Drug Class Review
on
Skeletal Muscle Relaxants

FINAL REPORT

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INTRODUCTION

Skeletal muscle relaxants are a heterogeneous group of medications commonly used to treat two different types of underlying conditions: spasticity from upper motor neuron syndromes and muscular pain or spasms from peripheral musculoskeletal conditions. Although they have by convention been classified into one group, the Food and Drug Administration (FDA) has approved only a few medications in this class for treatment of spasticity; the remainder are approved for treatment of musculoskeletal conditions.

Spasticity, although difficult to define precisely, is a clinical condition that has been described as "a motor disorder characterized by velocity dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex, as one component of the upper motor neuron syndrome."[1] The upper motor neuron syndrome is a complex of signs and symptoms that, in addition to spasticity, can be associated with exaggerated cutaneous reflexes, autonomic hyperreflexia, dystonia, contractures, paresis, lack of dexterity, and fatigability.[2] Spasticity from the upper motor neuron syndrome can result from a variety of conditions affecting the cortex or spinal cord. Some of the more common conditions associated with spasticity and requiring treatment include multiple sclerosis,[3] spinal cord injury,[4] traumatic brain injury, cerebral palsy, and post-stroke syndrome.[5] In many patients with these conditions, spasticity can be disabling and painful with a marked effect on functional ability and quality of life.[6]

Common musculoskeletal conditions causing tenderness and muscle spasms include fibromyalgia,[7] tension headaches,[8] myofascial pain syndrome, and mechanical low back or neck pain. If muscle spasm is present in these conditions, it is related to local factors involving the affected muscle groups. There is no hypertonicity or hyperreflexia, and the other symptoms associated with the upper motor neuron syndrome are not present. These conditions are commonly encountered in clinical practice and can cause significant disability and pain in some patients. Skeletal muscle relaxants are one of several classes of medications (including antidepressants, neuroleptics, anti-inflammatory agents, and opioids) frequently used to treat these conditions.[9-11]

Skeletal muscle relaxants have been approved for either treatment of spasticity or for treatment of musculoskeletal conditions. Drugs classified as skeletal muscle relaxants are baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, dantrolene, metaxalone, methocarbamol, orphenadrine, and tizanidine. Only baclofen, dantrolene, and tizanidine are approved for the treatment of spasticity. These three antispasticity medications act by different mechanisms: baclofen blocks pre- and post-synaptic $GABA_B$ receptors,[12, 13] tizanidine is a centrally acting agonist of $\alpha 2$ receptors,[14, 15] and dantrolene directly inhibits muscle contraction by decreasing the release of calcium from skeletal muscle sarcoplasmic reticulum.[16] Medications from other classes have also been used to treat spasticity. Diazepam, a benzodiazepine, was the first medication thought to be effective for spasticity. It acts by central blockade of $GABA_A$ receptors.[17, 18] Other medications used to treat spasticity but not formally approved for this indication include other benzodiazepines, clonidine, gabapentin, and botulinum toxin.[16]

The skeletal muscle relaxants carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, and orphenadrine have been approved for treatment of musculoskeletal disorders, but not for spasticity. They constitute a heterogeneous group of medications. Cyclobenzaprine is closely related to the tricyclic antidepressants,[19] carisoprodol

is metabolized to meprobamate,[20] methocarbamol is structurally related to mephenesin,[19] chlorzoxazone is a benzoxazolone derivative,[21] and orphenadrine is derived from diphenhydramine.[22] The mechanism of action for most of these agents is unclear, but may be related in part to sedative effects. These drugs are often used for treatment of musculoskeletal conditions whether muscle spasm is present or not.[11] Although there is some overlap between clinical usage (tizanidine in particular has been studied for use in patients with musculoskeletal complaints),[23] in clinical practice each skeletal muscle relaxant is used primarily for either spasticity or for musculoskeletal conditions.

In 2001, Senate Bill 819 was passed by the Oregon Legislature and signed into law by the Governor. The law mandates development of a Practitioner-Managed Prescription Drug Plan (PMPDP) for the Oregon Health Plan (OHP) and evidence-based reviews of the state's most expensive drug classes. The Oregon Health Resources Commission (OHRC) requested such a review of the skeletal muscle relaxant drug class in patients with spasticity as well as in patients with musculoskeletal conditions to determine whether there is evidence that one or more skeletal muscle relaxant is superior to others in terms of efficacy and safety.

This report was originally submitted in February 2003. It was subsequently revised in preparation for journal submission in June 2003. Seven placebo-controlled trials added to the report at that time are highlighted in red and italicized text in the tables and evidence tables. Data from an observational study regarding the association between chlorzoxazone and hepatotoxicity were also added to the report. Regular six-month updates for this report are scheduled. The first final update report, presented here, was completed in January 2004 from searches performed in October 2003. Trials identified during the update searches are also highlighted in red and italicized text in the tables and evidence tables. At the time that the update was conducted, the FDA had approved no new skeletal muscle relaxants.

Scope and Key Questions

The scope of the review and key questions were developed and refined with input from an OHC subcommittee of experts from around the state including pharmacists, primary care clinicians, neurologists, psychiatrists, and representatives of the public. In consultation with the subcommittee, we selected the following key questions to guide the review:

1. What is the comparative efficacy of different muscle relaxants in reducing symptoms and improving functional outcomes in patients with a chronic neurologic condition associated with spasticity, or a chronic or acute musculoskeletal condition with or without muscle spasms?

2. What are the comparative incidence and nature of adverse effects (including addiction and abuse) of different muscle relaxants in patients with a chronic neurologic condition associated with spasticity, or a chronic or acute musculoskeletal condition with or without muscle spasms?

3. Are there subpopulations of patients for which one muscle relaxant is more effective or associated with fewer adverse effects?

Several aspects of the key questions deserve comment:

Population. The population included in this review is adult or pediatric patients with spasticity or a musculoskeletal condition. We defined spasticity as muscle spasms associated with an upper motor neuron syndrome. Musculoskeletal conditions were defined as peripheral conditions resulting in muscle or soft tissue pain or spasms. We included patients with nocturnal leg cramps to determine whether medications in the skeletal muscle relaxant class are effective for this particular condition. We excluded obstetric and dialysis patients. Senate Bill 819 specifically excludes patients with HIV and patients with cancer. We also excluded patients with restless legs syndrome or nocturnal myoclonus.

Drugs. We included the following oral drugs classified as skeletal muscle relaxants: baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, dantrolene, metaxalone, methocarbamol, orphenadrine, and tizanidine. Because Senate Bill 819 specifically excludes drugs used to treat psychiatric conditions from this process, tricyclic antidepressants and benzodiazepenes were not considered primary drugs in this report. However, diazepam, clonazepam, and clorazepate were reviewed when they were compared in head-to-head studies with allowed skeletal muscle relaxants. Other medications used for spasticity but considered to be in another drug class, such as gabapentin (a neuroleptic) and clonidine (an antihypertensive), were also only reviewed when they were directly compared to an included skeletal muscle relaxant. Quinine was included only if it was compared to a skeletal muscle relaxant for treatment of nocturnal leg cramps.

The dose of skeletal muscle relaxants used in trials may affect either the efficacy or adverse event profile. One clinical trial[24] evaluated cyclobenzaprine 10 mg tid and 20 mg tid and found equivalent efficacy but increased adverse events with the higher dose. A study on dantrolene also found a 'ceiling' effect with dantrolene doses of 200 mg daily, with no increased efficacy but more side effects above that dose.[25] Most trials titrated skeletal muscle relaxants to the maximum tolerated dose or a pre-specified ceiling dose, but there are no standardized methods of titration and determining target doses.

Outcomes. The main efficacy measures were relief of muscle spasms or pain, functional status, quality of life, withdrawal rates, and adverse effects (including sedation, addiction, and abuse). We excluded non-clinical outcomes such as electromyogram measurements or spring tension measurements. There is no single accepted standard on how to measure the included outcomes. Clinical trials of skeletal muscle relaxants have often used different scales to measure important clinical outcomes such as spasticity, pain, or muscle strength.[26] Many trials have used unvalidated or poorly described methods of outcome assessment. Studies that use the same scale often report results differently (for example, mean raw scores after treatment, mean improvement from baseline, or number of patients "improved"). All of these factors make comparisons across trials difficult.

Spasticity is an especially difficult outcome to measure objectively. The most widely used standardized scales to measure spasticity in patients with upper motor neuron syndromes are the Ashworth[27] and modified Ashworth[28] scales. In these scales, the assessor tests the resistance to passive movement around a joint and grades it on a scale of 0 (no increase in tone) to 4 (limb rigid in flexion or extension). The modified Ashworth scale adds a "1+" rating between the 1 and 2 ratings of the Ashworth scale. For both of these scales, the scores are usually added for four lower and four upper limb joints, for a total possible score of 0-32, though scoring methods can vary. The Ashworth scale has been found to have moderate

reliability.[29] Some experts have pointed out that resistance to passive movement may measure tone better than it does spasticity and that the Ashworth scale and other 'objective' measures of spasticity may not correlate well with patient symptoms or functional ability.[30] Other areas of uncertainty regard the significance of the 1+ rating in the modified Ashworth scale and how a non-continuous ordinal variable should be statistically analyzed.[29] An important advantage of the Ashworth scale is that it is a consistent way to measure spasticity or tone across studies, and has been found to have moderate reproducibility.[29] Other measures of spasticity include the pendulum test, muscle spasm counts, and patient assessment of spasticity severity on a variety of numerical (e.g., 1-3, 1-4, 0-4) or categorical (e.g., none, mild, moderate, severe) scales. The best technique may be to perform both objective and subjective assessments of spasticity, but validated subjective assessment techniques of spasticity are lacking.

Muscle strength is usually assessed with the time-honored British Medical Research Council Scale, which is based on the observation of resistance provided by voluntary muscle activity and used in everyday clinical practice.[15] An assessor grades each muscle or muscle group independently on a scale of 0 (no observed muscle activation) to 5 (full strength). This scale was originally devised to test the strength of polio survivors. Data are not available regarding its reliability and validity in assessing spastic and weak patients.

Most studies measure pain using either visual analogue or categorical pain scales. Visual analogue scales (VAS) consist of a line on a piece of paper labeled 0 at one end, indicating no pain, and a maximum number (commonly 100) at the other, indicating excruciating pain. Patients designate their current pain level on the line. An advantage of VAS is that they provide a continuous range of values for relative severity. A disadvantage is that the meaning of a pain score for any individual patient depends on the patient's subjective experience of pain. This poses a challenge in objectively comparing different patients' scores, or even different scores from the same patient. Categorical pain scales, on the other hand, consist of several pain category options from which a patient must choose (e.g., no pain, mild, moderate, or severe). A disadvantage of categorical scales is that patients must choose between categories that may not accurately describe their pain. The best approach may be to utilize both methods.[31] Pain control (improvement in pain) and pain relief (resolution of pain) are also measured using visual analogue and categorical scales.

Studies can evaluate functional status using either disease-specific or non-specific scales. These scales measure how well an individual functions physically, socially, cognitively, and psychologically. Disease-specific scales tend to be more sensitive to changes in status for that particular condition, but non-specific scales allow for some comparisons of functional status between conditions. The most commonly used disease-specific measure of functional and disability status in patients with multiple sclerosis, for example, is the Kurtzke Extended Disability Status Scale (EDSS).[32] The EDSS measures both disability and impairment, combining the results of a neurological examination and functional assessments of eight domains into an overall score of 0-10 (in increments of 0.5). The overall score of the EDSS is heavily weighted toward ambulation and the inter-rater reliability has been found to be moderate.[32] Disease-specific scales are also available for fibromyalgia,[33, 34] low back pain, cerebral palsy, and other musculoskeletal and spastic conditions.

Scales that are not disease-specific include the Medical Outcomes Study Short Form-36 (SF-36), Short Form-12 (SF-12), or another multi-question assessment. Another approach to measuring function is to focus on how well the medication helps resolve problems in daily living that patients with spasticity or musculoskeletal conditions commonly face, such as

getting enough sleep or staying focused on the job. Some studies also report effects on mood and the preference for one medication over another.

The subcommittee selected the following adverse events for our review: somnolence or fatigue, dizziness, dry mouth, weakness, abuse, and addiction. We also paid special attention to reports of serious hepatic injury.[35] The subcommittee considered these the most common and potentially troubling adverse events in clinical practice. We recorded rates of these adverse events as well as rates of discontinuation of treatment due to a particular adverse effect. In some studies, only "serious" adverse events or adverse events "thought related to treatment medication" are reported. Many studies do not define these terms. We recorded any information about abuse and addiction, including rates of death and hospitalization when available.

Withdrawal rates. Because of inconsistent reporting of outcomes, withdrawal rates may be a more reliable surrogate measure for either clinical efficacy or adverse events in studies of skeletal muscle relaxants. High withdrawal rates probably indicate some combination of poor tolerability and ineffectiveness. An important subset is *withdrawal due to any adverse event* (those who discontinue specifically because of adverse effects).

Study types. We included controlled clinical trials to evaluate efficacy. The validity of controlled trials depends on how they are designed. Randomized, properly blinded clinical trials are considered the highest level of evidence for assessing efficacy.[36-38] Clinical trials that are not randomized or blinded or that have other methodologic flaws are less reliable. These are also discussed in our report with references to specific flaws in study design and data analysis.

Trials comparing one skeletal muscle relaxant to another provided direct evidence of comparative efficacy and adverse event rates. Trials comparing skeletal muscle relaxants to other active medications or placebos provided indirect comparative data.

To evaluate adverse event rates, we included clinical trials and large, high-quality observational cohort studies. Clinical trials are often not designed to assess adverse events, and may select patients at low risk for adverse events (in order to minimize dropout rates) or utilize methodology inadequate for assessing adverse events. Observational studies designed to assess adverse event rates may include broader populations, carry out observations over a longer time, utilize higher quality methodologic techniques for assessing adverse events, or examine larger sample sizes. We did not systematically review case reports and case series in which the proportion of patients suffering an adverse event could not be calculated.

METHODS

Literature Search

To identify articles relevant to each key question, we searched (in this order): the Evidence-Based Medicine Library (2002, Issue 1) (from the Cochrane Collaboration), MEDLINE (1966-2003), EMBASE (1980-2003), and reference lists of review articles. In electronic searches we combined terms for spasticity, conditions associated with spasticity, and musculoskeletal disorders with included skeletal muscle relaxants (see Appendix A for complete search strategy). In addition, the State of Oregon created and disseminated a protocol to pharmaceutical manufacturers for submitting clinical and economic evaluation data to the Evidence-based Practice Center. All citations were imported into an electronic database

(EndNote 6.0). Searches on the electronic databases were carried out through January 2003, using updates on electronic databases after the initial searches.

While this report was being prepared for journal submission in June 2003, additional studies were identified and added to the report. As part of the regularly scheduled update process, we conducted update searches in October 2003 of the Cochrane Library (through third quarter, 2003), MEDLINE (through October 2003), and Embase (through fourth quarter, 2003) starting from the end-date of the original searches. In electronic searches, we used the same search strategy as was used for the original report. Pharmaceutical manufacturers were again invited to submit dossiers, including citations, using a protocol issued by the State of Oregon (http://www.ohppr.state.or.us/index.htm). These submissions were reviewed to identify new citations not previously submitted.

Study Selection

All English-language titles and abstracts and suggested additional citations were reviewed for inclusion, using criteria developed by the research team with input from the subcommittee. We obtained full-text articles if the title and abstract review met the following criteria:

1. Systematic reviews of the clinical efficacy or adverse event rates of skeletal muscle relaxants for spasticity or musculoskeletal conditions OR
2. Randomized controlled trials that compared one of the included skeletal muscle relaxants listed to another included skeletal muscle relaxant, other antispasticity or muscle relaxant treatment (diazepam, gabapentin, clonidine, chlorazepate, clonazepam, or quinine), or placebo in adult patients with spasticity or musculoskeletal conditions OR
3. Randomized controlled trials and large, high quality observational studies that reported adverse event rates for one of the skeletal muscle relaxants listed above.

We then applied the same criteria to the full-text articles, ensuring that the clinical efficacy or adverse event rates from specific skeletal muscle relaxants were reported or could be calculated. While we preferred studies of longer duration, we had no lower limit on the length of follow-up, but excluded "single-dose studies" examining the effects of a single dose of medication rather than a course of treatment. We also excluded trials in which an included skeletal muscle relaxant was combined with an analgesic medication unless the comparison arm included the same analgesic medication and dose. We excluded abstracts and unpublished trials unless the unpublished data was submitted by a pharmaceutical company, and included only English-language studies.

Searches identified 3,847 citations: 335 from the Evidence-Based Medicine (Cochrane) Library, 1,155 from MEDLINE, 2,314 from EMBASE, and 43 from reference lists. We received no pharmaceutical company submissions. We identified 377 reports of clinical trials and excluded 227 of these (see Appendix B for detailed search results). Sixty-seven were excluded because they did not evaluate an included population, 148 were excluded because they did not evaluate an included intervention (skeletal muscle relaxant), seven were excluded because they did not evaluate an included outcome (spasms, pain, strength, functional ability, or adverse events), one was excluded because it was a single-dose study, and four were excluded because they were not English-language. We retrieved 150 reports on clinical trials

for more detailed evaluation. After this second review, we excluded 52: 39 because they did not evaluate an included intervention, one because it did not evaluate an included population, one because it did not contain original data, two because they did not evaluate an included outcome, six because of study design (results published in another reviewed trial, not a controlled trial, or no data), and three because they were not English-language. Ninety-eight reports presenting data for 101 randomized controlled trials provided usable data and are included in evidence tables. We also identified four relevant systematic reviews and three meta-analyses.

Seven placebo controlled-trials (reported in six publications) identified while this report was being prepared for journal submission were incorporated into the text of this report in June 2003.[39-44] These studies are highlighted in the tables and evidence tables. An observational study of hepatotoxicity associated with chlorzoxazone was also added in June 2003.[45]

In the update searches performed in October 2003, we found 590 citations. Twenty were from the Cochrane Central Register of Controlled Trials, 67 from Medline, and 501 from Embase. Two citations came from the reference list of a systematic review found in the update searches. We received no submissions from pharmaceutical companies. Of the citations found, 31 appeared to be trials, and of these 1(reporting results of two trials) met inclusion criteria.[46] Thirty trials were excluded for the following reasons: 8 did not evaluate an included patient population, 18 did not evaluate an included intervention, 1 was an abstract only, and 3 were non-English language. We also identified two separate reports of a single systematic review on muscle relaxants for acute low back pain.[47, 48] We did not identify any large, high-quality observational studies evaluating adverse events.

Data Abstraction

One reviewer abstracted the following data from included trials: study design, setting, population characteristics (including sex, age, race, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment (e.g., scales used), and results for each outcome. We recorded intention-to-treat results if available and the trial did not report high overall loss to follow-up. In trials with crossover, outcomes for the first intervention were recorded if available to minimize potential bias in results due to differential withdrawal prior to crossover. We also wanted to screen out the possibility of a "carryover" effect from the first treatment in studies without a washout period or "rebound" spasticity from withdrawal of the first intervention.[49] A second reviewer checked all data.

Quality Assessment

We assessed quality of trials based on the predefined criteria listed in Appendix C, which were submitted to the Health Resources Commission in December 2001 and updated in February 2003. We rated the internal validity of each trial based on methods used for randomization; allocation concealment and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. External validity of trials was assessed based on: adequate description of the study

population; similarity of patients to other populations to whom the intervention would be applied; control group receiving comparable treatment; funding source; and role of the funder.

Overall quality was assigned based on criteria developed by the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK).[37, 38] Trials with a fatal flaw in one or more categories were rated poor-quality. Trials that met all criteria were rated good-quality. The remainder were rated fair-quality. As the "fair-quality" category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are *unlikely* to be valid, while others are *probably* or *likely* to be valid. A "poor-quality" trial is not valid. The results are at least as likely to reflect flaws in the study design as they are true differences between the compared drugs. A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events.

Many of the studies we reviewed were conducted in the 1970s and early 1980s when standards for reporting clinical trial methodology were generally less stringent. Authors of these trials often did not discuss their methods in what would today be considered adequate detail.[26] This made rating the quality of these studies difficult, particularly when comparing their methods to more recent studies. In general, not reporting specific areas of methodology (such as randomization, allocation concealment, or blinding technique) was not considered a "fatal flaw," but did prevent a trial from achieving a "good" rating for that particular criterion.

Appendix D shows the criteria we used to rate studies reporting adverse events. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated studies as good-quality for adverse event assessment if they adequately met six or more of the seven pre-defined criteria, fair if they met three to five criteria, and poor if they met two or fewer criteria.

After assignment of quality ratings by the initial reviewer, a second reviewer independently assigned a quality rating. Overall quality rating and quality rating scores (for studies on adverse event assessment) were compared between reviewers. If overall quality ratings differed, the two reviewers came to consensus prior to assigning a final quality rating.

Data Synthesis

We constructed evidence tables showing study characteristics, quality ratings and results for all included studies. Poor-quality studies would usually be excluded from evidence tables, but we included them to ensure that the subcommittee is familiar with their limitations.

To assess the overall strength of evidence for a body of literature about a particular key question, we examined the consistency of study designs, patient populations, interventions, and results. Consistent results from good-quality studies across a broad range of populations suggest a high degree of certainty that the results of the studies were true (that is, the entire body of evidence would be considered "good-quality.") For a body of fair-quality studies, however, consistent results may indicate that similar biases are operating in all the studies. Unvalidated assessment techniques or heterogeneous reporting methods for important outcomes may weaken the overall body of evidence for that particular outcome or make it difficult to accurately estimate the true magnitude of benefit or harm.

RESULTS

Overview of included studies

We identified four systematic reviews[26, 50-52] (Table 1) and three meta-analyses (not systematic)[53-55] that evaluated the efficacy of skeletal muscle relaxants in patients with spasticity or musculoskeletal conditions (Evidence Tables 1 and 2). One systematic review evaluated the effectiveness of quinine for nocturnal leg cramps but did not evaluate other skeletal muscle relaxants, and thus was excluded from further review.[56] We identified 101 randomized trials evaluating included skeletal muscle relaxants for spasticity (55 trials reported in 54 publications, Tables 2 and 3) or for musculoskeletal conditions (46 trials reported in 44 publications, Tables 4 and 5).

The above results include 1 randomized trial evaluating included skeletal muscle relaxants for spasticity and 6 randomized trials (reported in 5 publications) for musculoskeletal conditions that were added to the report in June 2003.

In the update searches performed in October 2003, we identified one systematic review (reported in two different publications[47, 48]) (Table 1, Evidence Table 2) and two additional placebo-controlled randomized trials (reported in one publication[46]) (Table 5) meeting inclusion criteria. All of these studies evaluated skeletal muscle relaxants for musculoskeletal conditions.

Overview of systematic reviews and trials in patients with spasticity

Three systematic reviews evaluated skeletal muscle relaxants used to treat patients with spasticity (Table 1). One evaluated anti-spasticity agents in patients with multiple sclerosis,[26] one evaluated a variety of agents in patients with spinal cord injury,[52] and one evaluated tizanidine in patients with spasticity from different conditions.[51] We also identified two meta-analyses (not systematic) that evaluated the efficacy of tizanidine in patients with spasticity.[53, 55] These meta-analyses evaluated primarily unpublished trials conducted by the manufacturer of tizanidine (Evidence Table 1).

Of 55 trials evaluating included skeletal muscle relaxants in patients with spasticity, 17 were head-to-head trials of two skeletal muscle relaxants or a skeletal muscle relaxant versus another medication used to treat spasticity (Table 2). One publication reported results of two different head-to-head trials.[57] Eight trials directly compared tizanidine to baclofen.[49, 57-63] Another eight trials compared an included skeletal muscle relaxant to diazepam: Two trials evaluated tizanidine,[57, 64] three evaluated baclofen,[65-67] and three evaluated dantrolene.[68-70] We identified one trial of clonidine versus baclofen in patients with spinal cord injury.[71] We found no other head-to-head trials comparing an included skeletal muscle relaxant to gabapentin, clonidine, or other benzodiazepines. Of the included trials, ten used a crossover design[58, 60, 62, 65-71] and the remainder were parallel-group trials. The trials ranged in size from 13[66] to 105[64] enrollees, with an average of 38 enrollees (total enrolled=654). Ten of the trials focused on multiple sclerosis,[49, 57-60, 62, 63, 65, 67, 70] one on post-stroke or head trauma,[64] one on children with cerebral palsy,[69] one on spinal cord injury, [71] and the remainder on spasticity from various causes.[57, 61, 66, 68]

Except for one head-to-head trial lasting one year,[61] all of the trials were of relatively short duration, ranging from 2 to 8 weeks per intervention. All of the trials except one[71] were

published before 1990. One trial[67] enrolled only inpatients. The remainder enrolled outpatients or did not specify whether enrollees were in- or outpatients. The majority of trials recruited patients from specialty clinics, most commonly from neurology or rehabilitation practices, and the majority were single center. Race was not reported in any trial. Percentage of female enrolled patients ranged from 13% to 62%.[57, 67] The average age of enrollees ranged from 39 to 52 years. Although elderly patients were included in most trials, no head-to-head trial specifically evaluated only elderly patients. One trial included only children.[69]

In addition to one head-to-head trial[68] of dantrolene and diazepam that also included a placebo arm, we identified 38 additional placebo-controlled trials (Table 3). Fourteen evaluated baclofen,[72-85] 15 dantrolene,[86-100] six tizanidine,[101-106] one chlorzoxazone,[107] one methocarbamol,[39] and one cyclobenzaprine.[108] Conditions evaluated in these studies were multiple sclerosis, cervical myelopathy, cerebral palsy, post-stroke, traumatic brain injury, spinal cord injury, and spasticity from various causes. Nine placebo-controlled trials evaluated children[39, 80, 82, 87, 88, 91, 92, 97, 107] and one specifically evaluated elderly post-stroke patients.[78]

One poor-quality placebo-controlled trial of methocarbamol in children with cerebral palsy was incorporated into the above text in June 2003.[39] In the update searches of October 2003, no systematic reviews or clinical trials of skeletal muscle relaxants for spasticity meeting inclusion criteria were identified.

Overview of systematic reviews and trials in patients with musculoskeletal conditions

We identified no systematic reviews of different skeletal muscle relaxants in patients with musculoskeletal conditions. One systematic review compared cyclobenzaprine versus placebo in patients with low back pain.[50] This systematic review specifically excluded data on skeletal muscle relaxants other than cyclobenzaprine (Table 1). One meta-analysis of unpublished trials compared cyclobenzaprine to diazepam or placebo for various musculoskeletal conditions (Evidence Table 2).[55]

Of 46 trials of included skeletal muscle relaxants in patients with musculoskeletal conditions, 11 were head-to-head trials of two skeletal muscle relaxants (Table 4). One trial directly compared tizanidine to chlorzoxazone,[109] one trial compared cyclobenzaprine to methocarbamol,[19] and one trial compared cyclobenzaprine to carisoprodol.[110] Of eight trials that compared an included skeletal muscle relaxant to diazepam, five trials reported in four publications[111-114] evaluated cyclobenzaprine, one trial evaluated carisoprodol[115] and two trials[116, 117] evaluated tizanidine. We identified no head-to-head trials of orphenadrine, metaxalone, dantrolene, or baclofen in patients with musculoskeletal conditions. We also identified no head-to-head trials comparing an included skeletal muscle relaxant to quinine or another skeletal muscle relaxant in patients with nocturnal leg cramps. One trial[118] was excluded because it evaluated an included skeletal muscle relaxant versus chlormezanone, a medication not available or approved in the United States. Six others were excluded because they only evaluated the combination of a skeletal muscle relaxant and analgesic, or did not use an equivalent analgesic in each arm.[21, 119-123] One trial was excluded because it only compared one dose of cyclobenzaprine with another.[24]

The head-to-head trials ranged in size from 20[116] to 227[19] enrollees, with an average of 90 enrollees (total enrolled=724). All focused on patients with back or neck pain and spasms. One trial[113] focused on patients with chronic symptoms and the remainder evaluated patients

with acute symptoms. The duration of all head-to-head trials was short, ranging from seven[19] to 18[112] days. All of the trials were published before 1985. One trial[116] enrolled only inpatients. The remainder enrolled outpatients or did not specify whether enrollees were in- or outpatients. All were single center trials except one multicenter trial.[115] Race was reported in three trials and non-whites accounted for <15% of patients in these trials.[19, 110, 115] Percentage of female patients enrolled ranged from 30%[116] to over 55%[19]. The average age of enrollees ranged from 37 to 52 years. Although elderly patients were included in most head-to-head trials, no trial specifically evaluated only elderly patients and none included children.

In addition to six head-to-head trials (from five publications)[19, 111-114] including a placebo arm, we identified an additional 35 placebo-controlled trials (Table 5): Four evaluated carisoprodol,[124-127] 12 cyclobenzaprine,[40, 128-138] four metaxalone (in three publications),[42, 43, 139] one methocarbamol,[41] four orphenadrine,[22, 140-142] one baclofen,[143] two dantrolene,[144, 145] and seven tizanidine.[44, 146-151] Three trials evaluated a skeletal muscle relaxant with an equivalent analgesic in each arm and were included.[134, 141, 145] Most trials evaluated low back or neck syndromes alone or mixed with other musculoskeletal conditions. Other conditions specifically evaluated were fibromyalgia,[131, 135, 137] tension headaches or mixed headache conditions,[44, 136, 148, 150] and nocturnal leg cramps.[140] No placebo-controlled trials included children. One trial[148] of tension headaches only included women and one trial[140] evaluated orphenadrine in elderly patients with nocturnal leg cramps.

Six placebo controlled-trials (reported in five publications) were added to the report in June 2003 and incorporated into the above text.[40-44] In the update searches conducted in October 2003, we found one systematic review (reported in two publications) that evaluated the effectiveness of skeletal muscle relaxants and benzodiazepines for acute nonspecific low back pain.[47, 48] No head-to-head trials were identified. We also found two trials (reported in one publication) that evaluated the efficacy of different doses of cyclobenzaprine versus placebo.[46]

1. What is the comparative efficacy of different muscle relaxants in reducing symptoms and improving functional outcomes in patients with a chronic neurologic condition associated with spasticity, or a chronic or acute musculoskeletal condition with or without muscle spasms?

Patients with spasticity

Results of systematic reviews and meta-analyses

One good-quality systematic review[26] evaluated various anti-spasticity agents, including skeletal muscle relaxants, for treating symptoms of multiple sclerosis (Table 1 and Evidence Table 1). It identified 11 head-to-head and 12 placebo-controlled trials of skeletal muscle relaxants included in our review. Seven of the head-to-head trials compared tizanidine to baclofen (including one German-language trial, one unpublished trial and one abstract that were not included in our search). Other head-to-head trials included one trial comparing baclofen to diazepam, one trial comparing dantrolene to diazepam, and two trials comparing tizanidine to diazepam. Of the placebo-controlled trials, five evaluated baclofen, four

dantrolene, and three tizanidine. No evaluated trial was rated good quality. Three of the seven trials comparing tizanidine to baclofen and two of the four trials comparing included skeletal muscle relaxants to diazepam used the Ashworth scale as an outcome measure; all studies used unvalidated measures of muscle strength. In the seven trials of tizanidine vs. baclofen, no significant differences between interventions were found for functional status or for spasticity, spasms, or clonus. Only two of the seven trials reported changes in objective muscle power, with slightly more patients noting deterioration with baclofen than tizanidine. In the four trials of included skeletal muscle relaxants versus diazepam, no differences in efficacy were noted between interventions, but diazepam was usually associated with increased sedation or tiredness, and generally was less preferred. In the reviewed placebo-controlled trials, there was no pattern to suggest that one included skeletal muscle relaxant was any better than the others. Meta-analysis of placebo-controlled trials was not possible because of marked heterogeneity in study designs, interventions used, and outcomes measured.

One systematic review evaluated pharmacologic interventions for spasticity following spinal cord injury.[52] It was rated fair quality because the authors had not yet assessed 15 identified potentially relevant studies. Of the nine studies included, two were placebo-controlled trials evaluating baclofen or tizanidine. None of the included trials evaluated skeletal muscle relaxants head-to-head. No study was rated good quality. There was insufficient evidence to judge the comparative efficacy of tizanidine versus baclofen from these placebo-controlled studies.

One poor-quality systematic review[51] evaluated 20 studies of tizanidine versus baclofen (14 studies) or diazepam (6 studies) in patients with multiple sclerosis (12 studies), cerebrovascular disease (7), or amyotrophic lateral sclerosis (1). This systematic review included both published and unpublished trials and was rated poor-quality because it did not report methods used to identify trials, did not provide sufficient detail of included studies, and did not rate the quality of included studies. Although this systematic review found some evidence of increased effectiveness of tizanidine compared to baclofen and diazepam, it is not possible to determine whether these conclusions are valid.

Two fair-quality meta-analyses (not systematic reviews) evaluated unpublished trials on tizanidine versus baclofen or diazepam (Table 1).[53, 54] One meta-analysis[54] reported results from ten trials (n=270, seven trials versus baclofen and three versus diazepam) and the other[53] reported results of these plus one additional trial of tizanidine versus baclofen (n=288). Authors of these trials were employed by the pharmaceutical company marketing tizanidine in the U.S. These studies were rated fair-quality because they did not adequately report details of included studies (Evidence Table 1). Both studies evaluated the same trials, and found no significant differences between tizanidine and diazepam or baclofen for outcomes of tone (Ashworth scale) or muscle strength (summed BMRC strength scores).

No systematic reviews of skeletal muscle relaxants for spasticity meeting inclusion criteria were identified during the update process.

Results of head-to-head trials

None of the 17 head-to-head trials of skeletal muscle relaxant in patients with spasticity was rated good quality. All studies had at least two of the following methodological flaws: randomization technique not described, eligibility criteria not described, blinding technique not described, allocation concealment technique not described, or high loss to follow-up (Evidence

Table 3). Adequate blinding is an especially important factor in studies using subjective outcomes, such as patient preference, global assessments, spasm severity, or pain. One trial was rated poor-quality because it was not randomized and did not perform blinding; the remainder were rated fair-quality.[71] Possible confounding factors in these trials included different methods of medication titration or target doses, differential withdrawals during the first intervention period in crossover trials, and previous use of an intervention or other muscle relaxant, which was inconsistently reported. In crossover trials, results of the first intervention were usually not reported.

Of the eight trials of tizanidine vs. baclofen, average dose ranged from 11 mg/day [57] to 24 mg/day[59, 60, 63] and the dose of baclofen ranged from 15 mg/day[60] to 90 mg/day.[59] Most trials evaluated patients with multiple sclerosis, though one trial also evaluated patients with cervical myelopathy.[57] One also evaluated patients with syringomyelia[62]and another did not describe the underlying condition causing spasticity.[61]

In each of these eight trials, tizanidine and baclofen appeared to have roughly equivalent efficacy (Table 2 and Evidence Table 3). Outcomes measured included muscle tone, muscle spasm, clonus, functional assessments, patient or physician global assessments, and patient or physician preference. These outcomes were assessed using a variety of methods, including unvalidated or unspecified scales. Six trials[49, 57, 60-63] used the Ashworth scale to measure spasticity or tone, but methods of reporting these results were inconsistent and raw scores were usually not presented. In most trials, regardless of the method used to assess outcomes, patients receiving either baclofen or tizanidine reported significant improvements in spasticity, clonus, and overall improvement compared to baseline. The longest trial (52 weeks compared to 8 weeks or less for the other trials) reported results similar to shorter trials.[61] The overall withdrawal rate was higher with baclofen than with tizanidine in three out of seven trials[58, 60, 61] and roughly equivalent in the other four. Of the three trials with differential withdrawal rates, two had low numbers of overall withdrawals (five in each trial), making the significance of these differential rates difficult to assess. In two of the trials,[58, 61] withdrawals due to adverse events accounted for most of the observed differences in overall withdrawal rates (see below).

In the eight trials of tizanidine, baclofen, or dantrolene versus diazepam, there was no pattern to suggest that any of these skeletal muscle relaxants was superior to the others for assessed clinical outcomes including spasm, strength, functional status, or patient preference.(Table 2 and Evidence Table 3) Although one trial reported higher patient preference for baclofen over diazepam[67] and another for dantrolene over diazepam[70], unclear blinding techniques make these results difficult to interpret. Differences in study design, patient populations, outcomes evaluated, and similar efficacy of each skeletal muscle relaxant compared to diazepam in individual trials made it impossible to make accurate judgments about the comparative efficacy of tizanidine, baclofen, and dantrolene from these trials as a whole.

The one trial comparing baclofen to clonidine was rated poor-quality because it was not randomized and did not perform blinding.[104] This trial found no differences between baclofen and clonidine for spasticity and was not included in the tables.

In all head-to-head trials, external validity was difficult to assess. Numbers screened and enrolled were usually not reported, eligibility and exclusion criteria were often poorly specified, and funding sources were not stated. When exclusion criteria were reported, numbers of patients excluded for each criterion was not reported.

No head-to-head trials of skeletal muscle relaxants for spasticity meeting inclusion criteria were identified during the update process.

Results of placebo-controlled trials

None of the 38 placebo-controlled trials was rated good quality (Evidence Table 4). Main results from placebo-controlled trials for spasticity are summarized in Table 3, including results from the one head-to-head trial[68] that also had a placebo arm. Most of the placebo-controlled trials found either significant benefits or trends towards benefit from baclofen, dantrolene, and tizanidine compared to placebo for spasticity, functional ability, and strength. However, because of the use of unvalidated outcomes scales and inconsistent methods for reporting outcomes, the magnitude of benefit for each of these medications compared to placebo could not be accurately gauged. There was inadequate evidence from one trial[107] of chlorzoxazone (rated poor quality), one trial[108] of cyclobenzaprine (no significant differences), and one trial[39] of methocarbamol in children with cerebral palsy (rated poor quality) to show that these skeletal muscle relaxants are effective for treatment of spasticity. These three medications are not approved for this indication.

Meta-analysis could not be performed on the placebo-controlled trials because of marked differences in interventions (doses used and methods of titration), trial designs, populations studied, outcomes scales, and methods for reporting outcomes. No reliable conclusions about the comparative efficacy of different skeletal muscle relaxants can be drawn from these placebo-controlled trials.

One poor-quality trial was incorporated into the above text when this report was revised in June 2003.[39] No other placebo-controlled trials of skeletal muscle relaxants for spasticity meeting inclusion criteria were identified during the update process.

Summary

There is fair evidence from eight fair-quality head-to-head trials and one fair-quality meta-analysis of eight unpublished trials that tizanidine and baclofen are roughly equivalent for clinical efficacy. There is inadequate evidence from head-to-head or placebo-controlled trials to assess the comparative efficacy of dantrolene against that of tizanidine or baclofen. In trials that have directly compared baclofen, tizanidine, or dantrolene to diazepam, efficacy of each medication appears to be similar to diazepam. There is fair-quality evidence from placebo-controlled trials that tizanidine, baclofen, and dantrolene are effective in the treatment of spasticity. There is no evidence from clinical trials that other included skeletal muscle relaxants are effective for treatment of spasticity. Our findings are similar to those of a recent good-quality systematic review of antispasticity agents in multiple sclerosis.[26]

A single poor-quality placebo-controlled trial of methocarbamol in children with cerebral palsy was added to this report in June 2003. It did not change the conclusions of the original report. No other new studies regarding the efficacy of skeletal muscle relaxants and meeting inclusion criteria were identified during the update process.

Patients with musculoskeletal conditions

Results of systematic reviews and meta-analyses

One good-quality systematic review evaluated the efficacy of cyclobenzaprine versus placebo for treatment of back pain (Table 1 and Evidence Table 2).[50] This systematic review examined 14 trials of fair overall quality (one abstract and eight trials sponsored by a pharmaceutical company) and found that cyclobenzaprine was associated with better 'global improvement' scores at day 14 (odds ratio 4.7; 95% confidence interval (CI), 2.7-8.1) in ten trials that evaluated this outcome. For individual symptoms, the systematic review found a modest magnitude of improvement (effect size 0.38-0.58) compared to placebo by day 14 for five outcomes: local pain, muscle spasm, tenderness to palpation, range of motion, and activities of daily living. Information regarding other skeletal muscle relaxants evaluated in included trials (diazepam and methocarbamol) was specifically excluded from analysis in this systematic review.

One fair-quality meta-analysis evaluated the comparative efficacy of cyclobenzaprine, diazepam and placebo (Table 1 and Evidence Table 2).[55] This study summarized results of 20 unpublished short-term (2 week) trials performed in the U.S. in 1153 patients with muscle spasm; the authors were employed by Merck Laboratories. It included patients with post-traumatic injury, musculoskeletal strain, radiculopathy, and osteoarthritis. This meta-analysis was rated fair-quality because it did not adequately describe included trials and used an unvalidated method to measure 'global response'. This study found that the 'global response' was equivalent for cyclobenzaprine and diazepam (66% marked or moderate improvement) and significantly better than placebo (40%).

One systematic review (reported in two publications) identified during the update process evaluated the effectiveness of skeletal muscle relaxants and benzodiazepines for acute nonspecific low back pain (Table 1 and Evidence Table 1).[47, 48] It included 30 studies of various muscle relaxants or benzodiazepenes, with a total of 2884 patients evaluated. The systematic review was rated good quality. It found a pooled relative risk from 11 studies of skeletal muscle relaxants (excluding benzodiazepines) of 0.80 (95% CI, 0.71 to 0.89) for pain relief after 2 to 4 days and 0.49 (95% CI, 0.25 to 0.95) for global efficacy compared to placebo. It was not designed to specifically assess comparative efficacy, but reported that the various muscle relaxants appeared 'similar' in performance. This report generally gave higher quality ratings to studies than we did, (23/30 included trials rated good quality), which appeared to be due to more stringent methods we used to assign overall quality ratings. Following methods developed by the U.S. Preventive Services Task Force, we only rated studies good quality if they met all of our pre-specified criteria (see detailed methods in Appendix). Van Tulder et al, on the other hand, rated studies good quality if they met at least 6 out of 11 quality criteria. Of the thirty trials included in this systematic review, we did not review 14 of them. Two were excluded because they were foreign language.[152, 153] Both were placebo-controlled trials of tizanidine versus placebo. One[153] found no significant differences compared to placebo and one[152] found that tizanidine was superior to placebo. We excluded the rest of the studies because they evaluated interventions that were not included in our review (muscle relaxants not

available in the U.S., parenteral medications, benzodiazepines versus placebo, or differential use of non-steroidal anti-inflammatory agents or other pain medications in study arms).

Results of head-to-head trials

None of the 11 head-to-head trials was rated good-quality; all had at least two important methodological flaws (Evidence Table 5). All trials were rated fair except one trial of cyclobenzaprine versus diazepam that was rated poor because in addition to other flaws, it only reported results for 52 of the 105 enrollees and did not account for the other patients.[112] Of the fair-quality trials, the trial that appeared to be of best quality compared carisoprodol and diazepam.[115] In this trial the authors did not describe allocation concealment techniques and they used unvalidated methods for assessing outcomes. Carisoprodol was found to be significantly superior to diazepam using unvalidated methods to assess stiffness, tension, and relief, with average differences for carisoprodol compared to diazepam averaging about 0.5 on a 1-5 scale.[115] No significant differences were seen for pain, activity impairment, or sleep impairment.

In other head-to-head trials, a variety of methods were used for measuring outcomes, including various scales for pain (4, 5, or 9 point scales and visual analogue scales), tenderness, and functional status. Most assessment scales were unvalidated, and methods of reporting these outcomes were inconsistent. Functional status was either not measured or assessed using unstandardized and unvalidated methods. Doses of medications investigated were cyclobenzaprine 10 to 20 mg tid; tizanidine 2 to 8 mg tid, chlorzoxazone 500 mg tid, carisoprodol 350 mg qid, and diazepam 5 to10 mg tid (Table 4). In these trials, there was no clear evidence that one skeletal muscle relaxant was superior to any other for efficacy. In a trial comparing tizanidine and chlorzoxazone in patients with back pain,[109] there were no significant differences between treatments for muscle pain, muscle tension, tenderness, and activity. More patients reported 'excellent' overall results with tizanidine (57%) compared to chlorzoxazone (23%), but similar proportions of patients reported 'good or excellent' results (79% vs. 69%). A trial of cyclobenzaprine versus methocarbamol in patients with localized muscle spasm found that there were no significant differences in the proportion of patients reporting absent or mild muscle spasm, limitation of motion, or limitation of daily activities.[19] A slightly greater proportion of patients on cyclobenzaprine reported mild or absent local pain compared to methocarbamol (40% vs. 48%, p=.05), but only when patients with mild scores were excluded from analysis. In a trial of cyclobenzaprine versus carisoprodol in patients with acute back pain and spasms[110] there were no significant differences for pain, muscle stiffness, activity impairment, sleep impairment, tension, or relief scores compared to baseline.

Other head-to-head trials compared an included skeletal muscle relaxant to diazepam. Of the five trials[111-114] comparing cyclobenzaprine to diazepam, two trials[111, 114] (using unvalidated measures) found significant differences for most measurements of pain, muscle spasm, functional status, and 'global evaluations' that favored cyclobenzaprine. One other trial[114] reported decreased tenderness, decreased limitation of motion and better 'global evaluation' for cyclobenzaprine vs. diazepam, but not for other measures (muscle spasm, pain, functional ability). All three of these trials had some support from a manufacturer (Merck) and were published in the same book. For most outcomes that favored cyclobenzaprine, the magnitude of difference between treatments was greater at the end of week one than at the end of week two. In the other two trials comparing cyclobenzaprine to diazepam[112, 113] and the two

trials[116, 117] comparing tizanidine to diazepam, no significant differences were found for any clinical outcomes including pain, stiffness, or functional ability.

The trial[113] focusing on patients with chronic back or neck symptoms reported results similar to the other trials, which focused on acute back symptoms. In all head-to-head trials, the overall withdrawal rates ranged from 0% to 35%. In one trial, the overall withdrawal rate appeared significantly higher on cyclobenzaprine (12/34 [154]) compared to diazepam (3/32 [155]), but there was no significant difference in the withdrawal rate between interventions in other trials.

External validity was difficult to assess in these trials, for reasons similar to those described for head-to-head trials in patients with spasticity.

No head-to-head trials of skeletal muscle relaxants for musculoskeletal conditions meeting inclusion criteria were identified during the update process.

Results of placebo-controlled trials

None of the 35 placebo-controlled trials involving patients with musculoskeletal conditions was rated good quality (Evidence Table 6, includes results from six head-to-head trials with a placebo arm). Quality was generally at the same level or worse than the head-to-head trials. Most of these trials evaluated patients with acute neck or low back conditions, and most showed some evidence for clinical efficacy of evaluated skeletal muscle relaxants, but the magnitude of benefit was difficult to assess because of marked heterogeneity in study design, interventions, populations studied, and outcomes assessed (Table 5). Carisoprodol (four trials), cyclobenzaprine (17 trials, including head-to-head trials with a placebo arm), orphenadrine (four trials), metaxalone (four trials), and tizanidine (six trials) were evaluated in the highest number of trials, and most studies found significant benefits or trends towards benefit on active treatment compared to placebo. A small number of placebo-controlled trials evaluated baclofen (1 trial), methocarbamol (2), and dantrolene (2) for musculoskeletal conditions. Although trials of baclofen and dantrolene found significant benefits or trend toward benefit from active treatment, the data on metaxalone was mixed. The best fair-quality trial found no differences compared to placebo,[139] but a poor-quality trial[42] and two fair-quality trials reported in the same publication[43] did find benefits compared to placebo using unvalidated outcome measures. We identified no placebo-controlled trials evaluating chlorzoxazone.

Six placebo-controlled trials (reported in five publications) of skeletal muscle relaxants for musculoskeletal conditions were incorporated into the above text in June 2003.[40-44] None were rated good quality. The additional evidence (three trials) regarding the efficacy of metaxalone was difficult to interpret. Although all three trials found superior efficacy compared to placebo, two fair-quality trials[43] were reported by the same author in one publication, the other[42] was rated poor quality, and all used unvalidated outcomes measures. The best fair-quality trial, included in the original report, had found no significant benefit for metaxalone compared to placebo.[139] Other placebo-controlled trials added in June 2003 found superior efficacy for tizanidine versus placebo for muscle tension headaches,[44] cyclobenzaprine versus placebo for fibromyalgia,[40] and methocarbamol versus placebo for nonspecific muscle pain and spasm.[41]

In the update searches performed in October 2003, two randomized controlled trials (n=737 and 668) that evaluated the efficacy of different doses of cyclobenzaprine versus placebo were identified (Table 5 and Evidence Table 6).[46] Both trials received manufacturer

support, were short-term (7 days), and were rated fair quality for internal validity. Both used unvalidated outcomes measures for 'global impression of change', 'medication helpfulness', 'relief from starting backache', and proportion of 'responders'. In both trials, it was not clear if randomization and blinding techniques were adequate. One trial evaluated the efficacy and adverse events of cyclobenzaprine 5 mg po tid and 10 mg po tid compared to placebo. It found that the two cyclobenzaprine regimens were roughly equivalent for efficacy for the assessed outcomes. The second trial compared cyclobenzaprine 2.5 mg po tid and 5 mg po tid compared to placebo. It found that the 2.5 mg po tid regimen was not significantly different than placebo for assessed efficacy outcomes, but the 5 mg regimen was superior to placebo.

Summary

Data regarding comparative efficacy of skeletal muscle relaxants in patients with musculoskeletal conditions are quite limited. Most available data are in patients with acute neck or low back syndromes and evaluated carisoprodol, cyclobenzaprine, orphenadrine, tizanidine, and diazepam. Although the best of the fair-quality head-to-head trials found that carisoprodol was superior to diazepam for some clinical outcomes, there are no other head-to-head trials of these medications, and this trial used unvalidated methods to assess outcomes. It is not clear if cyclobenzaprine is superior to diazepam for clinical outcomes in patients with musculoskeletal conditions. One fair-quality meta-analysis of unpublished trials and two fair-quality head-to-head trials found that cyclobenzaprine and diazepam are roughly equivalent for clinical efficacy. On the other hand, three other fair-quality clinical trials found cyclobenzaprine superior to diazepam for at least some clinical outcomes, particularly in the first week of treatment. These three trials were published together, received some support from a manufacturer, and used unvalidated outcome measures, making further interpretation of the results difficult. There is insufficient evidence from other fair-quality head-to-head trials to suggest that any other skeletal muscle relaxant is more effective than others in patients with musculoskeletal conditions. Reviewed placebo-controlled trials were characterized by absence of good-quality studies and marked heterogeneity in terms of designs, patient populations, assessed outcomes, interventions, and results. These trials were not helpful in evaluating comparative efficacy. We were not able to perform meta-analyses on any sub-group of trials. These trials were generally of short duration and long-term data are lacking.

The body of evidence regarding the effectiveness of various skeletal muscle relaxants compared to placebo varies both in quality and quantity. There is fair-quality evidence from a total of 17 trials (none rated good quality) comparing cyclobenzaprine to placebo (including head-to-head trials with a placebo arm) that consistently found that cyclobenzaprine is more effective than placebo for various measures of pain relief, muscle spasm, or functional ability. These results are similar to a recent systematic review of 14 of these trials.[50] The body of evidence regarding tizanidine (six trials), carisoprodol (four trials), and orphenadrine (four trials) was also rated fair-quality but was not as robust. For each of these interventions there appeared to be a consistent trend favoring the active treatment compared to placebo. There is very limited data from head-to-head or placebo-controlled trials demonstrating the effectiveness of chlorzoxazone, methocarbamol, baclofen, or dantrolene in patients with musculoskeletal conditions. The data regarding metaxalone was mixed: although the best fair-quality trial found no benefit compared to placebo, one poor-quality trial and two other fair-quality trials found some benefit.

New evidence identified during the update process appears insufficient to significantly change the conclusions of the original report with regard to assessing the comparative efficacy of different skeletal muscle relaxants for musculoskeletal conditions. The systematic review was not designed to evaluate comparative efficacy, but its conclusions were similar to our report. No new head-to-head trials were identified, and none of the placebo-controlled trials were rated good quality. There is additional evidence from two fair-quality placebo-controlled trials that metaxalone is superior to placebo, though another fair-quality trial (reviewed in the original report) found no differences. In two placebo-controlled trials of different doses of cyclobenzaprine versus placebo, one found that cyclobenzaprine 5 mg po tid provided equivalent effectiveness to 10 mg po tid doses, and the other that cyclobenzaprine 2.5 mg po tid was not significantly superior to placebo.[46]

2. What are the comparative incidence and nature of adverse effects (including addiction and abuse) of different muscle relaxants in patients with a chronic neurologic condition associated with spasticity, or a chronic or acute musculoskeletal condition with or without muscle spasms?

Patients with spasticity

Results of systematic reviews and meta-analyses

We identified no systematic reviews that evaluated comparative adverse event rates from skeletal muscle relaxants in patients with spasticity. One meta-analysis of three placebo-controlled trials with 525 enrollees (284 on tizanidine) was rated poor-quality for adverse event assessment because no information about adverse event assessment methods was reported (Evidence Table 1).[53] Adverse events included 49% dry mouth, 48% somnolence, 41% asthenia, 16% dizziness, and 12% headache in patients on tizanidine compared to 10%, 10%, 16%, 4%, and 13% on placebo. Two patients had liver function abnormalities and three patients had hallucinations. No deaths were reported. Abuse or addiction were not evaluated. Withdrawal rates due to adverse events were 17% for tizanidine and 7% for placebo. This meta-analysis did not report adverse event data from other reviewed trials in which tizanidine was compared to diazepam or baclofen, but did report better 'global tolerability' (1-4 scale) with tizanidine (2.0) than with diazepam (2.6, p=0.001) or baclofen (2.3, p=0.008).

No systematic reviews of skeletal muscle relaxants for spasticity meeting inclusion criteria were identified during the update process.

Results of head-to-head trials

No head-to-head trial was rated good quality for adverse event assessment. In general, there was little evidence of rigorous adverse event assessment in these trials (Evidence Table 3). No trial appeared to have significantly better adverse event reporting methods than the others. The most frequently reported adverse event rates were for somnolence, weakness, dizziness, and dry mouth. For the same medication, adverse event rates varied between trials (Table 6). For example, rates of somnolence from baclofen in head-to-head trials of baclofen

and tizanidine ranged from 0%[63] to 80%[57] and weakness ranged from 7%[61] to 57%.[60] The observed ranges of adverse event rates could reflect differences in populations, dosing of medications in trials, use of a run-in period, the rigor of adverse event assessment, or other factors. No deaths or serious adverse events were reported in these trials. Rates of abuse and addiction were not evaluated. Interpretation of reported adverse event rates was limited by the short duration of follow-up.

For each skeletal muscle relaxant evaluated in head-to-head trials, rates across trials for common adverse events overlapped with rates found for other skeletal muscle relaxants (Table 6). In individual head-to-head trials of tizanidine and baclofen, however, several patterns emerged. In these eight trials, dry mouth was reported more frequently on tizanidine in five studies (roughly equivalent or not reported in the other three), but weakness was reported more frequently on baclofen in all seven studies in which it was reported (Table 5). No consistent patterns were seen for somnolence or dizziness. Withdrawal rates due to adverse events, an indicator of intolerable adverse events, were higher on baclofen than tizanidine (12/46 [156] vs. 4/46 [155]) in only one trial with significant numbers of withdrawals. Other trials had very low numbers of withdrawals due to adverse events or found no differences.

It was not possible to use trials directly comparing baclofen, dantrolene, or tizanidine with diazepam to assess comparative adverse event rates. Adverse events data were not reported or poorly reported in three trials.[66, 68, 69] In the remaining trials, no clear pattern of differential adverse events was apparent for any skeletal muscle relaxant. Withdrawals due to adverse events favored tizanidine over diazepam in one trial[64] (28% [15/54] vs. 12% [6/51]), but in other trials withdrawal rates were equivalent, not reported, or very few in number. The small number (two or three) of trials for each skeletal muscle relaxant, the wide ranges for adverse events (somnolence 11-67%, weakness 12-53%) on diazepam (the common comparator) in different trials, and the limited quality of adverse event assessment limit further interpretation of these data.

No head-to-head trials of skeletal muscle relaxants for spasticity meeting inclusion criteria were identified during the update process.

Results of placebo-controlled trials

Most placebo-controlled trials were rated poor or fair-quality for adverse event assessment (Evidence Table 4). Abuse or addiction was not evaluated. Three trials appeared to have more rigorous adverse event assessment[103, 105, 106] and were rated good quality. All three of these trials evaluated tizanidine. Rates of somnolence (41-54%) were similar in these trials but rates for other adverse events (dry mouth, dizziness, weakness, and withdrawal due to adverse events) ranged widely or were not consistently reported (Table 7). In one of the good-quality trials,[103] 3 patients (18%) developed elevations of transaminases (highest alanine transaminase 90) that were not thought to be clinically significant.

In general, placebo-controlled trials as a whole gave little additional information to compare adverse events of skeletal muscle relaxants in patients with spasticity. For each evaluated medication, adverse event rates overlapped for different skeletal muscle relaxants and had wide ranges across trials. For example, the rate of somnolence, the most consistently reported adverse event, ranged from 33-54% in trials of tizanidine, 0-78% for baclofen, and 15-88% for dantrolene. We were unable to define narrower ranges for adverse events by

stratifying trials according to dose because most trials titrated the medication, and it was not clear on which dose adverse events occurred. Withdrawal rates due to adverse events and rates of weakness were not consistently reported.

One poor-quality placebo-controlled trial of methocarbamol in children with cerebral palsy was added to the above text in June 2003 and did not change the above results.[39] No other placebo-controlled trials of skeletal muscle relaxants for spasticity meeting inclusion criteria were identified during the update process.

Results of observational studies

We identified two observational studies assessing rates of hepatic complications in patients on dantrolene.[35, 157] One study[35] published in 1990 collected all cases of dantrolene-associated hepatic injury that were reported to the manufacturer, regulatory authorities, or in the published literature. It was rated fair-quality for adverse event assessment because it relied primarily on spontaneously reported cases of hepatic injury. This study excluded 73 cases from analysis that could not be verified using pre-specified exclusion criteria and 36 cases in which dantrolene was not thought to be the cause of hepatic injury, leaving a total of 122 analyzable cases of dantrolene-associated hepatic injury. Of these, 47 had asymptomatic transaminase elevations, 12 also had mild hyperbilirubinemia, 36 had jaundice, and 27 fatalities occurred. Fifty-two percent (14/27) of the fatalities occurred in multiple sclerosis patients. Fatalities were associated with a higher mean dantrolene dose (582 mg/dL) than non-fatal cases (263 mg/dL). The risk of hepatic complications was estimated to be less than 9.0 cases per 100,000 prescriptions written for dantrolene, and fatal hepatic reactions 0.83 cases per 100,000 prescriptions. An earlier study (1977), which included results from placebo-controlled trials as well as spontaneously reported cases, estimated rates of 1.8% (16/1044) for any hepatic injury and 0.3% (3/1044) for a fatal outcome.[157] Differences between the two studies may be related in part to fewer spontaneously reported adverse events, higher doses of dantrolene in earlier studies, or increasingly selective use of dantrolene.

Tizanidine has been associated with hepatic aminotransaminase elevations that are usually asymptomatic and reversible with discontinuation of the medication. Postmarketing surveillance data submitted to the FDA indicate that tizanidine is associated with elevations of aminotransaminases greater than three times the upper limit of normal in 5% of patients, compared to 0.4% in placebo.[158] Of three deaths associated with liver failure in patients treated with tizanidine, one case was thought probably related to tizanidine and the other two occurred in patients on other hepatotoxic agents (dantrolene or carbamazepine) and were not clearly related to tizanidine. Based on these data, monitoring of aminotransferases was recommended during the first 6 months of treatment and periodically afterward. It was also recommended that tizanidine be used with caution in patients with impaired hepatic function. We found one other case report that reported a case of symptomatic jaundice associated with tizanidine that resolved after drug discontinuation.[159] We did not identify any observational studies estimating the rate of serious hepatic complications from baclofen.

We identified no other large or good-quality observational trials on adverse events from skeletal muscle relaxants in patients with spasticity. Although other serious adverse events (serious withdrawal symptoms,[160-164] overdose,[165-167] and seizure[168]) have been reported in case series, comparative rates for these events can not be estimated from these reports.

No large, high-quality observational studies of skeletal muscle relaxants for spasticity meeting inclusion criteria were identified during the update process.

Summary

Reliable data are lacking on comparative adverse event rates from skeletal muscle relaxants in patients with spasticity. In almost all trials evaluated, there was little or no evidence of rigorous adverse event assessment. There is limited fair-quality evidence from eight head-to-head trials that the adverse event profiles of tizanidine and baclofen are different, as most head-to-head trials of these two medications have found that more patients on tizanidine experienced dry mouth while more experienced weakness on baclofen. There was no clear evidence that intolerable adverse events were more frequent with tizanidine compared to baclofen. There was insufficient evidence to judge the comparative safety of other skeletal muscle relaxants in patients with spasticity. Serious side effects appeared rare, but there does appear to be a small but significant risk of serious (including fatal) dantrolene-related hepatic injury. Although asymptomatic, reversible elevations of aminotransaminases have been reported with tizanidine, serious or fatal hepatic injury appears extremely rare on this medication. Serious hepatic toxicity has not been associated with baclofen. Other serious adverse events (seizure, serious withdrawal, overdose) were reported in case studies or reports but we could not estimate comparative rates of these events.

One poor-quality placebo-controlled trial was added to the report in June 2003 and did not change the conclusions. No other new studies regarding the safety of skeletal muscle relaxants and meeting inclusion criteria were identified during the update process.

Patients with musculoskeletal conditions

Results of systematic reviews and meta-analyses

Adverse events from cyclobenzaprine have been evaluated in one systematic review and one meta-analysis (not systematic) (Evidence Table 2). Neither study rated the quality of included trials for adverse event assessment. The systematic review[50] evaluated rates of adverse events for cyclobenzaprine versus placebo. This systematic review did not rate the quality of included trials for adverse event assessment. It found significantly increased rates of drowsiness (20% vs. 2%, $p<0.001$), dry mouth (8% vs. 2%, $p=0.02$), dizziness (7% vs. 4%, $p=0.04$), and any adverse event (53% vs. 28%, $p=0.002$) in patients on cyclobenzaprine versus placebo. Withdrawals due to adverse events were not reported. The meta-analysis reported comparative rates of adverse events for cyclobenzaprine versus diazepam.[55] Rates of drowsiness (38%) and dry mouth (24%) were higher for cyclobenzaprine compared to diazepam (33% and 8%). Dizziness was reported more frequently in patients on diazepam (17%) compared to cyclobenzaprine (10%). Other adverse events and withdrawals due to adverse events were not reported.

The systematic review of skeletal muscle relaxants and benzodiazepines for non-specific low back pain that was identified during the update process did not report adverse event rates or withdrawal rates of individual included studies or specific skeletal muscle relaxants.[47, 48] It reported pooled relative risks of 1.50 (95% CI, 1.14 to 1.98) for any adverse event and 2.04 (95% CI, 1.23 to 3.37) for central nervous system adverse events from

nonbenzodiazepine skeletal muscle relaxants versus placebo in 11 trials (Table 1 and Evidence Table 1).

Results of head-to-head trials

No head-to-head trial was rated good quality for adverse event assessment. Overall quality of adverse event assessment was similar to that described for head-to-head trials in patients with spasticity. Abuse and addiction were not evaluated in these trials. No deaths were reported.

There was very limited data from head-to-head trials to assess comparative safety of skeletal muscle relaxants in patients with musculoskeletal conditions. Of 11 head-to-head trials, three trials reported almost no adverse event information[109, 112, 117]. In the eight head-to-head trials with more substantial adverse event data, there were too few direct comparisons for any clear patterns to emerge (Table 8). In the head-to-head trial of cyclobenzaprine versus methocarbamol, cyclobenzaprine was associated with more somnolence (58% vs. 31%), but the rate of withdrawals due to adverse events was equivalent (7% vs. 6%).[19] In the head-to-head trial of cyclobenzaprine and carisoprodol, dry mouth was more frequent with cyclobenzaprine (38% vs. 10%) and dizziness less frequent (8% vs. 26%).[110] Withdrawal rates due to adverse events were equal (8%).

The five head-to-head trials with adverse event data comparing cyclobenzaprine, carisoprodol, or tizanidine to diazepam are difficult to interpret because the rate of adverse events for diazepam varied greatly between trials. Rates of somnolence on diazepam, for example, were 13%,[113] 30%,[115] and 50%,[116] while respective rates for dizziness were 12%, 8%, and 50% despite similar doses of diazepam. Because of the wide disparity in adverse event rates from diazepam, reliable conclusions about the comparative adverse event rates of cyclobenzaprine and tizanidine could not be drawn from these trials. In all head-to-head trials, withdrawals due to adverse events were roughly equal or no withdrawals due to adverse events were reported.

No head-to-head trials of skeletal muscle relaxants for musculoskeletal conditions meeting inclusion criteria were identified during the update process.

Results of placebo-controlled trials

No placebo-controlled trial was rated good quality for adverse event assessment. Abuse and addiction were not evaluated. No deaths thought related to medication were reported. Serious adverse events were rare.

Adverse events were not reported consistently in these trials, and doses of medications and titration methods differed markedly between studies. For example, for baclofen, doses ranged from 5 mg tid up to 80 mg daily, with various methods for titrating doses. Wide and overlapping ranges for all commonly reported adverse events (somnolence, dizziness, dry mouth, withdrawals due to adverse events) were seen for carisoprodol, cyclobenzaprine, and tizanidine (Table 8). There was extremely limited adverse events data for orphenadrine (2 trials[140, 142] reported almost no adverse events and two[22, 141] did not report adverse event data), metaxalone, (no adverse event data from 3 trials[43, 139] and unclear adverse event rates from 1 other[42]) baclofen (only 1 trial[143]), methocarbamol (poor-quality and very limited adverse event data from one placebo-controlled trial[41]) or dantrolene (neither of 2 trials[144, 145] reported

adverse events). There was no pattern from placebo-controlled trials to suggest that any one muscle relaxant was superior to others for adverse events.

Six placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions were incorporated into the report in June 2003 and did not change the above results.[40-44] As with other placebo-controlled trials, the quality of adverse event assessment was generally poor.

Two trials found during the update searches in October 2003 evaluated the efficacy of different doses of cyclobenzaprine versus placebo.[46] Both were fair quality for adverse event assessment (adverse events not pre-specified or defined, adverse events only assessed by self-report, no statistical analysis of potential confounders). In both trials, adverse event rates were higher with increasing doses of cyclobenzaprine, compared to placebo (Table 9 and Evidence Table 6). One trial compared cyclobenzaprine 10 mg po tid and 5 mg po tid with placebo and found that withdrawal rates were higher for 10 mg po tid (13.7%) compared to 5 mg po tid (9.1%) and were due to increased adverse events (8.0% vs. 5.0%, $p<0.05$), primarily sedation. The second trial compared cyclobenzaprine 2.5 mg po tid and 5 mg po tid with placebo, and found that the 2.5 mg po tid regimen was associated with fewer adverse events (2.2%) than 5 mg (4.1%). Withdrawal rates, however, were higher in the cyclobenzaprine 2.5 mg po tid group than the 5 mg po tid group (9.0% vs. 6.8%, NS) and were due to increased discontinuations due to therapeutic ineffectiveness (4.5% vs. 0.9%, $p=0.036$).

Results of observational studies

We identified one study evaluating abuse risk in patients taking carisoprodol.[20] Carisoprodol is suspected of having a higher potential for abuse because of it metabolizes to meprobamate, a federally controlled substance. This study enrolled 40 patients taking carisoprodol for more than 3 months. It assessed the potential for abuse using an unvalidated six-item questionnaire and found that 20% of patients with no history of substance abuse history and 65% with a history of substance abuse responded yes to one or more questions, which the authors suggested indicated a tendency towards possible abuse. We identified no other observational studies assessing the risk of abuse or addiction from carisoprodol or other skeletal muscle relaxants in patients with musculoskeletal conditions. Most reports of abuse and addiction are from case reports.[169] A French report from 1997 noted that meprobamate was the most frequently cited drug in fatal pharmaceutical overdoses (19 cases, or 15.3%), but we were unable to find similar data on meprobamate or carisoprodol in the U.S.[170]

We identified one large observational study evaluating safety of cyclobenzaprine in 6311 patients.[171] This study enrolled about 2000 physicians and asked each to report any adverse events in five patients with musculoskeletal conditions. It was rated fair-quality for adverse event assessment. Rates of somnolence (16%), dry mouth (7%), dizziness (3%), and other adverse events were about 50% lower than in clinical trials and indicate that these data might not be as reliable as available clinical trial data for estimating true adverse events rates.

We identified one observational study of hepatotoxicity associated with chlorzoxazone.[45] This study reported one case in which a patient on a combination of chlorzoxazone and acetaminophen developed jaundice and abnormal liver function tests. This resolved when the medication was discontinued, but returned when the patient was rechallenged with chlorzoxazone, but not with acetaminophen. This study also obtained records from the FDA and found that 23 additional cases of hepatotoxicity associated with

chlorzoxazone had been reported since 1970. Eight cases were judged to be probably related to chlorzoxazone, including two fatal cases, while the remainder were possibly or doubtfully related. Most cases were mild and resolved after discontinuation of the medication, but a few cases reported very high elevations of serum transaminases, severe hepatitis on biopsy, or permanent liver damage. The FDA changed the labeling of chlorzoxazone to indicate that serious (including fatal) hepatotoxicity has been rarely reported in patients receiving chlorzoxazone, and that the medication should be discontinued promptly if signs or symptoms of this adverse reaction occur.[158] We found no data estimating rates of serious hepatotoxicity in patients treated with chlorzoxazone.

The hepatotoxic potential of tizanidine, a medication used for both spasticity and musculoskeletal conditions, was previously discussed. We identified no other large- or good-quality observational studies of comparative adverse event rates for skeletal muscle relaxants.

An observational study reviewing case reports of hepatotoxicity associated with chlorzoxazone was added to this report in June 2003 and described in the above text. It suggests an association between very rare, but potentially fatal (2 cases) hepatotoxicity and chlorzoxazone, but was not designed to calculate rates of this adverse event. No other large, good-quality observational studies of skeletal muscle relaxants for musculoskeletal conditions meeting inclusion criteria were identified during the update process

Summary

There is insufficient evidence to judge whether any skeletal muscle relaxant is safer than others in patients with musculoskeletal conditions. The data are quite limited both in quality and in quantity (only five head-to-head trials with adverse event data). Withdrawals due to adverse events (an indicator of intolerable adverse events) were similar in head-to-head trials. There was insufficient data to assess comparative abuse and addiction risk of skeletal muscle relaxants. Severe adverse events appeared rare and relative frequency could not be assessed. Chlorzoxazone and tizanidine have both rarely been associated with serious hepatotoxicity.

New evidence identified during the update process was insufficient to significantly change the conclusions of the original report with regard to the comparative safety of different skeletal muscle relaxants for musculoskeletal conditions. There appear to be very rare (two fatal) cases of hepatotoxicity associated with chlorzoxazone, but the rate of complications could not be calculated from the reviewed study. A systematic review of various muscle relaxants for nonspecific back pain did not report adverse event rates for individual trials or specific skeletal muscle relaxants. No new head-to-head trials were identified, and no placebo-controlled trial was rated good quality for adverse event assessment. One of these trials found that cyclobenzaprine 5 mg po tid was associated with fewer withdrawals and adverse events than 10 mg po tid, and another that cyclobenzaprine 2.5 mg po tid was associated with fewer adverse events but more overall withdrawals, due to ineffectiveness, than 5 mg po tid.[46]

3. Are there subpopulations of patients (specifically by race, age, sex, or different underlying conditions) with spasticity or chronic musculoskeletal conditions for which one skeletal muscle relaxant is more effective or associated with fewer adverse effects?

No clinical trials or observational studies were designed to compare the efficacy of skeletal muscle relaxants for different races, age groups, or genders. There is almost no information to judge the relative effectiveness or adverse event rates of skeletal muscle relaxants in these subpopulations. Race was rarely reported in the trials. When it was reported the overwhelming majority of patients were white. Women were well represented in the trials as were older patients, but the effect of gender or age on medication efficacy was not evaluated in any trial. Nine trials[69, 80, 82, 87, 88, 91, 92, 97, 107] evaluated children and two trials[78, 140] evaluated elderly patients. Accurate judgments about comparative efficacy and safety in these populations could not be made, however, because of the same problems with lack of good-quality trials and heterogeneity in interventions, outcomes assessed, and findings that were encountered in examining general efficacy and adverse events. In addition, fewer studies directly addressed these populations.

Most data from head-to-head trials were in patients with multiple sclerosis or acute neck and low back pain and were reviewed in the section on general efficacy and safety. Only small numbers of trials (usually placebo-controlled) specifically evaluated other underlying conditions. For example, of three placebo-controlled trials of patients with fibromyalgia, all investigated cyclobenzaprine.[131, 135, 137] Of four placebo-controlled trials in patients with tension headaches, three evaluated tizanidine[44, 148, 150] and one cyclobenzaprine.[136] Small numbers of trials, lack of high-quality studies, and heterogeneous designs and methods limited our ability to systematically evaluate skeletal muscle relaxants for these and other conditions including cerebral palsy (three trials[69, 87, 92]), spinal cord injury (two trials[104, 172]), and post-stroke patients (four trials[64, 78, 93, 94]) (see Table 3).

Because there is some evidence that different skeletal muscle relaxants are associated with different rates of somnolence, weakness, and dry mouth, specific patients might do better with one skeletal muscle relaxant compared to another. For example, in patients who are still ambulatory, it may be important to choose a skeletal muscle relaxant that does not cause excess weakness. This hypothesis, however, has not yet been evaluated in clinical trials or observational studies. There is also insufficient data to judge the comparative efficacy or safety of skeletal muscle relaxants in patients for whom one agent has failed or who have had intolerable side effects.

No study has assessed the comparative risk of abuse and addiction from skeletal muscle relaxants in patients with a prior history of substance abuse. In trials that specified exclusion criteria, patients with prior or suspected substance abuse were usually excluded.

Other special populations have typically been excluded from clinical trials and have not been well studied. In case reports, baclofen has been reported to cause toxicity in patients with impaired renal function, but there are insufficient data to compare rates of toxicity with other skeletal muscle relaxants in this population.[165] We found no trials involving patients with chronic liver disease. In one trial involving children with spasticity and epilepsy, dantrolene did not increase the frequency of seizures.[97]

No new studies evaluating skeletal muscle relaxants in different subpopulations were identified during the update process.

SUMMARY

Results for each of the key questions are summarized in Table 10. Most skeletal muscle relaxants were evaluated for either spasticity or musculoskeletal conditions; only tizanidine was evaluated in head-to-head and more than two placebo-controlled trials for both spasticity and musculoskeletal conditions. Most of the head-to-head trials were performed in patients with multiple sclerosis and patients with acute neck or low back pain; almost all of the evidence regarding efficacy and safety in patients with other conditions comes from placebo-controlled trials.

In general, there was insufficient evidence to prove that different skeletal muscle relaxants are associated with different efficacy or safety. The best available evidence suggests that tizanidine is roughly equivalent to baclofen for most clinical outcomes in patients with spasticity. The comparative efficacy for other skeletal muscle relaxants and other conditions has not been established. In patients with musculoskeletal conditions, the largest body of head-to-head data is for cyclobenzaprine versus diazepam in patients with musculoskeletal conditions, but this data was inconclusive regarding differences in comparative efficacy. The data on adverse events is insufficient to distinguish any skeletal muscle relaxant with regard to overall safety, though the adverse event profile may differ between medications. There appears to be a small but significant risk of dantrolene-associated serious (including fatal) hepatic injury. Tizanidine appears to be associated with asymptomatic, reversible elevations of aminotransferases, and both tizanidine and chlorzoxazone have been associated with rare cases of serious hepatotoxicity. The available literature provides no data regarding the comparative risk of abuse and addiction from skeletal muscle relaxants.

There may be other reasons (such as convenience, improved compliance, better sleep, or more consistent pain relief) for prescribing skeletal muscle relaxants, but these outcomes were not adequately assessed in the reviewed trials.

Essentially no data are available to assess comparative efficacy and adverse event risks in subpopulations of patients with spasticity or musculoskeletal conditions.

Based on additional trials reviewed and incorporated into the report in June 2003, and two other trials and a systematic review identified in update searches performed in October 2003, there does not appear to be new evidence that would significantly change the conclusions of the original report (Table 10). A new systematic review of skeletal muscle relaxants for non-specific low back pain was not designed to assess comparative efficacy, and did not report adverse event rates for specific trials or skeletal muscle relaxants. No new head-to-head trials were identified, and none of the placebo-controlled trials identified since the original report were rated good quality. Placebo-controlled trials did provide additional evidence regarding the efficacy of metaxalone, with two fair-quality trials finding superior efficacy compared to placebo (another fair-quality trial reviewed in the original report did not find superior efficacy compared to placebo). In addition, there appear to be very rare (two fatal) cases of hepatotoxicity associated with chlorzoxazone, but the rate of complications could not be calculated from the reviewed study. It does not appear that other reliable conclusions about the comparative efficacy or safety of different skeletal muscle relaxants can be drawn from the new data. One fair-quality randomized trial found that cyclobenzaprine 5 mg po tid provided equivalent effectiveness to 10 mg po tid doses, while being associated with fewer adverse events.[46] Another fair-quality randomized trial found that cyclobenzaprine 5 mg po tid but not 2.5 mg po tid was more effective than placebo, and associated with fewer withdrawals (due to

ineffectiveness) than the 2.5 mg po tid dose.[46] A previous trial found that cyclobenzaprine 20 mg tid was not more effective than 10 mg po tid, and associated with more adverse events.[24] This information could guide target doses in future trials, and similar information would be very useful for other skeletal muscle relaxants.

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Table 1. Overview of included systematic reviews on skeletal muscle relaxants

Author Year	Purpose of study	Skeletal muscle relaxants evaluated	Number of included studies and patients	Quality	Main findings
Systematic reviews					
Browning 2001[50]	Assess the effectiveness of cyclobenzaprine in low back pain	Cyclobenzaprine	14 trials 3315 patients on cyclobenzaprine	Good	Included studies of generally fair quality. Cyclobenzaprine moderately effective in improving symptoms compared to placebo. No information on comparative efficacy and safety.
Shakespeare 2001[26]	Assess the comparative effectiveness and tolerability of anti-spasticity agents in multiple sclerosis patients	Tizanidine Baclofen Dantrolene Diazepam*	36 trials (7 tizanidine vs. baclofen, 2 tizanidine vs. diazepam, 1 baclofen vs. diazepam, 1 dantrolene vs. diazepam) 1359 patients overall	Good	Included studies of fair or poor quality. Tizanidine more effective than baclofen for muscle strength in 2 out of 7 head-to-head trials, otherwise no significant differences in efficacy. No differences in efficacy between tizanidine, baclofen, and dantrolene compared to diazepam; diazepam associated with more sedation and less preferred.
van Tulder 2003[47,48]	Assess the effectiveness of muscle relaxants in the treatment of nonspecific low back pain	Tizanidine Cyclobenzaprine Carisoprodol Dantrolene Chlorzoxazone Baclofen Orphenadrine Diazepam* Tetrazepam*	30 trials (3 cyclobenzaprine vs. placebo, 6 tizanidine vs. placebo, 1 cyclobenzarpine vs. diazepam vs. placebo, 1 carisoprodol vs. diazepam, 1 tizanidine vs. chlorzoxazone, 1 dantrolene vs. placebo, 1 baclofen vs. placebo, 1 orphenadrine vs. placebo, 1 tizanidine vs. diazepam, 1 carisoprol vs. placebo, 1 carisoprodol vs. cyclobenzaprine, remainder evaluated interventions we excluded) 2884 patients overall	Good.	23/30 evaluated studies rated good quality (average score 6 on 0-11 scale) Nonbenzodiazepine muscle relaxants effective for pain relief and global efficacy, and associated with more adverse events, compared to placebo.

Table 1. Overview of included systematic reviews on skeletal muscle relaxants (continued)

Author Year	Purpose of study	Skeletal muscle relaxants evaluated	Number of included studies and patients	Quality	Main findings
Systematic reviews					
Taricco 2000[52]	Assess the effectiveness and safety of drugs for spasticity in spinal cord injury patients	Tizanidine Baclofen	9 trials (2 baclofen vs. placebo, 1 tizanidine vs. placebo) 218 patients overall	Fair. Some identified studies not assessed.	Included studies of fair or poor quality. Tizanidine more effective than placebo for Ashworth score but not for functional status. No difference between baclofen and placebo.
Lataste 1994[51]	Assess the comparative efficacy of tizanidine compared to other anti-spastic agents	Tizanidine Baclofen Diazepam*	20 trials (14 vs. baclofen, 6 vs. diazepam) 385 patients on tizanidine, 392 on baclofen or diazepam	Poor. Methods of search not reported, study quality not assessed, inufficient detail of included studies.	Unable to assess quality of included studies. No significant differences between tizanidine and baclofen or diazepam for muscle tone, muscle spasms, clonus, musle strength, functional status, or overall antispastic effect. Tizanidine slightly better tolerated than diazepam and baclofen. Withdrawals due to adverse events 4% on tizanidine vs. 9% on baclofen or diazepam.

Table 1. Overview of included systematic reviews on skeletal muscle relaxants (continued)

Author Year	Purpose of study	Skeletal muscle relaxants evaluated	Number of included studies and patients	Quality	Main findings
Meta-analyses					
Groves 1998[54]	Assess the efficacy and tolerability of tizanidine using unpublished trials held by the manufacturer	Tizanidine Baclofen Diazepam*	10 trials (7 vs. baclofen, 3 vs. diazepam) 270 patients overall	Fair. Insufficient detail of included studies and not clear if data combined appropriately.	No significant differences between tizanidine and baclofen or diazepam for spasticity by Ashworth score or mean change in muscle strength. 'Global tolerability to treatment' favored tizanidine compared to baclofen (p=0.008) and diazepam (p=0.001).
Wallace 1994[53]	Assess the efficacy and tolerability of tizanidine using unpublished trials held by the manufacturer	Tizanidine Baclofen Diazepam*	3 placebo-controlled trials with 525 patients 11 head-to-head studies (8 vs. baclofen, 3 vs. diazepam) with 270 patients	Fair. Insufficient detail of included studies and not clear if data combined appropriately	See results for Groves 1998 for results of head-to-head studies. In placebo-controlled studies, there were increased withdrawals due to adverse events (44/284 vs. 15/277) on tizanidine. Frequent adverse events on tizanidine were dry mouth (49%), somnolence (48%), asthenia (41%), dizziness (16%), headache (12%).
Nibbelink 1978[55]	Assess the efficacy of cyclobenzaprine using unpublished trials	Cyclobenzaprine Diazepam* Placebo	20 randomized trials 434 patients on cyclobenzaprine, 280 on diazepam, 439 on placebo	Fair. Insufficient detail of included studies and not clear if data combined appropriately	'Global response' equivalent for cyclobenzaprine and diazepam and significantly better than placebo. Muscle spasms, tenderness on palpation, limitation of motion, and limitation of daily living (but not local pain) significantly better in patients on cyclobenzaprine compared to diazepam at week 2 using unvalidated methods.

Table 2. Overview of head-to-head trials of skeletal muscle relaxants for spasticity

Interventions Dose	Study Year Quality	Population Number enrolled	Main outcomes assessed	Main results	Withdrawals (overall)
Tizanidine versus baclofen					
Tizanidine mean 17 mg/day **Baclofen mean 35 mg/day**	Bass 1988[58] **FAIR**	Multiple sclerosis 66	Spasticity: 6 point scale Strength: 6 point scale Functional status: Kurtzke functional scale Disability: Pedersen functional disability scale Preference: patient assessment	No significant differences between interventions for main outcomes	11% (5/46) 28% (13/46
Tizanidine titrated to 24 mg/day **Baclofen titrated to 60 mg/day**	Eyssette 1988[59] **FAIR**	Multiple sclerosis 100	Spasticity: 5 point scale Stretch reflex: 1-5 scale Functional status: Unspecified methods Efficacy and tolerability: Unspecified methods	No significant differences between interventions	16% (8/50) 12% (6/50)
Tizanidine 12-24 mg/day **Baclofen 15-60 mg/day**	Hoogstraten 1988[60] **FAIR**	Multiple sclerosis 16	Spasticity: Ashworth scale and patient self-report (5 point scale) Disability: Kurtzke Expanded Disability Status Scale Functional status: Kurtzke Functional Systems Incapacity status: Minimal record of disability for multiple sclerosis Ambulation: Ambulation index Clonus and reflexes: Unspecified methods Muscle strength and pain: 5 point scales Efficacy and tolerance: -3 to +3 scales	No significant differences between interventions (Ashworth scale scores not reported)	6% (1/16) 25% (4/16)
Tizanidine mean 20 mg/day **Baclofen mean 50 mg/day**	Medici 1989[61] **FAIR**	Spasticity due to various causes 30	Spasticity: Ashworth scale and patient self-report (4 point scale) Muscle strength: 5 point scale Clonus: 3 point scale Functional status: Kurtzke Expanded Disability Status Scale Global assessments: Unspecified methods	No significant differences between interventions (Ashworth scale scores not reported)	7% (1/15) 27% (4/15)
Tizanidine titrated to 16 mg/day **Baclofen titrated to 40 mg/day**	Newman 1982[62] **FAIR**	Multiple sclerosis (32) or syringomyelia (4) 36	Spasticity: Ashworth scale Functional status: Kurtzke and Pedersen scales	No significant differences between interventions (Ashworth scale scores not reported)	11% (4/36) 17% (6/36)

Table 2. Overview of head-to-head trials of skeletal muscle relaxants for spasticity (continued)

Interventions Dose	Study Year	Population Number enrolled	Main outcomes assessed	Main results	Withdrawals (overall)
Tizanidine mean 11 mg/day **Baclofen mean 51 mg/day**	Rinne 1980 (2)[57] **FAIR**	Multiple sclerosis (24) or cervical myelopathy (8) 32	Spasticity: Ashworth scale	No significant differences between interventions (Ashworth scale scores not reported)	6% (1/16) 6% (1/16)
Tizanidine 8 mg tid **Baclofen 20 mg tid**	Smolenski 1981[63] **FAIR**	Multiple sclerosis 21	Tone: Ashworth scale Spasticity: 5 point scale Muscle strength: 6 point scale Global assessment of change in condition: Unspecified methods Tolerance to medication: Unspecified methods	No significant differences between interventions (Ashworth scale scores not reported)	None reported
Tizanidine mean 23 mg/day **Baclofen mean 59 mg/day**	Stien 1987[49] **FAIR**	Multiple sclerosis 40	Tone/spasticity: Ashworth scale Functional status: Kurtzke Expanded Disability Status Scale Functional assessment: Pederson scale	No significant differences between interventions (Ashworth scale scores not reported)	6% (1/18) 5% (1/20)
Tizanidine, baclofen, or dantrolene versus diazepam					
Tizanidine mean 17 mg/day **Diazepam mean 20 mg/day**	Bes 1988[64] **FAIR**	Post-stroke or head-trauma 105	Spasticity: 5 point scale Functional status: walking distance Severity of spasms: 5 point scale Muscle strength: Unspecified methods Clonus: Unspecified methods	No significant differences between interventions	12% (6/51) 31% (17/54)
Tizanidine mean 14 mg/day **Diazepam mean 15 mg/day**	Rinne 1980 (1)[57] **FAIR**	Multiple sclerosis 30	Spasticity: Ashworth scale	No significant differences between interventions (Ashworth scale scores not reported)	0% (0/15) 27% (4/15)

Table 2. Overview of head-to-head trials of skeletal muscle relaxants for spasticity (continued)

Interventions Dose	Study Year	Population Number enrolled	Main outcomes assessed	Main results	Withdrawals (overall)
Baclofen 30 mg/day and 60 mg/day **Diazepam 15 mg/day and 30 mg/day**	Cartlidge 1974[65] FAIR	Multiple sclerosis 40	Spasticity: Ashworth scale	No significant differences between interventions (mean Ashworth score improvement 0.227 vs. 0.202 on high-doses)	Not clear
Baclofen mean 61 mg/day **Diazepam mean 27 mg/day**	From 1975[67] FAIR	Multiple sclerosis inpatients 16	Spasticity: Ashworth scale, clinical exam (unspecified methods) Clinical assesments of spasms, clonus, bladder function, walking: Unspecified methods Patient preference	No significant differences between interventions (Ashworth scale scores not reported)	6% (1/16) 0% (0/16)
Baclofen mean 47 mg/day **Diazepam 28 mg/day**	Roussan 1985[66] FAIR	Spasticity due to various causes 13	Global response to treatment: 0 (no improvement) to 3+ (marked improvement)	No significant differences between interventions	None reported
Dantrolene 100 mg qid **Diazepam 5 mg qid**	Glass 1974[68] FAIR	Spasticity due to various causes 16	Spasticity/tone: 6 point scale Reflexes: 6 point scale Clonus: 6 point scale Strength: 6 point scale	No significant differences between interventions	19% (3/16) 6% (1/16)
Dantrolene titrated to 75 mg qid **Diazepam titrated to 12 mg/day**	Nogen 1976[69] FAIR	Children with cerebral palsy 22	Tone: Unspecified method Tendon jerk: Unspecified method Clonus: Unspecified method Strength: Unspecified method Overall evaluation: Unspecified method	No significant differences between interventions	None reported
Dantrolene titrated to 75 mg qid **Diazepam titrated to 5 mg qid**	Schmidt 1976[70] FAIR	Multiple sclerosis 46	Spasticity: 6 point scale Clonus: 6 point scale Reflexes: 6 point scale Functional status: Methods not specified, derived from ACTH cooperative study	No significant differences between interventions for spasticity or clonus. Reflexes, station stability, and hand coordination favor dantrolene.	Not clear

Table 3. Overview of placebo-controlled trials of included skeletal muscle relaxants for spasticity

Medication	Trial Quality	Population Number enrolled	Main outcomes for spasticity/tone
Baclofen	Basmajian 1974[72] **FAIR**	Various spasticity 15	Favors baclofen based on "EMG and force recordings" (p not reported)
Baclofen	Basmajian 1975[73] **FAIR**	Various spasticity 14	Favors baclofen using unspecified method (p not reported)
Baclofen	Brar 1991[74] **FAIR**	Multiple sclerosis 38	Favors baclofen using Ashworth scale (p not reported)
Baclofen	Duncan 1976[75] **POOR**	M.S. or spinal cord lesions 25	Baclofen superior using 5 point scale (p<0.01)
Baclofen	Feldman 1978[76] **FAIR**	Multiple sclerosis 33	Baclofen superior using unspecified method (p not reported)
Baclofen	Hinderer 1990[77] **POOR**	Spinal cord lesions 5	No improvement on baclofen using unspecified method
Baclofen	Hulme 1985[78] **FAIR**	Post-stroke (elderly patients) 12	Not assessed; study stopped due to excess adverse events (somnolence)
Baclofen	Jones 1970[170] **FAIR**	Spinal cord injury 6	Favors baclofen using 5 point scale for spasm and spasm counts (p not reported)
Baclofen	McKinlay 1980[80] **FAIR**	Children with spasticity (criteria not specified) 20	No significant difference using Ashworth scale
Baclofen	Medaer 1991[81] **FAIR**	Post-stroke 20	Baclofen superior using Ashworth scale (p<0.001)
Baclofen	Milla 1977[82] **FAIR**	Various spasticity (children) 20	Baclofen superior using Ashworth scale (p<0.001)
Baclofen	Orsnes 2000[83] **FAIR**	Multiple sclerosis 14	No significant difference using Ashworth scale
Baclofen	Sachais 1977[84] **FAIR**	Multiple sclerosis 166	Baclofen superior using unspecified method (p<0.01)
Baclofen	Sawa 1979[85] **FAIR**	Multiple sclerosis 21	Baclofen superior using 6 point scale (p<0.001)
Dantrolene	Basmajian 1973[86] **POOR**	Upper motor neuron disease 25	Spasticity not assessed
Dantrolene	Chyatte 1973[87] **FAIR**	Athetoid cerebral palsy (children) 18	No measurable difference using 4 point scale

Table 3. Overview of placebo-controlled trials of included skeletal muscle relaxants for spasticity (continued)

Medication	Trials	Population Number enrolled	Main outcomes for spasticity/tone
Dantrolene	Denhoff 1975[80] **FAIR**	Various spasticity (children) 18	Dantrolene superior for "neurologic measurements" using unspecified methods (p<0.04)
Dantrolene	Gambi 1983[81] **FAIR**	Multiple sclerosis or myelopathy 24	Dantrolene superior using 6 point scale (p<0.05, raw data not reported)
Dantrolene	Gelenberg 1973[82] **POOR**	Multiple sclerosis 20	Spasticity assessed using unspecified method; outcomes not reported
Dantrolene	Glass 1974[54] **FAIR**	Various spasticity 16	Favors dantrolene for resistance to active stretch and tendon jerk using 6 point scales (p not reported)
Dantrolene	Haslam 1974[83] **FAIR**	Perinatal brain injury (children) 26	No statistical difference using 5 point scale
Dantrolene	Joynt 1980[84] **FAIR**	Cerebral palsy (children) 21	No statistical difference using 4 point scale
Dantrolene	Katrak 1992[85] **FAIR**	Post-stroke 38	No measurable difference using 0-6 motor assessment scale
Dantrolene	Ketel 1984[86] **POOR**	Post-stroke 18	Favors dantrolene, assessment method not reported
Dantrolene	Luisto 1982[87] **FAIR**	Various spasticity 17	Dantrolene superior using Ashworth scale (p=0.05)
Dantrolene	Monster 1974[88] **FAIR**	Various spasticity 200	Outcomes not clear, results for placebo not reported
Dantrolene	Nogen 1979[89] **FAIR**	Children with spasticity and epilepsy	No increased seizures on dantrolene; other outcomes not reported
Dantrolene	Sheplan 1975[90] **FAIR**	Various spasticity (all men) 18	Outcomes not clear (unspecified methods), results for placebo not reported
Dantrolene	Tolosa 1975[91] **FAIR**	Multiple sclerosis 23	Favors dantrolene using 7 point scale (p not reported)
Dantrolene	Weiser 1978[92] **FAIR**	Spinal cord disease 35	Dantrolene superior for spasms using unspecified scale (p<0.002); no differences for walking/staircase time
Tizanidine	Knutsson 1982[93] **FAIR**	Various spasticity 13	No significant difference using Ashworth scale
Tizanidine	Lapierre 1987[94] **FAIR**	Multiple sclerosis 66	No significant difference using unspecified method

Table 3. Overview of placebo-controlled trials of included skeletal muscle relaxants for spasticity (continued)

Medication	Trials	Population Number enrolled	Main outcomes for spasticity/tone
Tizanidine	Meythaler 2001[95] **FAIR**	Various spasticity 17	No significant difference using Penn Spasm Frequency Scale, favors tizanidine using Ashworth scale (p=0.006)
Tizanidine	Nance 1994[50] **FAIR**	Spinal cord injury 124	Tizanidine superior using Ashworth scale (p<0.0001) and pendulum test (p=0.004); no difference in daily spasm frequency
Tizanidine	Smith 1994[96] **FAIR**	Multiple sclerosis 220	No significant difference using Ashworth scale, 4 point scale, or daily counts
Tizanidine	UK Tizanidine Trial Group 1994[97] **FAIR**	Multiple sclerosis 187	Tizanidine superior using Ashworth scale (p=0.004)
Chlorzoxazone	Losin 1966[98] **POOR**	Various spasticity (children) 30	Outcomes not clear using 5 point scale
Cyclobenzaprine	Ashby 1972[100] **FAIR**	Various spasticity 15	No significant difference using 5 point scale
Methocarbamol	Bjerre 1971[99] **POOR**	Cerebral palsy (children) 44	No significant difference for overall condition using 3 point scale, methocarbamol superior for motor function (p<0.01) using Johnson scale for lower extremities but no significant difference for upper extremities

Table 4. Overview of head-to-head trials of skeletal muscle relaxants for musculoskeletal conditions

Interventions Dose	Study Year	Population Number enrolled	Main outcomes assessed	Main results	Overall withdrawals
Tizanidine versus chlorzoxazone					
Tizanidine 2 mg tid	Bragstad 1979[109]	Back spasms	Muscle tension: 4 point scale Pain intensity: 4 point scale Tenderness: 4 point scale Interference with normal activities: 4 point scale	No significant differences between interventions	0% (0/14)
Chlorzoxazone 500 mg tid	**FAIR**	120			8% (1/13)
Cyclobenzaprine versus methocarbamol					
Cyclobenzaprine 10 mg tid	Preston 1984[19]	Localized acute muscle spasm	Muscle spasm: 9 point scale Local pain and tenderness: 9 point scale Limitation of normal motion: 9 point scale Interference with normal activities: 9 point scale	No significant differences between interventions except slightly greater proportion of patients with improvement in local pain with cyclobenzaprine (48% vs. 40%)	14% (12/87)
Methocarbamol 1500 mg qid	**FAIR**	227			13% (12/94)
Cyclobenzaprine versus carisoprodol					
Cyclobenzaprine 10 mg qid	Rollings 1983[110]	Back spasms	Pain severity: 1-5 verbal rating scale and 0-100 visual analogue scale Muscle stiffness: VRS and VAS Activity impairment: VRS and VAS Sleep impairment: VRS and VAS Muslce tension: VRS and VAS	No significant differences between interventions	24% (9/37)
Carisoprodol 350 mg qid	**FAIR**	78			28% (11/39)
Carisoprodol, cyclobenzaprine or tizanidine versus diazepam					
Carisoprodol 350 mg qid	Boyles 1983[115]	Acute back sprain or strain with spasms	Muscle spasm: 5 point scale Tenderness: 5 point scale Mobility restriction: 5 point scale Pain, stiffness, activity, sleep impairment, tension: 5 point scales	Carisoprodol superior to diazpeam for muscle stiffness ($p<0.05$), tension ($p<0.05$), and relief ($p<0.05$) using 5 point scales; trend towards better overall relief (68% vs. 45%) with carisoprodol	10% (4/40)
Diazepam 5 mg qid	**FAIR**	80			12% (5/40)

Table 4. Overview of head-to-head trials of skeletal muscle relaxants for musculoskeletal conditions (continued)

Interventions Dose	Study Year	Population Number enrolled	Main outcomes assessed	Main results	Overall withdrawals
Cyclobenzaprine 10-20 mg tid **Diazepam 5-10 mg tid**	Aiken 1978a[111] **FAIR**	Acute back or neck spasms 117	Muscle spasm: 5 point scale Limitation of motion: 5 point scale Daily activities: 5 point scale Pain: 5 point scale Tenderness: 5 point scale Global response: 5 point scale (worse to marked improvement)	Cyclobenzaprine more effective than diazepam for muscle spasm, tenderness, limitation of motion at week 1 (p<0.05) and for pain, tenderness, limitation of motion, and global response at week 2 (p<0.05)	13% (5/38) 15% (6/40)
Cyclobenzaprine 10-20 mg tid **Diazepam 5 mg tid**	Basmajian 1978[112] **POOR**	Back or neck spasms 120	Muscle spasm: 5 point scale	No significant differences between interventions	Not reported
Cyclobenzaprine 10 mg tid **Diazepam 5 mg tid**	Brown 1978[113] **FAIR**	Back or neck spasms 49	Global evaluation: 5 point scale	No significant differences between interventions	None reported
Cyclobenzaprine 30-40 mg tid **Diazepam 15-20 mg/day**	Scheiner 1978 (1)[114] **FAIR**	Acute back or neck spasms 96	Muscle spasm: 5 point scale Pain: 5 point scale Tenderness: 5 point scale Limitation of motion: 5 point scale Daily activities: 5 point scale Global evaluation: 5 point scale (worse to marked improvement)	No significant differences between interventions except cyclobenzaprine more effective for tenderness at week 2 (p<0.05), limitation of motion at weeks 1 and 2 (p<0.01), and global evaluation (marked improvement) (p<0.01)	35% (12/34) 9% (3/32)
Cyclobenzaprine 30-40 mg tid **Diazepam 15-20 mg/day**	Scheiner 1978 (2)[114] **FAIR**	Acute back or neck spasms 75	Muscle spasm: 5 point scale Pain: 5 point scale Tenderness: 5 point scale Limitation of motion: 5 point scale Daily activities: 5 point scale Global evaluation: 5 point scale (worse to marked improvement)	Cyclobenzaprine more effective than diazepam (p<0.05) for all outcomes at weeks 1 and 2 except for muscle spasm and limitation of motion at week 1	8% (2/26) 21% (5/24)

Table 4. Overview of head-to-head trials of skeletal muscle relaxants for musculoskeletal conditions (continued)

Interventions Dose	Study Year	Population Number enrolled	Main outcomes assessed	Main results	Overall withdrawals
Tizanidine 4-8 mg tid **Diazepam 5-10 mg tid**	Fryda-Kaurimsky 1981[116] **FAIR**	Degenerative spinal disease with acute muscle spasm (inpatients) 20	Pain: 4 point scale Tenderness: 4 point scale Muscle spasm: 3 point scale Abnormal posture: 3 point scale Daily activities: 4 point scale Patient self-evaluation: 4 point scale	No significant differences between interventions	None reported
Tizanidine 4 mg tid **Diazepam 5 mg tid**	Hennies 1981[117] **FAIR**	Back or neck spasms 30	Pain: 4 point scale Muscle tension: Unspecified method Daily living activity: Unspecified method	No significant differences between interventions	7% (1/15) 0% (1/15)

Table 5. Overview of placebo-controlled trials of skeletal muscle relaxants for musculoskeletal conditions

Medication	Trials	Population Number enrolled	Main outcomes (included skeletal muscle relaxant versus placebo)
Carisoprodol	Baratta 1976[124] **FAIR**	Low back syndrome 105	No significant difference for pain using 4 point scale, carisoprodol superior to placebo for various functional measurements and for sleep
Carisoprodol	Cullen 1976[125] **FAIR**	Acute back or neck syndrome 65	Carisoprodol superior for pain, spasm, and limitation of movement using unspecified methods (all p<0.01)
Carisoprodol	Hindle 1972[126] **FAIR**	Low back syndrome (Mexican migrant workers) 48	Carisoprodol superior for pain, spasm, functional assessments using 4 point scales (all p<0.01) and pain intensity using 0-100 visual analogue scale (p<0.01)
Carisoprodol	Soyka 1979[127] **FAIR**	Acute neck or low back syndrome 414	Favors carisoprodol for muscle spasm (p=0.015) and functional assessment (p=0.04) using 5 point scales, no significant difference for sleep impairment using 4 point scale or pain using 5 point scale
Cyclobenzaprine	Aiken 1978a[128] **FAIR**	Acute neck or low back syndrome 117 (including diazepam arm)	Cyclobenzaprine superior to placebo for pain, tenderness, limitation of motion, daily activities, and global evaluation (all p<0.05) at end of week 2 using 5 point scales
Cyclobenzaprine	Aiken 1978b[125] **FAIR**	Acute neck or low back syndrome 50	Cyclobenzaprine superior to placebo for spasm, limitation of motion, daily activities (all p<0.01); pain/tenderness (p<0.05); and global evaluation (p not reported) using 5 point scales
Cyclobenzaprine	Baratta 1982[129] **FAIR**	Various acute muscle spasm 120	Cyclobenzaprine superior for local muscle spasm (p<0.01) and pain (p<0.01) using 5 point scale
Cyclobenzaprine	Basmajian 1978[112] **FAIR**	Various acute muscle spasm 120 (including diazepam arm)	No significant differences for task performance time or muscle spasms using 5 point scale
Cyclobenzaprine	Basmajian 1989[130] **FAIR**	Various acute muscle spasm 175	No significant differences for pain, muscle spasm, or functional measurements using unspecified methods
Cyclobenzaprine	Bennett 1988[131] **FAIR**	Fibromyalgia 120	Cyclobenzaprine superior for pain (p<0.02) using 1-10 visual analogue scale and sleep quality and fatigue using 5 point scale (p<0.02)
Cyclobenzaprine	Bercel 1977[132] **FAIR**	Neck or back pain >30 days 54	Favors cyclobenzaprine for spasm duration using 5 point scale (p not reported)
Cyclobenzaprine	Bianchi 1978[129] **FAIR**	Acute neck or low back syndrome 48	No significant differences at day 14; cyclobenzaprine superior to placebo for muscle consistency, tenderness, limitation of motion, and global evaluation (all p<0.01) and daily activities (p<0.05) at day 7
Cyclobenzaprine (5 mg tid and 10 mg tid)	Borenstein 2003 (1)[46] FAIR	Nonspecific low back pain 737	Cyclobenzaprine 5 mg tid and 10 mg tid superior to placebo using 5 point scales (p<0.05) for global change, medication helpfulness, and relief from starting backache.

Table 5. Overview of placebo-controlled trials of skeletal muscle relaxants for musculoskeletal conditions (continued)

Medication	Trials	Population Number enrolled	Main outcomes (included skeletal muscle relaxant versus placebo)
Cyclobenzaprine (2.5 mg tid and 5 mg tid)	Borenstein 2003 (2)[46] FAIR	Nonspecific low back pain 668	Cyclobenzaprine 5 mg tid superior to placebo using 5 point scales($p<0.03$) for global change, medication helpfulness, and relief from starting backache. No significant differences for cyclobenzaprine 2.5 mg tid versus placebo.
Cyclobenzaprine (+naprosyn in both arms)	Borenstein 1990[134] **POOR**	Acute low back syndrome 40	Cyclobenzaprine + naprosyn superior to naprosyn alone for functional capacity using 4 point scale ($p<0.05$) and muscle spasm using 4 point scale ($p<0.05$), no difference for resolution of pain (using 0-20 and 4 point scales)
Cyclobenzaprine	Brown 1978[113] **FAIR**	Chronic (>12 months) neck or low back pain	Cyclobenzaprine superior to placebo for global evaluation using 5 point scale (p not reported)
Cyclobenzaprine	Carette 1994[135] **FAIR**	Fibromyalgia 208	No significant difference for 6-month improvement using 0-10 visual analogue scale, pain using McGill Pain Questionnaire, functional disability, or psychological status
Cyclobenzaprine	Lance 1972[136] **POOR**	Chronic tension headache 20	Favors cyclobenzaprine using 3 point scale (p not reported)
Cyclobenzaprine	Preston 1984[19] **FAIR**	Acute local muscle spasm 227 (includes methocarbamol arm)	No differences for muscle spasm or limitation of motion; favors cyclobenzaprine for local pain and daily activities (p not reported) using 9 point scales
Cyclobenzaprine	Quimby 1989[40] **FAIR**	Fibromyalgia 40	Favors cyclobenzaprine using 5 point scale for patient rated stiffness and aching, patient rated poor sleep, and overall patient rating ($p<0.05$), no difference using 5 point scale for patient rated fatigue or muscle pain
Cyclobenzaprine	Reynolds 1991[137] **FAIR**	Fibromyalgia 12	No differences for tender point severity count using 5 point scale, pain using 7 point scale, fatigue using 7 point scale, sleepiness using Stanford Sleepiness Rating Scale
Cyclobenzaprine	Scheiner 1978 (1)[114] **FAIR**	Acute back or neck spasm 96	Cyclobenzaprine superior to placebo for muscle spasm, local pain, tenderness, limitation of motion, daily activities, and global evaluation ($p<0.01$) using 5 point scales
Cyclobenzaprine	Scheiner 1978 (2)[114] **FAIR**	Acute back or neck spasm 75	Cyclobenzaprine superior to placebo for muscle spasm, local pain, tenderness, limitation of motion, daily activities, and global evaluation ($p<0.01$) using 5 point scales
Cyclobenzaprine	Steingard 1980[138] **FAIR**	Back or neck spasm 121	No significant differences for global evaluation, pain, muscle spasm, or functional measurements using unspecified methods

Table 5. Overview of placebo-controlled trials of skeletal muscle relaxants for musculoskeletal conditions (continued)

Medication	Trials	Population Number enrolled	Main outcomes (included skeletal muscle relaxant versus placebo)
Metaxalone	Dent 1975[42] **POOR**	Acute skeletal muscle disorders (not specified) 228	Metaxolone superior for muscle spasm, local pain, limitation of normal motion, and interference with daily activities using unspecified scales
Metaxalone	Diamond 1966[139] **FAIR**	Muscle pain and spasm, unspecified locations 100	No significant difference using 5 point scale for muscle spasm or 4 point scale for pain
Metaxalone	Fathie 1964 (1)[43] **FAIR**	Low back pain 100	Metaxolone superior for global therapeutic response using 4 point scale, range of motion using 5 point scale, and palpable spasm using 5 point scale
Metaxalone	Fathie 1964 (2)[43] **FAIR**	Low back pain 100	Metaxolone superior for global therapeutic response using 4 point scale, range of motion using 5 point scale, and palpable spasm using 5 point scale
Methocarbamol	Preston 1984[19] **FAIR**	Acute local muscle spasm 227 (includes cyclobenzaprine arm)	No differences for muscle spasm; favors cyclobenzaprine for local pain, limitation of motion, and daily activities (p not reported) using 9 point scales
Methocarbamol	Tisdale 197541 **FAIR**	Acute local muscle spasm 180	Methocarbamol superior for muscle spasm and local pain at 48 hours using 5 point scales; methocarbamol superior for limitation of motion and daily activities at 1 week ($p<0.05$) but not for local pain ($p<0.10$) or muscle spasm (NS) using 5 point scales
Orphenadrine	Gold 1978[22] **POOR**	Acute low back syndrome 60	Orphenadrine superior for pain intensity ($p<0.01$) and pain relief ($p<0.01$)using unspecified methods
Orphenadrine	Latta 1989[140] **FAIR**	Nocturnal leg cramps (elderly) 59	Orphenadrine superior for number of nocturnal leg cramps in one month period
Orphenadrine (+paracetamol in both arms)	McGuinness 1983[141] **FAIR**	Various musculoskeletal conditions 32	Favors orphenadrine for pain, stiffness and function using 4 point scales (p not reported)
Orphenadrine	Valtonen 1975[142] **FAIR**	Low back or neck pain 200	No significant difference using 3-point scale for 'overall efffect'

Table 5. Overview of placebo-controlled trials of skeletal muscle relaxants for musculoskeletal conditions (continued)

Medication	Trials	Population Number enrolled	Main outcomes (included skeletal muscle relaxant versus placebo)
Baclofen	Dapas 1985[143] **FAIR**	Acute back syndrome 200	Baclofen superior for lumbar pain, tenderness, spasm, functional assessments using unspecifie methods (p<0.05)
Dantrolene	Casale 1988[144] **FAIR**	Chronic low back syndrome 20	Dantrolene superior for muscle spasm using "manual semiotic maneuvers" (p<0.001) and pain behavior using visual analogue scale (p<0.001)
Dantolene (+ ibuprofen in both arms)	Salvini 1986[145] **FAIR**	Neck or low back syndromes 60	Dantolene superior for muscle contracture using 4 point scale (p=0.04), strength using 5 point scale (p=0.05), no difference for pain on movement using 4 point scale
Tizanidine	Berry 1988a[146] **POOR**	Acute low back syndrome 105	Cyclobenzaprine superior for pain on movement (p=0.029), and pain at night (p=0.025) using 4 point scales, no differences for pain at rest or restriction of movement using 4 point scales
Tizanidine (+ ibuprofen in both arms)	Berry 1988b[147] **FAIR**	Acute low back syndrome 112	No significant differences for pain at night, pain at rest, or restriction of movement using 4 point scales
Tizanidine	Fogelholm 1992[148] **FAIR**	Tension headache (all women) 45	Tizanidine superior for headache severity using 0-100 visual analogue (p=0.018) scale and 5 point verbal rating scale (p=0.012) and for analgesic use using pill counts (p=0.001)
Tizanidine	Lepisto 1979[149] **FAIR**	Low back syndrome 30	Tizanidine superior for pain, muscle tension, tenderness using 4 point scales (p <0.05), no differences for limitation on movement using 4 point scale
Tizanidine	Murros 2000[150] **FAIR**	Tension headache 201	No statistical differences for headache severity using 100 mm visual analogue scale, days free of headache, daily duration of headache, or use of paracetamol
Tizanidine	Saper 2002[44] **FAIR**	Daily headaches 136 randomized	Tizanidine superior for headache index (headache days x average intensity x duration), mean headache days/week, average headache duration, average headache intensity using 5 point scale, pain using 100 mm visual snalogue scale, no difference for functional status using Migraine Disability Assessment questionnaire
Tizanidine (+ diclofenac in both arms)	Sirdalud Ternelin Asia-Pacific Study Group 1998[151] **FAIR**	Acute neck or low back syndromes 405	Tizanidine superior for pain using 4 point scale (p<0.05), spasm using 4 point scale (p<0.001), restriction of body movement using 4 point scale (p<0.001), no difference for sleep quality using 4 point scale

Table 6. Adverse events, head-to-head trials of skeletal muscle relaxants for spasticity

Study	Interventions	Somnolence or fatigue	Weakness	Dizziness or lightheadedness	Dry mouth	Withdrawals due to adverse events
Tizanidine versus baclofen						
Bass 1988[58]	Tizanidine mean 17 mg/day	29%	21%	Not reported	23%	9% (4/46)
	Baclofen mean 35 mg/day	19%	35%	Not reported	14%	26% (12/46)
Eysette 1988[59]	Tizanidine 24 mg/day	30%	Infrequent (data not reported)	Not reported	28%	6% (3/49)
	Baclofen 60 mg/day	20%	20%	Not reported	Infrequent (data not reported)	6% (3/49)
Hoogstraten 1988[60]	Tizanidine 12-24 mg/day	57%	33%	14%	36%	11% (1/9)
	Baclofen 15-60 mg/day	29%	57%	14%	14%	14% (1/7)
Medici 1989[61]	Tizanidine mean 20 mg/day	33%	0%	0%	7%	0% (0/15)
	Baclofen mean 50 mg/day	29%	7%	7%	0%	20% (3/15)
Newman 1982[62]	Tizanidine titrated to 16 mg/day	15%	8%	8%	0%	6% (2/36)
	Baclofen titrated to 40 mg/day	19%	15%	15%	4%	17% (6/36)
Rinne 1980 (2)[57]	Tizanidine mean 11 mg/day	62% (6% severe)	19% (0% severe)	25% (0% severe)	50%	6% (1/16)
	Baclofen mean 51 mg/day	80% (20% severe)	38% (40% severe)	60% (13% severe)	27%	6% (1/16)
Smolenski 1981[63]	Tizanidine 24 mg/day	45%	18%	None reported	9%	0% (0/11)
	Baclofen 60 mg/day	0%	30%	None reported	10%	0% (0/10)

Table 6. Adverse events, head-to-head trials of skeletal muscle relaxants for spasticity (continued)

Study	Interventions	Somnolence or fatigue	Weakness	Dizziness or lightheadedness	Dry mouth	Withdrawals due to adverse events
Stien 1987[49]	Tizanidine mean 23/day	33% (also includes weakness and dry mouth)	Not reported separately	Not reported	Not reported separately	6% (1/18)
	Baclofen mean 59 mg/day	25% (also includes weakness and dry mouth)	Not reported separately	Not reported	Not reported separately	4% (1/20)
Tizanidine, baclofen, or dantrolene versus diazepam						
Bes	Tizanidine mean 17 mg/day	44%	2%	None reported	11%	12% (6/51)
1988[64]	Diazepam mean 20 mg/day	44%	18%	None reported	3%	28% (15/54)
Rinne	Tizanidine mean 14 mg/day	53% (0% severe)	13% (8% severe)	7%	33%	0% (0/15)
1980 (1)[57]	Diazepam mean 15 mg/day	87% (47% severe)	53% (27% severe)	13%	0%	27% (4/15)
Cartlidge 1974[65]	Baclofen 30 mg/day and 60 mg/day	14%	11%	3%	3%	30% (11/37)
	Diazepam 15 mg/day and 30 mg/day	11%	16%	0%	0%	38% (14/37)
From	Baclofen mean 61 mg/day	31%	19%	6%	Not reported	6% (1/16)
1975[67]	Diazepam mean 21 mg/day	69%	12%	6%	Not reported	0% (0/16)
Roussan	Baclofen mean 47 mg/day	8%	Not reported	Not reported	Not reported	0% (0/13)
1985[66]	Diazepam mean 28 mg/day	38%	Not reported	Not reported	Not reported	0% (0/13)

Table 6. Adverse events, head-to-head trials of skeletal muscle relaxants for spasticity (continued)

Study	Interventions	Somnolence or fatigue	Weakness	Dizziness or lightheadedness	Dry mouth	Withdrawals due to adverse events
Glass	Dantrolene 100 mg qid	Not reported	Not reported	Not reported	Not reported	19% (3/16)
1974[68]	Diazepam 5 mg qid	Not reported	Not reported	Not reported	Not reported	6% (1/16)
Nogen 1976[69]	Dantrolene titrated to 75 mg qid	Not clear	Not reported	Not reported	Not reported	None reported
	Diazepam titrated to 12 mg/day	Not clear	Not reported	Not reported	Not reported	None reported
Schmidt	Dantrolene 75 mg qid	31%	67%	19%	Not reported	Not clear
1976[70]	Diazepam 5 mg qid	67%	76%	19%	Not reported	Not clear

Table 7. Adverse events, placebo-controlled trials of skeletal muscle relaxants for spasticity

Intervention	Study and year	Somnolence or fatigue	Dizziness or lightheadedness	Dry mouth	Withdrawals due to adverse events	Any adverse events
Baclofen 5 mg tid	Basmajian 1974[72]	0%	0%	0%	0%	None reported
Baclofen unclear dose	Basmajian 1975[73]	Not reported	Not reported	Not reported	12%	Not reported
Baclofen 5-20 mg/day	Brar 1991[74]	Not reported	Not reported	Not reported	Not reported by intervention	Not reported
Baclofen 5 mg tid to 100 mg/day	Duncan 1976[75]	12%	24%	12%	0%	60%
Baclofen 15-80 mg/day	Feldman 1978[76]	17%	Not reported	22%	0%	Not reported
Baclofen 40-80 mg/day	Hinderer 1990[77]	Not reported	Not reported	Not reported	Not reported	Not reported
Baclofen 10 mg tid	Hulme 1985[78]	78%	Not reported	Not reported	56%	78%
Baclofen 15-60 mg/day	Jones 1970[79]	Not clear	None reported	None reported	None reported	Not reported
Baclofen 0.5 mg/kg/day titrated to maximum 60 mg/day	McKinlay 1980[80]	60%	Not clear	None reported	0%	40%
Baclofen 30 mg/day	Medaer 1991[81]	5%	30%	None reported	None reported	50%
Baclofen 10 mg/day titrated up to 60 mg/day	Milla 1977[82]	20%	None reported	Not reported	0%	25%
Baclofen 5 mg tid titrated to 15 mg tid	Orsnes 2000[83]	36%	21%	None reported	None reported	64%
Baclofen 5 mg tid titrated to 80 mg/day	Sachais 1977[84]	71%	22%	Not reported	Not reported (36% overall)	Not reported
Baclofen 5 mg tid titrated to 60 mg/day	Sawa 1979[85]	29%	10%	5%	Not clear	71%

*Rated good quality for adverse event assessment

Table 7. Adverse events, placebo-controlled trials of skeletal muscle relaxants for spasticity (continued)

Intervention	Study and year	Somnolence or fatigue	Dizziness or lightheadedness	Dry mouth	Withdrawals due to adverse events	Any adverse events
Dantrolene unclear dose	Basmajian 1973[86]	'Almost all'	'Several'	Not reported	Not reported by intervention group	Not reported
Dantrolene 25-100 mg qid	Chyatte 1973[87]	Not reported	Not reported	Not reported	0%	Not reported
Dantrolene 1-3 mg/kg qid	Denhoff 1975[88]	Not reported	Not reported	Not reported	None reported	57%
Dantrolene 25 mg bid to 350 mg/day	Gambi 1983[89]	29%	Not reported	Not reported	9%	54%
Dantrolene 50-800 mg/day	Gelenberg 1973[90]	15%	55%	Not reported	None reported	Not reported
Dantrolene 4-12 mg/kg/day	Haslam 1974[91]	Not reported	Not reported	Not reported	0%	Not reported
Dantrolene 4-12 mg/kg/day	Joynt 1980[80]	Not reported	Not reported	Not reported	9%	91%
Dantrolene 25 mg bid to 50 mg qid	Katrak 1992[93]	70%	Not reported	Not reported	Not reported by intervention group	Not reported
Dantrolene mean 165 mg/day	Ketel 1984[94]	Not reported	Not reported	Not reported	25%	75%
Dantrolene 75 mg tid to 400 mg qid	Luisto 1982[95]	88%	24%	Not reported	Not reported by intervention group	100%
Dantrolene 50-100 mg qid	Monster 1974[96]	Not clear	Not clear	Not clear	Not clear (27% withdrawals overall)	Not reported
Dantrolene 6-8 mg/kg/day	Nogen 1979[97]	82%	Not reported	Not reported	None reported	Not reported
Dantrolene titrated to maximum 200 mg qid	Sheplan 1975[98]	Not clear	Not clear	Not clear	Not reported	Not reported
Dantrolene 100 mg/day titrated to 800 mg/day	Tolosa 1975[99]	Not clear	Not clear	Not clear	17%	Not reported
Dantrolene titrated to 100 mg qid	Weiser 1978[100]	23%	Included in somnolence	Not reported	11%	Not reported

*Rated good quality for adverse event assessment

Table 7. Adverse events, placebo-controlled trials of skeletal muscle relaxants for spasticity (continued)

Intervention	Study and year	Somnolence or fatigue	Dizziness or lightheadedness	Dry mouth	Withdrawals due to adverse events	Any adverse events
Tizanidine 10 mg/day	Knutsson 1982[101]	33%	None reported	17%	0%	Not reported
Tizanidine 2-32 mg/day	Lapierre 1987[102]	48%	3%	48%	Unclear	Not reported
Tizanidine 12-36 mg/day	Meythaler 2001*[103]	41%	Not reported	12%	0%	Not reported
Tizanidine 4-36 mg/day	Nance 1994[104]	41%	17%	39%	25%	81%
Tizanidine titrated to maximum 36 mg/day	Smith 1994*[105]	48%	19%	57%	13%	91%
Tizanidine mean 25 mg/day	UK Tizanidine Trial Group 1994*[106]	Not reported by intervention (54% overall)	Not reported	45%	13%	87%
Chlorzoxazone 20 mg/lb/day	Losin 1966[107]	None reported	Not reported	Not reported	Not reported	Not reported
Cyclobenzaprine 60 mg/day	Ashby 1972[108]	None reported	7%	7%	7%	Not reported
Methocarbamol mean 85 mg/kg/day	Bjerre 1971[39]	5%	Not reported	Not reported	Not reported	Not reported

*Rated good quality for adverse event assessment

Table 8. Adverse events, head-to-head trials of skeletal muscle relaxants for musculoskeletal conditions

Study	Interventions	Somnolence	Dry mouth	Dizziness or lightheadedness	Withdrawals due to adverse events	Any adverse event
Head-to-head trials of included skeletal muscle relaxants						
Bragstad 1979[109]	Tizanidine 2 mg tid	Not reported	Not reported	Not reported	None reported	0%
	Chlorzoxazone 500 tid	Not reported	Not reported	Not reported	None reported	15%
Preston, 1984[19]	Cyclobenzaprine 10 mg tid	58%	9%	Included in somnolence	7% (6/87)	42%
	Methocarbamol 1500 qid	31%	1%	Included in somnolence	6% (6/94)	31%
Rollings, 1983[110]	Cyclobenzaprine 10 mg qid	40%	38%	8%	8% (3/37)	65%
	Carisoprodol 350 mg qid	41%	10%	26%	8% (3/39)	62%
Head-to-head trials of included skeletal muscle relaxants versus diazepam						
Boyles, 1983[115]	Carisoprodol 350 mg qid	12%	Not reported	12%	2% (1/40)	22%
	Diazepam 5 mg qid	30%	Not reported	8%	5% (2/40)	35%
Aiken, 1978a[111]	Cyclobenzaprine 10-20 mg tid	66%	5%	18%	3% (1/38)	76%
	Diazepam 5-10 mg tid	68%	3%	21%	0% (0/40)	72%
Basmajian, 1978[112]	Cyclobenzaprine 10-20 mg tid	Not reported	Not reported	Not reported	None reported	Not reported
	Diazepam 5 mg tid	Not reported	Not reported	Not reported	None reported	Not reported
Brown, 1978[113]	Cyclobenzaprine 10 mg tid	44%	50%	25%	None reported	Not reported
	Diazepam 5 mg tid	13%	13%	12%	None reported	Not reported
Scheiner, 1978 (1)[114]	Cyclobenzaprine 30-40 mg/day	24%	29%	9%	None reported	32%
	Diazepam 15-20 mg/day	28%	6%	28%	None reported	28%
Scheiner, 1978 (2)[114]	Cyclobenzaprine 30-40 mg/day	83%	46%	17%	None reported	50%
	Diazepam 15-20 mg/day	67%	14%	52%	None reported	67%
Fryda-Kaurimsky, 1981[116]	Tizanidine 4-8 mg tid	10%	10%	10%	None reported	20%
	Diazepam 5-10 mg tid	50%	10%	50%	None reported	50%
Hennies, 1981[117]	Tizanidine 4 mg tid	None reported	None reported	None reported	7% (1/15)	7%
	Diazepam 5 mg tid	None reported	None reported	None reported	0% (0/15)	None reported

Table 9. Adverse events, placebo-controlled trials of skeletal muscle relaxants for musculoskeletal conditions

Intervention	Trials	Somnolence or fatigue	Dizziness or lightheadedness	Dry mouth	Withdrawals due to adverse events	Any adverse event
Carisoprodol 350 mg qid	Baratta 1976[124]	Not reported	Not reported	Not reported	Not reported	Not reported
Carisoprodol 350 mg qid	Cullen 1976[125]	12%	19%	Not reported	3%	Not reported
Carisoprodol 350 mg tid	Hindle 1972[126]	Not reported	Not reported	Not reported	None reported	Not reported
Carisoprodol 400 mg qid	Soyka 1979[127]	8%	18%	0%	1%	Not reported
Cyclobenzaprine 10-20 mg tid	Aiken 1978b[128]	84%	36%	4%	4%	96%
Cyclobenzaprine 10 mg tid	Baratta 1982[129]	31%	36%	10%	0%	43%
Cyclobenzaprine 10 mg bid	Basmajian 1989[130]	Not reported	Not reported	Not reported	None reported	Not reported
Cyclobenzaprine 10 mg qpm titrated to 40 mg/day	Bennett 1988[131]	55%	11%	92%	8%	89%
Cyclobenzaprine 20-40 mg/day	Bercel 1977[132]	33%	11%	4%	0%	Not reported
Cyclobenzaprine 10 mg tid	Bianchi 1978[129]	29%	4%	8%	None reported	42%
Cyclobenzaprine 5 mg tid Cyclobenzaprine 10 mg tid	Borenstein 2003 (1)[46]	29%^ 38%	3%^ 4%	21%^ 32%	5% 8%	55%^+ 62%
Cyclobenzaprine 2.5 mg tid Cyclobenzaprine 5 mg tid	Borenstein 2003 (2)[46]	20% 29%^	3% 3%^	14% 21%^	2% 4%	44% 55%^+
Cyclobenzaprine 10 mg tid (+naprosyn in both arms)	Borenstein 1990[134]	0%	5%	Not reported	None reported	20%
Cyclobenzaprine 10 mg qD titrated to 30 mg qD	Carette 1994[135]	4%	6%	None reported	14%	98%
Cyclobenzaprine 30-60 mg/day	Lance 1972[136]	20%	5%	16%	0%	Not reported
Cyclobenzaprine 10 mg qhs titrated to 30 mg qhs + 10 mg qam	Quimby 1989[40]	Not reported	Not reported	68%	4%	Not reported
Cyclobenzaprine 10 mg tid	Reynolds 1991[137]	Not reported	Not reported	Not reported	0%	Not reported
Cyclobenzaprine 30 mg/day	Steingard 1980[138]	24%	5%	12%	None reported	54%

*Unclear sample size, based on intervention sample of 90 patients
^Results pooled with other trial by Borenstein 2003
+Patients reporting more than 1 adverse event

Table 9. Adverse events, placebo-controlled trials of skeletal muscle relaxants for musculoskeletal conditions (continued)

Intervention	Trials	Somnolence or fatigue	Dizziness or lightheadedness	Dry mouth	Withdrawals due to adverse events	Any adverse event
Metaxalone 400 or 800 mg qid	Dent 1975*[42]	4%	3%	Not reported	9%	14%
Metaxalone 800 mg qid	Diamond 1966[139]	Not reported	Not reported	Not reported	None reported	Not clear
Metaxalone 800 mg qid	Fathie 1964 (1)[43]	Not reported	Not reported	Not reported	Not reported	Not reported
Metaxalone 800 mg qid	Fathie 1964 (2)[43]	Not reported	Not reported	Not reported	Not reported	Not reported
Methocarbamol 2000 mg qid initially, then 1000-1500 mg qid	Tisdale 1975[41]	Not reported	11%	Not reported	3%	Not clear
Orphenadrine 100 mg bid	Gold 1978[22]	Not clear	Not clear	Not clear	None reported	25%
Orphenadrine 100 mg qhs	Latta 1989[140]	0%	0%	0%	None reported	3%
Orphenadrine dose unclear (+paracetamol in both arms)	McGuinness 1983[141]	Not reported	Not reported	Not reported	7%	Not reported
Orphenadrine 100 mg bid	Valtonen 1975[142]	5%	4%	0%	Not reported	Not reported
Baclofen 30-80 mg/day	Dapas 1985[143]	49%	28%	5%	17%	68%
Dantrolene 25 mg/day	Casale 1988[144]	Not reported	Not reported	Not reported	None reported	Not reported
Dantolene 25 mg/day (+ ibuprofen in both arms)	Salvini 1986[145]	None reported	None reported	None reported	0%	3%
Tizanidine 4 mg tid (+ibuprofen both arms)	Berry 1988b [147]	22%	6%	6%	Not reported by intervention	Not reported

*Unclear sample size, based on intervention sample of 90 patients
^Results pooled with other trial by Borenstein 2003
+Patients reporting more than 1 adverse event

Table 9. Adverse events, placebo-controlled trials of skeletal muscle relaxants for musculoskeletal conditions (continued)

Intervention	Trials	Somnolence or fatigue	Dizziness or lightheadedness	Dry mouth	Withdrawals due to adverse events	Any adverse event
Tizanidine 4 mg tid	Berry 1988a[146]	22%	Not reported	Not reported	8%	41%
Tizanidine 6-18 mg/day	Fogelholm 1992[148]	'Frequent'	'Frequent'	Not reported	5%	Not reported
Tizanidine 2 mg/day	Lepisto 1979[149]	33%	0%	0%	Not reported	33%
Tizanidine 6-12 mg/day	Murros 2000[150]	17%	Not reported	22%	Not reported by intervention	11% (tolerated 'poorly')
Tizanidine mean 18 mg/day	Saper 2002[44]	46%	24%	22%	13%	Not reported
Tizanidine 2 mg bid (+diclofenac in both arms)	Sirdalud Ternelin Asia-Pacific Study Group 1988[151]	12%	3%	None reported	0%	Not reported

*Unclear sample size, based on intervention sample of 90 patients
^Results pooled with other trial by Borenstein 2003
+Patients reporting more than 1 adverse event

Table 10. Summary of evidence

Key Question	Condition	Level of Evidence	Conclusions
Efficacy			
1. What is the comparative efficacy of different muscle relaxants in reducing symptoms and improving functional outcomes in patients with a chronic neurologic condition associated with spasticity, or a chronic or acute musculoskeletal condition with or without muscle spasms?	Spasticity: comparative efficacy	FAIR for tizanidine vs. baclofen FAIR for tizanidine, baclofen, and dantrolene vs. diazepam POOR for dantrolene vs. tizanidine or baclofen and other skeletal muscle relaxants	8 fair-quality head-to-head trials and a fair-quality meta-analysis of unpublished trials consistenly found that tizanidine and baclofen are roughly equivalent for various measures of efficacy including spasms, functional status, and patient preference. Most of these trials evaluated patients with multiple sclerosis. Interpretation of trials was limited by lack of good-quality trials and heterogeneity in outcomes assessed, unvalidated methods to measure outcomes, and unstandardized methods of reporting results. 8 fair-quality head-to-head trials of dantrolene, tizandine, or baclofen compared to diazepam provide some evidence that each of these medications is similar in efficacy to diazepam, but judgments about comparative efficacy can not be made from these trials. Placebo-controlled trials were not helpful in assessing comparative efficacy. No additional trials were identified for the update.
	Spasticity: efficacy vs. placebo	FAIR for tizanidine, baclofen, and dantrolene vs. placebo	Tizanidine, baclofen, and dantrolene have consistently been found to be more effective than placebo in fair-quality clinical trials. Other skeletal muscle relaxants have not been adequately assessed for this condition. No additional trials were identified for the update.
	Musculoskeletal conditions: comparative efficacy	FAIR for cyclobenzaprine vs. diazepam POOR for comparative efficacy of other skeletal muscle relaxants	2 fair-quality head-to-head trials and 1 fair-quality meta-analysis of unpublished trials found that cyclobenzaprine and diazepam are roughly equivalent for various measures of efficacy including pain, spasm, and global response, but 3 other fair-quality trials found that cyclobenzaprine was superior to diazepam for most (2 trials) or some (1 trial) clinical outcomes. Most of these trials evaluated patients with neck or back pain or spasms. For other comparisons, the best fair-quality trial found that carisoprodol was superior to diazepam for several measures of efficacy, but used unstandardized outcomes scales. Other skeletal muscle relaxants have been directly compared in only 1 fair-quality trial or have been compared to diazepam, and comparative efficacy can not be accurately assessed. Placebo-controlled trials were not helpful in assessing comparative efficacy. No additional head-to-head trials were identified for the update. A systematic review of skeletal muscle relaxants for nonspecific back pain found they were 'similar' in efficacy, but was not designed to assess comparative efficacy.

Table 10. Summary of evidence (continued)

Key Question	Condition	Level of Evidence	Conclusions
Adverse events			
	Musculoskeletal conditions: efficacy vs. placebo	FAIR for cyclobenzaprine, carisoprodol, orphenadrine, and tizanidine vs. placebo POOR for other skeletal muscle relaxants vs. placebo	17 fair-quality trials consistently found cyclobenzaprine to be more effective than placebo for various measures of efficacy (pain relief, muscle spasms, functional status) in patients with musculoskeletal conditions. A good-quality systematic review of 14 trials reported similar findings. The body of evidence is not as robust for carisoprodol (4 trials), orphenadrine (4 trials), and tizanidine (6 trials), but these medications were also consistently found to be more effective than placebo. There is very limited or inconsistent data regarding the effectiveness of methocarbamol, metaxalone, dantrolene, chlorzoxazone, or baclofen compared to placebo. Two fair-quality trials were found for the update that compared different doses of cyclobenzaprine versus placebo. One found cyclobenzaprine 5 mg tid and 10 mg tid equally effective, and the other found 5 mg tid more effective than 2.5 mg tid (which was not significantly more effective than placebo). No judgments about comparative efficacy with other skeletal muscle relaxants could be made from this data.
2. What are the comparative safety of different muscle relaxants?	Spasticity	FAIR for tizanidine vs. baclofen FAIR for risk of hepatotoxicity from dantrolene and tizanidine POOR for other skeletal muscle relaxants	7 of 7 head-to-head trials of tizanidine vs. baclofen reporting rates of weakness found that tizanidine was associated with lower rates of weakness, while 5 of 7 head-to-head trials of tizanidine vs. baclofen reporting rates of dry mouth found that baclofen was associated with lower rates of dry mouth. Overall tolerability appears to be similar, as withdrawals due to adverse events (a marker of intolerable adverse events) were similar in all head-to-head trials except one. There was insufficient evidence from head-to-head or placebo-controlled trials to judge the comparative adverse event rates of other skeletal muscle relaxants. Serious hepatotoxicity with dantrolene has been found in observational studies, and tizanidine is associated with usually asymptomatic and reversible (rarely serious) hepatotoxicity. No additional trials were identified for the update.

Table 10. Summary of evidence (continued)

Key Question	Condition	Level of Evidence	Conclusions
Adverse events			
	Musculoskeletal conditions	POOR overall FAIR for risk of hepatoxicity from tizanidine and chlorzoxazone	There is insufficient evidence to accurately judge comparative adverse event rates from skeletal muscle relaxants in patients with musculoskeletal conditions. Direct comparisons of skeletal muscle relaxants in head-to-head trials were too limited in quantity and quality. Placebo-controlled trials showed no pattern of one skeletal muscle relaxant being superior to others and were generally of inferior quality compared to head-to-head trials. There are no data to judge comparative abuse or addiction risk. Tizanidine and chlorzoxazone are associated with usually reversible (rarely serious or fatal) hepatotoxicity, but data to estimate comparative event rates are not available. Other serious adverse events appear to be rare, but no assessment of comparative risk could be made. The systematic review and the two placebo-controlled trials found for the update provided no additional information to make judgments about comparative safety of different skeletal muscle relaxants. Cyclobenzaprine 5 mg tid was associated with fewer withdrawals due to adverse events and fewer overall adverse events than 10 mg tid in one fair-quality trial.
Subpopulations			
3. Are there subpopulations of patients for which one muscle relaxant is more effective or associated with fewer adverse effects?		POOR	There is almost no information to judge the comparative efficacy or safety of skeletal muscle relaxants in subpopulations defined by age, race, or gender. Almost all head-to-head trials have been done either in patients with multiple sclerosis or in patients with neck or low back syndromes, and there is insufficient evidence to judge the relative effectiveness or safety of skeletal muscle relaxants for other conditions. There are no studies to estimate the comparative risk of addiction or abuse in patients with prior substance abuse. Special populations (e.g. chronic liver disease, renal failure, or patients with seizures) have usually been excluded from clinical trials. No additional information about subpopulations was found for the update.

Evidence Table 1. Included systematic reviews and meta-analyses of skeletal muscle relaxants in patients with spasticity

Author Year	Aims	Time period covered and sources used in literature search	Eligibility criteria	Exclusion criteria	Funding source and role	Method of appraisal	Characteristics of identified articles
Systematic reviews							
Shakespeare 2001[26]	Assess the absolute and comparative efficacy and tolerability of anti-spasticity agents in multiple sclerosis (MS) patients	Through February 2001 (for MEDLINE) MEDLINE, EMBASE, reference lists, personal communications, drug manufacturers, manual searches of journals, collaborative MS trial registry, Cochrane database, National Health Service National Research Register	Double-blind, RCTs (either placebo-controlled or comparative studies)	<7 days duration	None	Independently abstracted by two reviewers and findings summarized	36/157 157 identified studies met inclusion criteria 23 placebo-controlled trials (5 oral baclofen, 4 dantrolene, 3 tizanidine, 3 botulinum toxin, 2 vigabitrin, 1 prazepam, 3 progabide, 1 brolitene, 1 L-threonine) 13 head-to-head trials met selection criteria (7 tizanidine vs. baclofen; 1 baclofen vs. diazepam, 1 diazepam vs. dantrolene, 2 ketazolam vs. diazepam, 2 tizanidine vs. diazepam) 1359 patients overall
Taricco 2000[52]	Assess the effectiveness and safety of drugs for the treatment of long term spasticity in spinal cord injury patients	Through 1998 CCTR, MEDLINE, EMBASE, CINAHL	All parallel and crossover RCTs including SCI patients with "severe spasticity"	RCTs with <50% of patients with SCI	None	Data independently abstracted by two reviewers using data extraction form	9 of 53 studies met inclusion criteria (1 oral baclofen, 4 intrathecal baclofen, 1 amytal and valium, 1 gabapentin, 1 clonidine, 1 tizanidine) 8 crossover studies, 1 parallel group trial 218 patients overall

RCT = Randomized Controlled Trial; CCTR = Cochrane Controlled Trials Registry; CINAHL = Cumulative Index to Nursing and Allied Health; SCI = Spinal Cord Injury

Evidence Table 1. Included systematic reviews and meta-analyses of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Population characteristics	Main results	Adverse events	Internal validity	Comments
Systematic reviews					
Shakespeare 2001[26]	Multiple sclerosis patients, age and severity varied between studies	Absolute and comparative efficacy and tolerability of anti-spasticity agents in multiple sclerosis is poorly documented and no recommendations can be made to guide prescribing. Included studies characterized by poor quality (though more recent studies are higher quality), heterogeneous study designs, interventions, outcomes, and methods of assessment. Unable to do quantitative meta-analysis.	Not systematically reviewed.	GOOD.	
Taricco 2000[52]	Crossover studies: 20/100 female, age range 16-62; 86/100 spinal cord injury, 14/100 multiple sclerosis Parallel study: 14/118 female, age range 15-69; mean duration of spinal cord injury 95 months	Tizanidine vs. placebo: Significant improvement of tizanidine for improving Ashworth score but now ADL performances Gabapentin, clonidine, diazepam, amytal, oral baclofen: No evidence for clinically significant effectiveness Unable to combine results because of poor quality, heterogeneous study designs, outcomes assessment, and method of reporting	Tizanidine vs. placebo: Increased drowsiness and xerostomia compared to placebo	FAIR. 14 retrieved studies had not yet been assessed.	

RCT = Randomized Controlled Trial; CCTR = Cochrane Controlled Trials Registry; CINAHL = Cumulative Index to Nursing and Allied Health; SCI = Spinal Cord Injury

Evidence Table 1. Included systematic reviews and meta-analyses of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Aims	Time period covered and sources used in literature search	Eligibility criteria	Exclusion criteria	Funding source and role	Method of appraisal	Characteristics of identified articles
Lataste 1994[51]	Assess the comparative therapeutic profile of tizanidine and other antispastic medications using data from 20 double-blind studies conducted during the development program of tizanidine between 1977 and 1987	1977-1987 Not clear what methods used to identify relevant studies through database search; also used Sandoz database	Double-blind controlled studies comparing tizanidine with another muscle relaxant.	Not specified.	Authors employed by Sandoz and Athena. Not reported if funder held data.	Not reported	Number of excluded studies not reported 20 trials of tizanidine vs. active control, ranging from 4-8 weeks (385 patients on tizanidine, 392 on active control) 10 studies vs. baclofen in multiple sclerosis 2 studies vs. diazepam in multiple sclerosis 3 studies vs. baclofen in cerebrovascular disease 4 studies vs. diazepam in cerebrovascular disease 1 study vs. baclofen in amyotrophic lateral sclerosis

RCT = Randomized Controlled Trial; CCTR = Cochrane Controlled Trials Registry; CINAHL = Cumulative Index to Nursing and Allied Health; SCI = Spinal Cord Injury

Evidence Table 1. Included systematic reviews and meta-analyses of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Population characteristics	Main results	Adverse events	Internal validity	Comments
Lataste 1994[51]	43-48% multiple sclerosis, 45-57% cerebrovascular disease, 0-7% amyotrophic lateral sclerosis Gender, age, race not reported	Tizanidine vs. active control (all studies included in analysis) Muscle tone (improved): 64% vs. 66% Muscle spasms (improved): 50% vs. 58% Clonus (improved): 46% vs. 56% Muscle strength (improved): 34% vs. 36% Neurologic function (Kurtzke scale) and functional disability (Pedersen's scale): No differences (data not reported) Overall assessment of antispastic effect (moderate, good, or excellent): 67.5% vs. 64.6% Overall assessment of antispastic effect (good or excellent): 37.5% vs. 33.0% Total Ashworth score: -0.39 (NS) Global tolerability: Favors tizanidine vs. baclofen or diazepam	Tizanidine vs. active controls Withdrawal (overall): 14% vs. 19% Withdrawal (adverse events): 4% vs. 9%	POOR. Methods of database search not reported. No quality assessment of included studies. No assessmentn of heterogeneity. Insufficient detail of included studies. Not clear if studies summarised appropriately: combined individual patient data for comparisons between interventions using 11/20 studies.	

RCT = Randomized Controlled Trial; CCTR = Cochrane Controlled Trials Registry; CINAHL = Cumulative Index to Nursing and Allied Health; SCI = Spinal Cord Injury

Evidence Table 1. Included systematic reviews and meta-analyses of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Aims	Time period covered and sources used in literature search	Eligibility criteria	Exclusion criteria	Funding source and role	Method of appraisal	Characteristics of identified articles
Meta-analyses (not systematic review)							
Groves 1998[54]	Assess the efficacy and tolerability of tizanidine using studies recorded by Sandoz (Novartis), the European sponsor of tizanidine trials	Time period covered not clear Records of Sandoz searched	Controlled, doubled-blind, randomized studies in which tizanidine was compared to a positive control. Studies had individual patient data, three key outcome measures (Ashworth Rating Scale, measure of muscle strength, and Global Tolerability to Treatment Rating), and patients had multiple sclerosis or other cerebrovascular lesions	Studies without measurement of muscle tone or individual data for muscle strength or tone, use of a nonstandard or incomplete scale for muscle strength or tone, no exam at six weeks, and one study in patients with amyotrophic lateral sclerosis.	Authors employed by Athena, which licenses tizanidine in North America, Ireland, and U.K. Not reported if funder held data.	Not reported	10 studies excluded. 11 included studies involving 270 patients 8 studies used baclofen as control, 3 used diazepam
Groves 1998[54]							

RCT = Randomized Controlled Trial; CCTR = Cochrane Controlled Trials Registry; CINAHL = Cumulative Index to Nursing and Allied Health; SCI = Spinal Cord Injury

Evidence Table 1. Included systematic reviews and meta-analyses of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Population characteristics	Main results	Adverse events	Internal validity	Comments
Meta-analyses (not systematic review)					
Groves 1998[54]	147 patients with multiple sclerosis 123 patients with other cerbrovascular lesions Mean age 38-48 years, 47-52% female, race not reported	Tizanidine vs. baclofen Mean change in total Ashworth score (scale 0 to 32): -3.2 vs. -3.0 (NS) Mean change in muscle strength (lower body Ashworth score, 0-160): -2.7 vs. -0.9 (p=0.07) Global Tolerability to Treatment (investigator rating, 1 (excellent) to 4 (poor): 2.0 vs. 2.3 (p=0.008) Tizanidine vs. diazepam Mean change in total Ashworth score: -5.6 vs. 4.0 (NS) Mean change in muscle strength: -4.4 vs. -2.7 (NS) Global Tolerability to Treatment: 1.8 vs. 2.6 (p=0.001)	Not reported	FAIR. No evaluation for heterogeneity. Insufficient detail of included studies. Not clear if studies summarised appropriately: combined all individual patient data for comparisons between interventions.	Included studies previously evaluated in meta-analysis by Wallace.

RCT = Randomized Controlled Trial; CCTR = Cochrane Controlled Trials Registry; CINAHL = Cumulative Index to Nursing and Allied Health; SCI = Spinal Cord Injury

Evidence Table 1. Included systematic reviews and meta-analyses of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Aims	Time period covered and sources used in literature search	Eligibility criteria	Exclusion criteria	Funding source and role	Method of appraisal	Characteristics of identified articles
Wallace 1994[53]	Combine data from three placebo-controlled and 11 active-controlled studies to evaluate efficacy of tizanidine	Time period covered not clear Sources used not clear, but appear to be unpublished data from studies sponsored by Sandoz	Not clear. Appear to be placebo controlled or active-controlled trials conducted by Sandoz.	Not reported	Authors employed by Athena, which licenses tizanidine in North America, Ireland, and U.K. Not reported if funder held data.	Not reported	3 placebo controlled studies (2 studies multiple sclerosis, 1 study spinal cord injury) with 525 evaluable patients 11 active-controlled studies (8 baclofen, 3 diazepam) with 5 studies on multiple sclerosis, 5 on patients with cerebral lesions, and 1 on amyotrophic lateral sclerosis with 288 patients

RCT = Randomized Controlled Trial; CCTR = Cochrane Controlled Trials Registry; CINAHL = Cumulative Index to Nursing and Allied Health; SCI = Spinal Cord Injury

Evidence Table 1. Included systematic reviews and meta-analyses of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Population characteristics	Main results	Adverse events	Internal validity	Comments
Wallace 1994[53]	Tizanidine vs. placebo: Mean age: 43.3 vs. 43.8 Gender: 53% female vs. 50% male Race (non-white): 11% vs. 11% Baseline demographics not reported for active-controlled studies	Tizanidine vs. placebo: Mean change in total Ashworth score for three lower-body muscle groups: -1.92 vs. -1.00 (p=0.01) Spasms and clonus: No statistically significant differences Global assessments: Placebo tolerated better than tizanidine, tizanidine more effective (NS) Muscle strength: No statistically significant differences Tizanidine vs. baclofen or valium (at end of week 6) Muscle strength: No difference at week 6 when all studies combined Global tolerance/patient assessment: No difference	Tizanidine vs. placebo Withdrawal (overall): 83/284 vs. 75/277 Withdrawal (adverse events): 44/284 vs. 15/277 Dry mouth: 49% vs. 27% Somnolence: 48% vs. 10% Asthenia: 41% vs. 16% Dizziness: 16% vs. 4% Headache: 12% vs. 13% UTI: 10% vs. 7% Insomnia: 8% vs. 8% Nausea: 7% vs. 7% Myasthenia: 6% vs. 6% Infection: 6% vs. 5% Adverse events for active-controlled trials not reported	FAIR. No evaluation for heterogeneity. Insufficient detail of included studies. Not clear if studies summarised appropriately: combined all individual patient data for comparisons between interventions.	Active-controlled trials later analyzed in meta-analysis by Groves.

RCT = Randomized Controlled Trial; CCTR = Cochrane Controlled Trials Registry; CINAHL = Cumulative Index to Nursing and Allied Health; SCI = Spinal Cord Injury

Evidence Table 2. Included systematic reviews and meta-analyses of skeletal muscle relaxants in patients with musculoskeletal conditions

Author Year	Aims	Time period covered and sources used in literature search	Eligibility criteria	Exclusion criteria	Funding source and role	Method of appraisal	Characteristics of identified articles
Systematic reviews							
Browning 2001[50]	Systematic review of cyclobenzaprine's effectiveness in the treatment of back pain	1966-1999 MEDLINE, PsycLit, CINAHL, EMBASE, AIDSLINE, HEALTHSTAR, CANCERLIT, Micromedix, Cochrane Library and Cochrane Database of Systematic Reviewers, Federal Research in Progress, reference lists, pharmaceutical companies contacted	Randomized, placebo-controlled, at least one group receiving cyclobenzaprine, and measurable outcomes reported	Not reported	None	Independently assessed by two reviewers using 6-item instrument	7 trials excluded 14 randomized placebo-controlled trials of 3315 patients on cyclobenzaprine; 6 studies also had diazepam as a control, 1 diflunisal, and 1 methocarbamol
Van Tulder 2003[48]	Systematic review of cyclobenzaprine's effectiveness in the treatment of back pain	through October 2001 (MEDLINE, EMBASE) or 2002 (Cochrane Library) MEDLINE, Cochrane Library, EMBASE	Randomized controlled trials and double-blind controlled clinical trials of patients with nonspecific low back pain receiving skeletal muscle relaxants of benzodiazepenes, reporting specified outcome measures	Studies of chlormezanone and botulinum toxin	University of Toronto and VU University Medical Center Amsterdam	Independently assessed by two reviewers using criteria (11-item instrument) recommended by the Cochrane Back Review Group.	27 studies excluded 30 trials of 2884 patients included (14 of these studies did not meet our inclusion criteria because they were non-English or evaluated excluded interventions)

Evidence Table 2. Included systematic reviews and meta-analyses of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Population characteristics	Main Results	Adverse events	Internal validity
Systematic reviews				
Browning 2001[50]	Acute back pain and muscle spasm of varying degrees; age, race, and gender not reported	All studies had at least one problem with rated quality. Mean quality score 4.3 (scale 1-8). Cyclobenzaprine vs. placebo: Global improvement (10 studies, pooled risk difference): 0.37 (95% CI, 0.24-0.50) No statistically different results (though trends favored cyclobenzaprine) for local pain, muscle spasm, tenderness to palpation, range of motion, and ADL at 3 days, 1 or 2 weeks.	Cyclobenzaprine vs. placebo (percentages) Drowsiness: 20% vs. 2%, p<0.001 Dry mouth: 8% vs. 2%, p=0.02 Dizziness: 7% vs. 4%, p=0.04 Nausea: 2% vs. 2%, p=0.70 Any: 53% vs. 28%, p=0.002	GOOD.
Van Tulder 2003[48]	Acute or chronic low back pain of varying degrees; age, race and gender reported for individual studies	All studies had at least two criteria for which it was rated inadequate. Mean quality score 6 (range 3-9, scale 0-11). Nonbezodiazepines versus placebo (11 studies, pooled relative risks) Pain relief after 2 to 4 days: 0.80 (95% CI, 0.71-0.89) Global efficacy after 2 to 4 days: 0.49 (95% CI, 0.25-0.95)	Nonbenzodiazepines versus placebo (11 studies, pooled relative risks) Overall adverse events: 1.50 (95% CI, 1.14-2.98) Central nervous system adverse events: 2.04 (95% CI, 1.23-3.37)	GOOD.

Evidence Table 2. Included systematic reviews and meta-analyses of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Aims	Time period covered and sources used in literature search	Eligibility criteria	Exclusion criteria	Funding source and role	Method of appraisal	Characteristics of identified articles
Meta-analysis							
Nibbelink 1978[55]	Assess the therapeutic response of cyclobenzaprine compared to diazepam and placebo	Time period covered not clear Not clear what methods used to identify relevant studies, but appears to include unpublished studies performed at Merck	Controlled clinical studies of patients with skeletal muscle spasm treated with cyclobenzaprine, diazepam, or placebo.	Studies outside the United States (3 studies) because of differences in protocol and data collection.	Authors employed by Merck. Not reported if funder held data.	Not reported	20 double-blind randomized trials of 1153 patients (434 cyclobenzaprine, 280 diazepam, 439 placebo) 46% posttraumatic, 14% musculoskeletal strain, 10% idiopathic, 8% postoperative, 6% osteoarthritis, 3% cervical root syndrome, 1% miscellaneous.

Evidence Table 2. Included systematic reviews and meta-analyses of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Population characteristics	Main Results	Adverse events	Internal validity
Meta-analysis			Muscle relaxants 'similar in performance'	
Nibbelink 1978[55]	46% posttraumatic, 14% musculoskeletal strain, 10% idiopathic, 8% postoperative, 6% osteoarthritis, 3% cervical root syndrome, 1% miscellaneous. Gender 535/1065 female, 186/1153 >50 years, race not reported	Cyclobenzaprine vs. diazepam vs. placebo Global response: Cyclobenzaprine and diazepam significantly better than placebo, no significant differences between cyclobenzaprine and diazepam. Cyclobenzaprine vs. diazepam (symptoms absent or mild at week 2) Muscle spasms: 42% vs. 29% (p=0.035) Local pain: 24% vs. 33% (NS) Tenderness on palpation: 26% vs. 39% (p=0.044) Limitation of motion: 30% vs. 50% (p=0.006) Limitation of daily living: 31% vs. 48% (p=0.030)	Cyclobenzaprine vs. diazepam vs. placebo Drowsiness: 39% vs. 33% vs. 12% Dry mouth: 24% vs. 8% vs. 4% Ataxia/dizziness: 10% vs. 17% vs. 6% Bad taste: 3% vs. 1% vs. 0.4% Nausea: 2% vs. 1% vs. 3% Withdrawals not reported for different interventions	FAIR. No evaluation for heterogeneity. Insufficient detail of included studies. Not clear if studies summarised appropriately: combined all individual patient data for comparisons between interventions.

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed	Population Characteristics
Bass 1988[58]	Randomized crossover trial Canada Single center	A: Tizanidine titrated to mean of 17.4 mg/day B: Baclofen titrated to mean of 35 mg/day 2 weeks washout, 3 weeks titration, 5 weeks maintenance, 1 week withdrawal, 3 weeks crossover titration, 5 weeks maintenance (8 weeks per intervention)	Patients with clinically definite multiple sclerosis interfering with activities of daily living, spasticity stable for >2 months	Not reported	Not reported Not reported 66	18 withdrew or excluded after randomization 48	Initial intervention: Tizanidine vs. baclofen Mean age (years): 50 vs. 52 Female gender: 15/32 vs. 16/30 Race: Not reported Paraperesis: 90% vs. 80% Status at entry progressive: 25% vs. 37% Duration of spasticity (years): 8.7 vs. 7.5 Severity severe: 22% vs. 30% Prior muscle relaxant use/baclofen: 14/32 vs. 14/30 Prior muscle relaxant use/diazapam: 6/32 vs. 4/30 Prior muscle relaxant use/any: 22/32 vs. 20/30
Bes 1988[64]	Randomized trial France Multicenter	A: Tizanidine mean 17 mg/day B: Diazepam mean 20 mg/day 2 weeks titration, 6 weeks maintenance	Spasticity interfering with daily activities following stroke or head trauma, stable for at least 2 months	Not reported	Not reported Not reported 105	23 91	Tizanidine vs. diazepam Mean age (years): 51 vs. 52 Female gender: 12/51 vs. 16/54 Race: Not reported Underlying condition/stroke: 46/51 vs. 43/54 Duration of symptoms (months): 20 vs. 23 Prior muscle relaxant use: 27% vs. 22%, specific medication not reported

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating	Outcomes
Bass 1988[58]	Spasms: 6 point ordinal scale Strength: 0 (normal) to 6 (no movement) Functional status: Kurtzke functional scale Disability: Pedersen functional disability scale Not clear when assessed	FAIR. Randomization, allocation concealment, blinding techniques not described, high loss to follow-up.	Tizanidine vs. baclofen Kurtzke functional scale (FS)/pyramidal (improvement >1): 2/48 vs. 2/48 (NS) Kurtzke FS/pyramidal (deterioration >1): 0/48 vs. 2/48 (NS) Kurtzke FS/cerebellar (improvement >1): 7/48 vs. 4/48 (NS) Kurtzke FS/cerebellar (deterioration >1): 3/48 vs. 7/48 (NS) Pedersen functional disability scale: No significant differences, raw data not reported Strength: No significant differences, raw data not reported Spasms: No significant differences (trend favored baclofen), raw data not reported Overall evaluation/patient (good or excellent): 13/53 (24%) vs. 20/51 (39%) (NS)
Bes 1988[64]	Spasticity: 1 (absent) to 5 (severe) Functional status: walking Severity of contraction: 1-5 scale Muscle strength: Not clear how rated Clonus: Not clear how rated Assessed at 2 and 8 weeks	FAIR. Randomization, allocation concealment, and blinding techniques not reported, high overall loss to follow-up.	Tizanidine vs. diazepam Walking distance on flat ground (improvement, in meters): 224 ($p<0.05$ vs. baseline) vs. 406 Duration of contractures: No significant differences between treatments Resolution of clonus: 14/29 (48%) vs. 8/20 (40%) Muscle strength/improvement in quadriceps: 36% vs. 27% (NS) Overall assessment/investigators (great or slight improvement): 37/45 (82%) vs. 30/36 (83%) (NS) Overall assessment/patients (great or slight improvement): 73% vs. 70% (NS)

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Adverse events	Funding Source and Role	Other comments
Bass 1988[58]	Tizanidine vs. baclofen Muscle weakness: 11/46 (21%) vs. 17/46 (35%) (p<0.01) Somnolence: 15/46 (29%) vs. 9/46 (19%) (p<0.01) Dry mouth: 12/46 (23%) vs. 7/46 (14%) (p<0.05) Spasms: 8/46 (15%) vs. 2/46 (4%) (p<0.05) Headaches: 1/46 vs. 5/46 (NS) Dizziness: 2/46 vs. 7/46 (NS) Light-headedness: 3/46 vs. 2/46 (NS) Irritability: 3/46 vs. 5/46 (NS) Insomnia: 8/46 vs. 3/46 (NS) Nausea: 2/46 vs. 6/46 (NS) Vomiting: 0/46 vs. 4/46 (NS) Constipation: 3/46 vs. 0/46 (NS) Bladder urgency: 3/46 vs. 7/46 (NS) Leg dysesthesia: 3/46 vs. 1/46 (NS) Adverse event requiring dose reduction: 46% vs. 63% Withdrawals (overall): 5/46 vs. 13/46 Withdrawals (due to adverse events): 4/46 (weakness) vs. 12/46 (7 weakness, 5 nausea)	Not reported	High loss to follow-up; not clear how patients lost to follow-up accounted for in statistical analysis. Results of first intervention period not reported separately. Raw data for results not reported.
Bes 1988[64]	Tizanidine vs. diazepam Drowsiness: 20/45 vs. 17/39 Fatigue: 9/45 vs. 10/39 Muscular weakness: 1/45 vs. 7/39 Orthostatic hypotension: 3/45 vs. 0/39 Vomiting: 2/45 vs. 2/39 Dry mouth: 5/45 vs. 1/39 Constipation: 2/45 vs. 2/39 Anxiety: 4/45 vs. 1/39 Sleep disturbance: 6/45 vs. 1/39 Disturbance of affect: 4/45 vs. 1/39 Overall tolerability: 61% vs. 54% Withdrawals (overall): 6/51 vs. 17/54 Withdrawals (due to adverse events): 6/51 vs. 15/54	Not reported	Specific prior muscle relaxants not reported. In patients on prior muscle relaxants, no difference between interventions for relief of spasticity. Not clear how withdrawn patients handled in data analysis.

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed	Population Characteristics
Cartlidge 1974[65]	Randomized crossover trial U.K. Single center	A: Baclofen 30 mg/day for 2 weeks and 60 mg/day for 2 weeks B: Diazepam 15 mg/day for 2 weeks and 30 mg/day for 2 weeks 4 weeks intervention, 4 weeks crossover	Spasticity, other eligibility criteria unclear	Not reported	Not reported Not reported 40	3 37	Age range (years): 22-61 Female gender: 19/40 Race: Not reported Underlying condition multiple sclerosis: 34/40 Baseline Ashworth score 3 or 4 in at least 1 lower limb Prior muscle relaxant use: Not reported
Eyssette 1988[59]	Randomized trial France Multicenter	A: Tizanidine titrated to 24 mg/day B: Baclofen titrated to 60 mg/day 2 weeks titration, 6 weeks maintenace	Patients age 18-70 with spasticity from multiple sclerosis	Not reported	Not reported Not reported 100	14/100 (14%) 86	Tizanidine vs. baclofen Mean age (years): 50 vs. 50 Female gender: 22/50 vs. 21/50 Race: Not reported Mean duration of gait disturbance (years): 11 vs. 13 Prior baclofen use: 73% overall, proportion for each group not reported

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating	Outcomes
Cartlidge 1974[65]	Spasticity: Ashworth scale	FAIR. Randomization, allocation concealment, blinding techniquest not described	Baclofen vs. diazepam Mean improvement in Ashworth score (low-dose vs. low-dose): 0.163 vs. 0.159 (NS) Mean improvement in Ashworth score (high-dose vs. high dose): 0.227 vs. 0.202 (NS) Patient's impressions (preferred): 19/37 vs. 15/37
Eyssette 1988[59]	Spasticity: 1 (absent) to 5 (spontaneous) Stretch reflex: 1-5 scale Locomotor function, patient's state in bed and in a chair, muscular strength, and difficulties with bladder control: unspecified methods General clinical status Overall efficacy and tolerability: unspecified methods Measured at 2 and 8 weeks	FAIR. Randomization, allocation concealment, blinding techniques not described.	Tizanidine vs. baclofen, results at 8 weeks Walking distance: No difference in ambulatory patients from baseline for either treatment (raw data not reported) Difficulty in transferring (improvement): 48% vs. 39% (NS) Difficulty in wheelchair use (improvement): 48% vs. 39% (NS) Difficulty in lying (improvement): 58% vs. 52% (NS) Flexor spasms (improvement): 55% vs. 48% (NS) Duration or angle of stretch reflex (improvement): No significant differences for any muscle group tested Clonus (no longer present): 8/28 vs. 6/28 Muscle strength at quadriceps (improvement): 34% vs. 29% (NS) Bladder function: No significant differences Overall status (improvement): 56% vs. 34% (significance not reported) Overall efficacy (very or moderately effective): 80% vs. 76% (NS) Overall efficacy (very effective): 42% vs. 24% (NS)

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Adverse events	Funding Source and Role	Other comments
Cartlidge 1974[65]	Baclofen vs. diazepam Sedation: 5/37 vs. 4/37 Weakness: 4/37 vs. 6/37 Lightheadedness: 1/37 vs. 0/37 Dry mouth: 1/37 vs. 0/37 Confusion: 2/37 vs. 1/37 Increasing stiffness: 2/37 vs. 3/37 Withdrawals (overall): Not clear Withdrawals (due to adverse events): 11/37 vs. 14/37	Not reported	
Eyssette 1988[59]	Frequent side effects: Tizanidine (n=50): 15 drowsiness, 14 dry mouth, 8 fatigue, 6 orthostatic hypotension, 7 insomnia Baclofen (n=50): 10 drowsiness, 12 fatigue, 10 muscular weakness, 9 disturbance of affect, 8 vomiting Tizanidine vs. baclofen Overall tolerability (well tolerated): 62% vs. 66% (NS) Withdrawals (overall): 8/50 vs. 6/50 Withdrawals (due to adverse events): 3/49 vs. 3/49	Not reported	73% of patients on baclofen prior to study entry, proportion in each intervention group not reported.

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed	Population Characteristics
From 1975[67]	Randomized crossover trial Denmark Single center	A: Baclofen titrated to mean dose 61 mg/day B: Diazepam titrated to mean dose 27 mg/day 4 weeks initial intervention, 4 weeks crossover	Not reported	Not reported	Not reported Not reported 17	1 withdrew 16	Baseline characteristics not reported for each intervention group Mean age (years): 51 Female gender: 10/16 Race: Not reported Multiple sclerosis inpatients Mean duration of illness (years): 18 Unable to walk more than short distances: 14/16 Prior muscle relaxant use: Not reported
Glass 1974[68]	Randomized crossover trial U.S. Single center	A: Dantrolene 100 mg qid B: Diazepam 5 mg qid C: Dantrolene 100 mg qid + diazepam 5 mg qid D: Placebo 4 2-week intervention periods	Not reported	Not reported	Not reported 62 16	5 withdrew 11	Demographics not reported Clinical conditions of patients enrolled not reported. In patients eligible, 39% CVA, 18% spinal cord injury, 12% MS, 4% CP, 4% miscellaneous (proportions not reported for each intervention group)

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating	Outcomes
From 1975[67]	Spasticity: Ashworth scale, clinical exam Clinical exam: Global assessment, physical exam Preferences: Patient preferences Assessed at start of trial, and at 3 and 4 weeks of each intervention period	FAIR. Randomization, allocation concealment, blinding techniques not described, unable to compare baseline characteristics between intervention groups	Baclofen vs. diazepam Ashworth score for lower limbs added for all patients receiving intervention (improvement): 21 vs. 23 Clinical assessment of flexor spasms, clonus, bladder function, walking: No significant differences Patient preference: 12/16 vs. 0/16 (4/16 had no preference)
Glass 1974[68]	Resistance to passive stretch: 1-6 scale (flaccid to marked resistance) Tendon jerk: 1-6 scale (absent to markedly hyperactive) Ankle clonus: 1-6 scale (absent to marked/sustained) General muscle strength: 1-6 scale (normal to paralyzed) Assessed weekly	FAIR. Randomization, allocation concealment, blinding techniques not described, high loss to follow-up, unable to compare baseline characteristics between intervention groups	Dantrolene vs. diazepam vs. dantrolene + diazepam vs. placebo Mean scores at end of treatment (no differences statistically significant between active treatments): Resistance to active stretch: 4.36 vs. 4.14 vs. 3.44 vs. 4.91 Tendon jerk: 3.70 vs. 3.00 vs. 2.70 vs. 5.45 Ankle clonus: 2.91 vs. 3.64 vs. 1.95 vs. 3.64 General muscle strength: 3.73 vs. 3.68 vs. 3.77 vs. 3.59

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Adverse events	Funding Source and Role	Other comments
From 1975[67]	Baclofen vs. diazepam Overall: 8/16 vs. 12/16 Sedation: 5/16 vs. 11/16 Depression: 2/16 vs. 0/16 Confusion: 0/16 vs. 1/16 Vertigo: 1/16 vs. 1/16 Nausea: 2/16 vs. 0/16 Weakness: 3/16 vs. 2/16 Withdrawal (overall): 1/16 vs. 0/16 Withdrawal (adverse event): 1/16 vs. 0/16	Not reported	Results of initial intervention period not reported.
Glass 1974[68]	Withdrawal (adverse event): 3/16 vs. 1/16 vs. 1/16 vs. 0/16	Not reported	Results of initial intervention not reported. Adverse events not assessed. Not clear why 46/62 eligible patients were not entered into study. Not clear if patients who withdrew from one intervention received other interventions.

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed	Population Characteristics
Hoogstraten 1988[60]	Randomized trial Crossover Netherlands Single center	A: Tizanidine titrated, range 12-24 mg/day B: Baclofen titrated, range 15-60 mg/day 2-3 weeks titration period, 4 weeks on titrated dose, washout period, then crossover (6-7 weeks each intervention)	Multiple sclerosis patients with stable spasticity for >2 months, Kurtzke expanded disability status score 4-7	Severe cardiac insufficiency, diastolic blood pressure >110, severe hypotension, chronic alcoholism, history of mental illness or pretreatment with diazepam or dantrolene	Not reported Not reported 16	5 14	Baseline characteristics not reported for each intervention group Mean age (years): 55 Female gender: 6/16 Race: Not reported Average Kurtzke EDSS score: 6.1 Mean duration of illness: Not reported Prior muscle relaxant use: Not reported
Medici 1989[61]	Randomized trial Uruguay Single center	A: Tizanidine titrated, mean dose 20 mg/day B: Baclofen titrated, mean dose 50 mg/day 2 weeks titration, 50 weeks maintenance	Outpatients with spasticity due to cerebrovascular disease	Heart disease, severe hypertension, orthostatic hypotension, alcoholism, insulin-dependent diabetes mellitus, impaired liver or renal function, abnormal blood chemistries, overt psychopathology	Not reported Not reported 30	2 deaths and 3 withdrawals 30	Tizanidine vs. baclofen Mean age (years): 50 vs. 49 Female gender: 4/15 vs. 2/15 Race: Not reported Duration of disability (years): 2.5 vs. 4.5 Type of disability: hemiparesis or hemiplegia): 14/15 vs. 15/15 Severity of spasticity (moderate or severe): 15/15 vs. 14/15 Severity of spasticity (severe): 7/15 vs. 4/15 Prior muscle relaxant use: Not reported

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating	Outcomes
Hoogstraten 1988[60]	Disability: Kurtzke Expanded Disability Status Scale Neurologic assessment of functional systems: Kurtzke Functional Systems Incapacitiy status: Minimal Record of Disability for Multiple Sclerosis Ambulation: Ambulation Index Spasticity/tone: Ashworth scale, patient self-report (0-5 scale) Reflexes/clonus Muscle strength Efficacy: -3 to +3 scale Tolerance: -3 to +3 scale	FAIR. Randomization technique not described, allocation concealment technique not described, inadequate blinding, unable to compare baseline characteristics between intervention groups	Tizanidine vs. baclofen No significant differences between interventions for overall efficacy, spasticity, spasms, mobility, or muscle strength (baseline scores not reported) Results for Ashworth score, Kurtzke scales not reported.
Medici 1989[61]	Neurologic exam: Kurtzke method Overall disability status: Kurtzke scale Tone: Ashworth scale, score 0 (normal)-4 Muscle spasms: 0 (normal) to 4 (severe) Clonus: 0 (normal) to 2 Decreased muscle strength: 0 (normal) to 5 Functional assessment of disability: Pedersen scale Patient self-assessment of disability: Mild, moderate, severe, very severe Physician global assessment of clinical changes: Worse, no change, improvement, marked improvement Global assessment of antispastic efficacy by physicians and patients Assessed at 3, 6, and 12 months	FAIR. Randomization, allocation concealment, blinding techniques not described.	Tizanidine vs. baclofen Neurological exam, overall disability status: No significant differences Muscle tone (improvement): 87% vs. 79% Muscle spasm (improvement): 62% vs. 83% Clonus (improvement): 71% vs. 80% Muscle strength (improvement): 53% vs. 21% Functional assessment (Pedersen scale) (improvement): 40% vs. 43% Patient global assessment of clinical changes: No significant differences between interventions (raw data not reported) Physician global assessment of clinical changes: No significant differences between interventions (raw data not reported) Global assessment/physician (good to excellent): 60% vs. 40% (NS) Global assessment/patient (good to excellent): 66% vs. 47% (p=0.057) Functional assessment and activities of daily living: No differences between interventions

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Adverse events	Funding Source and Role	Other comments
Hoogstraten 1988[60]	Tizanidine vs. baclofen Muscle weakness (first intervention period): 3/9 vs. 4/7 Somnolence (overall): 8/14 vs. 4/14 Dry mouth (overall): 5/14 vs. 2/14 Flushes (overall): 3/14 vs. 1/14 Nausea (overall): 2/14 vs. 3/14 Urine incontinence: 1/14 vs. 3/14 Dizziness (overall): 2/14 vs. 2/14 Sleep disturbance (overall): 2/14 vs. 0/14 Withdrawals (adverse events) during first intervention: 1/9 (depression) vs. 1/7 (weakness) Withdrawals (adverse events) during either intervention period: 1/16 vs. 4/16 (weakness)	Not reported	Data for Kurtzke scales and Ashworth scales not reported.
Medici 1989[61]	Tizanidine vs. baclofen Somnolence: 5/15 vs. 4/15 Drowsiness: 0/15 vs. 1/15 Dizziness: 0/15 vs. 1/15 Diarrhea: 1/15 vs. 0/15 Muscular instability: 1/15 vs. 3/15 Weakness: 0/15 vs. 1/15 Dry mouth: 1/15 vs. 0/15 Withdrawals (overall): 1/15 vs. 4/15 Withdrawals (adverse events, not including deaths): 0/15 vs. 3/15 (weakness and muscular instability) Deaths (not thought related to drugs): 1/15 vs. 1/15	Not reported	Long duration of intervention (50 weeks).

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed	Population Characteristics
Nance 1994[71]	Controlled clinical trial Canada Single center	A: Baclofen 20 mg qid B: Clonidine 0.05 mg bid C: Cyproheptadine 4 mg qid (results abstracted only for A and B)	Spinal cord injured patients with troublesome spasticity and original injury >1 year	Not reported	140 128 25	None reported 25	Age, gender, race not reported Severity: Frankel Grade A 11/25 Cervical injury: 16/25 Thoracic injury: 9/25 Prior muscle relaxant use: not reported
Newman 1982[62]	Randomized crossover trial U.K. Single center	A: Tizanidine titrated to 16 mg/day B: Baclofen titrated to 40 mg/day 2 week titration, 4 weeks maintenance, 2 weeks crossover titration, 4 weeks crossover maintenance (6 weeks per intervention)	Patients with spasticity, neurologically stable	Not reported	Not reported Not reported 36	10 26	Age, gender, race not reported Multiple sclerosis: 32/36 Syringomyelia: 4/36 Severity 'severe': 17/36 Prior muscle relaxant use: not reported
Nogen 1976[69]	Randomized crossover trial U.S. Single center	A: Dantrolene titrated to maximum 75 mg qid B: Diazepam titrated to maximum of 12 mg/day 3 weeks intervention, 3 weeks crossover	Children with cerebral palsy aged 2-8 years old, stable neurologically and physiologically	Children with contractures	Not reported Not reported 22	None reported 22	Age, gender, race not reported Severity and duration of illness not reported Prior muscle relaxant use: not reported

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating	Outcomes
Nance 1994[71]	Spasticity: Modified Ashworth scale using 1-5 scale and 0.5 gradations (raw data not reported) Spasticity: Video motion analysis of pendulum test Not clear when assessed	POOR. Does not appear randomized, allocation concealment technique not described, blinding not performed, unable to compare baseline characteristics between intervention groups	Baclofen vs. clonidine Spasticity (mean improvement): 0.8 vs. 0.8 Video motion analysis of pendulum test: No differences between treatments
Newman 1982[62]	Spasticity: Ashworth scale Functional status: Kurtzke and Pedersen scales Assessed at baseline and on days 7, 14, and 42 of each intervention	FAIR. Randomization, allocation concealment, blinding techniques not described, unable to compare baseline characteristics between intervention groups	Tizanidine vs. baclofen Lower limb knee spasticity/tone (better): 8/26 vs. 4/26 (NS) Lower limb knee spasticity/tone (better): 7/26 vs. 6/26 (NS) Lower limb ankle spasticity/tone (better): 8/26 vs. 4/26 (NS) Lower limb ankle spasticity/tone (better): 8/26 vs. 4/26 (NS) Functional status: Results not reported
Nogen 1976[69]	Tone: Unspecified method Tendon jerk: Unspecified method Clonus: Unspecified method Strength: Unspecified method Overall evaluation: Unspecified method Assessed twice weekly	FAIR. Randomizaton, allocation concealment, blinding techniques not described, unable to compare baseline characteristics between intervention groups	Dantrolene vs. diazepam Spasticity (best improvement on this medication): 9/22 vs. 7/22

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Adverse events	Funding Source and Role	Other comments
Nance 1994[71]	None reported	Not reported	Non-randomized clinical trial. Similar improvement noted on cyproheptadine.
Newman 1982[62]	Tizanidine vs. baclofen Drowsiness: 4/26 vs. 5/26 Dizziness: 2/26 vs. 4/26 Fatigue/lassitude: 1/26 vs. 1/26 Weakness: 2/26 vs. 4/26 Dry mouth: 0/26 vs. 1/26 Muscle pains: 4/26 vs. 5/26 Any adverse events: 17/26 vs. 17/26 Withdrawals (overall): 4/36 vs. 6/36 Withdrawals (adverse events): 2/36 vs. 6/36	Not reported	
Nogen 1976[69]	Not clear. 'Only side effects were lethargy and drowsiness which usually disappeared'	Not reported	

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed	Population Characteristics
Rinne (1) 1980[57]	Randomized trial Finland Single center	A: Tizanidine titrated, mean dose 14.3 mg/day B: Diazepam titrated, mean dose 15.0 mg/day 6 weeks	Not clear	Not reported	Not reported Not reported 30	4 withdrew 30	Tizanidine vs. diazepam Mean age (years): 42 vs. 40 Female gender: 9/15 vs. 10/15 Race: Not reported All patients had multiple sclerosis Disease severity "severe": 8/15 vs. 7/15 Duration of disease (years): 7 vs. 12 Prior muscle relaxant use: Not reported
Rinne (2) 1980[57]	Randomized trial Finland Single center	A: Tizanidine titrated, mean dose 11.2 mg/day B: Baclofen titrated, mean dose 51.3 mg/day 4 weeks	Not clear	Not reported	Not reported Not reported 32	2 withdrew 31	Tizanidine vs. baclofen Mean age (years): 47 vs. 46 Female gender: 10/16 vs. 8/16 Race: Not reported Multiple sclerosis (24) or cervical myelopathy (8) Disease severity "severe": 9/16 (A) vs. 9/16 (B) Duration of disease (years): 14 vs. 12 Prior muscle relaxant use: Not reported
Roussan 1985[66]	Randomized crossover trial U.S. Single center	A: Baclofen titrated, mean dose 47.3 mg/day B: Diazepam titrated, mean dose 28 mg/day 3 week washout, 5 week initial intervention, 3 week washout, 5 week crossover	Spasticity >3 months	Not reported	Not reported Not reported 13	None reported 13	Baseline characteristics not reported for each intervention group Mean age (years): 39 Female gender: 5/13 Race: Not reported 5 traumatic paraplegia, 7 multiple sclerosis, 1 transverse myelopathy Duration (years): 2-27 years Prior muscle relaxant use: Not reported

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating	Outcomes
Rinne (1) 1980[57]	Spasticity: Ashworth scale (numbers not reported) Assessed every 2 weeks	FAIR. Randomization technique not described, allocation concealment technique not described.	Tizanidine vs. diazepam Spasticity (marked improvement): 0/15 vs. 2/15 Spasticity (moderate or marked improvement): 5/15 vs. 5/15
Rinne (2) 1980[57]	Spasticity: Ashworth scale (numbers not reported) Assessed at 2 week intervals	FAIR. Randomization technique not described, allocation concealment technique not described.	Tizanidine vs. baclofen: Muscle tone (marked improvement): 1/16 vs. 2/15 Muscle tone (marked or moderate improvement): 4/16 vs. 3/15
Roussan 1985[66]	Global response to treatment: 0 (no improvement or worse) to 3+ (marked improvement) Assesssed weekly	FAIR. Randomization, treatment allocation, blinding techniques not described, unable to compare baseline characteristics between intervention groups.	Baclofen vs. diazepam Patient and physician preferences: No significant differences noted (trend favored diazepam)

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Adverse events	Funding Source and Role	Other comments
Rinne (1) 1980[57]	Tizanidine vs. diazepam, side effects at 2 weeks Drowsiness (severe): 0/15 vs. 7/15 Drowsiness (any): 8/15 vs. 13/15 Dry mouth: 5/15 vs. 0/15 Muscular weakness (severe): 1/15 vs. 4/15 Muscular weakness (any): 2/15 vs. 8/15 Dizziness: 1/15 vs. 2/15 Depression: 2/15 vs. 4/15 Constipation: 2/15 vs. 3/15 Overall tolerance (good or very good): 10/15 vs. 3/15 Withdrawal due to adverse event: 0/15 vs. 4/15 (weakness and drowsiness)	Not reported	May evaluate some of the same patients enrolled in Rinne (2). Outcome severity categories not defined.
Rinne (2) 1980[57]	Tizanidine vs. baclofen (side effects at two weeks) Drowsiness (severe): 1/16 vs. 3/15 Drowsiness (any): 10/16 vs. 12/15 Dry mouth: 8/16 vs. 4/15 Muscular weakness (severe): 0/16 vs. 5/15 Muscular weakness (any): 3/16 vs. 6/15 Dizziness (severe): 0/16 vs. 2/15 Dizziness (any): 4/16 vs. 9/15 Nausea: 3/16 vs. 5/15 Overall tolerance (good or very good): 7/16 vs. 6/16 Withdrawal due to adverse event: 1/16 (urticaria) vs. 1/16 (weakness)	Not reported	May evaluate some of the same patients enrolled in Rinne (1). Outcome severity categories not defined.
Roussan 1985[66]	Baclofen vs. diazepam Sedation: 1/13 vs. 5/13 Rebound spasticity: 7/13 vs. 3/13 Withdrawal: None reported	Not reported	

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed	Population Characteristics
Schmidt 1976[70]	Randomized trial Crossover U.S. Single center	A: Dantrolene titrated to 75 mg qid B: Diazepam titrated to 5 mg qid 2 weeks low dose initial intervention, 2 weeks higher dose initial intervention, 2 weeks low dose crossover, 2 weeks higher dose crossover (4 weeks per intervention)	Multiple sclerosis patients with moderate or severe spasticity but relatively less ataxia or weakness	Severe dementia, ataxia, or tremor	250 Not reported 46	4 withdrew 42	Demographics not reported Multiple sclerosis, moderate to severe spasticity Prior muscle relaxant use: No muscle relaxants or sedatives for 2 weeks before the study

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating	Outcomes
Schmidt 1976[70]	Physical functions: Spasticity, clonus, and reflexes measured on 0 (absent) to 5 (marked) scale; deltoid strength, hip flexor strength, station stability, hand coordination, hand speed, foot speed, walking speed measured using techniques from ACTH Cooperative study Patient self-report: Subjective reports of symptom improvement or deterioriation by patients Assessed at 2 week intervals	FAIR: Randomization and allocation concealment techniques not reported, unable to compare baseline characteristics between intervention groups.	Dantrolene vs. diazepam, results on higher doses Spasticity: 9.54 vs. 9.40 (NS) Reflexes: 19 vs. 22 (p=0.001, favors dantrolene) Clonus: 3.2 vs. 3.4 (NS) Deltoid strength: 47 vs. 50 (p=0.10, favors dantrolene) Hip flexor strength: 122 vs. 127 (NS) Hand coordination: 147 vs. 134 (p=0.01, favors diazepam) Station stability: 46 vs. 34 (p=0.01, favors dantrolene) Hand speed: 250 vs. 227 (NS) Foot speed: 240 vs. 226 (NS) Walking speed: 11 vs. 17 (NS) Muscle cramps or spasms by patient report (improved): 60% vs. 76% (NS) Stiffness by patient report (improved): 38% vs. 48% (NS) Patient preference: 22/42 vs. 13/42 (7 chose neither drug) Long-term (6 month) use: 11/35 vs. 12/35 (9 on no study drug)

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Adverse events	Funding Source and Role	Other comments
Schmidt 1976[70]	Dantrolene vs. diazepam Impaired gait: 52% vs. 75% Drowsiness: 31% vs. 67% Imbalance: 17% vs. 36% Incoordination: 10% vs. 29% Weakness: Not reported Withdrawals: 4 due to adverse events, intervention group not reported	Not reported	Results of initial intervention not reported separately. This appears to be the same study as Schmidt 1975, but some of the results and methodology are slightly different.

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed	Population Characteristics
Smolenski 1981[63]	Randomized trial Switzerland Single center	A: Tizanidine titrated to 8 mg tid B: Baclofen titrated to 20 mg tid Average doses not reported 6 weeks intervention	Multiple sclerosis with spasticity and stable for 2 months	Cardiac, renal, hepatic disease, hypertension, epilepsy, chronic alcoholism, diabetes mellitus, or overt psychiatric illness	Not reported Not reported 21	None reported 21	Tizanidine vs. baclofen Mean age (years): 53 vs. 55 Female gender: 6/11 vs. 5/10 Race: Not reported Mean duration of symptoms (years): 17 vs. 27 Spasticity severe: 6/11 vs. 6/10 Prior muscle relaxant use: Not reported

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating	Outcomes
Smolenski 1981[63]	Muscle strength: 0 (normal) to 5 (absence of voluntary movement) Muscle tone: Ashworth scale (0-4) Muscle spasms: 0 (normal) to 4 (all the time) Global assessment of change in condition Tolerance to medication Assessed weekly	FAIR: Randomization technique not described, treatment allocation technique not described, duration of illness appeared longer and more severe in baclofen group.	Tizanidine vs. baclofen Muscle tone and spasms (scores not reported): No significant differences Muscle strength (scores not reported): No significant differences Mean changes for functional abilities: No significant differences Physicians' assessments (improved) Overall spastic state: 10/11 vs. 9/10 Clonus: 5/11 vs. 5/10 Pain/stiffness: 9/11 vs. 7/10 Muscle strength: 5/11 vs. 5/10 Walking: 3/11 vs. 3/10 Bladder function: 3/11 vs. 0/10 Efficacy (good or excellent): 7/11 vs. 8/10 Tolerance (good or excellent): 10/11 vs. 9/10 Response compared to previous treatment (better): 7/11 vs. 5/10 Patients' global assessment of efficacy (good or excellent): 6/11 vs. 7/10 Patients' assessment of response compared to previous treatment (better): 6/11 vs. 4/10

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Adverse events	Funding Source and Role	Other comments
Smolenski 1981[63]	Tizanidine vs. baclofen Tiredness: 5/11 vs. 0/10 Weakness: 2/11 vs. 3/10 Dry mouth: 1/11 vs. 1/10 Ataxia: 1/11 vs. 0/10 Nausea: 0/11 vs. 1/10 Pyrosis: 0/11 vs. 1/10 Withdrawal: None reported	Not reported	Most patients previously on baclofen.

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed	Population Characteristics
Stien 1987[49]	Randomized trial Norway Single center	A: Tizanidine titrated, mean dose 23 mg/day B: Baclofen titrated, mean dose 59 mg/day 2 weeks titration, 4 weeks maintenance	Multiple sclerosis patients with stable disease for 3 months	Not reported	Not reported Not reported 40	2 withdrew 38	Tizanidine vs. baclofen Mean age (years): 50 vs. 45 Female gender: 9/18 vs. 12/20 Race: Not reported Multiple sclerosis patients in nursing home Duration of disease (years): 14 vs. 13 Severe spasticity: 5/18 vs. 10/20 Quadriparesis or quadriplegia: 8/18 vs. 12/20 Prior muscle relaxant use (baclofen): 10/18 vs. 16/20

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating	Outcomes
Stien 1987[49]	Neurologic disability: Kurtzke scale Functional assessment: Pederson scale Muscle tone: Ashworth scale Clonus: Unspecified method Strength: Unspecified method Overall response: Unspecified method Assessed weekly	FAIR: Randomization technique not described, allocation concealment technique not described, eligibility criteria not specified, tizanidine group appears to have had less severe baseline disease	Tizanidine vs. baclofen Neurologic disability (Kurtzke scale): No significant differences between interventions (raw data not reported) Functional disability (Pedersen's method): No significant differences between interventions (raw data not reported) Statistical significance between interventions not reported: Clonus (improvement): 7/18 vs. 9/20 Clonus (worse): 1/18 vs. 8/20 Muscular resistance (improvement): 13/18 vs. 13/20 Provoked or spontaneous spasms (improvement): 12/18 vs. 13/20 Muscle strength (improvement): 2/18 vs. 2/20 Overall response (good)/physician assessment: 2/18 vs. 4/20 Overall response (good)/patient assessment: 1/18 vs. 6/20

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Adverse events	Funding Source and Role	Other comments
Stien 1987[49]	Tizanidine vs. baclofen Tiredness, weakness, sleepiness, or dry mouth: 6/18 vs. 5/20 Withdrawals (adverse events): 1/18 (stiffness) vs. 1/20 (gastroenteritis) Rebound spasticity requiring re-initiation of medication: 1/18 vs. 5/20	Not reported	26/38 previously on baclofen. Abrupt discontinuation caused rebound spasticity in some patients requiring re-initiation of medication.

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Ashby 1972[108]	Randomized crossover trial Australia Single center Inpatient	A: Cyclobenzaprine 60 mg/day B: Placebo Two weeks	Patients with cerebral or spinal spasticity.	15 14	Spinal patients (5) age range 16-38 (mean not reported) Cerebral patients (10) age range 8-69 Gender not reported Race not reported 5 patients with stablecervical/thoracic spinal cord damage of at least nine months' duration 10 patients with brain damage of 2-18 months' duration Mean spasticity severity not reported Previous muscle relaxant use not reported
Basmajian 1974[72]	Randomized crossover trial United States Single center	A: Baclofen 5mg TID B: Placebo 5 weeks intervention, 1 week washout, 5 weeks crossover	Adult Outpatient Age 21-55 Spasticity for at least three months	15 11	Mean age not reported Gender ratio not reported Race not reported 8 Multiple Sclerosis 2 Traumatic paraplegia 1 Demyelinating spinal cord disease 1 Congenital quadriplegia Mean spasticity severity not reported Almost all patients had been on diazepam

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Ashby 1972[108]	Muscle Tone (0=no resistance; 1=slight; 2=moderate; 3=marked; 4=complete) Muscle Power (Medical Research Council Scale) Tendon Hyperreflexia (0=absent; +=reduced; ++ = normal; +++ = increased; ++++ = markedly increased) Clonus (recorded in seconds) Functional Changes (unspecified) *All above clinical assessments performed daily. EMG and other objective assessments performed on last day of each treatment period.	FAIR. Method of random assignment unspecified. Allocation concealment adequate (pharmacy-controlled). Baseline similarity not reported. Blinding technique not reported.	Cyclobenzaprine vs. placebo: "Improvement": 3/14 vs. 3/14 Tone (upper or lower limbs): No significant between group differences Clonus, strength, deep tendon reflexes: No significant between group differences	Cyclobenzaprine (A) vs. placebo (B) Withdrawals (due to adverse events): 1/14 (rash) vs. 0/14 Other adverse events reported Patient 1: truncal rash(B) Patient 2: dry mouth(A) Patient 3: dizziness while on A; nausea & vomiting while on B Patient 4: nausea & vomiting while on both A and B
Basmajian 1974[72]	Overall assessment of pain, motor status, and presence of spasms: methods not described Assessed weekly	FAIR. Randomization, allocation concealment techniques not reported. Unable to assess if intervention groups similar at baseline.	Baclofen vs. placebo Spasticity reduction "much superior or superior" (based on EMG and force recordings): 6/12 vs. 2/12 (4 inconclusive)	Withdrawals (overall): 4/12 (before intervention or early in treatment, group not specified) Withdrawal (adverse events): None No adverse events reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Basmajian 1975[73]	Randomized crossover trial United States Single center	A: Baclofen; dose not reported B: Placebo 4 weeks on treatment; 1 week washout or duration required to return to pretreatment spasticity level, 4 weeks crossover	Patients with spasticity from multiple sclerosis	14 11	Age range 21-55 Gender not reported Race not reported Spinal cord injuries Demyelinating spinal cord disease Multiple sclerosis Previous muscle relaxant use not reported
Basmajian 1973[86]	Crossover trial (not clear if randomized) United States Single center	A: Dantrolene 4 capsules/day, dose unclear B: Placebo 21 days treatment, then 21 days crossover	Motor spasticity caused by upper motor neuron disease	25 19	Age range 17-70 (mean age not provided) 70% female Race not provided 14 multiple sclerosis 5 spinal cord injury (4 of which were secondary to gunshot wounds) 4 other (stroke, dermoid cyst, meningioma) Severity not reported Previous muscle relaxant use not reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Basmajian 1975[73]	Overall assessment of antispastic activity: methods not described Weekly assessment	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Baclofen vs. placebo (includes results of Basmajian 1974 MS patients, n=8) Spasticity Reduction (at least slightly superior): 9/19 vs. 4/19 (5 no difference) Spastiticy Reduction (superior or much superior): 5/19 vs. 3/19	Not reported
Basmajian 1973[86]	Overall assessment of response to treatment by investigator: methods not described Assessments completed at end of each intervention and 7-10 days after study	POOR. Not clear if randomized, allocation concealment technique not described, unclear outcomes assessment, could not assess baseline differences between intervention groups.	Subjective overall clnical response: dantrolene preferred over placebo ($p<0.05$, raw data not reported)	Dantrolene vs. placebo Withdrawals (adverse events): 3/25 (weakness) vs. 1/25 (nausea and diarrhea) Frequent adverse events Weakness: "almost all patients" Dizziness: "several patients" Nausea: 2 patients Nausea and diarrhea: 3 patients

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Bjerre 1971[39]	Randomized crossover trial Sweden Single center	A: Methocarbamol mean 85 mg/kg/day B: Placebo 2 months intervention, 2 months crossover	Children with cerebral palsy	44 36	Mean age not reported (4-18 years old) Gender and race not reported Distribution of hemi-, di-, and quadriplegia 'largely equal', raw numbers not reported Prior muscle relaxant use not reported
Brar 1991[74]	Randomized crossover trial United States Single center	A: Baclofen titrated from 5 mg/day up to 20 mg/day B: Placebo C: Stretching* D: Baclofen + stretching* 10 weeks Outcomes for these interventions not abstracted	Patients age 24-54 with clinically definite, mild-moderate MS 5.5 or less on Kurtzke Expanded Disability Status Scale (EDSS) Clinically stable for three months or more	38 30	Mean age not reported 70% female Race not reported Multiple Sclerosis 43% minimal spasticity in both legs 57% minimal in one leg and moderate in the other Prior muscle relaxant use not reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Bjerre 1971[39]	Motor test: Method evaluating motor age (described by Johnson et al 1951) Overall condition: Improvement, same, or less than matched partner	POOR. Not clear if randomized. Allocation concealment and blinding techniques not described. Baseline characteristics not reported. High loss to follow-up or missing data (17/44). Results inadequately reported.	Methocarbamol vs. placebo Overall condition (better): 5/19 vs. 2/19 Motor test (improved >= 10 months): 13/36 vs. not reported (NS for upper limbs but p<0.01 for lower limbs)	Withdrawals: Not reported by intervention Methocarbamol only reported Any adverse event: Not reported Fatigue: 2/42 Weakness/hypotonia: 2/42 Nausea: 1/42 Rash: 1/42 Can't swallow pills: 6/42
Brar 1991[74]	Muscle tone (Ashworth Scale) Functional Ability (adapted from standard Minimal Record of Disability) Timing of assessment not reported	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described, intention-to-treat analysis not performed.	Baclofen vs. placebo Ashworth score (improved): 30% vs. 20% (p not reported) Ambulating (improved): 10% vs. 17% (NS) Climbing (improved): 20% vs. 13% (NS) Household activities (improved): 17% vs. 20% (NS)	Withdrawals (overall): 8 overall, intervention group not reported Withdrawals (adverse events): 1, intervention group not reported No other adverse event information provided

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Chyatte 1973[87]	Randomized crossover trial United States Single center	A: Dantrolene sodium: initial dose of 5-25 mg QID; maximum dose of 100 mg QID B: Placebo 4 weeks intervention, 4 weeks washout, 4 weeks crossover	Patients with athetoid cerebal palsy	18 17	53% female Age range of 7-38 years Race not reported 15 birth-related brain damage (hypoxia) 1 brain injury (2 years post-injury) 1 encephalitis (4 years post-illness) Quadriplegia in five patients Previous muscle relaxant use not reported
Denhoff 1975[88]	Randomized crossover trial United States Single Center	A: Dantrolene 1 mg/kg qid titrated to max of 3 mg/kg qid B: Placebo 6 week intervention, 2 weeks washout, 6 weeks crossover	Not reported	18 18	Age range 18 months to 12 years Female gender 43% Diagnoses Spastic quadriplegia: 15/28(54%) Spastic hemiplegia: 7/28(25%) Spastic diplegia: 4/28(14%) Mixed spasticity/athetosis: 1/28(4%) Mixed spasticity/rigidity: 1/28(4%) Degrees of severity Mild: 14/28(50%) Moderate: 5/28(18%) Severe: 9/28(32%)

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Chyatte 1973[87]	Overall clinical response: Includes spasticity (using unspecified 4-point scale) and motor function (unspecified scale) Activities of daily living: Included functional performance grading using 4-point scale (1=much easier; 2=easier; 3=no change; 4=more difficult) Timing of assessments not reported	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Dantrolene vs. placebo Overall clinical response: no results reported; numerical data from objective testing reported to be too "diffuse and variable" to analyze Improved motor control: 17/17 vs. 3/17 Better relaxation: 15/17 vs. 4/17 Less involuntary motion: 4/17 vs. 2/17 Improved excretory functions: 4/17 vs. 0/17 General improvement: 2/17 vs. 017	Dantrolene vs. placebo Withdrawals (overall): 0/17 vs. 1/18 Withdrawals (due to adverse events): 0 Numbers of adverse events not recorded for each intervention group
Denhoff 1975[88]	*Measurement scales not specified Neurological measurements: strength, spasticity, tendon jerk reflexes and clonus Orthopedic measurements: active/passive range of motion (degrees) Motor performance: observational Activities of daily living: scales unspecified; observational ratings made by both program staff and parents Behavioral functioning: scales unspecified; observational ratings made by both program staff and parents Cognitive measurements: obtained by subtests from McCarthy Scales of Children's Abilities and Peabody Picture Vocabulary Test	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Dantrolene vs. placebo Neurological measurements (moderate or marked change): 6/28 vs. 2/28; p<0.04 Motor performance (moderate or marked change): 5/28 vs. 6/28; p=NS Staff evaluations (moderate or marked change): 8/28 vs. 0/28; p<0.02 Parent evaluations (moderate or marked change): 9/28 vs. 3/28; p<0.03 Cognitive measurements: no statistically significant group differences found	Dantrolene vs. placebo Any adverse event: 16/28 vs. 7/28; p<0.03 Frequent adverse events: irritability, lethargy, drowsiness, general malaise, exacerbation of seizures (4)

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Duncan 1976[75]	Randomized crossover trial U.S. Single center	A: Baclofen 5 mg/TID titrated to max 100 mg/day B: Placebo 4 weeks intervention, 1 week washout, 4 weeks crossover	Duration of spasticity stability of 3 months or more	25 22	Average age: Multiple sclerosis group=36.4, non-multiple sclerosis group=38.8 Gender: 50% female Race: 100% White Diagnoses Multiple sclerosis: 11/22(50%) Other spinal cord lesions (including accidental and intraoperative trauma, compressive lesions and degenerative spinal cord disease): 11/22(50%) Extent of disability Ambulatory: 8/22 (36%) Paraplegia: 11/22(50%) Quadraplegia: 3/22(14%) Illness duration: MS patients=36.4, non-MS patients=5.1
Feldman 1978[76]	Randomized crossover trial United States Single center	A: Baclofen 15-80 mg/day B: Placebo 1 week washout, 4 weeks intervention, 1 week washout, 4 weeks crossover	Adult Established diagnosis of MS Spontaneous flexor contractions/spasticity for at least 3 months	33 23	Mean age 43 Gender not reported Race not reported Established diagnosis of Multiple Sclerosis Mean spasticity severity not reported. Previous muscle relaxant use not reported.

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Duncan 1976[75]	Resistance to passive movement: 5-point scale at the pretreatment visit (A=normal; E=immobile to passive movement) and change at each subsequent week rated using 5-point scale (1=worse; 5=marked improvement) Clonus: graded as none, minimal, moderate or severe at each visit Subjective impressions: included ratings of pain, use of spastic limbs, transfer activity, and general well-being Impression of current treatment: rated by patient in unspecified manner at end of each intervention phase Investigator therapy preference: rated before code broken	POOR. Randomization, allocation concealment, eligibility criteria, intention-to-treat analysis not performed. Blinding method described as providing baclofen and placebo tablets that were identical in size, shape, color and container.	Resistance to passive movement: A=11/20(55%) vs. B=1/20(5%), p<0.01 in increased resistance to passive movement Clonus: no consistent change seen in any patient; no significant between-group differences reported Subjective impressions: A=13(72%) vs. B=2(11%), p<0.01 in reduction of spasm frequency; A=9(75%) vs. B=0(0%), p<0.01 in reduction of nocturnal awakenings due to spasms; transfer activities reported as "generally improved", but no significant group differences were reported Impression of current treatment: Improvement reported as A=14/22(64%) vs. B=2/22(9%), p-value not reported but described as "significant" Investigator therapy preference: Improvement reported as A=14/22(64%) vs. B=0/22(0%), p-value not reported but described as "significant"	Withdrawals (due to adverse events): 2/25 patients on placebo Overall incidence: A=15, B=4 Frequent adverse events Lightheadedness: A=5, B=1 Nausea: A=5, B=1 Drowsiness: A=3, B=1 Dry Mouth: A=3, B=0 Weakness: A=2, B=0 Vomiting: A=1, B=0 Dizziness: A=1, B=1 Leg edema: A=1, B=0 Postural hypotension: A=1, B=0
Feldman 1978[76]	Daily spasm frequency: method unspecified Knee clonus: method unspecified Resistence to passive movement: a (normal resistance) to f (immobile) Ambulation/transfer activity: Method unspecified Spastic limb pain/use of spastic limb: Subjective method unspecified Functional assessment: Barthel Index	FAIR. Randomization and allocation concealment techniques not reported.	Baclofen vs. placebo Daytime spasms (improved): 13/18 (72%) vs. 2/18 (11%) Nocturnal awakenings (improved): 9/12 (75%) vs. 0/12 (0%) Resistance to passive movement (improved): 11/20 (55%) vs. 1/20 (5%) Patient assesment (overall improvement): 14/22 (64%) vs. 2/22 (9%)	Baclofen vs. placebo Withdrawals: None reported on treatment Frequent adverse events (n=23) Drowsiness: 4 vs. 4 Paresthesia: 5 vs. 2 Blurred vision: 2 vs. 2 Dry mouth: 5 vs. 1 3-year long-term study Drowsiness: 2 Dizziness: 2 Anorexia: 1 Nocturia: 1 Constipation: 3

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Gambi 1983[89]	Randomized crossover trial Italy Single center	A: Dantrolene 25 mg BID titrated to maximum of 350 mg/day B: Placebo 2 weeks washout, 5 weeks interention, 1 week washout, 5 weeks crossover	Not reported	24 24	Mean age 41.3 Female gender: 50% Race not reported Multiple sclerosis: 12 patients with a mean spasticity period of 7.2 years Degenerative myelopathies: 12 patients with a mean spasticity period of 5.7 years Previous muscle relaxant use not specified

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Gambi 1983[89]	Degree of spasticity: 6-point scale (1=marked hypotonicity; 6=marked hypertonicity) Muscular strength: 6-point scale (1=normal; 6-absent) Clonus: 6-point scale (1=absent; 6=markedly steady) Knee and ankle tendon reflexes: 6-point scale (1=absent; 6=marked hyperactive) Articular flexor movement: evaluated using a degree scale Physician final assessment: 4-point scale (1=none; 4=marked) Patient acceptibility: 3-point scale (1=poor; 3=excellent) Assessments completed at the beginning and end of each treatment cycle	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Dantrolene (A) vs. placebo (B) *Multiple sclerosis group* Degree of spasticity (reduction): A>B (p<0.05), data not reported Muscular strength: no significant differences Clonus: no significant differences Knee and ankle tendon reflexes: no significant differences Articular flexor movement: no significant differences Physician final assessment (of benefit): A>B (p<0.05) Patient acceptibility: no significant differences *Degenerative myelopathies group* Degree of spasticity (reduction): A>B (p<0.005), data not reported Muscular strength: no significant differences Clonus: no significant differences Knee and ankle tendon reflexes: no significant differences Physician final assessment (of benefit): A>B (p<0.005) Patient acceptibility: no significant group differences	Withdrawals (due to adverse events): A=2(9%) vs. B=3(13.6%) Any adverse event: 13/24 vs. 3/24 Headache: 2/24 vs. 1/24 Drowsiness: 7/24 vs. 2/24 Nausea: 4/24 vs. 0/24 Vomiting: 1/24 vs. 0/24 Gastric pain : 4/24 vs. 1/24 Malaise: 1/24 vs. 024 Muscular weakness: 3/24 vs. 1/24

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Gelenberg 1973[90]	Crossover (not clear if randomized) U.S. Single center	A: Dantrolene 50-800 mg (mean dose not reported) B: Placebo 5 weeks intervention, 1 to 3 weeks washout, 5 weeks crossover	Patients with moderate-severe spasticity secondary to multiple sclerosis.	20 20	Mean age=49 55% Male Race unreported Multiple Sclerosis Moderate-Severe Spasticity (Mean unreported) Previous muscle relaxant use not reported
Haslam 1974[91]	Randomized crossover trial United States Single center	A: Dantrolene 4mg/kg/day titrated to a maximum of 12mg/kg/day B: Placebo 2 weeks intervention, 10 days washoutk, 2 weeks crossover	Children with spasticity secondary to brain damage incurred at birth	26 23	Mean age (years): 6.5 65% female Race not reported Brain damage (e.g., prematurity, perinatal anoxia, kernicterus and neonatal meningitis) Mean IQ=45 Previous muscle relaxant use not reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Gelenberg 1973[90]	Spasticity, strength, clonus and tendon reflexes assessed weekly. Methods of assessment not specified.	POOR. Not clear if randomized. Allocation concealment technique not reported. Blinding technique may not have been adequate.	Dantrolene vs. placebo Patient preferred: 7/20 vs. 4/20 No other data provided	Dantrolene vs. placebo; n=20 Weakness: 15 vs. 0 Lightheadedness/drunkenness: 11 vs. 1 Nausea: 7 vs. 0 Dizziness: 6 vs. 0 Diarrhea: 6 vs. 0 Speech difficulty: 4 vs. 0 Drowsiness/lethargy: 3 vs. 0 Headache: 2 vs. 1 Short temper/irritable: 2 vs. 0 Photophobia: 1 vs. 0 Depression: 1 vs. 0 Cramps: 0 vs. 1
Haslam 1974[91]	Spasticity: 5-point scale for clonus (0=absent-4=sustained) Passive Movement: 0=full range to 4=severely restricted Spontaneous Movement: 0=normal to 4=none Tone: 0=normal to 4=marked increase Reflexes: 0=normal to 4=very brisk Scissoring: 0=absent to 4=paraplegia-in-flexion Motor functions: step climbing, sitting position time, hand-knee position, roll-over time as measured by physical therapists; methods unspecified Self-help skills: reach for/transfer objects, pegboard test, wheelchair operation as measured by physical therapists; methods unspecified Daily activities: bathing, bracing, dressing, wheelchair transfer as measured by nursing staff; methods unspecified Assessed on days 4, 8, 11 and 15 of each treatment period	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Dantrolene sodium vs. placebo Scissoring and reflexes: Improved in dantrolene vs. placebo, $p<0.05$, data not provided Passive range of motion, spontaneous range of motion, muscle spasticity: No differences between treatments	Withdrawals (overall): 3 (group not reported) Withdrawals (adverse events): 0 Frequent adverse events: minimal lethargy that resolved with first two days

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Hinderer 1990[77]	Randomized United States Single Center	A: Baclofen, 40-80 mg/day B: Placebo 2.5-4.5 weeks washout, 2 weeks titration, 2.5-4.5 weeks at target dose (80 mg) (multiple baseline single-subject research design)	Patients with spasticity	5 5	Age range of 20-42 100% male Race not reported Spinal cord lesions of unspecified traumatic etiologies Previous muscle relaxant use not specified
Hulme 1985[78]	Randomized crossover trial United Kingdom Single center Geriatric ward	A: Baclofen 10 mg TID B: Placebo 3-day titration, 18-day intervention, 7-day washout; 18 days crossover	Men and women over the age of 65 years in a geriatric ward who had muscle spasticity following a stroke	12 10	Gender: 7/12(58%) female Age range: 69-81 Race: not reported Baseline duration and severity of symptoms not reported
Jones 1970[170]	Randomized crossover trial Australia Single center	A: Baclofen 15 mg/day titrated to 60 mg/day B: Placebo 14 days intervention followed by 14 days crossover	Hospitalized patients with quadriparetic or quadriplegic spinal cord injury	6 6	Age range (years): 17-41 Female gender: 2/6 Race: not reported Duration of illness: 5/6 less than 12 months Prior muscle relaxant use: All previously on diazepam 15-30 mg/day

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Hinderer 1990[77]	Spasticity: unspecified method Anxiety: Beck Inventory Scale Assessed twice per week	POOR. Randomization, blinding techniques not described, intention-to-treat analysis not performed. Very small sample size. "Multiple baseline single-subjet research design" may be invalid.	Spasticity: 0 subjects demonstrated therapeutic reduction of spasticity measurements while taking baclofen Anxiety: 1/5 had significantly reduced Beck Inventory Score on baclofen	Not reported
Hulme 1985[78]	*Methods not specfied: Spasticity Psychomotor functioning Mobility Self-care capacity Assessments completed initially and at weekly intervals thereafter	FAIR. Allocation concealment, eligibility criteria, blinding techniques not described.	Study stopped due to excess withdrawals, no data to assess efficacy.	Withdrawals (adverse events): 5/9 (drowsiness) vs. 1/6 (stroke) Drowsiness: 7/9 vs. 0/6
Jones 1970[170]	Spasticity: 0 (normal) to 4 (rigid) Strength: British Medical Research Council Scale Ankle clonus: Duration Reflexes: 1 (normal) to 4 (markedly increased) Number of spasms Assessed daily	FAIR. Randomization, allocation concealment, blinding techniques not described.	Baclofen vs. placebo Muscle tone (improved): 5/6 vs. 0/6 Number of spasms: (fewer): 3/6 vs. 0/6 Reflexes: No differences	Baclofen vs. placebo Nausea: 5/6 vs. 2/6 Diarrhea: 2/6 vs. 2/6 Fatigue: Not clear Dizziness: None reported Dry mouth: None reported Weakness: None reported Any adverse event: Not clear Withdrawals: None reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Joynt 1980[92]	Randomized United States Single center	A: Dantrolene 4 mg/kg/day titrated to maximum of 12 mg/kg/day B: Placebo 6 weeks	Children with cerebal palsy and spasticity interfering with function	21 20	Children, mean ages not reported Gender: not reported Race: not reported Diagnostic etiologies Diplegia: 7/20(35%) Quadriplegia: 7/20(35%) Hemiplegia: 5/20(25%) Paraplegia: 1/20(5%) Previous muscle relaxant use: not reported
Katrak 1992[93]	Randomized crossover trial Australia Single center	A: Dantrolene 25 mg bid titrated to maximum 50 mg qid B: Placebo 2 weeks titration; 4 weeks maintenance; 1 week washout; 2 weeks crossover titration; 4 weeks crossover maintenance	Age 35-85; significant motor impairment; ability to comply with Cybex assessment	38 31	Average age 60.5 years 10% female Race not reported Within eight weeks post-CVA 14 left hemiparesis 17 right hemiparesis Previous muscle relaxant use not allowed

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Joynt 1980[92]	Family observations: muscle spasm, range of motion, activities of daily living, child's daily performance and drug's helpfulness; all rated using 9-point scale, with 5 being the pre-treatment baseline score (higher numbers indicated improvement) Tone: rated 0-6; 3=normal Clonus: rated 0-6; 0=normal Strength: rated 0-5; 5=normal Reflexes: rated 0-6; 3=normal Spasms: rated 0-3; 0=normal General activities of daily living: measured by various functional tests Mobility: measured by various functional tests Evaluated at weeks 3 and 6	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Dantrolene vs. placebo Spasm (improvement): 3/11 (27%) vs. 0/9, p=0.089 Range of motion (improvement): 7/11 (64%) vs. 2/9 (22%), p=0.064 Other family observations: No significant differences Physical examinations: no significant differences for Tone, Clonus, Strength, Reflexes, or Spasms General activities of daily living (improvement): 8/11 (72%) vs. 2/9 (22%) Mobility: no significant differences	Dantrolene vs. placebo Withdrawal (adverse events): 1/11 vs. 0/9 Any adverse events: 10/11 (91%) vs. 3/9 (33%), p<0.008 Frequent adverse events (intervention not specified): fatigue (n=5), drowsiness (n=3), anorexia (n=2), diarrhea (n=1) and vomiting (n=1)
Katrak 1992[93]	Tone: 0-5 scale (1=flaccid; 5=severe) Motor function: Motor Assessment Scale (eight areas of motor function on 0-6 scale) Activities of daily living: Barthel ADL scale Assessed at 1) Baseline; 2) completion of titration; 3) end of maintenance phase 1; 4) completion of washout; 5) completion of crossover titration; 6) completion of crossover maintenance phase; 7) completion of final washout	FAIR. Allocation concealment, blinding techniques not described.	Dantrolene vs. placebo Tone: No between-group differences Motor function: No between-group differences Activities of daily living: No between-group differences	Dantrolene vs. placebo Withdrawals (overall): 7 (group not specified) Lethargy/drowsiness: 14/20 vs. 6/20 (p=0.03) Slurred speach: 6/31 vs. 0/31 (p=0.01)

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Ketel 1984[94]	Randomized United States Single center	A: Dantrolene 25 mg BID or TIID titrated to average dose165.4mg B: Placebo Phase I: 6-week open-label dantrolene Phase II: randomized to 6 weeks of A or B	Patients with a history of cerebrovascular accident and limited return of function	18 14	Mean age of 61 Gender: Female=10/18(56%) Race: 100% White Cerebrovascular thrombosis: 17/18(94%) Cerebrovascular hemorrhage: 1/18 (6%) Left hemiparesis: 12/18 (67%) Right hemiparesis: 6/18(33%)
Knutsson 1982[101]	Randomized crossover trial Sweden Single center	A: Tizanidine, maximum 10 mg/day B: Placebo 3-4 weeks intervention, 3-4 weeks crossover	Not reported	13 12	Gender: 4/17 (24%) female Age range: 23-80 Race: not reported Illness duration: 2 months to 42 years Wheelchair-bound: 3/17 (18%) Walking-aid dependent: 8/17 (47%) Prior antispastic medication use Baclofen: 4/14 (29%) Dantrolene sodium: 1/4 (25%)

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Ketel 1984[94]	Neurological examination Spasticity: method not reported Strength: method not reported Clonus: method not reported Reflexes: method not reported Activities of daily living: method not reported Therapeutic goal Spasticity: method not reported Motor ability: method not reported Assessments completed at 3-week intervals	POOR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described, intention-to-treat analysis not performed. 7/9 patients randomized to placebo switched to dantrolene.	Dantrolene vs. placebo Neurological examination Spasticity improvement: 5/5 (100%) vs. 0/8 (0%) Strength improvement: 4/5 (80%) vs. 0/8 Clonus improvement: 5/5 (100%) vs. 0/9 Reflexes improvement: 5/5 (100%) vs. 0/8 Improvement in activities of daily living: 5/5 (100%) vs. 0/8 Therapeutic goal Spasticity improvement: 5/5(100%) vs. 0/9 Motor ability improvement: 5/5(100%) vs. 0/9	Dantrolene vs. placebo Withdrawals (due to adverse events): 3 Rebound spasticity: 0/5 vs. 7/9 (78%) Any adverse events:: 9/12(75%) vs. 1/9(11%) Frequent adverse events: lethargy, weakness, fatigue, drowsiness, depression, dizziness, diarrhea, periorbital rash
Knutsson 1982[101]	Resistance to passive movement: 5-point Ashworth scale Clonus: unspecified 3-point scale Functional disability: unspecified subjective assessment	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described, intention-to-treat analysis not performed.	Tizanidine vs placebo Passive resistance/Ashworth scale (improvement): 5/12 (42%) vs. 3/12 (25%), NS Clonus (improvement): 3/12 (25%) vs. 3/12 (25%), NS Functional disability (improvement): 1/12 (8%) vs. 2/12 (17%), NS	Withdrawals (due to adverse events): 1 (patient on placebo) Tizanidine vs. placebo Drowsiness: 4/12 (33%) vs. 3/13 (23%) Dry mouth: 2/12 (17%) vs. 1/13 (8%) Muscle weakness: 1/12 (8%) vs. 0 Sleep disturbance: 1/12 (8%) vs. 0 Increased dysphasia: 1/12 (8%) vs. 0 Nausea: 0 vs. 1/13 (8%) Nycturia: 0 vs. 1/13 (8%) Dyspnea: 1 vs. 1/13 (8%)

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Lapierre 1987[102]	Randomized Canada Single center	A: Tizanidine 2 mg/day titrated to maximum 32 mg/day B: Placebo 3-weeks titration, 5-weeks maintenance	Age between 18 and 60 years; definite diagnosis of multiple sclerosis; at least moderate degree of spasticity, severe enough to interfere with functional performance in daily life; stability of spasticity for two months or more	66 66	Tizanidine vs. placebo Mean age: 47.6 vs. 43.8 Gender: Female = 17 (52%) vs. 16 (48%) Race not reported Mean disease duration: 15.2 vs. 11.6 Severity "severe": 8 (25%) vs. 11 (33%) Monoparesis=7(22%) vs. 1(3%) Hemiparesis=0(0%) vs. 0(0%) Paraparesis=29(91%) vs. 32(97%) Previous muscle relaxant use not reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Lapierre 1987[102]	Neurological evaluation: included scoring of limb power, tone, deep tendon reflexes, clonus, cerebellar function, sensory function, mental status and cranial nerves (unspecified methods) Functional evaluation: included scoring of neurological status (Kurtzke), functional disability assessment (Kurtzke), ambulation index and upper extremities index Assessments at weeks 0, 2, 3 and 8	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Neurological evaluation: no significant between-group differences for any outcomes measures Neurological status scale/Kurtzke (improved): 3/33 vs. 3/33 Kurtzke EDSS: No between-group differences Cumulative limb tone score (change from baseline): 3.86 vs. 1.49, p<0.05 (favors tizanidine) Cumulative deep tendon reflex score (change from baseline): 1.14 vs. -0.20, p<0.01 (favors tizanidine) Investigator overall judgement of effectiveness (good to excellent): 27% vs. 10%	Tizanidine vs. placebo Withdrawals (overall): 5/33 (15%) vs. 2/33 (6%) Withdrawals (due to adverse events): clear data not provided Tolerability: 53% vs. 85% Frequent adverse events Drowsiness: 48% vs. 27% Dry mouth: 48% vs. 27% Abdominal pain: 2(6%) vs. 0(0%) Sleep disturbances: 2(6%) vs. 2(6%) Tremor: 2(6%) vs. 0(0%) Rash: 2(6%) vs. 2(6%) Bladder disturbances: 1(3%) vs. 1(3%) Dizziness: 1(3%) vs. 2(6%) Gait disturbances: 1(3%) vs. 1(3%) Hallucination: 1(3%) vs. 0(0%) Muscle weakness: 1(3%) vs. 2(6%) Constipation: 0(0%) vs. 2(6%)

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Losin 1966[107]	Randomized United States Single center Inpatient clinic	A: Chlorzoxazone, average dose of 20 mg/lb. body weight B: Placebo 9-10 weeks	Children with severe spasticity, mental retardation, and bedridden Concomitant use of anticonvulsants, antibiotics or vitamins allowed	30 27	Mean age (years): 10 Female gender: 37% Race not reported Diffuse encephalopathy: unknown cause (15), birth trauma (5), prematurity (3), postnatal meningoencephalitie (2), other (5) Previous muscle relaxant use not reported
Luisto 1982[95]	Randomized crossover trial Finland 2 centers	A: Dantrolene sodium 75mg TID titrated to 400 mg QID over 21 days B: Placebo 25 days intervention, 1 week washout, 25 days crossover	Patients with moderate-severe spasticity	17 14	Mean age (years): 38 Female gender: 24% Race not reported Spinal cord injuries: 9/17 Multiple sclerosis: 3/17 Other: 5/17 Spasticity duration (range): >1-15 years Moderate to severe spasticity Confined to bed or wheelchair: 15/17

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Losin 1966[107]	Limb posture, passive stretch resistance, pain: 4 point scale (0=normal, 1+=mildly abnormal, after which there were increasing degrees of severity up to 4+) General nursing care, feeding: 3 point scale ("+"=improvement, "0"=no change, "-"=worse) Timing of assessment not reported	POOR. Inadequate randomization (arbitrary assignment by investigator), one investigator not blinded, allocation concealment technique not described.	Chlorzoxazone vs. placebo Limb posture, passive stretch resistance, pain: "Improvement" in 3/5 on chlorzoxazone; no other data provided General nursing care, feeding: Spasticity severity increase for 2/3 on chlorzoxazone; no placebo data provided; no Feeding data provided	Withdrawals (overall): not reported Withdrawals (due to adverse events): not reported Frequent adverse events: sonorous respiration (1/6); light brown urine (5/0) Serious adverse events (resulting in death): aspiration pneumonia (1/2)
Luisto 1982[95]	Spasticity: 1 (flaccid) to 6 (marked) Muscle strength: 1 (normal) to 6 (paralyzed) Clonus: 1 (absent) to 6 (sustained, marked) Reflexes: 1 (absent) to 6 (hyperactive, marked) Functional evaluation (methods not specified)	FAIR. Randomization, allocation concealment techniques not reported.	Dantrolene sodium vs. placebo Spasticity (sum of scores): 33.5 vs. 71.5 (p=0.05) Strength (sum of scores): 57 vs. 48 (p=0.05) Clonus (sum of scores): 40.5 vs. 64.5 (p=0.05) Reflexes: 36 vs. 69 (p=0.05) Activities of daily living: No improvement on either treatment	Withdrawals (overall): 3 (intervention group not specified) Withdrawals (adverse events): 3 (at least 2 from dantrolene group) Dantrolene vs. placebo Any adverse events: 100% vs. 35% Drowsiness: 15/17 vs. 6/17 Dizziness/vertigo: 4/17 vs. 1/17/1 Headache: 3/17 vs. 0/17 Nausea: 3/17 vs. 1/17 Numbness in hands/feet: 3/17 vs. 0/17 Others adverse events occurred in 1 or 2 patients

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
McKinlay 1980[80]	Randomized crossover trial U.K. Single center School for physically handicapped children	A: Bacofen 0.5 mg/kg/day titrated to maximum dose 60 mg/day over 2 weeks B: Placebo 4 weeks titration/intervention, 2 weeks washout, 4 weeks crossover	Children with spasticity, no other criteria reported	20 18	Gender: "even sex distribution" (data not reported) Age range: 7-16 (mean not reported) Race: not reported Etiology Prenatal: 5 (25%) Perinatal: 10 (50%) Postnatal: 2 (10%) Unknown: 3 (15%)
Medaer 1991[81]	Randomized crossover trial Belgium Single center Multiple sclerosis and rehabilitation center	A: Baclofen titrated to mean 30 mg/day B: Placebo 6 week washout, 2 weeks titration, 4 weeks intervention, 1 week washout, 2 weeks crossover titration, 4 weeks crossover intervention	Post-stroke spasticity	20 20	Female gender: 13/20 Mean age: 65 Race not reported Hemiplegia: 18/20 Monoparesis: 2/20 Mean duration: 4 years Patients on prior antispasticity agents excluded

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
McKinlay 1980[80]	Muscle tone: Ashworth scale Tendon reflexes, extrapyramidal symptoms, cerebellar sympotms: graded clinically, methods not specified Manual dexterity: assessed using materials from standard tests (not specified) Speed of tongue movements: movement of tongue side-to-side 10 times Articulatory speed: time to say "buttercup" 10 times Assessments completed at initial visit and at weekly intervals Gait: Physiotherapist evaluation (method not specified) Muscle tone or better movement: Physiotherapist evaluation (method not specified)	FAIR. Allocation concealment, eligibility criteria, blinding techniques not described.	Baclofen vs. placebo Muscle tone: no significant differences Tendon reflexes: no significant differences Extrapyramidal symptoms: no significant differences Cerebellar symptoms: no significant differences Manual dexterity: no significant differences Speed of tongue movements: no significant differences Articulatory speed: no significant differences Muscle tone by physical therapy evaluation (improved): 14/20 vs. 5/20 (p=0.064) Gait (improved): 8/20 vs. 4/20	Baclofen vs. placebo Withdrawals (overall): 0 Any adverse event: 8/20 vs. 1/20 Drowsiness: 12/20 vs. 0/20 (p<0.001) "Sickness": overall 2 Dizziness: overall 2 Nocturnal enuresis: overall 2 Absence states: overall 2 Slurred speech: overall 2 Weakness: overall 1
Medaer 1991[81]	Muscle Tone: Ashworth Scale Functional Status: Oswestry Rating Scale, Incapacity Status Scale Clinical Global Impression Scale: 4 point scale Extrapyramidal symptoms, cerebellar symptoms, clonus, reflexes, walking ability, range of abduction, impariment of self-help, and impairment of dexterity: Unspecified scales Improvement in spasticity: Unvalidated 4 point scale Assessed before treatment and after each intervention period	FAIR. Randomization and allocation concealment techniques not described. Unable to determine baseline differences between intervention group.	Baclofen vs. placebo Mean scores after treatment Ashworth: 2.95 vs. 3.75 (p<0.001) Oswestry: 3.8 vs. 3.2 (p<0.014) Incapacity status scale: 12.4 vs. 12.8 (NS) Clinical global impression scale (moderate of excellent improvement): 65% vs. 40% (p=0.009) Preferred treatment: 6/20 vs. 1/20 (13 undecided or wanted neither treatment)	Withdrawals: None reported Baclofen vs. placebo Any adverse event: 10/20 vs. 3/20 Somnolence: 1/20 vs. 0/20 Weakness: 4/20 vs. 0/20 Dizziness: 6/20 vs. 0/20 Difficulty walking: 2/20 vs. 0/20 Confusion: 0/20 vs. 1/20

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Meythaler 2001[103]	Randomized crossover trial United States Single center Outpatient and inpatient rehabilitation center	A: Tizanidine 12-36 mg/day B: Placebo 6-weeks titration/treatment phase; 1-week taper; 1-week washout; 6-week crossover; 1-week taper; 1-week washout	Severe, chronic spastic hypertonia in at least 1 lower extremity (LE); spasticity of > 6 months' duration; Tone of >3 on Ashworth Scale Spasm of >2 on Penn Spasm Frequency Scale (PSFS); failure to respond satisfactorily to modalities and therapy for spasticity	17 17	Female gender: 3/17 (18%) Average age: 44 years Non-white race: 1/17 (6%) Black 7/17 (41%) hemiplegia 9/17 (53%) stroke 8/17 (47%) traumatic brain injury Tone >3 on Ashworth Scale Spasm >2 on Penn Spasm Frequency Scale (PSFS) 100% of patients had undergone a previous trial of oral baclofen and not responded adequately or could not tolerate the side effects
Milla 1977[82]	Randomized crossover trial U.K. Multicenter	A: Baclofen 10 mg/day titrated to maximum 30-40 mg/day in children aged 2-7 and 60 mg/day in children aged 8 and above B: Placebo 4-weeks intervention, 4-weeks crossover	Children with spasticity; aged 2-16	20 20	Female gender: 11/20 (55%) Mean age: not reported Race: not reported Functional disability Diplegia: 5/20(25%) Hemiplegia: 7/20(35%) Quadriplegia: 8/20(40%) Previous muscle relaxant use not reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Meythaler 2001[103]	Muscle Tone: Ashworth scale Spasticity: Penn Spasm Frequency Scale (PSFS) Deep tendon reflex: Using unspecified deep tendon reflex scale Range of Motion (ROM): Measured using goniometer Motor strength: Measured using International 6-point motor scale (0=absent; 5=normal) Mobility: Measured using FIM instrument and Craig Handicap Assessment and Reporting Technique (CHART) Assessments completed at start of arms 1 and 2 and at weeks 2, 4, 6, and 8 of treatment	FAIR. Randomization, allocation concealment, intention-to-treat analysis not described.	Tizanidine vs. placebo Muscle tone: A>B in reduction of lower extremity motor tone after 4 weeks of treatment (p=0.0006); A>B in reduction of upper extremity motor tone after 4 weeks of treatment (p=0.0007) (differences between interventions not reported) Spasticity: no significant differences Deep tendon reflex: no significant differences Range of Motion (ROM): no significant differences Motor strength: no significant differences Mobility: no significant differences Assessments completed at start of arms 1 and 2 and at weeks 2, 4, 6, and 8 of treatment	Withdrawals (adverse events): None Common adverse events on tizanidine Somnolence: 7/17 (41%) Increased LFT's: 3/17 (18%) Dry mouth: 2/17 (12%) Hypertonia: 2/17 (12%) Myasthenia 2/17 (12%) Pain 2/17 (12%) Other adverse events occurred in 1 patient
Milla 1977[82]	Records were kept of: 1) spasticity, 2) extra-pyramidal signs, 3)cerebellar signs, 4) clonus, 5) tendon reflexes, 6) walking ability, 7) passive limb movements, 8) degree of self-help and 9) manual dexterity *All assessment methods unspecified except spasticity (rated using Ashworth scale) Assessments completed at 7-day intervals	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described, intention-to-treat analysis not performed.	Baclofen vs. placebo Spasticity (improved): 14/20 (70%) vs. 2/20 (10%), p<0.001 Placebo group results not reported for other outcome measures	Baclofen vs. placebo Withdrawals (adverse events): 0 Any adverse event: 5/20 vs. 0/20 Sedation: 4/20 vs. 0/20 Hypotonia: 3/20 vs. 0/20

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Monster 1974[96]	Randomized crossover trial U.S. and Canada Multicenters	A: Dantrolene 50 mg QID titrated to 100 mg QID B: Placebo 5 weeks intervention, 5 weeks crossover	Patients with spasticity of various causes	200 147	Age: Range from 35 to 50 years depending on underlying diagnosis Female gender: About 50% Race not reported Spasticity secondary to spinal cord, stroke, "unclassified" and multiple sclerosis etiologies (proportion of each not reported) Previous muscle relaxant use not reported
Nance 1994[104]	Randomized U.S. and Canada Multicenter	A: Tizanidine 4 mg/day titrated to maximum 36 mg/day B: Placebo 3 weeks titration, 4 weeks maintenance, 1 week tapering (8 weeks intervention)	Patients 18 years or older with spinal cord injury, Frankel grade of A, B, or C and Ashworth scale score of 2 or greater in one or more muscle groups	124 118	Tizanidine vs. placebo Age range (years): 15-69 Female gender: 9/59 vs. 5/59 Non-white race: 31% vs. 36% Mean duration of spinal cord injury (months): 101 vs. 89 Frankel grade A: 32/59 vs. 34/59 Previous muscle relaxant use: not reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Monster 1974[96]	Overall clinical response (OCR): measured by 3-point scale (0=no/mild change; +1=moderate improvement; +2=marked improvement) Disability: methods not reported; included Activities of Daily Living (ADL) assessment Spasticity: various EMG measurements, including Clonus	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Dantrolene vs. placebo Overall clinical response (OCR): substantial improvement in 83% of patients on Dantrolene sodium (data/p-value not reported) Disability: substantial improvement in 43% of patients on Dantrolene sodium (data/p-value not reported) Spasticity: reduction in clonus in 90% of patients on Dantrolene sodium (data/p-value not reported)	Dantrolene sodium vs. placebo Withdrawals (overall): 53 (intervention not clear) Withdrawals (due to adverse events): less than 10% (exact number and intervention unclear) Frequent side effects: general malaise, fatigue, weakness, drowsiness, nausea, anorexia and dizziness (numbers not reported)
Nance 1994[104]	Spasticity: Ashworth scale and video motion analysis of the pendulum test Frequency of spasms Muscle strength: Unspecified method Functional status: modified Klein-Bell scale Global evaluation: Unspecified method Assessed at each visit	FAIR. Randomization, allocation concealment, blinding techniques not described. High dropout rate (78/118 completed trial)	Tizanidine vs. placebo Ashworth score (mean improvement): 4.41 vs. -0.44 (p<0.0001) Pendulum test (mean improvement) 13.32 vs. 1.50 (p=0.004) Daily spasm frequency: No difference at end of treatment Muscle strength: No differences Global evaluation: No significant differences Functional status (Klein-Bell): No differences	Tizanidine vs. placebo Withdrawals (overall): 21/59 (36%) vs. 19/59 (32%) Withdrawals (adverse events): 15/59 (25%) vs. 5/59 (8%) Any adverse event: 81% vs. 53% (p=0.002) Somnolence: 24/59 vs. 4/59 Dizziness: 10/59 vs. 2/59 Weakness: Not reported Dry mouth: 23/59 vs. 4/59 Asthenia: 18/59 vs. 9/59 Headache: 12/59 vs. 9/59 Diarrhea: 2/59 vs. 5/59

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Nogen 1979[97]	Randomized trial U.S. Single center	A: Dantrolene titrated to 5.6-7.9 mg/kg/day B: Placebo All patients titrated on dantrolene, 1 week washout, then unclear duration of intervention	Pediatric patients with spasticity and epilepsy	21 21	Age range: 7 months to 19 years Female gender: 11/22 Race: not reported Mental retardation: 19/22 Hypoxia at birth or in utero: 6/22 Hemiparesis: 8/22 Other diagnoses: Tumor, encephalitis, vascular malformation, hydrocephalus Anticonvulsant use: 9 phenobarbitol, 7 clonazepam, 13 phenytoin (7 patients more than one) Prior muscle relaxant use: not reported
Orsnes 2000[83]	Randomized crossover trial Denmark Multicenter	A: Baclofen 5 mg TID titrated to maximum 15 mg TID B: Placebo Titration to maximum tolerated dose (duration variable); 11 days maintenance; 1-week taper; 2-week washout; crossover titration; 11 days crossover maintenance; 1-week crossover taper	Patients with clinically definite MS	14 14	Median age=42 Clinically-definite MS; stable for at least one month Kurtzke's Expanded Disability Status Scale (EDSS) median score of 5 Neurologic Rating Scale (NRS) median score of 67 MS-impairment scale (MSIS) median score of 3 Ambulation index (AMB) median score of 3 Ashworth index of spasticity median score of 0.8 Previous muscle relaxant use not reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Nogen 1979[97]	Spasticity: Unspecified method Strength: Unspecified method Reflexes: Unspecified method Clonus: Unspecified method Functional status: Unspecified method Seizures: EEG and frequency	FAIR. Randomization, allocation concealment, blinding techniques not described	Dantrolene vs. placebo Seizure frequency (increased): 1/11 vs. 2/10 Spasticity and other outcomes not reported	Dantrolene vs. placebo Drowsiness: 9/11 vs. 0/10 Increased drooling: 3/11 vs. 0/10 Headaches: 2/11 vs. 0/10 Leg cramps: 1/11 vs. 0/10 Dizziness: Not reported Dry mouth: Not reported Weakness: Not reported Withdrawals (overall): 1, group not reported Withdrawals (adverse events): None reported
Orsnes 2000[83]	Postural stability: measured by force-plate Strength: Medical Research Council scale (0-5) Passive movement resistance: Ashworth scale (5-point scale) Tendon reflexes: 6-point scale (0=hyporeflexic; 5=severe clonus) Assessments before each of 2 treatment periods and after 11 days of treatment at the maximum dose	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Baclofen vs. placebo Postural stability: insignificant trends Strength: insignificant trends Passive movement resistance: insignificant trends Tendon reflexes: insignificant trends	Baclofen vs. placebo Withdrawals: not reported Any adverse event: 9/14 vs. 1/14 Fatigue: 5/14 vs. 1/14 Dizziness: 3/14 vs. 1/14 Better sleep: 2/14 vs. 0/14 Nausea: 1/14 vs. 0/14 Diarrhea :1/14 vs. 1/14 Other adverse events occurred in 1 patient

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Sachais 1977[84]	Randomized trial United States Multicenter Combined inpatient and outpatient setting	A: Baclofen, 5 mg tid (outpatients) or 10 mg tid (inpatients) titrated to 70-80mg/day B: Placebo 2-week titration, 5-week intervention	Inpatient or outpatient adults (18 years or older) Spasticity secondary to MS (duration not specified)	166 106	Mean age=43 59% Female 92% White 87% Outpatient Multiple Sclerosis Mean Disease Duration - 11 years One-Month Spasticity Stabilization - 70% Quadraplegia - 10/5 Paraplegia - 30/33 Hemiplegia - 6/3 Previous muscle relaxant use not reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Sachais 1977[84]	Mental State (Depression, Euphoria, Irritability); Flexor Spasms (Pain, Frequency); Resistance to Passive Joint Movement (Ankle Flexion, Ankle Extension, Knee Flexion, Knee Extension, Hip Abduction, Hip Extension); Tendon Stretch Reflexes (Left Knee Jerk, Right Knee Jerk); and Global Disease Severity - all assessed through unspecified methods at baseline and at weeks three and five Physician Global Impressions (5=marked; 4=moderate; 3=slight; 2=no change; 1=worse) - assessed at end of study Patient Self-Evaluation of Condition (0=little of the time to 3=all the time) and Disability (1=minimal to 6=very severe) - rated at baseline and final visit	FAIR. Randomization, allocation concealment, blinding techniques not described.	Baclofen (A) vs. placebo (B) Mental State: No significant differences for depression, euphoria, and irritability Flexor Spasms: Pain: -1.10 vs. -0.08 (p<0.001) Frequency: -0.63 vs. -0.14 (p<0.005) Resistance to Passive Joint Movements: Baclofen significantly better for ankle flexion, knee flexion, knee extension Global Disease Severity: -0.26 vs. -0.19 (NS) Physician's Assessment of Neurological Findings: No significant differences for ankle clonus or knee clonus Flexor spasms (improvement): 17/37 vs. 6/37 (p=<0.02) Patient Self-Evaluation ratings (improvement from baseline): Baclofen significantly better for muscle spasms, clonus, and stiffness	Baclofen vs. placebo Withdrawals (overall): 31/85 vs. 29/81 Withdrawals (adverse events): not reported Somnolence=71% vs. 36% Vertigo=22% vs. 7% Excessive Weakness=20% vs. 11% Headache=12% vs. 9% Frequenct Urination=12% vs. 1% Insomnia=11% vs. 9% Depression= 5% vs. 6% Lower Extremity Weakness=5% vs. 2% Nausea=16% vs. 6% Constipation=11% vs. 2% Vomiting=5% vs. 0%

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Sawa 1979[85]	Randomized crossover trial Canada Single center	A: Baclofen 5mg TID titrated to a maximum of 60mg B: Placebo 21-days intervention, 7-days washout, 21-days crossover	Patients with clinically definite MS of chronic myelopathy (presumed MS)	21 18	Mean age of 49 for males and 36 for females 29% male Race not reported Clinically definite MS of chronic myelopathy (presumed MS) Mean duration of illness of 14 years for males and 9 years for females Previous muscle relaxant use not reported
Sheplan 1975[98]	Randomized trial United States Single Center	A: Dantrolene titrated to maximum of 200mg QID 5-week intervention, 2-week washout, 5-week crossover	Males with spasticity of a neurological etiology	Not reported Not reported 18 enrolled	Mean age=47.8 100% male Race not reported Multiple sclerosis - 8 Stroke - 4 Cervical spondylosis - 3 Other - 3 Wheelchair-confined - 6 Previous muscle relaxant use not reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Sawa 1979[85]	Spasticity: 0 (normal) to 5 (in the absence of voluntary contraction, the leg will stay extended and require a significant degree of force to overcome the extensor spasticity)	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Baclofen vs. placebo Spasticity mean grade change (improvement in score): 1 vs. 0 (p not reported) Spasticity (improved): 13/18 vs. 0/18 (p<0.001) No other data reported	Baclofen vs. placebo Withdrawals (overall): 3/21 Withdrawals (adverse events): 1/21 (intervention not reported) Any adverse event: 71% vs. 19% Frequent Adverse Events in Baclofen Patients (n=21): Sedation(6), Headache(3), Mood Changes(4), Dizziness(2), Balance Disturbance(2), Weakness(3), Nausea(5), Vomiting(2), Diarrhea(1), Abdominal Pain(2), General Malaise(2), Dry Mouth(1), Weight Gain(1) Placebo patient adverse event data not reported
Sheplan 1975[98]	Spasticity: rigidity and clonus measured by unspecified methods carried out weekly Hyperreflexia: measured by tendo-achilles myotatic reflex Patient acceptance (improvement in activities of daily living): measured by unspecified methods	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Dantrolene vs. placebo Spasticity Clonus (complete remission): 78% vs. not reported Rigidity (complete remission): 50% vs. not reported Hyperreflexia (complete remission): 83% vs. not reported Patient acceptance: no data provided	No withdrawal data provided. Frequent adverse events: weakness, incoordination, "rubber legs", headache, dizziness, GI disturbance, somnolence, fatigue; no data provided

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Smith 1994[105]	Randomized trial United States Multicenter (14)	A: Tizanidine titrated to maximum 36 mg/day B: Placebo 2 weeks titration, 9 weeks maintenance, 1 week withdrawal	Patients with multiple sclerosis	256 220	Mean age (years): 45.3 62% female Race reported as being mostly White, but percentage unspecified. Muscle spasticity secondary to MS Average baseline spasticity severity values Tizanidine - 12.99 Placebo - 14.95 Previous muscle relaxant use not reported.
Tolosa 1975[99]	Randomized trial United States Single center	A: Dantrolene 25mg QID titrated to maximum 800 mg/day B: Placebo 8 weeks intervention	Patients with multiple sclerosis	23 23	Age, gender and race not reported Multiple sclerosis 48% severely disabled/confined to wheelchair Previous muscle relaxant use not reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Smith 1994[105]	Primary Efficacy: Mean muscle tone (Ashworth Scale) and type/frequency of muscle spasms/clonus (patient diaries) (0-3 scale) Secondary Efficacy Assessment: Deep tendon reflexes/clonus (unspecified scale), pain/disability secondary to muscle spasm/clonus (0-2 scale), muscle strength (British Medical Research Council scale), functional capacity (e.g. walking time, activities of daily living) (unspecified scale) and global evaluation of antispastic efficacy (11.5 cm visual analog scale) Assessed weekly titratio, every 3 weeks during maintenance, and 1 week after intervention	FAIR. Method of randomization not reported. Method of treatment allocation concealment not reported. Unspecified suspected treatment crossover deviations reported, high withdrawal/loss to follow-up.	Tizanidine vs. placebo Muscle tone/spasticity (change in Ashworth score, improvement): 2.03 vs. 2.73 (NS) Muscle tone/spasticity (improved): 60% vs. 58% (NS) Spasms/clonus daily count (percent improvement): -61 vs. -41 Patient global assessment (mean score): 5.91 vs. 4.33 (p=0.01) No other significant differences in secondary outcomes (improvements generally small)	Tizanidine vs. placebo Withdrawals (overall): 28/111 (25%) vs. 33/109 (30%) Withdrawals (adverse events): 14/111(13%) vs. 6/109 (6%) Any adverse event: 101/111(91%) vs. 66/109(61%) Dry mouth: 57% vs. 15% (p<0.001) Asthenia: 48% vs. 18% (p<0.001) Somnolence: 48% vs. 3% (p<0.001) Nervous system: 84% vs. 38% (p<0.001) Dizziness: 19% vs. 5% (p=0.001) Drug-induced hepatitis: 1/111 vs. 0/111 (resolved after drug discontinued) Severe hallucinations: 1/111 vs. 0/109 (resolved after drug discontinued) SGOT increase: 6(5%) vs. 0 (p=0.029)
Tolosa 1975[99]	Spasticity: (0=flaccid to 6=extreme resistance)	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Dantrolene vs. placebo Muscle Spasticity Reduction: 42% vs. 27% (signifiance not reported)	Dantrolene vs. placebo Withdrawals (overall): 2/12 vs. 0/11 Withdrawals (adverse events): 2/12 (weakness, diarrhea) vs. 0/11 Weakness: 50% vs. 9% Dizziness, vertigo and GI effects were noted as being "common," but no data reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
United Kingdom Tizanidine Trial Group 1994[106]	Randomized trial United Kingdom Multicenter (16)	A: Tizanidine mean dose 25 mg/day B: Placebo 3-week titration, 9-week intervention	Spasticity due to clinically-definite, lab-supported or probable MS. Stable MS during previous month.	187 187	Mean age (years): 47 vs. 47 Female gender: 63% vs. 67% Race not reported Multiple sclerosis patients: Mean baseline muscle tone score 18.5 vs. 16.8 1 patient (placebo) with previous Tizanidine treatment. All other patients, except 1 (placebo), had previously taken other unspecified medication(s) for spasticity.
Weiser 1978[100]	Randomized crossover trial United Kingdom Single center	A: Dantrolene 25 mg qid titrated to 100 mg qid B: Placebo 4 weeks intervention, 1 week washout, 4 weeks crossover	Symptomatic lower limb spasticity from spinal cord injury	35 27	Age range: 28 to 76 Female gender: 21/35 Race not reported Multiple sclerosis: 9/35 Myelopathy: 11/35 Hereditary spastic paraplegia: 8/35 Syringomyelia: 4/35 Other: 3/35 Severity and duration not reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
United Kingdom Tizanidine Trial Group 1994[106]	Primary Efficacy Assessment: Ashworth Scale administered weekly during 3-week titration phase; every three weeks during maintenance therapy; and at end of trial Secondary Efficacy Assessment: Muscle Strength: British Medical Research Council Scale Functional status/disability: Kurtzke Functional System Scale (FSS)/Kurtzke Expanded Disability Status Scale (EDSS) Reflexes: unspecified 8-point tendon reflex scale Spasms: unspecified 4-point spasm/spontaneous movement scale Timed 8 meter walking test	FAIR. Randomization method not reported. Allocation concealment technique not reported.	Tizanidine vs. Placebo Muscle Tone (sum Ashworth score) Change (%): 21 vs. 9 (p=0.004) Secondary Muscle Strength Change (%): +4 vs. +3 (NS) Muscle Spasm Frequency Change (%): -13 vs. -15 (NS) Muscle Spasm Pain Change (%): -10 vs. -4 (NS) Deep Tendon Reflexes Change (%): -9 vs. -4 (NS) Timed Walking Change (%): +4 vs. -10 (NS) No. of Steps Change (%): -3 vs. -3 (NS) Intermediate functions (improved): 20% vs. 10% Upper limb functions (improved): 6% vs. 5% Patient comfort (improved): 39% vs. 15% Sleep quality (improved): 43% vs. 33% Overall assessment by patient (very good or good): 28% vs. 14% (p=0.012)	Withdrawals (overall): 29/94 vs. 22/93 Withdrawals (due to adverse events): 12/94(13%) vs. 5/93(5%) Any adverse event: 87% vs. 61% Overall tolerability (very good or good): 40% vs. 85% Frequent adverse events Dry mouth: 45% vs. 0% Drowsiness: 54% of all patients in study
Weiser 1978[100]	Tone: 0 (normal) to 3 (pronounced hypertonia) Clonus: 0 (absent) to 2 (sustained) Number and severity (scale not specified) of spasms Walking performance: Time to walk 40 minutes and time to climb up and down 21 step staircase Gait: Not specified Weekly intervals	FAIR. Randomization, allocation concealment, blinding techniques not specified. Results reported for more patients than enrolled in trial for some outcomes.	Dantrolene vs. placebo Tone (treatment preferred): 14/24 vs. 3/24 (p=0.012) Knee clonus (treatment preferred): 17/40 vs. 5/40 (p=0.016) Ankle clonus (treatment preferred): 24/52 vs. 6/52 (p=0.002) Walking time: NS Staircase time: NS Gait (improved): 15/20 vs. 1/20 (p<0.004) Spasms (improved): 14/20 vs. 0/20 (p<0.002)	Dantrolene vs. placebo Withdrawals (any): 4/35 (11%) vs. 2/35 (6%) (2 not clear which intervention) Withdrawals (adverse events): 4/35 (11%) vs. 2/35 (6%) Drowsiness or 'lightheadedness': 8/35 vs. 0/35 Weakness: 8/35 vs. 2/35 Depression: 3/35 vs. not reported

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed
Aiken 1978a[111]	Randomized trial U.S. Single center	A: Cyclobenzaprine 10 mg tid titrated up to 20 mg tid B: Diazepam 5 mg tid titrated up to 10 mg tid C: Placebo 14 days intervention	Outpatients with moderate to severe acute (<30 days) muscle spasm associated with traumatic strains of the neck or low back	Central nervous system etiology, comorbid secondary conditions, pregnant women, receiving analgesics, steroids, or tranquilizers, conditions for which study drugs were contraindicated	Not reported Not reported 117	17 114
Basmajian 1978[112]	Randomized trial U.S. Single center	A: Cyclobenzaprine 10 mg tid titrated up to 20 mg tid (mean dose not reported) B: Diazepam 5 mg tid C: Placebo 18 days	Patients with clinically palpable muscle spasm, limitation of motion, limitation of activities of daily living, local pain, and tenderness on palpation	Other neurologic or general medical conditions	Not reported Not reported 120	15 105 completed study, but results only reported for 52
Boyles 1983[115]	Randomized trial U.S. Multicenter	A: Carisoprodol 350 mg qid B: Diazepam 5 mg qid 7 days	Outpatients between 19 and 65 years with acute (<7 days) sprain or strain of the lower back (no cervical involvement) with moderate pain and local spasm	Cervical strain, litigation, pregnant, nursing, allergy to interventions, patients requiring analgesics (except acetaminophen or aspirin), anti-inflammatories, or sedatives, history of drug abuse, chronic medical problems	Not reported Not reported 80	9 not analyzable 71

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Aiken 1978a[111]	Cyclobenzaprine vs. diazepam vs. placebo Age (>50 years): 4/37 vs. 3/38 vs. 7/39 Female gender: 18/37 vs. 13/38 vs. 22/39 Race: Not reported Posttraumatic: 35/37 vs. 35/38 vs. 34/39 Neck pain: 24/37 vs. 25/38 vs. 26/39 Back pain: 13/37 vs. 13/38 vs. 13/39 Severity (moderate/severe or severe): 27/37 vs. 25/38 vs. 20/39 Prior muscle relaxant use: Not reported	Muscle spasm on palpation: 1 (absent) to 5 (severe) scale Limitation of motion: 1 to 5 scale Limitation of activities of daily living: 1 to 5 scale Pain: 1 to 5 scale Tenderness on palpation: 1 to 5 scale Global response: 5 point scale (worse to marked improvement) Assessed at baseline, day 3, day 7, day 14	FAIR. Randomization, blinding, and allocation concealment techniques not described.
Basmajian 1978[112]	Age, gender, race: Not reported Cyclobenzaprine vs. diazepam vs. placebo Neck spasms: 10/34 vs. 10/36 vs. not described Lumbar spasms: 24/34 vs. 26/36 vs. not described Severity or duration: Not reported Prior muscle relaxant: Not reported	Muscle spasm: 1 (absent) to 5 (severe) scale Weighted mean of EMG index (these results not abstracted) Timing of evaluation not reported but appears to be at baseline and at end of intervention	POOR. Randomization and allocation concealment techniques not described; very high loss to follow-up and not clear how patients lost to follow-up analyzed; unable to compare baseline characteristics between intervention groups.
Boyles 1983[115]	Carisoprodol vs. diazepam Mean age (years): 39 vs. 39 Female gender: 53% vs. 51% Race (non-white): 8% vs. 14% Baseline severity (5 point verbal rating scale) Pain severity: 4.28 vs. 4.31 Impairment of activity: 4.14 vs. 4.29 Prior muscle relaxant use: Not reported	Muscle spasm: 1 (none) to 5 (severe) Tenderness: 1 (none) to 5 (severe) Mobility restriction: 1 (none) to 5 (severe) Pain, stiffness, activity, sleep impairment, tension: 5 point verbal rating scale (VRS) and 100 mm visual analogue scale Assessed at baseline and days 3 and 7 of treatment	FAIR. Allocation concealment technique not described.

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Outcomes	Adverse events	Funding Source and Role	Other comments
Aiken 1978a[111]	Cyclobenzaprine vs. diazepam vs. placebo Improvement in mean scores at weeks 1 and 2 Muscle spasm: 1.5** vs. 0.7 vs. 0.8; 1.9 vs. 1.4 vs. 1.3 Local pain: 1.0 vs. 0.6 vs. 0.7 and 1.5* vs. 1.2 vs. 1.1 Tenderness on palpation: 1.1* vs. 0.6 vs. 0.7; 1.5* vs. 1.2 vs. 1.1 Limitation of motion: 1.1* vs. 0.6 vs. 0.6; 1.6** vs. 1.3 vs. 1.1 Limitation of activities of daily living: 0.9** vs. 0.4 vs. 0.5; 1.4 # vs. 1.2 vs. 0.9 Total spasm score: 5.4** vs. 3.2 vs. 3.3 and 8.2** vs. 6.4 vs. 5.4 *p<0.05 for difference between cyclobenzaprine and diazepam **p<0.01 for difference between cyclobenzaprine and diazepam #p<0.05 for difference between cyclobenzaprine and placebo Global response (marked or moderate improvement): 28/37 vs. 15/38 vs. 16/39 Global response (marked improvement): 22/37 vs. 11/38 vs. 6/39 (p<0.01 for cyclobenzaprine vs. diazepam and placebo)	Cyclobenzaprine vs. diazepam vs. placebo Withdrawals (overall): 5/38 (13%) vs. 6/40 (15%) vs. 6/39 (15%) Withdrawals (adverse events): 1/38 (3%) vs. 0/40 vs. 0/39 Any adverse event: 29/38 (76%) vs. 28/38 (72%) vs. 25/39 (64%) Drowsiness: 25/38 vs. 26/38 vs. 18/39 Dizziness: 7/38 vs. 8/38 vs. 9/39 Nausea: 1/38 vs. 0/38 vs. 4/39 Dry mouth: 2/38 vs. 1/38 vs. 1/38 Lightheadedness: None reported	Editorial assistance provided by Merck, funding source otherwise not clear	
Basmajian 1978[112]	Cyclobenzaprine vs. diazepam vs. placebo Task performance time (% change from pretreatment): -12.5 vs -9.1 vs -6.5 (NS) Muscle spasm/back (change from pretreatment score): -1.0 vs. -1.0 vs -1.0 (NS) Muscle spasm/neck (change from pretreatment score): -0.9 vs. -0.7 vs. -0.7	Not reported	Not reported	
Boyles 1983[115]	Carisoprodol vs. diazepam (estimated from graphs) Mean improvement in VRS scores: Pain: 1.9 vs. 1.7 Muscle stiffness: 2.0 vs. 1.3 (p<0.05 at day 6) Activity impairment: 2.0 vs. 1.8 Sleep impairment: 2.0 vs. 1.8 Tension: 1.9 vs. 1.3 (p<0.05 at day 7) Relief: 4 vs. 3.2 (p<0.05 at day 6) (Similar results for visual analogue scales) Overall relief (very good to excellent): 68% vs. 45% (NS)	Carisoprodol vs. diazepam Drowsiness/tired: 5/40 vs. 12/40 Dizzy/blackout: 5/40 vs. 3/40 Headache: 2/40 vs. 1/40 Dry mouth: Not reported Any adverse event: 9/40 (22%) vs. 14/40 (35%) Withdrawals (overall): 4/40 vs. 5/40 Withdrawals (adverse event): 1/40 vs. 2/40	Not reported	

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed
Bragstad 1979[109]	Randomized trial Norway Single center	A: Tizanidine 2 mg po tid B: Chlorzoxazone 500 mg po tid 7 days	Spasms of the back muscles from degenerative lumbar disk disease	Impaired liver or renal function, severe hypertension, heart disease, epilepsy, cerebral insufficiency, or pregnant	Not reported Not reported 27	1 26
Brown 1978[113]	Randomized trial U.S. Single center	A: Cyclobenzaprine 10 mg po tid B: Diazepam 5 mg po tid C: Placebo 14 days	Moderate to severe pain in the lumbar or posterior cervical regions for more than 12 months	Not reported	Not reported Not reported 49	None reported 49
Fryda-Kaurimsky 1981[116]	Randomized trial Germany Single center	A: Tizanidine 4-8 mg po tid B: Diazepam 5-10 mg po tid 10 days	Inpatients with acute muscle spasm due to degenerative spinal disease	Not reported	Not reported Not reported 20	None reported 20

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Bragstad 1979[109]	Tizanidine vs. chlorzoxazone Mean age (years): 37 vs. 37 Female gender: 7/14 vs. 7/13 Race not reported Hospitalized: 2/14 vs. 5/13 Average muscle tension score: 2.57 vs. 2.69 Prior muscle relaxant use: Not reported	Muscle tension, pain intensity, tenderness, limitation of movement, protective posture, interference with normal activities: All rated on 0 (none) to 3 (severe) scale Baseline, 2, 3, 5, and 7 days of treatment	FAIR. Randomization and allocation concealment techniques not described.
Brown 1978[113]	20-64 years old 27/49 female Race not reported Demographics not reported for each intervention group Cyclobenzaprine vs. diazepam Underlying conditions Musculoskeletal strain: 4/16 vs. 4/16 Posttraumatic: 5/16 vs. 6/16 Postoperative: 6/16 vs. 5/16 Other: 1/16 vs. 1/16 Severity or duration: Not reported Prior muscle relaxant use: Not reported	Global evaluation: Worse, no change, slight improvement, moderate improvement, marked improvement Evaluated at 1 and 2 weeks	FAIR. Randomization, treatment allocation, blinding techniques not described; unable to compare baseline characteristics between intervention groups.
Fryda-Kaurimsky 1981[116]	Tizanidine vs. diazepam Mean age (years): 54 vs. 50 Female gender: 6/20 (30%) overall Race not reported Underlying condition Low back syndrome: 50% vs. 60% Low back and cervical syndrome: 30% vs. 20% Cervical syndrome: 20% vs. 20% Severity (severe): 50% vs. 50% Duration of degenerative spinal disease (days): 102 vs. 110 Prior muscle relaxant use: Not reported	Pain: 0 (none) to 3 (severe) Tenderness: 0 (none) to 3 (severe) Muscle spasm: 0 (normal) to 2 (markedly increased) Abnormal posture: 1 (slight, correction possible but slightly painful) to 3 (very marked, correction not possible) Day-to-day activities: 0 (normal) to 3 (immobile) Patient's self-evaluation: 0 (no incapacity) to 3 (severe incapacity) Restriction of movement (centimeters or degrees, measured in various joints) (not abstracted here) Assessed at baseline, 2, 3, 4, 5, and 7 days	FAIR. Randomization, treatment allocation, and blinding techniques not described.

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Outcomes	Adverse events	Funding Source and Role	Other comments
Bragstad 1979[109]	Tizanidine vs. chlorzoxazone Muscle pain (improvement): 1.43 vs. 1.58 (NS) Muscle tension (improvement): 1.86 vs. 2.25 (NS) Tenderness (improvement): 1.36 vs. 1.91 (NS) Limitation of movement (improvement): 1.00 vs. 1.25 (NS) Protective posture (improvement): 1.50 vs. 1.62 Prevention of normal activity (imprvoement): 1.43 vs. 1.64 (NS) Overall assessment/patient (good or excellent):11/14 (79%) vs. 9/13 (69%) Overall assessment/patient (excellent): 8/14 (57%) vs. 3/13 (23%)	Tizanidine vs. chlorzoxazone Any adverse events: 0/14 vs. 2/13 (diarrhea and fatigue) Withdrawal (overall): 0/14 vs. 1/13 Withdrawal (adverse events): None reported	Not reported	
Brown 1978[113]	Cyclobenzaprine vs. diazepam vs. placebo Global evaluation (marked or moderate improvement): 11/16 (69%) vs. 8/16 (50%) vs. 5/17 (29%) (NS for difference between active treatments) Global evaluation (marked improvement): 8/16 (50%) vs. 6/16 (38%) vs. 2/17 (12%)	Cyclobenzaprine vs. diazepam vs. placebo Drowsiness: 7/16 (p<0.05 vs. placebo) vs. 2/16 vs. 0/17 Dry mouth: 8/16 (p<0.05 vs. placebo) vs. 2/16 vs. 0/17 Dizziness: 4/16 (p<0.05 vs placebo) vs. 2/16 vs. 0/17 Withdrawals: None reported	Not reported	
Fryda-Kaurimsky 1981[116]	Tizanidine vs. diazepam Pain (improvement): 1.7 vs. 1.9 Tenderness (improvement): 1.8 vs. 1.8 Muscle spasm (improvement): 1.6 vs. 1.7 Day-to-day activities (improvement): 1.6 vs. 1.6 Patient's self-evaluation (improvement): 1.6 vs. 1.9 Combined scores for six variables pain, tenderness, spasm, abnormal posture, day-to-day activities, and self-evaluation (improvement): 8.5 vs. 9.1 (NS) Efficacy by physician evaluation (complete relief): 8/10 (80%) vs. 8/10 (80%)	Tizanidine vs. diazepam Any adverse effects: 2/10 vs. 5/10 Precordial discomfort: 1/10 vs. 0/10 Dry mouth: 1/10 vs. 1/10 Dizziness and fatigue: 1/10 vs. 5/10 Withdrawals: None	Not reported	

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed
Hennies 1981[117]	Randomized trial Germany Single center	A: Tizanidine 4 mg tid B: Diazepam 5 mg tid 7 day	Acute painful cervical or lumbar spasm	Liver or renal disease, cardiovascular disease, active infection or malignancy in spine, rheumatic disease, psychologically unstable, or pregnant	Not reported Not reported 30	1 30
Preston 1984[19]	Randomized trial U.S. Single center	A: Cyclobenzaprine 10 mg po tid B: Methocarbamol 1500 mg po qid C: Placebo 7 days	Localized muscle spasm due to pain secondary to traumatic or inflammatory causes of less than 14 days	Spasm due to disease of the spinal cord, cerebral disease, psychological causes; no injectable analgesics, skeletal muscle relaxants, tranquilizers, sedatives, or anti-inflammatories within last 48 hours, pregnancy, <18 years except with parental consent, other significant co-morbid medical conditions, alcohol or drug abuse, glaucoma	Not reported 232 227	30 197
Rollings 1983[110]	Randomized trial U.S. Single center	A: Cyclobenzaprine 10 mg po qid B: Carisoprodol 350 mg po qid 8 days	Outpatients between 19 and 65 with acute back strain (no neck involvement), moderate pain and local muscle spasm, tenderness and limited mobility, and <7 days duration	Cervical strain, patients involved in litigation, pregnant women, nursing mothers, women of childbearing potential not using contraceptives, known allergy or intolerance, patients requiring therapy other than bed rest or moist heat, patients requiring other medications for symptoms, known drug abuse, and other serious medical medications	Not reported Not reported 78	20 58

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Hennies 1981[117]	Tizanidine vs. diazepam Mean age (years): 46 vs. 49 Female gender: 11/15 vs. 9/15 Race: Not reported Score for pain (mean): 2.3 vs. 2.2 Score for spasm (mean): 2.3 vs. 2.1	Pain: 0 (absent) to 3 (severe) Tension: Unspecified method Protective posture: Unspecified method Daily living activity: Unspecified method Limitation of lumbar mobility: Centimeters Lasegue test: Degrees Patient self-assessment: Unspecified method Evaluated at baseline, day 3, and day 7	FAIR. Randomization and allocation concealment techniques not described.
Preston 1984[19]	Cyclobenzaprine vs. methocarbamol vs. placebo Mean age (years): 42 vs. 40 vs. 41 Female gender: 59% vs. 63% vs. 52% Non-white: 13% vs. 8% vs. 10% Duration of spasm (days): 3.8 vs. 3.8 vs. 4.3 Severity of muscle spasm (moderate or severe): 100% vs. 100% vs. 100% Prior muscle relaxant use: Not reported	Nine-point ordinal scale 0 (absent) to 8 (very severe) for following: Muscle spasm Local pain and tenderness Limitation of normal motion Interference with normal activities Baseline, interim visit, and at final visit (day 7)	FAIR. Randomization, allocation concealment techniques not described, high loss to follow-up and no intention-to-treat analysis; results excludes patients with initially mild scores from analysis.
Rollings 1983[110]	Cyclobenzaprine vs. carisoprodol Mean age (years): 43 vs. 41 Female gender: 10/28 (36%) vs. 17/30 (57%) Non-white: 13% vs. 11% Pain severity score: 4.07 vs. 3.89 Duration of symptoms: Not reported Prior muscle relaxant use: Not reported	Pain severity: Verbal rating scale (VRS) 1 (none) to 5 (severe) and visual analogue scale (VAS) 0 (none) to 100 (worse) Muscle stiffness: VRS and VAS Activity impairment: VRS and VAS Sleep impairment: VRS and VAS Tension: VRS and VAS Evaluated on days 4 and 8	FAIR: High loss to follow-up and no intention-to-treat analysis.

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Outcomes	Adverse events	Funding Source and Role	Other comments
Hennies 1981[117]	Tizanidine vs. diazepam Muscle tension (number improved): 9/11 vs. 12/15 (NS) Muscle tension (mean improvement in score): 1.5 vs. 1.2 Muscle pain (number improved): 13/14 vs. 11/15 (NS) Muscle pain (mean improvement in score): 1.7 vs. 1.1 Daily living activities (number improved): 13/14 vs. 14/15 (NS) Daily living activities (mean improvement in score): 1.7 vs. 1.4 Self-assessment (number improved): 13/14 vs. 12/15 (NS)	Tizanidine vs. diazepam Any adverse event: 1/15 vs. 0/15 Withdrawals (overall): 1/15 (7%) vs. 0% Withdrawals (adverse events): 1/15 (7%) vs. 0% Somnolence: None reported Dizziness: None reported Weakness: None reported Dry mouth: None reported	Not reported	Most patients on both treatments had improved by day 7.
Preston 1984[19]	Cyclobenzaprine vs. methocarbamol vs. placebo (study only reported results from first interim analysis and excluded patients with initially mild scores) Muscle spasm (absent or mild): 33% vs. 40% vs. 35% (NS for A vs. B) Local pain (absent or mild): 40% vs. 48% vs. 32% (p=0.05 for A vs. B) Limitation of motion (absent or mild): 35% vs. 49% vs. 34% (NS for A vs. B) Interference with daily activities (absent or mild): 41% vs. 48% vs. 32% (NS for A vs. B)	Cyclobenzaprine vs. methocarbamol vs. placebo Any adverse event: 37/87 (42%) vs. 29/94 (31%) vs. 7/46 (15%) Severe adverse event: 14/47 (30%) vs. 7/34 (21%) vs. 0 CNS adverse event (including drowsiness, dizziness): 60/87 (58%) vs. 30/94 (31%) vs. 2/46 (4%) Dry mouth: 8/87 (9%) vs. 1/94 (1%) vs. 1/46 (2%) Withdrawal (overall): 12/87 (14%) vs. 12/94 (13%) vs. 6/46 (13%) Withdrawal (adverse events): 6/87 (7%) vs. 6/94 (6%) vs. 1/46 (2%)	Not reported	By end of trial, most patients (including placebo) had improved. Results only reported for interim (day 1-4) visit.
Rollings 1983[110]	Cyclobenzaprine vs. carisoprodol (difference in scores from baseline) Pain (VRS): 1.6 vs. 1.9 (NS) Muscle stiffness (VRS): 1.5 vs. 1.6 (NS) Activity impairment (VRS): 1.6 vs. 1.7 (NS) Sleep impairment (VRS): 1.3 vs. 1.7 (NS) Tension (VRS): 1.1 vs. 1.0 (NS) Relief (VRS): 3.2 vs. 3.3 (NS) No significant differences in physician ratings for the above, or in assessment of overall improvement	Cyclobenzaprine vs. carisoprodol Any adverse event: 24/37 (65%) vs. 24/39 (62%) Drowsiness: 15/37 (40%) vs. 16/39 (41)% Dizzy: 3/37 (8%) vs. 10/39 (26%) Dry mouth: 14/37 (38%) vs. 4/39 (10%) (p<0.05) Headache: 1/37 (3%) vs. 3/39 (8%) Paresthesia: 0 vs. 3/39 (8%) Constipation: 3/37 (8%) vs. 1/39 (3%) Withdrawal (overall): 9/37 (24%) vs. 11/39 (28%) Withdrawal (due to adverse events): 3/37 (8%) vs 3/39 (8%)	Authors employed by A.H. Robins Company. Not clear if data held by funder.	

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed
Scheiner 1978 (1)[114]	Randomized trial U.S. Single center	A: Cyclobenzaprine 30-40 mg/day B: Diazepam 15-20 mg/day C: Placebo 14 days	Moderate to severe neck or low back muscle spasm of local origin and recent (<30 days) onset	Other serious medical or psychiatric conditions, spasticity of neurologic origin, pregnant patients, abnormal lab values, arthritic conditions	Not reported Not reported 96	18 96
Scheiner 1978 (2)[114]	Randomized trial U.S. Single center	A: Cyclobenzaprine 30-40 mg/day B: Diazepam 15-20 mg/day C: Placebo 14 days	Moderate to severe neck or low back muscle spasm of local origin and recent (<30 days) onset	Other serious medical or psychiatric conditions, spasticity of neurologic origin, pregnant patients, abnormal lab values, arthritic conditions	Not reported Not reported 75	10 69

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Scheiner 1978 (1)[114]	Cyclobenzaprine vs. diazepam vs. placebo Mean age (years): 33 vs. 38 vs. 36 Female gender: 10/34 vs. 12/32 vs. 12/30 Non-white: Not reported Duration <7 days: 34/34 vs. 31/32 vs. 26/30 Severity (severe): 6/34 vs. 8/32 vs. 5/30 Location back: 16/34 vs. 15/32 vs. 14/30 Location neck: 18/34 vs. 17/32 vs. 16/30 Posttraumatic: 15/34 vs. 9/32 vs. 13/30 Strain: 13/34 vs. 11/32 vs. 8/30 Other: 6/34 vs. 12/32 vs. 9/30 Prior muscle relaxant use: Not reported	Muscle spasm (consistency), local pain, tenderness, limitation of motion, and limitation of activities of daily living: All assessed using 1 (absent) to 5 (severe) scale Global evaluation: 5 point scale (worse to marked improvement) Assessed at baseline, day 7, and day 14	FAIR: Randomization and allocation concealment techniques not reported; high loss to follow-up in cyclobenzaprine group (12/34).
Scheiner 1978 (2)[114]	Cyclobenzaprine vs. diazepam vs. placebo Mean age (years): 35 vs. 32 vs. 34 Female gender: 6/24 vs. 6/21 vs. 15/24 Non-white: Not reported Duration <7 days: 17/24 vs. 17/21 vs. 13/24 Severity (severe): 1/24 vs. 1/21 vs. 1/24 Location back: 13/24 vs. 10/21 vs. 13/24 Location neck: 11/24 vs. 11/21 vs. 11/24 Posttraumatic: 18/24 vs. 13/21 vs. 14/24 Strain: 5/24 vs. 6/21 vs. 5/24 Other: 1/24 vs. 2/21 vs. 5/24 Prior muscle relaxant use: Not reported	Muscle spasm (consistency), local pain, tenderness, limitation of motion, and limitation of activities of daily living: All assessed using 1 (absent) to 5 (severe) scale Global evaluation: 5 point scale (worse to marked improvement) Range of motion: Goniometry (results not abstracted) Assessed at baseline, day 7, day 10, and day 14	FAIR: Randomization and allocation concealment techniques not reported.

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Outcomes	Adverse events	Funding Source and Role	Other comments
Scheiner 1978 (1)[114]	Cyclobenzaprine vs. diazepam vs. placebo Mean improvement in score at weeks 1 and 2 Muscle spasm: 1.4 vs. 0.9 vs. 0.5 and 2.5 vs. 1.9 vs. 1.1 Local pain: 1.3 vs. 0.9 vs. 0.4 and 2.4 vs. 1.8 vs. 1.2 Tenderness: 1.4 vs. 1.1 vs. 0.5 and 2.6 vs. 1.8 vs. 1.1 Limitation of motion: 1.5 vs. 1.0 vs. 0.5 and 2.5 vs. 1.8 vs. 0.9 Limitation of activities of daily living: 1.4 vs. 1.0 vs. 0.4 and 2.5 vs. 1.9 vs. 1.0 Differences significant for cyclobenzaprine and diazepam vs. placebo, not significant for cyclobenzaprine vs. diazepam except for tenderness on palpation at week 2 ($p<0.05$), and limitation of motion at weeks 1 and 2 ($p<0.01$) Global evaluation (marked or moderate improvement): 29/34 vs. 28/32 vs. 17/30 Global evaluation (marked improvement): 25/34 vs. 17/32 vs. 4/30 ($p<0.01$ for cyclobenzaprine vs. diazepam or placebo)	Cyclobenzaprine vs. diazepam vs. placebo Withdrawals (overall): 12/34 (35%) vs. 3/32 (9%) vs. 3/30 (10%) Withdrawals (adverse events): None reported Drowsiness: 8/34 vs. 9/32 vs. 3/30 Dry mouth: 10/34 vs. 2/32 vs. 0/30 Dizziness: 3/34 vs. 9/32 vs. 0/30 Ataxia: 0/34 vs. 3/32 vs. 0/30 Nausea: 0/34 vs. 0/32 vs. 1/30 Any side effect: 11/34 (32%) vs. 9/32 (28%) vs. 3/30 (10%)	Editorial assistance provided by Merck, funding source otherwise not clear	
Scheiner 1978 (2)[114]	Cyclobenzaprine vs. diazepam vs. placebo Mean improvement in score at weeks 1 and 2 Muscle spasm: 1.9 vs. 1.5 vs. 0.3 and 2.7 vs. 2.2 vs. 0.5 Local pain: 1.8 vs. 1.3 vs. 0.2 and 2.7 vs. 2.1 vs. 0.4 Tenderness: 2.0 vs. 1.4 vs. 0.2 and 2.7 vs. 2.1 vs. 0.4 Limitation of motion: 2.0 vs. 1.5 vs. 0.2 and 2.8 vs. 2.3 vs. 0.4 Limitation of activities of daily living: 2.0 vs. 1.5 vs. 0.2 and 2.8 vs. 2.2 vs. 0.4 Differences significant ($p<0.01$) for cyclobenzaprine and diazepam vs. placebo, and significant ($p<0.05$) for cyclobenzaprine vs. diazepam except NS for muscle spasm and limitation of motion at week 1 Global evaluation (marked or moderate improvement): 24/24 vs. 18/21 vs. 1/24 Global evaluation (marked improvement): 18/24 vs. 6/21 vs. 1/24 ($p<0.01$ for cyclobenzaprine vs. diazepam or placebo)	Cyclobenzaprine vs. diazepam vs. placebo Withdrawals (overall): 2/26 (8%) vs. 5/24 (21%) vs. 3/25 (12%) Withdrawals (adverse events): None reported Drowsiness: 20/24 vs. 14/21 vs. 1/24 Dry mouth: 11/24 vs. 3/21 vs. 1/24 Dizziness: 4/24 vs. 11/21 vs. 1/24 Ataxia: 0/24 vs. 2/21 vs. 0/24 Nausea: None reported Any side effect: 12/24 (50%) vs. 14/21 (67%) vs. 1/24 (4%)	Editorial assistance provided by Merck, funding source otherwise not clear	

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Aiken 1978b	Randomized trial United States Single center	A: Cyclobenzaprine 10 mg qD (range 20-60 mg qD) B: Placebo 2 weeks intervention	Outpatients with moderate to severe skeletal muscle spasm associated with traumatic strains of the neck and low back	50 44	Cyclobenzaprine vs. placebo Female gender: 12/25 vs. 10/25 Age (>45 years): 3/25 vs. 3/25 Race not reported Posttraumatic: 23/25 vs. 23/25 Neck: 14/25 vs. 15/25 Back: 11/25 vs. 10/25 Severity (severe): 13/25 vs. 6/25	Muscle spasm, limitation of activities of daily living, pain, tenderness: 1 (absent) to 4 (severe) Overall response: worse to excellent Assessed at day 3 or 4, 1 week, and 2 weeks
Baratta 1976[124]	Randomized trial United States Single center	A: Carisoprodol 350 mg QID B: Propoxyphene 65 mg QID C: Placebo 14 days	Patients with low back syndrome	105 94	Average age: A=38, B=36, C=37 Female gender: 18% vs. 31% vs 21% Non-white:Race: 9% vs. 22% vs. 10% Underlying conditions: lumbosacral sprain, cervical sprain, sacroiliac sprain, thoraco-lumbar sprain, thoraco-spinalis sprain Baseline severity and duration not reported Previous muscle skeletal relaxant use not reported	Functional measurements: flexion, extension, rotation, etc. Pain symptoms: active and passive Other symptoms: discomfort, stiffnes and anxiety Sleep patterns: early and middle insomnia and total hours of sleep *All assessed on 4 point scale Global improvement: rated by investigator using 3-point scale ("satisfactory", "mild", or "no relief") Assessments completed at baseline and 2x/week

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Aiken 1978b	FAIR. Allocation concealment, blinding techniques not described.	Cyclobenzaprine vs. placebo Mean scores at 2 weeks Spasm: 1.6 vs. 2.2 (p<0.01) Limitation of motion: 1.4 vs. 2.0 (p<0.01) Limitation of activities of daily living: 1.7 vs. 2.5 (p<0.01) Pain and tenderness: 1.9 vs. 2.5 (p<0.05) Global evaluation (excellent or good): 19/22 vs. 3/22 Global evaluation (excellent): 9/22 vs. 1/22	Cyclobenzaprine vs. placebo Withdrawals (all): 3/25 vs. 3/25 Withdrawals (adverse events): 1/25 vs. 0/25 Any adverse event: 24/25 vs. 12/25 Drowsiness: 21/25 vs. 3/25 Dizziness: 9/25 vs. 6/25 Weakness: 4/25 vs. 3/25 GI upset: 3/25 vs. 1/25 Sweating: 3/25 vs. 0/25 Dry mouth: 1/25 vs. 0/25
Baratta 1976[124]	FAIR. Allocation concealment, eligibility criteria, blinding techniques not described.	Results only for carisoprodol vs. placebo (p<0.01 unless noted) Flexion: 12.3 vs. 5.7 Back extension: 1.2 vs. -0.2 Passive sit-up: 44.4 vs. 13.9 Knee flex on abdomen: 39.3 vs. 6.6 Side bend to knee joint: 1.8 vs. 0.7 Squat off heels: 3.9 vs.1.4 Stiffness relief: 1.0 vs. 0.1 Discomfort relief: 0.8 vs. -0.1 Pain symptoms: no significant differences Sleep patterns: 1.0 vs. 0.2 (p=0.01) for falling asleep; 1.3 vs. 0.8 (p<0.02) in reducing number of awakenings Global improvement (satisfactory): 19/33(58%) vs. 4/29(14%) (p<0.01)	No adverse reactions were recorded for any of the patients in the study

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Baratta 1982[129]	Randomized United States # of centers not reported	A: Cyclobenzaprine 10mg TID B: Placebo 10 days or until patient became asymptomatic	Moderate-severe degree of muscle spasm for not longer than 30 days.	120 117	Cyclobenzaprine vs. placebo Mean age (years): 35 vs. 38 Female gender: 24/58 vs. 24.59 Race not reported 118 acute musculoskeletal strain 2 post-traumatic origin Moderate-severe spasticity Previous muscle relaxant use not reported	Muscle spasm Local pain Tenderness on palpitation Limitation of motion Limitation of activities of daily living *All recorded using 5-point rating scale (1=absent to 5=severe) Assessment #1 completed 2-3 hours post-first dose of test drug; #2 within days 2-4; #3 within days 5-7; #4 within days 8-12
Basmajian 1989[130]	Randomized Canada Multicenter (18)	A: Cyclobenzaprine 5mg bid + diflunisal 500mg bid B: Diflunisal 500mg bid C: Cyclobenzaprine 5mg bid D: Placebo 10 days	Patients with muscle spasm secondary to acute trauma or musculoskeletal strain of 7-10 days' duration.	175 175	Age not reported Gender not reported Race not reported Acute trauma or musculoskeletal strain of 7-10 days' duration Severity not reported Previous muscle relaxant use not reported	Presence of local pain; Presence of muscle spasm; Presence of muscle tenderness on palpation; Limitation of range of motion; Limitation of activities of daily living: Methods of assessments not reported Assessments completed at Baseline and at Days 2, 4 and 7-10

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Baratta 1982[129]	FAIR. Allocation concealment method not reported.	Flexeril vs. Placebo Muscle spasm mean decrease (mean score difference) Days 2-4: -0.7 vs. -0.2 (p<0.01) Days 5-7: -1.4 vs. -0.8 (p<0.01) Days 8-12: -1.9 vs. -1.2 (p<0.01) Local pain mean decrease (mean score difference) Days 2-4: -1.1 vs. -0.6 (p<0.01) Days 5-7: -1.6 vs. -1.0 (p<0.01) Days 8-12: -2.0 vs. -1.5 (p<0.01)	Withdrawal (due to adverse events): 0 Any adverse event: 25/58(43%) vs. 17/59(29%) <u>Frequent adverse events</u> A: n=58; B: n=59 Dizziness: 36% vs. 15% (p<0.01) Drowsiness: 31% vs. 10% (p<0.01) Nausea: 12% vs. 3% (NS) Dry mouth: 10% vs. 5% (NS) Sweating: 3% vs. 0 (NS) GI upset: 2% vs. 3% (NS) Fatigue: 2% vs. 0 (NS) Weakness: 2% vs. 2% (NS) Epigastric distress: 0 vs. 2% (NS)
Basmajian 1989[130]	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Presence of local pain: No significant between groups differences Presence of muscle spasm: No significant between groups differences Presence of muscle tenderness on palpation: No significant between groups differences Limitation of range of motion: No significant between groups differences Limitation of activities of daily living: No significant between groups differences Global response: No significant between groups differences except at Day 3(improvement rates): A=32/46(70%), B=24/40(60%), C=26/44(59%); (p=0.006)	Withdrawals: not reported Overall incidence: "no significant adverse events attributable to therapy"

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Bennett 1988[131]	Randomized United States Multi-center (2) Outpatient rheumatology clinics	A: Cyclobenzaprine: 10 mg qpm; titrated to a maximum dose of 40 mg/day B: Placebo 12 weeks	Musculoskeletal pain of at least three months' duration; presence of at least 7 tender points; increased shoulder/neck tension; morning fatigue secondary to sleep disturbance; am stiffness/aching accentuation	120 120	97% female Mean age of 49 Race not reported 44% primary fibrositis 56% fibrositis associated with trauma or arthritis Previous muscle relaxant use not reported	Patient symptoms: weekly assessment of local pain, sleep quality, am stiffness, and fatigue using a visual analog scale (1-10) Tender point analysis: rated using 5-point scale (1=absent; 5=severe) at weeks 1, 2, 4, 8 and 12 Muscle tightness/musculoskeletal pain: rated using 5-point scale (1=absent; 5=severe) at weeks 1, 2, 4, 8 and 12 Overall response to therapy: assessed by physician
Bercel 1977[132]	Randomized United States Single Center	A: Cyclobenzaprine, 20-40 mg (mean dose not reported) B: Placebo 2 weeks	Cervical or lumbosacral osteoarthritis (confirmed by x-ray) Moderate-severe muscle spasm for 30 days or longer	54 54	Mean age=54.4 56% female Race not reported 31 posterior neck spasm 23 lower back spasm Moderate-severe muscle spasticity Previous muscle relaxant use not reported	Muscle spasm duration (absent, mild, moderate, moderately severe, or severe) Global evaluation of therapeutic response (markedly, moderately, slightly) Ratings completed before and after treatment

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Bennett 1988[131]	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described, not performed. Intention-to-treat analysis utilized.	Cyclobenzaprine (A) vs. placebo (B) Patient symptoms: significant improvements in pain severity (A>B; p<0.02) and sleep quality (A>B; p<0.02) at weeks 2-12; no between-groups differentiation for morning stiffness; improvement in fatigue at weeks 2 and 4 (A>B; p<0.02) Tender point analysis: significant reduction in number and severity of tender points at week 2 and 4 (A>B; p<0.03) Muscle tightness/musculoskeletal pain: significant global pain improvement at weeks 2 and 4 (A>B; p<0.05) Overall response to therapy (n=117): A>B; p<0.04	Cyclobenzaprine vs. placebo Withdrawals (overall): 35% vs. 60% Withdrawals (due to adverse events): 8% vs. 5% Any adverse event: 89% vs. 64% (p=0.002) Frequent adverse events (n=62 vs. 58): dry mouth (57 vs. 17); drowsiness (34 vs. 17); constipation (8 vs. 2); dizziness (7 vs. 5); palpitation (7 vs. 4); tachycardia (5 vs. 4); fatigue (5 vs. 2); depression (5 vs. 2); headache (3 vs. 9); nausea (2 vs. 7); generalized pain (2 vs. 4)
Bercel 1977[132]	FAIR. Randomization technique not reported; treatment allocation concealment techniques not reported	Cyclobenzaprine vs. placebo Muscle spasm duration improvement Week 1: 81% vs. 41% (significance not reported) Week 2: 77% vs. 41% (significance not reported)	Withdrawals (due to adverse events): none <u>Frequent adverse events:</u> Cyclobenzaprine (n=27) vs. Placebo (n=27) Drowsiness: 9(33%) vs. 5(19%) Dry mouth: 1(4%) vs. 4(15%) Dizziness: 3(11%) vs. 0 Nausea: 1(4%) vs. 0 Ataxia/weakness: 1(4%) vs. 1(4%)

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Berry 1988a[147]	Randomized United Kingdom Multicenter (7)	A: Tizanidine, 4 mg TID + ibuprofen, 400 mg TID B: Placebo + ibuprofen, 400 mg TID 7 days	Patients with low back pain of at least moderate severity, of recent onset, with painful limitation of movement of the lumbar spine; aged 18-65	105 94	Tizanidine vs. placebo Mean age (years): 43 vs. 42 Female gender: 47% vs. 43% Race: not reported Functional disability and underlying severity: not reported Diagnostic etiologies: not reported	Limitation of movement: 4-point scale (severely, moderately, mildly restricted, not restricted) Sciatica: 4-point scale (absent, mild, moderate, severe) Pain: 4-point scale (none, mild, moderate, severe) Subjective assessments: overall helpfulness and whether patient was better or worse were rated by unspecified methods Assessments completed at baseline and days 3 and 7
Berry 1988b[146]	Randomized United Kingdom Multicenter (20)	A: Tizanidine, 4 mg tid B: Placebo 7 days	Patients aged 18-70 years with acute low-back pain of at least moderate severity, of recent onset, with or without sciatica, together with painful limitation of movement of the lumbar spine	112 96	Tizanidine vs. placebo Mean age (years): 44 vs. 38 Female gender: 49% vs. 49% Race: not reported Functional disability and mean severity: not reported Prior muscle relaxant use: Not reported	Restriction of movement: 4-point scale (severely, moderately, mildly restricted, not restricted) Sciatica: 4-point scale (absent, mild, moderate, severe) Pain: 4-point scale (none, mild, moderate, severe) on movement, at rest and at night Subjective assessments: overall helpfulness (no help, some help or very helpful) and rating of patient's condition compared to baseline (much better, better, same, worse, much worse) Assessments completed at baseline and days 3 and 7

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Berry 1988a[147]	POOR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described, intention-to-treat analysis not performed.	Tizanidine + ibuprofen (A) vs. placebo + ibuprofen (B) Pain at night (percent with moderate-severe severity): 18% vs. 37% (p=0.025) Pain at rest: no treatment differences Pain on movement (mean changes in diary visual analogue score assessment): 23 vs. 19 (p=0.029) Restriction of movement: no significant differences between groups Sciatica (marked improvement): A>B (p=0.002) at Day 3 of patients with moderate to severe pain at baseline Helpfulness of tablets (helpful): 88% vs. 69% (p=0.05) at day 3; between group difference not significant at day 7 Overall improvement: No significant between group differences reported	Withdrawals (due to adverse events): 6 Frequent adverse events (n=51) Central nervous system: A=17(33%), B=5(9%); p=0.025 Gastro-intestinal: A=3(6%), B=11(20%); p=0.002 Types of CNS adverse events in Group A: Drowsiness(n=10), Dry mouth(n=3), Tiredness(n=2), Light-headedness(n=2), Sedation(n=1), Vertigo(n=1)
Berry 1988b[146]	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Tizanidine vs. placebo Pain at night: no significant between group differences on patients' daily visual analogue scale assessments or four-point scale assessments Pain at rest: no significant between group differences shown in patients' diary visual analogue scale assessments Restriction of movement: no significant between group differences patients' daily visual analogue scale assessments or four-point scale assessments Sciatica: no significant between group differences Helpfulness of tablets: no significant between group differences	Withdrawals (due to adverse events): A=5/59(8%), B=1/54(2%) Overall incidence: A=24(41%), B=11(21%) Frequent adverse events Drowsiness and other central nervous system side-effects 19/59 (32%) (22% drowsiness) vs. 5/53(9%); p=0.003 Gastro-intestinal side-effects: B>A (p=0.018)

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Berry 1988b[146]	Randomized U.S. Single center	A: Cyclobenzaprine 10 mg tid B: Placebo 14 days	At least moderately severe acute muscle spasm of local origin	48 35	Cyclobenzaprine vs. placebo Female gender: 8/24 vs. 14/24 Mean age (years): 47 vs. 45 Race: not reported Mean duration (days): 4.1 vs. 3.5 Severity (moderate-severe): 19/24 vs. 21/24 Location back: 17/24 vs. 19/24	Muscle consistency, spontaneous local pain, tenderness, limitation of motion, limitation of activities of daily living, global evaluation: 1 (absent) to 5 (severe) Assessed during week 1 and at day 14
Borenstein 2003 (1)[46]	Randomized trial U.S. Multicenter	A: Cyclobenzaprine 5 mg po tid B: Cyclobenzaprine 10 mg po tid C: Placebo 7 days	Outpatients >18 years with acute (<14 days), moderate or moderately severe painful muscle spasm of the lumbar and/or cervical region	737 730	Cyclobenzaprine 5 mg po tid vs. 10 mg po tid vs. placebo Mean age (years): 42 vs. 42 vs. 42 Female gender: 57% vs. 57% vs. 59% Race (non-white): 14% vs. 12% vs. 14% Baseline serverity and duration: Not reported Lumbar pain: 66% vs. 65% vs. 63% Prior muscle relaxant use: Not reported	Patient rated global change: 0 (worsening) to 4 (marked improvement) scale Patient rated medication helpfulness: 0 (poor) to 4 (excellent) scale Patient rated relief from starting backache: 0 (no relief) to 4 (complete relief) scale Physician rating of muscle spasm: 0 (no hardness) to 4 (severe, boardlike hardness)

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Bianchi 1978[133]	FAIR. Blinding, allocation concealment techniques not reported.	Cyclobenzaprine vs. placebo Mean scores at day 7 and day 14 Muscle consistency: 1.3 vs. 2.2 (p<0.01); 1.0 vs. 1.3 (NS) Pain: 1.3 vs. 1.9 (p<0.05;1.0 vs. 1.3 (NS) Tenderness: 1.5 vs. 2. 3 (p<0.01) and 1.0 vs. 1.3 (NS) Limitation of motion: 1.5 vs. 2.3 (p<0.01); 1.0 vs. 1.3 (NS) LImitation of activities daily limitation:1.4 vs. 2.0 (p<0.05); 1.0 vs. 1.2 (NS) Global evaluation (complete or satisfactory relief): 20/22 vs.14/20 (p<0.01); 20/20 vs. 15/15 (NS) Global evaluation (complete relief): 17/22 vs. 6/20; 19/20 vs. 11/15	Cyclobenzaprine vs. placebo Any: 10/24 vs. 5/24 Withdrawals (overall): 4/24 vs. 9/24 Withdrawals (adverse events): None Drowsiness: 7/24 vs. 2/24 Dizziness: 1/24 vs. 1/24 Dry mouth: 2/24 vs. 0/24 Gastric pain: 0/24 vs. 1/24
Borenstein 2003 (1)[46]	FAIR. Not clear if allocation concealment and randomization techniques adequate (appears to be consecutive numbers).	Cyclobenzaprine 5 mg tid vs. 10 mg tid vs. placebo (results at end of treatment, 7 days) Global change: 2.88 vs. 2.82 vs. 2.47 (both active treatments p<0.001 compared to placebo) Medication helpfulness: 2.09 vs. 2.13 vs. 1.65 (both active treatments p<0.01 compared to placebo) Relief from starting backache: 2.37 vs. 2.38 vs. 2.00 (both active treatments p<0.03 vs. placebo) Withdrawals due to ineffectiveness: 2% (5/242) vs. 2% (5/249) vs. 4% (9/246)	Cyclobenzaprine 5 mg tid vs. 10 mg tid vs. placebo (pooled with results of another trial conducted by same authors) Somnolence: 29% vs. 38% vs. 10% Dry mouth: 21% vs. 32% vs. 7% Headache: 5% vs. 5% vs. 8% Asthenia/fatigue: 6% vs. 6% vs. 3% Nausea: 3% vs. 2% vs. 4% Dizziness: 3% vs. 4% vs. 2% >1 adverse event: 55% vs. 62% vs. 35% Cyclobenzaprine 5 mg tid vs. 10 mg tid vs. placebo (non-pooled) Withdrawals: 9% (22/242) vs. 14% (34/249) vs. 9% (221/246) Withdrawals due to adverse events: 5% (12/242) vs. 8% (20/249) vs. 2% (6/246)

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Borenstein 2003 (2)[46]	Randomized trial U.S. Multicenter	A: Cyclobenzaprine 2.5 mg po tid B: Cyclobenzaprine 5 mg po tid C: Placebo 7 days	Outpatients >18 years with acute (<7 days), moderate or moderately severe painful muscle spasm of the lumbar and/or cervical region	668 659	Cyclobenzaprine 2.5 mg po tid vs. 5 mg po tid vs. placebo Mean age (years): 44 vs. 43 vs. 42 Female gender: 60% vs. 55% vs. 56% Race (non-white): 14% vs. 9% vs. 10% Baseline serverity and duration: Not reported Lumbar pain: 55% vs. 64% vs. 62% Prior muscle relaxant use: Not reported	Patient rated global change: 0 (worsening) to 4 (marked improvement) scale Patient rated medication helpfulness: 0 (poor) to 4 (excellent) scale Patient rated relief from starting backache: 0 (no relief) to 4 (complete relief) scale Physician rating of muscle spasm: 0 (no hardness) to 4 (severe, boardlike hardness)

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Borenstein 2003 (2)[46]	FAIR. Not clear if allocation concealment and randomization techniques adequate (appears to be consecutive numbers).	Cyclobenzaprine 2.5 mg tid vs. 5 mg tid vs. placebo (results at end of treatment, 7 days) Global change: 2.63 vs. 2.82 vs. 2.41 (p<0.03 for 5 mg tid vs. placebo) Medication helpfulness: 1.72 vs. 2.00 vs. 1.50 (p<0.03 for 5 mg tid vs. placebo) Relief from starting backache: 2.03 vs. 2.24 vs. 1.72 (p<0.03 for 5 mg tid vs. placebl) Withdrawals due to ineffectiveness: 4% (10/223) vs. 1% (2/222) vs. 4% (10/223)	Cyclobenzaprine 2.5 mg tid vs. 5 mg tid vs. placebo (pooled with results of another trial conducted by same authors) Somnolence: 20% vs. 29% vs. 10% Dry mouth: 14% vs. 21% vs. 7% Headache: 7% vs. 5% vs. 8% Asthenia/fatigue: 4% vs. 6% vs. 3% Nausea: 4% vs. 3% vs. 4% Dizziness: 3% vs. 3% vs. 2% >1 adverse event: 44% vs. 55% vs. 35% Cyclobenzaprine 2.5 mg tid vs. 5 mg tid vs. placebo (non-pooled) Withdrawals: 9% (20/223) vs. 7% (15/222) vs. 9% (21/223) Withdrawals due to adverse events: 2% (5/223) vs. 4% (9/222) vs. 2% (4/223)

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Borenstein 1990[134]	Randomized Open-label # centers not reported	A=Naprosyn; 500 mg/day initially then 250 mg q 6 hrs B=Naprosyn + cyclobenzaprine 10 mg po q 8 hrs 14 days	Patients with mild-moderate acute low back pain (duration of 10 days or less), between the ages of 18 and 60.	40 40	Naprosyn vs. naprosyn + cyclobenzaprine Mean age (years): 32 vs. 37 Female gender: 35% vs. 25% Race not reported Acute mild-moderate low back pain Mean duration of pain before treatment (days): 2.5/3 Previous muscle relaxant use not reported	Functional Capacity: 0=usual activities performed without discomfort or difficulty to 3=usual activities could not be performed-scale completed daily by patient Muscle Spasm:: 0=none to 3=severe Tenderness to palpitation: 0=no pain to 3=withdraws Pain: Numerical scale: 0-20; also 0 (no pain) to 3 (severe pain) scale" - both scales completed daily Lumbosacral spine range of motion; straight-leg raising test; Schober's test; degree of difficulty in arising from a supine position Assessments completed at initial evaluation and at three follow-up visits (days 3, 7 and 14) Overall Efficacy: 0=poor to 4=excellent completed at final assessment by patient Overall remaining limitation of function: 0=none to 4=incapacitating

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Borenstein 1990[134]	POOR. Randomization, allocation concealment not described. Open-label study.	Naprosyn vs. naprosyn + cyclobenzaprine Functional Capacity (cumulative score for intervention): 15 vs. 9 (NS) Muscle Spasm: 3 vs. 2 (p=<0.05) Tenderness: 3 vs. 2.5 (p=<0.05) Days to resolution of pain: No significant difference between groups in Patient rating (12.5 vs. 8.5) or Physician Rating (14 vs. 7) No significant difference between groups in Days to maximum anterior flexion/extension (14 vs. 7) or Days to sit without pain (7 vs. 5) Schober's test range (cm): 2.0-7.0 vs. 4.5-6.0 (p<0.05) Other assessment results not reported	Naprosyn (n=20) vs. naprosyn + cyclobenzaprine (n=20) Withdrawals not reported Any adverse event: 4/20 vs. 12/20 (p<0.05) Drowsiness: 0 vs. 3/20 Dyspepsia: 1/20 vs. 2/20 Nervousness: 0/20 vs. 2/20 Others (reported by 1 patient each): abdominal pain, constipation, headaches, dizziness, diarrhea, dyspepsia/drowsiness, dyspepsia/diarrhea, dispepsia/dizziness

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Carette 1994[135]	Randomized Canada Multicenter (11)	A: Amitriptyline 10mg/day week 1, 25 mg/day weeks 2-12, 50 mg/day for last 12 weeks B: Cyclobenzaprine 10 mg/day week 1, 20mg/day weeks 2-12, 10 mg qam and 20mg qpm for last 12 weeks C: Placebo 6 months	18 years of age or older; American College of Rheumatology (1990) criteria; Score equal to or greater than 4 on at least one of two visual anolog scales measuring pain and global assessment of symptoms; normal lab results	208 186	Amitriptypline vs. cyclobenzaprine vs. placebo Mean age (years): 44.1 vs. 43.4 vs 47.1 Female gender: 92.9 vs. 95.1 vs. 92.9 Race not reported Fibromyalgia Duration of fibromyalgia (months): 60 vs. 36 vs. 60 months Patient global evaluation: 70.0 vs. 69.6 vs. 72.6	Visual analog assessments: Pain(0=none; 10=severe); Fatigue(0=none; 10=severe fatigue); Sleep(0=no difficulty; 10=extreme difficulty); Feeling on awakening(0=feeling find and refreshed; 10=feeling exhausted); Morning stiffness(0=none; 10=very severe); Global assessment of fibromyalgia (0=not troublesome at all; 10=extremely troublesome) McGill Pain Questionnaire Functional disability: Sickness Impact Profile (SIP); Health Assessment Questionnaire (HAQ) Psychological status: Arthritis Impact Measurement Scales (AIMS); MMPI Fibromyalgia point tenderness: 9-kg dolorimeter; global assessment of fibromyalgia using 10-cm visual analog scale (0=doing extremely well; 10=doing extremely poorly)
Casale 1988[144]	Randomized Italy Single center	A: Dantrolene sodium 25 mg/day B: Placebo 4 days	Patients suffering from chronic low back pain in the acute phase	20 20	Dantrolene (n=10) vs. placebo (n=10) Mean age (years): 47 vs. 47 Female gender: 30% vs. 20% Race not reported Illness duration (days): 12.4 vs. 14.7 Previous muscle relaxant use not reported	Muscle spasm: measured by means of manual semiotic maneuvers Pain behavior: measured by Scott and Huskinsson's visual analog scale (VAS) Muscle force: measured at knee and hip

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Carette 1994[135]	FAIR. Adequate method of randomization (table of random numbers) in blocks of 5; allocation concealment not described.	Amitriptyline vs. placebo results only One-month improvement: 21% vs. 0% (p=0.002) Six-month improvement: 36% `vs. 19% (p=0.08) Visual analog scale scores: Significant improvement for each variable (no data provided) McGill Pain Questionnaire: No significant difference except pain rating index at month 1 (no data) for cyclobenzaprine Functional disability (SIP, HAQ): No significant differences except SIP physical dimension score at month 3 (no data) for cyclobenzaprine Psychological status (AIMS, MMPI): No significant AIMS scores differences	Amitriptyline vs. cyclobenzaprine vs. placebo Withdrawals (overall): 14/82 vs. 24/78 vs. 14/40 Withdrawals (due to adverse events): 5/82 vs. 11/78 vs. 2/40 Any adverse events: 95% vs. 98% vs. 62% Frequent adverse events: somnolence (4 vs. 3 vs. 1); dizziness (0 vs. 5 vs. 1); abdominal pain (1 vs. 3 vs. 0); rash (1 vs. 1 vs. 0); headache (0 vs. 1 vs. 0); weight gain (1 vs. 0 vs. 0)
Casale 1988[144]	FAIR. Inadequate description of randomization, allocation concealment, and blinding techniques.	Dantrolene vs. placebo Muscle spasm (improvement): 85% vs. 10% by day 3 (p<0.001) Pain behavior (improvement): 90% at 3 days and 100% at 4 days vs. 40% (p<0.001; VAS pain measurement decrease in 50% vs. 8.6% (p<0.001) Muscle force: extension of the knee improvement in 77% vs. 8% (p<0.01)	Indication that patients did not report any weakness. No other information provided

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Cullen 1976[125]	Randomized United States Single center	A: Carisoprodol 350 mg qid B: Placebo 10 days	Patients with acute, traumatic conditions affecting the cervical, thoracic and lumbar regions of the back	65 63	Carisoprodol vs. placebo Mean age (years): 41 vs. 37 Female gender: 12/32 vs. 11/33 Non-white: 0/32 vs. 1/33 Primary diagnoses: Lumbosacral, cervical, sacroiliac, or thoracic sprain	Muscle pain: method not reported Muscle spasm: method not reported Limitation of motion: method not reported Patient improvement: rated on 4-point scale (none to severe) Global improvement: rated on 6-point scale (complete relief to worsened considerably) Assessments completed pretrial and on days 5 and 10
Dapas 1985[143]	Randomized United States Multicenter	A: Baclofen, 30-80 mg/day B: Placebo 14 days	Paravertebral muscle spasm and functional disability of less than 2 weeks' duration and at least moderate severity	200 178	Baclofen vs. placebo Mean age: 42 Female gender: 48% vs. 56% Race: Not reportedGender: Pain severity Moderate: 77/200(39%) Severe or extreme: 123/200(61%) Prior muscle relaxant use not reported	Efficacy variables included: 1) Lumbar pain; 2) Tenderness; 3) Paravertebral muscle spasm; 4) Interference with daily activity; 5) Global; 6) Physician's opinion; 7) Patient's opinion; 8) Active straight leg raising (degrees); 9) Forward flexion (inches) Assessment methods were not reported for any efficacy variables Assessments were completed at baseline and on two additional occasions during 14-day treatment period

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Cullen 1976[125]	FAIR. Allocation concealment, eligibility criteria, blinding techniques not described.	Carisoprodol (A) vs. placebo (B) Muscle pain (average) at Day 5: 2.1 vs. 2.7, p<0.01 At Day 10: 1.3 vs. 2.0, p<0.01 Muscle spasm (average) at Day 5: 1.5 vs. 2.2, p<0.01 At Day 10: 1.2 vs. 1.7, p<0.01 Limitation of motion (average) at Day 5: 1.6 vs. 2.4, p<0.01 At Day 10: 1.1 vs. 1.8, p<0.01 A=1.1, B=1.8 (p<0.01) Global improvemen (complete remission): 72% vs. 36% (p<0.01)	Carisoprodol (A, n=32) vs. placebo (B, n=33) Withdrawals (due to adverse events): A=1(dizziness), B=2(generalized giant hives, subarachnoid hemorrhage) Frequent adverse events Drowsiness: A=4, B=1 Dizziness: A=6, B=1
Dapas 1985[143]	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	In patients with 'severe' initial pain: A>B, (p<0.05) for all efficacy variables at Visit 2, except paravertebral muscle spasm and forward flexion; and for all efficacy variables at Visit 3 In patients with 'moderate' initial pain: A>B, (p<0.05) for 'Interference with daily activities' and 'Global limitation of function' at visit 2; no other significant between group differences were observed at visit 2 or 3	Baclofen vs. placebo Withdrawals (due to adverse events): 17/98 vs. 0/97 Any adverse events: 68% vs. 30%, p not reported but described as "significant" Frequent adverse events Sleepiness/fatigue: 49% vs. 21% Dizziness/lightheadedness: 28% vs. 2% Vertigo: 10% vs. 0% Nausea: 38% vs. 13% Dry mout: 5% vs. 1% Other adverse events occurring in < 10% of patients not reported here shown in table 4 of study

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Dent 1975[42]	Randomized U.S. Single center	A: Metaxalone 400 or 800 mg qid B: Placebo 7-9 days	Acute painful skeletal muscle disorders secondary to trauma and/or inflammation, with spasm for no longer than 14 days	228 176	Metaxalone vs. placebo Age: All over 18 years Other demographics not reported Baseline severity: Not reported Prior muscle relaxant use: Not reported	Muscle spasm: Scale not specified Local pain: Scale not specified Limitation of normal motion: Scale not specified Interference with daily activities: Scale not specified
Diamond 1966[139]	Randomized U.S. Single center	A: Metaxalone 800 mg qid B: Placebo (lactose) 10 days	Muscle spasm, pain, tenderness, and restriction of motion of acute onset, location not specified	100 100	Metaxalone vs. placebo Age range (years): 17-89 vs. 16-77 Female gender: 'Similar' Race: Not reported Baseline severity: Not reported Prior muscle relaxant use: Not reported	Muscle spasm: 5 point scale (worse to excellent) Pain: 4 point scale (not present prior to therapy, completely relieved by therapy, partially relieved by therapy, or unaffected by therapy) Assessed daily
Fathie (1) 1964[43]	Randomized U.S. Single center	A: Metaxalone 800 mg qid B: Placebo 7 days	Low back pain and discomfort	100 100	Demographics and baseline severity not reported	Global therapeutic response: 4 point scale (none to marked) Range of motion limitation: 5 point scale (absent to very severe) Palpable spasm: 5 point scale (absent to very severe) Assessed at baseline and at 7 days

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Dent 1975[42]	POOR. Allocation concealment and blinding techniques not described. Baseline characteristics of patients not reported. Reasons for exclusion unclear and high overall loss to follow-up (65/228); not clear if intention-to-treat.	Metaxalone vs. placebo (percent improved at final evaluation) Muscle spasm: 92% vs. 78% (p=0.02) Local pain or tenderness: 91% vs. 76% (p=0.02) Limitation of normal motion: 88% vs. 73% (p=0.02) Interference with daily activities: 88% vs. 75% (p=0.05) Global improvement, patient assessment: 86% vs. 68% (p=0.01)	Metaxalone vs. placebo (unclear sample sizes, based on sample size of 90 for metaxalone and 86 for placebo) Any adverse events: 14% (13/90) vs. 10% (9/86) Withdrawal (due to adverse events): 9% (8/90) vs. 5% (4/86) Withdrawal (Overall): Not reported Drowsiness: 4% (4/90) vs. 1% (1/86) Nausea: 4% (4/90) vs. 2% (2/86) Dizziness: 3% (3/90) vs. 0% Vertigo: 1% (1/90) vs. 0% Weakness: 1% (1/90) vs. 0%
Diamond 1966[139]	FAIR. Allocation concealment technique not described.	Metaxalone vs. placebo Spasm (excellent response): 11/50 (22%) vs. 12/50 (24%) (NS) Spasm (good or excellent response): 26/50 (52%) vs. 23/50 (46%) (NS) Pain (completely relieved): 14/50 (28%) vs. 13/50 (26%) (NS) Pain (completely or partially relieved): 33/50 (66%) vs. 36/50 (72%) (NS)	Not clear ('minor and related to vomiting and nausea')
Fathie (1) 1964[43]	FAIR. Not clear if allocation concealment technique adequate. Baseline characteristics of population not described.	Metaxalone vs. placebo (p values not reported) Global response (marked or moderate): 70% vs. 17% Range of motion (improved): 89% vs. 39% Palpable spasm (improved): 89% vs. 28%	Metaxalone vs. placebo Withdrawals (overall): 10% (5/51) vs. 6% (3/49 Adverse events not reported

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Fathie (2) 1964[43]	Randomized U.S. Single center	A: Metaxalone 800 mg qid B: Placebo 7 days	Low back pain and discomfort	100 100	Demographics and baseline severity not reported	Global therapeutic response: 4 point scale (none to marked) Range of motion limitation: 5 point scale (absent to very severe) Palpable spasm: 5 point scale (absent to very severe) Assessed at baseline and at 7 days
Fogelholm 1992[148]	Randomized crossover trial Finland Single center	A: Tizanidine, 6 mg/day to 18 mg/day B: Placebo 6 weeks intervention; 2 weeks washout; 6 weeks crossover	Women less than 60 years of age who had been treated in the past few years for chronic tension-type headache in the outpatient clinic of a neurology department	45 37	Gender: 100 percent female Median age: 47 years Race: not reported Baseline severity: not reported Prior muscle relaxant use not reported	Daily headache severity: documented in patient diary by marking a Visual Analogue Scale (VAS) of 100 mm (0 mm=no headache; 100 mm=the most severe headache) and also using a 5-point Verbal Rating Scale (VRS) (1=no headache; 5=most severe headache)
Gold 1978[22]	Randomized United States Single center	A: orphenadrine 100 mg BID B: phenobarbital 32 mg BID C: placebo 7 days	Patients with moderate-severe low-back syndrome pain that had been precipitated within 48 hours of study entry and was causing some degree of disability regarding work or normal activities	60 60	Age not reported Gender not reported Race not reported Severity not reported Previous muscle relaxant use not reported	Symptomotology/pain intensity: method not specified Pain relief: method not specified Assessments completed at days 2, 4 and 7

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Fathie 1964[43]	FAIR. Not clear if allocation concealment technique adequate. Baseline characteristics of population not described.	Metaxalone vs. placebo (p values not reported) Global response (marked or moderate): 76% vs. 28% Range of motion (improved): 90% vs. 47% Palpable spasm (improved): 84% vs. 47%	Metaxalone vs. placebo Withdrawals (overall): 10% (5/50) vs. 14% (7/50) Adverse events not reported
Fogelholm 1992[148]	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Tizanidine vs. placebo Daily headache severity Visual Analogue Scale (VAS) median sum: 408 vs. 680, p=0.018 Verbal Rating Scale (VRS) six-week sum: 70 vs. 81, p=0.012 Global Rating (milder headache): 90 vs. 60, p=0.001 Analgesic use (median # tablets): 4 vs. 10, p=0.001	Tizanidine vs. placebo Withdrawals (overall): 4/37 vs. 3/37 (1 not specified) Withdrawals (adverse events): 2 vs. 0 Tolerability (ratings of 'good' or 'moderately good'): 90% vs. 100%, p=0.007
Gold 1978[22]	POOR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described, outcomes assessment and patient population not described.	Orphenadrine vs. phenobarbital vs. placebo Overall improvement symptomotology/pain intensity A=7/20(35%)* B=3/20(15%)* C=0/20(0%) *>Placebo(p<0.01) Pain relief (at 48 hours) A=9/20(45%)* B=3/20(15%) C=4/20(20%) *>Phenobarbital or placebo (p<0.01)	Withdrawals not reported Any adverse effects A: 5/20(25%) B: 2/20(10%) C: 1/20(5%) <u>Frequent adverse events</u> A: 5 patients complained of heartburn, dry mouth, slight drowsiness or "high" feelings with shakiness or insomnia B: 2 patients complained of drowsiness C: 1 patient complained of sleepiness

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Hindle 1972[126]	Randomized United States Single center	A: carisoprodol 350 mg TID B: butabarbital 15 mg/day tid C: Placebo	Low back pain, not otherwise reported	48 43	Carisoprodol vs. batbarbital vs. placebo Gender (overall): 44% female Mean age (years): 37 vs. 35 vs. 44 Race: 100% hispanic Duration of symptoms 0-12 hours: 6% vs. 19% vs. 13% 12-24 hours: 88% vs. 69% vs. 75% 24-48 hours: 6% vs. 13% vs. 13%	Pain: 4-point scale (1=none; 4=severe) Spasm: 4-point scale (1=none; 4=severe) Interference with daily activities: 4-point scale (1=none; 4=severe) Limitation of motion: 4-point scale (1=none; 4=severe) Anxiety/tension: 4-point scale (1=none; 4=severe) Degree of limitation of motion: "finger to floor" test Pain intensity: 100 point VAS Global evaluation: assessment completed by investigator on 5-point scale (Excellent, Good, Fair, Poor, Worse) Assessments completed at baseline and at days 2 and 4
Lance 1972[136]	Randomized crossover Australia Single center	A: Cyclobenzaprine, 30-60 mg/day B: Placebo One month	Chronic tension headache, not otherwise reported	20 20	Age range: 19-66 Female center: 60% Race: not reported Illness duration range: mean 8 years Headache characteristics: 19/20(95%) bilateral; 13/20(65%) bifrontal; 2/20(10%) bitemporal; 1/20(5%) occipital; 3/20(15%) "all over the head"	Headache severity: rated on 3-point scale ("virtually headache free", "condition more than 50% improved", "condition unchanged")

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Hindle 1972[126]	FAIR. Allocation concealment, eligibility criteria, blinding techniques not described. Randomization conducted using a table of random numbers	Carisoprodol vs. placebo (average improvement at day 4) Pain: 1.4 vs. 0.0 (p=0.01) Spasm: 1.3 vs. 0.1 (p=0.01) Interference with daily activities: 1.9 vs. -0.3(p<0.01) Limitation of motion: 1.7 vs. 0.0 (p<0.01) Anxiety/tension: 1.0 vs.- 0.2 (p<0.01) Degree of limitation of motion: 19.6 vs. -1.3 (p=0.01) Pain intensity: 70.5 vs. 1.5 (p<0.01) Global evaluation: 1.5 vs. 0.0 (p<0.01) *Group B (Butabarbital) outcomes were not abstracted	Carisoprodol vs. placebo Withdrawals (due to adverse events): None Adverse events: None reported
Lance 1972[136]	POOR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described	<u>Cyclobenzaprine vs. placebo</u> <u>Headache severity</u> Virtually headache free: 25% vs. 0 More than 50% improved: 25% vs. 25% No change: 35% vs. 70% Withdrew: 15% vs. 5%	Withdrawals (due to adverse events): 0 vs. 1/20 Frequent adverse events (n=20) Drowsiness: A=4, B=5 Insomia: A=0, B=1 Heaviness in legs: A=1, B=0 Nausea: A=1, B=2 Epigastric discomfort: A=1, B=0 Dizziness: A=1, B=2 Dry mouth: A=4, B=0 Weight gain: A=1, B=1 Constipation: A=1, B=0 Frequency of micturition: A=1, B=0 Tremor: A=1, B=0 Blocked nose: A=2, B=1 Blurred vision: A=0, B=1

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Latta 1989[140]	Randomized crossover trial U.K. Single center	A: Orphenadrine 100 mg qhs B: Placebo 1 month intervention, 1 month crossover	Elderly patients in care facilities with painful nocturnal leg cramps	59 59	Mean age (years): 64 Female gender: 35/59 Race: Not reported Baseline severity of nocturnal leg cramps: Not reported Previous muscle relaxant use: Not reported	Number of nocturnal leg cramps in a 1 month period
Lepisto 1979[149]	Randomized Finland Single center Inpatient	A: Tizanidine 2 mg/day (n=15) B: Placebo (n=15) 7 days	Between age 18 and 62; suffering from moderate-severe muscle spasm of the lumbar (26 patients) or thoracic (4 patients) regions	30 28	Tizanidine vs. placebo Mean age (years): 42.5 vs. 40.8 Female gender: 47% vs. 53% Race not reported Lumbar muscle spasm: 87% vs. 87% Thoracic muscle spasm: 13% vs. 13% Previous muscle relaxant use not reported	The following were rated using a 4-point scale (absent, slight, moderate, severe): Pain in the back; Tenderness on palpation; Muscle tension; Limitation on movement; Protective posture Straight leg raising: measured in degrees Assessments performed before study entry and at days 2, 3, 5 and 7
McGuinness 1983[141]	Randomized England # of centers not reported	A: Orphenadrine + paracetamol, doses not reported B: Paracetamol alone Duration appears to be 10 days	Male or female patients; aged 18-70; suffering from painful musculoskeletal disorders	32 28	Orphenadrine + paracetamol vs. paracetamol Female gender: 64% vs. 36% Mean age (years): 35.7 vs. 41.9 Race: not reported <u>Diagnostic etiologies</u> Back pain: 57% vs. 57% Other pain: 43% vs. 43%	Assessments were made using a 4-point scale of severity, ranging from normality to severe distress and included (1) Pain; (2) Stiffness; and (3) Functional impairment These evaluations were carried out on the first attendance and at days 5 and 10

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Latta 1989[140]	FAIR. Randomizaton, allocation concealment, blinding techniques not described.	Orphenadrine vs. placebo (results of first intervention) Mean number of nocturnal leg cramps/1 month: 3.28 vs. 9.93 (p<0.0001)	No episodes of lightheadedness, dizziness, dry mouth, excess somnolence reported Any adverse event: 2/59 on orphenadrine Withdrawals (adverse events): None reported
Lepisto 1979[149]	FAIR. Randomization, allocation concealment, blinding techniques not described.	Pain in the back: no significant group differences Muscle tension (mean score decrease): Day 3=1.60 vs. 0.93 (p-value significant, but not reported); Day7=2.27 vs. 1.58 (p-value significant, but NR) Tenderness on palpation (mean score decrease): Day 2=0.53 vs. 0.27(p-value significant, but NR); Day 3=1.00 vs. 0.73(p-value significant, but NR) Limitation on movement: no significant group differences Protective posture: no significant group differences Straight leg raising (mean score decrease): Day 2=13 vs. 1.7(p-value significant, but NR) Physician's ratings: A better than B(p<0.001)	Tizanidine vs. placebo Any adverse event: 33% vs. 40% <u>Frequent adverse events</u> Light somnolence: 5/15 vs. 1/15 Dizziness: 0/15 vs. 3/15 Nausea: 0/15 vs. 1/15 Sweating: 0/15 vs. 1/15 Dry mouth: None reported
McGuinness 1983[141]	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	<u>Orphenadrine + paracetamol vs. paracetamol</u> <u>Pain (mean score improvement at day 10):</u> 1.2 vs. 0.8 <u>Stiffness (mean score improvement at day 10)</u>: 1.8 vs. 0.6 Function (mean score improvement at day 10): 2.0 vs. 1.0	Withdrawals (due to adverse events): 1(nausea) on combination No other adverse event information provided

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Murros 2000[150]	Randomized Finland # of centers: not reported	A: Tizanidine modified release (MR), 6 mg/day B: Tizanidine MR, 12 mg/day C: Placebo 6 weeks	Men and women, aged 18 or older, who fulfilled the International Headache Society criteria for chronic tension type headache (CTTH)	201 160	Tizanidine 6 mg vs. tizanidine 12 mg vs. placebo Mean age (years): 41 vs. 46 vs. 45 Female gender: 77% vs. 73% vs. 74% Race: not reported Mean headache duration (months): 90 vs. 116 vs. 92	Headache severity: measured using visual analogue scale (VAS) Days free of headache: method of measurement unspecified Daily duration of headache: method of measurement unspecified Use of paracetamol: method of measurement unspecified Assessments completed at weeks 2, 4 and 6
Quimby 1989[40]	Randomized trial U.S. Single center	A: Cyclobenzaprine 10 mg qhs titrated to 30 mg qhs + 10 mg qam B: Placebo 10-14 day washout, 6 weeks intervention	Fibromyalgia syndrome and no evidence of secondary causes of pain	45 40	Female gender: 40/40 Mean age (years): 45 Race: not reported Mean duration: 11 years Mean number of tender points: 7 No significant differences between groups for baseline severity, depression, sleep scales	Depression: Beck depression inventory Fatigue, stiffness, pain, sleep, overall rating: Minus 1 (got worse) to 3 (marked improvement) Assessed at baseline, 3 weeks, and 6 weeks

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Murros 2000[150]	FAIR. Randomization, allocation concealment, blinding techniques not described.	VAS: no significant group differences Days free of headache: no significant group differences Daily duration of headache: no significant group differences Use of paracetamol: no significant group differences	Withdrawals (due to adverse events): 14, group not specified Withdrawals (overall): 25, group not specified Frequent adverse events Tiredness: *A+B=21(17%) vs. C=9(15%) Dry mouth: *A+B=27(22%) vs. C=0 Tolerability (poor): *A+B=12/105 vs. 2/55 *A+B=all patients on active drug
Quimby 1989[40]	FAIR. Randomization and allocation concealment techniques not described	Fatigue: no significant group differences Pain: no significant group differences Patient rated stiffness and aching: favored cyclobenzaprine (p<0.05) Patient rated poor sleep: favored cyclobenzaprine (p<0.05) Patient overall rating: favored cyclobenzaprine (p<0.05)	Cyclobenzaprine vs. placebo Withdrawals (overall): 2/23 vs. 3/22 Withdrawals (adverse events): 1/23 vs. 1/22 Dry mouth: 13/19 vs. 6/18 Lightheadedness, weakness, fatigue: Not reported

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Reynolds 1991[137]	Randomized crossover Canada Single center Inpatient/Outpatient sleep disorders clinic	A: Cyclobenzaprine 10 mg TID B: Placebo 2 week washout, 4 weeks treatment, 2 weeks washout, 4 weeks crossover	Fibromyalgia and no previous cyclobenzaprine	12 9	Female gender: 83% Mean age: 43 Race: not reported Fibromyalgia severity: not reported	Tender point severity count: 16 anatomatic regions rated using 5-point scale (1=absent; 5=severe) Pain: 7-point scale (0-no pain; 6=worse possible pain) Fatigue: unspecified questionnaire which consisted of 7 statements (1=full of energy; 7=totally physically exhausted) Sleepiness: Stanford Sleepiness Rating Scale Sleep measurements: included Total sleep time, Latency Stage 2, Latency REM, Sleep efficiency, Alpha-non-REM, Movements, Stage Changes
Salvini 1986[145]	Randomized Italy Single center	A: Ibuprofen 200 mg TID + dantrolene 25 mg/day B: Ibuprofen 200 mg TID Eight days	Not reported	60 59	Low back pain (LBP) (n=30) Mean age (years): 47.1 Female gender: 53% Race not reported Cervicobrachialgia (CBA) (n=30) Mean age (years): 53.2 Female gender: 37% Race not reported Severity and duration of symptoms not reported.	Active and passive articular mobility: in angular degrees Muscle contracture: 4-point scale (0=absent; 3=severe) Muscle strength: 5-point scale (0=normal; 4=paralysis) Pain on movement: 4-point scale (0=absent; 3=severe without movement) Rest pain: 4-point scale (0=absent; 3=severe and constant) Physician judgment of effect: visual analog scale Patient judgment of effect: visual analog scale Assessments performed at days 0, 4 and 8

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Reynolds 1991	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Tender point severity count: no significant between group differences Pain: no significant between group differences Fatigue: no significant between group differences for am; A=4.4, B=5.1; p<0.05 Sleepiness: no significant between group differences Sleep measurements: no significant between group differences	Withdrawals (overall): 0 vs. 1 (1 withdrew during washout) Withdrawals (adverse events): 0 vs. 1 (excess sleepiness) Overall incidence: not reported Frequent adverse events: not reported
Salvini 1986[145]	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Dantrolene (A) vs. placebo (B) Low back pain patients Muscle contracture (after 4 days): A>B(p=0.04) Muscle strength (after 4 days): A>B(P=0.05) Pain on movement: no significant difference Rest pain: no significant difference Physician judgment of effect: A>B (p<0.01) Patient judgment of effect: A>B (p=0.01) Cervicobrachialgia patients Muscle contracture (after 4 days): A>B(p=0.001) Muscle strength (after 4 days): A>B(P=0.0006) Pain on movement: no significant difference Rest pain: A>B (p=0.01) Physician judgment of effect: A>B (p<0.001) Patient judgment of effect: A>B (p=0.001)	Dantrolene vs. placeboWithdrawals (due to adverse events): 0/30 vs. 1/30 Any adverse event: 1/30 vs. 2/30 Frequent adverse events=epigastric pain, heartburn

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Saper 2002[44]	Randomized United States Multicenter	A: Tizanidine titrated to mean 18 mg/day B: Placebo 4-week washout, 8-12 weeks intervention	Adults 18-65 years with at least 15 days of headaches per month for at least 3 months	200 enrolled initially 136 randomized 134 evaluated	Demographics not provided for each intervention ('did not differ') Female gender: 79% Mean age (years): 40 Race (non-white): 11% Tizanidine vs. placebo Headache type (migraine): 79% vs. 76% Intensity (severe): 23% vs. 18% Frequency (6-7 days/week): 45% vs. 47% Duration of headache (>5 years): 57% vs. 58%	Headache index: Headache days x average intensity x duration Mean headache days/week Severe headache days/week Average headache intensity: 1-5 scale Peak headache intensity: 1-5 scale Mean headache duration: hours/day Pain: 0-100 VAS Functional status: Migraine Disability Assessment (MIDAS) questionnaire Use of rescue analgesics/abortives Assessed at weeks 4, 8, and 12
Sirdalud Ternelin Asia-Pacific Study Group 1998[151]	Randomized Asia-Pacific region Multicenter (16) Type(s) of clinics: Not reported	A: tizanidine, 2 mg BID + diclofenac, 50 mg BID B: placebo + diclofenac, 50 mg BID 7-days	Men and women aged 18 to 70 years with acute pain in the back, neck or shoulder girdle, a clinical impression of m muscle spasms and onset of pain <7 days previously	405 361	Tizanidine + diclofenac vs. placebo + diclofenac Female gender: 49% vs. 54% Meean age (years): 40 vs. 40 Race: 100% asian-pacific Pain location Back: 53% vs. 50% Neck: 18% vs. 26% Shoulder: 29% vs. 24%	Pain: 4-point scale (0=absent; 3=severe) on palpitation, during movement, at night and at rest Severity of muscle spasm: 4-point scale (0=not present; 3=severe) Restriction of body movement: 4-point scale (0=no restriction; 3=marked restriction) Patients' self-assessment of disability due to pain: 5-point scale (0=no disability; 4=complete disability, need to stay in bed) Sleep quality: 4-point scale (0=no sleep disturbance; 3=>8 hours of daytime bed rest necessary) Overall efficacy: assessed by investigators using categorical scale Assessments completed at baseline, after 3 days and after 7 days

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Saper 2002[44]	FAIR. Randomization and allocation concealment techniques not adequately described. High overall withdrawal (85/136 randomized patients completed study)	Tizanidine vs. placebo (mean improvement between baseline and final visit, all p values based on repeated measures ANOVA) Headache index: 1.4 vs. 0.5 (p=0.002) Mean headache days/week: 1.7 vs. 1.2 (p=0.02) Severe headache days per week: 0.6 vs. 0.3 (p=0.02) Average headache intensity: 0.5 vs. 0.3 (p=0.01) Peak headache intensity: 0.7 vs. 0.4 (p=0.002) Mean headache duration: 2.4 vs. 1.2 (p=0.01) Pain (VAS score improvement): 22.4 vs. 8.7 (p=0.007) Functional status (MIDAS score): No differences Use of rescue analgesics/abortive agents: No differences	Tizanidine vs. placebo Withdrawals (overall): 23/71 (32%) vs. 19/63 (30%) Withdrawals (adverse events): 9/71 (13%) vs. 4/63 (6%) Somnolence: 46% vs. 5% Dizziness: 24% vs. 6% Dry mouth: 22% vs. 2% Asthenia: 20% vs. 3%
Sirdalud Ternelin Asia-Pacific Study Group 1998[151]	FAIR. Allocation concealment, eligibility criteria, blinding techniques not described. Randomization conducted using a table of random numbers	Tizanidine + diclofenac (A) vs. placebo + diclofenac (B) Pain(decrease from baseline scores): A>B (p<0.05) for rest, during movement and at night; A>B (p<0.001) on palpitation Severity of muscle spasm(mean values): Day 4: 0.77 vs. 1.20 (p<0.001); Day 8: 0.29 vs. 0.77(p<0.001) Restriction of body movement(mean values): Day 4: 0.72 vs. 0.94 (p<0.001); Day 8: 0.48 vs. 0.93 (p<0.001) Patients' self-assessment of disability due to pain(mean values): Day 4: 0.98 vs. 1.27 (p<0.001); Day 8: 0.61 vs. 0.92 (p<0.001) Sleep quality(mean values): no significant group differences at either Days 4 or 8 Overall efficacy (% good to very good): 72% vs. 58%(p<0.05)	Withdrawals (due to adverse events): 0 Frequent adverse events: GI adverse events: 12% vs. 32% (p<0.001) Central nervous system adverse events: 18% vs. 10% (p<0.05)

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Soyka 1979[127]	Randomized United States Multicenter	A: Soma compound (carisoprodol 200 mg + phenacetin 160 mg + caffeine 32 mg) 2 tabs qid B: Carisoprodol 400 mg qid C: Phenacetin/ Caffeine D: Placebo 6 days	Aged 18-65; suffering from acute, painful musculoskeletal condition of the lumbar and/or cervical region of not more than 7 days' duration; pain of moderate or greater severity	414 336	Soma compound vs. carisoprodol vs. phenacetin + caffeine vs. placebo Median age (years): 35 vs. 36 vs. 36 vs. 36 Female gender: 48% vs. 50% vs. 48% vs. 47% A=43(52%) male vs. 40(48%) Non-white: 13% vs. 9% vs. 6% vs. 8% Musculoskeletal etiology and severity not reported Previous muscle relaxant use not reported	Pain severity: 5-point scale (1=none; 5=very severe) Muscle spasm: 5-point scale (1=none; 5=very severe) Activity impairment: 5-point scale (1=none; 5=complete) Sleep impairment: 4-point scale (1=none; 4=severe) Global improvement: 8-point scale (1=complete improvement with no residual pain or impairment; 5=no change; 8=markedly worse or completely disabled) Assessments completed at days 3 and 6
Steingard 1980[138]	Randomized U.S. Multicenter	A: Cyclobenzaprine 30 mg/day B: Placebo 1-2 weeks	Acute muscle spasm of the neck or low back	121 106	Cyclobenzaprine vs. placebo Mean age (years): 38 vs. 37 Female gender: 26/59 vs. 25/52 Race: Not reported Musculoskeletal strain: 51/59 vs. 45/62 Others: Posttraumatic, idiopathic, cervical root syndrome Prior muscle relaxant use: Not reported	Global evaluation: Unspecified method Muscle spasm: Unspecified method Local pain: Unspecified method Tenderness on palpation: Unspecified method Limitation of motion: Unspecified method Functional status: Unspecified method Total symptom score: Unspecified method Assessed at baseline, and during weeks 1 and 2

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Soyka 1979[127]	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Carisoprodol vs. placebo results only Pain severity (mean improvement): 1.73 vs. 1.27 (p=0.08) Muscle spasm (day 6 mean improvement): 1.82 vs. 1.11 (p=0.015) Activity impairment (day 6 mean improvement): 1.75 vs. 1.18 (p=0.04) Sleep impairment: 1.45 vs. 0.75 (p=0.07) Global improvement (day 6 mean scores): 2.04 vs. 3.16 (0.02) Average symptomatic improvement(mean improvement): 1.69 vs. 1.08 (p=0.048)	Carisoprodol vs. placebo results only Withdrawals due to adverse events: 1/104 vs. 0/104 <u>Frequent adverse events</u> Dizziness: 18% vs. 3% Drowsiness: 8% vs. 1% Nausea: 2% vs. 1% Dry mouth: 0% vs. 0% Description of other adverse events which occurred in 1 % or less of the total patient population in Table XI
Steingard 1980[138]	FAIR. Not clear if randomized. Allocation concealment and blinding techniques not reported.	Cyclobenzaprine vs. placebo Global evaluation (marked improvement): 34% vs. 27% (NS) Global evaluation (marked or moderate improvement): 55% vs. 46% (NS) Muscle spasm (marked or moderate improvement): 62% vs. 60% (NS) Local pain (marked or moderate improvement): 62% vs. 53% (NS) Tenderness on palpation (marked or moderate improvement): 66% vs. 47% (NS) Limitation of motion (marked or moderate improvement): 55% vs. 43% (NS) Limitation of daily activities (marked or moderate improvement): 52% vs. 47% (NS) Total symptom score (improvement): 8.8 vs. 7.2 (NS)	Cyclobenzaprine vs. placebo Drowsiness: 24% vs. 3% Fatigue: 17% vs. 2% Dry mouth: 12% vs. 3% Dizziness: 5% vs. 2% Any adverse event: 54% vs. 23% Withdrawal (adverse event): None reported

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Tisdale 1975[41]	Randomized United States Single center	A: Methocarbamol 2000 mg qid initially, then 1000 to 1500 mg qid B: Placebo 7 to 8 days	Localized spasm due to pain secondary to traumatic or inflammatory causes, for less than 14 days, of at least moderate severity	180 166	Methocarbamol vs. placebo Mean age (years): 39 vs. 36 Female gender: 25% vs. 26% Non-white race: 8% vs. 9% Underlying cause (trauma): 88% vs. 84% Muscle spasm (very severe): 21% vs. 23% Local pain (very severe): 23% vs. 21% Prior muscle relaxant use: Not reported	Local pain, muscle spasm, limitation of motion, interference with daily activities: All rated on 5-point scale (verey severe to none) Assessed at baseline, 48 hours, and at end of study
Valtonen 1975[142]	Randomized Finland Single center	A: Orphenadrine 100 mg bid B: Placebo C: Chlormezanone D: Orphenadrine + acetaminophen (only results of A vs. B abstracted) 7 days	Low back or neck pain with tense, contracted muscles	200 (interventions A or B only) 200	Age, gender, race: Not reported Neck or cervical syndrome: 69% vs. 66% Back syndromes: 26% vs. 28% Ischial syndrome: 5% vs. 6% Prior muscle relaxant use: Not reported	Overall effect: 3 point scale (no effect to good pain relief)

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Tisdale 1975[41]	FAIR. Randomization and allocation concealment techniques not described.	Methocarbamol vs. placebo Muscle spasm at 48 hours (improved): 76% vs. 43% (p<0.005) Local pain at 48 hours (improved): 77% vs. 42% (p<0.005) Muscle spasm at 1 week (improved): 93% vs. 85% (NS) Local pain at 1 week (improved): 94% vs. 85% (p<0.10) Limitation of motion at 1 week (improved): 92% vs. 81% (p<0.05) Daily activities at 1 week (improved): 92% vs. 80% (p<0.05)	Methocarbamol vs. placebo Withdrawals (overall): 6% (5/90) vs. 10% (9/90) Withdrawals (adverse events): 3% (3/90) vs. 0% (0/90) Any adverse event: Not reported Dizziness, nausea: 11% (10/90) vs. 2% (2/90) Other adverse events not reported
Valtonen 1975[142]	FAIR. Blinding may not have been adequate (different frequency of dosing). Allocation concealment technique not described.	Orphenadrine vs. placebo Overall effect (moderate or good): 66% vs. 53% (NS) Overall effect (good): 26% vs. 25%	Orphenadrine vs. placebo Withdrawals: Not reported Any adverse event: Not reported Drowsiness: 5% vs. 4% Vertigo: 4% vs. 4% Dry mouth: 0% vs. 0% Weakness: Not reported Feeling unwell: 4% vs. 2% Rash: 0% vs. 3% Heart pains: 1% vs. 3% Diarrhea: 2% vs. 0%

Appendix A: Search Strategy

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2002>
Search Strategy:
---
1 central muscle relaxant$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (5)
2 (valium or diazepam or clonazepam or clorazepate or carisoprodol).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (3048)
3 (methocarbamol or baclofen or chlorzoxazone or cyclobenzaprine).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (226)
4 (dantrolene or metaxalone or orphenadrine or tizanidine).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (173)
5 (quinine or gabapentin or clonidine).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (2161)
6 1 or 2 or 3 or 4 or 5 (5450)
7 (muscle spasticity or muscle cramp or fibromyalgia or multiple sclerosis).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1969)
8 (headache or backache or back pain or stroke or cerebral palsy or spinal cord injur$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (13564)
9 (traumatic brain injur$ or chronic pain).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (679)
10 7 or 8 or 9 (15904)
11 6 and 10 (373)
12 from 11 keep 1-373 (373)

Database: MEDLINE
Search Strategy:
---
1 central muscle relaxant$.mp. or exp Muscle Relaxants, Central/ (25826)
2 valium.mp. or exp Diazepam/ (14422)
3 clonazepam.mp. or exp CLONAZEPAM/ (2512)
4 clorazepate.mp. (381)
5 carisoprodol.mp. or exp CARISOPRODOL/ (140)
6 methocarbamol.mp. or exp METHOCARBAMOL/ (117)
7 baclofen.mp. or exp BACLOFEN/ (3903)
8 chlorzoxazone.mp. or exp CHLORZOXAZONE/ (371)
9 exp Amitriptyline/ or cyclobenzaprine.mp. (4672)
10 dantrolene.mp. or exp DANTROLENE/ (1765)
11 metaxalone.mp. (8)
12 orphenadrine.mp. or exp ORPHENADRINE/ (412)
13 exp Clonidine/ or tizanidine.mp. (10497)
14 quinine.mp. or exp QUININE/ (5371)
15 gabapentin.mp. (1095)
16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (46894)
17 muscle spasticity.mp. or exp Muscle Spasticity/ (4089)
18 muscle cramp.mp. or exp Muscle Cramp/ (1391)
19 fibromyalgia.mp. or exp FIBROMYALGIA/ (2680)
20 multiple sclerosis.mp. or exp Multiple Sclerosis/ (23901)
21 headache.mp. or exp HEADACHE/ (27045)

Appendix A: Search Strategy (continued)

22 back pain.mp. or exp Back Pain/ (17104)
23 stroke.mp. or exp Cerebrovascular Accident/ (60106)
24 cerebral palsy.mp. or exp Cerebral Palsy/ (8713)
25 spinal cord injury.mp. or exp Spinal Cord Injuries/ (20602)
26 (traumatic brain injur$.mp. or exp brain injuries/) and trauma$.tw. (9604)
27 chronic pain.mp. (6066)
28 exp pain/ and chronic.tw. (14846)
29 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (181222)
30 16 and 29 (1872)
31 limit 30 to (human and english language) (1373)
32 from 31 keep 1-1373 (1373)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2002>
Search Strategy:
---

1 central muscle relaxant$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (5)
2 (valium or diazepam or clonazepam or clorazepate or carisoprodol).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (3048)
3 (methocarbamol or baclofen or chlorzoxazone or cyclobenzaprine).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (226)
4 (dantrolene or metaxalone or orphenadrine or tizanidine).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (173)
5 (quinine or gabapentin or clonidine).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (2161)
6 1 or 2 or 3 or 4 or 5 (5450)
7 (muscle spasticity or muscle cramp or fibromyalgia or multiple sclerosis).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1969)
8 (headache or backache or back pain or stroke or cerebral palsy or spinal cord injur$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (13564)
9 (traumatic brain injur$ or chronic pain).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (679)
10 7 or 8 or 9 (15904)
11 6 and 10 (373)
12 from 11 keep 1-373 (373)

Search Strategy for Skeletal Muscle Relaxants Update #1

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Database: EBM Reviews - Cochrane Central Register of Controlled Trials
<3rd Quarter 2003>
Search Strategy:
--------------------------------------------------------------------------
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1     (central muscle relaxant$ or valium or diazepam or clonezepam or
clorazepate or carisoprodol).mp. [mp=title, original title, abstract,
mesh headings, heading words, keyword] (2994)
2     (methocarbamol or baclofen or chlorzoxazone or cyclobenzaprine or
dantrolene).mp. [mp=title, original title, abstract, mesh headings,
heading words, keyword] (300)
3     (metaxalone or orphenadrine or tizanidine or quinine or
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gabapentin).mp. [mp=title, original title, abstract, mesh headings,
heading words, keyword] (630)
4     1 or 2 or 3 (3867)
5     (muscle spasticity or spastic muscle$ or muscle cramp$ or
fibromyalgia or multiple sclerosis).mp. [mp=title, original title,
abstract, mesh headings, heading words, keyword] (2170)
6     (headache or migraine or backache or back pain or stroke or
cerebral palsy or spinal cord injur$).mp. [mp=title, original title,
abstract, mesh headings, heading words, keyword] (15633)
7     (traumatic brain injur$ or chronic pain or intractable pain).mp.
[mp=title, original title, abstract, mesh headings, heading words,
keyword] (791)
8     5 or 6 or 7 (18218)
9     (chlormezanone or chlorphenesin or mephenesin or meprobamate or
tolperisone or zoxazolamine).mp. [mp=title, original title, abstract,
mesh headings, heading words, keyword] (204)
10     4 or 9 (4045)
11     8 and 10 (327)
12     from 11 keep 1-327 (327)

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Database: MEDLINE <1996 to October Week 2 2003>
Search Strategy:
--------------------------------------------------------------------------
---------
1     central muscle relaxant$.mp. or exp Muscle Relaxants, Central/
(4858)
2     valium.mp. or exp Diazepam/ (2005)
3     clonazepam.mp. or exp CLONAZEPAM/ (709)
4     clorazepate.mp. (41)
5     carisoprodol.mp. or exp CARISOPRODOL/ (27)
6     methocarbamol.mp. or exp METHOCARBAMOL/ (12)
7     baclofen.mp. or exp BACLOFEN/ (1523)
8     chlorzoxazone.mp. or exp CHLORZOXAZONE/ (271)
9     exp Amitriptyline/ or cyclobenzaprine.mp. (692)
10     dantrolene.mp. or exp DANTROLENE/ (503)
11     metaxalone.mp. (1)
12     orphenadrine.mp. or exp ORPHENADRINE/ (69)
13     exp Clonidine/ or tizanidine.mp. (2168)
14     quinine.mp. or exp QUININE/ (1620)
15     gabapentin.mp. (1148)
16     1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or
13 or 14 or 15 (10758)
17     muscle spasticity.mp. or exp Muscle Spasticity/ (1047)
18     muscle cramp.mp. or exp Muscle Cramp/ (276)
19     fibromyalgia.mp. or exp FIBROMYALGIA/ (1615)
20     multiple sclerosis.mp. or exp Multiple Sclerosis/ (9782)
21     headache.mp. or exp HEADACHE/ (11228)
22     back pain.mp. or exp Back Pain/ (7667)
23     stroke.mp. or exp Cerebrovascular Accident/ (32062)
24     cerebral palsy.mp. or exp Cerebral Palsy/ (2849)
25     spinal cord injury.mp. or exp Spinal Cord Injuries/ (7681)
26     (traumatic brain injur$.mp. or exp brain injuries/) and
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trauma$.tw. (4669)
27     chronic pain.mp. (3175)
28     exp pain/ and chronic.tw. (7460)
29     17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
or 28 (81969)
30     16 and 29 (752)
31     limit 30 to (human and english language) (552)
32     31 and 2003$.em. (71)
   33  from 32 keep 1-71 (71)
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Database: EMBASE Drugs & Pharmacology <1991 to 4th Quarter 2003>
Search Strategy:
--------------------------------------------------------------------------
---------
1      central muscle relaxant$.mp. or exp Central Muscle Relaxant/
(6278)
2      valium.mp. or exp Diazepam/ (14941)
3      clonazepam.mp. or exp CLONAZEPAM/ (5506)
4      clorazepate.mp. or exp CLORAZEPATE/ (655)
5      carisoprodol.mp. or exp CARISOPRODOL/ (181)
6      methocarbamol.mp. or exp METHOCARBAMOL/ (171)
7      baclofen.mp. or exp BACLOFEN/ (4157)
8      chlorzoxazone.mp. or exp CHLORZOXAZONE/ (496)
9      cyclobenzaprine.mp. or exp CYCLOBENZAPRINE/ (373)
10      dantrolene.mp. or exp DANTROLENE/ (1710)
11     metaxalone.mp. or exp METAXALONE/ (32)
12     exp ORPHENADRINE/ or orphenadrine.mp. (383)
13     tizanidine.mp. or exp TIZANIDINE/ (517)
14     quinine.mp. or exp QUININE/ (4146)
15     gabapentin.mp. or exp GABAPENTIN/ (3796)
16     1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or
13 or 14 or 15 (32634)
17     muscle spasticity.mp. or exp Spasticity/ (1367)
18     muscle cramp.mp. or exp Muscle Cramp/ (1679)
19     fibromyalgia.mp. or exp FIBROMYALGIA/ (1170)
20     multiple sclerosis.mp. or exp Multiple Sclerosis/ (8486)
21     headache.mp. or exp HEADACHE/ (28478)
22     back pain.mp. or exp Backache/ (4858)
23     stroke.mp. or exp STROKE/ (20425)
24     cerebral palsy.mp. or exp Cerebral Palsy/ (961)
25     spinal cord injury.mp. or exp Spinal Cord Injury/ (3933)
26     (exp brain injury/ and trauma$.mp.) or traumatic brain
injur$.mp. (2111)
27     chronic pain.mp. or exp Chronic Pain/ (4033)
28     17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
(72474)
29     16 and 28 (3358)
30     limit 29 to (human and english language) (2661)
31     30 and 2003$.em. (548)
32     from 31 keep 1-548 (548)
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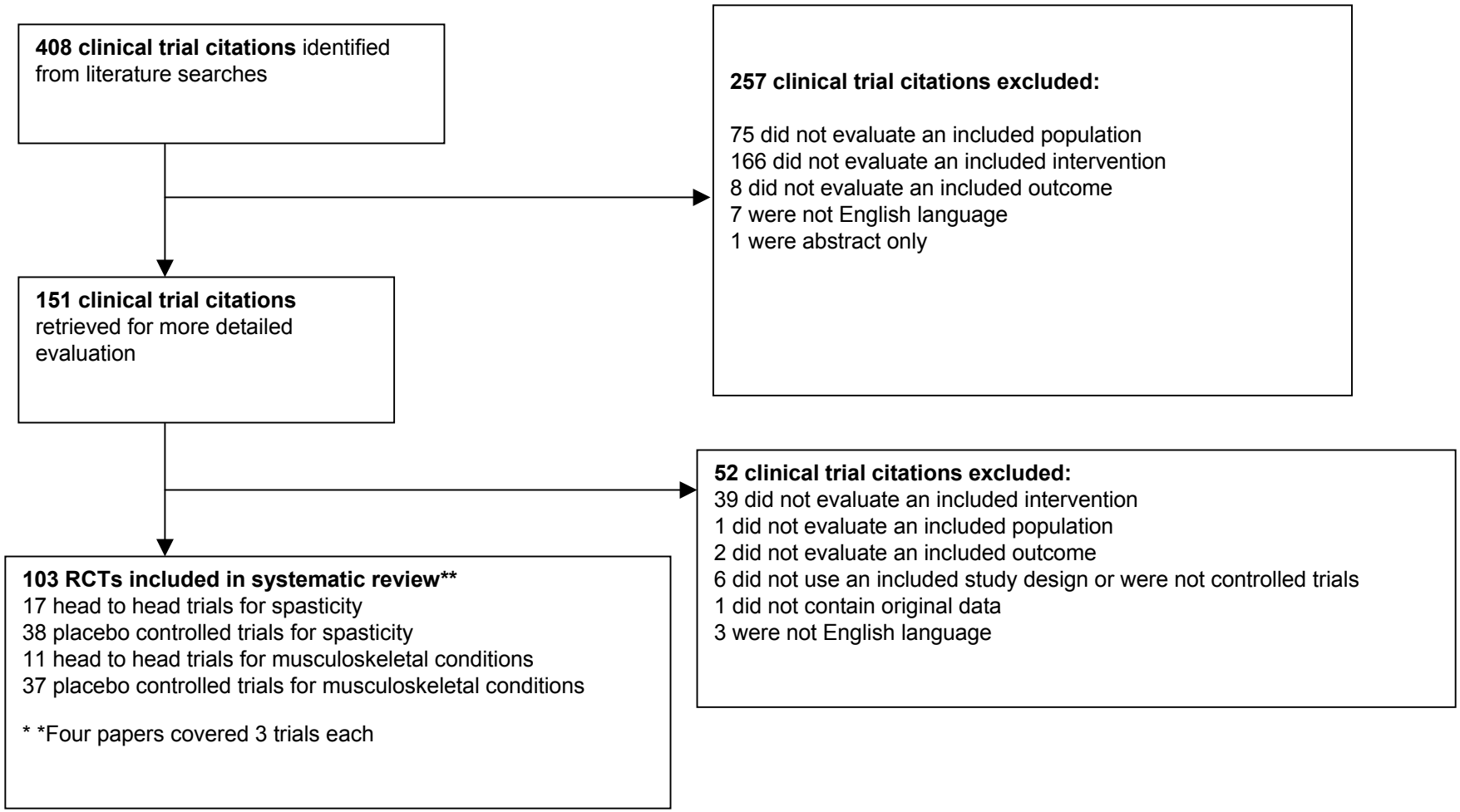
Appendix B. Clinical trials search results



Appendix C: Methods for Drug Class Reviews for Oregon Health Plan Practitioner-Managed Prescription Drug Plan

Oregon Evidence-based Practice Center

December 14, 2001
Updated February 4, 2003

Overview

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, in developing drug class reviews for the Oregon Health Plan Practitioner-Managed Prescription Drug Plan.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well-documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD. To ensure scientific rigor and relevance of the work, the Oregon EPC develops key questions and criteria for admissible evidence, and uses these to create a literature search strategy that best captures the appropriate evidence. To consider papers identified by the searches, the teams use the criteria for admissible evidence (explicit inclusion and exclusion criteria) to select papers that provide information to help answer the key questions. They abstract key data from these selected papers. The teams use established criteria to assess the internal validity of the evidence in each paper, as well as the total internal validity, external validity, and coherence of the evidence for each key question.

Key Questions and Inclusion/Exclusion Criteria

Key questions are essential in focusing the literature review on a manageable and clinically relevant topic. All key questions are reviewed and approved by the topic team in the process of assessing and refining the topic before the detailed literature review. The EPC teams work with the subcommittee members of the Oregon Health Resources Commission assigned to a particular drug class to finalize the key questions for that drug class.

We clearly document the criteria by which the team chooses to admit evidence on a given key question. Such criteria might include, for example, study design (e.g., randomized

controlled trials, cohort studies), setting, sample size, population studied, language(s) of publication, and year(s) of publication.

No generic criteria for admissible evidence have been established. Rather, the criteria are determined on a topic-by-topic and key question-by-key question basis, depending on the questions involved and the amount and quality of evidence available. All inclusion/exclusion criteria are reviewed and approved by the entire topic team.

Databases to Be Searched and Documenting Search Terms

At a minimum, all topics include a review of the English-language literature in MEDLINE and EMBASE bibliographic databases and the Cochrane Controlled Trials Register. Other databases (e.g., nursing or psychology databases) are searched as deemed necessary by the topic team. Evidence reviews document the databases used.

Search terms used for each key question, along with the yield associated with each term, are documented in a table or set of tables; these appear in the final evidence review.

Database of Abstracts

The EPC, for each review, establishes a database of all abstracts (i.e., both those included and those eventually excluded from the final set of full-text articles reviewed). Information captured in the database includes the key question(s) associated with each included abstract and reason for exclusion if the abstract does not meet inclusion criteria.

Abstraction Forms

Although the EPC has no standard or generic abstraction form, the following broad categories are always abstracted from included articles: study design, study participant description, quality information, and outcomes. Each team uses these (and, if indicated, other) general categories to develop an abstraction form specific to the topic at hand.

Double Abstraction of Included Articles

The EPC teams abstract only those articles that, after review of the entire article, meet criteria for both quality and focus on the key question at hand. Key articles are always read and checked by more than one team member. All reviewers are trained in the topic, the analytic framework and key questions, and the use of the abstraction instrument. Initial reliability checks are done for quality control.

Quality Criteria

Assessment of Internal Validity
To assess the internal validity of individual studies, the EPC adopted criteria for assessing the internal validity of individual studies from the US Preventive Services Task Force and the NHS Centre for Reviews and Dissemination.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alternation, case record numbers, birth dates or week days
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
        - On-site computer based system with a randomization sequence that is not readable until allocation
        - Other approaches sequence to clinicians and patients
    - Inferior approaches to concealment of randomization:
        - Use of alternation, case record numbers, birth dates or week days
        - Open random numbers lists
        - Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
    - Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of followup? (Give numbers at each stage of attrition.)

For Reports of Complications/Adverse Effects

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?

2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there non-biased and accurate ascertainment of events (independent ascertainer; validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

5. What was the funding source and role of funder in the study?

Economic Studies

Assessment of Internal Validity

Framing

1. Was a well-defined question posed in answerable form?

2. Was a comprehensive description of the competing alternatives given?

3. Are the interventions and populations compared appropriate?

4. Is the study conducted from the societal perspective?

5. Is the time horizon clinically appropriate and relevant to the study question?

Effects

1. Are all important drivers of effectiveness included?

2. Are key harms included?

3. Is the best available evidence used to estimate effectiveness?

4. Are long-term outcomes used?

5. Do effect measures capture preferences or utilities?

Costs

1. Are costs and outcomes measured accurately?
2. Are costs and outcomes valued credibly?
3. Are costs and outcomes adjusted for differential timing?
4. Are all appropriate downstream medical costs included?
5. Are charges converted to costs appropriately?
6. Are the best available data used to estimate costs? (like first question)
7. Are all important and relevant costs and outcomes for each alternative identified?

Results

1. Are incremental cost-effectiveness ratios presented?
2. Are appropriate sensitivity analyses performed?
3. How far do study results include all issues of concern to users?

Assessment of External Validity

1. Are the results generalizable to the setting of interest in the review?

Systematic Reviews:

1. Is the systematic review recent and relevant?
2. Is the review comprehensive in considering sources and in searching databases to find all relevant research?
3. Are inclusion/exclusion criteria reported relating to the primary studies that address the review question? If so, are they explicit and relevant?
4. Are the primary studies summarized appropriately?
5. Is sufficient detail of the primary studies presented?
6. Is there standard appraisal of the primary studies?
7. Is the validity of primary studies adequately assessed?

Appendix D. Quality abstraction tool for adverse events of muscle relaxants

Author	Study ____
Year published	
Citation	
Setting (country, single or multicenter, specialty or primary care clinic)	
Type of study (RCT, crossover, population-based, retrospective cohort, prospective cohort)	
INTERNAL VALIDITY	
Selection: 1: Study states "all patients" or "consecutive series" during specified time period (observational study) or describes and accounts for all patients deemed eligible (clinical trial) and has explicit inclusion and exclusion criteria applied to all eligible patients (all study types) 0: Selection not clear, biased selection, inclusion and exclusion criteria not specified, or unable to determine proportion of patients eligible for trial who withdrew or were not entered	
Loss to follow-up: 1: Low overall and differential loss to follow-up (<15% of study population or <25% difference between groups), able to compute adverse effects according to intention-to-treat if low loss to follow-up 0: High overall or differential loss to follow-up (>15% overall or >25% difference between groups), or unable to calculate intention-to-treat if low loss to follow-up	
Adverse events pre-specified and pre-defined: 1: Study reports definitions used for assessed adverse events in an explicit, reproducible fashion 0: Study does not meet above criteria	
Ascertainment techniques adequately described: 1: Study reports methods used to ascertain complications, including who ascertained, timing, and methods used 0: Study does not meet above criteria	
Non-biased and accurate ascertainment of adverse events: 1: Patients and assessors blinded to intervention and ascertainment techniques go beyond patient self-report alone 0: Study does not meet above criteria	
Statistical analysis of potential confounders: 1: Study examines more than 2 relevant confounders/risk factors using standard acceptable statistical techniques 0: Study does not meet above criteria	
Adequate duration of follow-up:	

Appendix D. Quality abstraction tool for adverse events of muscle relaxants

Author	Study ____
Year published	
Citation	
Setting (country, single or multicenter, specialty or primary care clinic)	
Type of study (RCT, crossover, population-based, retrospective cohort, prospective cohort)	
INTERNAL VALIDITY	
Selection: 1: Study states "all patients" or "consecutive series" during specified time period (observational study) or describes and accounts for all patients deemed eligible (clinical trial) and has explicit inclusion and exclusion criteria applied to all eligible patients (all study types) 0: Selection not clear, biased selection, inclusion and exclusion criteria not specified, or unable to determine proportion of patients eligible for trial who withdrew or were not entered	
Loss to follow-up: 1: Low overall and differential loss to follow-up (<15% of study population or <25% difference between groups), able to compute adverse effects according to intention-to-treat if low loss to follow-up 0: High overall or differential loss to follow-up (>15% overall or >25% difference between groups), or unable to calculate intention-to-treat if low loss to follow-up	
Adverse events pre-specified and pre-defined: 1: Study reports definitions used for assessed adverse events in an explicit, reproducible fashion 0: Study does not meet above criteria	
Ascertainment techniques adequately described: 1: Study reports methods used to ascertain complications, including who ascertained, timing, and methods used 0: Study does not meet above criteria	
Non-biased and accurate ascertainment of adverse events: 1: Patients and assessors blinded to intervention and ascertainment techniques go beyond patient self-report alone 0: Study does not meet above criteria	
Statistical analysis of potential confounders: 1: Study examines more than 2 relevant confounders/risk factors using standard acceptable statistical techniques 0: Study does not meet above criteria	
Adequate duration of follow-up:	

Appendix D. Quality abstraction tool for adverse events of muscle relaxants (continued)

EXTERNAL VALIDITY	
Adequate description of study population: 1: Study reports 2 or more demographic characteristics and both basic clinical characteristics of pain syndrome and average duration of pain 0: Study does not meet above criteria	
Does study report numbers screened and eligible (trial) or inception cohort (observational study)?	
Are exclusion criteria specified and numbers excluded for each criteria reported?	
Who is the funding source?	
Are authors employed by the funding source?	
Are data held by the funding source?	
Are patients in the study on opioids prior to study entry?	