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Drug therapy for pain in amyotrophic lateral sclerosis or motor neuron disease (Review)

Brettschneider J, Kurent J, Ludolph A

Brettschneider J, Kurent J, Ludolph A.
Drug therapy for pain in amyotrophic lateral sclerosis or motor neuron disease.
Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD005226.
DOI: 10.1002/14651858.CD005226.pub3.

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[Intervention Review]

Drug therapy for pain in amyotrophic lateral sclerosis or motor neuron disease

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Editorial group: Cochrane Neuromuscular Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 6, 2013.

Citation: Brettschneider J, Kurent J, Ludolph A. Drug therapy for pain in amyotrophic lateral sclerosis or motor neuron disease. *Cochrane Database of Systematic Reviews* 2013, Issue 6. Art. No.: CD005226. DOI: 10.1002/14651858.CD005226.pub3.

ABSTRACT

Background

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND), is the most common neurodegenerative disorder of the motor system in adults. Pain in ALS is a frequent symptom especially in the later stages of disease and can have a pronounced influence on quality of life and suffering. Treatment of pain therefore should be recognised as an important aspect of palliative care in ALS. This is an update of a review first published in 2008.

Objectives

To systematically review the evidence for the efficacy of drug therapy in relieving pain in ALS. We also aimed to evaluate possible adverse effects associated with the different drugs and their influence on survival and quality of life.

Search methods

On 2 July 2012, we searched the following databases: the Cochrane Neuromuscular Disease Group Specialized Register (2 July 2012), CENTRAL (2012, Issue 6 in *The Cochrane Library*), MEDLINE (January 1966 to June 2012), EMBASE (January 1980 to June 2012), CINAHL (January 1982 to June 2012), AMED (January 1985 to June 2012) and LILACS (January 1982 to June 2012). We checked the bibliographies of trials identified and contacted other disease experts to identify further published and unpublished trials.

Selection criteria

We searched for randomised or quasi-randomised controlled trials on drug therapy for pain in amyotrophic lateral sclerosis.

Data collection and analysis

We collected data using a specially designed form and analysed them using the Cochrane Review Manager software.

Main results

We found no randomised or quasi-randomised controlled trials on drug therapy for pain in ALS or MND.

Authors' conclusions

There is no evidence from randomised controlled trials about the management of pain in ALS. Further research on this important aspect of palliative care in ALS is needed. Randomised controlled trials should be initiated to determine the effectiveness of different analgesics for treatment of pain in ALS.

PLAIN LANGUAGE SUMMARY

Drug therapy for pain in amyotrophic lateral sclerosis or motor neuron disease

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND), is the most common neurodegenerative disorder of the motor system in adults. Pain is a frequent symptom and may have a pronounced impact on quality of life and suffering. Despite an extensive search of different medical databases, this review was not able to identify any randomised controlled trials on drug therapy for pain in ALS. Currently (to July 2012) no evidence exists for using one type of treatment over another.

BACKGROUND

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND), is the most common neurodegenerative disorder of the motor system in adults. The incidence is up to 2 per 100,000 population per year and age specific incidence and mortality rates peak between 55 and 75 years (Worms 2001). People with ALS show a combination of upper and lower motor neuron signs and death usually results from respiratory failure. Over 50% of people with ALS die within three years of the first symptom.

Although less of an issue in the earlier stages of the disease, pain has been reported to be a frequent symptom in the later stages of ALS (Ganzini 1999), where studies have reported pain to occur in up to 80% of cases (Gubbay 1985; Miller 1999; Newrick 1985; Saunders 1981; Wu 1998). Pain mainly affects the lower back, shoulders, neck and legs (Ganzini 1999; Wu 1998) and may have a dull or electrical character (Newrick 1984; Newrick 1985). Patients sometimes report pain of a different quality in different parts of the body. Although in most cases the severity of the pain is reported to be mild or moderate, severe pain is reported in 20% of patients (Ganzini 1999; Newrick 1985). It has been suggested that the intensity of pain increases with disease duration (Drory 2001).

The aetiology of pain in patients with ALS is not well understood. Musculoskeletal pain may arise in the later stages of disease as a result of stress on bones and joints that have lost their protective muscular sheath due to atrophy (Borasio 1997; Borasio 2001a). In addition, pain may be caused by muscle contractures and joint stiffness (Borasio 1997; Borasio 2001a). This may explain why pain seems to be a particular feature in the later stages of the disease. Pain may also arise from muscle cramps and muscle spasticity. Another cause of pain in patients with ALS seems to be skin pressure caused by immobility (Borasio 1997). In this context, decubitus ulcers have been reported in 16% of patients (Saunders 1981). Pain may also occur as a manifestation of the sensory disturbances which are reported to occur in up to 11% of patients (Lawyer 1953). Pathological involvement of sensory pathways in motor neuron disease has only infrequently been reported (Brownell 1970). A potentially associated chronic central pain syndrome was reported in a single patient (Drake 1983).

The first line treatment for pain in ALS is usually non-opioid analgesics, including acetaminophen, or non-steroidal anti-inflammatory agents (NSAIDs) (Ganzini 1999; Wu 1998). Opioid drugs are usually used if these drugs fail to relieve the pain (O'Brien 1992). Opioids may also be used for the symptomatic treatment of dyspnoea and coughing in MND (Neudert 2001; Oliver 1998). There is considerable discrepancy in the literature regarding the frequency of dosing and actual dose provided, as well as the routes of administration of opioids in ALS (Ganzini 1999; Neudert 2001; Wu 1998). Opioids are possibly more frequently used in patients treated in hospices or palliative care units (Neudert 2001). It is possible that some health professionals might be hesitant to use opioids for fear that they might hasten death by suppressing ventilation (Oliver 1998) and because patients and family caregivers might associate opiate drugs with terminal stages of disease and imminent death (Oliver 1998).

Continuing uncertainty over the indications, doses, application modes and side effects of pain medication in the palliative therapy of patients with ALS suggests that a systematic review of all randomised clinical trials concerning treatment of pain in ALS is required. The results will need to be considered in the context of non-randomised studies in the Discussion section of this review.

OBJECTIVES

The objective of this review was to systematically review the evidence for the efficacy of drug therapy in relieving pain in ALS. We also aimed to evaluate possible adverse effects associated with the different drugs and their influence on survival and quality of life.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised and quasi-randomised (alternate or other systematic allocation) controlled studies involving drug therapy administered to relieve pain in ALS or MND. We did not include studies of treatments for cramps in ALS or MND as this is the topic of another Cochrane review (Baldinger 2012).

Types of participants

All those with a clinical diagnosis of ALS or MND (pure mixed upper motor neuron and lower motor neuron degeneration with a supportive electromyogram) according to the revised El Escorial criteria (Brooks 2000)) and with any clinical pattern of the condition (e.g. bulbar or limb onset) who report experiencing pain.

Types of interventions

Any drug therapy, given by any route, in any dose, administered to relieve pain in ALS/MND.

Types of outcome measures

Primary outcomes

The primary outcome was patient reported pain relief after 24 hours (site, intensity, frequency and duration of pain) measured by a visual analogue scale, verbal or numerical rating scale, or any other validated assessment tool.

Secondary outcomes

The secondary outcome measures were:
(1) patient reported pain relief after seven days;
(2) adverse effects of treatment. An assessment of the severity and frequency of the reported adverse effects was made. Adverse effects were categorised into those severe enough to result in cessation of treatment (for example respiratory depression as an adverse effect of opioids) and those that were mild.

Wherever possible, we planned to transform visual analogue scales and any categorical outcomes and analyse them as dichotomous data.

Search methods for identification of studies

(1) We searched the Cochrane Neuromuscular Disease Group Specialized Register (2 July 2012), CENTRAL (2012, Issue 6 in *The Cochrane Library)*, MEDLINE (January 1966 to June 2012), EMBASE (January 1980 to June 2012), CINAHL (January 1982 to June 2012), AMED (January 1985 to June 2012) and LILACS (January 1982 to June 2012).

(2) In addition, we reviewed the results of the RCT searches of MEDLINE (January 1966 to June 2012) and EMBASE (January 1980 to June 2012) for well-designed published observational studies of pain therapy in terminal ALS, with controls, where the diagnosis was clearly stated, the interventions were clearly described and the outcomes were clearly reported for all patients. For example, we collected prospective cohort studies or case control studies with concurrent controls. We also considered retrospective case series of more than five participants where patients were treated consecutively. This strategy was deemed necessary because we suspected there would be few or no randomised controlled trials or quasi-randomised controlled trials on this particular topic, as we believed it would be unethical to design a placebo controlled trial for treatment of pain in ALS.

For this update, on 9 April 2013, we also searched the US national Institutes of Health registry ClinicalTrials.gov (http://clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/) for ongoing trials.

Electronic searches

The detailed search strategies are in the appendices:MEDLINE (Appendix 1), EMBASE (Appendix 2), CINAHL Plus (Appendix 3), AMED (Appendix 4), LILACS (Appendix 5), CENTRAL Appendix 6, ClinicalTrials.gov and WHO ICTRP (Appendix 7).

Searching other resources

We planned to check the bibliographies of trials identified and contacted other disease experts for further published and unpublished trials.

Data collection and analysis

Two authors (previously JB, JD Mitchell (JDM); for this update, JB and JK) checked all titles and abstracts identified by the searches for randomised or quasi-randomised trials. Two authors (previously JB, JDM; for this update, JB and JK) also checked all titles and abstracts identified by the searches for non-randomised evidence. The authors obtained the full texts of all potentially relevant studies and assessed them independently. Two authors extracted data independently onto a specially designed form (JB, JDM; not required for this update). One author (JB) entered the data into the software and two checked the data entered (JK, AL). All the authors decided which trials met the inclusion criteria for the review. Disagreement about inclusion was resolved by discussion and consensus between the authors.

Assessment of risk of bias in included studies

Had there been RCTs two authors would have independently assessed risk of bias using in the following domains using the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011):

- secure randomisation;
- allocation concealment;
- blinding of subject and observer;
- blinding of outcome assessors;
- completeness of follow up and intention-to-treat analysis;
- selective outcome reporting;
- other sources of bias.

We would have quantified the risk of bias as follows: Low risk of bias, High risk of bias, or Unclear risk of bias (insufficient detail reported, risk of bias unknown or the entry is not relevant to the study). Where there was an unclear risk of bias , we would have tried to obtain further information from the trial investigators.

Data collection

We designed a data collection form for the review and planned to collect the following data:

- publication details;
- participants: number of patients, gender, mean age, disease duration, clinical subtype of ALS (bulbar, limb, both bulbar and limb);
- trial quality characteristics;
- site of pain;
- cause of pain;
- duration of pain;
- description of intervention;
- outcome data;
- adverse effects.

We planned to obtain missing or additional data from the authors wherever possible.

Data analysis

The Cochrane Neuromuscular Disease Group guidelines were followed. We planned to analyse the data using Cochrane Review Manager software (currently RevMan 2012) and to report it according to the *Cochrane Handbook for Systematic Reviews of Interventions* (currently Higgins 2011)..

We aimed to calculate the risk ratio (RR) and corresponding 95% confidence intervals (CI) for dichotomous data and the mean difference (MD) and 95% confidence intervals (CI) for continuous data.
Analyses of subgroups identifying different drug treatments and different doses were to be carried out if sufficient data had been available. Wherever possible, we intended to compare different subgroups of pain medication.

We planned to test for heterogeneity across trials and if heterogeneity could be found we intended to undertake sensitivity analyses by repeating the calculation omitting trials that had low scores on individual quality items. If heterogeneity could not be explained by variation in trial quality we intended to use a random-effects approach to obtain the pooled estimates from the group of trials.

This review has a published protocol (Brettschneider 2005). If at a future update new trials emerge we will update the methodology according to Cochrane Collaboration guidance at that time.

RESULTS

Description of studies

The number of references retrieved by the new, current electronic searches for the review were: MEDLINE 151 (10 new papers), EMBASE = 229 (76 new papers), AMED = 8 (1 new paper), LILACS = 0, CINAHL Plus = 27 (6 new papers), CENTRAL = 13 and the

Cochrane NMD Group Specialised Register 15 (1 new paper). After screening, no randomised or quasi-randomised controlled trials on drug therapy for pain in ALS or MND were found. There was one randomised controlled study on gabapentin (which is often used for treatment of pain) in ALS, but pain was not an outcome measure in that study (Miller 2001). We could find no well designed published observational studies on pain therapy in ALS. We found one Cochrane review on treatment for spasticity in ALS/MND, although it identified no randomised trials examining the effectiveness of anti-spasticity drugs (Ashworth 2006).

In total there are 34 excluded studies. At this update we excluded Weber 2010, which is included in the Cochrane review of treatments for cramp in ALS (Baldinger 2012). We removed three reviews from the excluded studies tables (Ashworth 2006; Borasio 1997; Borasio 2001b).

We found 13 case series of more than five participants describing drug therapy for pain in ALS (Amtmann 2004; Bedlack 2009; Ganzini 1999; Ganzini 2002b; McClelland 2008; Neudert 2001; Newrick 1984; Newrick 1985; O'Brien 1992; Oliver 1996; Oliver 1998; Saunders 1981; Wu 1998).

Further data included case series (Adelman 2004; Abe 2008; Bradley 2001; de Castro-Costa 1999; Ganzini 1998; Hecht 2002; Jensen 2005; Tedman 1997; Trail 2003; Winter 2010) and case reports (de Carvalho 2001; Drake 1983; Shibata 2003) as well as surveys of expert opinion (Abe 2008; Borasio 2001a; Carter 2010; Chio 2001; Forshew 2003) or caregivers' experience (Ganzini 2002a; Maessen 2010; Mandler 2001) describing certain aspects such as causes, frequency, localisation or intensity of pain in ALS.

We found no relevant ongoing studies.

Risk of bias in included studies

No evidence above the level of case series was found.

Effects of interventions

We did not find any randomised or quasi-randomised controlled trials on drug therapy for pain in ALS or MND in the Cochrane Neuromuscular Disease Group Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, LILACS or AMED, or any other sources.

DISCUSSION

Frequency of pain

Evidence derived from case series, surveys of expert opinion and case reports showed pain in ALS to occur in between 3% and 78% of patients (Bradley 2001; Ganzini 1999; Maessen 2010; Winter 2010; Wu 1998). Frequency of pain has been shown to increase with ongoing disease (Hecht 2002).

Intensity and relevance of pain

Intensity of pain was shown to be mostly moderate in the earlier stages of ALS, though it was demonstrated to increase with ongoing disease (Adelman 2004; Ganzini 2002b). In a case series including 126 patients with MND, mean severity of pain was rated with 25.6 points on a 100 point visual analogue scale (20.8 to 30.4, 95% CI) (Clarke 2005). In the final stages of disease, pain was noted to be of severe intensity in up to 20% of patients (Ganzini 1998; Ganzini 1999; Ganzini 2002a; Ganzini 2002b). Agreement between patients and caregivers for ratings of pain level was shown to be high (Adelman 2004).

Pain in ALS was shown to correlate significantly with depression ratings (Tedman 1997). Depression was shown to be associated a significantly reduced quality of life in ALS (Lou 2003). Furthermore, suffering was statistically correlated with increasing pain, and pain was the most significant contributor to suffering in the final stages of disease (Ganzini 1999). There was a marked interference of pain with activities of daily living in ALS patients (Jensen 2005). In the final stages of disease, pain was associated with a patient's interest in assisted suicide (Ganzini 2002b).

Causes and localisation of pain

Most frequently, pain was found to be associated with reduced joint mobility, cramps or skin pressure caused by immobility (Borasio 1997; Borasio 2001b; de Castro-Costa 1999; Ganzini 1999; Neudert 2001; Newrick 1984). There were also case reports of a chronic central pain syndrome in ALS (Drake 1983) as well as a case of complex regional pain syndrome (CRPS) in an ALS patient without preceding trauma (Shibata 2003). Pain was most frequently localised in the lower back area, the legs, and in the shoulder and neck area of the patients (Ganzini 1999; Newrick 1985; Saunders 1981).

Therapy for pain

Acetaminophen or other NSAIDs were usually applied as first line treatment for pain in ALS (Saunders 1981; Wu 1998). Pain was often shown to be well controlled by these drugs in the earlier stages of disease (Saunders 1981). However, there was evidence that in the later stages of disease pain may not be controlled with these analgesics (Newrick 1984).

Although pain was shown to be common, especially in the later stages of disease, it was found to be frequently undertreated (Ganzini 1999; Mandler 2001). In a study by Ganzini and colleagues, only 77% of patients with pain received a specific treatment (Ganzini 1999). These patients were treated with opioids in 40%, NSAIDs in 44% and acetaminophen in 19% (Ganzini 1999).

Opioids were found to be an effective therapy for pain, which also showed beneficial effects on dyspnoea and insomnia (O'Brien 1992) (mean dose 30 (+/- 2.34) mg/24 hour oral morphine equivalent, mean duration of treatment 58 (+/- 18.51) days). Opioids were significantly more likely to be administered if patients were treated in a hospice or palliative care unit compared to those treated at home (Neudert 2001; Oliver 1996; Saunders 1981). There were distinct inter-country differences regarding the use of opioids: Neudert and colleagues observed morphine to be given to only 27% of a German ALS cohort as compared to 82% of a comparable UK cohort (Neudert 2001). A study in which oral morphine was used over an average of 95 days suggested that strong opioids could be used safely in palliative care and do not necessarily shorten life (Oliver 1998). One study reported that cannabis was effective at reducing pain in ALS (Amtmann 2004). However, only about 10% of ALS patients surveyed in this study reported using cannabis, distinctly fewer than observed in other severe diseases, such as multiple sclerosis, AIDS or cancer patients (Amtmann 2004).

Quinine may be an option for the treatment of muscle cramps in ALS in many countries, but is no longer approved for therapy of cramps in the United States as determined by the US Food and Drug Administration (FDA 2006; FDA 2010). A survey of members of the European ALS Research Group showed that for treatment of cramps, quinine sulphate was used in 58% of centres, benzodiazepines in 40%, magnesium in 25% and carbamazepine in 23% (Borasio 2001a). Separate Cochrane reviews on quinine for the treatment of muscle cramps (El Tawil 2010) and treatment for muscle cramps in ALS (Baldinger 2012) have been published. Gabapentin (Miller 2001) and tetrahydrocannabinol (Weber 2010) were observed to have no significant effect on muscle cramps. In contrast, a small open-label, non-controlled study suggested that levetiracetam 1500 mg twice daily may be effective in reducing the severity and frequency of cramps in ALS (Bedlack 2009). So far, there have been no randomised trials examining the effectiveness of the existing anti-spasticity drugs in ALS (Ashworth 2006). According to a survey of expert opinion, as a therapy for spasticity, baclofen was used in 100% of large centres, tizanidine in 36%, benzodiazepines in 21% and dantrolene in 29% (Chio 2001). A survey of members of the European ALS Research Group showed that for the treatment of spasticity, carbamazepine was used in 93%, tizanidine in 38%, dantrolene in 36% and benzodiazepines in 36% (Borasio 2001a). The effectiveness of these drugs on spasticity-associated pain was not monitored in either study. In a case series of eight ALS patients with intractable pain related to spasticity, intrathecal baclofen was able to achieve a pain score reduction in six patients, indicating that intrathecal application of baclofen could be an option to treat spasticity-related pain in patients that do not respond to oral therapy (McClelland 2008).

Though there is some evidence from animal models that riluzole could be beneficial in neuropathic pain (Coderre 2007; Sung 2003), this has not been demonstrated in humans so far (Pittenger 2008).

Pain as an underrated symptom in ALS

An important goal of treatment in patients with ALS is to relieve symptoms, diminish suffering and improve quality of life. The studies we reviewed showed pain in ALS to be common, especially in the later stages of disease and to have a pronounced influence on quality of life and suffering (Ganzini 1999; Ganzini 2002b; Tedman 1997). Treatment for pain, therefore, should be recognised as an important aspect of palliative care in ALS.

In contrast to its clinical relevance, data regarding the treatment for pain in ALS were found to be extremely scarce. As mentioned above, we found no randomised or quasi-randomised controlled trials or well-designed observational studies. This under-representation in the scientific literature in our opinion demonstrates that pain is still an underestimated symptom in ALS and may consequently be frequently undertreated.

We found data regarding pain in ALS not only to be scarce, but also frequently inconsistent when describing certain characteristics. For example, we found pronounced differences between studies describing the prevalence or severity of pain. These discrepancies may be partially due to differences among the cohorts included in the studies, for example, with regard to duration of disease.

Data regarding the effectiveness of different analgesics for therapy of pain in ALS were even rarer than data on the characteristics of pain in ALS or MND. The few available low evidence level studies seem to indicate that NSAIDs and acetaminophen, or both, may be effective for moderate pain frequently observed in the earlier stages of disease (Saunders 1981; Wu 1998). However, if these therapies prove to be insufficient, opioids seem to be an effective and well-tolerated alternative that could also alleviate other symptoms such as dyspnoea and anxiety (Neudert 2001; O'Brien 1992; Oliver 1998).

Treatment for pain in ALS is a common unresolved problem. In the absence of any evidence from randomised controlled trials, it is the authors' opinion that treatment for pain in ALS should follow the 1990 World Health Organization (WHO) Analgesic Ladder (WHO 1990). The WHO Analgesic Ladder includes a structured approach to the management of pain according to pain severity and the corresponding need for utilisation of drugs with the increasing potency required for effective pain control. The Analgesic Ladder includes the major categories of analgesic agents that this review has identified as being in use for patients with ALS or MND. The recommendation for using the WHO Analgesic Ladder is also consistent with the overall symptom management goals discussed in the evidence-based practice parameter for care of the patient with ALS developed by the American Academy of Neurology (Miller 1999).

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence from randomised controlled trials about the management of pain in ALS.

Implications for research

Further research on this important aspect of palliative care in ALS is needed. Randomised controlled trials should be initiated to determine the effectiveness of different analgesics for the treatment of pain in ALS. Treatment of pain should be included as an outcome measure in clinical trials using drugs with a known analgesic capacity.

ACKNOWLEDGEMENTS

The authors thank Ms Kate Jewitt, Ms Janice Fernandes and Mrs Rachel Barton for their invaluable support for this review. The Cochrane Neuromuscular Disease Group editorial base carried out searches.

The editorial base of the Cochrane Neuromuscular Disease Group is supported by the Motor Neuron Disease Association and the MRC Centre for Neuromuscular Disease.

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CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Abe 2008	Not a randomised trial
Adelman 2004	Not a randomised trial
Amtmann 2004	Not a randomised trial
Bedlack 2009	Not a randomised trial
Borasio 2001a	Not a randomised trial
Bradley 2001	Not a randomised trial
Carter 2010	Not a randomised trial
Chio 2001	Not a randomised trial
de Carvalho 2001	Not a randomised trial
de Castro-Costa 1999	Not a randomised trial
Drake 1983	Not a randomised trial
Forshew 2003	Not a randomised trial
Ganzini 1998	Not a randomised trial
Ganzini 1999	Not a randomised trial
Ganzini 2002a	Not a randomised trial
Ganzini 2002b	Not a randomised trial
Hecht 2002	Not a randomised trial
Jensen 2005	Not a randomised trial
Maessen 2010	Not a randomised trial
Mandler 2001	Not a randomised trial
McClelland 2008	Not a randomised trial
Neudert 2001	Not a randomised trial
Newrick 1984	Not a randomised trial
Newrick 1985	Not a randomised trial
O'Brien 1992	Not a randomised trial

Study	Reason for exclusion
Oliver 1996	Not a randomised trial
Oliver 1998	Not a randomised trial
Saunders 1981	Not a randomised trial
Shibata 2003	Not a randomised trial
Tedman 1997	Not a randomised trial
Trail 2003	Not a randomised trial
Weber 2010	A RCT of treatment for cramps in ALS
Winter 2010	Not a randomised trial
Wu 1998	Not a randomised trial

APPENDICES

Appendix 1. MEDLINE (OvidSP) search strategy

Database: Ovid MEDLINE(R) <1946 to June Week 3 2012>
Search Strategy:
---
1 randomized controlled trial.pt. (330201)
2 controlled clinical trial.pt. (84375)
3 randomized.ab. (233876)
4 placebo.ab. (132230)
5 drug therapy.fs. (1543331)
6 randomly.ab. (168558)
7 trial.ab. (242070)
8 groups.ab. (1106725)
9 or/1-8 (2867649)
10 (animals not (animals and humans)).sh. (3644610)
11 9 not 10 (2435542)
12 exp Motor Neuron Diseases/ (17466)
13 (moto$1 neuron$1 disease$1 or moto?neuron$1 disease).mp. (5793)
14 ((Lou Gehrig$1 adj5 syndrome$1) or (Lou Gehrig$1 adj5 disease)).mp. (64)
15 Amyotrophic Lateral Sclerosis.mp. (14118)
16 or/12-15 (21011)
17 (pain relie$ or pain therap$ or pain medicat$ or pain treat$ or analgesic$ or antiinflammatory agent or nsaid).mp. (114512)
18 exp Antiinflammatory Agents, Non-Steroidal/ (144357)
19 exp ANALGESICS/ (405157)
20 aspirin.tw. or ASPIRIN/ (48267)
21 salicylate.tw. or Salicylates/ (11649)
22 indomethacin.tw. or INDOMETHACIN/ (37834)
23 piroxicam.tw. or PIROXICAM/ (3162)
24 ketorolac.tw. or KETOROLAC/ (1856)
25 (tenoxicam or apazone or diclofenac or diflusinal or etodolac or fenoprofen or flurbiprofen or ibuprofen or ketoprofen or meclofenamate or nabumetone or naproxen or oxaprozin or phenylbutazone or sulindac or tolmetin or paracetamol or acetaminophen or APAP).mp. (48442)
26 exp NARCOTICS/ (81339)
27 (opioid$ or opiate$ or narcotic$).mp. (110252)
28 (morphinans or morphine or fentanyl or hydromorphone or oxycodone or pentazocine or methadone).mp. (72843)

29 codeine.tw. or CODEINE/ (5233)
30 (dihydrocodeine or dextromoramide or diamorphine or dextropropoxyphene or meptazinol or sufentanil or alfentanil or remifentanil or nalbuphine or dipipanone or pethidine or tramadol or buprenorphine).mp. (17410)
31 exp Antidepressive Agents, Tricyclic/ or (Tricyclic adj1 Antidepress$).tw. (31064)
32 (amitriptyline or desipramine or doxepine or clomipramine or levomepromazine or haloperidol or carbamazepine or gabapentin).mp. (50975)
33 exp Anesthesia Adjuvants/ (85623)
34 PAIN/pc, dt, th [Prevention and Control, Drug Therapy, Therapy] (30935)
35 or/17-34 (618590)
36 11 and 16 and 35 (151)

Appendix 2. EMBASE (OvidSP) search strategy

Database: Embase <1980 to 2012 Week 26>
Search Strategy:
---
1 crossover-procedure.sh. (34246)
2 double-blind procedure.sh. (109462)
3 single-blind procedure.sh. (16047)
4 randomized controlled trial.sh. (324293)
5 (random$ or crossover$ or cross over$ or placebo$ or (doubl$ adj blind$) or allocat$).tw,ot. (877566)
6 trial.ti. (132039)
7 or/1-6 (1004389)
8 (animal/ or nonhuman/ or animal experiment/) and human/ (1187619)
9 animal/ or nonanimal/ or animal experiment/ (3281792)
10 9 not 8 (2719455)
11 7 not 10 (920638)
12 limit 11 to embase (713539)
13 Motor Neuron Disease/ or Amyotrophic Lateral Sclerosis/ (22904)
14 (moto$1 neuron$1 disease$1 or moto?neuron$1 disease).mp. (8463)
15 ((Lou Gehrig$1 adj5 syndrome$1) or (Lou Gehrig$1 adj5 disease)).mp. (107)
16 amyotrophic lateral sclerosis.tw. (14103)
17 or/13-16 (25458)
18 (pain relie$ or pain therap$ or pain medicat$ or pain treat$ or analgesic$ or antiinflammatory agent or nsaid).mp. (250127)
19 exp Nonsteroidal Antiinflammatory Agent/ (377454)
20 exp ANALGESICS/ (566574)
21 aspirin.mp. or ASPIRIN/ (141880)
22 salicylate.mp. or Salicylates/ (21118)
23 indomethacin.mp. or INDOMETHACIN/ (67661)
24 piroxicam.mp. or PIROXICAM/ (9910)
25 ketorolac.mp. or KETOROLAC/ (7060)
26 (tenoxicam or apazone or diclofenac or diflusinal or etodolac or fenoprofen or flurbiprofen or ibuprofen or ketoprofen or meclofenamate or nabumetone or naproxen or oxaprozin or phenylbutazone or sulindac or tolmetin or paracetamol or acetaminophen or APAP).mp. (127135)
27 exp NARCOTICS/ (183153)
28 (opioid$ or opiate$ or narcotic$).mp. (142383)
29 (morphinans or morphine or fentanyl or hydromorphone or oxycodone or pentazocine or methadone).mp. (137993)
30 codeine.mp. or CODEINE/ (16242)
31 (dihydrocodeine or dextromoramide or diamorphine or dextropropoxyphene or meptazinol or sufentanil or alfentanil or remifentanil or nalbuphine or dipipanone or pethidine or tramadol or buprenorphine).mp. (70147)
32 exp Antidepressive Agents, Tricyclic/ or (Tricyclic adj1 Antidepress$).mp. (87917)
33 (amitriptyline or desipramine or doxepine or clomipramine or levomepromazine or haloperidol or carbamazepine or gabapentin).mp. (139460)
34 exp Anesthesia Adjuvants/ (650940)
35 PAIN/pc, dt, th [Prevention and Control, Drug Therapy, Therapy] (43081)
36 or/18-35 (1247542)
37 12 and 17 and 36 (229)

Appendix 3. CINAHL (EBSCOhost) search strategy

Tuesday, July 03, 2012 3:46:07 AM

S40 S38 and S39 6

S39 EM 201004- 815525
S38 S18 and S23 and S37 27
S37 S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 102707
S36 (MH "Pain/DT/PC/TH") 20767
S35 (MH "Anesthesia Adjuvants+") 7068
S34 amitriptyline or desipramine or doxepine or clomipramine or levomepromazine or haloperidol or carbamazepine or gabapentin or (antidepressive N3 tricyclic) 4968
S33 (MH "Antidepressive Agents, Tricyclic+") 2160
S32 dihydrocodeine or dextromoramide or diamorphine or dextropropoxyphene or meptazinol or sufentanil or alfentanil or remifentanil or nalbuphine or dipipanone or pethidine or tramadol or buprenorphine 3833
S31 morphinans or morphine or fentanyl or hydromorphone or oxycodone or pentazocine or methadone 11517
S30 opioid* or opiate* or narcotic* or codeine 19239
S29 (MH "Narcotics+") 20079
S28 tenoxicam or apazone or diclofenac or diflusinal or etodolac or fenoprofen or flurbiprofen or ibuprofen or ketoprofen or meclofenamate or nabumetone or naproxen or oxaprozin or phenylbutazone or sulindac or tolmetin or paracetamol or acetaminophen or APAP 6036
S27 aspirin or salicylic N2 acid or salicylate* or indomethacin or piroxicam or ketorolac 10101
S26 (MH "Analgesics+") 26665
S25 (MH "Antiinflammatory Agents, Non-Steroidal+") 17595
S24 pain N3 relief or pain N3 therap* or pain N3 treat* or analgesic* or antiinflammatory N3 agent* or nsaid 64781
S23 S19 or S20 or S21 or S22 4769
S22 (Lou Gehrig* W5 syndrome*) or (Lou Gehrig* w5 disease*) 30
S21 amyotrophic lateral sclerosis 1951
S20 motor neuron disease or motor neurone disease or motoneuron* disease or motorneuron* disease 465
S19 (MH "Motor Neuron Diseases+") 4516
S18 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 544729
S17 ABAB design* 76
S16 TI random* or AB random* 110869
S15 (TI (cross?over or placebo* or control* or factorial or sham? or dummy)) or (AB (cross?over or placebo* or control* or factorial or sham? or dummy)) 229065
S14 (TI (clin* or intervention* or compar* or experiment* or preventive or therapeutic) or AB (clin* or intervention* or compar* or experiment* or preventive or therapeutic)) and (TI (trial*) or AB (trial*)) 77341
S13 (TI (meta?analys* or systematic review*)) or (AB (meta?analys* or systematic review*)) 22527
S12 (TI (single* or doubl* or tripl* or trebl*) or AB (single* or doubl* or tripl* or trebl*)) and (TI (blind* or mask*) or AB (blind* or mask*)) 18089
S11 PT ("clinical trial" or "systematic review") 102544
S10 (MH "Factorial Design") 823
S9 (MH "Concurrent Prospective Studies") or (MH "Prospective Studies") 180529
S8 (MH "Meta Analysis") 14237
S7 (MH "Solomon Four-Group Design") or (MH "Static Group Comparison") 30
S6 (MH "Quasi-Experimental Studies") 5465
S5 (MH "Placebos") 7589
S4 (MH "Double-Blind Studies") or (MH "Triple-Blind Studies") 24428
S3 (MH "Clinical Trials+") 143550
S2 (MH "Crossover Design") 9355
S1 (MH "Random Assignment") or (MH "Random Sample") or (MH "Simple Random Sample") or (MH "Stratified Random Sample") or (MH "Systematic Random Sample") 56940

Appendix 4. AMED (OvidSP) search strategy

Database: AMED (Allied and Complementary Medicine) <1985 to June 2012>
Search Strategy:
---
1 amyotrophic lateral sclerosis/ or motor neuron disease/ (256)
2 (moto$1 neuron$1 disease$1 or moto?neuron$1 disease).mp. (163)
3 ((Lou Gehrig$1 adj5 syndrome$1) or (Lou Gehrig$1 adj5 disease)).mp. (2)
4 Amyotrophic Lateral Sclerosis.mp. (245)
5 or/1-4 (383)
6 (pain relie$ or (pain adj2 treatment)).mp. (2378)
7 (nonsteroidal anti-inflammatory agent$ or nonsteroidal analgesic$ or anti-inflammatory agent$ or NSAID$ or aspirin or salicylate$ or indomethacin or piroxicam or ketorolac or tenoxicam or apazone or diclofenac or diflunisal or etodolac or fenoprofen or flurbiprofen

or ibuprofen or ketoprofen or meclofenamate or nabumetone or naproxen or oxaprozin or phenylbutazone or sulindac or tolmetin or paracetamol or acetaminophen or APAP).mp. (1021)
8 exp Antiinflammatory agents/ (1657)
9 Narcotics/ (173)
10 exp Morphine/ (242)
11 exp Analgesics/ (1219)
12 (opioid$ or opiate$ or narcotic$ or morphinans or morphine or fentanyl or hydromorphone or oxycodone or pentazocine or methadone or codeine or dihydrocodeine or dextromoramide or diamorphine or dextropropoxyphene or meptazinol or sufentanil or alfentanil or remifentanil or nalbuphine or dipipanone or pethidine or tramadol or buprenorphine).mp. (1776)
13 or/6-12 (6277)
14 Pain/ (9274)
15 exp Therapy/ (31202)
16 14 and 15 (2030)
17 Antidepressive agents/ (239)
18 (amitriptyline or desipramine or doxepine or clomipramine or levomepromazine or haloperidol or carbamazepine or gabapentin).mp. (238)
19 or/13,16-18 (8225)
20 5 and 19 (8)

Appendix 5. LILACS search strategy

(Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask $ OR Tw mascar$)) OR Mh placebos OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct animal AND NOT (Ct human and Ct animal))) [Words] [Words] and (moto$ neuron$ disease$ OR motoneuron$ disease$ OR Mh Motor Neuron Disease or MND OR Mh amyotrophic lateral sclerosis OR amyotroph$ OR ALS) [Words] [Words] and (pain relie$ OR pain therap $ OR pain medicat$ OR pain treat$ OR analgesic$ OR Mh analgesics OR anti-inflammatory agent$ OR NSAID OR aspirin OR salicylate OR indomethacin OR piroxicam OR ketorolac OR tenoxicam OR apazone OR diclofenac OR diflunisal OR etodolac OR fenoprofen OR flurbiprofen OR ibuprofen OR ketoprofen OR meclofenamate OR nabumetone OR naproxen OR oxaprozin OR phenylbutazone OR sulindac OR tolmetin OR paracetamol OR acetaminophen OR APAP OR opioid OR opiate OR narcotics OR morphinans OR morphine OR fentanyl OR hydromorphone OR oxycodone OR pentazocine OR methadone OR codeine OR dihydrocodeine OR dextromoramide OR diamorphine OR dextropropoxyphene OR meptazinol OR sufentanil OR alfentanil OR remifentanil OR nalbuphine OR dipipanone OR pethidine OR tramadol OR buprenorphine OR supportive pain medication OR tricyclic antidepressant OR amitriptyline OR desipramine OR doxepine OR clomipramine OR levomepromazine OR haloperidol OR carbamazepine OR gabapentin) [Words]

Appendix 6. CENTRAL search strategy

#1MeSH descriptor Motor Neuron Disease explode all trees
#2"motor neuron disease" OR "motor neurone disease" OR "motoneuron disease" OR "motorneuron disease" OR "amyotrophic lateral sclerosis"
#3(Gehrig* NEAR syndrome*)
#4(Gehrig* NEAR disease*)
#5(#1 OR #2 OR #3 OR #4)
#6pain NEAR/3 relie* or pain NEAR/3 treatment or analgesic* or nonsteroidal or antiinflammatory agent or nsaid
#7aspirin or salicylates or indomethacin or piroxicam or ketorolac
#8tenoxicam or apazone or diclofenac or diflusinal or etodolac or fenoprofen or flurbiprofen or ibuprofen or ketoprofen or meclofenamate or nabumetone or naproxen or oxaprozin or phenylbutazone or sulindac or tolmetin or paracetamol or acetaminophen or APAP
#9MeSH descriptor Narcotics explode all trees
#10narcotic* or opioid* or opiate* or codeine
#11dihydrocodeine or dextromoramide or diamorphine or dextropropoxyphene or meptazinol or sufentanil or alfentanil or remifentanil or nalbuphine or dipipanone or pethidine or tramadol or buprenorphine
#12MeSH descriptor Analgesics explode all trees
#13analgesics or "supportive pain medication"
#14antidepressive NEAR/3 tricyclic
#15amitriptyline or desipramine or doxepine or clomipramine or levomepromazine or haloperidol or carbamazepine or gabapentin
#16anesthesia NEAR/2
adjuvant
#17MeSH descriptor Adjuvants, Anesthesia explode all trees
#18MeSH descriptor Anti-Inflammatory Agents, Non-Steroidal explode all trees

#19MeSH descriptor Pain, this term only with qualifiers: DT,PC,TH
#20(#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21(#5 AND #20)

Appendix 7. ClinicalTrials.gov and WHO ICTRP

amyotrophic lateral sclerosis AND pain

WHAT'S NEW

Date	Event	Description
11 April 2013	New citation required but conclusions have not changed	Searches updated to 3 July 2012. No RCTs identified for inclusion.
11 April 2013	New search has been performed	Minor revisions to text. Search for ongoing studies completed.

HISTORY

Protocol first published: Issue 2, 2005
Review first published: Issue 3, 2008

Date	Event	Description
2 August 2010	New search has been performed	Searches updated to May 2010. No randomised controlled trials identified. Some additional non-randomised studies referenced in the Discussion.
13 April 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

JB wrote the first draft of the manuscript and dealt with peer review revisions. AL, JK and JDM commented on drafts and agreed the final version of the review.

DECLARATIONS OF INTEREST

JB, JK: none known

AL and his institution has received research and other support from various sources, as follows, but none related to this review. AL has received lecture or consulting fees, travel support or honoraria from Biogen Idec, Merz Pharma, Nutricia, Novartis, Thierry Latran Foundation, Stifterverband; board membership fees from Biogen Idec; and fees for expert testimony from Teva. His institution has grants or grants pending from Biogen Idec, GSK, Teva, Merz Pharma. Royalties have been paid to AL or his institution from Thieme Verlag, Cambridge University Press.

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

- None, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

'Risk of bias' methodology updated. For the current update, we included searches for ongoing trials. We also included a clarification that studies of treatments for cramps are not included in the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Amyotrophic Lateral Sclerosis [*complications]; Motor Neuron Disease [complications]; Pain [*drug therapy]

MeSH check words

Adult; Humans