Review Article

Comparative Efficacy and Safety of Skeletal Muscle Relaxants for Spasticity and Musculoskeletal Conditions: A Systematic Review

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Abstract
Skeletal muscle relaxants are a heterogeneous group of medications 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 widely used for these indications, there appear to be gaps in our understanding of the comparative efficacy and safety of different skeletal muscle relaxants. This systematic review summarizes and assesses the evidence for the comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions. Randomized trials (for comparative efficacy and adverse events) and observational studies (for adverse events only) that included oral medications classified as skeletal muscle relaxants by the FDA were sought using electronic databases, reference lists, and pharmaceutical company submissions. Searches were performed through January 2003. The validity of each included study was assessed using a data abstraction form and predefined criteria. An overall grade was allocated for the body of evidence for each key question. A total of 101 randomized trials were included in this review. No randomized trial was rated good quality, and there was little evidence of rigorous adverse event assessment in included trials or observational studies. There is fair evidence that baclofen, tizanidine, and dantrolene are effective compared to placebo in patients with spasticity (primarily multiple sclerosis). There is fair evidence that baclofen and tizanidine are roughly equivalent for efficacy in patients with spasticity, but insufficient evidence to determine the efficacy of dantrolene compared to baclofen or tizanidine. There is fair evidence that although the overall rate of adverse effects between tizanidine and baclofen is similar, tizanidine is associated with more dry mouth and baclofen with more weakness. There is fair evidence that cyclobenzaprine, carisoprodol, orphenadrine, and tizanidine are effective compared to placebo in patients with

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musculoskeletal conditions (primarily acute back or neck pain). Cyclobenzaprine has been evaluated in the most clinical trials and has consistently been found to be effective. There is very limited or inconsistent data regarding the effectiveness of metaxalone, methocarbamol, chlorzoxazone, baclofen, or dantrolene compared to placebo in patients with musculoskeletal conditions. There is insufficient evidence to determine the relative efficacy or safety of cyclobenzaprine, carisoprodol, orphenadrine, tizanidine, metaxalone, methocarbamol, and chlorzoxazone. Dantrolene, and to a lesser degree chlorzoxazone, have been associated with rare serious hepatotoxicity. J Pain Symptom Manage 2004;28:140–175. *© 2004 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words
Muscle relaxants, central, muscle spasticity, meta-analysis, musculoskeletal diseases

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.

Spasticity from the upper motor neuron syndrome (a complex of signs and symptoms that can be associated with exaggerated reflexes, autonomic hyperreflexia, dystonia, contractures, paresis, lack of dexterity, and fatigability, in addition to spasticity) can result from a variety of conditions affecting the cortex or spinal cord.[1] Some of the more common conditions associated with spasticity include multiple sclerosis,[2] spinal cord injury,[3] traumatic brain injury, cerebral palsy, and post-stroke syndrome.[4] In many patients with these conditions, spasticity can be disabling and painful, with a marked effect on functional ability and quality of life.[5]

Common musculoskeletal conditions causing tenderness and muscle spasms include fibromyalgia,[6] tension headaches,[7] 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 affected muscle groups. 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 frequently used to treat these conditions.[8–10]

Drugs classified as skeletal muscle relaxants include baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, dantrolene, metaxalone, methocarbamol, orphenadrine, and tizanidine. Only baclofen, dantrolene, and tizanidine are approved for the treatment of spasticity. These three medications act by different mechanisms: baclofen blocks pre- and post-synaptic $GABA_B$ receptors,[11,12] tizanidine is a centrally-acting agonist of α2 receptors,[13,14] and dantrolene directly inhibits muscle contraction by decreasing the release of calcium from skeletal muscle sarcoplasmic reticulum.[15] Other medications used to treat spasticity but not formally approved for this indication include benzodiazepines, clonidine, gabapentin, and botulinum toxin.[15–17]

The skeletal muscle relaxants carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, and orphenadrine have been approved for the treatment of musculoskeletal disorders. Cyclobenzaprine is closely related to the tricyclic antidepressants,[18] carisoprodol is metabolized to meprobamate,[19] methocarbamol is structurally related to mephenesin,[18] chlorzoxazone is a benzoxazolone derivative,[20] and orphenadrine is derived from diphenhydramine.[21] 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.[10] Although there is some overlap between clinical usage (tizanidine in particular has been studied in patients with musculoskeletal conditions),[22] in clinical practice each skeletal muscle relaxant is used primarily for either spasticity or for musculoskeletal conditions.

There is little data regarding the comparative efficacy and safety of different skeletal muscle relaxants. 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 consultation with a multidisciplinary committee of experts, we selected the following key questions to guide the review:

What is the comparative efficacy of different muscle relaxants?
What is the comparative safety of different muscle relaxants?
Are there subpopulations of patients for which one muscle relaxant is more effective or associated with fewer adverse effects?

Methods

Literature Search

To identify articles relevant to each key question, we searched (in this order): the Evidence-Based Medicine Library (2003, Issue 1) (from the Cochrane Collaboration), MEDLINE (1966–January 2003), EMBASE (1980–January 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 on the Web site for complete search strategy). In addition, the State of Oregon created and disseminated a protocol to pharmaceutical manufacturers for submitting data. All citations were imported into an electronic database (EndNote 6.0).

Study Selection

All English-language titles and abstracts and suggested additional citations that met the following eligibility criteria were included:

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 excluded obstetric and dialysis patients, and patients with restless legs syndrome or nocturnal myoclonus. Senate Bill 819 specifically excludes patients with HIV and patients with cancer.

Drugs. We included the following oral drugs classified as skeletal muscle relaxants: baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, dantrolene, metaxalone, methocarbamol, orphenadrine, and tizanidine. Other medications used for spasticity but considered to be in another drug class, such as benzodiazepines, quinine, tricyclic antidepressants, gabapentin, and clonidine, were not considered primary drugs in this report, but were reviewed when they were directly compared to an included skeletal muscle relaxant. We excluded trials[20,23–27] in which an included skeletal muscle relaxant was combined with an analgesic medication unless the comparison arm included the same analgesic medication and dose, trials[28] which evaluated skeletal muscle relaxants not approved in the United States, and trials[29] which only compared one dose of an included skeletal muscle relaxant with another dose.

Outcomes. The main efficacy measures were relief of muscle spasms or pain, functional status, quality of life, withdrawal rates, and adverse effects (including sedation, weakness, 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. Spasticity is an especially difficult outcome to measure objectively. The most widely used standardized scales to measure spasticity are the Ashworth[30] and modified Ashworth[31] 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. 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. Many of these scales have not been validated.

Muscle strength is usually assessed with the British Medical Research Council (BMRC) scale, which is based on the observation of resistance provided by voluntary muscle activity.[14] An assessor grades each muscle or muscle group independently on a scale of 0 (no observed muscle activation) to 5 (full strength).

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. 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). 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. 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). Disease-specific scales are also available for other musculoskeletal and spastic conditions.[33,34] Scales that are not disease-specific include the Medical Outcomes Study Short Form-36 (SF-36), Short Form-12 (SF-12), and other multi-question assessments. 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.

We focused on the following common adverse events: somnolence or fatigue, dizziness, dry mouth, and weakness. We also paid special attention to reports of serious hepatic injury, abuse, and addiction.[35] 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 included information on hospitalizations and deaths when available.

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), which may indicate an intolerable adverse event.

Study Types. We included the following study types:

Systematic reviews of the clinical efficacy or adverse event rates of skeletal muscle relaxants for spasticity or musculoskeletal conditions, OR

Randomized controlled trials that compared one of the included skeletal muscle relaxants listed to another included skeletal muscle relaxant, an antispasticity medication from a different drug class, or placebo in adult patients with spasticity or musculoskeletal conditions, OR

Randomized controlled trials and large, high quality observational studies that reported adverse event rates for an included skeletal muscle relaxant.

We did not systematically review case reports and case series in which the proportion of patients suffering an adverse event could not be calculated. We excluded "single-dose" studies, abstracts and unpublished trials unless a pharmaceutical company submitted the full data.

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 crossover trials, 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.[36] A second reviewer checked all data.

Quality Assessment

We assessed the quality of included trials using predefined criteria (detailed methods available on the Web[37] or from the authors). Randomized, properly blinded clinical trials are considered the highest level of evidence for assessing efficacy.[38–40] Clinical trials that are not randomized or blinded or that have other methodologic flaws are less reliable. These are discussed in our report with references to specific flaws in study design and data analysis.

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 the 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).[39,40] 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 was 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.

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.[41] 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.

A particular randomized trial might receive two different ratings: one for efficacy and one for adverse events. Appendix D on the Web site 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. 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

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 on the Web site 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 in the English language.

Ninety-eight reports presenting data for 101 randomized controlled trials of patients with spasticity (55 trials reported in 54 publications) or musculoskeletal conditions (46 trials reported in 44 publications) provided usable data and were included. We also identified four relevant systematic reviews[41–44] and three relevant meta-analyses (not systematic).[45–47] In all 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 often not stated. When exclusion criteria were reported, numbers of patients excluded for each criterion were not reported.

Comparative Efficacy: Spasticity

Systematic Reviews and Meta-Analyses. Three systematic reviews evaluated skeletal muscle relaxants used to treat patients with spasticity (Table 1). One was a good-quality systematic review[41] of 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 (five trials of baclofen, four dantrolene, and three tizanidine) of included skeletal muscle relaxants. 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). Four other trials compared baclofen, dantrolene, or tizanidine to diazepam. No evaluated trial was rated good quality, and many trials used unvalidated measures of spasticity or muscle strength and inconsistent reporting methods. The authors found no pattern to suggest that one included skeletal muscle relaxant was any better than the others. Meta-analysis 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.[44] 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. There were no head-to-head trials, and no study was rated good quality. There was insufficient evidence to judge the comparative efficacy of tizanidine versus baclofen.

One systematic review[43] evaluated 20 studies of tizanidine versus baclofen (14 studies) or diazepam (6 studies) in patients with spasticity. This systematic review included both published and unpublished trials and was rated poor quality (see Table 1). 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.[45,46] Authors of these trials were employed by Athena Neurosciences (San Francisco, CA), a pharmaceutical

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[42]	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[41]	Assess the comparative effectiveness and tolerability of anti-spasticity agents in multiple sclerosis patients.	Tizanidine Baclofen Dantrolene Diazepam[a]	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.
Taricco 2000[44]	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[43]	Assess the comparative efficacy of tizanidine compared to other anti-spastic agents.	Tizanidine Baclofen Diazepam[a]	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, insufficient 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, muscle 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.

(*continued*)

Table 1
Continued

Author/Year	Purpose of Study	Skeletal Muscle Relaxants Evaluated	Number of Included Studies and Patients	Quality	Main Findings
Meta-analyses					
Groves 1998[46]	Assess the efficacy and tolerability of tizanidine using unpublished trials held by the manufacturer.	Tizanidine Baclofen Diazepam[a]	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[45]	Assess the efficacy and tolerability of tizanidine using unpublished trials held by the manufacturer.	Tizanidine Baclofen Diazepam[a]	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[47]	Assess the efficacy of cyclobenzaprine using unpublished trials.	Cyclobenzaprine Diazepam[a] 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.

[a]Comparator

company marketing tizanidine in the U.S., and analyzed the same trials (ten trials in one meta-analysis[46] and eleven in the other[45]). Both studies found no significant differences between tizanidine compared to diazepam orbaclofen for outcomes of tone (Ashworth scale) or muscle strength (summed BMRC strength scores).

Head-to-Head Trials. Of 55 trials evaluating included skeletal muscle relaxants in patients with spasticity, 17 (total enrolled = 654) were head-to-head trials of two skeletal muscle relaxants or a skeletal muscle relaxant versus another medication used to treat spasticity (Table 2). The majority (10) of the trials focused on patients with multiple sclerosis, but other clinical conditions (children with cerebral palsy,[48] post-stroke or head trauma,[49] spinal cord injury,[50] and spasticity from various causes[51–54]) were also evaluated. Except for one study lasting one year,[51] all of the head-to-head trials were of relatively short duration, ranging from 2 to 8 weeks per intervention. All of the trials except one[50] were published before 1990. Although elderly patients were included in most trials, no trial specifically evaluated only elderly patients. One trial included only children.[48]

None of the 17 head-to-head trials 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 comparing baclofen to clonidine that found no differences for spasticity was rated poor quality because it was not randomized and did not perform blinding, and was excluded from the tables.[55] The remainder were rated fair quality. 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.

In eight trials of tizanidine vs. baclofen, the average dose of tizanidine ranged from 11 mg/day[53] to 24 mg/day[56–58] and the dose of baclofen ranged from 15 mg/day[57] to 90 mg/day.[58] Most of these trials evaluated patients with multiple sclerosis. In each of these eight trials, tizanidine and baclofen appeared to have roughly equivalent efficacy (Table 2). 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[36,51,53,56,57,59] 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 compared to baseline. The longest trial (52 weeks compared to 8 weeks or less for the other trials) reported results similar to shorter trials.[51] The overall withdrawal rate was higher with baclofen than with tizanidine in three out of seven trials[51,57,60] 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,[51,60] withdrawals due to adverse events accounted for most of the observed differences in overall withdrawal rates (see section on adverse events).

There were no trials directly comparing dantrolene to baclofen or tizanidine. In the eight trials[48,49,52–54,61–63] 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). Differences in study design, patient populations, outcomes evaluated, and roughly 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.

Placebo-Controlled Trials. In addition to one head-to-head trial[54] that also included a placebo arm, we identified an additional 38 additional

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[60] 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[58] 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[57] 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[51] 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[59] 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)
Tizanidine mean 11 mg/day Baclofen mean 51 mg/day	Rinne 1980 (2)[53] 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[56] 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

(*continued*)

Table 2
Continued

Interventions/Dose	Study/Year/Quality	Population/Number Enrolled	Main Outcomes Assessed	Main Results	Withdrawals (overall)
Tizanidine mean 23 mg/day Baclofen mean 59 mg/day	Stien 1987[36] 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[49] 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)[53] Fair	Multiple sclerosis 30	Spasticity: Ashworth scale	No significant differences between interventions (Ashworth scale scores not reported).	0% (0/15) 27% (4/15)
Baclofen 30 mg/day and 60 mg/day Diazepam 15 mg/day and 30 mg/day	Cartlidge 1974[63] 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[61] 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[52] 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[54] 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[48] 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[62] 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[4] Fair	Various spasticity 15	Favors baclofen based on "EMG and force recordings" (P not reported).
Baclofen	Basmajian 1975[65] Fair	Various spasticity 14	Favors baclofen using unspecified method (P not reported).
Baclofen	Brar 1991[66] Fair	Multiple sclerosis 38	Favors baclofen using Ashworth scale (P not reported).
Baclofen	Duncan 1976[67] Poor	M.S. or spinal cord lesions 25	Baclofen superior using 5-point scale ($P < 0.01$).
Baclofen	Feldman 1978[68] Fair	Multiple sclerosis 33	Baclofen superior using unspecified method (P not reported).
Baclofen	Hinderer 1990[69] Poor	Spinal cord lesions 5	No improvement on baclofen using unspecified method.
Baclofen	Hulme 1985[70] Fair	Post-stroke (elderly patients) 12	Not assessed; study stopped due to excess adverse events (somnolence).
Baclofen	Jones 1970[71] Fair	Spinal cord injury 6	Favors baclofen using 5-point scale for spasm and spasm counts (P not reported).
Baclofen	McKinlay 1980[72] Fair	Children with spasticity (criteria not specified) 20	No significant difference using Ashworth scale.
Baclofen	Medaer 1991[73] Fair	Post-stroke 20	Baclofen superior using Ashworth scale ($P < 0.001$).
Baclofen	Milla 1977[74] Fair	Various spasticity (children) 20	Baclofen superior using Ashworth scale ($P < 0.001$).
Baclofen	Orsnes 2000[75] Fair	Multiple sclerosis 14	No significant difference using Ashworth scale.
Baclofen	Sachais 1977[76] Fair	Multiple sclerosis 166	Baclofen superior using unspecified method ($P < 0.01$).
Baclofen	Sawa 1979[77] Fair	Multiple sclerosis 21	Baclofen superior using 6-point scale ($P < 0.001$).
Dantrolene	Basmajian 1973[78] Poor	Upper motor neuron disease 25	Spasticity not assessed.
Dantrolene	Chyatte 1973[79] Fair	Athetoid cerebral palsy (children) 18	No measurable difference using 4-point scale.
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.

(*continued*)

Table 3
Continued

Medication	Trial/Quality	Population/Number Enrolled	Main Outcomes for Spasticity/Tone
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 21	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.
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.

placebo-controlled trials (Table 3). Fourteen evaluated baclofen,[64–77] 15 dantrolene,[78–92] six tizanidine,[55,93–97] one chlorzoxazone,[98] one methocarbamol,[99] and one cyclobenzaprine.[100] 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[72,74,79,80,83,84,89,98,99] and one specifically evaluated elderly post-stroke patients.[70] We identified no placebo-controlled trials of carisoprodol, metaxalone, or orphenadrine in patients with spasticity.

None of the placebo-controlled trials was rated good quality (Evidence Table 4). Main results from placebo-controlled trials for spasticity are summarized in Table 3. 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 relative magnitude of benefit for each of these medications could not be compared across studies. There was inadequate evidence from one trial[98] of chlorzoxazone (rated poor quality), one trial[100] of cyclobenzaprine (no significant differences), and one trial[99] 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 comparative efficacy can be drawn from these placebo-controlled trials.

Comparative Efficacy: Musculoskeletal Conditions

Systematic Reviews and Meta-Analyses. We identified no systematic reviews comparing different skeletal muscle relaxants in patients with musculoskeletal conditions.

One good-quality systematic review evaluated the efficacy of cyclobenzaprine versus placebo for treatment of back pain (Table 1 and Evidence Table 2).[42] This systematic review examined 14 trials of fair overall quality 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). 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 was specifically excluded from analysis in this systematic review.

One fair-quality meta-analysis evaluated the comparative efficacy of cyclobenzaprine, diazepam and placebo.[47] 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 study found that the unvalidated outcome measure 'global response' was equivalent for cyclobenzaprine and diazepam (66% marked or moderate improvement) and significantly better than placebo (40%).

Head-to-Head Trials. Of 46 trials of included skeletal muscle relaxants in patients with musculoskeletal conditions, 11 (total enrolled = 724) were head-to-head trials (Table 4). All of the head-to-head trials focused on patients with back or neck pain and spasms. One trial[101] focused on patients with chronic symptoms and the remainder evaluated patients with acute symptoms. The duration of all head-to-head trials ranged from seven[18] to 18[102] days. All of the trials were published before 1985. Although elderly patients were included in most trials, no trial specifically evaluated only elderly patients and none included children.

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

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 Chlorzoxazone 500 mg tid	Bragstad 1979[103] Fair	Back spasms 120	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) 8% (1/13)
Cyclobenzaprine versus Methocarbamol					
Cyclobenzaprine 10 mg tid Methocarbamol 1500 mg qid	Preston 1984[18] Fair	Localized acute muscle spasm 227	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) 13% (12/94)
Cyclobenzaprine versus Carisprodol					
Cyclobenzaprine 10 mg qid Carisoprodol 350 mg qid	Rollings 1983[104] Fair	Back spasms 78	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 Muscle tension: VRS and VAS	No significant differences between interventions.	24% (9/37) 28% (11/39)
Carisoprodol, Cyclobenzaprine or Tizandine versus Diazepam					
Carisoprodol 350 mg qid Diazepam 5 mg qid	Boyles 1983[105] Fair	Acute back sprain or strain with spasms 80	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 diazepam 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) 12% (5/40)
Cyclobenzaprine 10–20 mg tid Diazepam 5–10 mg tid	Aiken 1978a[107] 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)

(*continued*)

Table 4
Continued

Interventions/Dose	Study/Year	Population/ Number Enrolled	Main Outcomes Assessed	Main Results	Overall Withdrawals
Cyclobenzaprine 10–20 mg tid	Basmajian 1978[102]	Back or neck spasms	Muscle spasm: 5-point scale	No significant differences between interventions.	Not reported
Diazepam 5 mg tid	Poor	120			
Cyclobenzaprine 10 mg tid	Brown 1978[101]	Back or neck spasms	Global evaluation: 5-point scale	No significant differences between interventions.	None reported
Diazepam 5 mg tid	Fair	49			
Cyclobenzaprine 30–40 mg tid	Scheiner 1978 (1)[106]	Acute back or neck spasms	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)
Diazepam 15–20 mg/day	Fair	96			9% (3/32)
Cyclobenzaprine 30–40 mg tid	Scheiner 1978 (2)[106]	Acute back or neck spasms	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)
Diazepam 15–20 mg/day	Fair	75			21% (5/24)
Tizanidine 4–8 mg tid	Fryda-Kaurimsky 1981[108]	Degenerative spinal disease with acute muscle spasm (inpatients)	Pain: 4-point scale Tenderness: 4-point scale Muscle spasm: 3-point scale	No significant differences between interventions.	None reported
Diazepam 5–10 mg tid	Fair	20	Abnormal posture: 3-point scale Daily activities: 4-point scale		
Tizanidine 4 mg tid	Hennies 1981[109]	Back or neck spasms	Pain: 4-point scale Muscle tension: Unspecified method	No significant differences between interventions.	7% (1/15)
Diazepam 5 mg tid	Fair	30	Daily living activity: Unspecified method		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[121] 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[122] 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[123] 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[124] 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[125] 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[126] 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[102] 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[127] Fair	Various acute muscle spasm 175	No significant differences for pain, muscle spasm, or functional measurements using unspecified methods.
Cyclobenzaprine	Bennett 1988[114] 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[128] 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 (+naprosyn in both arms)	Borenstein 1990[110] 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[101] 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[115] 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[117] Poor	Chronic tension headache 20	Favors cyclobenzaprine using 3-point scale (P not reported).
Cyclobenzaprine	Preston 1984[18] 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[130] 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.

(*continued*)

Table 5
Continued

Medication	Trials	Population/Number Enrolled	Main Outcomes (Included Skeletal Muscle Relaxant versus Placebo)
Cyclobenzaprine	Reynolds 1991[113] 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)[106] 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)[106] 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[131] Fair	Back or neck spasm 121	No significant differences for global evaluation, pain, muscle spasm, or functional measurements using unspecified methods.
Metaxalone	Dent 1975[133] 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[135] 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)[134] 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)[134] 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[18] 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 1975[141] 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[21] 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[120] 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[111] Fair	Various musculoskeletal conditions 32	Favors orphenadrine for pain, stiffness and function using 4-point scales (P not reported).
Orphenadrine	Valtonen 1975[132] Fair	Low back or neck pain 200	No significant difference using 3-point scale for 'overall effect'.
Baclofen	Dapas 1985[140] Fair	Acute back syndrome 200	Baclofen superior for lumbar pain, tenderness, spasm, functional assessments using unspecifie methods ($P < 0.05$).
Dantrolene	Casale 1988[142] 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 ($P < 0.001$).
Dantrolene (+ ibuprofen in both arms)	Salvini 1986[12] Fair	Neck or low back syndromes 60	Dantrolene 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[137] 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.

(*continued*)

Table 5
Continued

Medication	Trials	Population/Number Enrolled	Main Outcomes (Included Skeletal Muscle Relaxant versus Placebo)
Tizanidine	Berry 1988b[136] 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[116] 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[138] 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[118] 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[119] 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 analogue scale, no difference for functional status using Migraine Disability Assessment questionnaire.
Tizanidine	Sirdalud Ternelin Asia-Pacific Study Group 1988[139] 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.

did not account for the other patients.[102] A variety of methods was 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 varied between trials.

There was no clear evidence from head-to-head trials that one skeletal muscle relaxant was superior to any other. Three trials evaluated one included skeletal muscle relaxant versus another, but each evaluated a different comparison. In a trial comparing tizanidine and chlorzoxazone in patients with back pain,[103] 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.[18] In a trial of cyclobenzaprine versus carisoprodol in patients with acute back pain and spasms,[104] there were no significant differences for pain, muscle stiffness, activity impairment, sleep impairment, tension, or relief scores compared to baseline.

Eight other head-to-head trials compared an included skeletal muscle relaxant to diazepam. Of these, the trial that appeared to be of best quality compared carisoprodol and diazepam.[105] This trial was still rated fair quality because the authors did not describe allocation concealment techniques and used unvalidated methods for assessing outcomes. Carisoprodol was significantly superior to diazepam for stiffness, tension, and relief, with average differences about 0.5 on a 1–5 scale.[105] No significant differences were seen for pain, activity impairment, or sleep impairment.

Of five trials[101,102,106,107] comparing cyclobenzaprine to diazepam, two[106,107] found significant differences (using unvalidated measures) for most measurements of pain, muscle spasm,

functional status, and 'global evaluations' that favored cyclobenzaprine. One other trial[106] reported decreased tenderness, decreased limitation of motion and better 'global evaluation' for cyclobenzaprine versus diazepam, but not for other measures (muscle spasm, pain, functional ability). All three of these trials had some support from a manufacturer (Merck Sharp & Dohme, West Point, Pennsylvania, USA) 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 1 than at the end of Week 2. Two other trials comparing cyclobenzaprine to diazepam[101,102] and two trials[108,109] comparing tizanidine to diazepam found no significant differences for any clinical outcomes including pain, stiffness, or functional ability.

The trial[101] focusing on patients with chronic back or neck symptoms reported results similar to the other trials. The overall withdrawal rates in all head-to-head trials ranged from 0% to 35%. In one trial,[106] the overall withdrawal rate appeared significantly higher on cyclobenzaprine (12/34 [35%]) compared to diazepam (3/32 [9%]), but there was no significant difference in the withdrawal rate between interventions in other trials.

We identified no head-to-head trials of orphenadrine, metaxalone, dantrolene, or baclofen in patients with musculoskeletal conditions.

Placebo-Controlled Trials. In addition to six head-to-head trials (from five publications)[18,101,102,106,107] with a placebo arm, we identified an additional 35 placebo-controlled trials (Table 5). Three trials evaluated a skeletal muscle relaxant with an equivalent analgesic in each arm.[110–112] Most trials evaluated low back or neck syndromes alone or mixed with other musculoskeletal conditions. Other conditions evaluated were fibromyalgia,[113–115] tension headaches or mixed headache conditions,[116–119] and nocturnal leg cramps.[120] No trial included children.

In general, placebo-controlled trials were not helpful in assessing comparative efficacy. None of the placebo-controlled trials involving patients with musculoskeletal conditions was rated good quality (Table 5 and Evidence Table 6). The comparative efficacy of each skeletal muscle relaxant was also difficult to assess because of marked heterogeneity in study design, interventions, populations studied, and outcomes assessed.

Carisoprodol (four trials[121–124]), cyclobenzaprine (18 trials reported in 17 publications[18,101,102,106,107,110,113–115,117,125–131] including five head-to-head trials with a placebo arm), orphenadrine (four trials[21,111,120,132]), metaxalone (four trials in three publications[133–135]), and tizanidine (six trials[116,118,119,136–139]) were evaluated in the highest number of trials. A smaller number of trials evaluated baclofen (1 trial[140]), methocarbamol (2 trials[18,141]), and dantrolene (2 trials[112,142]). Although most of these trials found significant benefits or trends towards benefit on active treatment compared to placebo, cyclobenzaprine has been evaluated and consistently found effective in substantially more trials than the other skeletal muscle relaxants. The data on metaxalone, on the other hand, was mixed. The best fair-quality trial found no differences compared to placebo,[135] but a poor-quality trial[133] and two lesser fair-quality trials[134] reported some benefits compared to placebo using unvalidated outcome measures. We identified no placebo-controlled trials evaluating chlorzoxazone.

Comparative Safety: Spasticity

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 was rated poor quality for adverse event assessment because no information about adverse event assessment methods was reported (Table 1).[45] 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 had hallucinations. No deaths were reported. Abuse or addiction was not evaluated. Withdrawal rates due to adverse events were 17% for tizanidine and 7% for placebo.

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

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[60]	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[58]	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[57]	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[51]	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[59]	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)[53]	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[56]	Tizanidine 24 mg/day	45%	18%	None reported	9%	0% (0/11)
	Baclofen 60 mg/day	0%	30%	None reported	10%	0% (0/10)
Stien 1987[36]	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 1988[49]	Tizanidine mean 17 mg/day	44%	2%	None reported	11%	12% (6/51)
	Diazepam mean 20 mg/day	44%	18%	None reported	3%	28% (15/54)
Rinne 1980 (1)[53]	Tizanidine mean 14 mg/day	53% (0% severe)	13% (8% severe)	7%	33%	0% (0/15)
	Diazepam mean 15 mg/day	87% (47% severe)	53% (27% severe)	13%	0%	27% (4/15)
Cartlidge 1974[63]	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 1975[61]	Baclofen mean 61 mg/day	31%	19%	6%	Not reported	6% (1/16)
	Diazepam mean 21 mg/day	69%	12%	6%	Not reported	0% (0/16)
Roussan 1985[52]	Baclofen mean 47 mg/day	8%	Not reported	Not reported	Not reported	0% (0/13)
	Diazepam mean 28 mg/day	38%	Not reported	Not reported	Not reported	0% (0/13)
Glass 1974[54]	Dantrolene 100 mg qid	Not reported	Not reported	Not reported	Not reported	19% (3/16)
	Diazepam 5 mg qid	Not reported	Not reported	Not reported	Not reported	6% (1/16)
Nogen 1976[48]	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 1976[62]	Dantrolene 75 mg qid	31%	67%	19%	Not reported	Not clear
	Diazepam 5 mg qid	67%	76%	19%	Not reported	Not clear

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%[56] to 80%,[53] and weakness ranged from 7%[51] to 57%.[57] 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.

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. 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 [26%] vs. 4/46 [9%]) 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 comparing baclofen, dantrolene, or tizanidine with diazepam to assess comparative adverse event rates between these three medications. Adverse events data were not reported or poorly reported in three trials.[48, 52, 54] 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[49] (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.

Placebo-Controlled Trials. Most placebo-controlled trials showed little evidence of rigorous adverse event assessment. Abuse or addiction was not evaluated. Three trials appeared to have more rigorous adverse event assessment[95–97] 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,[95] 3 patients (18%) developed elevations of transaminases (highest alanine transaminase 90) that were not thought to be clinically significant.

In general, placebo-controlled trials 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. 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.

Observational Studies. We identified two observational studies assessing rates of hepatic complications in patients on dantrolene.[35, 143] 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, using pre-specified inclusion criteria. It found 122 cases of dantrolene-associated hepatic injury, with 27 fatalities. 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 nonfatal 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

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[64]	0%	0%	0%	0%	None reported
Baclofen unclear dose	Basmajian 1975[65]	Not reported	Not reported	Not reported	12%	Not reported
Baclofen 5–20 mg/day	Brar 1991[66]	Not reported	Not reported	Not reported	Not reported by intervention	Not reported
Baclofen 5 mg tid to 100 mg/day	Duncan 1976[66]	12%	24%	12%	0%	60%
Baclofen 15–80 mg/day	Feldman 1978[68]	17%	Not reported	22%	0%	Not reported
Baclofen 40–80 mg/day	Hinderer 1990[69]	Not reported	Not reported	Not reported	Not reported	Not reported
Baclofen 10 mg tid	Hulme 1985[70]	78%	Not reported	Not reported	56%	78%
Baclofen 15–60 mg/day	Jones 1970[71]	Not clear	None reported	None reported	None reported	Not reported
Baclofen 0.5 mg/kg/day titrated to maximum 60 mg/day	McKinlay 1980[72]	60%	Not clear	None reported	0%	40%
Baclofen 30 mg/day	Medaer 1991[73]	5%	30%	None reported	None reported	50%
Baclofen 10 mg/day titrated up to 60 mg/day	Milla 1977[74]	20%	None reported	Not reported	0%	25%
Baclofen 5 mg tid titrated to 15 mg tid	Orsnes 2000[75]	36%	21%	None reported	None reported	64%
Baclofen 5 mg tid titrated to 80 mg/day	Sachais 1977[76]	71%	22%	Not reported	Not reported (36% overall)	Not reported
Baclofen 5 mg tid titrated to 60 mg/day	Sawa 1979[77]	29%	10%	5%	Not clear	71%
Dantrolene unclear dose	Basmajian 1973[78]	'Almost all'	'Several'	Not reported	Not reported by intervention group	Not reported
Dantrolene 25–100 mg qid	Chyatte 1973[79]	Not reported	Not reported	Not reported	0%	Not reported
Dantrolene 1–3 mg/kg qid	Denhoff 1975[80]	Not reported	Not reported	Not reported	None reported	57%
Dantrolene 25 mg bid to 350 mg/day	Gambi 1983[81]	29%	Not reported	Not reported	9%	54%
Dantrolene 50–800 mg/day	Gelenberg 1973[82]	15%	55%	Not reported	None reported	Not reported
Dantrolene 4–12 mg/kg/day	Haslam 1974[83]	Not reported	Not reported	Not reported	0%	Not reported
Dantrolene 4–12 mg/kg/day	Joynt 1980[84]	Not reported	Not reported	Not reported	9%	91%
Dantrolene 25 mg bid to 50 mg qid	Katrak 1992[85]	70%	Not reported	Not reported	Not reported by intervention group	Not reported
Dantrolene mean 165 mg/day	Ketel 1984[86]	Not reported	Not reported	Not reported	25%	75%
Dantrolene 75 mg tid to 400 mg qid	Luisto 1982[87]	88%	24%	Not reported	Not reported by intervention group	100%
Dantrolene 50–100 mg qid	Monster 1974[88]	Not clear	Not clear	Not clear	Not clear (27% withdrawals overall)	Not reported
Dantrolene 6–8 mg/kg/day	Nogen 1979[89]	82%	Not reported	Not reported	None reported	Not reported
Dantrolene titrated to maximum 200 mg qid	Sheplan 1975[90]	Not clear	Not clear	Not clear	Not reported	Not reported
Dantrolene 100 mg/day titrated to 800 mg/day	Tolosa 1975[91]	Not clear	Not clear	Not clear	17%	Not reported

(*continued*)

Table 7
Continued

Intervention	Study and Year	Somnolence or Fatigue	Dizziness or Lightheadedness	Dry Mouth	Withdrawals Due to Adverse Events	Any Adverse Events
Dantrolene titrated to 100 mg qid	Weiser 1978[92]	23%	Included in somnolence	Not reported	11%	Not reported
Tizanidine 10 mg/day	Knutsson 1982[93]	33%	None reported	17%	0%	Not reported
Tizanidine 2–32 mg/day	Lapierre 1987[94]	48%	3%	48%	Unclear	Not reported
Tizanidine 12-36 mg/day	Meythaler 2001[a95]	41%	Not reported	12%	0%	Not reported
Tizanidine 4-36 mg/day	Nance 1994[55]	41%	17%	39%	25%	81%
Tizanidine titrated to maximum 36 mg/day	Smith 1994[a96]	48%	19%	57%	13%	91%
Tizanidine mean 25 mg/day	UK Tizanidine Trial Group 1994[a97]	Not reported by intervention (54% overall)	Not reported	45%	13%	87%
Chlorzoxazone 20 mg/lb/day	Losin 1966[98]	None reported	Not reported	Not reported	Not reported	Not reported
Cyclobenzaprine 60 mg/day	Ashby 1972[100]	None reported	7%	7%	7%	Not reported
Methocarbamol mean 85 mg/kg/day	Bjerre 1971[99]	5%	Not reported	Not reported	Not reported	Not reported

[a]Rated good quality for adverse event assessment.

(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.[143] Differences between the two studies may be related in part to higher doses of dantrolene in earlier studies, increasingly selective use of dantrolene, or different methods used to find cases.

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.[144] 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. We found one other case report that reported a case of symptomatic jaundice associated with tizanidine that resolved after drug discontinuation.[145]

We identified no other large, good-quality observational trials on adverse events from skeletal muscle relaxants in patients with spasticity. Although other serious adverse events (serious withdrawal symptoms,[146–150] overdose,[151–153] and seizure[154]) have been reported in case reports and series, rates cannot be estimated from these reports.

Comparative Safety: Musculoskeletal Conditions

Systematic Reviews and Meta-Analyses. No systematic review or meta-analysis compared adverse events between different skeletal muscle relaxants in patients with musculoskeletal conditions. 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[42] evaluated rates of adverse events for cyclobenzaprine versus placebo (Table 1). As expected, it found significantly increased rates of drowsiness, dry mouth, dizziness, and any adverse event 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.[47] 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.

Head-to-Head Trials. There was very limited data from head-to-head trials to assess comparative safety of skeletal muscle relaxants in patients with musculoskeletal conditions (Table 8). Of 11 head-to-head trials, three trials reported almost no adverse event information.[102, 103, 109] Of the remainder, quality of adverse event assessment was generally poor. Reliable conclusions about the comparative adverse event rates could not be drawn from these trials. In all head-to-head trials, withdrawals due to adverse events were roughly equal or none were reported. Abuse and addiction were not evaluated, and no deaths were reported.

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%).[18] 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%).[104]

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%,[101] 30%,[105] and 50%,[108] while respective rates for dizziness were 12%, 8%, and 50% despite similar doses of diazepam.

Placebo-Controlled Trials. There was no pattern from placebo-controlled trials to suggest that any one muscle relaxant was superior to others for adverse events (Table 9). Quality of adverse event assessment was generally poor. Abuse and addiction were not evaluated. No deaths thought related to medication were reported, and 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. There were extremely limited adverse events data for orphenadrine (2 trials[120, 132] reported almost no adverse events and two[21,111] did not report adverse event data), metaxalone, (no adverse event data from 3 trials[134,135] and unclear adverse event rates from 1 other[133]) baclofen (only 1 trial[140]), methocarbamol (poor quality and very limited adverse event data from one placebo-controlled trial[141]) or dantrolene (neither of 2 trials[112,142] reported adverse events).

Observational Studies. We found no observational studies evaluating abuse risk of carisoprodol or other skeletal muscle relaxants using validated measures, though one study used an unvalidated questionnaire to estimate abuse "risk."[19] Reports of abuse and addiction are from case reports and series.[155] A French study from 1997 noted that meprobamate (a metabolite of carisoprodol) 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.[156]

We identified one large, fair-quality observational study evaluating safety of cyclobenzaprine in 6311 patients.[157] This study enrolled about 2,000 physicians and asked each to report any adverse events in five patients with musculoskeletal conditions. Rates of somnolence (16%), dry mouth (7%), dizziness (3%), and other adverse events were about 50% lower than in clinical trials and might not be reliable for estimating true adverse events rates.

We identified one observational study of hepatotoxicity associated with chlorzoxazone.[158] The authors of this study reported on one case of reversible hepatotoxicity associated with chlorzoxazone, and also found 23 additional cases of hepatotoxicity reported to the FDA since 1970. Eight cases (two fatal) were judged to be probably related to chlorzoxazone, while

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[103]	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[18]	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[104]	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[105]	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[107]	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[102]	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[101]	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)[106]	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)[106]	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[108]	Tizanidine 4-8 mg tid	10%	10%	10%	None reported	20%
	Diazepam 5-10 mg tid	50%	10%	50%	None reported	50%
Hennies, 1981[109]	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[121]	Not reported	Not reported	Not reported	Not reported	Not reported
Carisoprodol 350 mg qid	Cullen 1976[122]	12%	19%	Not reported	3%	Not reported
Carisoprodol 350 mg tid	Hindle 1972[123]	Not reported	Not reported	Not reported	None reported	Not reported
Carisoprodol 400 mg qid	Soyka 1979[124]	8%	18%	0%	1%	Not reported
Cyclobenzaprine 10–20 mg tid	Aiken 1978b[125]	84%	36%	4%	4%	96%
Cyclobenzaprine 10 mg tid	Baratta 1982[126]	31%	36%	10%	0%	43%
Cyclobenzaprine 10 mg bid	Basmajian 1989[127]	Not reported	Not reported	Not reported	None reported	Not reported
Cyclobenzaprine 10 mg qpm titrated to 40 mg/day	Bennett 1988[114]	55%	11%	92%	8%	89%
Cyclobenzaprine 20–40 mg/day	Bercel 1977[128]	33%	11%	4%	0%	Not reported
Cyclobenzaprine 10 mg tid	Bianchi 1978[129]	29%	4%	8%	None reported	42%
Cyclobenzaprine 10 mg tid (+naprosyn in both arms)	Borenstein 1990[110]	0%	5%	Not reported	None reported	20%
Cyclobenzaprine 10 mg qD titrated to 30 mg qD	Carette 1994[115]	4%	6%	None reported	14%	98%
Cyclobenzaprine 30–60 mg/day	Lance 1972[117]	20%	5%	16%	0%	Not reported
Cyclobenzaprine 10 mg qhs titrated to 30 mg qhs + 10 mg qam	Quimby 1989[130]	Not reported	Not reported	68%	4%	Not reported
Cyclobenzaprine 10 mg tid	Reynolds 1991[113]	Not reported	Not reported	Not reported	0%	Not reported
Cyclobenzaprine 30 mg/day	Steingard 1980[131]	24%	5%	12%	None reported	54%
Metaxalone 400 or 800 mg qid	Dent 1975[a133]	4%	3%	Not reported	9%	14%
Metaxalone 800 mg qid	Diamond 1966[135]	Not reported	Not reported	Not reported	None reported	Not clear
Metaxalone 800 mg qid	Fathie 1964 (1)[134]	Not reported	Not reported	Not reported	Not reported	Not reported
Metaxalone 800 mg qid	Fathie 1964 (2)[134]	Not reported	Not reported	Not reported	Not reported	Not reported
Methocarbamol 2000 mg qid initially, then 1000–1500 mg qid	Tisdale 1975[141]	Not reported	11%	Not reported	3%	Not clear
Orphenadrine 100 mg bid	Gold 1978[21]	Not clear	Not clear	Not clear	None reported	25%
Orphenadrine 100 mg qhs	Latta 1989[120]	0%	0%	0%	None reported	3%
Orphenadrine dose unclear (+paracetamol in both arms)	McGuinness 1983[111]	Not reported	Not reported	Not reported	7%	Not reported
Orphenadrine 100 mg bid	Valtonen 1975[132]	5%	4%	0%	Not reported	Not reported
Baclofen 30–80 mg/day	Dapas 1985[140]	49%	28%	5%	17%	68%
Dantrolene 25 mg/day	Casale 1988[142]	Not reported	Not reported	Not reported	None reported	Not reported
Dantrolene 25 mg/day (+ ibuprofen in both arms)	Salvini 1986[112]	None reported	None reported	None reported	0%	3%
Tizanidine 4 mg tid (+ibuprofen both arms)	Berry 1988 (1)[137]	22%	6%	6%	Not reported by intervention	Not reported
Tizanidine 4 mg tid	Berry 1988 (2)[136]	22%	Not reported	Not reported	8%	41%
Tizanidine 6–18 mg/day	Fogelholm 1992[116]	'Frequent'	'Frequent'	Not reported	5%	Not reported
Tizanidine 2 mg/day	Lepisto 1979[138]	33%	0%	0%	Not reported	33%
Tizanidine 6–12 mg/day	Murros 2000[118]	17%	Not reported	22%	Not reported by intervention	11% (tolerated 'poorly')
Tizanidine mean 18 mg/day	Saper 2002[119]	46%	24%	22%	13%	Not reported
Tizanidine 2 mg bid (+diclofenac in both arms)	Sirdalud Ternelin Asia-Pacific Study Group 1988[139]	12%	3%	None reported	0%	Not reported

[a]Unclear sample size, based on intervention sample of 90 patients.

the rest were possibly or doubtfully related. Most cases were mild and resolved after discontinuation of the medication, but a few were associated with very high elevations of serum transaminases, severe hepatitis, or permanent liver damage. 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.

Subpopulations

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 safety 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, older patients, and children were all included in some studies, but the effect of gender or age on comparative efficacy was not evaluated in any study or group of studies.

Most trials were in adult patients with multiple sclerosis or acute neck and low back pain. Small numbers of trials, lack of high-quality studies, and heterogeneous designs and methods severely limit our ability to systematically evaluate skeletal muscle relaxants for other patient populations and underlying conditions.

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.

Patients with renal and hepatic disease have typically been excluded from clinical trials. In case reports, baclofen toxicity has been seen in patients with impaired renal function.[151] 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.[89]

Summary of Results

Results for each of the key questions are summarized in Table 10. Only tizanidine was found effective in a substantial number of trials for both spasticity and musculoskeletal conditions. Most of the head-to-head trials were performed in patients with multiple sclerosis or 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 overall efficacy. Dantrolene, baclofen, and tizanidine all appear effective in patients with spasticity. 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, cyclobenzaprine has consistently been found to be effective in the most clinical trials. There is little published data demonstrating the effectiveness of chlorzoxazone, metaxalone, methocarbamol, dantrolene, or baclofen for musculoskeletal conditions.

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 and some medications are associated with rare but serious adverse events. There is a small risk of serious (including fatal) hepatic injury associated with dantrolene and chlorzoxazone. Tizanidine appears to be associated with asymptomatic, reversible elevations of aminotransferases. Despite concerns about the potential risk of abuse from carisoprodol because of its metabolism to meprobamate, the available literature provides no data regarding the comparative risk of abuse and addiction from skeletal muscle relaxants.

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

Discussion

Unlike other drug classes such as statins, angiotensin-converting enzyme inhibitors, or beta-blockers, the skeletal muscle relaxants are a heterogeneous group of medications that are not chemically related. Because of this,

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 consistently 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 cannot be made from these trials. Placebo-controlled trials were not helpful in assessing comparative efficacy.
	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.
	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. Interpretation of these 3 trials is unclear because they all used unvalidated outcome measures, had the same manufacturer support, and were published in the same book. 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 cannot be accurately assessed from these data. Placebo-controlled trials were not helpful in assessing comparative efficacy.
	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.

(*continued*)

Table 10
Continued

Key Question	Condition	Level of Evidence	Conclusions
Adverse events			
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.
	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.
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.

there may be important differences in efficacy or safety that need to be considered in choosing a medication to treat patients with spasticity or musculoskeletal conditions. The current available literature provides only limited evidence to guide the prescribing physician in choosing an initial skeletal muscle relaxant, particularly for patients with musculoskeletal conditions. For these patients, clinicians might choose to avoid medications (chlorzoxazone, methocarbamol, metaxalone, dantrolene, and baclofen) for which there is very limited published evidence regarding their clinical effectiveness.

A major limitation of the literature is that clinical trials of skeletal muscle relaxants have often used unvalidated or poorly described methods to measure important clinical outcomes such as spasticity, pain, or muscle strength.[41] Studies that have used the same scale often reported 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.

Even if standardized methods of reporting outcomes were adopted, the optimal methods to measure important clinical outcomes are not clear. The most common standardized methods for measuring spasticity, for example, are the Ashworth and modified Ashworth scales. 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.[159] Some experts, however, have suggested 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.[160] The best technique may be to perform both objective and subjective assessments of spasticity, as well as for other important clinical outcomes such as pain and weakness. Validated subjective assessment techniques, however, are currently lacking. Standardized methods for measuring and reporting important clinical outcomes would be helpful in facilitating meaningful comparisons across studies.

Other limitations of the literature are relatively small numbers of head-to-head trials, lack of high-quality studies, generally poor quality of adverse event assessment, typically short duration of follow-up, and heterogeneity in study design and interventions. In addition, few studies have adequately evaluated functional outcomes.

Other specific areas have not been adequately investigated. For example, patients who are still ambulatory might do better with one skeletal muscle relaxant compared to another, because of differential risk profiles. There are also no 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. There may be other reasons (convenience, improved compliance, better sleep, or more consistent pain relief) for choosing a specific skeletal muscle relaxant, but these outcomes have not been adequately assessed.

The lack of high-quality evidence regarding this class of medications is concerning given their wide use. Without better evidence regarding differential efficacy or safety, payers may be forced to rely disproportionately upon cost as a differentiating factor in choosing between medications in this class. We hope this report helps to highlight remaining gaps in our understanding of this important class of medication and that studies to fill these gaps will be supported and undertaken.

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