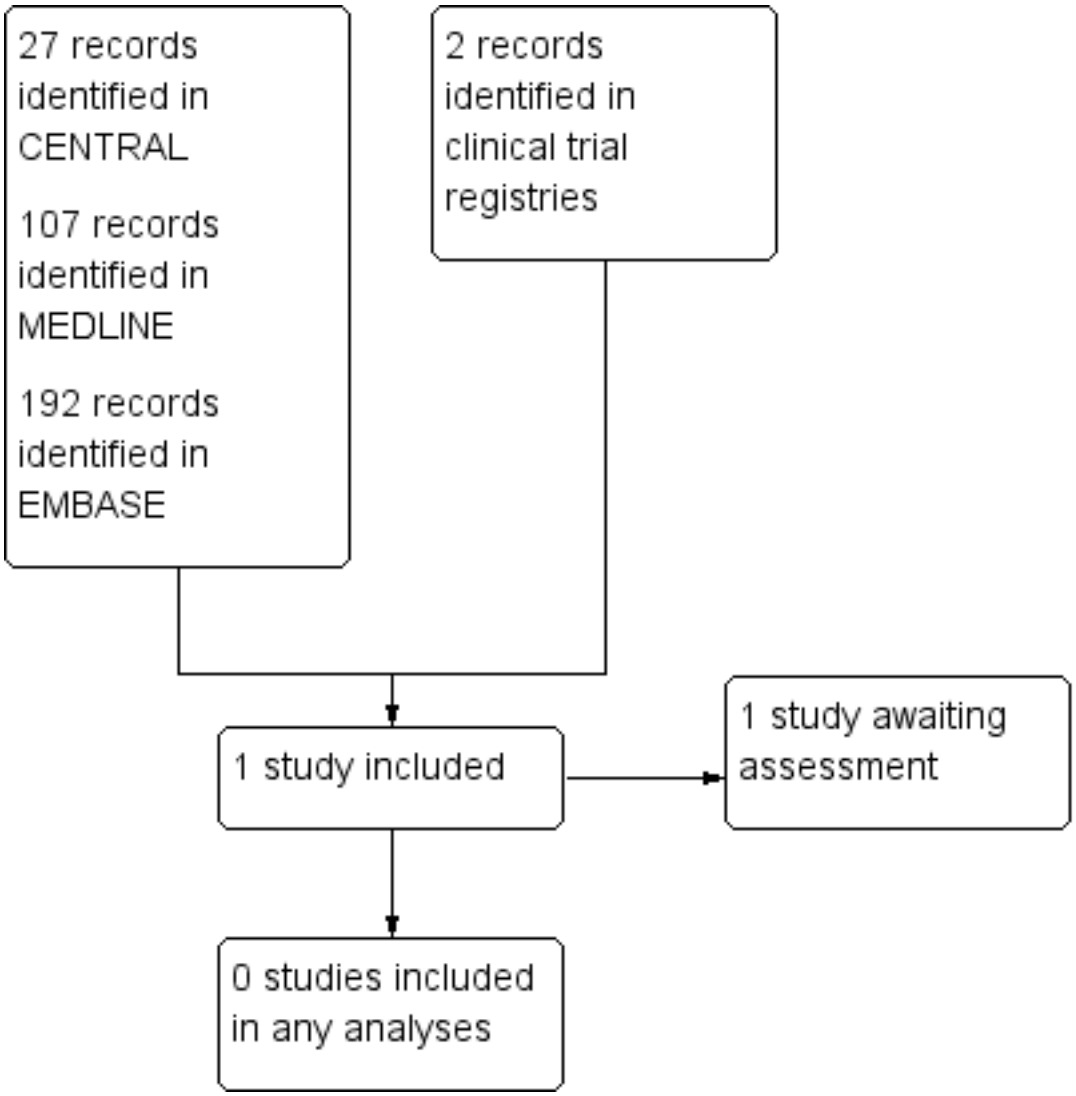
RESULTS

Description of studies

Results of the search

We identified 27 references in the search of CENTRAL, 107 in MEDLINE, and 192 in EMBASE. No relevant published studies were found for any type of chronic neuropathic pain. The manufacturers of milnacipran did not provide any additional information to that retrieved in our searches for the previous version of this review (Derry 2012a). The searches of the clinical trial registries identified two studies of milnacipran in neuropathic pain. One had results and is included (NCT01225068). The other had no results, and is included in the Characteristics of ongoing studies table (NCT01288937). It was a small study of 52 participants with idiopathic neuropathy pain (Figure 1).

Figure 1. Study flow diagram.



Included studies

The single included study was small, with 40 participants with a history of chronic low back pain radiating to the leg or buttocks (NCT01225068). Milnacipran 100 mg to 200 mg daily was compared with placebo over six weeks. This was a shorter time than we had specified in the methods, but we included it because of the absence of any other trial data.

Details are in the Characteristics of included studies table.

Excluded studies

We had no studies to exclude, as the randomised studies we found clearly described the pain condition in which they were conducted.

Risk of bias in included studies

There were inadequate details for randomisation, allocation concealment, or blinding to make any sensible evaluation of any risk of bias, except the high risk of bias because of its small size. The included study scored 3/5 on the Oxford Quality Scale.

Effects of interventions

There was no first- or second-tier evidence of efficacy, and the results from the single included study represent the minimum information required for third-tier evidence.

In that study there were no differences between milnacipran and placebo for mean pain score at the end of the study (six weeks). Participants experiencing any adverse event were numerically higher with milnacipran (14/20) than placebo (10/20), but the numbers were too small to draw any conclusions. There was only one serious adverse event, which occurred with placebo.

DISCUSSION

Summary of main results

We found only a single study, with a very small number of participants who had chronic low back pain with a neuropathic component. This represents third-tier evidence of very low quality. No benefits or harms of milnacipran in neuropathic pain in adults were discernible in this single study.

Overall completeness and applicability of evidence

The evidence was trivial in amount, and was not applicable to clinical practice.

Quality of the evidence

The quality of evidence was poor, as best we could judge from incomplete reporting on a clinical trials register. The single study was described as randomised and double blind, although there were no details of the methods used. The only efficacy results available used mean data from a completer analysis. The small size is a concern, because of high risk of bias in very small studies. Although we intended to include studies of eight weeks' duration or longer, we included one study of six weeks because there was no other study with any results.

Potential biases in the review process

We carried out a comprehensive search and feel it is unlikely that we have missed a body of evidence for efficacy in neuropathic pain conditions.

Agreements and disagreements with other studies or reviews

The results here are in agreement with a previous version of this review (Derry 2012a). We found no other relevant reviews. Milnacipran is not mentioned in other reviews of antidepressants (Finnerup 2015; Saarto 2007).

AUTHORS' CONCLUSIONS

Implications for practice

For people with neuropathic pain

The was insufficient evidence to suggest milnacipran has any efficacy in any neuropathic pain condition.

For clinicians

The was insufficient evidence to suggest milnacipran has any efficacy in any neuropathic pain condition.

For policy makers

The was insufficient evidence to suggest milnacipran has any efficacy in any neuropathic pain condition, and it should not be recommended.

For funders

The was insufficient evidence to suggest milnacipran has any efficacy in any neuropathic pain condition. Establishing whether milnacipran had any efficacy would require large clinical trials in several different conditions, and cost at least several million pounds, dollars, or euros. There is no obvious reason for this sort of expenditure.

Implications for research

General

There are no implications for research in general.

Design

There are no implications for design of studies.

Measurement (endpoints)

There are no implications for measurement.

Comparison between active treatments

As milnacipran is not an established active treatment (not obviously better than placebo), it cannot be compared with other treatments with established efficacy.

ACKNOWLEDGEMENTS

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CHARACTERISTICS OF STUDIES

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

NCT01225068

Methods	Randomised, double blind, placebo-controlled, parallel-group, 6 weeks
Participants	History of low back pain for a minimum of 6 months with radiation to leg or buttocks VAS pain > 50/100 N = 40 Age 18 to 70 years (mean 48 years) 50% female
Interventions	Titration to 2 x 50 mg milnacipran daily (n = 20), or placebo (n = 20) Option to increase to 2 x 100 mg daily after 2 weeks
Outcomes	PI at 6 weeks: 100 mm VAS Adverse events Serious adverse events

NCT01225068 *(Continued)*

Notes	Oxford Quality Score: R = 1, DB = 1, W = 1. Total = 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Method of blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis, with 20% attrition in milnacipran group
Size	High risk	20 participants per treatment group

N: number of participants in study; n: number of participants in treatment arm; PI: pain intensity; VAS: visual analogue scale.

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

NCT01288937

Trial name or title	A placebo controlled, randomized, double blind trial of milnacipran for the treatment of idiopathic neuropathy pain
Methods	Randomised, double-blind, placebo-controlled, parallel-group, 11 weeks
Participants	Patients with signs and symptoms of a peripheral neuropathy, with either abnormal nerve conductions or abnormal epidermal nerve fibre density with neuropathic pain Age 18 to 80 years Pain ≥ 6 months Estimated N = 52
Interventions	Titration to 2 x 50 mg milnacipran daily, or placebo
Outcomes	Change in average 11-point Likert pain scale (0 to 10) Change in Rand-36 Item Quality of Life Scale
Starting date	November 2010
Contact information	Thomas H Brannagan, MD

NCT01288937 *(Continued)*

Notes	Active but not recruiting (December 2013). No study results posted, February 2015

N: number of participants in study

APPENDICES

Appendix 1. Methodological considerations for chronic pain

There have been several recent changes in how the efficacy of conventional and unconventional treatments is assessed in chronic painful conditions. The outcomes are now better defined, particularly with new criteria for what constitutes moderate or substantial benefit (Dworkin 2008); older trials may only report participants with 'any improvement'. Newer trials tend to be larger, avoiding problems from the random play of chance. Newer trials also tend to be of longer duration, up to 12 weeks, and longer trials provide a more rigorous and valid assessment of efficacy in chronic conditions. New standards have evolved for assessing efficacy in neuropathic pain, and we are now applying stricter criteria for the inclusion of trials and assessment of outcomes, and are more aware of problems that may affect our overall assessment. To summarise some of the recent insights that must be considered in this new review:

1. Pain results tend to have a U-shaped distribution rather than a bell-shaped distribution. This is true in acute pain (Moore 2011a; Moore 2011b), back pain (Moore 2010c), and arthritis (Moore 2010b), as well as in fibromyalgia (Straube 2010); in all cases average results usually describe the experience of almost no-one in the trial. Data expressed as averages are potentially misleading, unless they can be proven to be suitable.
2. As a consequence, we have to depend on dichotomous results (the individual either has or does not have the outcome) usually from pain changes or patient global assessments. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group has helped with their definitions of minimal, moderate, and substantial improvement (Dworkin 2008). In arthritis, trials of less than 12 weeks duration, and especially those shorter than eight weeks, overestimate the effect of treatment (Moore 2010b); the effect is particularly strong for less effective analgesics, and this may also be relevant in neuropathic-type pain.
3. The proportion of patients with at least moderate benefit can be small, even with an effective medicine, falling from 60% with an effective medicine in arthritis to 30% in fibromyalgia (Moore 2009; Moore 2010b; Moore 2013b; Moore 2014c; Moore 2014b; Straube 2008; Sultan 2008). A Cochrane review of pregabalin in neuropathic pain and fibromyalgia demonstrated different response rates for different types of chronic pain (higher in diabetic neuropathy and postherpetic neuralgia and lower in central pain and fibromyalgia) (Moore 2009). This indicates that different neuropathic pain conditions should be treated separately from one another, and that pooling should not be done unless there are good grounds for doing so.
4. Individual patient analyses indicate that patients who get good pain relief (moderate or better) have major benefits in many other outcomes, affecting quality of life in a significant way (Hoffman 2010; Moore 2010d; Moore 2014a).
5. Imputation methods such as last observation carried forward (LOCF), used when participants withdraw from clinical trials, can overstate drug efficacy especially when adverse event withdrawals with drug are greater than those with placebo (Moore 2012b).

Appendix 2. Search strategy for CENTRAL (via CRSO)

1. (Milnacipran or Ixel or Savella or Dalcipran or Toledomin):TI,AB,KY (616)
2. MESH DESCRIPTOR pain EXPLODE ALL TREES (29786)
3. MESH DESCRIPTOR Peripheral Nervous System Diseases EXPLODE ALL TREES (2534)
4. MESH DESCRIPTOR Somatosensory Disorders EXPLODE ALL TREES (699)
5. MESH DESCRIPTOR Neuralgia EXPLODE ALL TREES (597)
6. ((pain* or discomfort*) and (central or complex or nerv* or neuralg* or neuropath*)):TI,AB,KY (8558)
7. ((neur* or nerv*) and (compress* or damag*)):TI,AB,KY (1765)
8. #2 OR #3 OR #4 OR #5 OR #6 OR #7 (37465)
9. #1 AND #8 (27)

Appendix 3. Search strategy for MEDLINE (via Ovid)

1. exp PAIN/ (306193)
2. exp PERIPHERAL NERVOUS SYSTEM DISEASES/ (115068)
3. exp SOMATOSENSORY DISORDERS/ (16091)
4. exp NEURALGIA/ (13852)
5. ((pain* or discomfort*) adj10 (central or complex or nerv* or neuralg* or neuropath*)).mp. (38237)
6. ((neur* or nerv*) adj6 (compress* or damag*)).mp. (47759)

7. 1 or 2 or 3 or 4 or 5 or 6 (449378)
8. (milnacipran or Ixel or Savella or Dalcipran or Toledomin).mp. (2781)
9. randomized controlled trial.pt. (376175)
10. controlled clinical trial.pt. (88531)
11. randomized.ab. (274544)
12. placebo.ab. (146796)
13. drug therapy.fs. (1708719)
14. randomly.ab. (194627)
15. trial.ab. (284610)
16. groups.ab. (1250317)
17. or/10-17 (3208598)
18. 6 and 9 and 18 (107)

Appendix 4. Search strategy for EMBASE (via Ovid)

1. exp PAIN/ (876575)
2. exp PERIPHERAL NERVOUS SYSTEM DISEASES/ (52410)
3. exp SOMATOSENSORY DISORDERS/ (67304)
4. exp NEURALGIA/ (72992)
5. ((pain* or discomfort*) adj10 (central or complex or nerv* or neuralg* or neuropath*)).mp. (79896)
6. ((neur* or nerv*) adj6 (compress* or damag*)).mp. (67830)
7. or 1-6 (1012989)
8. Milnacipran/ (13089)
9. (milnacipran or Ixel or Savella or Dalcipran or Toledomin).mp. (13326)
10. 8 or 9 (13326)
11. crossover-procedure/ (39290)
12. double-blind procedure/ (116416)
13. randomized controlled trial/ (346881)
14. (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or (doubl* adj blind*) or assign* or allocat*).tw. (1210076)
15. 11 or 12 or 13 or 14 (1287159)
16. 7 and 10 and 15 (192)

WHAT'S NEW

Date	Event	Description
29 May 2019	Amended	Contact details updated.
11 October 2017	Review declared as stable	See Published notes.

HISTORY

Review first published: Issue 7, 2015

Date	Event	Description
20 October 2015	Amended	Reference to Cording 2015 updated.
6 July 2015	Review declared as stable	This review will be assessed for further updating in 2020.

Date	Event	Description
23 February 2015	New search has been performed	New searches run and two new studies identified. One small unpublished study included and one small ongoing study awaiting classification.
23 February 2015	New citation required but conclusions have not changed	Title changed from Milnacipran for neuropathic pain and fibromyalgia in adults to Milnaciran for neuropathic pain in adults. Previous review split into two new reviews, with separate reviews dealing with neuropathic pain and with fibromyalgia.

CONTRIBUTIONS OF AUTHORS

RAM and SD wrote the protocol.

Dipender Gill (review author of original review) and TP carried out searches, assessed studies for inclusion for the original review, and SD, DG, and TP extracted data and carried out analyses. RAM acted as arbitrator. All authors were involved in writing the review.

RAM and SD carried out the searches and assessed studies for inclusion for this update. RAM and SD extracted data. PJW acted as arbitrator. All authors were involved in writing the review. It is unlikely that any update will be required in the future.

DECLARATIONS OF INTEREST

SD has no conflicts relating to this review or any similar product.

TP has no conflicts relating to this review or any similar product.

RAM has no conflicts relating to this review or any similar product.

PJW has no conflicts relating to this review or any similar product.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this update in 2015 there have been minor changes in methods, principally relating to risk of bias assessment.

In the previous review we included analyses of two composite efficacy outcomes that were not prespecified in the protocol, but these applied only to studies in fibromyalgia. We chose to do this because they more closely reflect what is desirable in clinical practice (what patients want), and because they were calculated using BOCF, without imputation for missing data, which reflects the situation in clinical practice (if you cannot take the medication you cannot get any benefit from it).

NOTES

No new studies likely to change the conclusions are expected. Therefore, this review has now been stabilised following discussion with the authors and editors. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics [*administration & dosage] [adverse effects]; Back Pain [*drug therapy]; Chronic Pain [*drug therapy]; Cyclopropanes [*administration & dosage] [adverse effects]; Fibromyalgia [drug therapy]; Milnacipran; Neuralgia [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans