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Muscle Relaxants for Nonspecific Low Back Pain: A Systematic Review Within the Framework of the Cochrane Collaboration

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Study Design. A systematic review of randomized and/or double-blinded controlled trials.

Summary of Background Data. The use of muscle relaxants in the management of nonspecific 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 nonspecific low back pain.

Methods. A computer-assisted search of the Cochrane Library (Issue 2, 2002), MEDLINE (1966 up to October 2001), and EMBASE (1988 up to October 2001) 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. Randomized and/or double-blinded controlled trials, involving patients diagnosed with nonspecific low back pain, treated with muscle relaxants as monotherapy or in combination with other therapeutic methods, were included for review. Two reviewers independently carried out the methodologic 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.

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 nonbenzodiazepines, and 2 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 low back pain on short-term pain relief. The pooled relative risk for nonbenzodiazepines *versus* placebo after 2 to 4 days was 0.80 (95% confidence interval: 0.71 to 0.89) for pain relief and 0.49 (95% confidence interval: 0.25 to 0.95) for global efficacy. Adverse events, however, with a relative risk of 1.50 (95% confidence interval: 1.14 to 1.98) were significantly more prevalent in patients receiving muscle relaxants and especially the central nervous system adverse effects (relative risk 2.04; 95% confidence interval: 1.23 to 3.37). The various muscle relaxants were found to be similar in performance.

Conclusions. Muscle relaxants are effective in the management of nonspecific 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 nonsteroidal anti-inflammatory drugs. [Key words: systematic review, Cochrane Collaboration, effectiveness, muscle relaxants, low back pain] **Spine 2003;28:1978–1992**

Muscle relaxants are one of the many treatments currently employed in the management of nonspecific low back pain (LBP). Thirty-five percent of patients visiting a primary care physician for LBP are prescribed muscle relaxants.[1] 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 LBP. Antispasmodics can be subclassified into benzodiazepines and nonbenzodiazepines.

Benzodiazepines (*e.g.*, diazepam, tetrazepam) are used as anxiolytics, sedatives, hypnotics, anticonvulsants, and/or skeletal muscle relaxants.[2] 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.

Nonbenzodiazepines include a variety of drugs that can act at the brain stem or spinal cord level.[2] 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.[3] 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 antianxiety 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 endplate, 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.[4] 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 favor the combination of antispasmodics with nonsteroidal anti-inflammatory drugs (NSAIDs).[5]

Antispasticity medications are used to reduce spasticity that interferes with therapy or function, such as in cerebral palsy, multiple sclerosis, and spinal cord injuries.[6] 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.[7]

The use of muscle relaxants for low back pain continues to be a source of controversy among 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.[8] 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.[9] Despite this, 91% of physicians report using muscle relaxants even if they are conditionally discouraged by guidelines.[10]

The role of muscle spasm in the pathophysiology of LBP 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.[11] Others view muscle spasm as a protective physiologic response that should not be inhibited by muscle relaxants.[12] Muscle spasm secondary to a pathologic 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[13]; however, there is a lack of good quality research on the clinical application of these drugs.[14]

Objectives

The aim of this systematic review was to determine if muscle relaxants are effective in the treatment of nonspecific LBP. The following comparisons were investigated:

1) Muscle relaxants *versus* placebo

2) Muscle relaxants *versus* paracetamol/acetaminophen

3) Muscle relaxants *versus* NSAIDs

4) Muscle relaxants *versus* mscle relaxants

5) Muscle relaxants + analgesics/NSAIDs *versus* placebo + analgesics/NSAIDs

■ Methods

Criteria for Considering Studies for This Review

Types of studies. Only randomized controlled trials (RCTs) and double-blind controlled clinical trials (CCTs) were included.

Types of Participants. Only trials involving patients diagnosed with "nonspecific low back pain" were included. Nonspecific LBP was defined as pain localized between the scapulas and inferior gluteal folds that may or may not radiate down towards the knees, for which specific etiologies such as infections, neoplasms, metastases, osteoporosis, fractures, rheumatological disorders, neurologic disorders, and other relevant pathologic entities have been ruled out clinically.

Trials involving patients with various musculoskeletal disorders were included if results were presented separately for the subgroup of LBP patients or if more than 50% of the study population consisted of LBP patients.

Types of Interventions. The use of muscle relaxants as monotherapy or in combination with other therapeutic methods was 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.[15] 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)
- Physiologic 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 Strategy for Identification of Studies. A computer-assisted search of the Cochrane Library (Issue 2, 2002), MEDLINE (up to October 2001), and EMBASE (up to October 2001) was carried out. These databases were searched using the algorithm recommended in the Cochrane Collaboration Handbook[16] and the Back Review Group. Pertinent references cited in the identified articles were also screened as well as references of other systematic reviews.[13,14,17] 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.

General Procedure of the Review. The review started with a literature search. Studies meeting the inclusion criteria were screened and analyzed for methodologic quality. This was followed by the extraction and analysis of the relevant data. The selection of studies, methodologic quality assessment, and data extraction were carried out by two independent reviewers. Nineteen studies that were originally identified in MEDLINE, EMBASE, and the Cochrane Library were independently assessed by one pair of reviewers (T.T. and M.vT.). Eleven studies[4,5,18-26] identified through reference checking were included at a later stage and were independently assessed by another pair of reviewers (M.vT. and S.S.; A.F. and S.S.). Results at each stage were compared and discrepancies were resolved in a consensus meeting.

Methodologic Quality Assessment. The methodologic quality of each RCT was assessed using the criteria recommended by the Cochrane Back Review Group.[27] 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 randomization
3) Similarity of baseline characteristics
4) Blinding of patients
5) Blinding of care provider
6) Equal cointerventions
7) Adequate compliance
8) Identical timing of outcome assessment
9) Blinded outcome assessment
10) Withdrawals and dropouts adequate
11) Intention-to-treat analysis

All items were scored as positive (+), negative (−), or unclear (?). High quality was defined as fulfilling 6 or more of the 11 quality criteria. A sensitivity analysis in which the effect of variations in the cutoff point distinguishing studies of high and low methodologic quality was conducted. We did not contact the authors for additional information because most studies had been published many years ago with only 7 studies published in or after 1990.

Data Extraction. The data extraction was carried out by the same reviewers who performed the quality assessment using a standardized 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 LBP (duration of symptoms less than 12 weeks) and chronic LBP (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, nonbenzodiazepine antispasmodics, or antispasticity drug), the doses administered, and the frequency and duration of the administration of the treatments were 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 was regarded positive (in favor 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.[28,29] We considered a clinically important difference in VAS to be >16 mm or

>30% decrease. For an 11-point NRS, this was 2 points or more.

Data Analysis. 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 an RR smaller than 1 indicated a positive effect of muscle relaxants. For example, an RR of 0.74 (95% CI 0.55–0.98) means that the chance of "not getting pain relief" is 26% less in the muscle relaxants group compared to the placebo group, with a CI of 2% to 45%. The data entered in the meta-analyses were adversive 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, nonbenzodiazepines, and antispasticity drugs), for various outcome measures, and for various follow-up moments.

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

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

Literature Search and Study Selection
The computer-assisted literature search produced a yield of 7 references in the Cochrane Library, 25 in MEDLINE, and 25 in EMBASE. Taking into account 11 articles that were cross-referenced in the 3 databases, a net total of 46 articles were found to be potentially eligible. Further assessment of the articles and application of the inclusion and exclusion criteria resulted in 19 articles. Eleven additional studies were identified through reference checking,[4,5,18,26] resulting in a total of 30 studies.

Not all studies included in the systematic review of cyclobenzaprine for back pain[13] 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 LBP patients or if more than 50% of the study population consisted of LBP patients.

A total of 28 studies[30–57] identified in electronic databases or through reference checking were excluded.

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 *versus* placebo

1a) Benzodiazepines *versus* placebo[25,58–60]

1b) Nonbenzodiazepines *versus* placebo[4,18,19,23,59,61–66]

1c) Antispasticity *versus* placebo[67,68]

2) Muscle relaxants *versus* paracetamol/acetaminophen (no studies)

3) Muscle relaxants *versus* NSAIDs (no studies)

4) Muscle relaxants *versus* muscle relaxants[18,20,22,24,59,64,69,70]

5) Muscle relaxants + analgesics/NSAIDs *versus* placebo + analgesics/NSAIDs[5,21,71–74]

Other Comparisons
Other studies compared ethoheptazine plus meprobamate plus aspirin *versus* NSAID (mefenamic acid),[75] orphenadrine *versus* phenobarbital,[63] orphenadrine plus paracetamol *versus* aspirin,[76] and diazepam plus paracetamol-codeine *versus* levomepromazine plus paracetamol-codeine.[26] These studies are summarized in Table 1, but not included in the results section because they could not be classified in one of the predefined comparisons.

Methodologic Quality of Included Studies
The median score for methodologic quality of all the included studies was 6 with a range of 3 to 9 (Table 2). Using a cutoff point of 6 out of 11 criteria, 23 of the 30 studies (77%) were of high quality.[4,5,18–23,25,58,61,62,64–71,73,74,76]

The most common methodologic 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 randomization (80% scored "negative" or "unclear")
- Nonequivalent cointerventions (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 reviewers for each study demonstrated a reviewer concurrence rate of 73%. The disagreement in 27% of the scores could be attributed to subtle differences in interpretation of the criteria. This

Table 1. Methodological Quality Assessment of Randomized and Double-Blind Controlled Trials on the Effectiveness of Muscle Relaxants for Nonspecific Low Back Pain

Reference	1	2	3	4	5	6	7	8	9	10	11	Total
Arbus[58]	–	?	–	+	+	?	?	+	+	+	+	6
Baptista[18]	–	–	?	+	+	–	–	+	+	+	+	6
Baratta[61]	–	+	+	+	+	–	–	+	+	+	–	6
Basmajian[59]	–	?	–	+	+	–	–	+	+	–	–	4
Berry[62]	–	?	+	+	+	?	?	+	+	+	+	7
Berry[71]	–	?	+	+	+	?	–	+	+	+	+	7
Bianchi[19]	?	+	+	+	+	?	?	+	+	–	?	6
Borenstein[72]	–	?	–	–	–	?	?	+	–	+	+	3
Boyles[69]	–	+	+	+	+	+	?	+	+	+	–	8
Bragstad[20]	?	?	+	+	+	+	–	+	+	+	–	7
Casale[67]	+	?	+	+	+	+	–	+	+	+	+	9
Corts Giner[21]	–	–	+	+	+	–	–	+	+	+	+	7
Dapas[68]	–	?	+	+	+	+	+	+	+	–	–	7
Gold[63]	–	?	–	+	+	–	–	+	+	–	–	4
Hennies[22]	?	?	+	+	+	+	–	+	+	+	–	7
Hindle[64]	+	+	–	+	+	–	–	+	+	+	–	7
Hingorani[73]	–	?	–	+	+	–	–	+	+	+	+	6
Hingorani[76]	–	–	–	+	+	–	–	+	+	+	+	6
Klinger[65]	–	?	–	+	+	+	+	+	+	+	?	7
Lepisto[23]	–	?	+	+	+	+	?	+	+	+	+	8
Moll[60]	–	?	–	+	+	–	–	+	+	+	–	5
Pipino[24]	?	?	+	–	?	+	–	+	?	+	+	5
Pratzel[4]	–	?	+	+	+	+	+	+	+	–	–	7
Rollings[70]	–	+	+	+	+	+	+	+	+	–	–	8
Salzmann[25]	?	?	?	+	+	+	+	+	+	–	?	6
Sirdalud[5]	–	?	+	+	+	+	?	+	+	?	–	6
Sweetman[75]	–	?	+	+	+	–	–	+	+	–	–	5
Tervo[74]	–	+	+	+	+	–	–	–	+	+	–	6
Weber[26]	–	–	?	+	+	?	–	?	+	–	–	3
Wörz[66]	–	?	–	+	+	–	–	+	+	+	+	6

1) Adequate allocation concealment, 2) Adequate method of randomization, 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.
+ = positive; − = negative; ? = unclear.

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.

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 explicit 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 precommercial name of the muscle relaxant drug, such as DS 103-282 for tizanidine.

Data on sample size, age and gender, type and duration of symptoms, and setting are summarized in Table 1. Twenty-four studies included patients with acute LBP and 6 studies chronic LBP.[4,24,25,58,59,66] 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.

Eight studies were identified which included benzodiazepines,[22,25,26,58-60,69,73] 23 studies nonbenzodiazepines,[4,5,18-24,59,61-66,69-72,74-76] and 2 studies antispasticity drugs.[67,68]

Five studies made use of injection therapy. In one of these studies, the efficacy of a single intravenous injection was evaluated,[65] whereas in the other four studies, an intramuscular injection was followed by oral medication.[24,60,73,74]

Effectiveness of Muscle Relaxants

Benzodiazepines Versus Placebo. Four studies were identified, one on acute LBP[60] and three on chronic LBP.[25,58,59]

Acute Low Back Pain. 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 for short-term pain relief and better overall improvement, but is associated with substantially more central nervous system side effects.[60]

Table 2. Characteristics of Randomized and Double-blind Controlled Trials on the Effectiveness of Muscle Relaxants for Nonspecific Low Back Pain

Study	Design and participants	Interventions	Outcomes
Arbus[58]	Randomized, placebo-controlled, double-blind trial. Sponsored by Sanofi. N = 50; Male/Female (%): ? Age: 18–80 years. Diagnosis: chronic LBP with or without radiological abnormality. Placebo responders were excluded. Setting: outpatient.	(I) Tetrazepam 50 mg t.i.d./10 days. N = 25. (R) Placebo t.i.d./10 days. N = 24.	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.]
Baptista[18]	Multicenter, double-blind, placebo controlled trial. Sponsorship: none declared. N = 267; Male/Female (%): 35.6/60.4. Age: 17–64 years; mean = 41.7 years. Diagnosis: painful spasms of paravertebral muscles (acute LBP). Setting: outpatient.	(I1) Tizanidine 2 mg t.i.d./8 days. N = 89. (I2) Tizanidine 4 mg t.i.d./8 days. N = 89. (R) Placebo t.i.d./8 days. N = 89.	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.
Baratta[61]	Randomized, placebo-controlled, double-blind trial. Merck Sharp & Dohme performed statistical evaluation of data. 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.	(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.	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.]. 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].
Basmajian[59]	Randomized, placebo-controlled, double-blind trial. Supported by Merck Sharp & Dohme. N = 76; Male/Female (%): ? Mean age: ? Diagnosis: Chronic LBP. Muscle spasm, limitation of motion and ADL, pain and tenderness on palpation. Setting: outpatient.	(I1) 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.	No measurement of pain, global efficacy or activity of daily living. Mean decrease of muscle spasm (1–5 point scale) from baseline to days 13–18: (I1): 3.2 to 2.2; (I2): 2.9 to 1.9; (R): 3.2 to 2.1. [no differences among groups]
Berry[62]	Randomized, placebo-controlled, double-blind trial. Sandoz Ltd. supplied medication. TIL (Medical) Ltd. Organized and monitored study. N = 112; Male/Female (%): 51/49. Mean age: 41 (16–69) Diagnosis: Acute LBP. Setting: Primary care.	(I) Tizanidine 4 mg t.i.d./7 days. N = 59. (R) Placebo t.i.d./7 days. N = 53.	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].
Berry[71]	Randomized, placebo-controlled, double-blind trial. Sandoz Ltd. supplied medication; TIL (Medical) Ltd. Organized and monitored study. N = 105; Male/Female (%): 55/45. Age: 42.5 (20–66) Diagnosis: Acute LBP. Setting: Primary care.	(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.	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].
Bianchi[19]	Randomized, placebo-controlled, double-blind trial. Merck Sharp & Dohme provided editorial assistance. 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.	(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.	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 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 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].
Borenstein[72]	Randomized, open-label trial. Supported by Merck Sharp & Dohme. N = 40; Male/Female (%): 70/30 Mean age: 34.5 (20–57) Diagnosis: Acute, mild to moderate LBP. Setting: outpatient.	(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.	Pain (0 to 20 NRS), descriptive pain scale (from 0 to 3), no. 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.]. Functional capacity (0–3 scale): (I): 9; (R): 15. [no differences]. Global efficacy (0 = poor to 4 = excellent). [no differences].

(Table continues)

Table 2. Continued

Study	Design and participants	Interventions	Outcomes
Boyles[69]	Randomized, double-blind trial. N = 80; Male/Female (%): 48/52 Mean age: 39 (19–65) Diagnosis: Acute LBP. Setting: outpatient.	(I1) Carisoprodol 350 mg q.i.d./7 days. N = 40. (I2) Diazepam 5 mg q.i.d./7 days. N = 40.	Pain (100-mm VAS) day 7—baseline (I): 58 (I2): 48; muscle stiffness (I): 59 (I2): 42; activity (I): 58 (I2): 41; overall relief: (I): 75, (I2): 56. [stat. sign. For muscle stiffness, activity, and relief]. Overall improvement (very good + excellent): (I): 70%, (I2): 45%.
Bragstad[20]	Randomized, double-blind trial. Sponsorship not declared, but most likely Sandoz Ltd supplied the medication. 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).	(I1) Tizanidine 2 mg t.i.d., 7 days. N = 14. (I2): Chlorzoxazone 500 mg t.i.d., 7 days. N = 13.	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.
Casale[67]	Randomized, placebo-controlled, double-blind trial. Medication supplied by Boots-Formenti Pharmaceuticals. N = 20; Male/Female (%): 75/25; Mean age: 46.9 (37–58) Diagnosis: acute episode of chronic LBP. Setting: secondary care.	(I) Dantrolene sodium 25 mg o.i.d./4 days, N = 10. (R) Placebo o.i.d./4 days. N = 10.	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%. Pain behavior stat. sign. Better in (I) than (R) on day 4.
Corts Giner[21]	Placebo-controlled, double-blind trial. Sponsorship: none declared. 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: ?	(I) Tizanidine 4 mg t.i.d. + paracetamol 500 mg/7 days. N = 26. (R) Placebo t.i.d. + paracetamol 500 mg/7 days. N = 24.	Pain (4-point scale) on movement at baseline, day 3 and 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.
Dapas[68]	Randomized, placebo-controlled, double-blind trial. Sponsored by Ciba-Geigy. 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.	(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.	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.
Gold[63]	Randomized, placebo-controlled, double-blind trial. Supported by Riker Laboratories, Inc. N = 60; Male/Female (%): ? Mean age: ? Diagnosis: Acute LBP and muscle spasms. Setting: outpatient.	(I) Orphenadrine 100 mg b.i.d./7 days. N = 20. (R1) Phenobarbital 32 mg b.i.d./7 days. N = 20. (R2) Placebo b.i.d./7 days. N = 20.	Reduced pain at 2 days: (I): 9/20; (R1): 3/20; (R2): 4/20 [(I) stat. sign. better than (R1) and (R2)]. Overall improvement at 2 days: (I): 7/20; (R1): 3/20; (R2): 0/20. [(I) stat. sign. better than (R2)].
Hennies[22]	Randomized, double-blind trial. Sponsorship not declared but most likely Sandoz Ltd supplied medication. N = 30; Male/Female (%): 33/67 Mean age: 47.5 (25–70) Diagnosis: Acute spasm of back (80%) and neck (20%) muscles, actual no. of weeks of duration unknown. Setting: 'ambulant patients'.	(I1) Tizanidine, 4 mg t.i.d., 7 days. N = 15. (I2) Diazepam 5 mg t.i.d., 7 days. N = 15.	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. 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.
Hindle[64]	Randomized, placebo-controlled, double-blind trial. Medications were provided by Wallace Pharmaceuticals. 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.	(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. Note: 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 complaints than the other groups.	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)].

(*Table continues*)

Table 2. Continued

Study	Design and participants	Interventions	Outcomes
Hingorani[73]	Double-blind, placebo-controlled trial. Roche Ltd. acknowledged for their "help and cooperation." N = 50; Male/Female (%): 80/20 Mean age: ? Diagnosis: Acute LBP severe enough to require admission to hospital. Setting: secondary care. All patients were hospitalized and treated with complete bed rest and 8/25 in (I) and 6/25 in (R) received additional therapy.	(I) Diazepam injections: 10 mg IM/6 hrs/24 hrs. Oral: 2 mg q.i.d./5 days plus calcium aspirin 10 g 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.	Subjective results (pain and tenderness), no. 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].
Hingorani[76]	Randomized, placebo-controlled, double-blind trial. Cooperation and assistance from Riker Laboratories Inc. is acknowledged. N = 99; Male/Female (%): 61/39 Mean age: 43.5 Diagnosis: Acute LBP of sufficient severity to require inpatient treatment. Setting: secondary care.	(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.	Number of patients with improvement in pain (4-point scale) at the end of the trial: (I): 37 (R): 34 [no differences].
Klinger[65]	Randomized, placebo-controlled, double-blind trial. Four authors were affiliated with the Clinical Research Department of Riker Laboratories. N = 80; Male/Female (%): 81/19 Mean age: 33.8 (14–62) Diagnosis: Acute LBP and muscle spasms. Setting: tertiary care.	(I) Orphenadrine 60 mg intravenously, single dose. N = 40. (R) Placebo intravenously, single dose. N = 40.	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)].
Lepisto[23]	Randomized, placebo-controlled, double-blind trial. Sponsorship: none declared. 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.	(I): Tizanidine 2 mg, t.i.d., 7 days. N = 15. (R): Placebo, t.i.d., 7 days. N = 15.	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]. 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]. Patient's assessment of overall response (excellent, good, moderate, poor): (I): 6, 6, 2, 1 (R): 2, 4, 7, 2 [no difference].
Moll[60]	Randomized, placebo-controlled, double-blind trial. Sponsorship not declared. N = 68; Male/Female (%): 56/44 Mean age: 45.6 (23–72) Diagnosis: Acute LBP Setting: ?	(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. Note: Groups were not similar at baseline.	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)]
Pipino[24]	Randomized single-blind clinical trial. Sponsorship: none declared. 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.	(I1) Pridinol mesilate 4 mg IM injection b.i.d. × 3 days followed by 2 mg b.i.d. orally × 4 days. N = 60. (I2) Thiocolchicoside 4 mg IM injection b.i.d. × 3 days followed by 8 mg b.i.d. orally × 4 days. N = 60.	Mean (SD) pain intensity (VAS) at baseline, day 4 and day 7: (I1): 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.
Pratzel[4]	Randomized, placebo-controlled, double-blind trial. One of the authors affiliated with Strathmann AG. 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.	(I) Tolperisone 100 mg t.i.d., 21 days. N = 67. (R) Placebo t.i.d./21 days. N = 70.	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)].
Rollings[70]	Randomized, placebo-controlled, double-blind trial. Sponsorship: none declared. 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.	(I1) Carisoprodol 350 mg q.i.d./7 days. N = 39. (I2) Cyclobenzaprine 10 mg q.i.d./7 days. N = 39.	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. Overall improvement (very good to excellent) at end of treatment: (I): 70%, (I2): 70%. No differences between groups.

(Table continues)

Table 2. Continued

Study	Design and participants	Interventions	Outcomes
Salzmann[25]	Randomized, placebo-controlled double-blind trial. Sponsored by Sanofi Winthrop. 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.	(I): Tetrazepam 50 mg t.i.d./14 days plus physiotherapy. N = 79. (R): Placebo t.i.d/14 days plus physiotherapy. N = 73.	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]. Data only presented for 103 patients in per protocol analysis.
Sirdalud[5]	Randomized, placebo-controlled, double-blind trial. Sponsored by Novartis Pharma AG, Basel. 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 pain. Setting: not specified.	(I) Tizanidine 2 mg plus diclofenac 50 mg b.i.d./7 days. N = 185. (R) Placebo plus diclofenac 50 mg b.i.d./7 days. N = 176.	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.]
Sweetman[75]	Randomized, placebo-controlled, double-blind trial. Sponsorship: none declared. N = 122; Male/Female (%): 53/47 Mean age: 41.3 (?) Diagnosis: Acute LBP (1–28 days). Setting: Outpatient.	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.	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].
Tervo[74]	Randomized, placebo-controlled, double-blind trial. Sponsorship: none declared. 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.	(I) Orphenadrine 60 mg (2 ml) IM followed by orphenadrine (35 mg) + paracetamol (450 mg) 2 tablets t.i.d., 7 days. N = 25. (R) Saline 2 ml IM followed by paracetamol (450 mg) 2 tablets t.i.d., 7 days. N = 25.	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). Note: Baseline measurements, 15 minutes after injection.
Weber[26]	Double-blind, controlled clinical trial. Sponsorship: none declared. N = 78; Male/Female (%): 60/40 Mean age: 46.2 (I) and 47.4 (R) Diagnosis: Acute lumbago-sciatica and cervical pain; majority LBP Setting: Secondary care—hospital.	(I) Diazepam t.i.d (7 mg, 7 mg, 10 mg)/6 days + paralgin Forte (paracetamol 400 mg, codeine 20 mg, promethazine 5 mg) t.i.d./3 days, then prn. N = 33. (R) Levomepromazine t.i.d (7.5 mg + 7.5 mg + 15 mg) 6 days + paralgin Forte t.i.d./3 days, then prn. N = 45.	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].
Wörz[66]	Randomized, placebo-controlled, double-blind trial. One author affiliated with ASTA Medica. N = 107; Male/Female (%): 43/57 Mean age: 49.7 Diagnosis: Chronic LBP Setting: ?	Chlormezanone. Excluded from this review. (I) Flupirtin 100 mg q.i.d./7 days. N = 53. (R) Placebo q.i.d./7 days. N = 54.	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)].

Chronic Low Back Pain. The 2 high quality trials on chronic LBP[25,58] showed that there is strong evidence (2 trials; 222 people) that tetrazepam 50 mg 3 times daily is more effective than placebo for patients with chronic LBP for short-term pain relief and overall improvement. The pooled RRs and 95% CIs for pain intensity were 0.82 (0.72–0.94) after 5 to 7 days follow-up and 0.71 (0.54–0.93) after 10 to 14 days. The pooled RR and 95% CI for overall improvement was 0.63 (0.42–0.97) after 10 to 14 days follow-up. One high quality trial[58] showed that there is moderate evidence (1 trial; 50 people) that tetrazepam is more effective than placebo for 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 for short-term decrease of muscle spasm.[59]

Nonbenzodiazepines Versus Placebo

Eleven studies were identified, eight on acute LBP[18,19,23,61–65] and three on chronic LBP.[4,59,66]

Acute Low Back Pain. One high quality study on acute LBP[65] showed that there is moderate evidence (1 trial; 80 people) that a single intravenous injection of 60 mg orphenadrine is more effective than placebo for immediate relief of pain and muscle spasm for patients with acute LBP.

Three high quality[23,61,62] and 1 low quality trial[63] showed that there is strong evidence (4 trials; 294 people) that oral nonbenzodiazepines are more effective than placebo for patients with acute LBP for short-term pain relief, global efficacy, and improvement of physical outcomes. The pooled RR and 95% CIs for pain intensity

were 0.80 (0.71–0.89) after 2 to 4 days (4 trials; 294 people) and 0.58 (0.45–0.76) after 5 to 7 days follow-up (3 trials; 244 people). The pooled RR and 95% CIs for global efficacy were 0.49 (0.25–0.95) after 2 to 4 days (4 trials; 222 people) and 0.68 (0.41–1.13) after 5 to 7 days follow-up (4 trials; 323 people). The pooled RR and 95% CIs for physical outcomes were 0.76 (0.66–0.88) after 2 to 4 days (3 trials; 252 people) and 0.55 (0.40–0.77) after 5 to 7 days follow-up (3 trials; 251 people).

Of the three high quality trials[18,19,64] that could not be included in the statistical pooling due to insufficient data, 1 large trial (267 people) reported no differences after 3 and 7 days in pain relief and global efficacy between tizanidine and placebo.[18] Two small trials (48 people each) reported that oral nonbenzodiazepines are more effective than placebo regarding pain intensity, global efficacy, and muscle spasm after 7 and 14 days[19] and on pain intensity after 4 days.[64] However, in the last trial, groups were not similar at baseline, which may have biased the results.

Strong evidence from all 8 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 (1.14–1.98), 2.04 (1.23–3.37) and 0.95 (0.29–3.19), 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 Low Back Pain. One high quality trial[66] showed that there is moderate evidence (1 trial; 107 people) that flupirtine is more effective than placebo for patients with chronic LBP for short-term pain relief and overall improvement after 7 days, but not for reduction of muscle spasm. One high quality trial[4] showed that there is moderate evidence (1 trial; 112 people) that tolperisone is more effective than placebo for patients with chronic LBP for short-term overall improvement after 21 days, but not for pain relief and reduction of muscle spasm. The low quality trial[59] 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.

Antispasticity Drugs Versus Placebo

Acute Low Back Pain. Two high quality trials[67,68] showed that there is strong evidence (2 trials; 220 people) that antispasticity muscle relaxants are more effective than placebo for patients with acute LBP for short-term pain relief and reduction of muscle spasm after 4 days. One high quality trial[68] also showed that there is moderate evidence that antispasticity muscle relaxants

are more effective than placebo for patients with acute LBP for short-term pain relief, reduction of muscle spasm, and overall improvement after 10 days.

Muscle Relaxants Versus Paracetamol/Acetaminophen

No RCTs or double-blind trials were identified.

Muscle Relaxants Versus Nonsteroidal Anti-Inflammatory Drugs

No RCTs or double-blind trials were identified.

Muscle Relaxants versus Muscle Relaxants

Eight studies were identified, five high quality[20,22,64,69,70] and three low quality trials.[18,24,59]

Carisoprodol. This muscle relaxant was investigated in two high quality studies on acute LBP. The first study compared carisoprodol with diazepam.[69] Carisoprodol was superior in performance on all outcome parameters measured. Comparison of carisoprodol with cyclobenzaprine-hydrochloride in the second study revealed no statistically significant differences between the two treatments.[70]

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.[20] No differences were found between the treatments.

Cyclobenzaprine-Hydrochloride. Cyclobenzaprine was compared with diazepam in a low quality trial on chronic LBP, but no significant differences between the treatments were identified.[59] There was also no significant difference between cyclobenzaprine and carisoprodol in one high quality study on acute LBP.[70]

Diazepam. In comparison with carisoprodol, diazepam was found to be inferior in performance for muscle spasm, global efficacy, and functional status in a high quality trial on acute LBP.[69] 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 7 days.[22]

Tizanidine. This muscle relaxant was compared with chlorzoxazone and diazepam in two very small high quality trials.[20,22] 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.[24]

Muscle Relaxants + Analgesics/NSAIDs versus Placebo + Analgesics/NSAIDs

Six studies were identified on acute LBP, five high quality[5,21,71,73,74] and one low quality trial.[72] Five trials evaluated nonbenzodiazepines and only one trial benzodiazepines.[73]

Acute Low Back Pain. Three high quality trials showed that there is strong evidence (3 trials; 560 people) that

tizanidine plus analgesics[21] or NSAIDs[5,71] is more effective than placebo plus analgesics or NSAIDs for patients with acute LBP for short-term pain relief and decrease of muscle spasm after 3 to 4 and 7 to 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.[74] 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.[72] Data on adverse events from four studies (556 people) were pooled.[5,71,72,74] Using the random effects model, the RR and 95% CI was 1.34 (0.67–2.67), 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 (1.05–5.63) and 0.54 (0.26–1.14), 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.[73]

Preplanned Subgroup Analyses

Low Back Pain With and Without Sciatica and Muscle Spasms. No trials specifically addressed sciatica. We could not perform a subgroup 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 did not mention muscle spasm reflect in reality patients without muscle spasm.

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 3 times daily) or were found to be too heterogeneous in terms of control interventions and outcome parameters to be able to make any comparisons.

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.[68] 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.[73] No difference was found between the two treatments in this trial.

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 10 mg every 6 hours for 24 hours.[73] 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 60 mg of orphenadrine administered intramuscularly followed by oral tablets plus paracetamol compared with placebo. There was no difference in global efficacy. Dropout rate in this trial was high.[74]

One high quality study using 60 mg of orphenadrine administered intravenously compared to placebo found significant relief of pain and spasm 45 minutes after a single injection.[65]

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.[60]

The other low quality trial showed no differences between pridinol mesilate and thiocolchicoside intramuscular followed by oral tablets.[24]

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.[59,63] 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 3 studies from low to high quality.[24,60,75] 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 *versus* placebo for chronic LBP changed from strong to moderate, and the moderate evidence on muscle spasm to limited. The evidence that flupirtine 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 Study 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 that 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.[77]

Methodologic Quality

Using a cutoff point of 6 out of 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 methodologic flaws involved the concealment of treatment allocation, compliance, and randomization 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 "randomized," which does not give the reader confidence that a trial has been properly randomized or that the randomization 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 that must be equally divided between study groups to prevent bias. This was also true of cointerventions. In 18 of the 30 trials (60%), cointerventions 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 methodologic 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 nonbenzodiazepines 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 fewer trials than for nonbenzodiazepines. The evidence of benzodiazepines for acute and nonbenzodiazepines 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,[13] which showed that cyclobenzaprine is more effective than placebo at the price of greater adverse effects. An exception was dantrolene sodium,[67] one of the antispasticity muscle relaxants identified in the review. 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[67] 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.[78]

Although a positive treatment effect was found for antispasticity muscle relaxants, for acute LBP the clinical relevance of this finding for the LBP population is questionable as these medications are typically prescribed for neurologic 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 methods, specifically analgesics/NSAIDs.[79] 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 nonbenzodiazepines 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 LBP as cited in the United Kingdom, American, and Dutch guidelines[17,80,81] and other guidelines.[9]

Chlorzoxazone is implicated in 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 hospitalized because of these conditions and 1147 patients hospitalized for other reasons. Data were 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, whereas only 1 among the control group used this drug. Based on the findings in this study, chlormezanone was discontinued in 1996 worldwide.[15]

Minimally Clinical Important Difference

When evaluating the effectiveness of a treatment intervention, statistical significance is a necessary but insufficient criterion.[28,29] 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.[28,82] 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.[28,29,83]

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.[82] 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 vs. placebo or vs. active treatments), and whose 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 et al[28] suggest that a 2-point or 30% reduction on an 11-point pain intensity rating scale relates to clinical importance for individuals with chronic pain, and Gallagher et al[84] found the MCID for acute abdominal pain to be 16 mm on a pain intensity visual analogue scale (95% CI 13–18 mm). Because of the heterogeneity of how data were reported, differences in scales used, and lack of relevant criteria for MCID in the LBP population and specifically in acute LBP, 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[28,84]; 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.[83] Thus, to facilitate more easily understandable clinical importance of results of efficacy trials, we suggest future trials incorporate the recommendation of Farrar et al[28] that investigators report the proportion of subjects who observe a clinically important improvement in the groups being compared.

■ Conclusions

Implications for Practice

The results of this review illustrate strong evidence that nonbenzodiazepines are effective for acute LBP. The evidence on benzodiazepines for acute and nonbenzodiazepines 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.

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 LBP. These agents could potentially induce the same beneficial effects as those that act through the central nervous system, but without the associated side ef-

fects. Future studies should focus on reducing the incidence and severity of side effects.

> ### ■ Key Points
>
> - A systematic review of 30 randomized and double-blinded controlled trials was performed.
> - The effectiveness of muscle relaxants for nonspecific LBP was evaluated.
> - Muscle relaxants are effective in the management of acute and chronic nonspecific LBP, but the adverse effects require that they be used with caution.

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