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[Intervention Review]

Muscle relaxants for non-specific low-back pain

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ABSTRACT

Background

The use of muscle relaxants in the management of non-specific low back pain is controversial. It is not clear if they are effective, and concerns have been raised about the potential adverse effects involved.

Objectives

The aim of this review was to determine if muscle relaxants are effective in the treatment of non-specific low back pain.

Search methods

A computer-assisted search of the Cochrane Library (Issue 3, 2002), MEDLINE (1966 up to October 2002) and EMBASE (1988 up to October 2002) was carried out. These databases were searched using the algorithm recommended by the Cochrane Back Review Group. References cited in the identified articles and other relevant literature were screened.

Selection criteria

Randomised and/or double-blinded controlled trials, involving patients diagnosed with non-specific low back pain, treated with muscle relaxants as monotherapy or in combination with other therapeutic modalities, were included for review.

Data collection and analysis

Two authors independently carried out the methodological quality assessment and data extraction of the trials. The analysis comprised not only a quantitative analysis (statistical pooling) but also a qualitative analysis ("best evidence synthesis"). This involved the appraisal of the strength of evidence for various conclusions using a rating system based on the quality and outcomes of the studies included. Evidence was classified as "strong", "moderate", "limited", "conflicting" or "no" evidence.

Main results

Thirty trials met the inclusion criteria. Twenty-three trials (77%) were of high quality, 24 trials (80%) were on acute low back pain. Four trials studied benzodiazepines, 11 non-benzodiazepines and two antispasticity muscle relaxants in comparison with placebo. Results showed that there is strong evidence that any of these muscle relaxants are more effective than placebo for patients with acute LBP on short-term pain relief. The pooled RR for non-benzodiazepines versus placebo after two to four days was 0.80 [95% CI; 0.71 to 0.89] for pain relief and 0.49 [95% CI; 0.25 to 0.95] for global efficacy. Adverse events, however, with a relative risk of 1.50 [95% CI; 1.14 to 1.98] were significantly more prevalent in patients receiving muscle relaxants and especially the central nervous system adverse effects (RR 2.04; 95% CI; 1.23 to 3.37). The various muscle relaxants were found to be similar in performance.

Authors' conclusions

Muscle relaxants are effective in the management of non-specific low back pain, but the adverse effects require that they be used with caution. Trials are needed that evaluate if muscle relaxants are more effective than analgesics or non-steroidal anti-inflammatory drugs.

PLAIN LANGUAGE SUMMARY**Muscle relaxants for non-specific low-back pain**

Muscle relaxants are effective for short-term symptomatic relief in patients with acute and chronic low back pain. However, the incidence of drowsiness, dizziness and other side effects is high. Muscle relaxants must be used with caution and it must be left to the discretion of the physician to weigh the pros and cons and to determine whether or not a specific patient is a suitable candidate for a course of muscle relaxants. Large high quality trials are needed that directly compare muscle relaxants to analgesics or NSAIDs and future studies should focus on reducing the incidence and severity of side effects.

BACKGROUND

Muscle relaxants are one of the many treatments currently employed in the management of non-specific low back pain. Thirty-five percent of patients visiting a primary care physician for low back pain are prescribed muscle relaxants (Cherkin 1998). The term "muscle relaxants" is very broad and includes a wide range of drugs with different indications and mechanisms of action. Muscle relaxants can be divided into two main categories: antispasmodic and antispasticity medications.

Antispasmodics are used to decrease muscle spasm associated with painful conditions such as low back pain. Antispasmodics can be subclassified into benzodiazepines and non-benzodiazepines.

Benzodiazepines (e.g., diazepam, tetrazepam) are used as anxiolytics, sedatives, hypnotics, anticonvulsants, and/or skeletal muscle relaxants (Jackson 1993). In general, there is no evidence that any one benzodiazepine is more effective than another if adequate dosage is given; however, pharmacokinetic differences between the drugs may be important considerations in prescription choice.

Non-benzodiazepines include a variety of drugs that can act at the brain stem or spinal cord level (Jackson 1993). The mechanisms of action with the central nervous system are still not completely understood. Cyclobenzaprine is structurally similar to the tricyclic antidepressants; however, it has strong side effects such as sedation (Lofland 2001). It is currently believed that cyclobenzaprine acts in the brain stem rather than at the spinal cord level. Carisoprodol and metaxalone have moderate antispasmodic effects and are mildly sedative. Carisoprodol blocks interneuronal activity in the descending reticular formation and spinal cord. Carisoprodol is metabolized to meprobamate. Meprobamate was introduced as an anti-anxiety agent in 1955 and is prescribed primarily to treat anxiety, tension, and associated muscle spasms. Its onset and duration of action are similar to the intermediate-acting barbiturates; however, therapeutic doses of meprobamate produce less sedation and toxicity than barbiturates. Excessive use can result in psychological and physical dependence. Chlorzoxazone acts at the spinal cord and subcortical levels, inhibiting multisynaptic reflex arcs. The mechanism of action of methocarbamol in humans has not been established, but may be due to central nervous system depression. It has no direct action on the contractile mechanism of striated muscle, the motor end plate or the nerve fiber. Cyclobenzaprine and orphenadrine have anticholinergic activity (which is responsible for some side effects such as dry mouth). Tolperisone has a lidocaine-like activity and stabilizes nerve membranes. It blocks in a dose-dependent manner mono- and polysynaptic reflexes at the spinal level. Tolperisone is supposed to mediate muscle relaxation without concomitant sedation or withdrawal phenomena (Pratzel 1996). Some antispasmodic drugs (e.g. Tizanidine) have showed in animal studies that in addition to muscle relaxant and antinociceptive effect they have also gastroprotective effects which may favour the combination of antispasmodics with non-steroidal anti-inflammatory drugs (NSAIDs) (Sirdalud 1998).

Antispasticity medications are used to reduce spasticity that interferes with therapy or function, such as in cerebral palsy, multiple sclerosis and spinal cord injuries (Rosche 2002). The mechanism of action of the antispasticity drugs with the peripheral nervous system (e.g., dantrolene sodium) is the blockade of the

sarcoplasmic reticulum calcium channel. This reduces calcium concentration and diminishes actin-myosin interaction. Baclofen is a gamma-aminobutyric acid (GABA) derivative with central nervous system action. It inhibits transmission at spinal level and also depresses the central nervous system (Abbruzzese 2002).

The use of muscle relaxants for low back pain continues to be a source of controversy amongst physicians, mainly because of their side effects. In addition to sedation, potential adverse effects include drowsiness, headache, blurred vision, nausea and vomiting. Potential for abuse and dependency has also been reported (Elder 1991). The controversy is evident in the recommendations found in national clinical guidelines for the management of low back pain in primary care. Some guidelines recommend muscle relaxants alone or in combination with NSAIDs as optional, others clearly do not recommended using them (Koes 2001). Despite this, 91 per cent of physicians report using muscle relaxants even if they are conditionally discouraged by guidelines (Di Iorio 2000).

The role of muscle spasm in the pathophysiology of low back pain is also controversial. Low back pain is generally considered to be the result of a self-perpetuating cycle of pain and spasm. Some physicians have questioned this model and thus, the efficacy of muscle relaxants (Johnson 1989). Others view muscle spasm as a protective physiologic response that should not be inhibited by muscle relaxants (Littrell 1993). Muscle spasm secondary to a pathological lesion in the lumbosacral region (e.g. facet joints, discs, muscles or ligaments) will immobilize the back and therefore contribute to the healing process.

Controversies surrounding muscle relaxants have resulted in some resistance to their use in patient care. Studies have been published which suggest a potential role for muscle relaxants in clinical practice (Browning 2001); however, there is a lack of good quality research on the clinical application of these drugs (Van Tulder 1997a). This review aims to provide evidence on the efficacy and effectiveness of muscle relaxants in the management of non-specific low back pain.

OBJECTIVES

The aim of this systematic review was to determine if muscle relaxants are effective in the treatment of non-specific low back pain. The following comparisons were investigated:

- 1) Muscle relaxants vs. Placebo
- 2) Muscle relaxants vs. Paracetamol/Acetaminophen
- 3) Muscle relaxants vs. NSAIDs
- 4) Muscle relaxants vs. Muscle relaxants
- 5) Muscle relaxants + Analgesics/NSAIDs vs. Placebo + Analgesics/NSAIDs

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) and double-blind controlled clinical trials (CCTs) were included.

Types of participants

Only trials involving patients diagnosed with "non-specific low back pain" were included. Non-specific low back pain was defined as pain localised between the scapulae and inferior gluteal folds which may or may not radiate down towards the knees, for which specific etiologies such as infections, neoplasms, metastases, osteoporosis, fractures, rheumatological disorders, neurological disorders and other relevant pathological entities have been ruled out clinically.

Trials involving patients with various musculoskeletal disorders were included if results were presented separately for the subgroup of low back pain patients or if more than 50 per cent of the study population consisted of low back pain patients.

Types of interventions

The use of muscle relaxants as monotherapy or in combination with other therapeutic modalities were included. The muscle relaxants that are included in this review are: benzodiazepines (diazepam and tetrazepam), non-benzodiazepines antispasmodics (cyclobenzaprine, carisoprodol, chlorzoxazone, meprobamate, methocarbamol, metaxalone, orphenadrine, tizanidine and flupirtine), and antispasticity drugs (baclofen and dantrolene sodium). We excluded the muscle relaxant chlormezanone (Trancopal) from this review because this drug was discontinued worldwide in 1996 by its manufacturer, due to confirmed serious and rare cutaneous reactions (toxic epidermal necrolysis) associated with this drug (Roujeau 1995). We also excluded botulinum toxin, because it is not usually classified as a muscle relaxant.

Types of outcome measures

Trials using one or more of the following outcome measures were included:

- Pain intensity (e.g., visual analogue scale (VAS) or numerical rating scale (NRS)) at rest or during the day.
- Global measure (overall improvement, proportion of patients recovered) assessed by the patient
- Back pain specific functional status (e.g., Roland Disability Questionnaire, Oswestry Scale)
- Return to work (return to work status, number of days off work)
- Physiological outcomes (e.g., muscle spasm, range of motion, spinal flexibility, Lasegue test or muscle strength)
- Generic functional status (e.g., SF-36, Nottingham Health Profile, Sickness Impact Profile)

Search methods for identification of studies

A computer-assisted search of the Cochrane Library (Issue 3, 2002), MEDLINE (up to October 2002) and EMBASE (up to October 2002) was carried out. These databases were searched using the algorithm recommended in the Cochrane Collaboration Handbook (Dickersin 1994) and the Back Review Group. Pertinent references cited in the identified articles were also screened as well as references of other systematic reviews (Bigos 1994; Van Tulder 1997a; Browning 2001). A language restriction excluding studies not published in English, Dutch, German, Spanish or Portuguese was applied to the selection process, because the authors were not able to read and understand any other languages. If possible, studies

published in other languages will be included in a future update of this review. See [Appendix 1](#) and [Appendix 2](#).

Data collection and analysis

General procedure of the review

The review started with a literature search. Studies meeting the inclusion criteria were screened and analysed for methodological quality. This was followed by the extraction and analysis of the relevant data. The selection of studies, methodological quality assessment and data extraction were carried out by two independent authors. Twenty studies that were originally identified in MEDLINE, EMBASE and the Cochrane Library were independently assessed by one pair of authors (TT and MvT). Ten studies (Baptista 1988; Bianchi 1978; Bragstad 1979; Corts Giner 1989; Lepisto 1979; Pipino 1991; Pratzel 1996; Salzmann 1992; Sirdalud 1998; Weber 1980) were included at a later stage and were independently assessed by another pair of reviewers (MvT and SS; AF and SS). Results at each stage were compared and discrepancies were resolved in a consensus meeting.

Methodological quality assessment

The methodological quality of each RCT was assessed using the criteria recommended by the Cochrane Back Review Group (Van Tulder 1997b). The studies were not blinded for authors, institutions or the journals in which the studies were published. A pilot test was conducted using a trial on NSAIDs for back pain that is not included in the present systematic review. Only the criteria pertaining to internal validity were applied:

- 1) Adequate allocation concealment,
- 2) Adequate method of randomisation,
- 3) Similarity of baseline characteristics,
- 4) Blinding of patients,
- 5) Blinding of care provider,
- 6) Equal co-interventions,
- 7) Adequate compliance,
- 8) Identical timing of outcome assessment,
- 9) Blinded outcome assessment,
- 10) Withdrawals and drop outs adequate,
- 11) Intention-to-treat analysis.

All items were scored as positive (+), negative (-) or unclear (?). High quality was defined as fulfilling six or more of the 11 quality criteria. A sensitivity analysis in which the effect of variations in the cut-off point distinguishing studies of high and low methodological quality was conducted. We did not contact the authors for additional information because most studies had been published many years ago with only seven studies published in or after 1990.

Data extraction

The data extraction was carried out by the same authors who performed the quality assessment using a standardised data extraction sheet. The studies were not blinded for authors, institutions or journals in which the studies were published. A pilot test was conducted using a trial on NSAIDs for back pain that is not included in the present systematic review.

The following data were extracted from the studies:

1) Characteristics of the studies

The sponsors of the study and their contributions as well as authors affiliations.

2) Characteristics of study population

Data pertaining to the sample sizes, and gender and age of the patients in the samples. The diagnosis of the patients was also noted. A distinction was made between acute/subacute low back pain (duration of symptoms less than 12 weeks) and chronic low back pain (duration of symptoms 12 weeks or more). The presence or absence of sciatica and muscle spasms was also recorded.

3) Characteristics of interventions

The muscle relaxants investigated and the reference treatments to which they were compared were noted. Specifically, the type of muscle relaxant (benzodiazepine, non-benzodiazepine antispasmodics or antispasticity drug), the doses administered and the frequency and duration of the administration of the treatments was registered.

4) Characteristics of outcomes

The outcome parameters used in the various trials and the performance of the treatments as recorded on these parameters was extracted. The performance of the treatments were regarded positive (in favour of intervention) if the difference from the control group was statistically significant ($p < 0.05$). For pain outcomes, we considered pain at rest (first) and pain during the day (second). With regard to global improvement, if the authors reported both physician's and patient's opinion, we extracted only the patient's opinion. If they reported only the physician's assessment, then we used this data. We also assessed whether there was a clinically important difference of pain outcomes. (Farrar 2000; Farrar 2001) We considered a clinically important difference in VAS to be $>16\text{mm}$ or $>30\%$ decrease. For a 11-points NRS this was 2 points or more.

Data analysis

A qualitative analysis ("best evidence synthesis") was conducted using a rating system consisting of the following levels of evidence: Level 1 - strong evidence: generally consistent findings in multiple high quality trials

Level 2 - moderate evidence: generally consistent findings in multiple low quality trials and/or one high quality trial

Level 3a - limited evidence: only one low quality trial

Level 3b - conflicting evidence: inconsistent findings in multiple trials

Level 4 - no evidence: no RCTs and no double-blind trials

A quantitative or meta-analysis was conducted if studies provided sufficient data. The results were tabulated and formally tested for homogeneity. If data were statistically heterogeneous, reasons for heterogeneity were explored. Data were pooled using the random effects model. The results were plotted as relative risks (RR) with corresponding 95% confidence intervals (95% CI). All RRs were calculated so that a RR smaller than 1 indicated a positive effect of muscle relaxants. For example, a RR of 0.74 (95%CI 0.55 to 0.98) means that the chance of "not getting pain relief" is 26% less in the muscle relaxants group compared to the placebo group, with a confidence interval of 2% to 45%. The data entered in the meta-analyses were adverse outcomes, that is: number of patients with "no pain relief", "no global improvement", "no improvement in muscle spasms", etc. The analyses were performed separately for drug types (benzodiazepines, non-benzodiazepines and antispasticity drugs), for various outcome measures and for various follow-up moments.

Subgroup analyses were planned for the following combinations:

- a) Low back pain with and without sciatica or muscle spasms
- b) Different doses of muscle relaxants
- c) Ambulant versus bed rest patients
- d) Injection versus oral therapy

RESULTS

Description of studies

Results of the literature search and selection

The computer-assisted literature search produced a yield of seven references in the Cochrane Library, 25 in Medline and 25 in Embase. Taking into account 11 articles that were cross-referenced in the three databases, a net total of 46 articles were found to be potentially eligible. Further assessment of the articles and application of the in- and exclusion criteria resulted in 22 articles. Eight additional studies were identified through reference checking (Baptista 1988; Bianchi 1978; Bragstad 1979; Corts Giner 1989; Lepisto 1979; Pipino 1991; Salzmann 1992; Sirdalud 1998), resulting in a total of 30 studies.

Not all studies included in the systematic review of cyclobenzaprine for back pain (Browning 2001) were included in the present review, because some of them had included a mixed population of patients with various musculoskeletal disorders. We only included studies if results were presented separately for low back pain patients or if more than 50% of the study population consisted of low back pain patients (see Table "Characteristics of excluded studies").

The following studies were identified in the comparisons investigated (some studies included more than one comparison, so the total is more than 30):

1) Muscle relaxants vs. placebo

1a) Benzodiazepines vs. placebo (4 studies: Arbus 1990; Basmajian 1978; Moll 1973; Salzmann 1992)

1b) Non-benzodiazepines vs. placebo (11 studies: Baptista 1988; Barrata 1982; Basmajian 1978; Berry 1988a; Bianchi 1978; Gold 1978; Hindle 1972; Klinger 1988; Lepisto 1979; Pratzel 1996; Worz 1996)

1c) Antispasticity vs. placebo (2 studies: Casale 1988; Dapas 1983)

2) Muscle relaxants vs. paracetamol/Acetaminophen (no studies)

3) Muscle relaxants vs. NSAIDs (no studies)

4) Muscle relaxants vs. muscle relaxants (8 studies: Baptista 1988; Basmajian 1978; Boyles 1983; Bragstad 1979; Hennies 1981; Hindle 1972; Pipino 1991; Rollings 1983)

5) Muscle relaxants + analgesics/NSAIDs vs. placebo + analgesics/NSAIDs (6 studies: Berry 1988b; Borenstein 1990; Corts Giner 1989; Hingorani 1966; Sirdalud 1998; Tervo 1976)

Other comparisons

Other studies compared ethoheptazine plus meprobamate plus aspirin vs. NSAID (mefenamic acid) (Sweetman 1987), orphenadrine vs. phenobarbital (Gold 1978), orphenadrine plus paracetamol vs. aspirin (Hingorani 1971), and diazepam plus paracetamol - codeine vs. levomepromazine plus paracetamol - codeine (Weber 1980). These studies are summarized in the table with "characteristics of included studies", but not included in the results section because they could not be classified in one of the predefined comparisons.

Study characteristics

Twenty-two studies declared at least one relationship with the pharmaceutical industry. These relationships varied from authors affiliated with the pharmaceutical industry, drugs supplied by the industry, support received (in terms of statistical evaluations, medical, scientific and editorial assistance) and explicitly declaration that the study was conducted with grants from the pharmaceutical industry or was directly conducted by them. In eight studies there was nothing declared with regards to any relationship with the pharmaceutical industry, but in some studies they used the pre-commercial name of the muscle relaxant drug, such as DS 103 - 282 for tizanidine.

Sample characteristics

Data on sample size, age and gender, type and duration of symptoms, and setting are summarized in the table with "characteristics of included studies". Twenty-four studies included patients with acute LBP and six studies chronic LBP (Arbus 1990; Basmajian 1978; Pipino 1991; Pratzel 1996; Salzmänn 1992; Worz 1996). No studies specifically reported on patients with sciatica. Fourteen studies explicitly stated that the population to be treated had to be diagnosed with muscle spasms. However, the accuracy of this diagnosis was not discussed in any of these studies.

Interventions

Eight studies were identified which included benzodiazepines (Arbus 1990; Basmajian 1978; Boyles 1983; Hennies 1981; Hingorani

1966; Moll 1973; Salzmänn 1992; Weber 1980); 23 studies non-benzodiazepines (Baptista 1988; Barrata 1982; Basmajian 1978; Berry 1988a; Berry 1988b; Bianchi 1978; Borenstein 1990; Boyles 1983; Bragstad 1979; Corts Giner 1989; Gold 1978; Hennies 1981; Hindle 1972; Hingorani 1971; Klinger 1988; Lepisto 1979; Pipino 1991; Pratzel 1996; Rollings 1983; Sirdalud 1998; Sweetman 1987; Tervo 1976; Worz 1996); and 2 studies antispasticity drugs (Casale 1988; Dapas 1983).

Five studies made use of injection therapy. In one of these studies the efficacy of a single intravenous injection was evaluated (Klinger 1988), while in the other four studies an intramuscular injection was followed by oral medication (Hingorani 1966; Moll 1973; Pipino 1991; Tervo 1976).

Risk of bias in included studies

The median score for methodological quality of all the included studies was 6 with a range of 3-9. Using a cut-off point of 6 out of 11 criteria, 23 of the 30 studies (77%) were of high quality (Arbus 1990; Baptista 1988; Barrata 1982; Berry 1988a; Berry 1988b; Bianchi 1978; Boyles 1983; Bragstad 1979; Casale 1988; Corts Giner 1989; Dapas 1983; Hennies 1981; Hindle 1972; Hingorani 1966; Hingorani 1971; Klinger 1988; Lepisto 1979; Pratzel 1996; Rollings 1983; Salzmänn 1992; Sirdalud 1998; Tervo 1976; Worz 1996). See Figure 1.

Figure 1. Summary of risks of bias

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias): All outcomes - patients?	Blinding (performance bias and detection bias): All outcomes - providers?	Blinding (performance bias and detection bias): All outcomes - outcome assessors?	Incomplete outcome data (attrition bias): All outcomes - drop-outs?	Incomplete outcome data (attrition bias): All outcomes - ITT analysis?	Similarity of baseline characteristics?	Co-interventions avoided or similar?	Compliance acceptable?	Timing outcome assessments similar?
Arbus 1990	?	-	+	+	+	+	+	-	?	?	+
Baptista 1988	-	?	+	+	+	+	+	?	-	-	+
Barrata 1982	+	-	+	+	+	+	-	+	-	-	-
Basmajian 1978	?	-	+	+	+	-	-	-	-	-	+
Berry 1988a	?	-	+	+	+	+	+	+	?	?	+
Berry 1988b	?	-	+	+	+	+	+	+	?	-	+
Bianchi 1978	+	?	+	+	+	-	?	+	?	?	+
Borenstein 1990	?	-	-	-	-	+	+	-	?	?	+
Boyles 1983	+	-	+	+	+	+	-	+	+	?	+
Bragstad 1979	?	?	+	+	+	+	-	+	+	-	+
Casale 1988	?	+	+	+	+	+	+	+	+	-	+
Corts Giner 1989	-	?	+	+	+	+	+	+	-	-	+
Dapas 1983	?	-	+	+	+	-	-	+	+	+	+
Gold 1978	?	-	+	+	+	-	-	-	-	-	+
Hennies 1981	?	?	+	+	+	+	-	+	+	-	+

Figure 1. (Continued)

Hennies 1981	?	?	+	+	+	+	-	+	+	-	+
Hindle 1972	+	+	+	+	+	+	-	-	-	-	+
Hingorani 1966	?	-	+	+	+	+	+	-	-	-	+
Hingorani 1971	-	?	+	+	+	+	+	-	-	-	+
Klinger 1988	?	-	+	+	+	+	?	-	+	+	+
Lepisto 1979	?	?	+	+	+	+	+	+	+	?	+
Moll 1973	?	-	+	+	+	+	-	-	-	-	+
Pipino 1991	?	?	-	?	?	+	+	+	+	-	+
Pratzel 1996	?	-	+	+	+	-	-	+	+	+	+
Rollings 1983	+	-	+	+	+	-	-	+	+	+	+
Salzmann 1992	?	?	+	+	+	-	?	?	+	+	+
Sirdalud 1998	?	?	+	+	+	?	-	+	+	?	+
Sweetman 1987	?	-	+	+	+	-	-	+	-	-	+
Tervo 1976	+	-	+	+	+	+	-	+	-	-	-
Weber 1980	-	?	+	+	+	-	-	?	?	-	?
Worz 1996	?	-	+	+	+	+	+	-	-	-	+

The most common methodological shortcomings in the studies involved (in order of frequency):

- Inadequate concealment of the drug allocation procedures (93% scored 'negative' or 'unclear')
- Failing to evaluate compliance (83% scored 'negative' or 'unclear')
- Inadequate method of randomisation (80% scored 'negative' or 'unclear')
- Non-equivalent co-interventions (60% scored 'negative' or 'unclear')
- Failing to apply intention-to-treat analysis (60% scored 'negative' or 'unclear')
- Dissimilarity of the baseline characteristics (47% scored 'negative' or 'unclear')
- Inadequate dropouts (33% scored 'negative' or 'unclear')

Almost all studies had identical timing of outcome measures (90%) and had adequately blinded patients (93%), outcome assessments (93%) and care provider (93%).

Comparison of the scores by the authors for each study demonstrated a author concurrence rate of 73%. The disagreement in 27% of the scores could be attributed to subtle differences in interpretation of the criteria. This was reflected in the systematic nature of the discrepancies in scoring. Random errors in reading of the articles and recording of the assessments, as well as ambiguities in the presentation of information in the articles also

played a role. All disagreements were resolved in a consensus meeting.

Effects of interventions

1a) Benzodiazepines vs. placebo

Four studies were identified, one on acute LBP (Moll 1973) and three on chronic LBP (Arbus 1990; Basmajian 1978; Salzmann 1992).

Acute LBP

The one low quality trial on acute LBP showed that there is limited evidence (1 trial; 50 people) that an intramuscular injection of diazepam followed by oral diazepam for 5 days is more effective than placebo for patients with acute LBP on short-term pain relief and better overall improvement, but is associated with substantially more central nervous system side effects (Moll 1973).

Chronic LBP

The two high quality trials on chronic LBP (Arbus 1990; Salzmann 1992) showed that there is strong evidence (2 trials; 222 people) that tetrazepam 50 mg t.i.d. is more effective than placebo for patients with chronic LBP on short-term pain relief and overall improvement. The pooled RRs and 95% CIs for pain intensity were 0.82 (0.72 to 0.94) after 5-7 days follow-up and 0.71 (0.54 to 0.93) after 10-14 days. The pooled RR and 95% CI for overall improvement was 0.63 (0.42 to 0.97) after 10-14 days follow-up. One high quality trial (Arbus 1990) showed that there is moderate evidence (1 trial; 50 people) that tetrazepam is more effective than placebo on short-

term decrease of muscle spasm. One low quality trial showed that there is limited evidence (1 trial; 76 people) that there is no difference between diazepam and placebo on short-term decrease of muscle spasm (Basmajian 1978).

1b) Non-benzodiazepines vs. placebo

Eleven studies were identified, eight on acute LBP (Baptista 1988; Barrata 1982; Berry 1988a; Bianchi 1978; Gold 1978; Hindle 1972; Klinger 1988; Lepisto 1979) and three on chronic LBP (Basmajian 1978; Pratzel 1996; Worz 1996).

Acute LBP

One high quality study on acute LBP (Klinger 1988) showed that there is moderate evidence (1 trial; 80 people) that a single intravenous injection of 60 mg orphenadrine is more effective than placebo in immediate relief of pain and muscle spasm for patients with acute LBP.

Three high quality (Barrata 1982; Berry 1988a; Lepisto 1979) and one low quality trial (Gold 1978) showed that there is strong evidence (4 trials; 294 people) that oral non-benzodiazepines are more effective than placebo for patients with acute LBP on short-term pain relief, global efficacy and improvement of physical outcomes. The pooled RR and 95% CIs for pain intensity was 0.80 (0.71 to 0.89) after 2-4 days (4 trials; 294 people) and 0.58 (0.45 to 0.76) after 5-7 days follow-up (3 trials; 244 people). The pooled RR and 95% CIs for global efficacy was 0.49 (0.25 to 0.95) after 2-4 days (4 trials; 222 people) and 0.68 (0.41 to 1.13) after 5-7 days follow-up (4 trials; 323 people). The pooled RR and 95% CIs for physical outcomes was 0.76 (0.66 to 0.88) after 2-4 days (3 trials; 252 people) and 0.55 (0.40 to 0.77) after 5-7 days follow-up (3 trials; 251 people).

Of the three high quality trials (Baptista 1988; Bianchi 1978; Hindle 1972) that could not be included in the statistical pooling due to insufficient data, one large trial (267 people) reported no differences after 3 and 7 days in pain relief and global efficacy between tizanidine and placebo (Baptista 1988). Two small trials (48 people each) reported that oral non-benzodiazepines are more effective than placebo regarding pain intensity, global efficacy and muscle spasm after 7 and 14 days (Bianchi 1978) and on pain intensity after 4 days (Hindle 1972). However, in the last trial groups were not similar at baseline which may have biased the results.

Strong evidence from all eight trials on acute LBP (724 people) showed that muscle relaxants are associated with more total adverse effects and central nervous system adverse effects than placebo, but not with more gastrointestinal adverse effects; RRs and 95% CIs were 1.50 (1.14 to 1.98), 2.04 (1.23 to 3.37) and 0.95 (0.29 to 3.19), respectively. The most commonly and consistently reported adverse events involving the central nervous system were drowsiness and dizziness. For the gastrointestinal tract this was nausea. The incidence of other adverse events associated with muscle relaxants was negligible.

Chronic LBP

One high quality trial (Worz 1996) showed that there is moderate evidence (1 trial; 107 people) that flupirtin is more effective than placebo for patients with chronic LBP on short-term pain relief and overall improvement after 7 days, but not on reduction of muscle spasm. One high quality trial (Pratzel 1996) showed that there is moderate evidence (1 trial; 112 people) that tolperisone

is more effective than placebo for patients with chronic LBP on short-term overall improvement after 21 days, but not on pain relief and reduction of muscle spasm. The low quality trial (Basmajian 1978) showed that there is limited evidence (1 trial; 76 people) that there is no difference on short-term reduction of muscle spasm after 18 days between cyclobenzaprine and placebo for patients with chronic LBP. The two high quality trials did not show a difference in side effects.

1c) Antispasticity drugs vs. placebo

Acute LBP

Two high quality trials (Casale 1988; Dapas 1983) showed that there is strong evidence (2 trials; 220 people) that antispasticity muscle relaxants are more effective than placebo for patients with acute LBP on short-term pain relief and reduction of muscle spasm after 4 days. One high quality trial (Dapas 1983) also showed that there is moderate evidence that antispasticity muscle relaxants are more effective than placebo for patients with acute LBP on short-term pain relief, reduction of muscle spasm, and overall improvement after 10 days.

2) Muscle relaxants vs. paracetamol/acetaminophen

No RCTs or double-blind trials were identified.

3) Muscle relaxants vs. NSAIDs

No RCTs or double-blind trials were identified.

4) Muscle relaxants vs. muscle relaxants

Eight studies were identified, 5 high quality (Boyles 1983; Bragstad 1979; Hennies 1981; Hindle 1972; Rollings 1983) and three low quality trials (Baptista 1988; Basmajian 1978; Pipino 1991).

Carisoprodol

This muscle relaxant was investigated in two high quality studies on acute low back pain. The first study compared carisoprodol with diazepam (Boyles 1983). Carisoprodol was superior in performance on all the outcome parameters measured. Comparison of carisoprodol with cyclobenzaprine-hydrochloride in the second study revealed no statistically significant differences between the two treatments (Rollings 1983).

Chlorzoxazone

This muscle relaxant was compared with tizanidine in one high quality study in a very small sample of patients (27 people) with degenerative lumbar disc disease (Bragstad 1979). No differences were found between the treatments.

Cyclobenzaprine-hydrochloride

Cyclobenzaprine was compared with diazepam in a low quality trial on chronic low back pain, but no significant differences between the treatments were identified (Basmajian 1978). There was also no significant difference between cyclobenzaprine and carisoprodol in one high quality study on acute low back pain (Rollings 1983).

Diazepam

In comparison with carisoprodol, diazepam was found to be inferior in performance on muscle spasm, global efficacy and functional status in a high quality trial on acute low back pain (Boyles 1983). In a very small high quality trial (30 people) comparing diazepam with

tizanidine there were no differences in pain, functional status and muscle spasm after seven days (Hennies 1981).

Tizanidine

This muscle relaxant was compared with chlorzoxazone and diazepam in two very small high quality trials (Bragstad 1979; Hennies 1981). Both trials did not find any differences in pain, functional status and muscle spasm after 7 days.

Pridinol mesilate

One low quality trial showed no differences between this muscle relaxant and thiocolchicoside on pain relief and global efficacy (Pipino 1991).

5) Muscle relaxants + analgesics/NSAIDs vs. placebo + analgesics/NSAIDs

Six studies were identified on acute LBP, five high quality (Berry 1988b; Corts Giner 1989; Hingorani 1966; Sirdalud 1998; Tervo 1976) and one low quality trial (Borenstein 1990). Five trials evaluated non-benzodiazepines and only one trial benzodiazepines (Hingorani 1966).

Acute LBP

Three high quality trials showed that there is strong evidence (3 trials; 560 people) that tizanidine plus analgesics (Corts Giner 1989) or NSAIDs (Berry 1988b; Sirdalud 1998) is more effective than placebo plus analgesics or NSAIDs for patients with acute LBP on short-term pain relief and decrease of muscle spasm after 3-4 and 7-8 days. The other high quality trial showed no difference on global efficacy, but the orphenadrine plus paracetamol group had statistically significantly fewer disability days than the placebo plus paracetamol group (Tervo 1976). The low quality trial showed statistically significantly greater decrease of muscle spasm for cyclobenzaprine plus NSAIDs after 14 days, but no differences on pain intensity and global efficacy (Borenstein 1990). Data on adverse events from four studies (556 people) were pooled (Berry 1988b; Borenstein 1990; Sirdalud 1998; Tervo 1976). Using the random effects model the RR and 95% CI was 1.34 [95%CI 0.67 to 2.67] indicating that there was no statistically significant difference in total adverse effects. However, the RRs and 95% CIs for central nervous system and gastrointestinal adverse effects were 2.44 (1.05 to 5.63) and 0.54 (0.26 to 1.14), respectively, showing that combination therapy was responsible for significantly more central nervous system adverse effects.

One high quality trial showed no differences on subjective and objective outcomes between a benzodiazepine (diazepam) plus calcium aspirin versus placebo plus calcium aspirin (Hingorani 1966).

Pre-planned subgroup analyses

a) Low back pain with and without sciatica and muscle spasms

No trials specifically addressed sciatica. We could not perform a sub-group analysis of the studies in which muscle spasms were identified because the accuracy of these measurements is not described and because we cannot assume that the trials that didn't mention muscle spasm reflect in reality patients without muscle spasm.

b) Different doses of muscle relaxants

Various muscle relaxants were investigated in multiple studies, but the studies either included the same doses (for example, all studies evaluating cyclobenzaprine used a dose of 10 mg t.i.d.) or were found to be too heterogeneous in terms of control interventions and outcome parameters to be able to make any comparisons.

c) Ambulant patients versus bed rest patients

Two high quality studies involved patients prescribed bed rest. One study compared an antispasticity muscle relaxant (baclofen) with placebo and incorporated bed rest in the therapeutic regimen (Dapas 1983). In comparison with placebo there was significant relief of pain and improvement in terms of global efficacy. Relief of spasm did not reach statistical significance. The second study investigated a benzodiazepine (diazepam) plus calcium aspirin versus placebo plus calcium aspirin and involved patients treated with complete bed rest (Hingorani 1966). No difference was found between the two treatments in this trial.

d) Injection therapy

Five studies made use of injection therapy, of which four evaluated an intramuscular injection followed by oral medication compared with placebo or another muscle relaxant. No trial compared injection with oral medication.

The first high quality study made use of an initial course of diazepam therapy administered intramuscularly at a dose of 10mg every six hours for 24 hours (Hingorani 1966). This was followed by a course of oral therapy plus calcium aspirin. No differences were found between the diazepam and placebo groups at the end of the trial, and the effect of the injection therapy was not clear.

The second high quality study found shorter duration of disability with 60mg of orphenadrine administered intramuscularly followed by oral tablets plus paracetamol compared with placebo. There was no difference in global efficacy. Drop-out rate in this trial was high (Tervo 1976).

One high quality study using 60mg of orphenadrine administered intravenously compared to placebo found significant relief of pain and spasm 45 minutes after one single injection (Klinger 1988).

One low quality trial showed a better therapeutic effect with intramuscular diazepam followed by oral tablets compared with placebo, but groups were different at baseline (Moll 1973).

The other low quality trial showed no differences between pridinol mesilate and thiocolchicoside intramuscular followed by oral tablets (Pipino 1991).

Sensitivity analysis

A best case analysis was carried out in which internal validity criteria that were scored as unclear ("?") were scored as positive. This obviously increased the number of high quality studies and resulted in only two studies still being considered low quality (Basmajian 1978; Gold 1978). This procedure changed the results of benzodiazepines versus placebo for acute LBP from limited to moderate evidence, but had no consequences for any of the other results.

Lowering the threshold distinguishing higher and lower quality studies from 6 out of 11 criteria to 5 out of 11 criteria changed

three studies from low to high quality (Moll 1973; Pipino 1991; Sweetman 1987). This produced the same consequences described in the paragraph above, changing the results of benzodiazepines versus placebo for acute LBP from limited to moderate evidence.

Raising the threshold from 6 out of 11 to 7 out of 11 criteria consequently decreased the number of high quality studies; 10 trials with quality score of 6 were considered low quality in this sensitivity analysis. The evidence on pain relief and global efficacy for tetrazepam vs. placebo for chronic LBP changed from strong to moderate, and the moderate evidence on muscle spasm to limited. The evidence that flupirtin is more effective than placebo for patients with chronic LBP changed from moderate to limited. There were no other implications on results.

DISCUSSION

Literature search and selection

The results of this review must be interpreted against several potential sources of bias involving the literature search and selection process. A language restriction was applied to the selection process in which studies not published in English, Dutch, German, Spanish or Portuguese were not admitted for further review. Although we acknowledge that systematic reviews should aim at inclusion of all relevant trials, independent of language, identifying trials published in any language is difficult, time consuming and costly. We will attempt to include other language trials in a future update of this review. In addition, no efforts were undertaken to track down and include the results of unpublished studies. It was noted that no studies were identified which demonstrated negative results for muscle relaxants. This suggests the possibility of publication bias. It has been demonstrated that medication trials with positive outcomes are more likely to be published (Gotzsche 1987).

Methodological quality analysis

Using a cut-off point of 6/11 criteria, 77% of the included studies were found to be of high quality. A large proportion of these high quality studies fulfilled six criteria indicating that there is still room for improvement in the quality of execution and reporting of trials involving muscle relaxants. The most common methodological flaws involved the concealment of treatment allocation, compliance and randomisation procedure, which were only adequate in 2, 4 and 6 of the 30 trials, respectively. Most authors failed to explicitly specify the method or person responsible for concealing the treatment allocation and did not evaluate compliance or failed to explicitly report compliance data. Taking into account the type of side effects associated with muscle relaxants and the fact that the majority of the studies involved patients treated outside the controlled environment of a secondary care setting (i.e. outpatient or primary care setting), more attention should have been devoted to compliance. Compliance gives an indication of the tolerability and acceptability of these drugs to patients. In many studies, authors merely stated that the trial was "randomised", which does not give the reader confidence that a trial has been properly randomised or that the randomisation procedure was adequate. Finally in 13 of the 30 studies (43%) the baseline status of the patients in the various trial arms was found not to be similar. Very often this was the result of authors failing to report information on relevant prognostic factors which must be equally divided between study groups to prevent bias. This

was also true of co-interventions. In 18 of the 30 trials (60%) co-interventions were either not avoided or not equally distributed between study groups making it difficult to assess the significance of the trial outcomes. To reduce the impact of these methodological deficiencies on the quality of the review, the authors of the various trials could have been contacted to request missing information and data. This however seemed futile, as many of the studies were over a decade old, rendering the possibility of locating the authors and receiving the desired information unlikely.

Performance of muscle relaxants versus placebo

The results demonstrate strong evidence for significant symptomatic relief and overall improvement within a week of therapy for non-benzodiazepines for acute LBP. Regarding benzodiazepines, there was strong evidence for short-term pain relief and overall improvement with tetrazepam for chronic LBP. However, tetrazepam is only available in some European countries and in Mexico. Also, the evidence for benzodiazepines comes from less trials than for non-benzodiazepines. The evidence of benzodiazepines for acute and non-benzodiazepines for chronic LBP is less convincing.

The results of the review indicate that muscle relaxants could be of benefit to patients, reducing the duration of their discomfort and accelerating recovery. These findings are consistent with the results of a systematic review on cyclobenzaprine for back pain (Browning 2001) which showed that cyclobenzaprine is more effective than placebo at the price of greater adverse effects. An exception was dantrolene sodium, one of the antispasticity muscle relaxants identified in the review (Casale 1988). In comparison with placebo, this drug demonstrated more significant relief of pain and spasm with no side effects at the dose used. The study by Casale involved a very small sample size ($n = 20$), rendering the applicability of the results uncertain. Although dantrolene circumvents the central nervous system and thus avoids the characteristic side effects, it is associated with severe hepatotoxicity and muscular weakness (Van der Kuy 1997).

Although a positive treatment effect was found for antispasticity muscle relaxants for acute LBP the clinical relevance of this finding for the low back pain population is questionable as these medications are typically prescribed for neurological disorders such as cerebral palsy, multiple sclerosis and spinal cord injuries.

Performance of muscle relaxants versus muscle relaxants

The results of the analysis of the various muscle relaxants identified in this review showed that one high quality study found carisoprodol to be superior to diazepam. None of the other muscle relaxants was superior to another. They were all similar in performance adhering to the characteristic pattern of good efficacy and limited tolerability.

Muscle relaxants as adjunctive therapy

It has been suggested in the literature that muscle relaxants in practice could be more useful as an adjunct to other therapeutic modalities, specifically analgesics/NSAIDs (Elenbaas 1980). This was confirmed in this review. There was strong evidence that combination with analgesics or NSAIDs improved and accelerated recovery, but at the cost of increased central nervous system adverse effects.

Adverse effects

The results indicate that muscle relaxants are associated with adverse events. Central nervous system events were more prevalent in patients on muscle relaxants with the most common complaints being drowsiness and dizziness. These effects were consistently reported with all benzodiazepines and non-benzodiazepines reviewed. The incidence of other central nervous system events was negligible. For the gastrointestinal events, the difference with placebo was not significant with the most common complaint being nausea. These adverse effects, especially those involving the central nervous system adverse effects, indicate that muscle relaxants must be used with caution. These findings concur with the recommendations on use of muscle relaxants in the management of low back pain as cited in the UK, American and Dutch guidelines (Bigos 1994; Faas 1996; Waddell 1996) and other guidelines (Koes 2001). Although conclusions cannot be made about this risk of dependency from the trials included in this review, there is sufficient indirect evidence from other sources that a substantial risk of dependency can develop when using muscle relaxants. Health care professionals should be reluctant in prescribing muscle relaxants, particularly in patients who are prone to addiction.

Chlorzoxazone is implicated to serious (including fatal) hepatocellular toxicity, however this is a rare event. Another drug, chlormezanone has been implicated in the genesis of Stevens-Johnson syndrome and toxic epidermal necrolysis. Rare side effects are rarely seen in clinical trials with small sample sizes. A case-control study compared 245 people who were hospitalised because of these conditions and 1147 patients hospitalised for other reasons. Data was obtained through surveillance networks in France, Germany, Italy and Portugal. Among the 245 cases, 13 (5%) used chlormezanone 1 to 21 days before the index day, while only one among the control group used this drug. Based on the findings in this study, chlormezanone was discontinued in 1996 world-wide (Roujeau 1995).

Minimally clinical important difference

When evaluating the effectiveness of a treatment intervention, statistical significance is a necessary but insufficient criterion (Farrar 2000; Farrar 2001). The issue of clinical importance must also be considered, a concept that adds to the challenge of interpreting results of trials to guide patient care (Farrar 2000; Beaton 2002). But what constitutes a clinically importance change or difference in scores in an outcome of interest? For outcomes such as survival, death or hospitalization, the answer may be clear, but for subjective outcomes such as pain, clinical importance is often difficult to determine (Farrar 2000; Farrar 2001; Testa 2000).

The concept termed minimally clinical importance difference (MCID) has varying definitions. They all contain the common idea of being the smallest change or difference in scores that has been defined in some way as being important (Beaton 2002). Among other things, the determination of a MCID is dependent on the nature of scores compared (e.g. within or between group), population (e.g. acute or chronic LBP), intervention (e.g. muscle relaxants versus placebo or versus active treatments), and who's perspective of importance is taken into consideration (e.g. patient or clinician). Attempts to ascertain MCID values for pain intensity in the LBP population revealed a paucity of literature. Although not necessarily generalizable to the population of the current review,

Farrar (Farrar 2000) suggests that a two point or 30% reduction on an 11-point pain intensity rating scale relates to clinical importance for individuals with chronic pain and Gallagher (Gallagher 2002) found the MCID for acute abdominal pain to be 16mm on a pain intensity visual analogue scale (95% CI, 13-18mm). Because of the heterogeneity of how data were reported, differences in scales used, lack of relevant criteria for MCID in the low back pain population and specifically in acute low back pain, we were not able to include the MCID in our results. In the trials we reviewed, most studies reported pain outcome data as a summary statistic for each group (i.e., mean scores). If the differences in the scores had been large, the clinical importance may have been more obvious but because the changes were often small, it was difficult to determine what should be considered clinically important. This has to do in part with the nature of a mean score when considering whether to apply the results to an individual patient (Farrar 2000; Gallagher 2002); for example, if a mean change of 10 mm in pain on a VAS in a population is required before the treatment can be considered to produce an important effect, it does not imply that the same change of 10 mm is clinically important for an individual, (Testa 2000). Thus, to facilitate more easily understandable clinical importance of results of efficacy trials, we suggest future trials incorporate the recommendation of Farrar (Farrar 2000) that investigators report the proportion of subjects who observe a clinically important improvement in the groups being compared.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review illustrate strong evidence that non-benzodiazepines are effective for acute LBP. The evidence on benzodiazepines for acute and non-benzodiazepines for chronic LBP is less convincing. It is unknown if muscle relaxants are more effective than analgesics or NSAIDs, because there are no trials that directly compared these drugs. Muscle relaxants must be used with caution. The mechanism by which they induce their beneficial effects is also responsible for the intractable side effects associated with the central nervous system (drowsiness, dizziness). Furthermore, the risk of long-term dependence of muscle relaxants is substantial. Other systematic reviews have shown that analgesics and NSAIDs are also effective for acute LBP without having a high risk of dependency. Clinical guidelines have therefore recommended not using muscle relaxants for acute LBP or using them only for a selection of patients that do not respond to analgesics or NSAIDs. It must be left to the discretion of the physician to weigh the pros and cons, taking into account the needs and preferences of the individual patient, to determine whether or not a specific patient is a suitable candidate for a course of muscle relaxants.

Implications for research

Large high quality trials are needed that directly compare muscle relaxants to analgesics or NSAIDs. Another area of interest is the use of peripherally acting muscle relaxants for low back pain. These agents could potentially induce the same beneficial effects as those that act through the central nervous system, but without the associated side effects. Future studies should focus on reducing the incidence and severity of side effects.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Arbus 1990

Methods	Randomised, placebo-controlled, double-blind trial. Sponsored by Sanofi.
Participants	N = 50 Male/Female (%): ? Age: 18-80 Diagnosis: Chronic LBP with or without radiological abnormality. Placebo responders were excluded. Setting: outpatient.
Interventions	(I) Tetrazepam 50 mg t.i.d. / 10 days. N=25. (R) Placebo t.i.d. / 10 days. N=24.
Outcomes	Mean (SD) pain at baseline, day 7 and day 14 (from 1 to 5): (I) 3.4 (0.82), 2.5 (0.94) and 1.73 (1.31); (R): 3.36 (0.62), 3.1 (0.71) and 2.38 (1.08). [stat. sign. day 7] Number of patients with difference in pain scores of at least 1 point at day 7 and day 14: (I): 4 and 15; (R): 1 and 8. [stat. sign. day 7 and 14] Number of patients with at least 1.5 points decrease in muscle spasm (score 1 to 3), at day 7 and day 14: (I): 2 and 11; (R): 0 and 4. [stat. sign. day 7 and 14] Overall efficacy by physician: (I): 64%, (R): 29.2%. [stat. sign.]
Notes	Other outcomes measured in this trial: Pain assessed by physician. Significant on day 7 ($p < 0.02$) but no longer on day 14 ($p = 0.25$). Range of motion (finger-floor distance, cm) at baseline, day 7 and day 14: (I): 29 (+/- 14), 22 (+/- 13), 16.9 (+/- 11.8); (R): 33.8 (+/- 14.6), 32.1 (+/- 14.1), 25.7 (+/- 13.3). [no difference between groups]

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear from text
Allocation concealment (selection bias)	High risk	C - Inadequate
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias)	Low risk	

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Arbus 1990 (Continued)

All outcomes - outcome assessors?

Incomplete outcome data (attrition bias)	Low risk
All outcomes - drop-outs?	

Incomplete outcome data (attrition bias)	Low risk
All outcomes - ITT analysis?	

Similarity of baseline characteristics?	High risk
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Co-interventions avoided or similar?	Unclear risk	Unclear from text
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Compliance acceptable?	Unclear risk	Unclear from text
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Timing outcome assessments similar?	Low risk
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Baptista 1988

Methods	Multicentre, double-blind, placebo controlled trial. Sponsorship: none declared.
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Participants	N=267 Male/Female (%): 35.6/60.4 Age: 17-64. Mean=41,7 Diagnosis: painful spasms of paravertebral muscles (acute LBP). Setting: outpatient.
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Interventions	(I) Tizanidine 2mg t.i.d. / 8 days. N=89. (I2) Tizanidine 4mg t.i.d. / 8 days. N=89. (R) Placebo t.i.d. / 8 days. N=89.
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Outcomes	No differences in percentage pain at rest, muscle spasm and daily inactivity at baseline, day 3 and day 7. Global measure of improvement at day 7: (inefficacious + somewhat efficacious) / (satisfactory + excellent): (I): 29/47; (R): 32/43.
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Notes	The authors found a statistically significant difference between groups on percentage of spontaneous pain in relation to baseline for the group of patients with "moderate pain" only on day 3 (tizanidine 6mg/d = 48%, placebo = 68%). The authors concluded that tizanidine is effective.
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Risk of bias

Bias	Authors' judgement	Support for judgement
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Random sequence generation (selection bias)	High risk	
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Baptista 1988 (Continued)

Allocation concealment (selection bias)	Unclear risk	D - Not used
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	Low risk	
Similarity of baseline characteristics?	Unclear risk	Unclear from text
Co-interventions avoided or similar?	High risk	
Compliance acceptable?	High risk	
Timing outcome assessments similar?	Low risk	

Barrata 1982

Methods	Randomised, placebo-controlled, double-blind trial. Merck Sharp & Dohme performed statistical evaluation of data.
Participants	N = 120 Male/Female (%): 59/41 Mean age: 36 (21-60) Diagnosis: Acute LBP. Patients with moderate to severe degree of muscle spasm and local pain. Setting: Primary care.
Interventions	(I) Cyclobenzaprine 10 mg t.i.d. - q.i.d. / 10 days. N=58. (R) Placebo t.i.d. - q.i.d. / 10 days. N=59.
Outcomes	Proportion of patients who showed improvement (> 2 points): in pain, at days 2-4, 5-7 and 8-12: (I): 21%, 53% and 81%; (R): 0%, 15% and 49% [stat. sign.] Proportion of patients improved (> 2 points) in muscle spasm, at days 2-4, 5-7 and 8-12: (I): 10%, 44% and 72%; (R): 0%, 8% and 39% [stat. sign.] Physicians' global evaluation (5-point ordinal scale): (I): 23, 18, 10, 7 and 0; (R): 2, 13, 24, 20 and 0. [stat. sign.].

Barrata 1982 (Continued)

Proportion of patients improved (>2 points) in ADL at days 2-4, 5-7 and 8-12: (I): 21%, 53% and 78%; (R): 2%, 28% and 47%. [significant on days 5-7 and 8-12].

Notes The analysis of mean decreases in the ordinal scales is not appropriate.
The analysis of proportions is appropriate, and the difference of 2 points is clinically important.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	High risk	C - Inadequate
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	High risk	
Similarity of baseline characteristics?	Low risk	
Co-interventions avoided or similar?	High risk	
Compliance acceptable?	High risk	
Timing outcome assessments similar?	High risk	

Basmajian 1978

Methods Randomised, placebo-controlled, double-blind trial.
Supported by Merck Sharp & Dohme.

Participants N = 76
Male/Female (%): ?

Basmajian 1978 (Continued)

Mean age: ?

Diagnosis: Chronic LBP. Patients with clinically palpable muscle spasm, limitation of motion, limitation of ADL, local pain and tenderness on palpation.

Setting: outpatient.

Interventions	(I) Cyclobenzaprine 10 mg t.i.d. / 14 days. N=34. (I2) Diazepam 5 mg t.i.d. / 14 days. N=36. (R) Placebo t.i.d. / 14 days. N=35.
Outcomes	Mean decrease of muscle spasm (1-5 point scale) from baseline to days 13-18: (I): 3.2 to 2.2; (I2): 2.9 to 1.9; (R): 3.2 to 2.1. [no differences among groups]
Notes	No measurement of pain, global efficacy or activity of daily living.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear from text
Allocation concealment (selection bias)	High risk	C - Inadequate
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	High risk	
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	High risk	
Similarity of baseline characteristics?	High risk	
Co-interventions avoided or similar?	High risk	
Compliance acceptable?	High risk	
Timing outcome assessments similar?	Low risk	

Berry 1988a

Methods	Randomised, placebo-controlled, double-blind trial. Sandoz Ltd. supplied medication. TIL (Medical) Ltd. organized and monitored study.
Participants	N = 112 Male/Female (%): 51/49 Mean age: 41 (16-69) Diagnosis: Acute LBP. Setting: Primary care.
Interventions	(I) Tizanidine 4 mg t.i.d. / 7days. N=59. (R) Placebo t.i.d. / 7days. N=53.
Outcomes	Pain at night, at rest and on movement. Mean (SD) pain at rest (diary; 100 mm VAS) at baseline, day 3 and day 7: (I): 51 (29.4), 39 (29.6) and 19 (23.2); (R): 51(26.9), 34 (27.9) and 19 (22.9) [no differences]. Proportion of patients improved (4-point scale), on day 3 and 7: (I): 47%, 75% (R): 37%, 63%. [stat. sign. on day 7]. Global efficacy: (I): very helpful at day 3 = 17%, some help at day 7 = 84%; (R): very helpful at day 3 = 8% and some help at day 7 = 44%. [no differences].
Notes	Other outcomes: no differences in rescue analgesic consumption (aspirine) and restriction of movement.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear from text
Allocation concealment (selection bias)	High risk	C - Inadequate
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	Low risk	
Similarity of baseline characteristics?	Low risk	

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Berry 1988a (Continued)

Co-interventions avoided or similar?	Unclear risk	Unclear from text
Compliance acceptable?	Unclear risk	Unclear from text
Timing outcome assessments similar?	Low risk	

Berry 1988b

Methods	Randomised, placebo-controlled, double-blind trial. Sandoz Ltd. supplied medication; TIL (Medical) Ltd. organized and monitored study.
Participants	N = 105 Male/Female (%): 55/45 Age: 42.5 (20-66) Diagnosis: Acute LBP. Setting: Primary care.
Interventions	(I) Tizanidine 4 mg plus ibuprofen 400 mg t.i.d. / 7 days. N=51. (R) Placebo plus ibuprofen 400 mg t.i.d. / 7 days. N=54.
Outcomes	Mean (SD) change in pain at rest (diary; 100 mm VAS) from baseline to day 3 and day 7: (I): 18 (25.3) and 29 (43.3); (R): 16 (24.9) and 33 (32.9). [no differences]. Proportion of patients with moderate + severe pain / no pain + mild pain at rest, on day 3 and day 7: (I): 5/46 and 3/43; (R): 15/39 and 12/40) [stat. sign.] Global efficacy (% improved) on day 3 and day 7: (I) 76% and 85%; (R): 67% and 81%. [no statistical testing].
Notes	Other outcomes: pain on movement stat. sign. better in (I) than (R) on day 3, not day 7. No differences in pain at night, % of patients with moderate + severe pain and restriction of movement.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear from text
Allocation concealment (selection bias)	High risk	C - Inadequate
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias)	Low risk	

Berry 1988b (Continued)

All outcomes - outcome assessors?

Incomplete outcome data (attrition bias)
All outcomes - drop-outs?

Low risk

Incomplete outcome data (attrition bias)
All outcomes - ITT analysis?

Low risk

Similarity of baseline characteristics?

Low risk

Co-interventions avoided or similar?

Unclear risk Unclear from text

Compliance acceptable?

High risk

Timing outcome assessments similar?

Low risk

Bianchi 1978

Methods

Randomised, placebo-controlled, double-blind trial.
Merck Sharp & Dohme provided editorial assistance.

Participants

N = 48
Male/Female (%): 54/46
Mean age: 46 (19-67)
Diagnosis: Acute LBP (75%) or neck pain (25%). Moderate to severe muscle spasm.
Setting: Outpatient.

Interventions

(I) Cyclobenzaprine 10 mg t.i.d. - q.i.d. / 14 days. N=24.
(R) Placebo t.i.d. - q.i.d. / 14 days. N=24.

Outcomes

Mean spontaneous pain (1-5 point scale) at baseline, day 7 and day 14: (I): 3.7, 1.3, 1.0 (R): 3.6, 1.9, 1.3 [stat. sign. on day 7, not day 14].
Mean muscle consistency (1 to 5) at baseline, day 7 and day 14: (I): 3.7, 1.3, 1.0 (R): 3.9, 2.2, 1.3 [stat. sign. on day 7, not on day 14].
Mean limitation of daily activities (1 to 5) at baseline, day 7 and day 14: (I): 1.4, 1.0 (R): 2.0, 1.2 [stat. sign. on day 7, not on day 14].
Global improvement (4-point scale) on day 4, 7 and 14: complete + satisfactory / unsatisfactory + worsening: (I): 20/3, 20/2 and 20/0; (R): 9/13, 14/6 and 15/0 [stat. sign. on day 4 and 7, not on day 14].

Notes

Other outcomes:
pain on palpation and limitation of motion stat. sign. better in (I) on day 7, not on day 14.

Risk of bias

Bias	Authors' judgement	Support for judgement
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Random sequence generation (selection bias)	Low risk	
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Bianchi 1978 (Continued)

Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	High risk	
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	Unclear risk	Unclear from text
Similarity of baseline characteristics?	Low risk	
Co-interventions avoided or similar?	Unclear risk	Unclear from text
Compliance acceptable?	Unclear risk	Unclear from text
Timing outcome assessments similar?	Low risk	

Borenstein 1990

Methods	Randomised, open-label trial. Supported by Merck Sharp & Dohme.
Participants	N = 40 Male/Female (%): 70/30 Mean age: 34.5 (20-57) Diagnosis: Acute, mild to moderate LBP. Setting: outpatient.
Interventions	(I) Cyclobenzaprine 10 mg / 8 hrs / 14 days plus naproxen 500 mg initially, followed by 250 mg / 6 hrs / 14 days. N=20. (R) Placebo plus naproxen 500 mg initially, followed by 250 mg / 6 hrs / 14 days. N=20.
Outcomes	Pain (0 to 20 NRS). [no difference between groups]. Descriptive pain scale (from 0 to 3). [no difference between groups]. Number of days to resolution of pain: (I): 8.5, (R): 12.5. [no differences] Muscle spasm (0=none to 3=severe). (I): 2.0; (R): 3.0. [stat. sign.].

Muscle relaxants for non-specific low-back pain (Review)

Borenstein 1990 (Continued)

Functional capacity (0-3 scale): (I): 9; (R): 15. [no differences].
Global efficacy (0=poor to 4=excellent). [no differences].

Notes	Other outcomes: Tenderness to palpation and Schober's test stat. sign. better in (I). No differences in ROM.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (selection bias)	Unclear risk	Unclear from text
Allocation concealment (selection bias)	High risk	C - Inadequate
Blinding (performance bias and detection bias) All outcomes - patients?	High risk	
Blinding (performance bias and detection bias) All outcomes - providers?	High risk	
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	High risk	
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - ITT analy- sis?	Low risk	
Similarity of baseline char- acteristics?	High risk	
Co-interventions avoided or similar?	Unclear risk	Unclear from text
Compliance acceptable?	Unclear risk	Unclear from text
Timing outcome assess- ments similar?	Low risk	

Boyles 1983

Methods	Randomised, double-blind trial.
Participants	N = 80

Muscle relaxants for non-specific low-back pain (Review)

Boyles 1983 (Continued)

Male/Female (%): 48/52
Mean age: 39 (19-65)
Diagnosis: Acute LBP.
Setting: outpatient.

Interventions	(I1) Carisoprodol 350 mg q.i.d. / 7 days. N=40. (I2) Diazepam 5mg q.i.d. / 7 days.N=40.
Outcomes	Pain (100-mm VAS) day 7 - baseline (I): 58 (I2): 48; muscle stiffness (I): 59 (I2): 42; activity (I): 58 (I2): 41; sleep impairment (I): 52 (I2): 40; tension (I): 51 (I2):38 and overall relief: (I): 75, (I2): 56. [stat. sign. for muscle stiffness, activity, tension and relief]. Overall improvement (very good + excellent): (I): 70%, (I2): 45%.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	High risk	C - Inadequate
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	High risk	
Similarity of baseline characteristics?	Low risk	
Co-interventions avoided or similar?	Low risk	
Compliance acceptable?	Unclear risk	Unclear from text
Timing outcome assessments similar?	Low risk	

Bragstad 1979

Methods	Randomised, double-blind trial. Sponsorship not declared, but most likely Sandoz Ltd supplied the medication.
Participants	N = 27 Male/Female (%): ? Mean age: 37 (21-63) Diagnosis: Acute LBP and muscle spasms of disc origin. Setting: secondary care - hospitalized (7), ambulant (20).
Interventions	(I1) Tizanidine 2 mg t.i.d, 7 days. N=14. (I2): Chlorzoxazone 500 mg t.i.d, 7 days. N=13.
Outcomes	Difference (4-point scale) at baseline and day 7 for pain (I): 2.29, 0.83 (I2): 2.31, 0.73, for muscle tension (I): 2.57, 0.71 (I2): 2.69, 0.44; for limitation of movement (I): 2.0, 1.0 (I2): 2.15, 0.9. [no differences]. Overall effectiveness by patient at end of the trial: excellent/good (I):11 (I2): 9; moderate/poor (I):3 (I2): 3.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear from text
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	High risk	
Similarity of baseline characteristics?	Low risk	
Co-interventions avoided or similar?	Low risk	

Muscle relaxants for non-specific low-back pain (Review)

Bragstad 1979 (Continued)

Compliance acceptable?	High risk
Timing outcome assessments similar?	Low risk

Casale 1988

Methods	Randomised, placebo-controlled, double-blind trial. Medication supplied by Boots-Formenti Pharmaceuticals.
Participants	N = 20 Male/Female (%): 75/25 Mean age: 46.9 (37-58) Diagnosis: acute episode of chronic LBP. Setting: Secondary care.
Interventions	(I) Dantrolene sodium 25 mg o.i.d. / 4 days, N=10. (R) Placebo o.i.d. / 4 days. N=10.
Outcomes	Pain during maximal voluntary movements (% variation on VAS): (I): 50%; (R): 8.6%. [stat. sign.] Muscle spasm (5-points) proportion improved on day 3 and 4: (I): 85%, 85%; (R): 10%, 30%.
Notes	Other outcomes: Pain behavior stat. sign. better in (I) than (R) on day 4.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear from text
Allocation concealment (selection bias)	Low risk	A - Adequate
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	Low risk	
Incomplete outcome data (attrition bias)	Low risk	

Casale 1988 (Continued)

All outcomes - ITT analysis?

Similarity of baseline characteristics?	Low risk
Co-interventions avoided or similar?	Low risk
Compliance acceptable?	High risk
Timing outcome assessments similar?	Low risk

Corts Giner 1989

Methods	Placebo-controlled, double-blind trial. Sponsorship: none declared.
Participants	N=50 Male/Female (%): 46/54 Mean age: 50 (range 32-63) in muscle relaxant group and 53 (41-68) in placebo group. Diagnosis: Acute LBP. Setting: ?
Interventions	(I) Tizanidine 4mg t.i.d. + paracetamol 500mg / 7 days. N=26. (R) Placebo t.i.d. + paracetamol 500mg / 7 days. N=24.
Outcomes	Pain (4-point scale) on movement at baseline, day 3 and day 7: (I): 2.0, 1.1, 0.3; (R): 2.0, 1.8, 1.4. Pain at rest: (I): 1.8, 0.6, 0.2; (R): 1.8, 1.2, 1.0; Pain at night: (I): 1.8, 0.3, 0.1; (R): 1.7, 1.0, 0.8. [stat. sign.] Muscle spasm (4-point scale) at baseline, day 3 and day 7: (I): 2.0, 1.1, 0.3; (R): 2.1, 1.7, 1.5. [stat. sign.]. Activity daily living (4-point scale) at baseline, day 3 and day 7: (I): 2.0, 0.8, 0.5; (R): 1.9, 1.6, 1.2. [stat. sign.]. Global efficacy (1=excellent, 2=good, 3=moderate and 4=poor) at the end of treatment: (I): 20, 3, 0, 3; (R): 4, 3, 3, 14.
Notes	Other outcomes: ROM stat. sign. better in (I) than (R) at day 3 and 7.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	
Allocation concealment (selection bias)	Unclear risk	D - Not used
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	

Muscle relaxants for non-specific low-back pain (Review)

Corts Giner 1989 (Continued)

Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	Low risk
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	Low risk
Similarity of baseline characteristics?	Low risk
Co-interventions avoided or similar?	High risk
Compliance acceptable?	High risk
Timing outcome assessments similar?	Low risk

Dapas 1983

Methods	Randomised, placebo-controlled, double-blind trial. Sponsored by Ciba-Geigy.
Participants	N = 200 Male/Female (%): 48/52 Mean age: 42.2 (17-74) Diagnosis: Acute LBP; muscle spasm and functional disability < 2 wks of at least moderate severity. Setting: outpatient.
Interventions	(I) Baclofen 10 mg, 1-2 tablets t.i.d. -q.i.d. / 10 days. N=100. (R) Placebo 1-2 tablets t.i.d. -q.i.d. / 10 days. N=100.
Outcomes	For group of patients with severe pain at baseline (63 baclofen, 60 placebo): Local pain (5-point scale) at baseline, day 4 and day 10: (I): 4.1, 2.6, 2.0 (R): 4.1, 3.0, 2.5 [stat. sign.] Muscle spasm (5-point scale) at baseline, day 4 and day 10: (I): 3.8, 2.5, 1.5 (R): 3.8, 2.8, 2.0 [stat. sign. on day 10]. Patient's opinion (5-point scale) at baseline, day 4 and day 10: (I): 4.0, 2.7, 1.8 (R): 4.0, 3.0, 2.2 [stat. sign.] Data for patients with moderate pain (N=77) not given. Authors reported that baclofen was sign. better in daily activity on day 4. No differences on day 10.
Notes	Other outcomes: Active SLR and ROM stat. sign. better in (I) than (R) at day 10.

Risk of bias

Bias	Authors' judgement	Support for judgement
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Dapas 1983 (Continued)

Random sequence generation (selection bias)	Unclear risk	Unclear from text
Allocation concealment (selection bias)	High risk	C - Inadequate
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	High risk	
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	High risk	
Similarity of baseline characteristics?	Low risk	
Co-interventions avoided or similar?	Low risk	
Compliance acceptable?	Low risk	
Timing outcome assessments similar?	Low risk	

Gold 1978

Methods	Randomised, placebo-controlled, double-blind trial. Supported by Riker Laboratories, Inc.
Participants	N = 60 Male/Female (%): ? Mean age: ? Diagnosis: Acute LBP and muscle spasms. Limited work and daily activities. Setting: outpatient.
Interventions	(I) Orphenadrine 100 mg b.i.d. / 7 days. N=20. (RI) Phenobarbital 32 mg b.i.d. / 7 days. N=20. (R2) Placebo b.i.d. / 7 days. N=20.
Outcomes	Reduced pain at 2 days: (I): 9/20; (R1): 3/20; (R2): 4/20 [I stat. sign. better than R1 and R2].

Muscle relaxants for non-specific low-back pain (Review)

Gold 1978 (Continued)

Overall improvement at 2 days: (I): 7/20; (R1): 3/20; (R2): 0/20. [I stat. sign. better than R2].

Notes Other data not shown. Authors concluded that orphenadrine is better than placebo and phenobarbital based on the results after 48-hrs.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear from text
Allocation concealment (selection bias)	High risk	C - Inadequate
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	High risk	
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	High risk	
Similarity of baseline characteristics?	High risk	
Co-interventions avoided or similar?	High risk	
Compliance acceptable?	High risk	
Timing outcome assessments similar?	Low risk	

Hennies 1981

Methods Randomised, double-blind trial.
Sponsorship not declared but most likely Sandoz Ltd supplied medication.

Participants N = 30
Male/Female (%): 33/67
Mean age: 47.5 (25-70)

Muscle relaxants for non-specific low-back pain (Review)

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Hennies 1981 (Continued)

Diagnosis: Acute spasm of back (80%) and neck (20%) muscles, actual no. of weeks of duration unknown).
Setting: 'ambulant patients'.

Interventions	(I1) Tizanidine, 4mg t.i.d., 7 days. N=15. (I2) Diazepam 5mg t.i.d., 7 days. N=15.
Outcomes	Pain (4-point scale) at baseline, day 3 and day 7: (I): 2.3, 1.3, 0.6; (R): 2.2, 1.7, 1.1. Number of cases with pain improvement on day 3 and 7: (I): 13, 13; (R): 8, 11. [stat. sign. on day 3]. Percentage of pain relief at end of trial: (I): 77.4%, (R): 47.8%. Patient self assessment of pain (4-point scale) at baseline, day 3 and day 7: (I): 2.2, 1.1, 0.5; (R): 2.2, 1.7, 1.0. Number of cases with self assessment of pain on day 3 and 7: (I): 12, 13; (R): 8, 12. Number of cases with improvement of muscle tension on day 3 and 7: (I): 10, 9; (R): 11, 12. Daily activities at baseline and after 7 days: (I): 2.1, 0.4, (R): 2.2, 0.8. Number of cases with improvement of daily activities on day 3 and 7: (I): 12, 13; (R): 10, 14.
Notes	Other outcomes: Forward flexion and lateral flexion stat. sign. better in (I) than (R) on day 3 and 7. The analysis of covariance always showed a sign. difference in favour of tizanidine in all parameters evaluated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear from text
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	High risk	
Similarity of baseline characteristics?	Low risk	
Co-interventions avoided or similar?	Low risk	

Muscle relaxants for non-specific low-back pain (Review)

Hennies 1981 (Continued)

Compliance acceptable?	High risk
Timing outcome assessments similar?	Low risk

Hindle 1972

Methods	Randomised, placebo-controlled, double-blind trial. Medications were provided by Wallace Pharmaceuticals.
Participants	N = 48 Male/Female (%): 56/44 Mean age: 38.4 (18-70) Diagnosis: Acute LBP. Mexican migrant farm laborers with acute lumbar strain and spasm Setting: outpatient.
Interventions	(I) Carisoprodol 350 mg q.i.d. / 4 days. N=16. (R1) Butabarbital 15 mg q.i.d. / 4 days. N=16. (R2) Placebo q.i.d. / 4 days. N=16.
Outcomes	Pain (100 mm VAS) at baseline, day 2 and day 4: (I): 86.0, 33.0, 15.5; (R1): 75.2, 58.7, 49.1 (R2): 65.5, 58.5, 64.0. [(I) stat. sign. better than (R1) and (R2)]. Muscle spasm (4-point scale) at baseline, day 2 and day 4: (I): 3.1, 2.4, 1.8 (R1): 3.1, 2.8, 2.6 (R2): 3.0, 2.9, 2.9. [no differences]. Interference with daily activities (4-point scale) at baseline, day 2 and day 4: (I): 3.7, 2.4, 1.8 (R1): 3.3, 2.9, 2.7 (R2): 3.1, 3.1, 3.4. [(I) stat. sign. better than (R2)]. Number of patients with global improvement excellent/good (I): 12 (R1): 2 (R2): 2. [(I) stat. sign. better than (R1) and (R2)].
Notes	The three groups were significantly different at baseline on scores of pain, daily activities, global severity and patient estimate of pain. The carisoprodol group showed more severe factors than the other groups. Other outcomes: Pain evaluated by investigator stat. sign. better in (I) than (R2) at day 2 and 4. No differences in limitation of motion.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	A - Adequate
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias)	Low risk	

Muscle relaxants for non-specific low-back pain (Review)

Hindle 1972 (Continued)

All outcomes - outcome assessors?

Incomplete outcome data (attrition bias) All outcomes - drop-outs?	Low risk
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	High risk
Similarity of baseline characteristics?	High risk
Co-interventions avoided or similar?	High risk
Compliance acceptable?	High risk
Timing outcome assessments similar?	Low risk

Hingorani 1966

Methods	Double-blind, placebo-controlled trial. Roche Ltd. acknowledged for their "help and cooperation".
Participants	N = 50 Male/Female (%): 80/20 Mean age: ? Diagnosis: Acute LBP severe enough to require admission to hospital. Causes were: lumbar spondylosis (28 patients), prolapsed intervertebral disk (19), post-laminectomy (2) and sprain (1) Setting: secondary care.
Interventions	(I) Diazepam injections: 10 mg IM / 6 hrs / 24 hrs Oral: 2 mg q.i.d. / 5 days plus calcium aspirin 10g t.i.d. / 5 days. N=25. (R) Placebo injections: water IM / 6 hrs / 24 hrs Oral: placebo q.i.d. / 5 days plus calcium aspirin 10 g t.i.d. / 5 days. N=25.
Outcomes	Subjective results (pain and tenderness), number of patients improved, no change and worse at the end of treatment: (I) 19, 5, 1 (R): 18, 5, 2. [no differences]. Objective results (range of motion, straight leg raising and neurological signs), number of patients improved, no change and worse at the end of treatment: (I): 16, 7, 2 (R): 15, 8, 2. [no differences].
Notes	All patients were hospitalized and treated with complete bed rest and 8/25 in (I) and 6/25 in (R) received additional therapy.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear from text

Muscle relaxants for non-specific low-back pain (Review)

Hingorani 1966 (Continued)

Allocation concealment (selection bias)	High risk	C - Inadequate
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	Low risk	
Similarity of baseline characteristics?	High risk	
Co-interventions avoided or similar?	High risk	
Compliance acceptable?	High risk	
Timing outcome assessments similar?	Low risk	

Hingorani 1971

Methods	Randomised, placebo-controlled, double-blind trial. Cooperation and assistance from Riker Laboratories Inc. is acknowledged.
Participants	N = 99 Male/Female (%): 61/39 Mean age: 43.5 Diagnosis: Acute LBP of sufficient severity to require inpatient treatment. Causes were: prolapsed intervertebral disc, acute sprain, spondylarthrosis and spondylolisthesis and acute post-laminectomy backache. Setting: secondary care.
Interventions	(I) Orphenadrine 35 mg + paracetamol 450 mg 2 tablets t.i.d. / 7 days. N=48. (R) Aspirin 100 mg t.i.d. / 7 days. N=50.
Outcomes	Number of patients with improvement in pain (4-point scale) at the end of the trial: (I): 37 (R): 34 [no differences].
Notes	Other outcomes:

Muscle relaxants for non-specific low-back pain (Review)

Hingorani 1971 (Continued)

no differences in tenderness and SLR. Mean improvement in finger-floor distance stat. sign. better in (I) than (R).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	
Allocation concealment (selection bias)	Unclear risk	D - Not used
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	Low risk	
Similarity of baseline characteristics?	High risk	
Co-interventions avoided or similar?	High risk	
Compliance acceptable?	High risk	
Timing outcome assessments similar?	Low risk	

Klinger 1988

Methods	Randomised, placebo-controlled, double-blind trial. Four authors were affiliated with the Clinical Research Department of Riker Laboratories.
Participants	N = 80 Male/Female (%): 81/19 Mean age: 33.8 (14-62) Diagnosis: Acute LBP and muscle spasms. Setting: tertiary care.

Muscle relaxants for non-specific low-back pain (Review)

Klinger 1988 (Continued)

Interventions	(I) Orphenadrine 60 mg intravenously, single dose. N=40. (R) Placebo intravenously, single dose. N=40.
Outcomes	Number of patients with self assessment of pain as none, slight, moderate or severe (45 min. after injection): (I): 5, 30, 5, 0 (R): 0, 4, 31, 5. Physician's assessment of spasm (% , better): (I): 95% (R): 10%. [(I) stat. sign. better than (R)] Global improvement (% , better): (I): 92% (R): 12% [(I) stat. sign. better than (R)].
Notes	Other outcomes: No difference in physician's assesement of pain 45 min. after injection. Global improvement by physician (I) stat. sign. better than (R).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear from text
Allocation concealment (selection bias)	High risk	C - Inadequate
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	Unclear risk	Unclear from text
Similarity of baseline characteristics?	High risk	
Co-interventions avoided or similar?	Low risk	
Compliance acceptable?	Low risk	
Timing outcome assessments similar?	Low risk	

Lepisto 1979

Methods	Randomised, placebo-controlled, double-blind trial. Sponsorship: none declared.
Participants	N=30 Male/Female(%): 50/50. Mean age: 42.5 (18-62) (I) and 40.8 (27-59) (R) Diagnosis: moderate to severe acute spasms due to disk prolapse in lumbar (n=26) and thoracic (n=4) regions. Setting: secondary care - hospitalized patients.
Interventions	(I): Tizanidine 2mg, t.i.d., 7 days. N=15. (R): Placebo, t.i.d., 7 days. N=15.
Outcomes	Mean back pain (4-point scale) at baseline, days 2, 3, 5 and 7: (I): 2.5, 2.0, 1.7, 1.3, 1.0 (R): 2.6, 2.2, 1.9, 1.4, 1.0. [no difference]. Number of patients with decreased pain on days 2, 3, 5 and 7: (I): 8, 9, 11, 13. (R): 6, 10, 13, 12. [no difference]. Mean score of muscle spasm (4-point scale), at baseline, days 2, 3, 5 and 7. (I): 2.9, 1.9, 1.3, 1.0, 0.7 (R): 2.7, 2.3, 1.8, 1.2, 1.2. [stat. sign. only on day 3]. Number of patients with decreased spasm on days 2, 3, 5 and 7: (I): 15, 15, 15, 15 (R): 6, 10, 14, 12 [stat. sign. on days 2, 3 and 7]. Patient's assessment of overall response (excellent, good, moderate, poor): (I): 6, 6, 2, 1 (R): 2, 4, 7, 2 [no difference].
Notes	Some outcomes (e.g. overall improvement) were not statistically significant, but difference was important. This might be due to lack of power. Other outcomes: no difference in limitation of movement. Physician's assessment of overall response stat. sign. better in (I).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear from text
Allocation concealment (selection bias)	Unclear risk	D - Not used
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	Low risk	

Lepisto 1979 (Continued)

Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	Low risk	
Similarity of baseline characteristics?	Low risk	
Co-interventions avoided or similar?	Low risk	
Compliance acceptable?	Unclear risk	Unclear from text
Timing outcome assessments similar?	Low risk	

Moll 1973

Methods	Randomised, placebo-controlled, double-blind trial Sponsorship not declared
Participants	N = 68 Male/Female (%): 56/44 Mean age: 45.6 (23-72) Diagnosis: Acute LBP Setting: ?
Interventions	(I) Diazepam IM injection 10 mg (2 ml) + 2 tablets t.i.d. for 5 days. Day 5-10 2 tablets t.i.d. or less if good response. N=33. (R) Placebo IM injection (2 ml) + 2 placebo tablets t.i.d. for 5 days. Day 5-10 2 placebo tablets t.i.d. or less if good response. N=35.
Outcomes	Patients' assessment 1 hr after IM injection, 24 hrs, between 48-72 hs and either at day 5 or day 10 to 14. Therapeutic effect at end of treatment period (0=no, 1=moderate, 2=good, 3=very good). Mean (SD) and number of patients with scores of 2 and 3: (I): 1.8 (1.2) 21; (R): 0.3 (0.8) 6. [(I) stat. sign better than (R)]
Notes	Groups were not similar at baseline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear from text
Allocation concealment (selection bias)	High risk	C - Inadequate
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias)	Low risk	

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Moll 1973 (Continued)

All outcomes - providers?

Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	Low risk
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	High risk
Similarity of baseline characteristics?	High risk
Co-interventions avoided or similar?	High risk
Compliance acceptable?	High risk
Timing outcome assessments similar?	Low risk

Pipino 1991

Methods	Randomized single-blind clinical trial. Sponsorship: none declared.
Participants	N=120 Male/Female (%): 42.5/57.5 Mean age: 54.4 (20-77) (I) and 51.7 (24-76) (R) Diagnosis: chronic LBP with muscle spasm Setting: secondary care - inpatients and outpatients.
Interventions	(I1) Pridinol mesilate 4mg IM injection b.i.d. x 3 days followed by 2mg b.i.d. orally x 4 days. N=60. (I2) Thiocolchicoside 4mg IM injection b.i.d x 3 days followed by 8mg b.i.d. orally x 4 days. N=60.
Outcomes	Mean (SD) pain intensity (VAS) at baseline, day 4 and day 7: (I): 62.8 (10.8); 45.8 (12.4); 30.0 (13.9); (I2) 63.5 (10.8); 46.4 (12.4); 30.1 (15.5). [no differences]. Patient rated global efficacy: (I) 47/60 = good & very good; (I2) 39/60 = good & very good.
Notes	Other outcomes: no differences in fingertip-floor distance at day 4 and 7.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear from text

Pipino 1991 (Continued)

Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes - patients?	High risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Unclear risk	Unclear from text
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Unclear risk	Unclear from text
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	Low risk	
Similarity of baseline characteristics?	Low risk	
Co-interventions avoided or similar?	Low risk	
Compliance acceptable?	High risk	
Timing outcome assessments similar?	Low risk	

Pratzel 1996

Methods	Randomised, placebo-controlled, double-blind trial. One of the authors affiliated with Strathmann AG.
Participants	N = 112 Male/Female (%): 78/27 Mean age: 50.8 (I) and 47.8 (R) Diagnosis: chronic LBP with painful reflex muscle spasms. Setting: secondary care - rehabilitation centers.
Interventions	(I) Tolperisone 100 mg t.i.d., 21 days. N=67. (R) Placebo t.i.d./ 21 days. N=70.
Outcomes	Clinical global impression of efficacy on day 10 and day 21 (1=very good, 4=ineffective) (I): 2.65, 2.20 (R): 2.85, 2.45. [no differences]. Number of patients with overall assessment of efficacy by the patient after 21 days: very good / good / moderate/ ineffective: (I): 15, 17, 19, 5; (R): 6, 21, 15, 14. [(I) sign. better than (R)].

Pratzel 1996 (Continued)

Notes Other outcomes: pressure pain threshold sign. more improved in (I) at day 10 and day 21.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear from text
Allocation concealment (selection bias)	High risk	C - Inadequate
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	High risk	
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	High risk	
Similarity of baseline characteristics?	Low risk	
Co-interventions avoided or similar?	Low risk	
Compliance acceptable?	Low risk	
Timing outcome assessments similar?	Low risk	

Rollings 1983

Methods	Randomised, placebo-controlled, double-blind trial. Sponsorship: none declared.
Participants	N = 78 Male/Female (%): 53/47 Mean age: 42 (19-65) Diagnosis: Acute LBP of at least moderate intensity with muscle spasms of 7 days or less. Setting: outpatient.

Muscle relaxants for non-specific low-back pain (Review)

Rollings 1983 (Continued)

Interventions	(I1) Carisoprodol 350 mg q.i.d. / 7 days. N=39. (I2) Cyclobenzaprine 10 mg q.i.d. / 7 days. N=39.
Outcomes	Pain (100 mm VAS) at baseline and day 8: (I): 70, 30; (I2): 74, 28. Muscle spasm: (I): 64, 22; (I2): 67, 25. Activity impairment: (I): 74, 32; (I2): 76, 26. Physician's evaluation of muscle spasm using a 5-point scale, at baseline, day 4 and day 8: (I): 3.46, 2.39, 1.83; (I2): 3.77, 2.74, 2.0. Overall improvement (very good to excellent) at end of treatment: (I): 70%, (I2): 70%. No differences between groups.
Notes	Other outcomes: no difference in physician's evaluation of mobility restriction and overall improvement.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	High risk	C - Inadequate
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	High risk	
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	High risk	
Similarity of baseline characteristics?	Low risk	
Co-interventions avoided or similar?	Low risk	
Compliance acceptable?	Low risk	
Timing outcome assessments similar?	Low risk	

Salzmann 1992

Methods	Randomised, placebo-controlled double-blind trial. Sponsored by Sanofi Winthrop
Participants	N=152 Male/Female (%): 59/41 Mean age: 44.4(I) and 46.3 (R) Diagnosis: chronic LBP without benefit from physiotherapy Setting: secondary care - outpatient.
Interventions	(I): Tetrazepam 50 mg t.i.d / 14 days plus physiotherapy. N=79. (R): Placebo t.i.d / 14 days plus physiotherapy. N=73.
Outcomes	Percentage of patients reporting >66.6% reduction of daytime pain at day 3, 7 and 14: (I): 7.3, 29.1, 45.5; (R): 2.1, 8.3, 27.1. [stat. sign. difference at day 7]. Clinical global impression (marked, moderate, slight / unchanged, deteriorated) at baseline, day 3, 7 and 14: (I): 5/50, 39/16, 46/9, 45/8 (R): 1/47, 31/17, 41/7, 39/9 [no differences].
Notes	Other outcomes: no difference in mobility measures (rotation, flexion, finger-floor distance, Schober test) and overall improvement in % (response in at least two of three pain and mobility criteria) on day 3, 7. Medication most helpful: (I): 84% (R): 56%. [stat. sign.]. Data only presented for 103 patients in per protocol analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear from text
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	High risk	
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	Unclear risk	Unclear from text
Similarity of baseline characteristics?	Unclear risk	Unclear from text

Salzmann 1992 (Continued)

Co-interventions avoided or similar?	Low risk
Compliance acceptable?	Low risk
Timing outcome assessments similar?	Low risk

Sirdalud 1998

Methods	Randomised, placebo-controlled, double-blind trial. Sponsored by Novartis Pharma AG, Basel.
Participants	N= 405 Male/Female (%): 48/52 Mean age: 40 Diagnosis: patients with local pain syndromes (back, neck or shoulder) of recent onset and clinically discernible muscle spasms; > 50% low back Setting: not specified.
Interventions	(I) Tizanidine 2mg plus diclofenac 50mg b.i.d. / 7 days. N=185. (R): Placebo plus diclofenac 50mg b.i.d. / 7 days. N=176.
Outcomes	Mean pain at rest (4-point scale) at baseline, day 4 and day 8: (I): 1.98, 0.89, 0.53 (R): 1.87, 1.21, 0.92. [stat. sign.]. Mean muscle tension (4-point scale at baseline, day 4 and day 8: (I): 1.98, 0.77, 0.29 (R): 1.99, 1.20, 0.77. [stat. sign.]. Mean disability score (5-point scale) at baseline, day 4 and day 8: (I): 2.01, 0.98, 0.61 (R): 1.97, 1.27, 0.92. [stat. sign.]. Overall assessment of efficacy at end of treatment (good/very good): (I): 72% (R): 58% [stat. sign.]
Notes	Other outcomes: pain at movement, pain at night, pain at palpation and restriction of movement stat. sign. at day 4 and day 8.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear from text
Allocation concealment (selection bias)	Unclear risk	D - Not used
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias)	Low risk	

Muscle relaxants for non-specific low-back pain (Review)

Sirdalud 1998 (Continued)

All outcomes - outcome assessors?

Incomplete outcome data (attrition bias) All outcomes - drop-outs?	Unclear risk	Unclear from text
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	High risk	
Similarity of baseline characteristics?	Low risk	
Co-interventions avoided or similar?	Low risk	
Compliance acceptable?	Unclear risk	Unclear from text
Timing outcome assessments similar?	Low risk	

Sweetman 1987

Methods	Randomised, placebo-controlled, double-blind trial. Sponsorship: none declared.
Participants	N = 122 Male/Female (%): 53/47 Mean age: 41.3 (?) Diagnosis: Acute LBP (1- 28 days). Setting: Outpatient.
Interventions	Chlormezanone: excluded from this review (I) Meprobamate 150 mg plus ethoheptazine 75 mg plus aspirin 250 mg 2 tablets t.i.d. / 7 days. N=40. (R) Mefenamic acid 500 mg t.i.d. / 7 days. N=40.
Outcomes	Number of patients experiencing moderate and severe pain at baseline, day 1 and day 7: (I):25/40, 17/40, 8/41; (R): 27/37, 19/32, 6/39 [no differences]. Pain diary (4-point scale) (25% failed to complete). Day 0 and day 7: 1.45, 0.8; (R): 1.4, 0.7. [no differences] Patient's overall assessment (some and marked improvement) on day 7: (I2): 22; (R): 24 [no difference].
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear from text
Allocation concealment (selection bias)	High risk	C - Inadequate

Muscle relaxants for non-specific low-back pain (Review)

Sweetman 1987 (Continued)

Blinding (performance bias and detection bias) All outcomes - patients?	Low risk
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	High risk
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	High risk
Similarity of baseline characteristics?	Low risk
Co-interventions avoided or similar?	High risk
Compliance acceptable?	High risk
Timing outcome assessments similar?	Low risk

Tervo 1976

Methods	Randomised, placebo-controlled, double-blind trial. Sponsorship: none declared.
Participants	N = 50 Male/Female (%): 34/66 Mean age: ? Diagnosis: Acute LBP. 38/50 no previous episodes. 37/50 acute onset of symptoms. 16/50 work injury. Setting: outpatient.
Interventions	(I) Orphenadrine 60 mg (2ml) IM followed by orphenadrine (35 mg) + paracetamol (450 mg) 2 tablets t.i.d., 7 days. N=25. (R) Saline 2ml IM followed by paracetamol (450 mg) 2 tablets t.i.d., 7 days. N=25.
Outcomes	Mean (SE) duration of disability: (I): 8.6 (0.6) days; (R): 12.9 (1.2) days. [stat. sign.]. Subjective impressions of the treatments: no difference between groups (15 minutes after injection and in the first follow-up visit).
Notes	Baseline measurements, 15 minutes after injection. Follow-up visits at 14-21 days only 36%. Because of high drop-out rate these data were not analysed. Other outcomes: objective clinical examinations (patient's gait, sitting posture, scoliosis, spinal flexion, muscle spasm and Lasegue) no differences.

Tervo 1976 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	High risk	C - Inadequate
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	High risk	
Similarity of baseline characteristics?	Low risk	
Co-interventions avoided or similar?	High risk	
Compliance acceptable?	High risk	
Timing outcome assessments similar?	High risk	

Weber 1980

Methods	Double-blind, controlled clinical trial. Sponsorship: none declared.
Participants	N = 78 Male/Female (%): 60/40 Mean age: 46.2 (I) and 47.4 (R) Diagnosis: Acute lumbagosciatica and cervical pain; majority LBP Setting: Secondary care - hospital.
Interventions	(I) Diazepam t.i.d (7mg, 7mg, 10mg) / 6 days + paralgin Forte (paracetamol 400mg, codeine 20 mg, promethazine 5mg) t.i.d. / 3 days, then prn. N=33.

Muscle relaxants for non-specific low-back pain (Review)

Weber 1980 (Continued)

(R) Levomepromazine t.i.d (7.5mg + 7.5mg + 15mg) 6 days + paralgin Forte t.i.d. / 3 days, then prn. N=45.

Outcomes	Pain intensity (10-point scale) daily during 6 days. (I) 21/33 patients with satisfactory effect ; mean grade 5.30 (R) 26/45 satisfactory effect; mean grade 5.82. [no differences].	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	
Allocation concealment (selection bias)	Unclear risk	D - Not used
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	High risk	
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	High risk	
Similarity of baseline characteristics?	Unclear risk	Unclear from text
Co-interventions avoided or similar?	Unclear risk	Unclear from text
Compliance acceptable?	High risk	
Timing outcome assessments similar?	Unclear risk	Unclear from text

Worz 1996

Methods	Randomised, placebo-controlled, double-blind trial. One author affiliated with ASTA Medica.	
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Worz 1996 (Continued)

Participants	N = 107 Male/Female (%): 43/57 Mean age: 49.7 Diagnosis: Chronic LBP Setting: ?
Interventions	(I) Flupirtin 100 mg q.i.d. / 7 days. N=53. (I2) Chlormezanone. Excluded from this review. (R) Placebo q.i.d. / 7 days. N=54.
Outcomes	Reduction in pain intensity by 2 categories (5-point verbal scale) at day 7: (I): 54.3%; (R): 33.4%. [no difference]. Reduction in muscle spasm by 2 categories (5-point verbal scale) at day 7 (I): 47.8%; (R): 33.4%. [no differences]. Overall assessment by the physician (very good + good + satisfactory): (I): 84.8%; (R): 54.3%. [(I) better than (R)].
Notes	Other outcomes: Assessment of general health no figures reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear from text
Allocation concealment (selection bias)	High risk	C - Inadequate
Blinding (performance bias and detection bias) All outcomes - patients?	Low risk	
Blinding (performance bias and detection bias) All outcomes - providers?	Low risk	
Blinding (performance bias and detection bias) All outcomes - outcome assessors?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - drop-outs?	Low risk	
Incomplete outcome data (attrition bias) All outcomes - ITT analysis?	Low risk	
Similarity of baseline characteristics?	High risk	
Co-interventions avoided or similar?	High risk	

Muscle relaxants for non-specific low-back pain (Review)

Worz 1996 (Continued)

Compliance acceptable? High risk

Timing outcome assessments similar? Low risk

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Aiken 1978a	Neck and low back pain; less than 50% low back pain.
Aiken 1978b	Neck and low back pain; less than 50% low back pain.
Aoki 1995	Japanese study. Excluded by language restriction criterion.
Asia-Pacific 1998	Mixed study population of back and neck pain.
Basmajian 1988	Study population included patients with neck and back pain; unknown percentage back pain.
Bercel 1977	Osteoarthritis of back and neck; unknown percentage back pain.
Bobulesco 1970	French study. Excluded by language restriction criterion.
Bouchier-Hayes 1984	Study population included patients with back and neck pain; unknown percentage back pain.
Brown 1978	Neck and back pain; unknown percentage back pain.
Fryda-Kaurimsky 1981	Study population included patients with back and neck pain; unknown percentage back pain.
Gabric 1992	Serbocroatian study. Excluded by language restriction criterion.
Hasue 1997	Japanese study. Excluded by language restriction criterion.
Hofferberth 1990	Drug: chlormezanone
Kuroki 1995	Japanese study. Excluded by language restriction criterion.
Larouche 1999	Back and neck pain. Excluded because it is an abstract.
Marcel 1990	French study. Excluded by language restriction criterion.
McGuinness 1969	Study population included patients with various musculoskeletal disorders; less than 50% back pain.
McGuinness 1983	Study population included patients with various musculoskeletal disorders; less than 50% back pain.
Meignany 1991	French study. Excluded by language restriction criterion.
Middleton 1984	Drug: chlormezanone
Nibbelink 1978	Neck and back pain; less than 50% back pain.

Study	Reason for exclusion
Preston 1984	Muscle spasm and pain of posttraumatic and inflammatory origin; unknown percentage back pain.
Scheiner 1978	Neck and back pain; less than 50% back pain.
Stehmann 1990	French study. Excluded by language restriction criterion.
Steingard 1980	Neck and low back pain; unknown percentage low back pain.
Tessari 1968	Italian study. Excluded by language restriction criterion.
Valtonen 1975	Neck and back pain; less than 50% back pain.
Vernon 1972	Study population consisted of a mix of musculoskeletal syndromes; percentage of back pain unknown.
Yakhno 1994	Russian study. Excluded by language restriction criterion.

DATA AND ANALYSES

Comparison 1. Benzodiazepines versus placebo for chronic low back pain

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain (dichotomous)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 : 5 - 7 days follow-up	2	152	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.72, 0.94]
1.2 : 8-14 days follow-up	2	146	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.54, 0.93]
2 Global efficacy (dichotomous, assessed by the patient)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 : 8 - 14 days follow-up	2	151	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.42, 0.97]

Analysis 1.1. Comparison 1 Benzodiazepines versus placebo for chronic low back pain, Outcome 1 Pain (dichotomous).

Study or subgroup	Muscle relaxant n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 : 5 - 7 days follow-up					
Arbus 1990	21/25	23/24		49.79%	0.88[0.72,1.06]
Salzmann 1992	39/55	44/48		50.21%	0.77[0.64,0.93]
Subtotal (95% CI)	80	72		100%	0.82[0.72,0.94]
Total events: 60 (Muscle relaxant), 67 (Placebo)					
Heterogeneity: Tau ² =0; Chi ² =0.91, df=1(P=0.34); I ² =0%					
Test for overall effect: Z=2.84(P=0)					
			Favours myorelaxant	0.2 0.5 1 2 5	Favours placebo

Analysis 1.2. Comparison 1 Benzodiazepines versus placebo for chronic low back pain, Outcome 2 Global efficacy (dichotomous, assessed by the patient).

Comparison 2. Non-benzodiazepines versus placebo for acute low back pain

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain (dichotomous)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 : 2-4 days follow-up	4	294	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.71, 0.90]
1.2 : 5-7 days follow-up	3	244	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.45, 0.76]
2 Muscle spasm	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 : 2-4 days follow-up	2	146	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.01, 8.40]
2.2 : 5-7 days follow-up	2	146	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.41, 0.74]
3 Physical outcomes (e.g. limitation of motion)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 : 2-4 days follow-up	3	252	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.66, 0.88]
3.2 : 5-7 days follow-up	3	251	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.40, 0.77]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Global efficacy (assessed by the patient)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 : 2-4 days follow-up	4	222	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.25, 0.96]
4.2 : 5-7 days follow-up	4	323	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.41, 1.13]
5 Adverse events	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Total	8	724	Risk Ratio (M-H, Random, 95% CI)	1.50 [1.14, 1.98]
5.2 Central Nervous System	8	724	Risk Ratio (M-H, Random, 95% CI)	2.04 [1.23, 3.37]
5.3 Gastrointestinal	7	692	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.29, 3.19]

Analysis 2.1. Comparison 2 Non-benzodiazapines versus placebo for acute low back pain, Outcome 1 Pain (dichotomous).

Analysis 2.2. Comparison 2 Non-benzodiazapines versus placebo for acute low back pain, Outcome 2 Muscle spasm.

Analysis 2.3. Comparison 2 Non-benzodiazapines versus placebo for acute low back pain, Outcome 3 Physical outcomes (e.g. limitation of motion).

Analysis 2.4. Comparison 2 Non-benzodiazapines versus placebo for acute low back pain, Outcome 4 Global efficacy (assessed by the patient).

Analysis 2.5. Comparison 2 Non-benzodiazapines versus placebo for acute low back pain, Outcome 5 Adverse events.

Comparison 3. Non-benzodiazepines versus placebo for chronic low back pain

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse Events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Total	2	246	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.67, 1.57]

Analysis 3.1. Comparison 3 Non-benzodiazepines versus placebo for chronic low back pain, Outcome 1 Adverse Events.

Comparison 4. Non-benzodiazepines + analgesics/NSAIDs versus placebo + analgesics/NSAIDs for acute low back pain

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain (dichotomous)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 : 2-4 days follow-up	2	469	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.37, 1.09]
2 Global efficacy (assessed by the patient)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 : 2-4 days follow-up	2	155	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.13, 1.32]
2.2 : 5-7 days follow-up	2	148	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.08, 1.77]
3 Adverse events	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Total	3	506	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.62, 2.75]
3.2 Central Nervous System	3	506	Risk Ratio (M-H, Random, 95% CI)	2.77 [1.18, 6.46]
3.3 Gastrointestinal	3	506	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.23, 1.00]

Analysis 4.1. Comparison 4 Non-benzodiazepines + analgesics/NSAIDs versus placebo + analgesics/NSAIDs for acute low back pain, Outcome 1 Pain (dichotomous).

Analysis 4.2. Comparison 4 Non-benzodiazepines + analgesics/NSAIDs versus placebo + analgesics/NSAIDs for acute low back pain, Outcome 2 Global efficacy (assessed by the patient).

Analysis 4.3. Comparison 4 Non-benzodiazepines + analgesics/NSAIDs versus placebo + analgesics/NSAIDs for acute low back pain, Outcome 3 Adverse events.

APPENDICES

Appendix 1. MEDLINE search strategy

- 1.randomized controlled trial.pt.
- 2.controlled clinical trial.pt.
- 3.randomized controlled trials.sh.
- 4.random allocation.sh.
- 5.double blind method.sh.
- 6.single blind method.sh.
- 7.1 or 2 or 3 or 4 or 5 or 6
- 8.(animal not (human and animal)).sh.
- 9.7 not 8
- 10.clinical trial.pt.
- 11.exp clinical trials/
- 12.(clin\$ adj25 trial\$).ti,ab.
- 13.((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
- 14.placebos.sh.
- 15.placebo\$.ti,ab.
- 16.random\$.ti,ab.
- 17.research design.sh.
- 18.volunteer\$.ti,ab.
- 19.10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
- 20.19 not 8
- 21.20 not 9
- 22.9 or 21
- 23.back pain.sh.
- 24.low back pain.sh.
- 25.back pain.ti,ab.
- 26.backache.ti,ab.
- 27.23 or 24 or 25 or 26
- 28.muscle relaxants, central.sh.
- 29.benzodiazepines.sh.
- 30.muscle relaxant\$.ti,ab.
- 31.benzodiazepine\$.ti,ab.
- 32.28 or 29 or 30 or 31
- 33.27 and 32
- 34.22 and 33

Appendix 2. EMBASE search strategy

- 1.clinical article/
- 2.clinical study/
- 3.clinical trial/
- 4.controlled study/
- 5.randomized controlled trial/
- 6.major clinical study/
- 7.double blind procedure/
- 8.multicenter study/
- 9.single blind procedure/
- 10.phase 3 clinical study/
- 11.phase 4 clinical study/
- 12.crossover procedure/
- 13.placebo/
- 14.or/1-13
- 15.allocat\$.ti,ab.
- 16.assign\$.ti,ab.
- 17.blind\$.ti,ab.
- 18.(clinic\$ adj25 (study or trial)).ti,ab.
- 19.compar\$.ti,ab.
- 20.control\$.ti,ab.
- 21.cross?over.ti,ab.
- 22.factorial\$.ti,ab.

23.follow?up.ti,ab.
 24.placebo\$.ti,ab.
 25.prospective\$.ti,ab.
 26.random\$.ti,ab.
 27.((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
 28.trial.ti,ab.
 29.(versus or vs).ti,ab.
 30.or/15 29
 31.14 or 30
 32.human/
 33.nonhuman/
 34.animal/
 35.animal experiment/
 36.33 or 34 or 35
 37.32 and 36
 38.31 not 36
 39.31 and 37
 40.38 or 39
 41.backache/
 42.low back pain/
 43.lumbago/
 43.back pain.ti,ab.
 44.backache.ti,ab.
 45.Lumbago.ti,ab.
 46.or/41-45
 47.muscle relaxants/
 48.benzodiazepines/
 49.muscle relaxant\$.ti,ab.
 50.benzodiazepine\$.ti,ab.
 51.or/47-50
 52.46 and 51
 53.52 and 40

FEEDBACK

from Ana Royer et al, 26 February 2017

Summary

Comment: We appreciated this extensive review, as this is a common medical condition that we frequently observe as not being optimally managed.

Currently, we are reviewing the use of cyclobenzaprine for pain as part of another project. In the process, we read your article and specifically evaluated the 3 included studies comparing cyclobenzaprine to placebo. We would like to address a few points from this review.

First, we noted that 17 studies were excluded from the review because their results were not presented separately for low back pain patients or because less than 50% of the study population consisted of low back pain patients. We believe that this likely led to many low back pain patients being excluded from the analyses, whose data may be valuable and may add to our knowledge of the condition. Thus, we feel that these studies should be included. In order to determine whether the results are affected by inclusion of patients with other types of pain, sensitivity analyses can be performed.

Secondly, we would like to address the assessments for risk of bias due to blinding. When reviewing the included trials that compared cyclobenzaprine to placebo, we noted that they were all assessed as having a low risk of bias. However, although the studies are described as double-blind, it is not clear in the publications as to who was blinded. The main description of blinding reported was regarding the appearance and/or packaging of the medication. For example, in the Baratta 1982 trial publication, it is mentioned that the patient and the investigator were blinded; however, the role(s) of the investigator were not explicitly stated. Separate individuals may have been responsible for assessing outcomes and/or providing care to patients, and if this is the case, it is unclear whether they were appropriately blinded. The lack of information provided in these publications makes it challenging to not only determine the overall risk of bias due to inadequate blinding, but also to judge the distinct risks of detection and performance biases.

Furthermore, when reviewing the risks of bias of the 3 studies comparing cyclobenzaprine to placebo, we judged there was a high risk of compromised blinding of patients, personnel, and outcome assessors. This is due to the high rate of observed adverse drug reactions (ADRs) with cyclobenzaprine. The occurrence of ADRs with cyclobenzaprine was shown to be as high as 43%, a 14% increase compared to placebo, in the Baratta 1982 trial (1). Additionally, the rates of ADRs were significantly greater with cyclobenzaprine compared to placebo

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in the Basmajian 1978 and Bianchi 1978 trials (2,3). We feel that it is important to factor in the detection and performance biases that could result from unblinding with observation of ADRs, especially when many of the efficacy outcomes in these pain studies were highly subjective. A trial by Quimby et al., which also compared cyclobenzaprine to placebo but in patients with fibromyalgia, demonstrated the significant impact that cyclobenzaprine ADRs can have on unblinding (4). Although it was designed as a randomized double-blinded trial, 67.5% of patients guessed the identity of the test drug correctly, and physicians were able to guess correctly for 77.5% of their patients. Dry mouth, which was an ADR that occurred in 47.5% of the patients, was statistically related to the guesses of both the patients and physicians. Therefore, it is very likely that unblinding due to ADRs occurred in all the studies included in your review that compared cyclobenzaprine to placebo. The risk of unblinding is important, as empirical studies have shown that a lack of blinding in randomized trials is associated with an exaggeration of estimated intervention effects by an average of 9%, measured as odds ratio (5). This estimated effect has been shown to be even more biased in trials with subjective outcomes (6). A recent systematic review by Hrobjartsson et al. found that, in randomized controlled trials involving subjective measurement scales, the use of non-blinded assessors exaggerated the pooled effect size by 68% (7).

To demonstrate the potentially large effect of unblinding on results, we took a finding from the Baratta 1982 trial as an example. In this trial, the proportion of patients whose muscle spasm improved on days 2-4 was greater by 10% in the cyclobenzaprine group, as compared to placebo. If this result was exaggerated by 68%, the "true" effect of cyclobenzaprine on improvement of muscle spasm was only 3.2%.

Thus, the impact of unblinding on the risk of bias should not be taken lightly, and accounting for this bias could greatly diminish the statistical and/or clinical significance of reported results. The Cochrane Handbook also states that, regardless of whether blinding was attempted in trials, a trial should be labelled as having a high risk of bias due to blinding if blinding likely could have been broken and if this likely could have influenced the outcome. While our feedback focuses mainly on cyclobenzaprine studies, it is probable that these issues apply to other trials included in your review, as they looked at other muscle relaxants that similarly are associated with easily identifiable ADRs.

In conclusion, we believe that several studies that were excluded from the review should be included, and that the trials' risks of bias due to blinding warrant reassessment.

We hope that you will kindly consider our feedback, and we thank you very much again for conducting this review.

Sincerely,

Anna Royer, B.Sc.(Pharm); Jia (Shermaine) Ngo, B.Sc.(Pharm); Hilary Wu, B.Sc. (Pharm), ACPR; Aaron M Tejani, B.Sc.(Pharm), PharmD

References:

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Reply

March 20, 2017

Thank you for taking the time to provide feedback on this review. A new team of authors is in the process of updating the review and will take your comments into consideration. Your comments are aligned with the [Furlan 2015](#) method guidelines.

Contributors

Shireen Harbin, Managing Editor, Cochrane Back and Neck

from Dr Claus Manniche, October 2004

Summary

The report recommends the usage of muscle relaxants for both acute and chronic spinal pain.

There are no references to the frequently observed physical and psychological dependency which the majority of the drugs of this type promote. These side-effects have been clearly described in the literature from both a qualitative and quantitative viewpoint. No reservations or modifications can be seen in the recommendations regarding the serious side-effects of the long-term usage of these drugs. Due to the fact that a potentially significant percentage of the potential users of these drugs develop chronic pain syndromes combined with the fact that a planned short-term prescription will frequently result in a lifelong dependency leads us to question the appropriateness of overall conclusions of the report as well as its inherent deficiencies.

It is our considered opinion - in accordance with the official policy in Denmark - that this family of drugs should simply not be used for the group of patients.

This issue has been discussed with the leadership of the Nordic Cochrane Institute. It has been recommended that this letter be the first step in the process of attaining a modification in the content of the report.

We look forward to receiving a comprehensive response to this letter and enclose a copy of a commentary which will be published in Spine in November, 2004.

Sincerely,

Claus Manniche, MD, professor and Alan Jordan, DC, PhD

To Spine , November, 2004: Back Pain and Muscle Relaxants and The Cochrane Collaboration

MV Tulder et al (1) recently published a Cochrane Collaboration report in Spine dealing with the prescription of muscle relaxants for low-back pain. The conclusions of this report can also be read on the Cochrane library's home page.

The following conclusion was arrived at based upon the results of 30 controlled short-term studies:

"Muscle relaxants are effective in the management of acute and chronic non-specific low back pain, but the adverse effects (most often drowsiness and dizziness) require that they be used with caution."

The Danish MTV-report (2) published in 1999, arrived at a different conclusion:

"Muscle relaxants, for example diazepam, should play no role in the treatment of back pain. The possible positive effects are greatly overshadowed by the risk of physical and psychological dependency, even after short term usage."

The clear difference in these conclusions (1,2) both of which were formed after a thorough analyses, is a prime example of how important it is to carry out the classical MTV process which includes an analysis of the long term side effects and other risks in conjunction with the utilisation of a technology, in addition to reviewing all of the scientific literature relating to possible clinical effects. In this case, 40 years clinical experience regarding the utilisation of muscle relaxants has abundantly demonstrated the massive problems associated with its usage, first and foremost the frequently seen physical and psychological dependence (3). The risk of extremely strong withdrawal symptom is great. As regards low back pain, these risks are in all likelihood increased due to the fact that low back pain frequently develops into chronic symptoms which in turn result in long term medication dependence. It is well known and commonplace for patients to "force" their physicians to renew their prescriptions.

It would have been appropriate if this Cochrane analysis included a discussion of the considerable published literature regarding the overuse and dependence related to drugs of this type and furthermore had incorporated these important factors into its recommendations.

The Danish Ministry of Health has recently begun several initiatives relating to the prescription of muscle relaxants. Among the steps taken are placing this family of drugs on a " national watch list" with the goal of reducing utilisation. This initiative has been instigated due to the widely accepted opinion that there are great risks related to the daily clinical usage of drugs in this group (4).

The recommendations of the MTV report of 1999 (2) are about to be reviewed. It is likely that the recommendations regarding muscle relaxants will remain unchanged. The risks are still greater than the possible benefits.

Claus Manniche, MD, professor and Alan Jordan, DC, PhD
Spine Centre, Ringe, Denmark

References:

1. Tulder MW, Touray T, Furlan AD, Solway S and Bouter LM. Muscle relaxants for non-specific low back pain: A systematic review within the framework of the Cochrane collaboration. Spine 2003; 28: 1978-92.

2. Manniche C, Ankjaer-Jensen A, Olesen A et al. Low Back Pain in a MTV-perspective. National Health Department, Copenhagen 1999.
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Reply

- November 2004

Thank you for taking the time to read and comment on our Muscle Relaxants for LBP Cochrane Review. The Editorial Board discussed your concerns at our last meeting and submit this response.

You express concern that there is no reference in the review to the adverse effects of muscle relaxants. Adverse effects are addressed in each comparison and again in the discussion, under 'adverse effects'.

The conclusions of the review state that "The results of this review illustrate strong evidence that non-benzodiazepines are effective for acute LBP. The evidence on benzodiazepines for acute and non-benzodiazepines for chronic LBP is less convincing. It is unknown if muscle relaxants are more effective than analgesics or NSAIDs, because there are no trials that directly compared these drugs. Muscle relaxants must be used with caution. The mechanism by which they induce their beneficial effects is also responsible for the intractable side effects associated with the central nervous system (drowsiness, dizziness). Therefore, it must be left to the discretion of the physician to weigh the pros and cons, taking into account the needs and preferences of the individual patient, to determine whether or not a specific patient is a suitable candidate for a course of muscle relaxants."

You argue specifically that this review has left out an important discussion of the published literature on the overuse and dependency associated with the prescription of muscle relaxants, in particular as it relates to the use of benzodiazepines.

One of our Editorial Board members looked at your cited references from the Danish Ministry of Health. The almost exclusive focus of these Danish publications is on the treatment of insomnia and anxiety and not on low back pain. None of these publications appear to contain a systematic review of the literature regarding side effects from the use of benzodiazepines, but represent descriptive data based on the Danish prescription habits by medical doctors and overuse by patients, in particular those who are already drug abusers.

Let us emphasize that the primary purpose of Cochrane systematic reviews is to provide a comprehensive and unbiased review of the literature. As such, they can help inform healthcare policy, but were never intended to replace national clinical guidelines or medical technology assessment initiatives, which usually factor in such elements as national, societal, and economic preferences.

Contributors

Editorial Board, Cochrane Back Review Group

WHAT'S NEW

Date	Event	Description
20 March 2017	Feedback has been incorporated	Feedback received February 2017. Response added March 2017. See Feedback section.

HISTORY

Protocol first published: Issue 3, 2000

Review first published: Issue 3, 2000

Date	Event	Description
20 June 2008	Amended	Converted to new review format.
30 April 2005	New search has been performed	Issue 3, 2005: extra precautions about the potential for dependency were added to the discussion section and to the Reviewers' conclusions.
1 November 2004	Feedback has been incorporated	Feedback added: 28 September 2004

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Date	Event	Description
		Response to feedback added: 1 November 2004 See Feedback section.

CONTRIBUTIONS OF AUTHORS

Tony Touray and Maurits van Tulder identified and selected studies, assessed the methodological quality of studies, performed the data extraction, and conducted the data analyses. Andrea Furlan and Sherra Solway were involved in assessing the methodological quality of selected studies, data extraction and in the writing and editing of the final review document. Lex Bouter was involved in writing of the review protocol and in writing of the final review.

DECLARATIONS OF INTEREST

One of the authors (Lex Bouter) is co-ordinating editor of the Cochrane Back Review Group. Editors are required to conduct at least one Cochrane review. This requirement ensures that editors are aware of the processes and commitment needed to conduct reviews. None of the editors are first authors. This involvement does not seem to be a source of conflict of interest in the Back Review Group. Any editor who is a author is excluded from editorial decisions on the review in which they are contributors.

SOURCES OF SUPPORT

Internal sources

- Institute for Research in Extramural Medicine, Netherlands.
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- Health Insurance Board, Netherlands.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Chronic Disease; Low Back Pain [*drug therapy]; Muscle Relaxants, Central [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans