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Antiepileptic drugs for chronic non-cancer pain in children and adolescents (Review)

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[Intervention Review]

Antiepileptic drugs for chronic non-cancer pain in children and adolescents

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ABSTRACT

Background

Pain is a common feature of childhood and adolescence around the world, and for many young people, that pain is chronic. The World Health Organization (WHO) guidelines for pharmacological treatments for children's persisting pain acknowledge that pain in children is a major public health concern of high significance in most parts of the world. While in the past, pain was largely dismissed and was frequently left untreated, views on children's pain have changed over time, and relief of pain is now seen as important.

We designed a suite of seven reviews on chronic non-cancer pain and cancer pain (looking at antidepressants, antiepileptic drugs, non-steroidal anti-inflammatory drugs, opioids, and paracetamol) in order to review the evidence for children's pain utilising pharmacological interventions in children and adolescents.

As the leading cause of morbidity in the world today, chronic disease (and its associated pain) is a major health concern. Chronic pain (that is pain lasting three months or longer) can occur in the paediatric population in a variety of pathophysiological classifications (nociceptive, neuropathic, or idiopathic) relating to genetic conditions, nerve damage pain, chronic musculoskeletal pain, and chronic abdominal pain, and for other unknown reasons.

Antiepileptic (anticonvulsant) drugs, which were originally developed to treat convulsions in people with epilepsy, have in recent years been used to provide pain relief in adults for many chronic painful conditions and are now recommended for the treatment of chronic pain in the WHO list of essential medicines. Known side effects of antiepileptic drugs range from sweating, headache, elevated temperature, nausea, and abdominal pain to more serious effects including mental or motor function impairment.

Objectives

To assess the analgesic efficacy and adverse events of antiepileptic drugs used to treat chronic non-cancer pain in children and adolescents aged between birth and 17 years, in any setting.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online, MEDLINE via Ovid, and Embase via Ovid from inception to 6 September 2016. We also searched the reference lists of retrieved studies and reviews as well as online clinical trial registries.

Selection criteria

Randomised controlled trials, with or without blinding, by any route, treating chronic non-cancer pain in children and adolescents, comparing any antiepileptic drug with placebo or an active comparator.

Data collection and analysis

Two review authors independently assessed studies for eligibility. We planned to use dichotomous data to calculate risk ratio and number needed to treat for one additional event, using standard methods if data were available. We assessed the evidence using GRADE and created two 'Summary of findings' tables.

Main results

We included two studies with a total of 141 participants (aged 7 to 18 years) with chronic neuropathic pain, complex regional pain syndrome type 1 (CRPS-I), or fibromyalgia. One study investigated pregabalin versus placebo in participants with fibromyalgia (107 participants), and the other study investigated gabapentin versus amitriptyline in participants with CRPS-I or neuropathic pain (34 participants). We were unable to perform any quantitative analysis.

Risk of bias for the two included studies varied, due to issues with randomisation (low to unclear risk), blinding of outcome assessors (low to unclear risk), reporting bias (low to unclear risk), the size of the study populations (high risk), and industry funding in the 'other' domain (low to unclear risk). We judged the remaining domains of sequence generation, blinding of participants and personnel, and attrition as low risk of bias.

Primary outcomes

One study (gabapentin 900 mg/day versus amitriptyline 10 mg/day, 34 participants, for 6 weeks) did not report our primary outcomes.

The second study (pregabalin 75 to 450 mg/day versus placebo 75 to 450 mg/day, 107 participants, for 15 weeks) reported no significant change in pain scores for pain relief of 30% or greater between pregabalin 18/54 (33.3%), and placebo 16/51 (31.4%), P = 0.83 (very low-quality evidence). This study also reported Patient Global Impression of Change, with the percentage of participants feeling "much or very much improved" with pregabalin 53.1%, and placebo 29.5% (very low-quality evidence).

Secondary outcomes

In one small study, adverse events were uncommon: gabapentin 2 participants (2 adverse events); amitriptyline 1 participant (1 adverse event) (6-week trial). The second study reported a higher number of adverse events: pregabalin 38 participants (167 adverse events); placebo 34 participants (132 adverse events) (15-week trial) (very low-quality evidence).

Withdrawals due to adverse events were infrequent in both studies: pregabalin (4 participants), placebo (4 participants), gabapentin (2 participants), and amitriptyline (1 participant) (very low-quality evidence).

Serious adverse events were reported in both studies. One study reported only one serious adverse event (cholelithiasis and major depression resulting in hospitalisation in the pregabalin group) and the other study reported no serious adverse events (very low-quality evidence).

There were few or no data for our remaining secondary outcomes.

Quality of evidence

For the outcomes with available data, we downgraded the quality of the evidence by three levels to very low-quality due to too few data and the fact that the number of events was too small to be meaningful.

Authors' conclusions

This review identified only two small studies, with insufficient data for analysis.

As we could undertake no meta-analysis, we were unable to comment about efficacy or harm from the use of antiepileptic drugs to treat chronic non-cancer pain in children and adolescents. Similarly, we could not comment on our remaining secondary outcomes: Carer Global Impression of Change; requirement for rescue analgesia; sleep duration and quality; acceptability of treatment; physical functioning; and quality of life.

We know from adult randomised controlled trials that some antiepileptics, such as gabapentin and pregabalin, can be effective in certain chronic pain conditions.

PLAIN LANGUAGE SUMMARY

Antiepileptic drugs for chronic non-cancer pain in children and adolescents

Bottom line

We are uncertain as to whether antiepileptic drugs provide pain relief for chronic non-cancer pain in children and adolescents. We do not have evidence to suggest that one type of antiepileptic drug is more effective than another.

Background

Children can experience chronic or recurrent pain related to genetic conditions, nerve damage, muscle or joint pain, stomach pain, or for other unknown reasons. Chronic pain is pain that lasts three months or more and is commonly accompanied by changes in lifestyle and functional abilities, as well as by signs and symptoms of depression and anxiety.

Antiepileptic (anticonvulsant) drugs were originally developed to treat epilepsy, but some of these drugs have been shown to provide pain relief in some chronic painful conditions in adults.

Study characteristics

In September 2016 we searched for clinical trials in which antiepileptic drugs were used to treat chronic pain. We found two studies with a total of 141 participants (aged 7 to 18 years) with chronic neuropathic pain, complex regional pain syndrome type 1, or fibromyalgia, which they had for more than 3 months.

Key results

One study looked at pregabalin versus placebo for people with fibromyalgia, and found no significant change in pain scores. The other study evaluated gabapentin compared to amitriptyline, but did not report our specified pain outcomes.

Side effects were uncommon, and only mild reactions (such as nausea, dizziness, drowsiness, tiredness, and abdominal discomfort): pregabalin 38 participants, gabapentin 2 participants, amitriptyline 1 participant, and placebo 34 participants. Only 11 participants withdrew due to these mild side effects (4 pregabalin, 2 gabapentin, 1 amitriptyline, 4 placebo).

Quality of the evidence

We rated the quality of the evidence from studies using four levels: very low, low, moderate, or high. Very low-quality evidence means that we are very uncertain about the results. High-quality evidence means that we are very confident in the results.

The available evidence in this review was of very low-quality due to a lack of data and small study sizes.

Summary of findings for the main comparison. Gabapentin compared with amitriptyline for chronic non-cancer pain

Gabapentin compared with amitriptyline for chronic non-cancer pain

Patient or population: children and adolescents (birth to 17 years of age) with chronic non-cancer pain

Settings: primary care

Intervention: gabapentin

Comparison: amitriptyline

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Amitriptyline	Gabapentin				
Participant-reported pain relief of 30% or greater	No data	No data	N/A	N/A	-	No evidence to support or refute[b]
Participant-reported pain relief of 50% or greater	No data	No data	N/A	N/A	-	No evidence to support or refute[b]
Patient Global Impression of Change: much improved or very much improved	No data	No data	N/A	N/A	-	No evidence to support or refute[b]
Any adverse events	1/17	2/17	N/A	34 participants (1 study)	⊕⊖⊖⊖ **very low[a]**	
Serious adverse events	0/17	0/17	N/A	34 participants (1 study)	⊕⊖⊖⊖ **very low[a]**	
Withdrawals due to adverse events	1/17	2/17	N/A	34 participants (1 study)	⊕⊖⊖⊖ **very low[a]**	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **N/A:** not applicable; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded three levels due to too few data and number of events were too small to be meaningful.
[b]No data available for this outcome, and therefore no GRADE rating has been applied and there is no evidence to support or refute.

Summary of findings 2. Pregabalin compared with placebo for chronic non-cancer pain

Pregabalin compared with placebo for chronic non-cancer pain

Patient or population: children and adolescents (birth to 17 years of age) with chronic non-cancer pain

Settings: multicentre, USA (28 primary care centres), India (5 primary care centres), Taiwan (2 primary care centres), and Czech Republic (1 primary care centre)

Intervention: pregabalin

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Placebo	Pregabalin				
Participant-reported pain relief of 30% or greater**	16/51	18/54	N/A	107 participants (1 study)	⊕⊖⊖⊖ **very low[a]**	
Participant-reported pain relief of 50% or greater**	4/51	9/54	N/A	107 participants (1 study)	⊕⊖⊖⊖ **very low[a]**	
Patient Global Impression of Change: much improved or very much improved**	15/51	29/54	N/A	107 participants (1 study)	⊕⊖⊖⊖ **very low[a]**	

Adverse events	34/53	38/54	N/A	107 participants (1 study)	⊕⊝⊝⊝ **very low**[a]
Serious adverse events	0/53	1/54	N/A	107 participants (1 study)	⊕⊝⊝⊝ **very low**[a]
Withdrawals due to adverse events	4/53	4/54	N/A	107 participants (1 study)	⊕⊝⊝⊝ **very low**[a]

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded three levels due to too few data and number of events were too small to be meaningful.
[b]No data available for this outcome, and therefore no GRADE rating has been applied and there is no evidence to support or refute.

BACKGROUND

Pain is a common feature of childhood and adolescence around the world, and for many young people, that pain is chronic. The World Health Organization (WHO) guidelines for pharmacological treatments for persisting pain in children acknowledge that pain in children is a major public health concern of high significance in most parts of the world (WHO 2012). While in the past, pain was largely dismissed and was frequently left untreated, views on children's pain have changed over time, and relief of pain is now seen as important. Since the 1970s, studies comparing child and adult pain management have revealed a variety of responses to pain, fuelling the need for a more in-depth focus on paediatric pain (Caes 2016).

Infants (zero to 12 months), children (1 to 9 years), and adolescents (10 to 18 years), WHO 2012, account for 27% (1.9 billion) of the world's population (United Nations 2015); the proportion of those aged 14 years and under ranges from 12% (in Hong Kong) to 50% (in Niger) (World Bank 2014). However, little is known about the pain management needs of this population. For example, in the Cochrane Library, approximately 12 reviews produced by the Cochrane Pain, Palliative and Supportive Care Review Group in the past 18 years have been specifically concerned with children and adolescents, compared to over 100 reviews specific to adults. Additional motivating factors for investigating children's pain include the vast amount of unmanaged pain in the paediatric population and the development of new technologies and treatments. We convened an international group of leaders in paediatric pain to design a suite of seven reviews in chronic pain and cancer pain (looking at antidepressants, antiepileptic drugs, non-steroidal anti-inflammatory drugs, opioids, and paracetamol as priority areas) in order to review the evidence under a programme grant for children's pain utilising pharmacological interventions in children and adolescents (Appendix 1).

This review is based on a template for reviews of pharmacotherapies used to relieve pain in infants, children, and adolescents. The aim is for all reviews to use the same methods, based on new criteria for what constitutes reliable evidence (Appendix 2) (Moore 2010a; Moore 2012). This review focused on antiepileptic drugs to treat chronic non-cancer pain.

Description of the condition

This review focused on chronic non-cancer pain experienced by children and adolescents as a result of any type of chronic disease that occurs throughout the global paediatric population. Children's level of pain can be mild, moderate, or severe, and pain management is an essential element of patient management during all care stages of chronic disease.

As the leading cause of morbidity in the world today, chronic disease (and its associated pain) is a major health concern. Chronic pain can arise in the paediatric population in a variety of pathophysiological classifications: nociceptive, neuropathic, or idiopathic. Chronic pain is pain that lasts three months or longer and can be accompanied by changes in lifestyle, personality, and functional abilities, as well as by signs and symptoms of depression (Ripamonti 2008).

Whilst diagnostic and perioperative procedures performed to treat chronic diseases are a known common cause of pain in these patients, this review did not cover perioperative pain or adverse effects of treatments such as mucositis.

Description of the intervention

Evidence for the use of antiepileptic (anticonvulsant) drugs, which were originally developed and manufactured to treat convulsions and convulsive disorders in people with epilepsy, to provide pain relief in many chronic painful conditions has existed since the 1960s (Blom 1962; Wiffen 2013). Phenytoin was used as long ago as the 1940s to treat trigeminal neuralgia (Ryder 2005). Antiepileptic drugs are now recommended for the treatment of both convulsive disorders and chronic pain in the WHO list of essential medicines (WHO 2015).

Antiepileptic drugs are available worldwide and have been found to reduce the chronic pain associated with fibromyalgia, neuropathic pain, and other kinds of chronic pain. Antiepileptic drugs include, but are not limited to, carbamazepine, clonazepam, diazepam, ethosuximide, lorazepam, magnesium sulphate, midazolam, phenobarbital, phenytoin, and valproic acid (sodium valproate) (WHO 2015).

Routes of administration include oral tablets, oral liquids, gels, rectal solutions, parenteral formulations, intravenous injections, and intramuscular injections (WHO 2015). Recommended doses for children vary depending on the drug, age of the child, and painful condition.

Known side effects of antiepileptic drugs range from sweating, headache, elevated temperature, nausea, and abdominal pain to more serious adverse effects including mental or motor function impairment, physical or congenital abnormalities if taken during pregnancy, and on rare occasions death from haematological reactions.

The use of antiepileptic drugs to treat chronic pain in children is likely to be outside the product licence in most countries.

How the intervention might work

Different antiepileptic drugs have different mechanisms of action, not all of which are well understood, especially in terms of how a given drug produces pain relief in any particular individual with any particular chronic pain condition.

In general, antiepileptic drugs are thought to reduce the ability of the neuron to fire at high frequency (Chong 2000). The two standard explanations are enhanced gamma-aminobutyric acid (GABA) inhibition (valproate, clonazepam), or a stabilising effect on neuronal cell membranes, possibly by modulating ion channels. A third possibility is action via N-methyl-D-aspartate (NMDA) receptor sites (Dickenson 2007).

The mechanisms of action of specific drugs are as follows.

- Gabapentin is thought to act by binding to calcium channels and modulating calcium influx. This mode of action confers antiepileptic, analgesic, and sedative effects. Recent research indicates that gabapentin acts by blocking new synapse formation (Eroglu 2009). Clear-cut explanations are not available.
- Pregabalin has a mechanism of action similar to gabapentin, binding to calcium channels and modulating calcium influx as

well as influencing GABAergic neurotransmission. It is more potent than gabapentin and is therefore used at lower doses. Again, clear-cut explanations are not available.

- Lamotrigine is chemically unrelated to other antiepileptic agents. It is thought to exert its antiepileptic effect via sodium channels. There is some evidence that agents that block sodium channels are useful in the treatment of neuropathic pain (McCleane 2000). More recently it has been shown that neuronal alpha-4-beta2-nicotinic acetylcholine receptors may be a target for lamotrigine, and this may mediate its antiepileptic effects (Zheng 2010).
- Lacosamide is a functionalised amino acid molecule that selectively enhances the slow inactivation of voltage-gated sodium channels and interacts with the collapsin-response mediator protein-2 (Beydoun 2009; Errington 2008). Voltage-gated sodium channels play an important role in the excitability of nociceptors.
- Carbamazepine and its keto analogue oxcarbazepine are also thought to work by blocking voltage-gated sodium channels, making the cells less excitable.
- There is no consensus as to how phenytoin exerts any analgesic effects. It may involve voltage-gated sodium channel blockade.
- Valproate is thought to influence GABAergic neurotransmission. It is also thought to block sodium and calcium channels. Although their mechanism of action in pain relief is not yet fully understood, increasing levels of GABA and stabilisation of cell membranes probably result in a reduction of pain signals being processed in the brain. A number of other putative mechanisms of action have been suggested based on the effects on signal transduction in neurons (Toth 2005).
- It has been suggested that clonazepam works by antagonising hyperexcitability of neurotransmission through the enhancement of inhibitory GABAergic signalling pathways.
- Topiramate has been shown to block activity-dependent, voltage-gated sodium channels; enhance the action of GABAreceptors; inhibit L-type voltage-gated calcium channels; presynaptically reduce glutamate release; and postsynaptically block kainate/α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Chong 2003).

Why it is important to do this review

The paediatric population is at risk of inadequate management of pain (AMA 2013). Some conditions that would be aggressively treated in adult patients are being managed with insufficient analgesia in younger populations (AMA 2013). Although there have been repeated calls for best evidence to treat children's pain, such as Eccleston 2003, there are no easily available summaries of the most effective paediatric pain relief.

This review formed part of a Programme Grant addressing the unmet needs of people with chronic pain, commissioned by the National Institute for Health Research (NIHR) in the UK. This topic was identified in June 2015 during consultation with experts in paediatric pain. Please see Appendix 1 for full details of the meeting. The standards used to assess evidence in chronic pain trials have changed substantially in recent years, with particular attention being paid to trial duration, withdrawals, and statistical imputation following withdrawal, all of which can substantially alter estimates of efficacy. The most important change was to encourage a move from using average pain scores, or average change in pain scores, to the number of people who have a large decrease in pain (by at least 50%). Pain intensity reduction of 50% or more has been shown to correlate with improvements in comorbid symptoms, function, and quality of life (Moore 2011a). These standards are set out in the reference guide for pain studies (AUREF 2012).

OBJECTIVES

To assess the analgesic efficacy and adverse events of antiepileptic drugs used to treat chronic non-cancer pain in children and adolescents aged between birth and 17 years, in any setting.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised controlled trials, with or without blinding, and participant- or observer-reported outcomes.

Full journal publication was required, with the exception of online clinical trial results, summaries of otherwise unpublished clinical trials, and abstracts with sufficient data for analysis. We included studies published in any language. We excluded abstracts (usually meeting reports) or unpublished data, non-randomised studies, studies of experimental pain, case reports, and clinical observations.

Types of participants

We included studies of infants, children, and adolescents, aged from birth to 17 years old, with chronic or recurrent pain (lasting for three months or longer), arising from genetic conditions, neuropathy, or other conditions. These included but were not limited to chronic musculoskeletal pain and chronic abdominal pain.

We excluded studies of perioperative pain, acute pain, cancer pain, headache, migraine, and pain associated with primary disease or its treatment.

We planned to include studies of participants with more than one type of chronic pain, in which case we would analyse results according to the primary condition.

Types of interventions

We included studies reporting interventions prescribing antiepileptic drugs for the relief of chronic non-cancer pain; by any route, in any dose, with comparison to a placebo or any active comparator.

Types of outcome measures

In order to be eligible for inclusion in this review, studies had to report pain assessment, as well as meeting the other selection criteria.

We included trials measuring pain intensity and pain relief assessed using validated tools such as numerical rating scale (NRS), visual analogue scale (VAS), Faces Pain Scale - Revised (FPS-R), Colour Analogue Scale (CAS), or any other validated numerical rating scale.

We were particularly interested in Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (PedIMMPACT) definitions for moderate and substantial benefit in chronic pain studies (PedIMMPACT 2008). These were defined as: at least 30% pain relief over baseline (moderate); at least 50% pain relief over baseline (substantial); much or very much improved on Patient Global Impression of Change scale (PGIC) (moderate); very much improved on PGIC (substantial).

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

We also recorded any reported adverse events. We planned to report the timing of outcome assessments.

Primary outcomes

1. Participant-reported pain relief of 30% or greater
2. Participant-reported pain relief of 50% or greater
3. PGIC much or very much improved

In the absence of self reported pain, we considered the use of 'other-reported' pain, typically by an observer such as a parent, carer, or healthcare professional (Stinson 2006; von Baeyer 2007).

Secondary outcomes

We identified the following with reference to the PedIMMPACT recommendations, which suggest core outcome domains and measures for consideration in paediatric acute and chronic/recurrent pain clinical trials (PedIMMPACT 2008),

1. Carer Global Impression of Change
2. Requirement for rescue analgesia
3. Sleep duration and quality
4. Acceptability of treatment
5. Physical functioning as defined by validated scales
6. Quality of life as defined by validated scales
7. Any adverse events
8. Withdrawals due to adverse events
9. 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.

Search methods for identification of studies

We developed the search strategy with our Information Specialist based on previous strategies used by the Cochrane Pain, Palliative and Supportive Care Review Group and carried out the searches.

Electronic searches

We searched the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) (via the Cochrane Register of Studies Online) searched on 6 September 2016;
- MEDLINE (via Ovid) 1947 to week 2 September 2016, searched 6 September 2016;Embase (via Ovid) 1974 to week 2 September 2016, searched 6 September 2016.

We used medical subject headings (MeSH) or equivalent and text word terms. We restricted our search to randomised controlled trials and clinical trials. There were no language or date restrictions. We restricted our search to published papers only and excluded conference abstracts and meeting reports. The focus of the key words in our search terms was on chronic pain and anticonvulsant pharmacological agents. We tailored searches to individual databases. The search strategies for MEDLINE, Embase, and CENTRAL are in Appendix 3, Appendix 4, and Appendix 5, respectively.

Searching other resources

We searched ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/) for ongoing trials, on 6 September 2017. In addition, we checked reference lists of reviews and retrieved articles for additional studies, and performed citation searches on key articles. We planned to contact experts in the field for unpublished and ongoing trials. We planned to contact study authors for additional information where necessary.

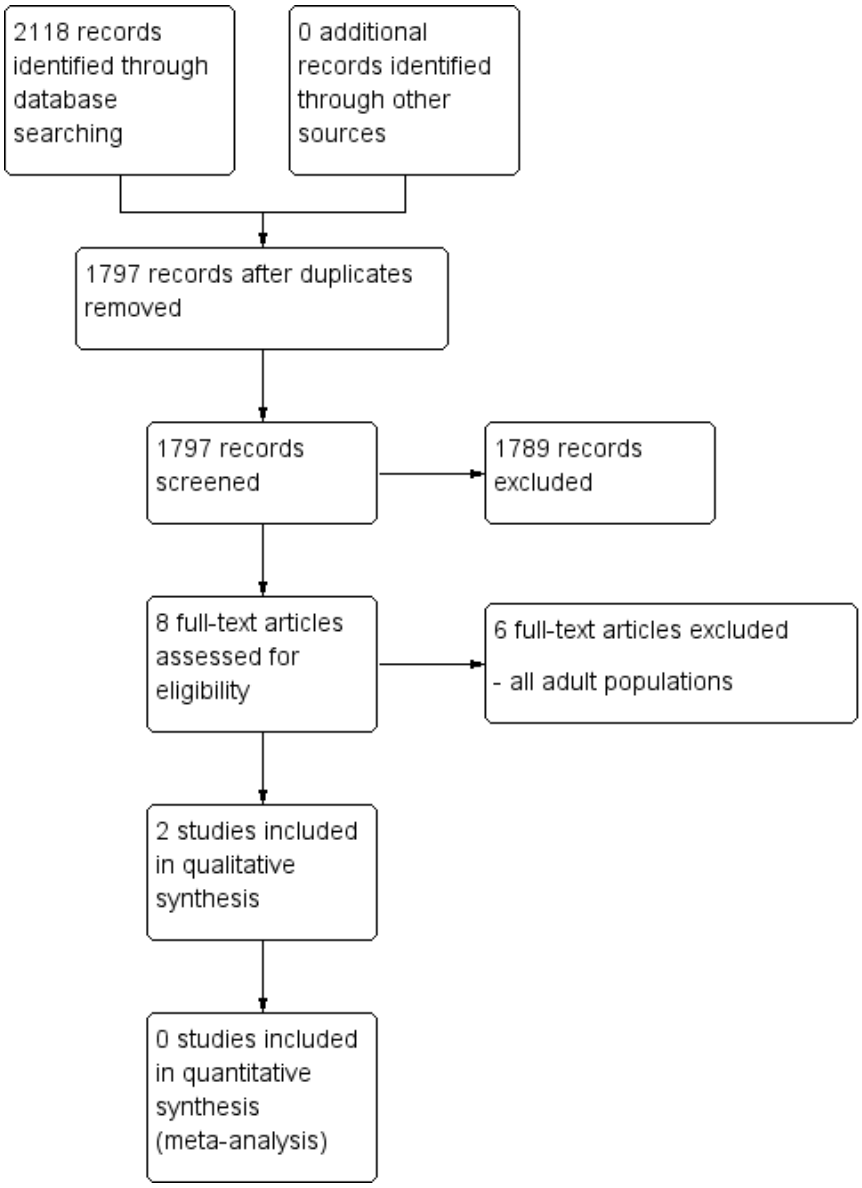
Data collection and analysis

We planned to perform separate analyses according to particular chronic pain conditions. We planned to combine different chronic pain conditions in analyses for exploratory purposes only.

Selection of studies

Two review authors independently determined study eligibility by reading the abstract of each study identified by the search. Review authors independently eliminated studies that clearly did not satisfy the inclusion criteria, and obtained full copies of the remaining studies. Two review authors independently read these studies to select those that met the inclusion criteria, a third review author adjudicating in the event of disagreement. We did not anonymise the studies in any way before assessment. We included a PRISMA flow chart (Figure 1) to illustrate the results of the search and the process of screening and selecting studies for inclusion in the review (Moher 2009), as recommended in section 11.2.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We included studies in the review irrespective of whether measured outcome data are reported in a 'usable' way.

Figure 1. Study flow diagram.



Data extraction and management

We obtained full copies of the studies, and two review authors independently carried out data extraction. Where these data were available, data extraction included information about the pain condition, number of participants treated, drug and dosing regimen, study design (placebo or active control), study duration and follow-up, analgesic outcome measures and results, withdrawals, and adverse events (participants experiencing any adverse event or serious adverse event). We planned to collate multiple reports of the same study, so that each study rather than each report was the unit of interest in the review. We collected characteristics of the included studies in sufficient detail to populate a 'Characteristics of included studies' table.

We used a template data extraction form and checked for agreement before entry into Cochrane's statistical software Review Manager 5 (RevMan 2014).

If a study had more than two intervention arms, we planned to only include the intervention and control groups that met the eligibility criteria. If multi-arm studies were included, we planned to analyse multiple intervention groups in an appropriate way that avoided arbitrary omission of relevant groups and double-counting of participants.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We completed a 'Risk of bias' table for each included study using the Cochrane 'Risk of bias' tool in Review Manager 5 (RevMan 2014).

We assessed the following for each study. Any disagreements were resolved by discussion between review authors or by consulting a third review author when necessary.

1. Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (i.e. any truly random process, e.g. random number table; computer random number generator); or unclear risk of bias (when the method used to generate the sequence was not clearly stated). We excluded studies that used a non-random process and were therefore at high risk of bias (e.g. 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 (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); or unclear risk of bias (when the method was not clearly stated). We excluded studies that did not conceal allocation and were therefore at a high risk of bias (e.g. open list).
3. Blinding of participants and personnel (checking for possible performance bias). We assessed any methods used to blind the participants and personnel from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study states that the participants and personnel involved were blinded to treatment groups); unclear risk of bias (study does not state whether or not participants and personnel were blinded to treatment groups); or high risk of bias (participants or personnel were not blinded) (as stated in Types of studies, we still included trials with or without blinding, and participant- or observer-reported outcomes).
4. Blinding of outcome assessment (checking for possible detection bias). We assessed any methods used to blind the outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (e.g. study states that it was single-blinded and describes the method used to achieve blinding of the outcome assessor); unclear risk of bias (study states that outcome assessors were blinded but does not provide an adequate description of how this was achieved); or high risk of bias (outcome assessors were not blinded) (as stated in Types of studies, we still included trials with or without blinding, and participant- or observer-reported outcomes).
5. 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 of bias (i.e. less than 10% of participants did not complete the study or 'baseline observation carried forward' (BOCF) analysis was used, or both); unclear risk of bias (used 'last observation carried forward' (LOCF) analysis); or high risk of bias (used 'completer' analysis).
6. Selective reporting (checking for possible reporting bias). We assessed the methods used to report the outcomes of the study as: low risk of bias (if all planned outcomes in the protocol or methods were reported in the results); unclear risk of bias (if there was not a clear distinction between planned outcomes and reported outcomes); high risk of bias (if some planned outcomes from the protocol or methods were clearly not reported in the results).
7. Size of study (checking for possible biases confounded by small size (Dechartres 2013; Dechartres 2014; McQuay 1998; Nüesch 2010; Thorlund 2011)). We assessed studies as being at low risk of bias (200 participants or more per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); or high risk of bias (fewer than 50 participants per treatment arm).
8. Other bias. We assessed studies for any additional sources of bias such as early stopping or baseline imbalances as low, unclear, or high, and provided rationale.

Measures of treatment effect

Where dichotomous data were available, we planned to calculate a risk ratio (RR) with 95% confidence interval (CI) and meta-analyse the data as appropriate. We planned to calculate numbers needed to treat for an additional beneficial outcome (NNTBs) where appropriate (McQuay 1998); for unwanted effects the NNTB becomes the number needed to treat for an additional harmful outcome (NNTH) and would be calculated in the same manner. Where continuous data were reported, we planned to use appropriate methods to combine these data in the meta-analysis.

Unit of analysis issues

We planned to accept randomisation to the individual participant only. We planned to split the control treatment arm between active treatment arms in a single study if the active treatment arms were not combined for analysis. We only accepted studies with minimum 10 participants per treatment arm.

Dealing with missing data

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

Assessment of heterogeneity

We planned to identify and measure heterogeneity as recommended in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to deal with clinical heterogeneity by combining studies that examined similar conditions. We planned to undertake and present a meta-analysis only if we judged participants, interventions, comparisons, and outcomes to be sufficiently similar to ensure a clinically meaningful answer. We planned to assess statistical heterogeneity visually and by using the I^2 statistic (L'Abbé 1987). When I^2 was greater than 50%, we planned to consider the possible reasons.

Assessment of reporting biases

We assessed the risk of reporting bias, as recommended in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

The aim of this review is to use dichotomous outcomes of known utility and of value to patients (Hoffman 2010; Moore 2010b; Moore 2010c; Moore 2010d; Moore 2013a). The review did not depend on what the authors of the original studies chose to report or not, though clearly difficulties would arise in studies failing to report any dichotomous results. We extracted and used continuous data, which probably reflected efficacy and utility poorly, and is useful for illustrative purposes only (Appendix 6; Appendix 7).

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 a number needed to treat (NNT) of 10 or higher) (Moore 2008).

Data synthesis

We planned to use a fixed-effect model for meta-analysis. We planned to use a random-effects model for meta-analysis if there was significant clinical heterogeneity and we considered it appropriate to combine studies. We planned to conduct our analysis using the primary outcomes of pain and adverse events, and to calculate the NNTHs for adverse events. We planned to use the Cochrane software program Review Manager 5 (RevMan 2014).

Quality of the evidence

To analyse data, two review authors independently rated the quality of each outcome. We planned to use the GRADE approach to assess the quality of the body of evidence related to each of the key outcomes, and to report our judgement in a 'Summary of findings' table per Chapter 12 of the *Cochrane Handbook* (Appendix 8) (Higgins 2011).

In addition, there may be circumstances where the overall rating for a particular outcome would need to be adjusted as recommended by GRADE guidelines (Guyatt 2013a). For example, if there were so few data that the results were highly susceptible to the random play of chance, or if studies used LOCF imputation in circumstances where there were substantial differences in adverse event withdrawals, one would have no confidence in the result, and would need to downgrade the quality of the evidence by three levels, to very low quality. In addition, in circumstances where no data were reported for an outcome, we planned to report that there was no evidence to support or refute (Guyatt 2013b).

'Summary of findings' table

We included a 'Summary of findings' table as set out in the Cochrane Pain, Palliative and Supportive Care Review Group's author guide (AUREF 2012), and recommended in section 4.6.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to justify and document all assessments of the quality of the body of evidence.

In an attempt to interpret reliability of the findings for this systematic review, we attempted to assess the summarised data using the GRADE guidelines (Appendix 8) to rate the quality of the body of evidence of each of the key outcomes listed in Types of outcome measures per Chapter 12 of the *Cochrane Handbook* (Guyatt 2011; Higgins 2011), as appropriate. Utilising the explicit criteria against study design, risk of bias, imprecision, inconsistency, indirectness, and magnitude of effect, we planned to summarise the evidence in an informative, transparent and, succinct 'Summary of findings' table or 'Evidence profile' table (Guyatt 2011).

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses where a minimum number of data were available (at least 200 participants per treatment arm). We planned to analyse according to age group; geographical location or country; type of control group; baseline measures; frequency, dose, and duration of drugs; and nature of drug.

We planned to investigate whether the results of subgroups were significantly different by inspecting the overlap of confidence intervals and by performing the test for subgroup differences available in Review Manager 5.

Sensitivity analysis

We did not plan to carry out any sensitivity analysis because the evidence base is known to be too small to allow reliable analysis; we did not plan to pool results from chronic pain of different origins in the primary analyses. We planned to examine details of dose escalation schedules in the unlikely circumstance that this could provide some basis for a sensitivity analysis.

RESULTS

Description of studies

Results of the search

A PRISMA flow diagram of the search results is shown in Figure 1.

The three main database searches revealed 2118 records of titles and abstracts, of which 321 duplicates were removed. Our searches of ClinicalTrials.gov and the WHO ICTRP yielded no additional eligible studies.

We screened the remaining 1797 titles and abstracts for eligibility, of which 1789 were removed as ineligible studies.

We retrieved the full-text reports of the eight remaining studies. We deemed six as ineligible. We identified no ongoing studies. Two studies fulfilled the eligibility criteria and provided data. As they investigated different antiepileptic drugs and type of chronic pain condition, we could enter neither study into a quantitative meta-analysis.

Included studies

See Characteristics of included studies.

Arnold 2016 investigated 107 participants in a multicentre (36 centres), randomised, double-blind, placebo-controlled, parallel-group study. Participants had a diagnosis of fibromyalgia according to Yunus and Masi criteria with a mean daily pain score of ≥ 4 out of 10. Ages ranged from 12 to 17 years, and 86% were female. The flexible dose of oral pregabalin was administered as 75 to 450 mg/day, and flexible-dose placebo tablets were administered in a similar regimen. The study duration was 15 weeks, whereby 4 doses were optimised over 3 weeks based on efficacy and tolerability to 75, 150, 300, 450 mg/day, remaining at that dose for 12 weeks. People were excluded if they had pain due to other conditions, systemic inflammatory musculoskeletal disorders, rheumatic diseases other than fibromyalgia, serious active infections, untreated endocrine disorders, prior participation in a clinical trial of pregabalin, history of failed treatment with pregabalin, unstable mental health conditions, active malignancy, immunocompromised, or history of drug abuse. Authors used a baseline observation carried forward (BOCF) method for missing data.

Brown 2016 investigated 34 participants in a single-centre, randomised, double-blind, controlled by active comparator, parallel-group study. Participants had a diagnosis of complex regional pain syndrome type 1 (CRPS-I) or neuropathic pain

and were recommended for pharmacological treatment with either gabapentin or amitriptyline by their clinical physician. Ages ranged from 7 to 18 years, and 82% were female. A fixed dose of oral gabapentin was administered as 900 mg/day (300 mg at 3 separate times), and fixed-dose oral amitriptyline was administered as a single evening dose of 10 mg/day with placebo capsules administered to this group at the other two dosing time points. People were excluded if they were lactose intolerant; pregnant; previously using either gabapentin or amitriptyline for the treatment of CRPS-I or neuropathic pain; or had health conditions requiring the regular use of anticholinergics, antihypertensives, anticonvulsants, H2 receptor antagonists, antidepressants, sympathomimetics, thyroxine replacement, or antacids that might interact adversely with one of the study medications. Authors used a baseline observation carried forward (BOCF) method for missing data.

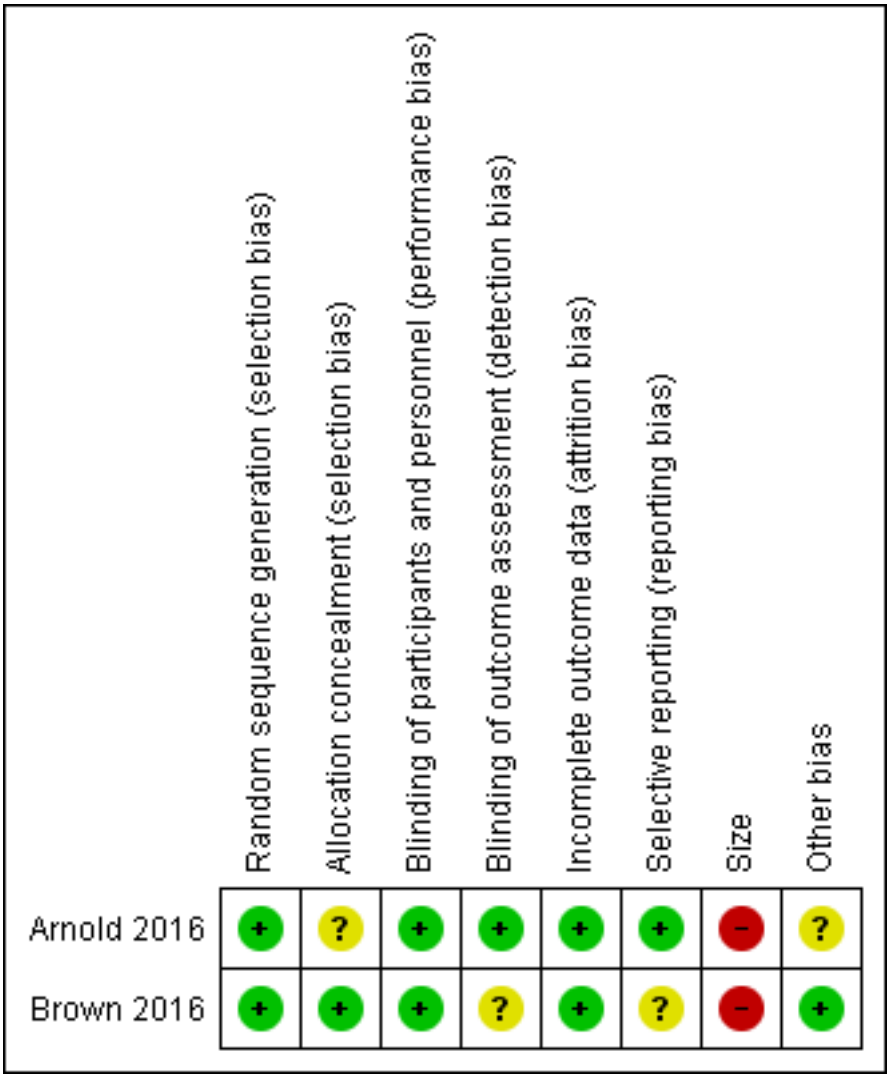
Excluded studies

We excluded six studies in this review. Upon reading the full texts of Kalita 2014, Ogawa 2010, Pramod 2011, Ries 2003, To 2002, and Yilmaz 2015, we discovered the age ranges were on average 18 years and above, with a small number of participants who were 15 to 17 years old. All six studies were randomised controlled trials investigating the use of antiepileptic drugs to treat chronic pain, but unfortunately primarily in adult participants.

Risk of bias in included studies

A summary of the 'Risk of bias' assessment is available in Figure 2. See Characteristics of included studies for full details of 'Risk of bias' assessments.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

Both studies used computer-generated randomisation methods, with a 1:1 ratio of sequence to randomise participants. We judged both studies as at low risk of selection bias for random sequence generation.

Allocation concealment

Brown 2016 adequately described the methods used to conceal treatment allocation to the participants. We judged this study as at low risk of selection bias for allocation concealment.

Arnold 2016 did not adequately describe the methods used to conceal treatment allocation to the participants. We judged this study as at unclear risk of selection bias for allocation concealment.

Blinding

Performance bias

Both studies adequately described the methods used to maintain blinding in both participants and study personnel from knowledge of the treatment groups (Arnold 2016; Brown 2016). We judged both studies as at low risk of performance bias.

Detection bias

Arnold 2016 described adequate methods used to blind outcome assessors. We judged this study as at low risk of detection bias.

Brown 2016 did not provide adequate information regarding how the outcomes were assessed. We judged this study as at unclear risk of detection bias.

Incomplete outcome data

Both studies adequately accounted for all participants from the recruitment stage, through randomisation until follow-up, including counting all withdrawals (Arnold 2016; Brown 2016). We judged both studies as at low risk of attrition bias.

Neither study displayed an unclear or high risk of attrition bias.

Selective reporting

Arnold 2016 reported on all planned outcomes as initially listed in the methods section. We judged this study as at low risk of reporting bias.

Brown 2016 did not report on all planned outcomes as initially listed in the methods section. Some secondary outcomes, for example disruption of school, social, and sports, were not reported. We judged this study as at unclear risk of selection bias.

Other potential sources of bias

Size

Arnold 2016 investigated a total of 107 participants, however fewer than 50 participants per treatment arm completed the study. We judged this study as at high risk of bias for size.

Brown 2016 investigated a total of 34 participants, and fewer than 50 participants per treatment arm for both randomisation and completion of the study. We also judged this study as at high risk of bias for size.

Other

We found no other potential sources of bias in Brown 2016. We judged this study as at low risk of other bias. Arnold 2016 reported funding for the study and medical writing support from Pfizer as well as the majority of the author team to be Pfizer employees. We judged this study as at unclear risk of other bias.

Effects of interventions

See: **Summary of findings for the main comparison** Gabapentin compared with amitriptyline for chronic non-cancer pain; **Summary of findings 2** Pregabalin compared with placebo for chronic non-cancer pain

Results and outcomes of the individual studies are shown in Appendix 6 and Appendix 7.

Comparison 1: Antiepileptic drugs versus active comparator

One study, Brown 2016, investigated antiepileptic drugs compared with an active comparator (gabapentin versus amitriptyline) in people with CRPS-I or neuropathic pain.

Primary outcomes

No data were reported for our primary outcomes: participant-reported pain relief of 30% or greater; participant-reported pain relief of 50% or greater; and PGIC much or very much improved.

Due to the lack of evidence, we were unable to judge the quality (no evidence to support or refute).

Secondary outcomes

Sleep duration and quality

Brown 2016 reported the average decrease in sleep score on a 5-point Likert scale mean (±standard deviation) (m (±SD)). For completed participants, the mean decrease in sleep score for 14 gabapentin participants was 0.46 (±1.60), and for 12 amitriptyline participants 1.25 (±1.86); P = 0.75. For all participants, the mean decrease in sleep score for 17 gabapentin participants was 0.38 (±1.45), and for 17 amitriptyline participants 0.88 (±1.69); P = 0.77 (very low-quality evidence).

Any adverse event

Brown 2016 reported the number of participants who experienced at least 1 adverse event: 1 for gabapentin (1 event) and 2 for amitriptyline (1 event per participant) (p = 0.77). Adverse events in all studies, across active treatment and comparator groups, were considered to be a mild reaction, such as nausea, dizziness, drowsiness, tiredness, and abdominal discomfort (very low-quality evidence).

Withdrawals due to adverse events

Total withdrawals were low: 2 out of 17 in the gabapentin group and 1 out of 17 in the amitriptyline group (very low-quality evidence) (Brown 2016).

Withdrawals due to adverse events were low: 2 out of 17 in the gabapentin group and 1 out of 17 in the amitriptyline group (very low-quality evidence) (Brown 2016).

Serious adverse events

Brown 2016 reported no serious adverse events for gabapentin (0 out of 17) and amitriptyline (0 out of 17) groups (very low-quality evidence).

Other secondary outcomes

No data were reported for our remaining secondary outcomes: Carer Global Impression of Change; requirement for rescue analgesia; acceptability of treatment; physical functioning as

defined by validated scales; and quality of life as defined by validated scales (no evidence to support or refute).

Quality of the evidence

There is no evidence to support or refute the use of antiepileptic drugs versus an active comparator across our primary outcomes.

The quality of evidence for antiepileptic drugs versus an active comparator across our secondary outcomes is very low-quality, due to too few data and the fact that the number of events was too small to be meaningful.

See Summary of findings for the main comparison.

Comparison 2: Antiepileptic drugs versus placebo

One study, Arnold 2016, investigated antiepileptic drugs compared with a placebo (pregabalin versus placebo).

Primary outcomes

Participant-reported pain relief of 30% or greater

Arnold 2016 reported no significant change in pain scores for pain relief of 30% or greater between pregabalin 18/54 (33.3%) and placebo 16/51 (31.4%), p = 0.83. The authors of Arnold 2016 reported in their conclusions that "pregabalin did not significantly improve the mean pain score in adolescents with FM [fibromyalgia]". For mean pain scores, see Appendix 6 (very low-quality evidence).

Participant-reported pain relief of 50% of greater

Arnold 2016 reported no significant change in pain scores for pain relief of 50% or greater between pregabalin 9/54 (16.7%) and placebo 4/51 (7.8%), p = 0.179 (very low-quality evidence).

PGIC much or very much improved

Arnold 2016 reported much or very much improved pain scores for pregabalin 53.1% and placebo 29.5% (p = 0.013) (very low-quality evidence).

Secondary outcomes

Carer Global Impression of Change

Arnold 2016 reported Parent GIC much or very much improved responses for pregabalin responders (51.0%) compared with placebo responders (25.0%) (p = 0.011) (very low-quality evidence).

Sleep duration and quality

Arnold 2016 reported the average decrease in sleep score on an 11-point numerical rating scale m (±SD) at baseline: pregabalin: 5.8 (1.6) and placebo: 5.6 (2.5); at week 8 treatment difference: -1.01 (95% confidence interval (CI) -1.73 to -0.30), P = 0.006; at week 10 treatment difference: P = 0.037; at week 15 treatment difference: -0.17 (95% CI -0.95 to 0.61). The overall treatment difference was -0.48 (95% CI -1.02 to 0.06), p = 0.081 (very low-quality evidence).

Physical functioning

Arnold 2016 reported an FIQ-C (Fibromyalgia Impact Questionnaire for children) total score of least squares mean difference between gabapentin and amitriptyline: -2.46 (95% CI -6.87 to 1.95), p = 0.270 (very low-quality evidence).

Any adverse events

Arnold 2016 reported total adverse events as 167 events in the pregabalin group and 132 events in the placebo group. Arnold 2016 also reported the number of participants who experienced an adverse event as 38 (70.4%) in the pregabalin group and 34 (64.2%) in the placebo group (very low-quality evidence).

Withdrawals due to adverse events

Arnold 2016 reported total withdrawals as 10 (19%) pregabalin and 17 (32%) placebo. Total withdrawals due to adverse events in Arnold 2016 were low: 4 (7%) pregabalin and 4 (8%) placebo (very low-quality evidence).

Serious adverse events

Arnold 2016 reported serious adverse events experienced by one participant (2%) for the pregabalin group (cholelithiasis and major depression resulting in hospitalisation), and none for the placebo group (very low-quality evidence).

Other secondary outcomes

No data were reported for our remaining secondary outcomes: requirement for rescue analgesia; acceptability of treatment; physical functioning as defined by validated scales; and quality of life as defined by validated scales (no evidence to support or refute).

Quality of the evidence

The quality of evidence for antiepileptic drugs versus placebo across our primary outcomes is very low-quality, due to too few data and the fact that the number of events was too small to be meaningful.

The quality of evidence for antiepileptic drugs versus placebo across some of our secondary outcomes is very low-quality, due to too few data and the fact that the number of events was too small to be meaningful. For the remaining secondary outcomes, there was no evidence to support or refute the use of antiepileptic drugs to treat chronic non-cancer pain in children and adolescents.

See Summary of findings 2.

DISCUSSION

Summary of main results

We included two studies in this review that reported data from 141 participants (aged 7 to 18 years), comparing gabapentin versus amitriptyline, or pregabalin versus placebo.

The two studies were not comparable by pain condition or by type of antiepileptic drug, therefore we were unable to complete any quantitative analysis of our outcomes.

Risk of bias for the two included studies varied, due to issues with randomisation (low to unclear risk), blinding of outcome assessors (low to unclear risk), reporting bias (low to unclear risk), the size of the study populations (high risk), and industry funding in the 'other' domain (low to unclear risk). We judged the remaining domains of sequence generation, blinding of participants and personnel, and attrition as low risk of bias.

There is no evidence from randomised controlled trials to suggest that antiepileptic drugs are effective in treating chronic non-cancer

pain in children or adolescents, nor do we have evidence to suggest that one antiepileptic drug is more effective than another. We were unable to comment on harm.

Overall completeness and applicability of evidence

This review identified only a small number of studies (two), with insufficient data for meta-analysis. Arnold 2016 investigated pregabalin versus placebo for people with fibromyalgia, and Brown 2016 investigated gabapentin versus amitriptyline in people with CRPS-I or neuropathic pain.

As we could undertake no meta-analysis, we are unable to comment on efficacy or harm from the use of antiepileptic drugs to treat chronic non-cancer pain in children and adolescents. Similarly, we cannot comment on our remaining secondary outcomes: Carer Global Impression of Change, requirement for rescue analgesia, sleep duration and quality, acceptability of treatment, physical functioning, and quality of life.

We know from adult randomised controlled trials that some antiepileptics, such as gabapentin and pregabalin, can be effective in certain chronic neuropathic pain conditions (Wiffen 2013). However, we suggest that these drugs be used with caution in children and only by those with suitable expertise.

The suite of reviews

This review is part of a suite of reviews on pharmacological interventions for chronic pain and cancer-related pain in children and adolescents (Appendix 1). Taking a broader view on this suite of reviews, some pharmacotherapies (investigated in our other reviews) are likely to provide more data than others. The results were thus as expected considering that randomised controlled trials in children are known to be limited. The results have the potential to inform policymaking decisions for the funding of future clinical trials into antiepileptic drug treatment of child and adolescent pain, therefore any results (large or small) are important in order to capture a snapshot of the current evidence for antiepileptic drugs.

Quality of the evidence

Of the two included studies, only one clearly described randomisation methods, and only one was clearly described as double-blind, however both studies provided information about withdrawals, dropouts, and adverse events.

The two studies recruited participants with adequate baseline pain and used clinically useful outcome measures. Only Arnold 2016 reported our prespecified primary outcomes of pain relief at 30% or greater and 50% or greater. Brown 2016 reported a difference between mean pain scores, with limited data to arrive at any results.

The studies themselves were of moderate quality, however the number of studies and sample sizes for the comparisons were somewhat limited, given what is known about study size and estimates of effect for outcomes derived from studies with few participants and events (Dechartres 2013; Dechartres 2014; McQuay 1998; Nüesch 2010; Thorlund 2011).

There was no evidence to support or refute the use of antiepileptic drugs, versus an active comparator, for primary outcomes. The evidence was very low-quality for secondary outcomes for this comparison due to too few data and the fact that the number of events was too small to be meaningful.

The quality of evidence for antiepileptic drugs versus placebo was very low-quality (for primary and secondary outcomes), due to too few data and the fact that the number of events was too small to be meaningful.

Potential biases in the review process

We carried out extensive searches of major databases using broad search criteria, and also searched two large clinical trial registries. We consider it to be unlikely that we have missed relevant studies.

Agreements and disagreements with other studies or reviews

We were not able to identify any published systematic reviews on this topic.

AUTHORS' CONCLUSIONS

Implications for practice

General

We identified two randomised controlled trials, however we were unable to analyse these to determine whether to support or refute the use of antiepileptic drugs to treat chronic non-cancer pain in children and adolescents.

This is disappointing as children and adolescents with chronic non-cancer pain have specific needs for analgesia. While extrapolating from adult data may be possible, it could also compromise effectiveness and safety.

Despite the lack of evidence of long-term effectiveness and safety, clinicians prescribe antiepileptic drugs to children and adolescents when medically necessary, based on extrapolation from adult guidelines, when perceived benefits in conjunction with other multimodalities improve a child's care. However, extrapolating from adult data may be unreliable, and risks compromising safety in children and adolescents. It is important to consider recent suggestions and government warnings about the risks of antiepileptic drugs towards mental health and suicide when used in children (FDA 2008). Until new evidence emerges, individual clinician judgement, and informed consent regarding off-licence use of antiepileptic drugs for children and adolescents with chronic non-cancer pain, will continue to be necessary.

Appropriate medical management is necessary in disease-specific conditions such as incurable progressive degenerative conditions of Duchenne muscular dystrophy, osteogenesis imperfecta, congenital degenerative spine, and neurodegenerative conditions such as spasticity/dystonia in mitochondrial Leigh's disease, leukoencephalopathy, and severe cerebral palsy.

In current practice, antiepileptic drugs are given to young children and adolescents, despite the lack of evidence and although no antiepileptic is licensed for use in pain in those below 18 years of age. Our only current source is the World Health Organization guideline on the pharmacological treatment of persisting pain in children with medical illnesses (WHO 2012).

The rationale for the use of antiepileptic agents for management of chronic neuropathic pain is based on their effectiveness on damaged nervous system (e.g. postherpetic neuralgia). Their use in chronic pain disorders is based on the assumption that there is dysfunction of nervous system (e.g. CRPS, juvenile fibromyalgia, etc.). A common mechanism evoked among the various symptomatically overlapping chronic pain disorders is central sensitisation. In general, chronic pain disorders are poorly defined, particularly in the paediatric population, because of unclear pathoaetiology, poor response to commonly used analgesics, and medical models of care. Chronic pain disorders are associated with multiple somatic symptoms that are usually influenced by the psychosocial stressors that shape the overall pain experience, and are therefore optimally managed by a multidisciplinary approach.

The case definitions, and especially diagnostic criteria of various disorders, have not been fully validated in the paediatric population and are extrapolated from adult experience, for example the CRPS Budapest criteria have yet to be validated in children and adolescents, and central sensitisation in juvenile fibromyalgia is not reliably confirmed and the diagnosis relies on clinical criteria.

For children and adolescents with chronic non-cancer pain

The amount and quality of evidence around the use of antiepileptic drugs for treating chronic non-cancer pain is very low. This means that at present, treatment is based on clinical experience and advice from respected authorities. We could make no judgement about adverse events or withdrawals.

For clinicians

The amount and quality of evidence around the use of antiepileptic drugs for treating chronic non-cancer pain is very low. This means that at present, treatment is based on clinical experience and advice from respected authorities. We could make no judgement about adverse events or withdrawals.

For policymakers

The amount and quality of evidence around the use of antiepileptic drugs for treating chronic non-cancer pain is very low. This means that at present, treatment is based on clinical experience and advice from respected authorities. We could make no judgement about adverse events or withdrawals.

For funders

The amount and quality of evidence around the use of antiepileptic drugs for treating chronic non-cancer pain is very low. This means that at present, treatment is based on clinical experience and advice from respected authorities. We could make no judgement about adverse events or withdrawals.

Implications for research

General

The lack of robust evidence of efficacy and safety found in this review highlights the need to design and fund high quality and clinically relevant research on this topic. The heterogenous nature of pain in children needs to be recognised and presents challenges in designing research studies.

Overall, there appears to be a gap between how antiepileptic drugs are used in clinical practice to treat chronic non-cancer pain in children and adolescents, and how this drug class has been investigated in prospective clinical trials.

The challenge is to develop clinician- and patient-informed trial protocols examining clinically-meaningful, patient-centred outcomes.

Design

Several methodological issues stand out.

The first is the use of outcomes of value to children with chronic non-cancer pain. Existing trials are designed more for purposes of registration and marketing than informing and improving clinical practice, that is the outcomes are often average pain scores or statistical differences, and rarely how many individuals achieve satisfactory pain relief. In the case where pain is initially mild or moderate, consideration needs to be given to what constitutes a satisfactory outcome.

The second issue is the time taken to achieve good pain relief. We have no information about what constitutes a reasonable time to achieve a satisfactory result. This may best be approached initially with a Delphi methodology.

The third issue is design. Studies with a cross-over design often have significant attrition, therefore parallel-group designs may be preferable. The use of suitable validated scales is important.

The fourth issue is size. The studies need to be suitably powered to ensure adequate data after the effect of attrition due to various causes. Much larger studies of several hundred participants or more are needed.

There are some other design issues that might be addressed. Most important might well be a clear decision concerning the gold-standard treatment comparator.

An alternative approach may be to design large registry studies. This could provide an opportunity to foster collaboration among paediatric clinicians and researchers, in order to create an evidence base.

Measurement (endpoints)

Trials need to consider the additional endpoint of 'no worse than mild pain' as well as the standard approaches to pain assessment.

Primary outcomes need to be outcomes of value to children with chronic non-cancer pain and their families. To help them make decisions about drug treatment, families seek to know what chance their child has of achieving relief that is meaningful to them. There is as yet no patient-defined level of pain relief, or improvement in function, that is considered meaningful. This could be addressed in future using Delphi methodology.

As a surrogate, expert consensus recommends reporting the proportion of participants achieving at least 30% or 50% pain relief, but only one of the two included studies did so. Consideration could also be given to reporting the proportion of participants achieving the endpoint of ‘no worse than mild pain’ and ‘no pain’. The endpoint might depend on whether participants are selected for having severe pain at baseline, or whether children whose pain is

mild-moderate are included. For fluctuating conditions, endpoints might be proportion of pain-free days, or days in which pain does not reach a specific level (PedIMMPACT 2008).

Time to achieve benefit was not reported, yet this is of great interest to children and families. Where drugs have equal efficacy, a drug with earlier onset might still be considered 'superior' by consumers. Future research should measure and report the time to achieve outcome and the longevity of benefits.

Other

The obvious study design of choice is the prospective randomised trial, but other pragmatic designs may be worth considering. Studies could incorporate initial randomisation but a pragmatic design in order to provide immediately relevant information on effectiveness and costs. Such designs in pain conditions have been published (Moore 2010e).

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REFERENCES

References to studies included in this review

Arnold 2016 *{published data only}*

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CHARACTERISTICS OF STUDIES

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

Arnold 2016

Methods	**Allocation:** randomised
	Blinding: double-blind
	Controlled: placebo
	Centre: multi
	Arm: 2 arms, parallel groups

Arnold 2016 *(Continued)*

	Imputation: BOCF **Study dates:** 55-month trial (May 2010 to December 2014)
Participants	**Inclusion criteria:** adolescents with fibromyalgia, Yunus and Masi diagnostic criteria, mean daily pain rating NRS score of ≥ 4 (0 to 10). **Exclusion criteria:** pain due to other conditions, systemic inflammatory MSK disorders, rheumatic diseases other than fibromyalgia, serious active infections, untreated endocrine disorders, prior participation in a clinical trial of pregabalin, history of failed treatment with pregabalin, mental health conditions, active malignancy, immunocompromised, or history of drug abuse. **Baseline characteristics** **N =** 107 **Age:** 12 to 17 years **Gender:** male (15); female (92) **Number randomised:** intervention (54); placebo (53) **Number completed:** intervention (44); placebo (36) **Setting and location:** 36 centres in the USA (28), India (5), Taiwan (2), and Czech Republic (1)
Interventions	**Intervention group (N = 54):** flexible-dose pregabalin 75 to 450 mg/day **Control group (N = 53):** flexible-dose placebo 75 to 450 mg/day **Study duration:** 15 weeks' duration including 4 phases: doses were optimised over 3 weeks based on efficacy and tolerability to 75, 150, 300, 450 mg/day. Remaining at that dose for 12 weeks.
Outcomes	**Primary outcomes** 1. Mean pain score (NRS 0 to 10) **Secondary outcomes** 1. Change in pain score by week 2. Change in pain score at week 15 3. PGIC (Patient Global Impression of Change)
Notes	**Sources of funding:** sponsored by Pfizer. Medical writing support was provided. Trial registrations: NCT01020474; NCT01020526.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Subjects were randomized 1:1 to receive pregabalin or matched placebo according to a computer-generated pseudo-random code using the method of random permuted blocks."
Allocation concealment (selection bias)	Unclear risk	**Comment:** no information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "this was a double-blind study", "pregabalin or matched placebo was administered twice daily"

Arnold 2016 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "Under this approach, a blinded assessment of the change in mean pain score of the 95 subjects who had been randomized at that point was conducted"
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** all participants were accounted for.
Selective reporting (reporting bias)	Low risk	**Comment:** all planned outcomes listed in the methods were reported in the results.
Size	High risk	**Comment:** total participants > 50 per treatment arm randomised. Participants < 50 per treatment arm completed.
Other bias	Unclear risk	**Comment:** see notes above for details on Pfizer funding.

Brown 2016

Methods	**Allocation:** randomised **Blinding:** double-blind **Controlled:** active comparator **Centre:** single **Arm:** 2 arms, parallel groups **Imputation:** BOCF **Study dates:** 38-month trial (April 2006 to July 2010)
Participants	**Inclusion criteria:** CRPS-I or neuropathic pain and recommendation for pharmacological treatment with gabapentin or amitriptyline by a clinic physician during the patient's intake appointment. **Exclusion criteria:** unable to speak English, lactose intolerant, pregnant, previously using either gabapentin or amitriptyline for the treatment of CRPS-I or neuropathic pain or if they were unable to swallow a size “0” gelatin capsule. Children were also excluded if study medications were contraindicated by additional health conditions or the treatment of such conditions, including the regular use of any of the following medications or classes of medications: anticholinergics, antihypertensives, anticonvulsants, H2 receptor antagonists, antidepressants, sympathomimetics, thyroid replacements, antacids, and analgesics. **Baseline characteristics** **N =** 34 **Age:** 7 to 18 years **Gender:** male (6); female (28) **Number randomised:** intervention (17); active comparator (17) **Number completed:** intervention (15); active comparator (14) **Setting and location:** Chronic Pain Clinic (The Hospital for Sick Children, Toronto, Canada)
Interventions	**Intervention group (N = 17):** oral gabapentin 900 mg/day (300 mg x 3). **Control group (N = 17):** oral amitriptyline 10 mg/day.

Brown 2016 *(Continued)*

	Study duration: 6 weeks.
Outcomes	**Primary outcomes** 1. Change in usual pain intensity from baseline to 6 weeks as measured by the Child Health Assessment Questionnaire **Secondary outcomes** 1. Disruption of sleep, school, social, and sports (Likert scale) 2. Adverse events
Notes	**Sources of funding:** Canadian Institutes of Health Research (CIHR) New Emerging Team (NET) Grant (GHL-63209).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "The randomization sequence generation was completed by the research support service pharmacist (not involved in patient care) and the allocation list was concealed from the participants and the study team" **Quote:** "Since some neuropathic pain conditions disproportionately affect boys and girls, randomization was stratified by sex to ensure that equivalent numbers of boys and girls were randomized to each treatment group. The randomization sequence of 1:1 ratio of amitriptyline to gabapentin was a block 4 design with the possible sequence combinations (e.g., AABB, ABAB) assigned a number and then a point on a page of printed random numbers picked"
Allocation concealment (selection bias)	Low risk	**Quote:** "The research support pharmacy held the allocation sequence schedule, with a copy of participant-specific medications in sealed manila envelopes available to the research coordinator for emergency purposes or unblinding at the end of the study period"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "To maintain blinding due to differences in dosing frequency for the two study drugs, participants were prescribed one capsule at night (~20:00 h) for the first 3 days, then added a second capsule in the morning (~08:00 h) for the next 3 days and then added a third capsule mid-afternoon (~14:00 h) for the remainder of the trial. Children randomized to the amitriptyline group received amitriptyline in the evening pill and placebo in the morning and afternoon pills; while children randomized to gabapentin received 300 mg of gabapentin in each pill." **Quote:** "Both study and placebo medications were made to be similar in composition, odour, colour and taste by over encapsulating the untouched original dosage form with a larger opaque hard gelatin capsule (7.34 ml in length) and filling any space with lactose powder."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** insufficient information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** all participants were accounted for.
Selective reporting (reporting bias)	Unclear risk	**Comment:** not all planned outcomes were reported; disruption of school, social, and sports not reported.

Brown 2016 *(Continued)*

Size	High risk	**Comment:** total participants < 50 per treatment arm randomised and completed.
Other bias	Low risk	**Comment:** no other potential sources of bias.

BOCF: baseline observation carried forward; **CPRS-I:** complex regional pain syndrome type 1; **MSK:** musculoskeletal; **NRS:** numerical rating scale

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

Study	Reason for exclusion
Kalita 2014	Participants: adult population
Ogawa 2010	Participants: adult population
Pramod 2011	Participants: adult population
Ries 2003	Participants: adult population
To 2002	Participants: adult population
Yilmaz 2015	Participants: adult population

APPENDICES

Appendix 1. Meeting for NIHR Programme Grant agenda on pain in children

Date

Monday 1st June 2015

Location

International Association of the Study of Pain (IASP) Conference, Seattle, USA

Delegates

Allen Finlay, Anna Erskine, Boris Zernikow, Chantal Wood, Christopher Eccleston, Elliot Krane, George Chalkaiadis, Gustaf Ljungman, Jacqui Clinch, Jeffrey Gold, Julia Wager, Marie-Claude Gregoire, Miranda van Tilburg, Navil Sethna, Neil Schechter, Phil Wiffen, Richard Howard, Susie Lord.

Purpose

National Institute for Health Research (NIHR) (UK) Programme Grant - *Addressing the unmet need of chronic pain: providing the evidence for treatments of pain*.

Proposal

Nine reviews in pharmacological interventions for chronic pain in children and adolescents: Children (5 new, 1 update, 1 overview, and 2 rapid) self-management of chronic pain is prioritised by the planned NICE guideline. Pain management (young people and adults) with a focus on initial assessment and management of persistent pain in young people and adults.

We propose titles in paracetamol, ibuprofen, diclofenac, other NSAIDs, and codeine, an overview review on pain in the community, 2 rapid reviews on the pharmacotherapy of chronic pain, and cancer pain, and an update of psychological treatments for chronic pain.

Key outcomes

The final titles: (1) opioids for cancer-related pain (Wiffen 2017), (2) opioids for chronic non-cancer pain (Cooper 2017a), (3) antiepileptic drugs for chronic non-cancer pain (Wiffen 2017b - this review), (4) antidepressants for chronic non-cancer pain (Cooper 2017b), (5) non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain (Eccleston 2017), (6) non-steroidal anti-inflammatory drugs (NSAIDs) for cancer-related pain (Cooper 2017c), (7) paracetamol for chronic non-cancer pain (Cooper 2017d).

PICO

Patients: children, aged 3 to 12, chronic pain defined as pain persisting for 3 months (NB: now changed to: birth to 17 years to include infants, children and adolescents)

Interventions: by drug class including antiepileptic drugs, antidepressants, opioids, NSAIDs, paracetamol

Comparisons: maintain a separation of cancer and non-cancer, exclude headache, in comparison with placebo and or active control

Outcomes: we will adopt the IMMPACT criteria

Appendix 2. 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. We 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 2010d), and arthritis (Moore 2010c), 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 2010c); 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 2010c; Moore 2013b; 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 (Moore 2010b; 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 2012).

Appendix 3. MEDLINE search strategy (via Ovid)

1. exp Child/
2. exp Adolescent/
3. exp Infant/
4. (child* or boy* or girl* or adolescen* or teen* or toddler* or preschooler* or pre-schooler* or baby or babies or infant*)..tw
5. 1 or 2 or 3 or 4
6. exp Anticonvulsants/
7. (carbamazepine or clobazam or clonazepam or ethosuximide or gabapentin or lacosamide or lamotrigine or levetiracetam or oxcarbazepine or phenytoin or pregabalin or rufinamide or topiramate or valproate or vigabatrin or zonisamide).mp.
8. 6 or 7
9. exp Pain/
10. pain*.tw
11. 9 or 10

12.5 and 8 and 11
13.randomized controlled trial.pt.
14.controlled clinical trial.pt.
15.randomized.ab.
16.placebo.ab.
17.drug therapy.fs.
18.randomly.ab.
19.trial.ab.
20.groups.ab.
21.13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22.exp animals/ not humans.sh.
23.21 nor 22
24.12 and 23

Appendix 4. Embase search strategy (via Ovid)

1. exp Child/
2. exp Adolescent/
3. exp Infant/
4. (child* or boy* or girl* or adolescen* or teen* or toddler* or preschooler* or pre-schooler* or baby or babies or infant*).tw.
5. 1 or 2 or 3 or 4
6. exp anticonvulsive agent/
7. (carbamazepine or clobazam or clonazepam or ethosuximide or gabapentin or lacosamide or lamotrigine or levetiracetam or oxcarbazepine or phenytoin or pregabalin or rufinamide or topiramate or valproate or vigabatrin or zonisamide).mp.
8. 6 or 7
9. exp Pain/
10. pain*.tw
11. 5 and 8 and 10
12. random$.tw.
13. factorial$.tw.
14. crossover$.tw.
15. cross over$.tw.
16. cross-over$.tw.
17. placebo$.tw.
18. (doubl$ adj blind$).tw.
19. (singl$ adj blind$).tw.
20. assign$.tw.
21. allocat$.tw.
22. volunteer$.tw.
23. Crossover Procedure/
24. double-blind procedure.tw.
25. Randomized Controlled Trial/
26. Single Blind Procedure/
27. or/12-26
28. (animal/ or nonhuman/) not human/
29. 27 not 28
30. 11 and 29

Appendix 5. CENTRAL search strategy (via Cochrane Register of Studies Online)

1. MESH DESCRIPTOR Child EXPLODE ALL TREES
2. MESH DESCRIPTOR Adolescent EXPLODE ALL TREES
3. MESH DESCRIPTOR Infant EXPLODE ALL TREES
4. (child* or boy* or girl* or adolescen* or teen* or toddler* or preschooler* or pre-schooler* or baby or babies or infant*):TI,AB,KY
5. #1 OR #2 OR #3 or #4

6. MESH DESCRIPTOR Anticonvulsants EXPLODE ALL TREES
7. (carbamazepine or clobazam or clonazepam or ethosuximide or gabapentin or lacosamide or lamotrigine or levetiracetam or oxcarbazepine or phenytoin or pregabalin or rufinamide or topiramate or valproate or vigabatrin or zonisamide):TI,AB,KY
8. #6 OR #7
9. MESH DESCRIPTOR Pain EXPLODE ALL TREES
10. pain*:TI,AB,KY
11. #9 OR #10
12. #5 AND #8 AND #11

Appendix 6. Summary of efficacy in individual studies

Study	Treatment	Pain outcome	Other efficacy outcome
Arnold 2016	**Intervention group (N = 54):** flexible-dose pregabalin 75 to 450 mg/day **Control group (N = 53):** flexible-dose placebo 75 to 450 mg/day **Study duration:** 15 weeks' duration involving 4 phases: doses were optimised over 3 weeks based on efficacy and tolerability to 75, 150, 300, 450 mg/day. Remaining at that dose for 12 weeks.	**Participant-reported pain relief of 30% or greater:** Pregabalin: 18/54 (33.3%) Placebo: 16/51 (31.4%) P = 0.83 **Participant-reported pain relief of 50% or greater:** Pregabalin: 9/54 (16.7%) Placebo: 4/51 (7.8%) P = 0.179 **PGIC much or very much improved:** Pregabalin: 53.1% Placebo: 29.5%	**Carer Global Impression of Change:** Pregabalin: 51.0% Placebo: 25.0% p = 0.011 **Requirement for rescue analgesia:** no data **Sleep duration and sleep quality:** 11-point numerical rating scale *BASELINE* Pregabalin: 5.8 (1.6) m (SD). Placebo: 5.6 (2.5) m (SD). *WEEK 8*: treatment difference: -1.01 (95% CI -1.73 to -0.30); P = 0.006. *WEEK 10*: treatment difference: P = 0.037. *WEEK 15*: treatment difference -0.17 (95% CI -0.95 to 0.61). *OVERALL*: treatment difference: -0.48 (95% CI -1.02 to 0.06); P = 0.081. **Acceptability of treatment:** Pregabalin: no data Placebo: no data **Physical functioning:** Fibromyalgia Impact Questionnaire for children total score: least squares mean difference: -2.46 (95% CI -6.87 to 1.95); P = 0.270. **Quality of life:** Pregabalin: no data Placebo: no data

(Continued)

Brown 2016	**Intervention group (N = 17):** oral gabapentin 900 mg/day (300 x 3) **Control group (N = 17):** oral amitriptyline 10 mg/day **Study duration:** 6 weeks	**Participant-reported pain relief of 30% or greater:** no data **Participant-reported pain relief of 50% or greater:** no data **PGIC much or very much improved:** no data	**Carer Global Impression of Change:** no data **Requirement for rescue analgesia:** no data **Sleep duration and sleep quality:** Average decrease in sleep score on 5-point Likert scale *Completed participants m (SD)* Gabapentin: 0.46 (1.60); n = 14 Amitriptyline: 1.25 (1.86); n = 12 *All participants m (SD)* Gabapentin: 0.38 (1.45); n = 17 Amitriptyline: 0.88 (1.69); n = 17 **Acceptability of treatment:** no data **Physical functioning:** no data **Quality of life:** no data

CI: confidence interval; **m:** mean; **N:** number of participants; **PGIC:** Patient Global Impression of Change; **SD:** standard deviation

Appendix 7. Summary of adverse events and withdrawals in individual studies

Study	Treatment	Adverse events	Withdrawals
Arnold 2016	**Intervention group (N = 54):** flexible-dose pregabalin 75 to 450 mg/day **Control group (N = 53):** flexible-dose placebo 75 to 450 mg/day **Study duration:** 15 weeks' duration involving 4 phases: doses were optimised over 3 weeks based on efficacy and tolerability to 75, 150, 300, 450 mg/day. Remaining at that dose for 12 weeks.	**Total adverse events:** Pregabalin: 167 Placebo: 132 **No. participants with any adverse event:** Pregabalin: 38/54 Placebo: 34/53 **No. participants with serious adverse events:** Pregabalin: 1/54 Placebo: 0/53	**Total all-cause withdrawals:** Pregabalin: 10/54 Placebo: 17/53 **Withdrawals due to adverse events:** Pregabalin: 4/54 Placebo: 4/53

(Continued)

Brown 2016	**Intervention group (N = 17):** oral gabapentin 900 mg/day (300 x 3) **Control group (N = 17):** oral amitriptyline 10 mg/day **Study duration:** 6 weeks	**Total adverse events:** Gabapentin: 2/17 Amitriptyline: 1/17 **No. participants with any adverse event:** Gabapentin: 2/17 Amitriptyline: 1/17 **No. participants with serious adverse events:** Gabapentin: 0/17 Amitriptyline: 0/17	**Total all-cause withdrawals:** Gabapentin: 2/17 Amitriptyline: 3/17 **Withdrawals due to adverse events:** Gabapentin: 2/17 Amitriptyline: 1/17

CI: confidence interval; **m:** mean; **N:** number of participants; **SD:** standard deviation

Appendix 8. GRADE guidelines

Some advantages of utilising the GRADE process are (Guyatt 2008):

- transparent process of moving from evidence to recommendations;
- clear separation between quality of evidence and strength of recommendations;
- explicit, comprehensive criteria for downgrading and upgrading quality of evidence ratings; and
- clear, pragmatic interpretation of strong versus weak recommendations for clinicians, patients, and policymakers.

The GRADE system uses the following criteria for assigning grades of evidence:

- high: we are very confident that the true effect lies close to that of the estimate of the effect;
- moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;
- low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect; and
- very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We will decrease the grade if there is:

- serious (-1) or very serious (-2) limitation to study quality;
- important inconsistency (-1);
- some (-1) or major (-2) uncertainty about directness;
- imprecise or sparse data (-1); or
- high probability of reporting bias (-1).

We will increase the grade if there is:

- strong evidence of association - significant risk ratio of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1);
- very strong evidence of association - significant risk ratio of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2);
- evidence of a dose response gradient (+1); or
- all plausible confounders would have reduced the effect (+1).

"In addition, there may be circumstances where the overall rating for a particular outcome would need to be adjusted per GRADE guidelines (Guyatt 2013a). For example, if there were so few data that the results were highly susceptible to the random play of chance, or if studies used LOCF imputation in circumstances where there were substantial differences in adverse event withdrawals, one would have no confidence in the result, and would need to downgrade the quality of the evidence by three levels, to very low quality. In circumstances

where no data were reported for an outcome, we planned to report the level of evidence as 'no evidence to support or refute' (Guyatt 2013b)."

WHAT'S NEW

Date	Event	Description
19 February 2020	Amended	Clarification added to Declarations of interest.
18 March 2019	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 2, 2017
Review first published: Issue 8, 2017

Date	Event	Description
7 June 2019	Amended	We amended the GRADE methods for assessing no evidence, for consistency with the other reviews in this series.
4 July 2018	Amended	Searches updated with terms relating to 'infants'. We did not identify any new studies.
14 August 2017	Amended	References for some reviews from the suite amended to reflect correct publication Issue.

CONTRIBUTIONS OF AUTHORS

TC and PW registered the title.

TC, PW, and Christopher Eccleston wrote the template protocol for the suite of children's reviews, of which this review is a part.

All authors contributed to writing the protocol, and all authors agreed on the final version.

All authors were responsible for data extraction, analysis, and writing of the Discussion for the full review.

All authors will be responsible for the completion of updates.

DECLARATIONS OF INTEREST

PW: none known.

TC: none known.

LH: none known.

JC: none known; JC is a specialist paediatric pain physician and treats patients with complex pain.

RH: none known; RH is a specialist paediatric pain clinician and treat patients with chronic pain.

EK has received consulting fees for attending a research strategy meeting from Pfizer, Inc. (2015) and for protocol and research consultation from Mallinckrodt Pharmaceuticals, Inc. (2014), AstraZeneca, Inc. (2014), and Collegium Pharma (2016); EK is a specialist paediatric pain clinician and treats patients with chronic pain.

SL: none known; SL is a specialist paediatric pain clinician and treats patients with chronic pain.

NS (Sethna) has received grants from Gebauer Company for the conduct of animal studies using a topical anaesthetic (2015). NS has offered consultant expertise to Pfizer in designing a multicentre study for use of gabapentin in treatment of neuropathic pain in children (2015). NS is a co-investigator with an ongoing multicentre Phase 3 trial of an experimental drug SMNRX [antisense oligonucleotide] for treatment of infants and children with spinal muscle atrophy (2012 to present). NS is an anaesthesiologist and manages paediatric patients with chronic pain.

NS (Schechter): none known; NS is a developmental paediatrician and treats children and adolescents with pain; NS directs the Chronic Pain Clinic at Boston Children's Hospital and is on the faculty at Harvard Medical School.

CW: none known; CW is a paediatrician and anaesthesiologist; CW specialises in pain and treats children and adults presenting chronic pain; CW also treats patients in palliative care.

This review was identified in a 2019 audit as not meeting the current definition of the Cochrane Commercial Sponsorship policy. At the time of its publication it was compliant with the interpretation of the existing policy. As with all reviews, new and updated, at update this review will be revised according to 2020 policy update.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK.

  NIHR Programme Grant, Award Reference Number: 13/89/29 (Addressing the unmet need of chronic pain: providing the evidence for treatments of pain)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not consider studies with fewer than 10 participants per treatment arm for inclusion in this review, as is standard practice for this group.

In the protocol we stated the age inclusion criterion as birth to 17 years old. One trial reported participants as being between 7 and 18 years of age. We decided to include the study rather than miss data on the participants who were under 18 years of age, who constituted most of the participants in the study.

NOTES

A restricted search in March 2019 did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating in five years. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitates major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Amines [adverse effects] [*therapeutic use]; Amitriptyline [adverse effects] [*therapeutic use]; Anticonvulsants [adverse effects] [*therapeutic use]; Chronic Pain [*drug therapy]; Complex Regional Pain Syndromes [*drug therapy]; Cyclohexanecarboxylic Acids [adverse effects] [*therapeutic use]; Fibromyalgia [*drug therapy]; Gabapentin; Neuralgia [*drug therapy]; Pregabalin [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; gamma-Aminobutyric Acid [adverse effects] [*therapeutic use]

MeSH check words

Adolescent; Child; Humans