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[Intervention Review]

Interventions for treating neuropathic pain in people with sickle cell disease

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ABSTRACT

Background

Pain is the hallmark of sickle cell disease (SCD) and it can be severe, frequent and unpredictable. Although nociceptive pain is more common, at times, people with SCD may have neuropathic pain. The latter can occur due to peripheral or central nerve injury. This review is focused on identifying treatment of only painful sensory neuropathy in people with SCD.

Objectives

To determine the effectiveness and safety of any pharmacological or non-pharmacological therapies for treating neuropathic pain in people with SCD.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register, compiled from electronic database searches and handsearching of journals and conference abstract books. We also searched trial registries, the reference lists of relevant articles and reviews and contacted experts in the field.

Date of last search: 31 January 2019.

Selection criteria

Randomised controlled trials (RCTs) (parallel or cross-over in design), quasi-RCTs of pharmacological or non-pharmacological therapies for treating neuropathic pain in people with SCD compared to placebo or another intervention in any category (i.e. pharmacological or non-pharmacological).

Data collection and analysis

Two review authors independently assessed all trials identified by the searches and extracted relevant data. Two authors independently assessed the risk of bias in the selected trials using the Cochrane risk of bias tool. Two review authors independently rated the quality of the evidence for each outcome using the GRADE guidelines.

Main results

One RCT of 22 participants with SCD, conducted in the USA was included in this review. Participants were randomly assigned to either pregabalin ($n = 11$) or placebo ($n = 11$). Oral pregabalin was administered at an initial dose of 75 mg twice daily. The drug was titrated at increments of 75 mg to a maximum of 600 mg daily or decreased by 75 mg per day if necessary, based on clinical presentation and pain level. Neuropathic pain was assessed using self-reports on the Leeds Assessment of Neuropathic Symptoms and Signs (S-LANNS) scale and the Neuropathic Pain Symptom Inventory (NPSI), where higher scores were indicative of more pain. Outcomes included self-reported pain, quality of life and withdrawal due to adverse effects measured at baseline and monthly for three months post-intervention. The overall risk of bias was low with a high risk of bias due to attrition.

In relation to this reviews primary outcomes, for self-reported neuropathic pain relief, given the paucity of data, we are very uncertain whether there is a difference between the pregabalin and placebo groups at the end of three months as measured by the S-LANSS scale, mean difference (MD) -2.00 (95% confidence interval (CI) -9.18 to 5.18), or the NPSI scale, MD -11.10 (95% CI -33.97 to 11.77) (very low-quality evidence). There was no report of 'Patient Global Impression of Change' in the included trial.

Although the mean quality of life scores (Short Form-36) at three months showed small increases in seven of the eight domains post-intervention in the pregabalin group as compared to the placebo group, this was very low-quality evidence and we are very uncertain whether pregabalin increases quality of life. Neither of our pre-defined outcomes of 'time to improvement of symptoms' or 'changes in sleep quality', were measured in the included trial.

While treatment-related adverse effects appeared higher in pregabalin group than the placebo group at three months, this was very low-quality evidence and we are very uncertain whether there is a difference, RR 1.33 (95% CI 0.39 to 4.62) (very low-quality evidence). There was one withdrawal for adverse effects in the pregabalin group while three people withdrew or dropped out from the placebo group due to adverse effects and complications and hospitalisation related to SCD.

Authors' conclusions

The included trial provided very low-quality evidence. Self-reported pain relief was greater in the pregabalin group compared to the placebo control group but only using the S-LANSS scale and we are very unsure whether there is a difference. While the pregabalin group tended to have improved quality of life over the duration of the trial, this was very low-quality evidence and we are uncertain whether there is a difference. Adverse effects and withdrawals were similar across the treatment and placebo control group in trial. There are both insufficient trials addressing this review question and insufficient outcomes addressed in the single included RCT. Therefore, there is still a significant gap in evidence on interventions for neuropathic pain in people with SCD.

PLAIN LANGUAGE SUMMARY

Treatments for neuropathic pain in persons with sickle cell disease

Review question

We reviewed the evidence about the effect and safety of drug, or other therapies, for treating pain due to nerve damage (neuropathic pain) in people with sickle cell disease (SCD).

Background

Pain is the most common complication of SCD. Some of this pain may be due to damage to nerves and this pain needs to be treated differently from the usual sickle cell pain. The usual medications such as ibuprofen or morphine may not be effective in managing this nerve pain. This trial aimed to examine how safe and effective medications or other alternative treatments are for nerve pain in people with SCD.

Search date

The evidence is current to: 31 January 2019.

Study characteristics

After a detailed search of scientific literature, we identified one trial that was eligible for inclusion. In this trial people with SCD who were diagnosed to have neuropathic pain were randomly put into groups to take either a drug named pregabalin or a placebo (no active medication) treatment.

Key results

The trial was conducted in the USA and included 22 participants with SCD, with 11 people in the pregabalin group and 11 in the placebo drug group. Assessments were measured at baseline and monthly for three months.

Self-reported neuropathic pain relief and quality of life scores (Short Form-36) were no different between the pregabalin and placebo groups. The outcomes of time to improvement of symptoms and changes in sleep quality were not measured in the included trial. Few unwanted effects were noted and the numbers of these were not different between participants who were given pregabalin versus those given placebo.

In conclusion, the effect of pregabalin on SCD neuropathic pain was no different to placebo. We are unable to make firm conclusions regarding our objectives on the basis of a single small trial which only addressed three of our seven prespecified outcomes. Larger, well-conducted trials of different treatments for neuropathic pain in people with SCD need to be carried out.

Quality of the evidence

The evidence in this review was assessed as very-low quality. The single trial in this review lost more than 15% of participants to follow-up over three months. We downgraded the level of evidence due to lack of clarity in how the participants were assigned to the pregabalin or the placebo group and due to the small number of events and participants in the trial.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings - Pharmacological intervention (pregabalin) versus placebo for treating neuropathic pain in people with sickle cell disease

Pregabalin compared to placebo for treating neuropathic pain in people with sickle cell disease

Patient or population: adults and children with sickle cell disease experiencing neuropathic pain

Settings: outpatient sickle cell disease clinic

Intervention: pregabalin

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Pregabalin				
Self-reported pain relief - NPSI: ranges from 0 to 100. Higher scores are indicative of neuropathic pain. Follow-up: 3 months	The mean NPSI Score in the placebo group was 32.6 points	The mean NPSI score in the pre-gabalin group was 11.10 points lower (95% CI -33.97 lower to 11.77 higher)		16 (1 study)	⊕⊕⊕⊖ very low ^{1,2,3}	No significant difference between pregabalin and placebo groups in self-reported pain events.
Self-reported pain relief - S-LANSS: Possible total scores range from 0 to 24, and a score of 12 or higher is indicative of neuropathic pain. Follow-up: 3 months	The mean S-LANSS score in the placebo group was 7.9 points	The mean S-LANSS score in the pre-gabalin group was 2.00 points lower (95% CI -9.18 lower to 5.18 higher)		16 (1 study)	⊕⊕⊕⊖ very low ^{1,2,3}	No significant difference between pregabalin and placebo groups in self-reported pain events.
PGIC Follow-up: 3 months	See comment	See comment	N/A	N/A	N/A	This outcome was not measured.
Time to improvement of symptoms	See comment	See comment	N/A	N/A	N/A	This outcome was not measured.

Follow-up: 3 months						
Change in QoL	See comment	See comment	NA	16	⊕⊕⊕⊖ very low ^{1,2,3}	There was no significant difference in any of the 8 QoL subscales between the pregabalin and placebo groups.
Follow-up: 3 months				(1 study)		
Changes in sleep quality as measured by sleep questionnaires	See comment	See comment	N/A	N/A	N/A	This outcome was not measured.
Follow-up: 3 months						
Treatment-related adverse effects	273 per 1000	363 per 1000	RR 1.33 (95% CI 0.39 lower to to 4.62 higher)	22	⊕⊕⊕⊖ very low ^{1,2,3}	
Follow-up: 3 months		(106 to 1261)		(1 study)		

The basis for the **assumed risk** is the event rate in the control group unless otherwise stated in the comments and footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **NA:** not applicable; **NPSI:** Neuropathic Pain Symptoms Inventory; **PGIC:** Patient Global Impression of Change; **QoL:** quality of life; **S-LANSS:** Leeds Assessment of Neuropathic Symptoms and Signs

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

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

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

Very low quality: we are very uncertain about the estimate.

1. Downgraded once due to key risk of bias domain random sequence generation which might influence primary outcomes.
2. Downgraded once due to imprecision: small number of events/participants and large CI around the relative effect.
3. Downgraded once due to indirectness: majority female and all over 18.

BACKGROUND

Description of the condition

Sickle cell disease (SCD) refers to a group of genetic disorders of haemoglobin which occur when the sickle gene is inherited either homozygously or heterozygously with another abnormal haemoglobin gene. This monogenic disorder results when the 17th nucleotide in the β -globin chain changes from thymine to adenine resulting in the 6th amino acid becoming valine instead of glutamic acid (Rees 2010). In the deoxygenated state, this mutation leads to polymerisation of sickle haemoglobin and subsequent red cell sickling. The disorder is multisystemic and presents with many acute complications, as well as progressive organ damage. Overall survival is reduced (Wierenga 2001), although this continues to improve. Despite optimising available treatment, life expectancy is still almost 20 years shorter than in the general population (Serjeant 2013).

Although the disease originated in sub-Saharan Africa and the Indian subcontinent, the disease is now global (Stuart 2004) and has been declared a public health burden by the World Health Organization (WHO) (WHO 2009). Estimates show that approximately 5% of the world's population carries a haemoglobinopathy gene (Piel 2013a) and the prevalence of the disease at birth is expected to rise as a result of improving survival and increasing migration to higher-income countries (Piel 2013b).

Pain is the hallmark of SCD and it can be severe, frequent and unpredictable (Ballas 2012). The acute painful crisis is the most frequent reason for healthcare visits by both children and adults with SCD (Ballas 2005). Acute painful crises increase in frequency as people get older and more frequent crises have been associated with an increased mortality rate. The vaso-occlusion seen in SCD leads to a cycle of hypoxia, ischaemia and tissue injury which causes the activation of nociceptive pathways, stimulating peripheral afferent pathways and resulting in a perception of pain (Ballas 2012). Recurrent and irreversible tissue damage can lead to bone infarction, avascular necrosis (hip or shoulder) and arthritis, resulting in chronic pain; other complications such as leg ulceration and chronic osteomyelitis may also result in chronic pain (Ballas 2011a). However, most people with SCD who suffer from chronic pain do not have an obvious anatomic source. As the understanding of the diverse pathophysiological mechanisms behind underlying SCD pain evolves, it is becoming apparent that chronic pain is more frequent than previously thought (Smith 2010); and may occur in up to 29% to 40% of adolescents and adults with SCD, which profoundly affects health-related quality of life (QoL). Both the acute and chronic pain suffered by people with SCD are associated with significant psychological complications such as depression and anxiety and reduced overall health-related QoL (McClish 2005).

Although nociceptive pain is more common, at times, people with SCD may have neuropathic pain. In general, neuropathy is the presence of nerve damage which may either be symptomatic or asymptomatic, i.e. neuropathy may be present without the presence of pain and may only be detected by careful clinical examination or neurophysiological testing. When symptomatic, however, symptoms may be sensory or motor or both. Motor symptoms may be negative, e.g. weakness or atrophy, or positive, e.g. twitching (fasciculations). Sensory involvement is not necessarily painful; individuals may report negative sensory symptoms, e.g. numbness, but may also report positive sensory symptoms, e.g. tingling, itching,

crawling sensations or pins and needles, which itself may or may not be unpleasant (dysaesthetic). When pain is present, it may be burning or lancinating in quality, typically implying either differential small-fibre involvement (burning) or larger-fibre involvement (lancinating pain). In most situations, it is indeed neuropathic pain that is the most common and most disabling feature of peripheral neuropathic involvement. The International Association for the Study of Pain defines neuropathic pain as "pain caused by a lesion or disease of the somatosensory system" (Jensen 2011). They further define that a lesion or disease of the central somatosensory system (e.g. thalamic origin) may lead to 'central neuropathic pain' and of the peripheral nervous system to 'peripheral neuropathic pain'. The former is comparatively rare and typically both forms result from the same pathophysiological processes. Neuropathic pain can be persistent and long-lasting as once nerve injury has occurred it may be irreversible.

In SCD neuropathic pain can occur due to peripheral or central nerve injury, and it has been hypothesised to occur from vaso-occlusion of vasa nervorum of nerves (Ballas 2012). Emerging neurobiological data suggest that SCD pain has a complex aetiology that includes neuropathic components (Brandow 2015a). This is evidenced by the pain descriptors that individuals use (i.e. burning, lancinating, sticking, numbness, tingling) and accumulating neurobiological evidence in both the sickle cell mouse model and people with SCD, that SCD pain has features of peripheral and central nervous system sensitisation resulting in pain hypersensitivity and neuropathic pain (Ballas 2007; Ballas 2012; Brandow 2017). Furthermore, in SCD symptoms of neuropathy may be present without any associated 'neuropathic pain' and assessments should be able to differentiate between the two (Ballas 2013). Screening questionnaires reveal that 30% to 40% of people with SCD report neuropathic pain and the presence of neuropathic pain is associated with older age and is more common in females (Brandow 2014; Brandow 2015b).

It is important to make the distinction between nociceptive and neuropathic pain as their pathophysiological mechanisms differ and hence therapies need to be tailored appropriately. This review is focused on identifying treatment of only painful sensory neuropathy in people with SCD.

Description of the intervention

Neuropathic pain from any cause, including non-SCD causes, can be quite difficult to treat and is not likely to be amenable to any one intervention (Finnerup 2015; Kalso 2013).

Opioids are the backbone of treatment for both acute and chronic SCD pain (Ballas 2007); however, their effectiveness is not well studied and opioids can be associated with numerous adverse events, including opioid-induced hypersensitivity. Furthermore, the effectiveness of these drugs for treating neuropathic pain in SCD is unclear. The National Institute for Health and Care Excellence (NICE) guidelines recommend amitriptyline, duloxetine, gabapentin or pregabalin as initial treatments for neuropathic pain (National 2013).

Hydroxyurea is a ribonucleotide reductase inhibitor and is one of the two drugs approved for treating SCD. A Cochrane Review has shown benefits for prevention of pain and other severe complications of SCD (Nevitt 2017) as has further research in both adults

(Charache 1997) and children (Heeney 2010; McGann 2011; Ware 1999).

In July 2017, L-Glutamine was approved for preventing acute complications in people with SCD. Along with pharmacological agents (such as opioids and non-steroidal anti-inflammatory agents (NSAIDs)) non-pharmacological interventions, such as cognitive behavioural therapy, herbal treatments, relaxation therapy, and acupuncture have also shown benefit in managing acute SCD pain (Ballas 2007; Ballas 2011b; Lutz 2015).

In this review, we will assess the effectiveness and safety of all pharmacological and non-pharmacological interventions that have been used to treat neuropathic pain in SCD.

How the intervention might work

Different classes of pharmacological agents intended for use in managing pain have different mechanisms of action and so it is important to assess their effectiveness in managing neuropathic pain in SCD – both individually and as part of combination therapy.

The consensus statement of the Canadian Pain Society provides one useful approach to summarising the pharmacological and non-pharmacological management of neuropathic pain by mode of action (Moulin 2007).

Pharmacological interventions include, but are not limited to:

- tricyclic antidepressants, which block the hyperalgesic effect of n-methyl-d-aspartate (NMDA) agonists;
- anticonvulsants such as gabapentin and pregabalin, which bind to calcium channels in the dorsal horn resulting in inhibition of excitatory neurotransmitters;
- venlafaxine and duloxetine, which act as serotonin noradrenaline re-uptake inhibitors (SNRIs);
- topical lidocaine, which is a sodium channel blocker and has minimal adverse effects;
- opioids with the analgesic effect of binding to mu- and kappa-opioid receptors and blocking the release of substance P neurotransmitters;
- cannabinoids with anti-inflammatory and central analgesic properties;
- invasive techniques, which may be used after failure of standard treatments and include intravenous lidocaine and opioid spinal infusions via implantable pumps as well as spinal cord stimulation;
- NSAIDs, which act by inhibiting the production of prostaglandins which cause inflammation at sites of tissue damage.

As neuropathic pain is expected to be of long-term nature and because pharmacological agents may have various adverse events, many individuals seek non-pharmacological treatments. Studies in SCD have shown some limited benefits of non-pharmacological treatments (Lutz 2015). Some of these treatments are also associated with the lowering of anxiety and depression and improvements in coping skills (Edwards 2010; Hildenbrand 2014). While these studies have looked at the effects in SCD pain in general, it remains to be seen if there is benefit of their use for treating neuropathic pain in people with SCD.

Non-pharmacologic interventions include:

- psychological treatments such as cognitive or behavioural therapies which attempt to assess and modify the thoughts and behaviours associated with pain (Morley 1999);
- physiotherapy and exercise, which may improve mood and increase pain tolerance (Anshel 1994);
- TENS (transcutaneous electrical nerve stimulation); which stimulates nerve endings and utilises central and peripheral mechanisms to decrease hyperalgesia (Vance 2014).

Why it is important to do this review

Pain in SCD can be very difficult to manage and often does not respond to either opioids or other commonly-used classes of analgesics. As mechanisms that underlie neuropathic pain differ from other kinds of pain present in SCD (i.e. Ischaemic, inflammatory resulting in nociceptive pain), therapy that is directed specifically at neuropathic pain may be required for a subset of patients. Neuropathic pain has been shown to be difficult to treat in conditions other than SCD. Thus, it is important to systematically review the existing evidence to assess the effectiveness of any therapies, whether pharmacological or non-pharmacological, for treating neuropathic pain in people with SCD.

OBJECTIVES

To determine the effectiveness and safety of any pharmacological or non-pharmacological therapies for treating neuropathic pain in people with SCD.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised, controlled trials (RCTs) and quasi-RCTs. Cross-over trials were considered.

Types of participants

People with any type of SCD (all ages, both genders, all genotypes) who described experiencing pain symptoms associated with neuropathic pain (that is, pain described as burning or lancinating), or where trial investigators described participants as having 'neuropathic pain'. We excluded trials with individuals who may have had other co-morbidities that could potentially lead to neuropathic pain, e.g. diabetes mellitus and cancer-related neuropathy.

As described above, the diagnosis of neuropathic pain could be based on clinician opinion, based on pain classification assessments, such as the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale or the PainDETECT questionnaire (Brandow 2014), or use of classical neuropathic pain descriptors such as lancinating, tingling or burning. The named scales are neuropathic pain screening measures that have not been specifically validated in people with SCD.

Types of interventions

We made provisions to include trials where any pharmacological or non-pharmacological treatment is compared to either placebo or to another intervention in any category (i.e. pharmacological or non-pharmacological). Treatment duration should have been at

least two weeks. All doses, routes and trial settings were to be included.

Types of outcome measures

Primary outcomes

1. Self-reported pain relief of:
 - a. 30% or greater (moderate);
 - b. 50% or greater (substantial).
2. Patient Global Impression of Change (PGIC):
 - a. much or very much improved (moderate);
 - b. very much improved (substantial).

We have used the definitions from the the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) for moderate and substantial benefit in chronic pain studies (Dworkin 2008). These are recommendations for assessing pain outcomes since pain responses are not usually normally distributed.

Secondary outcomes

1. Time to improvement of symptoms
2. Change in psychosocial outcomes (e.g. QoL, activities of daily living, depression or anxiety (or both), or coping (all assessed using any well-validated measures or expert diagnosis))
3. Changes in sleep quality as measured by sleep questionnaires
4. Treatment-related adverse effects
 - a. number of people experiencing serious adverse effects (any significant event, e.g. leading to hospitalisation, death, or significant disability)
 - b. number of people experiencing other adverse effects
 - c. number of withdrawals due to any adverse events (including serious adverse events)
5. Withdrawal from treatment due to lack of efficacy

Search methods for identification of studies

We conducted a comprehensive search for all relevant published and unpublished trials without restrictions on language, year or publication status.

Electronic searches

The review authors identified relevant trials from the Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register using the terms: (sickle cell OR (haemoglobinopathies AND general)) AND pain.

The Haemoglobinopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library) and weekly searches of MEDLINE. Unpublished work is identified by

searching the abstract books of five major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the Caribbean Public Health Agency Annual Scientific Meeting (formerly the Caribbean Health Research Council Meeting); and the National Sickle Cell Disease Program Annual Meeting. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's [website](#).

Date of last search: 31 January 2019.

We also searched the following databases, trials registries and resources:

- Caribbean Public Health Agency (CARPHA) EVIDeNce Portal (<http://carphaevidenceportal.bvsalud.org/>);
- US National Institutes of Health Ongoing Trials Register Clinicaltrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (<http://apps.who.int/trialsearch/>);
- EU Clinical Trials Register (www.clinicaltrialsregister.eu/).

Please refer to [Appendix 1](#) for full search strategies. All additional searches were conducted in January 2019.

Searching other resources

We screened the references of included trials and any relevant systematic reviews identified for further references to relevant trials. We also contacted noted experts in the field conducting relevant trials.

Data collection and analysis

Selection of studies

We compiled the database search results using Endnote and discarded duplicates of same record. We then exported data from the search database to Microsoft Excel to facilitate screening.

Two review authors (CG and AB) independently assessed each trial identified by the search for eligibility by reading its title and abstract. A third author (MA) provided consensus as needed. We discarded trials that clearly did not meet inclusion criteria, and obtained full-text copies of the remaining trials. We attempted to link multiple reports of the same trials. We did not anonymise trials before assessment. Two authors (MA, CG) independently read full reports and selected relevant trials meeting eligibility criteria. We presented a PRISMA flow chart in the full review ([Figure 1](#)) (Moher 2009), as well as a list of excluded trials for those trials not excluded at the title and abstract screening phase that a reader may plausibly expect to see in the included studies section of the review ([Higgins 2011a](#)).

Figure 1. Flow Diagram

Data extraction and management

Two review authors (MA, CG) independently extracted data using the data extraction template from the Cochrane Cystic Fibrosis and Genetic Disorders Group; we resolved disagreements by discussion with a third author (DF).

We extracted data on age, sex, genotype of participants and self-reported change in pain as assessed by multiple pain scales. We also collected information about the number of participants in each trial, drug and dosing regimens, trial design (placebo or active control), trial duration and follow-up, withdrawals and adverse events. We entered the extracted data directly into the Review Manager software (RevMan 2014).

We searched for multiple reports of the same trial to include as a single unit of interest in the review. We collected characteristics of the included trials and populated a table of 'Characteristics of included studies' in the full review. We reported on the primary outcome of change in pain (pain reduction) at time periods greater than two weeks as available in the included trial.

Assessment of risk of bias in included studies

Two authors used the Cochrane risk of bias tool (MA and DF) to assess risk of bias in six domains (Higgins 2011b):

1. selection bias – sequence generation and allocation concealment;

2. performance bias – blinding of participants and personnel;
3. detection bias – blinding of outcome assessment;
4. attrition bias - incomplete outcome data;
5. reporting bias; and
6. other bias.

Two review authors (MA, DF) collated judgements and rationale for each bias domain in a tabular form. We categorised risk of bias judgements according to 'low', 'high', or 'unclear' risk according to the Cochrane criteria (Higgins 2011b).

Measures of treatment effect

We performed statistical analyses using Review Manager 5 (RevMan) (RevMan 2014).

Continuous data

For primary and secondary outcomes (e.g. self-reported pain score, QoL) that were reported on a continuous scale, we calculated the estimate of treatment effect as the mean difference (MD) with 95% CIs. We used means and standard deviations (SD). For future updates, if additional trials are identified where continuous scores measuring the same outcome but in a variety of ways (e.g. different scales to measure anxiety) are pooled, we will use the standardised mean difference (SMD) with 95% CIs (Deeks 2011). We assessed whether data were skewed as per chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

Dichotomous data

For dichotomous data (e.g. treatment-related adverse events), we calculated risk ratios (RR) with 95% confidence intervals (CI) using number of events in the intervention group and the control group.

Time-to-event data

Should future update of this review include trials with time-to-event data (e.g. time-to-improvement of symptoms), we will use survival analysis to calculate hazard ratios of the intervention effect on such outcomes as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

Unit of analysis issues

For future updates of this review, if we include additional trials, making a meta-analysis possible, we will give consideration to the following unit of analysis issues.

Unit of analysis for included trials will be at the participant level where there is no evidence of clustering by pain outcome or trial design in the case of cluster RCTs.

Clustering may be introduced by included trials that report multiple pain events per participant. Where this clustering effect is present, we will use the number of trial clusters and an estimate of the intraclass correlation co-efficient to inflate the standard errors (SEs) associated with each clustered trial (Cooper 2016).

Cluster-randomised trials

For any trials included in the future, if clustered randomisation has been used, evidence that trial investigators have presented their results after appropriately controlling for clustering effects (e.g. using techniques such as robust SEs or multilevel modelling) will be examined. If it is unclear whether a cluster-randomised trial has used appropriate statistical techniques for clustering, we will contact trial investigators for further information. Where appropriate statistical techniques are not used, we will request individual participant data and re-analyse these using techniques to control for clustering. Following this, we will undertake a meta-analysis of effect sizes and SEs in RevMan using the generic inverse method (Deeks 2011).

Studies with multiple treatment groups

We aimed to summarise separately pharmacological and non-pharmacological treatment groups. Within the pharmacological treatment group, we planned to combine the different medications if the mechanisms of action were similar.

Cross-over trials

If we had included trials, we would have analysed data from the first period as carry over of the treatment effect would have been likely to affect the comparative efficacy of the intervention. If needed, we will contact trial authors for first-period data.

Dealing with missing data

Data reported by the single included RCT were complete. We describe attrition in the [Characteristics of included studies](#) table.

In future versions of the review, we will request any additional data that may be required from the trial authors if data presented in published paper are insufficient. Where possible, we will undertake an intention-to-treat (ITT) analysis. Where we assume missing values

are not missing at random (e.g. withdrawal due to adverse events or serious adverse events) we will use the imputation of the mean approach to replace missing values. We do not expect data missing at random, such as in the instance of loss of record with pain assessment, to be related to the actual pain outcome. In these instances we will analyse available data without any adjustment for missing values (Higgins 2008).

Assessment of heterogeneity

We did not assess heterogeneity as we only included a single trial in the analysis of the review. We intend to assess heterogeneity in future updates of this review using the criteria below, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

We will visually inspect heterogeneity using the combined data presented in the forest plots, and by considering the I^2 statistic (Higgins 2003). The Chi^2 values and a P value less than 0.10 will constitute statistical heterogeneity as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). The I^2 statistic reflects the likelihood that variation of results across trials are due to heterogeneity rather than by chance, and we plan to interpret this using the following simple classification:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

In addition to the I^2 value, we will observe (a) the magnitude and direction of effects; and (b) the strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a CI for I^2).

Assessment of reporting biases

We addressed selective outcome reporting by comparing outcomes described in the methods of the published report with those reported in the results.

We did not consider a funnel plot for assessing publication bias as the requisite number of included trials (at least 10) was not met (Sterne 2011).

Data synthesis

A meta-analysis was not possible for this review as only one trial met the pre-planned inclusion criteria. We entered relevant data on reported outcomes into RevMan to calculate effect estimates supported by a description of trial findings. For future updates of the review, we plan to add to the analysis using a fixed-effect model for meta-analysis where there is no evidence of substantial heterogeneity between trials. In the event of substantial heterogeneity between trials, we will use a random-effects model.

Two review authors (DF and MA) independently rated the quality of the evidence for each outcome using the guidelines provided in chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011).

Subgroup analysis and investigation of heterogeneity

We did not conduct any subgroup analysis but consider the following subgroups to be important for future updates of this review:

1. age (children under 18 years versus adults 18 years and older);
2. drug class (for pharmacological interventions).

Sensitivity analysis

In this current version of the review, we were unable to conduct a meta-analysis or sensitivity analysis with only one included trial. Future update of this review will consider sensitivity analysis on the basis of:

1. imputation of missing values using the mean;
2. fixed-effect versus random-effects models where there are likely unimportant heterogeneity (0% to 40%) in both models;
3. trial design, where the effect of blinded versus unblinded trials on outcomes are assessed.

Summary of findings table

We generated a summary of findings table with the following outcomes.

1. Self-reported pain relief
2. PGIC
3. Time to improvement of symptoms
4. Change in QoL
5. Changes in sleep quality as measured by sleep questionnaires
6. Treatment-related adverse effects

We planned to present a summary of findings table for each comparison made (e.g. pharmacological and non-pharmacological interventions in future reviews) but are currently only able to present a table on a pharmacological intervention.

The summary of findings table includes a comment and brief description of the GRADE approach as used to assess the quality of the body of evidence (Schünemann 2011). We took guidance in developing the summary of findings table from the GRADE Handbook (GRADE 2013).

RESULTS

Description of studies

See 'Characteristics of included studies' and 'Characteristics of excluded studies'.

Results of the search

The search of the Group's trials register identified 182 references of which 31 (representing 14 trials) were selected for full text assessment after initial screening. Only one full text was assessed as meeting the criteria to be included in this review (Figure 1).

Included studies

See [Characteristics of included studies](#).

Design and sample size and setting

The single included trial was a RCT with two arms having 22 participants randomly assigned to either pregabalin (n = 11) or placebo (n = 11) (Schlaeger 2017). The trial was conducted in the USA with participants recruited from an outpatient SCD clinic.

Participants

There were 22 participants included; the majority of participants were female (n = 16) and of African descent with mean age of 33.1 years ranging from 18 to 82 years.

Disease status for all participants was as follows: homozygous S (SS) genotype = 15; heterozygous SC genotype = 6; sickle-beta thalassaemia genotype (SBThal) = 1. In the placebo group there were six participants with SS and five with SC; in the pregabalin group there were nine participants with SS, one with SC and one with SBThal.

Intervention

The intervention was pregabalin given orally with an initial dose of 75 mg twice daily. The pregabalin was titrated at increments of 75 mg to a maximum of 600 mg daily or decreased by 75 mg per day if necessary based on clinical presentation and pain level.

Outcomes

The single included trial reported on one of this reviews two primary outcomes, self-reported pain. Of the five secondary outcomes, only QoL and withdrawal due to adverse effects were measured and reported by the trial.

The trial did not report on PGIC in pain, time to improvement of pain, changes in sleep quality and withdrawal due to lack of efficacy. The outcomes were assessed at baseline and monthly up to three months.

Excluded studies

See [Characteristics of excluded studies](#).

A total of 13 trials were excluded as the population was not being defined as having neuropathic pain or neuropathic pain descriptors such as burning or lancinating pain (Co 1979; Ezenwa 2016; Ezenwa 2018; Gil 1996; Hollins 2012; Horst 2016; Howard 2018; Matthie 2018; Myers 1999; Osunkwo 2012; Wallen 2014; Wang 1988).

Risk of bias in included studies

A graphical display of the risk of bias assessment is presented in an a figure (Figure 2). The single trial had issues with incomplete outcome data (more than 20% attrition rate) and 'unclear' description of random sequence generation which affected the overall risk of bias. The other domains were assessed as being at low risk of bias.

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

Allocation

Sequence generation

The single included RCT was assessed as being at unclear risk of bias for allocation bias. Insufficient information was provided on how the allocation was carried out.

Allocation concealment

There was a low risk of bias for this domain as only the external pharmacist was aware of the allocation code.

Blinding

The included trial was described as a "double-blind pilot study". The individuals responsible for participant care were blinded as the allocation was centralised and the initial dose of the medication was similar for both groups. No information was given on the physical appearance of the medication given to the pregabalin and placebo control groups. The participants also had no knowledge of which group they were assigned to. Outcome assessors were also unaware of which group received the intervention versus the placebo as this was only known by the pharmacist responsible for sequence generation.

Overall, the trial was assessed as being at low risk of bias for blinding of participants, personnel and outcome assessors.

Incomplete outcome data

There was 27% loss to follow-up, however, dropouts were similar in both groups and appropriately described. The trial authors did not report an intention-to-treat analysis and therefore, we assessed this trial as being at high risk of bias for incomplete outcome data.

Selective reporting

We did not have access to the trial protocol and were therefore unable to assess reporting bias. The risk of bias for this domain is unclear.

Other potential sources of bias

The trial was not perceived as having any other potential source of bias.

Effects of interventions

See: [Summary of findings for the main comparison](#) Summary of findings - Pharmacological intervention (pregabalin) versus placebo for treating neuropathic pain in people with sickle cell disease

The Schlaeger trial (22 participants) assessed the management of sickle cell pain using pregabalin versus placebo over three months (Schlaeger 2017). Self-reported pain relief was assessed using the S-LANNS and the NPSI which are both validated tools for examining neuropathic pain.

Pregabalin versus placebo

Primary outcomes

1. Pain relief

The included trial reported on pain relief at baseline, one, two and three months (Analysis 1.1; Analysis 1.2). Notably, the single included study (22 participants) by Schlaeger did not report on the pain outcome as defined in the current review protocol. They instead reported a decline in neuropathic pain in the pregabalin group with 18% of participants reporting a S-LANSS score of over 12 (indicative of neuropathic pain) at baseline as compared to 13% at three months. Conversely, neuropathic pain was reported by 27% of controls at baseline and 38% at the end of trial, suggesting an increase in neuropathic pain in the placebo group. When compared to placebo, there were no differences observed at any time point; at three months the mean pain score was two points lower, MD -2.00 (95% CI -9.18 lower to 5.18 higher) (very low-quality evidence) (Analysis 1.1) for participants in the pregabalin group. Similarly, as assessed by the NPSI, participants' self-reported pain showed no difference between groups, although there was a decline in pain score from baseline to end of the trial for both the placebo and pregabalin group. The MD of 11 points between the pregabalin and placebo group was not statistically significant, MD -11.10 (95% CI -33.97 lower to 11.77 higher) (very low-quality evidence) (Analysis 1.1).

2. Patient Global Impression of Change (PGIC)

There was no report of PGIC in the single RCT included in this review (Schlaeger 2017).

Secondary outcome

1. Time to improvement of symptoms

There was no report given on this outcome in the included trial (Schlaeger 2017).

2. Change in psychosocial outcomes

a. QoL

The included trial assessed QoL using the SF-36 instrument and reported data at baseline, one, two and three months (Table 1) (Analysis 1.1; Analysis 1.2). Higher SF-36 scores indicate higher QoL and less disability. Overall, the placebo group and the pregabalin group reported similar SF-36 mean scores at baseline and the three time points of the trial. The MD in SF-36 specific domain mean scores varied between the pregabalin and placebo groups. Whereas for the treatment group, the mean SF-36 domain scores increased with time for seven of the eight domains (the only exception was for 'physical function' domain where the mean score fell), the scores decreased for four domains (physical health-role limitation, emotional health-role limitations, emotional well-being, and social functioning) of the eight studied domains for the placebo group. At three months, none of the MDs, however, were statistically significant (very low-quality evidence) (Analysis 1.3).

b. Activities of daily living, depression or anxiety (or both), or coping

There was no assessment or report on any other psychosocial outcome in the included trial (Schlaeger 2017).

3. Changes in sleep quality as measured by sleep questionnaire

This outcome was not assessed in the included trial (Schlaeger 2017).

4. Treatment-related adverse effects

a. Number of people experiencing serious adverse effects

There were two reported cases of hospitalisations due to sickle cell pain or complications of the disease with these participants being subsequently dropped from the placebo arm of the trial (Schlaeger 2017). In addition, two other participants withdrew from the trial due to adverse events (one in the placebo group and one in the pregabalin group) at the three-month visit.

b. Number of people experiencing other adverse effects

Overall, by three months, there were seven reported cases of adverse effects. In the pregabalin group there were four cases of adverse events, two due to sleepiness; two due to dizziness and drowsiness, with one of the two also complaining of dry mouth; and one had stomach cramps after ingesting the trial medication (but when taken after meals the participant felt better). In the placebo control group, three participants reported adverse events; one due to sleepiness; one due to light-headedness; and one due to sleepiness and a mild tingling sensation in the fifth digit of the right hand (Schlaeger 2017). We found that the risk of adverse events, although higher in the pregabalin group, was not significantly different from the placebo group, RR 1.33 (95% CI 0.39 lower to 4.62 higher) (very low-quality evidence) (Analysis 1.4).

c. Number of withdrawals due to any adverse events (including serious adverse events)

Four participants left the trial, two for complications related to SCD and two for adverse events related to treatment or placebo (Schlaeger 2017).

5. Withdrawal from treatment due to lack of efficacy

There was no report of withdrawal due to a lack of efficacy (Schlaeger 2017).

DISCUSSION

Summary of main results

The authors of this review screened 182 references (abstract and titles) of which just one was trial (22 participants) was included (Schlaeger 2017).

Regarding self-reported neuropathic pain relief, given the paucity of data, we are very uncertain whether there is a difference between the pregabalin and placebo groups at the end of three months as measured by both the S-LANSS and the NPSI scales (very low-quality evidence). There was no report of 'Patient Global Impression of Change' in the included trial. We are also very uncertain whether there is a difference in various QoL domains over the duration of the trial, between the pregabalin and placebo groups. Similar numbers of treatment-related adverse effects and withdrawals were seen across both groups in trial. No other outcomes were reported on in this trial.

Overall completeness and applicability of evidence

The evidence from this synthesis, while consistent with our review question, is inadequate to inform practice and has limited generalisability. The single trial in this review focused on an adult population (18 years and older) addressing a single pharmacological intervention versus placebo for SCD-related neuropathic pain (Schlaeger 2017). The trial had a fairly small number of participants and was of short duration, and therefore the evidence it provides is insufficient to form robust conclusions as to which is the most effective intervention for treating neuropathic pain in people with SCD. Hence, there remains a significant gap in the evidence on interventions for treating neuropathic pain in this population.

Quality of the evidence

The evidence from this review has been assessed as very-low quality. The review includes only one pilot trial with 22 participants (with over 15% loss to follow-up or dropouts over three months) (Schlaeger 2017). This recent trial adhered for the most part to the Consolidated Standards of Reporting Trials (CONSORT) (Moher 2010). The evidence was at 'high' risk of bias for incomplete outcome data and 'unclear' risk of bias for random sequence generation. All other domains were assessed as being at 'low' risk of bias. As a result of the risk of bias assessment, the level of evidence was downgraded as appropriate randomisation might impact the trial findings (Summary of findings for the main comparison). The level of evidence was further downgraded due to the small number of events and few participants in the trial, which was additionally affected by high levels of attrition. The trial was also downgraded once due to indirectness, with the majority being female and all over 18 years of age. Therefore, we were unable to make robust conclusions regarding our objectives on the basis of a single included trial which only addressed three of the seven pre-specified outcomes.

Potential biases in the review process

Standard systematic review methodology and guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* was employed to reduce bias in the review process (Higgins 2011c). This included the use of at least two review authors in every aspect of identifying potential trials, deciding on inclusion and exclusion of trials, extracting data, and conducting analyses. However, a few potential sources of bias may remain.

Publication bias

A comprehensive search of both published and unpublished sources was undertaken to find relevant trials. However, we did not make contact with drug companies for data on RCTs which might not show up readily in our search of the published and grey litera-

ture. There is therefore some limited potential that some trials were missed.

Agreements and disagreements with other studies or reviews

There are very few studies addressing the efficacy of interventions for neuropathic pain in persons with SCD and we found no existing review with which to compare our findings.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient rigorous evidence on which to base concrete conclusions about interventions for neuropathic pain in people with sickle cell disease (SCD). In light of this, current interventions used by clinicians must balance potential benefits against any possible adverse effects of treatment in this population. Additionally, more randomised control trials (RCTs) evaluating the effectiveness of different interventions for neuropathic pain in SCD are urgently needed. Our review has highlighted a major gap in the evidence pool and highlights the need for caution and the conscientious use of currently available interventions for treating neuropathic pain in people with SCD. The single RCT of pregabalin versus placebo for treating neuropathic pain in people with SCD presented very low-quality evidence and we are unsure whether there is a treatment difference. This pilot trial was not sufficiently powered to identify a significant effect of this intervention in people with SCD and it remains to be seen if the trend to improvement shown in this trial can be duplicated or strengthened by more robust studies in the future.

Implications for research

This systematic review has identified a major gap in the research area of treatments for managing neuropathic pain in people with SCD. Well-conducted RCTs are needed to follow on from this pilot trial and to assess the effectiveness and possible adverse effects of the different interventions for treating neuropathic pain in people with SCD.

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REFERENCES

References to studies included in this review

Schlaeger 2017 {published data only}

Schlaeger JM, Molokie RE, Yao Y, Suarez ML, Golembiewski J, Wilkie DJ, et al. Management of sickle cell pain using pregabalin: a pilot study. *Pain Management Nursing* 2017;**18**(6):391-400. [CFGD Register: SC317]

References to studies excluded from this review

Co 1979 {published data only}

Co LL, Schmitz TH, Havdala H, Reyes A, Westerman MP. Acupuncture: an evaluation in the painful crises of sickle cell anaemia. *Pain* 1979;**7**(2):181-5. [CFGD Register: SC24]

Ezenwa 2016 {published data only}

Ezenwa M, Yao Y, Molokie R, Engeland C, Wang Z, Suarez M, et al. Feasibility of an internet-enabled tablet-based guided imagery for stress and pain reduction intervention in adults with sickle cell disease. *Journal of Pain* 2015;**16**(4 Suppl 1):S101. [CFGD Register: SC307a]

* Ezenwa MO, Yao Y, Engeland CG, Molokie RE, Wang ZJ, Suarez ML, et al. A randomized controlled pilot study feasibility of a tablet-based guided audio-visual relaxation intervention for reducing stress and pain in adults with sickle cell disease. *Journal of Advanced Nursing* 2016;**72**(6):1452-63. [CFGD Register: SC307b]

Ezenwa 2018 {published data only}

Ezenwa M, Yao Y, Nguyen M, Mandernach M, Hunter C, Yoon S, et al. The effects of relaxation intervention on pain, stress, and autonomic responses among adults with sickle cell pain in the outpatient setting. *Journal of Pain* 2018;**19**(3 Supplement 1):S18-9. [CFGD Register: SC337]

Gil 1996 {published data only}

* Gil KM, Carson JW, Sedway JA, Porter LS, Schaeffer JJ, Orringer E. Follow-up of coping skills training in adults with sickle cell disease: analysis of daily pain and coping practice diaries. *Health Psychology* 2000;**19**(1):85-90. [CFGD Register: SC39b]

Gil KM, Wilson JJ, Abrams MA, Orringer E, Clark WC, Janal MN. Coping skills training in adults with sickle cell disease: post-intervention and 3-month follow-up results. The National Sickle Cell Disease Program Annual Meeting; 1996 March. 1996:08. [CFGD Register: SC39c]

Gil KM, Wilson JJ, Edens JL, Webster DA, Abrams MA, Orringer E, et al. Effects of cognitive coping skills training on coping strategies and experimental pain sensitivity in African American adults with sickle cell disease. *Health Psychology* 1996;**15**(1):3-10. [CFGD Register: SC39a]

Hollins 2012 {published data only}

Hollins M, Stonerock GL, Kisaalita NR, Jones S, Orringer E, Gil KM. Detecting the emergence of chronic pain in sickle

cell disease. *Journal of Pain and Symptom Management* 2012;**43**(6):1082-93. [CFGD Register: SC250]

Horst 2016 {published data only}

Horst J, Frei-Jones M, Deych E, Shannon W, Kharasch ED. Pharmacokinetics and analgesic effects of methadone in children and adults with sickle cell disease. *Pediatric Blood & Cancer* 2016;**63**(12):2123-30. [CFGD Register: SC311]

Howard 2018 {published data only}

Howard J, Inusa B, Lioffi C, Jacob E, Murphy PB, Hart N, et al. Prevention of morbidity in sickle cell disease--qualitative outcomes, pain and quality of life in a randomised cross-over pilot trial of overnight supplementary oxygen and auto-adjusting continuous positive airways pressure (poms2a): study protocol for a randomised controlled trial. *Trials* 2015;**16**:376. [CFGD Register: SC328d]

Howard J, Inusa B, Lioffi C, Rees DC, Thein SL, Cheng E, et al. Prevention of morbidity in sickle cell disease (POMS 2): a pilot study of nocturnal respiratory support shows that auto-adjusting positive airways pressure is safe and is preferred to oxygen therapy. *Blood* 2015;**126**(23):993. [CFGD Register: SC328c]

* Howard J, Slee AE, Skene S, Inusa B, Kawadler J, Downes M, et al. Overnight auto-adjusting continuous airway pressure +standard care compared with standard care alone in the prevention of morbidity in sickle cell disease phase II (POMS2b): study protocol for a randomised controlled trial. *Trials* 2018;**19**(1). [CFGD Register: SC328a]

Inusa B, Howard J, Chakravorty S, Pelidis M, Thein SL, Kirkham FJ. Prevention of morbidity in sickle cell disease phase II (improvement of pain and quality of life in children with sickle cell disease with auto-adjusting continuous positive airways pressure: phase II) (poms 2B pediatric cohort). *Blood* 2017;**130**(Supplement 1):3537. [CFGD Register: SC328b]

Inusa B, Stotesbury H, Koelbel M, Kawadler J, Howard J, Rees D, et al. Prevention of morbidity in sickle cell disease phase II (POMS 2B paediatric cohort): improvement of pain and quality of life in children with sickle cell disease with auto-adjusting continuous positive airways pressure. *British Journal of Haematology* 2018;**181**(Supplement 1):115-6. [CFGD Register: SC328h]

Kawadler J, Lioffi C, Inusa B, Clark C, Rees D, Pelidis M, et al. Reduced cortical thickness in patients with Sickle Cell Disease and a high pain burden: baseline results from the Prevention of Morbidity in Sickle Cell Anaemia (POMS2b) trial. *British Journal of Haematology* 2017;**176**(Suppl 1):18. [CFGD Register: SC328e]

Kolbel M, Stotesbury H, Kawadler J, Howard J, Inusa B, Rees D, et al. Does auto-adjusting positive airway pressure (APAP) aid memory and learning in children with sickle cell disease and sleep disordered-breathing?. *British Journal of Haematology* 2018;**181**(Suppl 1):113. [CFGD Register: SC328a]

Slee A, Stotesbury H, Kawadler J, Koelbel M, Chakravorty S, Pelidis M, et al. Prevention of morbidity in sickle cell disease

phase 2 (poms 2B pediatric): improvement of cognition in children with sickle cell disease with auto-adjusting continuous positive airways pressure: a single-blind, randomized, controlled phase II trial. *British Journal of Haematology* 2018;**181**(Supplement 1):31. [CFGD Register: SC328i]

Slee AE, Kawadler JM, Koelbel M, Stotesbury H, Rees DC, Pelidis M, et al. Prevention of morbidity in sickle cell disease phase II (improvement of cognition in children with sickle cell disease with auto-adjusting continuous positive airways pressure: phase II) (poms 2B paediatric cohort). *Blood* 2017;**130**(Supplement 1). [CFGD Register: SC328j]

Stotesbury H, Kawadler J, Inusa B, Pelidis M, Chakravorty S, Rees D, et al. Neurocognitive deficits in Sickle Cell Disease: links with nocturnal oxygen desaturation in adolescents, but not children. *British Journal of Haematology* 2017;**176**(Suppl 1):89. [CFGD Register: SC328f]

Matthie 2018 {published data only}

Matthie N, Jenerette C, Griest Pell TJ, Lane D, Fu P, Margevicius S, et al. The Effects of a Single Electronic Music Improvisation Session on the Pain of Adults with Sickle Cell Disease: a Mixed Methods Pilot Study. *Journal of Music Therapy* 2018;**55**(2):156-85. [CFGD Register: SC344]

Myers 1999 {published data only}

Myers CD, Robinson ME, Guthrie TH, Lamp SP, Lottenberg R. Adjunctive approaches for sickle cell chronic pain. *Alternative Health Practitioner* 1999;**5**(3):203-12. [CFGD Register: SC151]

Osunkwo 2012 {published data only}

Osunkwo I, Dampier C, Seydafkan S, Cherry K, Ghosh S, Eckman J, et al. Randomized double blind study evaluating response to high dose vitamin D therapy in pediatric sickle cell disease. *American Journal of Hematology* 2011;**86**(10):E19. [Abstract no.: 028; CFGD Register: SC231b]

Osunkwo I, Ziegler T, Alvarez J, George J, Cherry K, Rhodes J, et al. A randomized double blind, placebo controlled study of vitamin D to ameliorate sickle cell chronic pain. *Journal of Pain* 2012;**13**(4 Suppl 1):S73. [Abstract no.: 388; CFGD Register: SC231c]

* Osunkwo I, Ziegler TR, Alvarez J, McCracken C, Cherry K, Osunkwo CE, et al. High dose vitamin D therapy for chronic pain in children and adolescents with sickle cell disease: results of a randomized double blind pilot study. *British Journal of Haematology* 2012;**159**(2):211-5. [CFGD Register: SC231a]

Palermo 2018 {published data only}

Palermo TM, Dudeney J, Santanelli JP, Carletti A, Zempsky WT. Feasibility and acceptability of internet-delivered cognitive behavioral therapy for chronic pain in adolescents with sickle cell disease and their parents. *Journal of Pediatric Hematology/Oncology* 2018;**40**(2):122-7. [CFGD Register: SC325]

Wallen 2014 {published data only}

Wallen GR, Handel D, Mendoza J, Chestnut W, Nichols J, Yates J, et al. A randomized pilot study exploring hypnosis as a pain and symptom management strategy in patients with sickle cell disease. 35th Anniversary Convention of the National Sickle

Cell Disease Program; 2007 Sep 17-22; Washington DC, USA. 2007:261. [CFGD Register: SC205a]

* Wallen GR, Middleton KR, Ames N, Brooks AT, Handel D. Randomized trial of hypnosis as a pain and symptom management strategy in adults with sickle cell disease. *Integrative Medicine Insights* 2014;**9**:25-33. [CFGD Register: SC205b]

Wallen GR, Velumylyum S, Middleton KR, Todaro A, Ames N, Miller-Davis C, et al. Hypnosis as a potential adjunct mind-body intervention in adults with sickle cell disease. *American Journal of Hematology* 2012;**87**(7):E43. [CFGD Register: SC205c]

Wang 1988 {published data only}

* Wang WC, George SL, Wilimas JA. Transcutaneous electrical nerve stimulation treatment of sickle cell pain crises. *Acta Haematologica* 1988;**80**(2):99-102. [CFGD Register: SC90a]

Wang WC, Parker LJ, George SL, Harber JR, Presbury GJ, Wilimas JA. Transcutaneous electrical nerve stimulation (TENS) treatment of sickle cell painful crises. *Blood* 1985;**5**. [Abstract no.: 154; CFGD Register: SC90b]

Additional references

Anshel 1994

Anshel MH, Russell KG. Effect of aerobic and strength training on pain tolerance, pain appraisal and mood of unfit males as a function of pain location. *Journal of Sports Sciences* 1994;**12**(6):535-47.

Ballas 2005

Ballas SK, Lusardi M. Hospital readmission for adult acute sickle cell painful episodes: frequency, etiology, and prognostic significance. *American Journal of Hematology* 2005;**79**(1):17-25.

Ballas 2007

Ballas SK. Current issues in sickle cell pain and its management. <http://asheducationbook.hematologylibrary.org/content/2007/1/97.full> (accessed 29 January 2017):97-105. [DOI: 10.1182/asheducation-2007.1.97]

Ballas 2011a

Ballas SK. Defining the phenotypes of sickle cell disease. *Hemoglobin* 2011;**35**(5-6):511-9.

Ballas 2011b

Ballas SK. Update on pain management in sickle cell disease. *Hemoglobin* 2011;**35**(5-6):520-9.

Ballas 2012

Ballas SK, Gupta K, Adams-Graves P. Sickle cell pain: a critical reappraisal. *Blood* 2012;**120**(18):3647-56.

Ballas 2013

Ballas SK, Darbari DS. Neuropathy, neuropathic pain, and sickle cell disease. *American Journal of Hematology* 2013;**88**(11):927-9.

Brandow 2014

Brandow AM, Farley RA, Panepinto JA. Neuropathic pain in patients with sickle cell disease. *Pediatric Blood & Cancer* 2014;**61**(3):512-7.

Brandow 2015a

Brandow AM, Farley RA, Panepinto JA. Early insights into the neurobiology of pain in sickle cell disease: A systematic review of the literature. *Pediatric Blood & Cancer* 2015;**62**(9):1501-11.

Brandow 2015b

Brandow AM, Farley RA, Dasgupta M, Hoffmann RG, Panepinto JA. The use of neuropathic pain drugs in children with sickle cell disease is associated with older age, female sex, and longer length of hospital stay. *Journal of Pediatric Hematology/Oncology* 2015;**37**(1):10-5.

Brandow 2017

Brandow AM, Zappia KJ, Stucky CL. Sickle cell disease: a natural model of acute and chronic pain. *Pain* 2017;**158** Suppl 1:S79-84.

Charache 1997

Charache S. Mechanism of action of hydroxyurea in the management of sickle cell anemia in adults. *Seminars in Hematology* 1997;**34**(3 Suppl 3):15-21.

Cooper 2016

Cooper TE, Hambleton IR, Ballas SK, Wiffen PJ. Pharmacological interventions for painful sickle cell vaso-occlusive crises in adults. *Cochrane Database of Systematic Reviews* 2016, Issue 5. [DOI: [10.1002/14651858.CD012187](https://doi.org/10.1002/14651858.CD012187)]

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG on behalf of the Cochrane Statistical Methods Group. Chapter 9: Analysing data and undertaking meta-analysis. In: Higgins JPT, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Dworkin 2008

Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *Journal of Pain* 2008;**9**(2):105-21.

Edwards 2010

Edwards LY, Edwards CL. Psychosocial treatments in pain management of sickle cell disease. *Journal of the National Medical Association* 2010;**102**(11):1084-94.

Finnerup 2015

Finnerup, NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurology* 2015;**14**(2):162-73.

GRADE 2013

Schünemann H, Brożek J, Guyatt G, Oxman A, editor(s). *GRADE Handbook*. http://gdt.guidelinedevelopment.org/central_prod/_design/client/handbook/handbook.html (accessed 20 June 2017).

Heeney 2010

Heeney MM, Ware RE. Hydroxyurea for children with sickle cell disease. *Hematology/Oncology Clinics of North America* 2010;**24**(1):199-214.

Higgins 2011a

Higgins JPT, Deeks JJ, editor(s). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011b

Higgins JPT, Altman DG, Sterne JAC, editor(s) on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011c

Higgins JPT, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hildenbrand 2014

Hildenbrand AK, Nicholls EG, Daly BP, Marsac ML, Tarazi R, Deepti R. Psychosocial and pharmacological management of pain in pediatric sickle cell disease. *Postgraduate Medicine* 2014;**126**(2):123-33.

Jensen 2011

Jensen TS, Baron R, Haanpaa M, Kalso E, Loeser JD, Rice AS, et al. A new definition of neuropathic pain. *Pain* 2011;**152**(10):2204-5.

Kalso 2013

Kalso E, Aldington DJ, Moore RA. Drugs for neuropathic pain. *BMJ* 2013;**347**:f7339.

Lutz 2015

Lutz B, Meiler SE, Bekker A, Tao YX. Updated mechanisms of sickle cell disease-associated chronic pain. *Translational Perioperative and Pain Medicine* 2015;**2**:8-17.

McClish 2005

McClish DK, Penberthy LT, Bovbjerg VE, Roberts JD, Aisiku IP, Levenson JL, et al. Health related quality of life in sickle cell patients: the PiSCES project. *Health and Quality of Life Outcomes* 2005;**3**:50.

McGann 2011

McGann PT, Ware RE. Hydroxyurea for sickle cell anemia: what have we learned and what questions still remain?. *Current Opinion in Hematology* 2011;**18**(3):158-65.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009;**6**(7):e1000097.

Moher 2010

Moher, David, Hopewell, Sally, Schulz, Kenneth F, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* Vol. 340:c869. [DOI: <https://doi.org/10.1136/bmj.c869>]

Morley 1999

Morley SJ, Eccleston C, Williams A. Systematic review and meta-analysis of randomised controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. *Pain* 1999;**80**(1-2):1-13.

Moulin 2007

Moulin DE, Clark AJ, Gilron I, Ware MA, Watson CP, Sessle BJ, et al. Pharmacological management of chronic neuropathic pain —consensus statement and guidelines from the Canadian Pain Society. *Pain Research & Management* 2007;**12**(1):13-21. [DOI: [10.1155/2007/730785](https://doi.org/10.1155/2007/730785).]

National 2013

National Institute for Health and Care Excellence. NICE. National Institute for Health and Care Excellence. Neuropathic pain – pharmacological management. The pharmacological management of neuropathic pain in adults in non-specialist settings. <https://www.nice.org.uk/guidance/cg173/evidence/neuropathic-pain-pharmacological-management-full-guideline-191621341> (accessed 20 June 2017).

Nevitt 2017

Nevitt SJ, Jones AP, Howard J. Hydroxyurea (hydroxycarbamide) for sickle cell disease. *Cochrane Database of Systematic Reviews* 2017, Issue 4. [DOI: [10.1002/14651858.CD002202.pub2](https://doi.org/10.1002/14651858.CD002202.pub2)]

Piel 2013a

Piel FB, Patil AP, Howes RE, Nyangiri OA, Gething PW, Dewi M, et al. Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. *Lancet* 2013;**381**(9861):142-51.

Piel 2013b

Piel FB, Hay SI, Gupta S, Weatherall DJ, Williams TN. Global burden of sickle cell anaemia in children under five, 2010-2050: modelling based on demographics, excess mortality, and interventions. *PLoS Med* 2013;**10**:e1001484.

Rees 2010

Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. *Lancet* 2010;**376**(9757):2018-31.

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Schünemann 2011

Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al on behalf of the Cochrane Applicability and Recommendations Methods Group and the Cochrane Statistical Methods Group. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Serjeant 2013

Serjeant GR. The natural history of sickle cell disease. *Cold Spring Harbour Perspectives in Medicine* 2013;**3**:a011783.

Smith 2010

Smith WR, Scherer M. Sickle-cell pain: advances in epidemiology and etiology. *Hematology. American Society of Hematology. Education Program* 2010;**2010**:409-15.

Sterne 2011

Sterne JAC, Egger M, Moher D, editor(s) on behalf of the Cochrane Bias Methods Group. Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Stuart 2004

Stuart MJ, Nagel RL. Sickle-cell disease. *Lancet* 2004;**364**(9442):1343-60.

Vance 2014

Vance CG, Dailey DI, Rakel BA, Sluka KA. Using TENS for pain control: the state of the evidence. *Pain Management* 2014;**4**(3):197-209.

Ware 1999

Ware RE, Zimmerman SA, Schultz WH. Hydroxyurea as an alternative to blood transfusions for the prevention of recurrent stroke in children with sickle cell disease. *Blood* 1999;**94**(9):3022-6.

WHO 2009

World Health Organization. Recognition of sickle cell anaemia as a public health problem. Sixty-Third Session. A/RES/63/237. Geneva, 2009:1-2.

Wierenga 2001

Wierenga KJ, Hambleton IR, Lewis NA. Survival estimates for patients with homozygous sickle-cell disease in Jamaica: a clinic-based population study. *Lancet* 2001;**357**(9257):680-3.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Schlaeger 2017

Methods	Pilot RCT; parallel design
Participants	<p>22 participants</p> <p>Sex: male: 6 (placebo: 2, pregabalin: 4); female: 16 (placebo: 9; pregabalin: 7)</p> <p>Age: mean (SD) all participants: 33.1 (9.9) years (placebo: 34.1 (9.5) years; pregabalin: 32.0 (10.7) years. Range 18 - 82 years</p> <p>Disease status all participants: homozygous S (SS) genotype= 15; heterozygous SC genotype = 6; sickle-beta thalassaemia genotype (SBThal) = 1 (placebo: SS: 6; SC: 5; SBThal: 0; pregabalin: SS: 9; SC: 1; SBThal: 1)</p> <p>Pregabalin group:</p> <p>at 1 month (n = 9) (1 withdrew without taking pregabalin, 1 withdrew for side effects)</p> <p>at 2 months (n = 8) (1 was dropped-combative behavior)</p> <p>at 3 months (n = 8)</p> <p>Placebo group:</p> <p>at 1 month (n = 11)</p> <p>at 2 months (n = 10) (withdrew for side effects)</p> <p>at 3 months (n = 8) (1 dropped-SCD symptoms/hospitalization, 1 missing due to hospitalization for sickle-cell pain)</p>
Interventions	<p>Treatment group: pregabalin, dose and frequency of administration: initial dose: 75 mg twice daily; increased by 75 mg increments, to a maximum of 600 mg daily, or decreased the dose by 75 mg per day if necessary based on clinical presentation and pain level</p> <p>Control group: placebo</p> <p>Duration of treatment: 3 months</p> <p>Length of follow-up: not stated</p>
Outcomes	<p>Self-reported pain (NPSI, S-LANNS); QoL (QOL SF-36), adverse events, withdrawals due to adverse events</p> <p>Time points of measurements: baseline, 1 month, 2 months, 3 months</p>
Notes	<p>Eligibility criteria</p> <p>(a) diagnosed with SCD, receiving ongoing care at the clinic</p> <p>(b) aged 18 - 82 years old</p> <p>(c) a history of SCD pain that was not well controlled (pain now score ≥ 4 on a 0 - 10 scale at registration)</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The University of Illinois Hospital and Health Sciences System experimental pharmacist randomly assigned participants'. No explanation of how the participants were randomly assigned by the pharmacist

Schlaeger 2017 (Continued)

Allocation concealment (selection bias)	Low risk	Pharmacist was the only person with knowledge of group assignment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as a double-blind pilot study The prescribing physician was blind to the study drug treatment (pregabalin or placebo), the physician was not blind to the dose (in mg), which allowed all participants' doses to be titrated Initial dose of 75 mg twice daily and increments of 75 mg was similar for both groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Pharmacist was the only person with knowledge of group assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	27% loss to follow-up Numbers completing the 3-month trial: pregabalin 8/11; placebo 8/11 (for further information, see 'Interventions' in above table)
Selective reporting (reporting bias)	Unclear risk	Unable to assessed as protocol could not be accessed
Other bias	Low risk	Unlikely from the publication

NPSI: Neuropathic Pain Symptom Inventory

QoL: quality of life

RCT: randomised controlled trial

SCD: sickle cell disease

S-LANNS: Leeds Assessment of Neuropathic Symptoms and Signs scale

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Co 1979	SCD population without neuropathic pain
Ezenwa 2016	SCD population without neuropathic pain
Ezenwa 2018	SCD population without neuropathic pain
Gil 1996	SCD population without neuropathic pain
Hollins 2012	SCD population without neuropathic pain
Horst 2016	SCD population without neuropathic pain
Howard 2018	Neuropathic pain not measured
Matthie 2018	SCD population without neuropathic pain
Myers 1999	SCD population without neuropathic pain
Osunkwo 2012	SCD population without neuropathic pain

Study	Reason for exclusion
Palermo 2018	Neuropathic pain not measured
Wallen 2014	SCD population without neuropathic pain
Wang 1988	SCD population without neuropathic pain

SCD: sickle cell disease

DATA AND ANALYSES

Comparison 1. Pharmacological intervention (pregabalin) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Self-reported pain relief - S-LANSS	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 at 1 month	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 at 2 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 at 3 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Self-reported pain relief - NPSI	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 at 1 month	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 at 2 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 at 3 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Quality of life (at 3 months)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Physical function	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Role limitation as a result of physical health	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Role limitation as a result of emotional problems	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 Energy or fatigue	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.5 Emotional well-being	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.6 Social functioning	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.7 Pain	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.8 General health	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Treatment-related adverse events (at 3 months)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Pharmacological intervention (pregabalin) versus placebo, Outcome 1 Self-reported pain relief - S-LANSS.

Study or subgroup	Pregabalin		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
1.1.1 at 1 month						
Schlaeger 2017	9	6.2 (6.8)	11	9.8 (6.1)		-3.6[-9.32,2.12]
1.1.2 at 2 months						
Schlaeger 2017	8	5.9 (4.1)	10	10.8 (8.4)		-4.9[-10.83,1.03]
1.1.3 at 3 months						
Schlaeger 2017	8	5.9 (3.9)	8	7.9 (9.6)		-2[-9.18,5.18]
					-100 -50 0 50 100	Favours pregabalin Favours placebo

Analysis 1.2. Comparison 1 Pharmacological intervention (pregabalin) versus placebo, Outcome 2 Self-reported pain relief - NPSI.

Study or subgroup	Pregabalin		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
1.2.1 at 1 month						
Schlaeger 2017	9	18.9 (13.8)	11	32.8 (21.5)		-13.9[-29.48,1.68]
1.2.2 at 2 months						
Schlaeger 2017	8	16 (14.8)	10	31.5 (25.3)		-15.5[-34.24,3.24]
1.2.3 at 3 months						
Schlaeger 2017	8	21.5 (14.2)	8	32.6 (29.8)		-11.1[-33.97,11.77]
					-100 -50 0 50 100	Favours pregabalin Favours placebo

Analysis 1.3. Comparison 1 Pharmacological intervention (pregabalin) versus placebo, Outcome 3 Quality of life (at 3 months).

Study or subgroup	Pregabalin		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
1.3.1 Physical function						
Schlaeger 2017	8	60 (17.9)	8	67 (18.6)		-7[-24.89,10.89]
1.3.2 Role limitation as a result of physical health						
					-100 -50 0 50 100	Favours pregabalin Favours placebo

Analysis 1.4. Comparison 1 Pharmacological intervention (pregabalin) versus placebo, Outcome 4 Treatment-related adverse events (at 3 months).

ADDITIONAL TABLES

Table 1. Change in psychosocial outcomes: SF-36 data (at 1 and 2 months)

Quality of life		Pregabalin group* (mean (SD))	Control group* (mean (SD))
Physical function	At 1 month	67.8 (19.1)	59.5 (25.0)
	At 2 months	56.3 (22.0)	65.5 (22.4)
Role imitation as a results of physical health	At 1 month	48.7 (39.4)	47.7 (48.0)
	At 2 months	56.3 (47.7)	50.0 (45.6)
Role imitation as a results of emotional problems	At 1 month	92.1 (22.5)	72.7 (46.7)

Table 1. Change in psychosocial outcomes: SF-36 data (at 1 and 2 months) *(Continued)*

	At 2 months	95.8 (11.8)	56.7 (44.6)
Energy/fatigue	At 1 month	49.4 (17.8)	42.3 (27.5)
	At 2 months	38.9 (22.6)	47.0 (28.8)
Emotional well-being	At 1 month	73.3 (20.3)	72.7 (18.4)
	At 2 months	81.0 (8.2)	64.0 (27.5)
Social functioning	At 1 month	62.5 (23.4)	63.6 (28.2)
	At 2 months	64.1 (25.4)	60.0 (28.7)
Pain	At 1 month	57.0 (27.2)	57.3 (20.3)
	At 2 months	56.6 (31.9)	50.0 (18.9)
General health	At 1 month	38.7 (18.3)	44.2 (22.7)
	At 2 months	37.8 (21.8)	45.7 (23.7)

At 1 month: pregabalin group = 9 participants; control group = 11 participants

At 2 months: pregabalin group = 8 participants; control group = 10 participants

APPENDICES

Appendix 1. Electronic searching

Database/ Resource	Strategy
CARPHA EvIDeNce Portal	Search subject: sickle AND pain* Limit your search by language: No limits (<i>default option "documents written in English" unticked</i>)
ClinicalTrials.gov	Other terms: pain Study Type: Interventional Studies Condition/ Disease: sickle
WHO ICTRP	sickle AND pain*
EU Clinical Trials Register	sickle AND pain*

CONTRIBUTIONS OF AUTHORS

Task	Author(s) responsible
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Protocol stage: draft the protocol	Monika Asnani (MA) Damian Francis (DF) Amanda Brandow (AB) Christine Hammond Gabbadon (CG) Amza Ali (AA)
Review stage: select which trials to include (2 + 1 arbiter)	CG, AB, Arbiter (MA)
Review stage: extract data from trials (2 people)	AB, CG, AA
Review stage: enter data into RevMan	DF, MA
Review stage: carry out the analysis	DF, MA
Review stage: interpret the analysis	DF, MA, AB, CG, AA
Review stage: draft the final review	DF, MA, AB, CG, AA
Update stage: update the review	MA, DF, AB, CG, AA

Review Guarantor: MA

DECLARATIONS OF INTEREST

Monika R Asnani, Damian K Francis, Christine EO Hammond Gabbadon, Sheik A Ali: none known.

Amanda M Brandow: is employed as an academic physician by the Medical College of Wisconsin. She receives funding from the National Institutes of Health/National Heart Lung and Blood Institute to support her research in sickle cell disease.

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INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics [*therapeutic use]; Anemia, Sickle Cell [*complications]; Neuralgia [*drug therapy] [*etiology]; Pregabalin [*therapeutic use]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Humans