Drug Class Review on Skeletal Muscle Relaxants for Spasticity and Musculoskeletal Conditions

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The Agency for Healthcare Research and Quality has not yet seen or approved this report.

INTRODUCTION

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

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

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

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

The skeletal muscle relaxants carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, and orphenadrine have been approved for treatment of

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

In 2001, the Oregon Legislature passed Senate Bill 819, which mandated the development of a Practitioner-Managed Prescription Drug Plan (PMPDP) for the Oregon Health Plan (OHP). As part of this process, it required that an evidence-based review of the state's most expensive drug classes be performed. The Oregon Health Resources Commission (OHRC) requested a review of the skeletal muscle relaxant drug class in patients with spasticity as well as in patients with musculoskeletal conditions. The OHRC requested information about whether there is evidence that one or more skeletal muscle relaxant is superior to others in terms of efficacy and safety.

Scope and Key Questions

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

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

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

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

Several aspects of the key questions deserve comment:

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

Senate Bill 819 specifically excludes patients with HIV and patients with cancer. We also excluded patients with restless legs syndrome or nocturnal myoclonus.

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

The dose of skeletal muscle relaxants used in trials may affect either the efficacy or adverse event profile. One clinical trial[24] evaluated cyclobenzaprine 10 mg tid and 20 mg tid and found equivalent efficacy, but increased adverse events with the higher dose. A study on dantrolene also found a 'ceiling' effect with dantrolene doses of 200 mg daily, with no increased efficacy but more side effects above that dose.[25] Most trials titrated skeletal muscle relaxants to the maximum tolerated dose or a pre-specified ceiling dose, but methods of titration and target doses have not been standardized.

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

Spasticity is an especially difficult outcome to measure objectively. The most widely used standardized scales to measure spasticity in patients with upper motor neuron syndromes are the Ashworth[27] and modified Ashworth[28] scales. In these scales, the assessor tests the resistance to passive movement about a joint and grades it on a scale of 0 (no increase in tone) to 4 (limb rigid in flexion or extension). The modified Ashworth scale adds a "1+" rating between the 1 and 2 ratings of the Ashworth scale. For both of these scales, the scores are usually added for four lower and four upper limb joints, for a total possible score of 0-32, though scoring methods can vary. The Ashworth scale has been found to have moderate reliability.[29] Some experts have pointed out that resistance to passive movement may be a better measure of tone than spasticity and that the Ashworth scale and other 'objective' measures of spasticity may not correlate well with patient symptoms or functional ability.[30] Other areas of uncertainty regard the significance of the 1+ rating in the modified Ashworth scale and how a non-continuous ordinal variable should be statistically analyzed.[29] An important advantage of the Ashworth scale is that it is a consistent way to measure spasticity or tone across studies, and has been found to have moderate reproducibility.[29] Other measures of spasticity include the pendulum test, muscle spasm counts, and patient assessment of spasticity

severity on a variety of numerical (e.g., 1-3, 1-4, 0-4) or categorical (e.g., none, mild, moderate, severe) scales. The best technique may be to perform both objective and subjective assessments of spasticity, but validated subjective assessment techniques of spasticity are lacking.

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

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

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

Scales that are not disease-specific include the Medical Outcomes Study Short Form-36 (SF-36), Short Form-12 (SF-12), or another multi-question assessment. Another approach to measuring function is to focus on how well the medication helps problems in daily living commonly faced by patients with spasticity or musculoskeletal conditions, such as getting enough sleep or staying focused on the job. Some studies also report effects on mood and the preference for one medication over another.

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

subcommittee specifically requested that we examine whether skeletal muscle relaxants differ in the risk of abuse and addiction. We recorded any information about abuse and addiction, including rates of death and hospitalization when available.

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

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

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

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

METHODS

Literature Search

To identify articles relevant to each key question, we searched, in order, the Evidence-Based Medicine Library (2002, Issue 1) (from the Cochrane Collaboration), MEDLINE (1966-2003), EMBASE (1980-2003), and reference lists of review articles. In electronic searches, we combined terms for spasticity, conditions associated with spasticity, and musculoskeletal disorders with included skeletal muscle relaxants (see Appendix A for complete search strategy). In addition, the State of Oregon created and disseminated a protocol to pharmaceutical manufacturers for the submission of clinical and economic evaluation data to the Evidence-based Practice Center. All citations were imported into an electronic database (EndNote 6.0). Searches on the electronic databases were carried out through January 2003, using updates on electronic databases after the initial searches.

Study Selection

All English-language titles and abstracts and suggested additional citations were reviewed for inclusion, using criteria developed by the research team with input from the

subcommittee. We obtained full-text articles if the title and abstract review met the following eligibility criteria:

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

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

Searches identified 3,838 citations: 335 from the Evidence-Based Medicine (Cochrane) Library, 1,155 from MEDLINE, 2,314 from EMBASE, and 34 from reference lists. We received no pharmaceutical company submissions. We identified 368 reports of clinical trials and excluded 227 of these (see Appendix B for detailed search results). Sixty-seven were excluded because they did not evaluate an included population, 148 were excluded because they did not evaluate an included intervention (skeletal muscle relaxant), eight were excluded because they did not evaluate an included outcome (spasms, pain, strength, functional ability, or adverse events), and four were excluded because they were not English-language. We retrieved 141 reports on clinical trials for more detailed evaluation. After this second review, we excluded 48: 36 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, five because of study design (results published in another reviewed trial, not a controlled trial, or no data), and three because they were not English-language. Ninety-three reports presenting data for 95 randomized controlled trials provided usable data and are included in evidence tables. We also identified four relevant systematic reviews and three meta-analyses.

Data Abstraction

One reviewer abstracted the following data from included trials: study design, setting, population characteristics (including sex, age, race, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment (e.g., scales used), and results for each outcome. We recorded intention-to-treat results if available and the trial did not report high overall loss to follow-up. In trials with crossover, outcomes for the first intervention were

recorded if available. This was because of the potential for differential withdrawal prior to crossover biasing subsequent results and the possibility of either a "carryover effect" (from the first treatment) in studies without a washout period, or "rebound" spasticity[39] from withdrawal of the first intervention. A second reviewer checked all data.

Quality Assessment

We assessed quality of trials based on the predefined criteria listed in Appendix C, which were submitted to the Health Resources Commission in December 2001 and updated in February 2003. We rated the internal validity of each trial based on the 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 adequately describing the study population, similarity of patients to other populations to whom the intervention would be applied, control group receiving comparable treatment, funding source, and role of the funder.

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

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

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

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

Data Synthesis

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

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

RESULTS

Overview of included studies

We identified four systematic reviews[26, 40-42] (Table 1) and three meta-analyses (not systematic)[43-45] that evaluated the efficacy of skeletal muscle relaxants in patients with spasticity or musculoskeletal conditions (Evidence Tables 1 and 2). One systematic review evaluated the effectiveness of quinine for nocturnal leg cramps, but did not evaluate other skeletal muscle relaxants, and was excluded from further review.[46] We identified 95 randomized trials that evaluated included skeletal muscle relaxants for spasticity (54 trials reported in 53 publications, Tables 2 and 3) or for musculoskeletal conditions (41 trials reported in 40 publications, Tables 4 and 5).

Overview of systematic reviews and trials in patients with spasticity

Three systematic reviews evaluated skeletal muscle relaxants in patients with spasticity (Table 1). One evaluated anti-spasticity agents in patients with multiple sclerosis,[26] one evaluated a variety of agents in patients with spinal cord injury,[42] and one evaluated tizanidine in patients with spasticity from different conditions.[41] We also identified two meta-analyses (not systematic) that evaluated the efficacy of tizanidine in patients with spasticity.[43, 45] These meta-analyses evaluated primarily unpublished trials conducted by the manufacturer of tizanidine (Evidence Table 1).

Of 54 trials that evaluated included skeletal muscle relaxants in patients with spasticity, 17 were head-to-head trials of one skeletal muscle relaxant versus another (Table 2). One publication reported results of two different head-to-head trials.[47] Eight trials directly compared tizanidine to baclofen.[39, 47-53] Another eight trials compared an included skeletal muscle relaxant to diazepam: Two trials evaluated tizanidine,[47, 54] three evaluated baclofen,[55-57] and three evaluated dantrolene.[58-60] We identified one trial of clonidine and baclofen in patients with spinal cord injury.[61] We found no other head-to-head trials comparing an included skeletal muscle relaxant to gabapentin, clonidine, or other benzodiazepines. Of the

included trials, ten used a crossover design,[48, 50, 52, 55-61] and the remainder were parallel-group trials. The trials ranged in size from 13[56] to 105[54] enrollees, with an average of 38 enrollees (total enrolled=654). Ten of the trials focused on multiple sclerosis,[39, 47-50, 52, 53, 55, 57, 60] one post-stroke or head trauma,[54] one children with cerebral palsy,[59] one spinal cord injury, [61] and the remainder spasticity from various causes.[47, 51, 56, 58]

Except for one head-to-head trial lasting one year,[51] all of the trials were of relatively short duration, ranging from 2 to 8 weeks per intervention. All of the trials except one[61] were published before 1990. One trial[57] enrolled only inpatients; the remainder enrolled outpatients or did not specify whether enrollees were in- or outpatients. The majority of trials recruited patients from specialty clinics, most commonly from neurology or rehabilitation practices, and the majority were single center. Race was not reported in any trial. Females ranged from 13%[51] to 62%[47, 57] of enrolled patients. The average age of enrollees ranged from 39 to 52 years. Although elderly patients were included in most trials, no head-to-head trial specifically evaluated only elderly patients. One trial included only children.[59]

In addition to one head-to-head trial[58] of dantrolene and diazepam that also included a placebo arm, we identified 37 additional placebo-controlled trials (Table 3). Fourteen evaluated baclofen,[62-75] 15 dantrolene,[76-90] six tizanidine,[91-96] one chlorzoxazone,[97] and one cyclobenzaprine.[98] 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. Eight placebo-controlled trials evaluated children[70, 72, 77, 78, 81, 82, 87, 97] and one specifically evaluated elderly post-stroke patients.[68]

Overview of systematic reviews and trials in patients with musculoskeletal conditions

We identified no systematic reviews of different skeletal muscle relaxants in patients with musculoskeletal conditions. One systematic review compared cyclobenzaprine versus placebo in patients with low back pain.[40] This systematic review specifically excluded data on skeletal muscle relaxants other than cyclobenzaprine (Table 1). One meta-analysis of unpublished trials compared cyclobenzaprine to diazepam or placebo for various musculoskeletal conditions (Evidence Table 2).[45]

Of 41 trials of included skeletal muscle relaxants in patients with musculoskeletal conditions, 11 were head-to-head trials of one skeletal muscle relaxant versus another (Table 4). One trial directly compared tizanidine to chlorzoxazone,[99] one trial compared cyclobenzaprine to methocarbamol,[19] and one trial cyclobenzaprine to carisoprodol.[100] Of eight trials that compared an included skeletal muscle relaxant to diazepam, five trials reported in four studies[101-104] evaluated cyclobenzaprine, one trial evaluated carisoprodol[105] and two trials[106, 107] evaluated tizanidine. We identified no head-to-head trials of orphenadrine, metaxalone, dantrolene, or baclofen in patients with musculoskeletal conditions. We also identified no head-to-head trials comparing an included skeletal muscle relaxant to quinine or another skeletal muscle relaxant in patients with nocturnal leg cramps. One trial[108] was excluded because it evaluated an included skeletal muscle relaxant versus chlormezanone, a medication not available or approved in the United States. Three other were excluded because they compared one skeletal muscle relaxant to the combination of a skeletal muscle relaxant and analgesic.[21, 109, 110] One trial was excluded because it only compared one dose of cyclobenzaprine with another.[24]

The head-to-head trials ranged in size from 20[106] to 227[19] enrollees, with an average of 90 enrollees (total enrolled=724). All focused on patients with back or neck pain and spasms; one trial[103] focused on patients with chronic symptoms and the remainder evaluated patients with acute symptoms. The duration of all head-to-head trials was short, ranging from seven[19] to 18[102] days. All of the trials were published before 1985. One trial[106] enrolled only inpatients; the remainder enrolled outpatients or did not specify whether enrollees were in- or outpatients. All were single center trials except one multicenter trial.[105] Race was reported in three trials and non-whites accounted for <15% of patients in these trials.[19, 100, 105] Females ranged from 30%[106] to over 55%[19] of enrolled patients. The average age of enrollees ranged from 37 to 52 years. Although elderly patients were included in most head-to-head trials, no trial specifically evaluated only elderly patients and none included children.

In addition to six head-to-head trials (from five publications)[19, 101-104] that included a placebo arm, we also identified 30 placebo-controlled trials (Table 5). Four evaluated carisoprodol,[111-114] 12 cyclobenzaprine,[115-126] one metaxalone,[127] four orphenadrine,[22, 128-130] one baclofen,[131] two dantrolene,[132, 133] and six tizanidine.[134-139] Three trials evaluated a skeletal muscle relaxant with an equivalent analgesic in each arm and were included.[121, 129, 133] Most trials evaluated low back or neck syndromes alone or mixed with other musculoskeletal conditions; some other conditions specifically evaluated were fibromyalgia,[118, 122, 125] tension headaches,[123, 136, 138] and nocturnal leg cramps.[128] No placebo-controlled trials included children; one trial[136] of tension headaches only included women and one trial[128] evaluated orphenadrine in elderly patients with nocturnal leg cramps.

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

Patients with spasticity

Results of systematic reviews and meta-analyses. One good-quality systematic review[26] evaluated various anti-spasticity agents, including skeletal muscle relaxants, for multiple sclerosis (Table 1 and Evidence Table 1). It identified 11 head-to-head and 12 placebo-controlled trials of skeletal muscle relaxants included in our review. Seven of the head-to-head trials compared tizanidine to baclofen (including one German-language trial, one unpublished trial and one abstract that were not included in our search). Other head-to-head trials were one trial comparing baclofen to diazepam, one trial comparing dantrolene to diazepam, and two trials comparing tizanidine to diazepam. Of the placebo-controlled trials, five evaluated baclofen, four dantrolene, and three tizanidine. No evaluated trial was rated good quality. Three of the seven trials comparing tizanidine to baclofen and two of the four trials comparing included skeletal muscle relaxants to diazepam used the Ashworth scale as an outcome measure; all studies used unvalidated measures of muscle strength. In the seven trials of tizanidine vs. baclofen, no significant differences between interventions were found for functional status or for spasticity, spasms, or clonus. Only two of the seven trials reported changes in objective muscle power, with slightly more patients noting deterioration with baclofen than tizanidine. Similarly, slightly more patients reported weakness with baclofen

than tizanidine. In the four trials of included skeletal muscle relaxants versus diazepam, no differences in efficacy were noted between interventions, but diazepam was usually associated with increased sedation or tiredness, and generally was less preferred. In the reviewed placebo-controlled trials, there was no pattern to suggest that one included skeletal muscle relaxant was any better than others. Marked heterogeneity in study designs, interventions used, and outcomes measured made meta-analysis of placebo-controlled trials impossible.

One systematic review evaluated pharmacologic interventions for spasticity following spinal cord injury.[42] It was rated fair quality because the authors had not yet assessed 15 identified potentially relevant studies. Of the nine studies included, two were placebo-controlled trials evaluating baclofen or tizanidine. None of the included trials evaluated skeletal muscle relaxants head-to-head. No study was rated good quality. There was insufficient evidence to judge the comparative efficacy of tizanidine versus baclofen from these placebo-controlled studies.

One poor-quality systematic review[41] evaluated 20 studies of tizanidine versus baclofen (14 studies) or diazepam (6 studies) in patients with multiple sclerosis (12 studies), cerebrovascular disease (7), or amyotrophic lateral sclerosis (1). This systematic review included both published and unpublished trials and was rated poor-quality because it did not report methods used to identify trials, did not provide sufficient detail of included studies, and did not rate the quality of included studies. Although it 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 11 unpublished trials on tizanidine (n=137) versus baclofen (n=8) or diazepam (n=3) (Table 1).[43, 44] Authors of these trials were employed by the pharmaceutical company marketing tizanidine in the U.S. These studies were rated fair-quality because they did not adequately report details of included studies (Evidence Table 1). Both studies evaluated the same trials, and found no significant differences between tizanidine and diazepam or baclofen for outcomes of tone (Ashworth scale) or muscle strength (summed BMRC strength scores).

Results of head-to-head trials. None of the 17 head-to-head trials of skeletal muscle relaxant in patients with spasticity was rated good quality. All studies had at least two of the following methodological flaws: randomization technique not described, eligibility criteria not described, blinding technique not described, allocation concealment technique not described, or high loss to follow-up (Evidence Table 3). Adequate blinding is an especially important factor in studies using subjective outcomes, such as patient preference, global assessments, spasm severity, or pain. One trial was rated poor-quality because it was not randomized and did not perform blinding; the remainder were rated fair-quality.[61] Possible confounding factors in these trials included different methods of medication titration or target doses, differential withdrawals during the first intervention period in crossover trials, and previous use of an intervention or other muscle relaxant, which was inconsistently reported. In crossover trials, results of the first intervention were usually not reported.

Of the eight trials of tizanidine vs. baclofen, average dose ranged from 11 mg/day [47] to 24 mg/day[49, 50, 53] and the dose of baclofen ranged from 15 mg/day[50] to 90 mg/day.[49] Most trials evaluated patients with multiple sclerosis, though one trial also evaluated patients with cervical myelopathy,[47] one also evaluated patients with syringomyelia,[52]and another did not describe the underlying condition causing spasticity.[51]

In each of these eight trials, tizanidine and baclofen appeared roughly equivalent for efficacy (Table 2 and Evidence Table 3). Outcomes measured included muscle tone, muscle spasm, clonus, functional assessments, patient or physician global assessments, and patient or physician preference. These outcomes were assessed using a variety of methods, including unvalidated or unspecified scales. Six trials[39, 47, 50-53] used the Ashworth scale to measure spasticity or tone, but methods of reporting these results were inconsistent and raw scores were usually not presented. In most trials, regardless of the method used to assess outcomes, patients receiving either baclofen or tizanidine reported significant improvements in spasticity, clonus, and overall improvement compared to baseline. The longest trial (52 weeks compared to 8 weeks or less) reported results similar to shorter trials.[51] The overall withdrawal rate was higher with baclofen than with tizanidine in three out of seven trials,[48, 50, 51] 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,[48, 51] withdrawals due to adverse events accounted for most of the observed differences in overall withdrawal rates (see below).

In the eight trials of tizanidine, baclofen, or dantrolene versus diazepam, there was no pattern to suggest that any of these skeletal muscle relaxants was superior to the others for assessed clinical outcomes including spasm, strength, functional status, or patient preference.(Table 2 and Evidence Table 3) Although one trial reported higher patient preference for baclofen over diazepam[57] and another for dantrolene over diazepam[60], unclear blinding techniques make these results difficult to interpret. Differences in study design, patient populations, outcomes evaluated, and similar efficacy of each skeletal muscle relaxant compared to diazepam in individual trials made it impossible to make accurate judgments about the comparative efficacy of tizanidine, baclofen, and dantrolene from these trials as a whole.

The one trial comparing baclofen to clonidine was rated poor-quality because it was not randomized and did not perform blinding.[94] This trial found no differences between baclofen and clonidine for spasticity and was not included in the Tables.

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

Results of placebo-controlled trials. None of the 37 placebo-controlled trials was rated good quality (Evidence Table 4). Main results from placebo-controlled trials for spasticity are summarized in Table 3, including results from the one head-to-head trial[58] that also had a placebo arm. Most of the placebo-controlled trials found either significant benefits or trends towards benefit from baclofen, dantrolene, and tizanidine compared to placebo for spasticity, functional ability, and strength. However, because of the use of unvalidated outcomes scales and inconsistent methods for reporting outcomes, the magnitude of benefit for each of these medications compared to placebo could not be accurately gauged. There was inadequate evidence from 1 trial[97] of chlorzoxazone (rated poor quality) and one trial[98] of cyclobenzaprine (no significant differences) to show that these skeletal muscle relaxants are effective for treatment of spasticity. These two medications are not approved for this indication.

Meta-analysis could not be performed on the placebo-controlled trials because of marked differences in interventions (doses used and methods of titration), trial designs,

populations studied, outcomes scales, and methods for reporting outcomes. No reliable conclusions about the comparative efficacy of different skeletal muscle relaxants can be drawn from these placebo-controlled trials.

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

Patients with musculoskeletal conditions

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

One fair-quality meta-analysis evaluated the comparative efficacy of cyclobenzaprine, diazepam and placebo (Table 1 and Evidence Table 2).[45] This study summarized results of 20 unpublished short-term (2 week) trials performed in the U.S. in 1153 patients with muscle spasm; the authors were employed by Merck Laboratories. It included patients with post-traumatic injury, musculoskeletal strain, radiculopathy, and osteoarthritis. This meta-analysis was rated fair-quality because it did not adequately describe included trials and used an unvalidated method to measure 'global response'. This study found that the 'global response' was equivalent for cyclobenzaprine and diazepam (66% marked or moderate improvement) and significantly better than placebo (40%).

Results of head-to-head trials. None of the 11 head-to-head trials was rated good-quality; all had at least two important methodological flaws (Evidence Table 5). All trials were rated fair except one trial of cyclobenzaprine versus diazepam that was rated poor because in addition to other flaws, it only reported results for 52 of the 105 enrollees, and did not account for these patients.[102] Of the fair-quality trials, the trial that appeared to be of best quality compared carisoprodol and diazepam.[105] In this trial, allocation concealment techniques were not described and unvalidated methods of assessing outcomes were used. Carisoprodol was found to be significantly superior to diazepam using unvalidated methods to assess stiffness, tension, and relief, with average differences for carisoprodol compared to diazepam averaging

about 0.5 on a 1-5 scale.[105] No significant differences were seen for pain, activity impairment, or sleep impairment.

In other head-to-head trials, a variety of methods were used for measuring outcomes, including various scales for pain (4, 5, or 9 point scales and visual analogue scales), tenderness, and functional status. Most assessment scales were unvalidated, and methods of reporting these outcomes were inconsistent. Functional status was either not measured or assessed using unstandardized and unvalidated methods. Doses of medications investigated were cyclobenzaprine 10 to 20 mg tid; tizanidine 2 to 8 mg tid, chlorzoxazone 500 mg tid, carisoprodol 350 mg qid, and diazepam 5 to10 mg tid (Table 4). In these trials, there was no clear evidence that one skeletal muscle relaxant was superior to any other for efficacy. In a trial comparing tizanidine and chlorzoxazone in patients with back pain,[99] 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 proportion of patients reporting absent or mild muscle spasm, limitation or motion, or limitation of daily activities.[19] A slightly greater proportion of patients on cyclobenzaprine reported mild or absent local pain compared to methocarbamol (40% vs. 48%, p=.05), but only when patients with mild scores were excluded from analysis. In a trial of cyclobenzaprine versus carisoprodol in patients with acute back pain and spasms[100] there were no significant differences between interventions for pain, muscle stiffness, activity impairment, sleep impairment, tension, or relief scores compared to baseline.

Other head-to-head trials compared an included skeletal muscle relaxant to diazepam. Of the five trials[101-104] comparing cyclobenzaprine to diazepam, two trials[101, 104] found significant differences for most measurements of pain, muscle spasm, functional status, and 'global evaluations' that favored cyclobenzaprine, but used unvalidated measures. One other trial[104] reported decreased tenderness, and limitation of motion and better 'global evaluation' for cyclobenzaprine vs. diazepam, but not for other measures (muscle spasm, pain, functional ability). All three of these trials had some support from a manufacturer (Merck) and were published in the same book. For most outcomes that favored cyclobenzaprine, the magnitude of difference between treatments was greater at the end of week one than at the end of week two. In the other two trials comparing cyclobenzaprine to diazepam[102, 103] and the two trials[106, 107] comparing tizanidine to diazepam, no significant differences were found for any clinical outcomes including pain, stiffness, or functional ability.

The results of the one trial[103] that focused on patients with chronic back or neck symptoms reported results similar to the other trials, which focused on acute back symptoms. In all head-to-head trials, the overall withdrawal rates ranged from 0% to 35%. In one trial, the overall withdrawal rate appeared significantly higher on cyclobenzaprine (12/34 [35%]) compared to diazepam (3/32 [9%]), but there was no significant difference between interventions in other trials.

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

Results of placebo-controlled trials. None of the 30 placebo-controlled trials in patients with musculoskeletal conditions was rated good quality (Evidence Table 6, includes results from six head-to-head trials with a placebo arm). Quality was generally at the same level as the head-to-head trials or worse. Most of these trials evaluated patients with acute neck or low back conditions, and most showed some evidence for clinical efficacy of evaluated skeletal muscle relaxants, but the magnitude of benefit was difficult to assess because of marked heterogeneity in study design, interventions, populations studied, and outcomes assessed (Table 5). Carisoprodol (four trials), cyclobenzaprine (17 trials, including head-to-head trials with a placebo arm), orphenadrine (four trials), and tizanidine (six trials) were evaluated in the highest number of trials, and most studies found significant benefits or trends towards benefit on active treatment compared to placebo. A small number of placebo-controlled trials evaluated baclofen (1 trial), metaxolone (1), methocarbamol (1), and dantrolene (2) for musculoskeletal conditions. Although trials of baclofen and dantrolene found significant benefits or trend towards benefit from active treatment, the single trial of metaxalone found no differences compared to placebo.[127] We identified no placebo-controlled trials evaluating chlorzoxazone.

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

The body of evidence regarding the effectiveness of various skeletal muscle relaxants compared to placebo varies both in quality and quantity. There is fair-quality evidence from a total of 17 trials (none rated good quality) comparing cyclobenzaprine to placebo (including head-to-head trials with a placebo arm) that consistently found that cyclobenzaprine is more effective for various measures of pain relief, muscle spasm, or functional ability. These results are similar to a recent systematic review of 14 of these trials.[40] The body of evidence regarding tizanidine (six trials), carisoprodol (four trials), and orphenadrine (four trials) was also rated fair-quality but was not as robust. For each of these interventions there appeared to

be a consistent trend favoring the active treatment compared to placebo. There is very limited data from head-to-head or placebo-controlled trials demonstrating the effectiveness of methocarbamol, chlorzoxazone, baclofen, or dantrolene in patients with musculoskeletal conditions. Metaxalone was not shown to be effective in the one available placebo-controlled trial.

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

Patients with spasticity

Results of systematic reviews and meta-analyses. We identified no systematic reviews that evaluated comparative adverse event rates from skeletal muscle relaxants in patients with spasticity. One meta-analysis of three placebo-controlled trials with 525 enrollees (284 on tizanidine) was rated poor-quality for adverse event assessment because no information about adverse event assessment methods was reported (Evidence Table 1).[43] Adverse events included 49% dry mouth, 48% somnolence, 41% asthenia, 16% dizziness, and 12% headache in patients on tizanidine compared to 10%, 10%, 16%, 4%, and 13% on placebo. Two patients had liver function abnormalities and three patients had hallucinations. No deaths were reported. Abuse or addiction was not evaluated. Withdrawal rates due to adverse events were 17% for tizanidine and 7% for placebo. This meta-analysis did not report adverse event data from other reviewed trials in which tizanidine was compared to diazepam or baclofen, but did report better 'global tolerability' (1-4 scale) with tizanidine (2.0) than with diazepam (2.6, p=0.001) or baclofen (2.3, p=0.008).

Results of head-to-head trials. No head-to-head trial was rated good-quality for adverse event assessment. In general, there was little evidence of rigorous adverse event assessment in these trials (Evidence Table 3). No trial appeared to have significantly better adverse event reporting methods than the others. The most frequently reported adverse event rates were for somnolence, weakness, dizziness, and dry mouth. For the same medication, adverse event rates varied between trials (Table 6). For example, rates of somnolence from baclofen in head-to-head trials of baclofen and tizaninde ranged from 0%[53] to 80%,[47] and weakness ranged from 7%[51] to 57%.[50] The observed ranges of adverse event rates could reflect differences in populations, dosing of medications in trials, use of a run-in period, the rigor of adverse event assessment, or other factors. No deaths or serious adverse events were reported in these trials. Rates of abuse and addiction were not evaluated. Interpretation of reported adverse event rates was limited by the short duration of follow-up.

For each skeletal muscle relaxant evaluated in head-to-head trials, rates across trials for common adverse events overlapped with rates found for other skeletal muscle relaxants (Table 6). In individual head-to-head trials of tizanidine and baclofen, however, several patterns emerged. In these eight trials, dry mouth was reported more frequently on tizanidine in five studies (roughly equivalent or not reported in the other three), but weakness was reported more

frequently on baclofen in all seven studies in which it was reported (Table 5). No consistent patterns were seen for somnolence or dizziness. Withdrawal rates due to adverse events (an indicator of intolerable adverse events), however, 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 directly comparing baclofen, dantrolene, or tizanidine with diazepam to assess comparative adverse event rates. Adverse events data were not reported or poorly reported in three trials.[56, 58, 59] 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[54] (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.

Results of placebo-controlled trials. Most placebo-controlled trials were rated poor or fair-quality for adverse event assessment (Evidence Table 4). Abuse or addiction was not evaluated. Three trials appeared to have more rigorous adverse event assessment[93, 95, 96] 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,[93] 3 patients (18%) developed elevations of transaminases (highest alanine transaminase 90) that were not thought to be clinically significant.

In general, placebo-controlled trials as a whole gave little additional information to compare adverse events of skeletal muscle relaxants in patients with spasticity. For each evaluated medication, adverse event rates overlapped for different skeletal muscle relaxants and had wide ranges across trials. For example, the rate of somnolence, the most consistently reported adverse event, ranged from 33-54% in trials of tizanidine, 0-78% on baclofen, and 15-88% on dantrolene. We were unable to define narrower ranges for adverse events by stratifying trials according to dose because most trials titrated the medication, and it was not clear on which dose adverse events occurred. Withdrawal rates due to adverse events and rates of weakness were not consistently reported.

Results of observational studies. We identified two observational studies assessing rates of hepatic complications in patients on dantrolene.[35, 140] One study[35] published in 1990 collected all cases of dantrolene-associated hepatic injury that were reported to the manufacturer, regulatory authorities, or in the published literature. It was rated fair-quality for adverse event assessment because it primarily relied on spontaneously reported cases of hepatic injury. This study excluded 73 cases from analysis that could not be verified using pre-specified exclusion criteria and 36 cases in which dantrolene was not thought to be the cause of hepatic injury, leaving a total of 122 analyzable cases of dantrolene-associated hepatic injury. Of these, 47 had asymptomatic transaminase elevations, 12 also had mild hyperbilirubinemia, 36 had

jaundice, and 27 fatalities occurred. Fifty-two percent (14/27) of the fatalities occurred in multiple sclerosis patients. Fatalities were associated with a higher mean dantrolene dose (582 mg/dL) than non-fatal cases (263 mg/dL). The risk of hepatic complications was estimated to be less than 9.0 cases per 100,000 prescriptions written for dantrolene, and fatal hepatic reactions 0.83 cases per 100,000 prescriptions. An earlier study (1977), which included results from placebo-controlled trials as well as spontaneously reported cases, estimated rates of 1.8% (16/1044) for any hepatic injury and 0.3% (3/1044) for a fatal outcome.[140] Differences between the two studies may in part be related to fewer spontaneously reported adverse events, higher doses of dantrolene in earlier studies, or increasingly selective use of dantrolene. We did not identify any observational studies that estimated the rates of hepatic complications from tizanidine or baclofen.

We identified no other large or good-quality observational trials on adverse events from skeletal muscle relaxants in patients with spasticity. Although other serious adverse events (serious withdrawal symptoms,[141-145] overdose,[146-148] and seizure[149]) have been reported in case series, comparative rates for these events can not be estimated from these reports.

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

Patients with musculoskeletal conditions

Results of systematic reviews and meta-analyses. Adverse events from cyclobenzaprine have been evaluated in one systematic review and one meta-analysis (not systematic) (Evidence Table 2). Neither study rated the quality of included trials for adverse event assessment. The systematic review[40] evaluated rates of adverse events for cyclobenzaprine versus placebo. This systematic review did not rate the quality of included trials for adverse event assessment. It found significantly increased rates of drowsiness (20% vs. 2%, $p<0.001$), dry mouth (8% vs. 2%, $p=0.02$), dizziness (7% vs. 4%, $p=0.04$), and any adverse event (53% vs. 28%, $p=0.002$) in patients on cyclobenzaprine versus placebo. Withdrawals due to adverse events were not reported. The meta-analysis reported comparative rates of adverse events for cyclobenzaprine versus diazepam.[45] 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.

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

There was very limited data from head-to-head trials to assess comparative safety of skeletal muscle relaxants in patients with musculoskeletal conditions. Of 11 head-to-head trials, three trials reported almost no adverse event information[99, 102, 107]. In the eight head-to-head trials with more substantial adverse event data, there were too few direct comparisons for any clear patterns to emerge (Table 8). In the head-to-head trial of cyclobenzaprine versus methocarbamol, cyclobenzaprine was associated with more somnolence (58% vs. 31%), but the rate of withdrawals due to adverse events was equivalent (7% vs. 6%).[19] In the head-to-head trial of cyclobenzaprine and carisoprodol, dry mouth was more frequent with cyclobenzaprine (38% vs. 10%) and dizziness less frequent (8% vs. 26%).[100] Withdrawal rates due to adverse events were equal (8%).

The five head-to-head trials with adverse event data comparing cyclobenzaprine, carisoprodol, or tizanidine to diazepam are difficult to interpret because the rate of adverse events for diazepam varied greatly between trials. Rates of somnolence on diazepam, for example, were 13%,[103] 30%,[105] and 50%,[106] while respective rates for dizziness were 12%, 8%, and 50% despite similar doses of diazepam. Because of the wide disparity in adverse event rates from diazepam, reliable conclusions about the comparative adverse event rates of cyclobenzaprine and tizanidine could not be drawn from these trials. In all head-to-head trials, withdrawals due to adverse events were roughly equal or no withdrawals due to adverse events were reported.

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

Adverse events were not reported consistently in these trials, and doses of medications and titration methods differed markedly between studies. For example, for baclofen, doses ranged from 5 mg tid up to 80 mg daily, with various methods for titrating doses. Wide and overlapping ranges for all commonly reported adverse events (somnolence, dizziness, dry mouth, withdrawals due to adverse events) were seen for carisoprodol, cyclobenzaprine, and tizanidine (Table 8). There was extremely limited adverse events data for orphenadrine (2 trials[128, 130] reported almost no adverse events and two[22, 129] did not report adverse event data), metaxalone,(no adverse event data from 1 trial[127]) baclofen (only 1 trial[131]), or dantrolene(neither of 2 trials[132, 133] reported adverse events). There was no pattern from placebo-controlled trials to suggest that any one muscle relaxant was superior to others for adverse events.

Results of observational studies. We identified one study evaluating abuse risk in patients taking carisoprodol.[20] Carisoprodol is suspected of having a higher potential for abuse because of its metabolism to meprobamate, a federally controlled substance that is now rarely prescribed. This study enrolled 40 patients taking carisoprodol for more than 3 months. It assessed the potential for abuse using an unvalidated six-item questionnaire and found that 20% of patients with no history of substance abuse history and 65% with a history of substance abuse responded yes to one or more questions, which the authors suggested indicated a

tendency towards possible abuse. We identified no other observational studies assessing the risk of abuse or addiction from carisoprodol or other skeletal muscle relaxants in patients with musculoskeletal conditions. Most reports of abuse and addiction are from case reports.[150] A French report from 1997 noted that meprobamate was the most frequently cited drug in fatal pharmaceutical overdoses (19 cases, or 15.3%), but we were unable to find similar data on meprobamate or carisoprodol in the U.S.[151]

We identified one large observational study evaluating safety of cyclobenzaprine in 6311 patients.[152] This study enrolled about 2000 physicians and asked each to report any adverse events in five patients with musculoskeletal conditions. It was rated fair-quality for adverse event assessment. Rates of somnolence (16%), dry mouth (7%), dizziness (3%), and other adverse events were about 50% lower than in clinical trials and indicate that these data might not be as reliable as available clinical trials data for estimating true adverse events rates.

We identified no other large- or good-quality observational studies of comparative adverse event rates for skeletal muscle relaxants.

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

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

No clinical trials or observational studies were designed to compare the efficacy of skeletal muscle relaxants for different races, age groups, or genders. There is almost no information to judge the relative effectiveness or adverse event rates of skeletal muscle relaxants in these subpopulations. Race was rarely reported in the trials; when it was reported the overwhelming majority of patients were white. Women were well represented in the trials as were older patients, but the effect of gender or age on medication efficacy was not evaluated in any trial. Nine trials[59, 70, 72, 77, 78, 81, 82, 87, 97] evaluated children and two trials[68, 128] evaluated elderly patients, but accurate judgments about comparative efficacy and safety in these populations cannot be made because of the same problems with lack of good-quality trials and heterogeneity in interventions, outcomes assessed, and findings that were encountered in examining general efficacy and adverse events, with the additional limitation of fewer available studies.

Information regarding comparative efficacy and safety of skeletal muscle relaxants for different underlying conditions is also not available. Most data from head-to-head trials were in patients with multiple sclerosis or acute neck and low back pain and were reviewed in the section on general efficacy and safety. Only small numbers of trials (usually placebo-controlled) specifically evaluated other conditions. For example, of three placebo-controlled trials of patients with fibromyalgia, all investigated cyclobenzaprine.[118, 122, 125] Of three

placebo-controlled trials in patients with tension headaches, two evaluated tizanidine[136, 138] and one cyclobenzaprine.[123] Small numbers of trials, lack of high-quality studies, and heterogeneous designs and methods limited our ability to systematically evaluate skeletal muscle relaxants for these and other conditions including cerebral palsy (three trials[59, 77, 82]), spinal cord injury (two trials[94, 153]), and post-stroke patients (four trials[54, 68, 83, 84]) (see Table 3).

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

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

Other special populations have typically been excluded from clinical trials and have not been well studied. In case reports, baclofen has been reported to cause toxicity in patients with impaired renal function in case reports, but there are insufficient data to compare rates of toxicity with other skeletal muscle relaxants in this population.[146] We found no trials in patients with chronic liver disease. In one trial of children with spasticity and epilepsy, dantrolene did not increase the frequency of seizures.[87]

SUMMARY

Results for each of the key questions are summarized in Table 10. Most skeletal muscle relaxants were evaluated for either spasticity or musculoskeletal conditions; only tizanidine was evaluated in head-to-head and more than two placebo-controlled trials for both spasticity and musculoskeletal conditions. Metaxalone was not found to be effective for low back or neck spasms in the one clinical trial in which it was evaluated. Most of the head-to-head trials were performed in patients with multiple sclerosis and patients with acute neck or low back pain; almost all of the evidence regarding efficacy and safety in patients with other conditions comes from placebo-controlled trials.

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

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

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

REFERENCES

1. Lance JW. Symposium synopsis. In: Feldman, RG, Young RR, Koella WP, editors. Spasticity: disordered motor control. Chicago: Yearbook Medical; 1980. p. 485-494.

2. Young RR. Spasticity: a review. Neurology 1994;44:(11 Suppl 9):S12-20.

3. Andersson PB, Goodkin DE. Current pharmacologic treatment of multiple sclerosis symptoms. West J Med 1996;165:(5):313-317.

4. Burchiel KJ, Hsu FP. Pain and spasticity after spinal cord injury: mechanisms and treatment. Spine 2001;26:(24 Suppl):S146-60.

5. Barnes MP. Medical management of spasticity in stroke. Age Ageing 2001;30:(Suppl. 1):13-16.

6. Anonymous. Spasticity. Lancet 1989;2:(8678-8679):1488-1490.

7. Leventhal LJ. Management of fibromyalgia. Ann Intern Med 1999;131:(11):850-858.

8. Redillas C, Solomon S. Prophylactic pharmacological treatment of chronic daily headache. Headache 2000;40:(2):83-102.

9. Deyo RA, Bergman J, Phillips WR. Drug therapy for back pain: Which drugs help which patients? Spine 1996;21:(24):2840-2850.

10. Arnold LM, Keck PE, Jr., Welge JA. Antidepressant treatment of fibromyalgia. A meta-analysis and review. Psychosomatics 2000;41:(2):104-113.

11. Cherkin DC, Wheeler KJ, Barlow W, et al. Medication use for low back pain in primary care. Spine 1998;23:(5):607-614.

12. Brogden RN, Speight TM, Avery GS. Baclofen: a preliminary report of its pharmacological properties and therapeutic efficacy in spasticity. Drugs 1974;8:(1):1-14.

13. Davidoff RA. Antispasticity drugs: mechanisms of action. Ann Neurol 1985;17:(2):107-16.

14. Wagstaff AJ, Bryson HM. Tizanidine. A review of its pharmacology, clinical efficacy and tolerability in the management of spasticity associated with cerebral and spinal disorders. Drugs 1997;53:(3):435-52.

15. Nance PW. Tizanidine: An alpha2-agonist imidazoline with antispasticity effects. Todays Ther Trends 1997;15:(1):11-25.

16. Kita M, Goodkin DE. Drugs used to treat spasticity. Drugs 2000;59:(3):487-95.

17. Cook JB, Nathan PW. On the site of action of diazepam in spasticity in man. J Neurol Sci 1967;5:(1):33-7.

18. Davidoff RA. Pharmacology of spasticity. Neurology 1978;28:(9 Pt 2):46-51.

19. Preston EJ, Miller CB, Herbertson RK. A double-blind, multicenter trial of methocarbamol (Robaxin(TM)) and cyclobenzaprine (Flexeril(TM)) in acute musculoskeletal conditions. Todays Ther Trends 1984;1:(4):1-11.

20. Reeves RR, Carter OS, Pinkofsky HB, et al. Carisoprodol (soma): abuse potential and physician unawareness. J Addict Dis 1999;18:(2):51-6.

21. Azoury FJ. Double-blind study of Parafon Forte and Flexeril in the treatment of acute skeletal muscle disorders. Curr Ther Res 1979;26:189-97.

22. Gold RH. Orphenadrine citrate: Sedative or muscle relaxant? Clin Ther 1978;1:(6):451-453.

23. Smith HS, Barton AE. Tizanidine in the management of spasticity and musculoskeletal complaints in the palliative care population. Am J Hosp Palliat Care 2000;17:(1):50-8.

24. Santandrea S, Montrone F, Sarzi-Puttini P, et al. A double-blind crossover study of two cyclobenzaprine regimens in primary fibromyalgia syndrome. J Int Med Res 1993;21:(2):74-80.

25. Meyler WJ, Bakker H, Kok JJ, et al. The effect of dantrolene sodium in relation to blood levels in spastic patients after prolonged administration. J Neurol Neurosurg Psychiatry 1981;44:(4):334-9.

26. Shakespeare DT, Boggild M, Young C. Anti-spasticity agents for multiple sclerosis. Cochrane Database of Systematic Reviews 2001(4):CD001332.

27. Ashworth B. Preliminary trial of carisoprodal in multiple sclerosis. Practitioner 1964;192:540-542.

28. Bohannon RW, Smith MB. Inter rater reliability of a modified Ashworth Scale of muscle spasticity. Phys Ther 1987;67:206-207.

29. Pandyan AD, Johnson GR, Price CI, et al. A review of the properties and limitations of the Ashworth and modified Ashworth Scales as measures of spasticity. Clin Rehabil 1999;13:(5):373-83.

30. Landau WM. Tizanidine and spasticity. Neurology 1995;45:(12):2295-6.

31. McQuay HJ. Opioid use in chronic pain. Bandolier 2002;http://www.jr2.ox.ac.uk/bandolier/booth/painpag/wisdom/S31.html.

32. Sharrack B, Hughes RAC. Clinical scales for multiple sclerosis. J Neurol Sci 1996;135:1-9.

33. Simms RW, Felson DT, Goldenberg DL. Development of preliminary criteria for response to treatment in fibromyalgia syndrome. J Rheumatol 1991;18:(10):1558-63.

34. Mannerkorpi K, Ekdahl C. Assessment of functional limitation and disability in patients with fibromyalgia. Scand J Rheumatol 1997;26:(1):4-13.

35. Chan CH. Dantrolene sodium and hepatic injury. Neurology 1990;40:(9):1427-32.

36. Harris RP, Helfand M, Woolf SH, et al. Current methods of the third U.S. Preventive Services Task Force. Am J Prev Med 2001;20:(3S):21-35.

37. Anonymous. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews CRD Report Number 4 (2nd edition). York, UK: NHS Centre for Reviews and Dissemination; 2001. Report No.: 4 (2nd edition).

38. Mulrow CD, Oxman A. How to conduct a Cochrane systematic review. Version 3.0.2. In: San Antonio Cochrane Collaboration; 1997.

39. Stien R, Nordal HJ, Oftedal SI, et al. The treatment of spasticity in multiple sclerosis: a double-blind clinical trial of a new anti-spastic drug tizanidine compared with baclofen. Acta Neurol Scand 1987;75:(3):190-4.

40. Browning R, Jackson JL, O'Malley PG. Cyclobenzaprine and back pain: a meta-analysis. Arch Intern Med 2001;161:(13):1613-20.

41. Lataste X, Emre M, Davis C, et al. Comparative profile of tizanidine in the management of spasticity. Neurology 1994;44:(11 Suppl 9):S53-9.

42. Taricco M, Adone R, Pagliacci C, et al. Pharmacological interventions for spasticity following spinal cord injury. Cochrane Database of Systematic Reviews 2000(2):CD001131.

43. Wallace JD. Summary of combined clinical analysis of controlled clinical trials with tizanidine. Neurology 1994;44:(11 Suppl 9):S60-8; discussion S68-9.

44. Groves L, Shellenberger MK, Davis CS. Tizanidine treatment of spasticity: a meta-analysis of controlled, double-blind, comparative studies with baclofen and diazepam. Adv Ther 1998;15:(4):241-51.

45. Nibbelink DW, Strickland SC, McLean LF, et al. Cyclobenzaprine, diazepam and placebo in the treatment of skeletal muscle spasm of local origin. Clin Ther 1978;1:(6):409-424.

46. Man-Son-Hing M, Wells G, Lau A. Quinine for nocturnal leg cramps: a meta-analysis including unpublished data. J Gen Intern Med 1998;13:(9):600-6.

47. Rinne UK. Tizanidine treatment of spasticity in multiple sclerosis and chronic myelopathy. Curr Ther Res Clin Exp 1980;28:(6 I):827-836.

48. Bass B, Weinshenker B, Rice GP, et al. Tizanidine versus baclofen in the treatment of spasticity in patients with multiple sclerosis. Can J Neurol Sci 1988;15:(1):15-9.

49. Eyssette M, Rohmer F, Serratrice G, et al. Multi-centre, double-blind trial of a novel antispastic agent, tizanidine, in spasticity associated with multiple sclerosis. Curr Med Res Opin 1988;10:(10):699-708.

50. Hoogstraten MC, van der Ploeg RJ, vd Burg W, et al. Tizanidine versus baclofen in the treatment of spasticity in multiple sclerosis patients. Acta Neurol Scand 1988;77:(3):224-30.

51. Medici M, Pebet M, Ciblis D. A double-blind, long-term study of tizanidine ('Sirdalud') in spasticity due to cerebrovascular lesions. Curr Med Res Opin 1989;11:(6):398-407.

52. Newman PM, Nogues M, Newman PK, et al. Tizanidine in the treatment of spasticity. Eur J Clin Pharmacol 1982;23:(1):31-5.

53. Smolenski C, Muff S, Smolenski-Kautz S. A double-blind comparative trial of new muscle relaxant, tizanidine (DS 103-282), and baclofen in the treatment of chronic spasticity in multiple sclerosis. Curr Med Res Opin 1981;7:(6):374-83.

54. Bes A, Eyssette M, Pierrot-Deseilligny E, et al. A multi-centre, double-blind trial of tizanidine, a new antispastic agent, in spasticity associated with hemiplegia. Curr Med Res Opin 1988;10:(10):709-18.

55. Cartlidge NE, Hudgson P, Weightman D. A comparison of baclofen and diazepam in the treatment of spasticity. J Neurol Sci 1974;23:(1):17-24.

56. Roussan M, Terrence C, Fromm G. Baclofen versus diazepam for the treatment of spasticity and long-term follow-up of baclofen therapy. Pharmatherapeutica 1985;4:(5):278-84.

57. From A, Heltberg A. A double-blind trial with baclofen (Lioresal) and diazepam in spasticity due to multiple sclerosis. Acta Neurol Scand 1975;51:(2):158-66.

58. Glass A, Hannah A. A comparison of dantrolene sodium and diazepam in the treatment of spasticity. Paraplegia 1974;12:(3):170-4.

59. Nogen AG. Medical treatment for spasticity in children with cerebral palsy. Child Brain 1976;2:(5):304-8.

60. Schmidt RT, Lee RH, Spehlmann R. Comparison of dantrolene sodium and diazepam in the treatment of spasticity. J Neurol Neurosurg Psychiatry 1976;39:(4):350-6.

61. Nance PW. A comparison of clonidine, cyproheptadine and baclofen in spastic spinal cord injured patients. J Am Paraplegia Soc 1994;17:(3):150-6.

62. Basmajian JV, Yucel V. Effects of a GABA--derivative (BA-34647) on spasticity. Preliminary report of a double-blind cross-over study. Am J Phys Med 1974;53:(5):223-8.

63. Basmajian JV. Lioresal (baclofen) treatment of spasticity in multiple sclerosis. Am J Phys Med 1975;54:(4):175-7.

64. Brar SP, Smith MB, Nelson LM, et al. Evaluation of treatment protocols on minimal to moderate spasticity in multiple sclerosis. Arch Phys Med Rehab 1991;72:(3):186-9.

65. Duncan GW, Shahani BT, Young RR. An evaluation of baclofen treatment for certain symptoms in patients with spinal cord lesions. A double-blind, cross-over study. Neurology 1976;26:(5):441-6.

66. Feldman RG, Kelly-Hayes M, Conomy JP, et al. Baclofen for spasticity in multiple sclerosis. Double blind crossover and three year study. Neurology 1978;28:(11):1094-8.

67. Hinderer SR. The supraspinal anxiolytic effect of baclofen for spasticity reduction. Am J Phys Med Rehabil 1990;69:(5):254-8.

68. Hulme A, MacLennan WJ, Ritchie RT, et al. Baclofen in the elderly stroke patient its side-effects and pharmacokinetics. Eur J Clin Pharmacol 1985;29:(4):467-9.

69. Jones K, Castleden CM. A double-blind comparison of quinine sulphate and placebo in muscle cramps. Age Ageing 1983;12:(2):155-8.

70. McKinlay I, Hyde E, Gordon N. Baclofen: A team approach to drug evaluation of spasticity in childhood. Scott Med J 1980;25:(SYMP.):S26-S28.

71. Medaer R, Hellebuyk H, Van DBE, et al. Treatment of spasticity due to stroke. A double-blind, cross-over trial comparing baclofen with placebo. Acta Ther 1991;17:(4):323-331.

72. Milla PJ, Jackson AD. A controlled trial of baclofen in children with cerebral palsy. J Int Med Res 1977;5:(6):398-404.

73. Orsnes G, Crone C, Krarup C, et al. The effect of baclofen on the transmission in spinal pathways in spastic multiple sclerosis patients. Clin Neurophysiol 2000;111:(8):1372-9.

74. Sachais BA, Logue JN, Carey MS. Baclofen, a new antispastic drug. A controlled, multicenter trial in patients with multiple sclerosis. Arch Neurol 1977;34:(7):422-8.

75. Sawa GM, Paty DW. The use of baclofen in treatment of spasticity in multiple sclerosis. Can J Neurol Sci 1979;6:(3):351-4.

76. Basmajian JV, Super GA. Dantrolene sodium in the treatment of spasticity. Arch Phys Med Rehab 1973;54:(2):61-4.

77. Chyatte SB, Birdsong JH, Roberson DL. Dantrolene sodium in athetoid cerebral palsy. Arch Phys Med Rehab 1973;54:(8):365-8.

78. Denhoff E, Feldman S, Smith MG, et al. Treatment of spastic cerebral palsied children with sodium dantrolene. Dev Med Child Neurol 1975;17:(6):736-742.

79. Gambi D, Rossini PM, Calenda G, et al. Dantrolene sodium in the treatment of spasticity caused by multiple sclerosis or degenerative myelopathies: A double-blind, cross-over study in comparison with placebo. Curr Ther Res 1983;33:(5):835-840.

80. Gelenberg AJ, Poskanzer DC. The effect of dantrolene sodium on spasticity in multiple sclerosis. Neurology 1973;23:(12):1313-5.

81. Haslam RH, Walcher JR, Lietman PS, et al. Dantrolene sodium in children with spasticity. Arch Phys Med Rehab 1974;55:(8):384-8.

82. Joynt RL, Leonard JA, Jr. Dantrolene sodium suspension in treatment of spastic cerebral palsy. Dev Med Child Neurol 1980;22:(6):755-67.

83. Katrak PH, Cole AM, Poulos CJ, et al. Objective assessment of spasticity, strength, and function with early exhibition of dantrolene sodium after cerebrovascular accident: a randomized double-blind study. Arch Phys Med Rehab 1992;73:(1):4-9.

84. Ketel WB, Kolb ME. Long-term treatment with dantrolene sodium of stroke patients with spasticity limiting the return of function. Curr Med Res Opin 1984;9:(3):161-9.

85. Luisto M, Moller K, Nuutila A, et al. Dantrolene sodium in chronic spasticity of varying etiology. Acta Neurol Scand 1982;65:(4):355-62.

86. Monster AW. Spasticity and the effect of dantrolene sodium. Arch Phys Med Rehab 1974;55:(8):373-83.

87. Nogen AG. Effect of dantrolene sodium on the incidence of seizures in children with spasticity. Child Brain 1979;5:(4):420-5.

88. Sheplan L, Ishmael C. Spasmolytic properties of dantrolene sodium: Clinical evaluation. Mil Med 1975;140:(1):26-29.

89. Tolosa ES, Soll RW, Loewenson RB. Treatment of spasticity in multiple sclerosis with dantrolene. JAMA 1975;233:(10):1046.

90. Weiser R, Terenty T, Hudgson P, et al. Dantrolene sodium in the treatment of spasticity in chronic spinal cord disease. Practitioner 1978;221:(1321):123-7.

91. Knutsson, E, Martensson, et al. Antiparetic and antispastic effects induced by tizanidine in patients with spastic paresis. J Neurol Sci 1982;53:(2):187-204.

92. Lapierre Y, Bouchard S, Tansey C, et al. Treatment of spasticity with tizanidine in multiple sclerosis. Can J Neurol Sci 1987;14:(3 Suppl):513-7.

93. Meythaler JM, Guin-Renfroe S, Johnson A, et al. Prospective assessment of tizanidine for spasticity due to acquired brain injury. Arch Phys Med Rehab 2001;82:(9):1155-63.

94. Nance PW, Bugaresti J, Shellenberger K, et al. Efficacy and safety of tizanidine in the treatment of spasticity in patients with spinal cord injury. North American Tizanidine Study Group. Neurology 1994;44:(11 Suppl 9):S44-S52.

95. Smith C, Birnbaum G, Carter JL, et al. Tizanidine treatment of spasticity caused by multiple sclerosis: results of a double-blind, placebo-controlled trial. Neurology 1994;44:(11 Suppl 9):S34-42; discussion S42-3.

96. Anonymous. A double-blind, placebo-controlled trial of tizanidine in the treatment of spasticity caused by multiple sclerosis. United Kingdom Tizanidine Trial Group. Neurology 1994;44:(11 Suppl 9):S70-78.

97. Losin S, McKean CM. Chlorzoxazone (paraflex) in the treatment of severe spasticity. Dev Med Child Neurol 1966;8:(6):768-9.

98. Ashby P, Burke D, Rao S, et al. Assessment of cyclobenzaprine in the treatment of spasticity. J Neurol Neurosurg Psychiatry 1972;35:(5):599-605.

99. Bragstad A, Blikra G. Evaluation of a new skeletal muscle relaxant in the treatment of lower back pain (A Comparison of DS 103-282 with Chlorzoxazone). Curr Ther Res Clin Exp 1979;26:(1).

100. Rollings HE, Glassman JM, Soyka JP. Management of acute musculoskeletal conditions - Thoracolumbar strain or sprain: A double-blind evaluation comparing the efficacy and safety of carisoprodol with cyclobenzaprine hydrochloride. Curr Ther Res 1983;34:(6):917-928.

101. Aiken DW. A comparative study of the effects of cyclobenzaprine, diazepam and placebo in the treatment of acute musculoskeletal conditions of the low back. In: Clinical Evaluation of Flexaril. Minneapolis, MN: Postgraduate Medicine Communications; 1978. p. 34-38.

102. Basmajian JV. Cyclobenzaprine hydrochloride effect on skeletal muscle spasm in the lumbar region and neck: two double-blind controlled clinical and laboratory studies. Arch Phys Med Rehab 1978;59:(2):58-63.

103. Brown BR, Jr., Womble J. Cyclobenzaprine in intractable pain syndromes with muscle spasm. JAMA 1978;240:(11):1151-2.

104. Scheiner JJ. Cyclobenzaprine in the treatment of local muscle spasm. In: Clinical Evaluation of Flexeril. Minneapolis, MN: Postgraduate Medicine Communications; 1978. p. 39-48.

105. Boyles WF. Management of acute musculoskelatal conditions. Todays Ther Trends 1983;1:1-16.

106. Fryda-Kaurimsky Z, Muller-Fassbender H. Tizanidine (DS 103-282) in the treatment of acute paravertebral muscle spasm: a controlled trial comparing tizanidine and diazepam. J Int Med Res 1981;9:(6):501-5.

107. Hennies OL. A new skeletal muscle relaxant (DS 103-282) compared to diazepam in the treatment of muscle spasm of local origin. J Int Med Res 1981;9:(1):62-8.

108. Middleton RS. A comparison of two analgesic muscle relaxant combinations in acute back pain. Br J Clin Pract 1984;38:(3):107-9.

109. McMillen JI. A double-blind study of Parafon Forte(TM) and Flexeril(TM) in the treatment of acute skeletal muscle disorders of local origin. Curr Ther Res 1980;28:(2):164-172.

110. Miller AR. A comparative study of Parafon Forte tablets and soma compund in the treatment of painful skeletal muscle conditions. Curr Ther Res Clin Experi 1976;19:(4):444-50.

111. Baratta RR. A double-blind comparative study of carisoprodol, propoxyphene, and placebo in the management of low back syndrome. Curr Ther Res Clin Exp 1976;20:(3):233-40.

112. Cullen AP. Carisoprodol (Soma) in acute back conditions: a double blind, randomized, placebo controlled study. Curr Ther Res 1976;20:(4II):557-562.

113. Hindle TH. Comparison of carisoprodol, butabarbital, and placebo in treatment of the low back syndrome. Calif Med 1972;117:(2):7-11.

114. Soyka JP, Maestripieri LR. Soma compound (carisoprodol plus phenacetin and caffeine) in the treatment of acute, painful musculoskeletal conditions. Curr Ther Res 1979;26:(2):165-180.

115. Aiken DW. Cyclobenzaprine in the treatment of acute skeletal muscle spasm of local origin. In: Clinical Evaluation of Flexeril. Minneapolis, MN: Postgraduate Medicine Communications; 1978. p. 30-33.

116. Baratta RR. A double-blind study of cyclobenzaprine and placebo in the treatment of acute musculoskeletal conditions of the low back. Curr Ther Res 1982;32:(5):646-652.

117. Basmajian JV. Acute back pain and spasm. A controlled multicenter trial of combined analgesic and antispasm agents. Spine 1989;14:(4):438-9.

118. Bennett RM, Gatter RA, Campbell SM, et al. A comparison of cyclobenzaprine and placebo in the management of fibrositis. A double-blind controlled study. Arthritis Rheum 1988;31:(12):1535-42.

119. Bercel NA. Cyclobenzaprine in the treatment of skeletal muscle spasm in osteoarthritis of the cervical and lumbae spine. Curr Ther Res 1977;22:462-468.

120. Bianchi M. Evaluation of cyclobenzaprine for skeletal muscle spasm of local origin. In: Clinical evaluation of Flexeril. Minneapolis, MN: Postgraduate Medicine Communications; 1978. p. 25-29.

121. Borenstein DG, Lacks S, Wiesel SW. Cyclobenzaprine and naproxen versus naproxen alone in the treatment of acute low back pain and muscle spasm. Clin Ther 1990;12:(2):125-31.

122. Carette S, Bell MJ, Reynolds WJ, et al. Comparison of amitriptyline, cyclobenzaprine, and placebo in the treatment of fibromyalgia: A randomized, double-blind clinical trial. Arthritis Rheum 1994;37:(1):32-40.

123. Lance JW, Anthony M. Cyclobenzaprine in the treatment of chronic tension headache. Med J Aust 1972;2:(25):1409-11.

124. Quimby LG, Gratwick GM, Whitney CD, et al. A randomized trial of cyclobenzaprine for the treatment of fibromyalgia. J Rheumatol Suppl 1989;19:140-3.

125. Reynolds WJ, Moldofsky H, Saskin P, et al. The effects of cyclobenzaprine on sleep physiology and symptoms in patients with fibromyalgia. J Rheumatol 1991;18:(3):452-4.

126. Steingard PM, Schildberg WL, Peterson KD. Multiclinic study of a muscle relaxant for treatment of acute musculoskeletal disorders. Osteopath Ann 1980;8:(10):44-58.

127. Diamond S. Double-blind study of metaxalone; use as skeletal-muscle relaxant. JAMA 1966;195:(6):479-80.

128. Latta D, Turner E. An alternative to quinine in nocturnal leg cramps. Curr Ther Res Clin Exp 1989;45:(5):833-837.

129. McGuinness BW. A double-blind comparison in general practice of a combination tablet containing orphenadrine citrate and paracetamol ('Norgesic') with paracetamol alone. J Int Med Res 1983;11:(1):42-5.

130. Valtonen EJ. A controlled clinical trial of chlormezanone, orphenadrine, orphenadrine/paracetamol and placebo in the treatment of painful skeletal muscle spasms. Ann Clin Res 1975;7:(2):85-8.

131. Dapas F, Hartman SF, Martinez L, et al. Baclofen for the treatment of acute low-back syndrome. A double-blind comparison with placebo. Spine 1985;10:(4):345-9.

132. Casale R. Acute low back pain. Symptomatic treatment with a muscle relaxant drug. Clin J Pain 1988;4:(2):81-88.

133. Salvini S, Antonelli S, De MG, et al. Dantrolene sodium in low back pain and cervico brachialgia treatment: A controlled study. Curr Ther Res Clin Exp 1986;39:(2):172-177.

134. Berry H, Hutchinson DR. A multicentre placebo-controlled study in general practice to evaluate the efficacy and safety of tizanidine in acute low-back pain. J Int Med Res 1988;16:(2):75-82.

135. Berry H, Hutchinson DR. Tizanidine and ibuprofen in acute low-back pain: results of a double-blind multicentre study in general practice. J Int Med Res 1988;16:(2):83-91.

136. Fogelholm R, Murros K. Tizanidine in chronic tension-type headache: a placebo controlled double-blind cross-over study. Headache 1992;32:(10):509-13.

137. Lepisto P. A comparative trial of DS 103-282 and placebo in the treatment of acute skeletal muscle spasms due to disorders of the back. Curr Ther Res 1979;26:(4):454-459.

138. Murros K, Kataja M, Hedman C, et al. Modified-release formulation of tizanidine in chronic tension-type headache. Headache 2000;40:(8):633-7.

139. Anonymous. Efficacy and gastroprotective effects of tizanidine plus diclofenac versus placebo plus diclofenac in patients with painful muscle spasms. Curr Ther Res 1998;59:(1):13-22.

140. Utili R, Biotnott JK, Zimmerman HJ. Dantrolene-associated hepatic injury: incidence and character. Gastroenterology 1977;72:610-616.

141. Rivas DA, Chancellor MB, Hill K, et al. Neurological manifestations of baclofen withdrawal. J Urol 1993;150:(6):1903-5.

142. Kofler M, Arturo Leis A. Prolonged seizure activity after baclofen withdrawal. Neurology 1992;42:(3 Pt 1):697-8.

143. Garabedian-Ruffalo SM, Ruffalo RL. Adverse effects secondary to baclofen withdrawal. Drug Intell Clin Pharm 1985;19:(4):304-6.

144. Kirubakaran V, Mayfield D, Rengachary S. Dyskinesia and psychosis in a patient following baclofen withdrawal. Am J Psychiatry 1984;141:(5):692-3.

145. Mandac BR, Hurvitz EA, Nelson VS. Hyperthermia associated with baclofen withdrawal and increased spasticity. Arch Phys Med Rehab 1993;74:(1):96-7.

146. Chen KS, Bullard MJ, Chien YY, et al. Baclofen toxicity in patients with severely impaired renal function. Ann Pharmacother 1997;31:(11):1315-1320.

147. Ghose K, Holmes KM, Matthewson K. Complications of baclofen overdosage. Postgrad Med J 1980;56:(662):865-7.

148. Lipscomb DJ, Meredith TJ. Baclofen overdose. Postgrad Med J 1980;56:(652):108-9.

149. Zak R, Solomon G, Petito F, et al. Baclofen-induced generalized nonconvulsive status epilepticus. Ann Neurol 1994;36:(1):113-4.

150. Elder NC. Abuse of skeletal muscle relaxants. Am Fam Physician 1991;44:(4):1223-1226.

151. Gaillard Y, Baillault F, Pepin G. Meprobamate overdosage: a continuing problem. Sensitive GC-MS quantitation after solid phase extraction in 19 fatal cases. Forensic Sci Int 1997;86:(3):173-180.

152. Nibbelink DW, Strickland SC. Cyclobenzaprine (Flexeril(TM)): Report of a postmarketing surveillance program. Curr Ther Res Clin Exp 1980;28:(6 I):894-903.

153. Jones RF, Burke D, Marosszeky JE, et al. A new agent for the control of spasticity. J Neurol Neurosurg Psychiatry 1970;33:(4):464-8.