Drug Class Review on Skeletal Muscle Relaxants

Preliminary Scan Report #6

May 2014

Last Report: Update 2 (May 2005)

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Scan conducted by:
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OBJECTIVE

The purpose of the preliminary updated literature scan process is to provide the Drug Effectiveness Review Project participants with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with consideration of allocating resources. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the U.S. Food and Drug Administration (FDA) since the last scan. Other important studies could exist.

Date of Last Update Report

Original Report: September 2003
Update #1: January 2004
Update #2: May 2005 (searches through November 2004)

Date of Last Preliminary Update Scan Report

Update #3 Preliminary Scan #1: February 2007
Update #3 Preliminary Scan #2: March 2008
Update #3 Preliminary Scan #3: June 2009
Update #3 Preliminary Scan #4: September 2010
Update #3 Preliminary Scan #5: May 2013 (searches through April Week 3 2013)

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Oregon Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, pain care specialists, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The Participating Organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Participating Organizations approved the following key questions to guide this 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?

Inclusion Criteria

Populations

- 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 however, excluded patients with restless legs syndrome or nocturnal myoclonus.
- Obstetric and dialysis patients were also excluded.

Interventions

Table 1. Included interventions*

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Brand name</th>
<th>Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baclofen</td>
<td>Generic</td>
<td>Oral tablet</td>
</tr>
<tr>
<td>Carisoprodol</td>
<td>Soma®</td>
<td>Oral tablet</td>
</tr>
<tr>
<td>Chlorzoxazone</td>
<td>Parafon Forte® DSC</td>
<td>Oral tablet</td>
</tr>
<tr>
<td>Cyclobenzaprine hydrochloride</td>
<td>Amrix®</td>
<td>Extended release oral capsule</td>
</tr>
<tr>
<td>Cyclobenzaprine hydrochloride</td>
<td>Generic</td>
<td>Oral tablet</td>
</tr>
<tr>
<td>Dantrolene</td>
<td>Dantrium®</td>
<td>Oral capsule</td>
</tr>
<tr>
<td>Metaxalone</td>
<td>Skelaxin®</td>
<td>Oral tablet</td>
</tr>
<tr>
<td>Methocarbamol</td>
<td>Robaxin®, Robaxin-750</td>
<td>Oral tablet</td>
</tr>
<tr>
<td>Orphenadrine</td>
<td>Generic</td>
<td>Extended release oral tablet</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>Zanaflex®</td>
<td>Oral tablet and oral capsule</td>
</tr>
</tbody>
</table>

Study designs

- Controlled clinical trials/randomized controlled trials
- Comparative effectiveness reviews

Comparators: Effectiveness and harms of individual skeletal muscle relaxants

- Benzodiazepines were not considered primary drugs in this report. However, diazepam, clonazepam, and clorazepate were reviewed when they were compared in head-to-head studies with any of the skeletal muscle relaxants listed above.
- 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 only included if it was compared to a skeletal muscle relaxant.
Effectiveness outcomes

- Relief of muscle spasms or pain, functional status, quality of life
- Non-clinical outcomes such as electromyogram measurements or spring tension measurements were excluded.

Harms outcomes

- Somnolence or fatigue, dizziness, dry mouth, weakness, abuse, and addiction
- Withdrawal rates and adverse events
- We also paid special attention to reports of serious hepatic injury.

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from 2013 through May 14, 2014 using terms for included drugs and limited to humans, English language, controlled clinical trials and randomized clinical trials. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) (http://www.effectivehealthcare.ahrq.gov/), the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/), the VA Evidence-based Synthesis Program (http://www.hsrd.research.va.gov/publications/esp/reports.cfm), and University of York Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/crdreports.htm).

Study Selection

The reviewer assessed abstracts of citations identified from literature searches for inclusion using the criteria described above.

RESULTS

New Drugs

New drugs identified in this Preliminary Update Scan
None

New drugs identified in previous Preliminary Update Scan(s)
Amrix® (cyclobenzaprine hydrochloride, 15 mg and 30 mg extended-release oral tablet): indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions in adult patients (02/11/2007).

Soma® (carisoprodol, 250 mg oral capsule): indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions in adults (9/13/2007).
New Indications

New indications identified in this Preliminary Update Scan
None

Identified in previous Preliminary Update Scan(s)
None

New Safety Alerts

Identified in this Preliminary Update Scan
None

Identified in previous Preliminary Update Scan(s)
Dantrium (dantrolene sodium) Oral Capsule: July 2012

BOXED WARNING

- Spontaneous reports suggest a higher proportion of hepatic events with fatal outcome in elderly patients receiving Dantrium. However, the majority of these cases were complicated with confounding factors such as intercurrent illnesses and/or concomitant potentially hepatotoxic medications.

Comparative Effectiveness Reviews

Reviews identified in this Preliminary Update Scan
None

Reviews identified in previous Preliminary Update Scan(s)
None

Randomized Controlled Trials

Trials identified since the most recent scan
Medline searches resulted in 10 citations, none of which were relevant to the key questions and populations of interest in this scan. Table 2 includes all placebo-controlled trials that were identified in previous preliminary update scans. Appendix A includes the abstracts for each relevant trial identified in previous preliminary update scans.

Table 2. Previously identified potentially relevant trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Drugs/Comparisons</th>
<th>Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malanga, 2009</td>
<td>Cyclobenzaprine ER vs. placebo (report of two trials)</td>
<td>Low back and neck pain</td>
<td></td>
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<tr>
<td>Serfer, 2010</td>
<td>Carisoprodol vs. placebo</td>
<td>Low back spasm</td>
<td></td>
</tr>
<tr>
<td>Mathew 2005</td>
<td>Diazepam vs. placebo</td>
<td>Motor function in children with cerebral palsy</td>
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</table>
Ketenci 2005 | Thiocolchicoside vs. Tizanidine vs. placebo | Low back pain associated with muscle spasm

**Summary**

There is no new evidence on skeletal muscle relaxants since the last preliminary update scan. No new head-to-head trials, placebo controlled trials, or comparative effectiveness reviews pertaining to existing drugs were identified in this preliminary update scan.
Appendix A. Abstracts of relevant trials and systematic reviews of skeletal muscle relaxants identified in previous scans (N=5)

Placebo-Controlled Trials (N=4)


Objectives of this study were to assess efficacy and effects on psychomotor performances of thiocolchicoside (TCC) and tizanidine (TZ) compared to placebo. Patients complaining of acute low back pain (LBP) associated with muscle spasm were enrolled in this randomised, double-blind clinical trial, comparing the effects of oral TCC, TZ and placebo on psychomotor performances assessed by a visual analogue scale of tiredness, drowsiness, dizziness and alertness and by psychometric tests after 2 and 5-7 days of treatment. The efficacy assessments, both TCC and TZ, were more effective than placebo in improving pain at rest, hand-to-floor distance, Schober test and decreased paracetamol consumption. There were significant differences among the treatment groups in favour of TCC compared to TZ in visual analog scale-parameters. TZ-induced reduction of psychomotor performances of the patients was confirmed by psychometric tests, which showed significant differences among groups. This study showed that TCC is at least as effective as TZ in the treatment of acute LBP, while it appears devoid of any sedative effect in contrast to TZ.


OBJECTIVE: To evaluate efficacy and tolerability of once-daily cyclobenzaprine extended release (CER) 15- and 30-mg capsules in patients with muscle spasm associated with acute, painful musculoskeletal conditions. METHODS: Two identically designed, randomized, double-blind, placebo- and active-controlled, parallel-group studies in patients aged 18-75 years with muscle spasm associated with neck or back pain. Patients received CER 15 or 30 mg once daily, cyclobenzaprine immediate release (CIR) 10 mg three times daily, or placebo for 14 days. Primary efficacy measures were patient's rating of medication helpfulness and physician's clinical global assessment of response to therapy at day 4. Secondary measures were patient's rating of medication helpfulness and physician's clinical global assessment of response (days 8 and 14), relief from local pain, global impression of change, restriction in activities of daily living, restriction of movement, daytime drowsiness, quality of nighttime sleep (days 4, 8, and 14), and quality of life (days 8 and 14). RESULTS: A total of 156/254 randomized patients in study 1 and 174/250 in study 2 completed 14 days of treatment. Significant improvements in patient's rating of medication helpfulness and physician's clinical global assessment of response to therapy at day 4. Significant improvements with CER 30 mg versus placebo (CER 30 mg, study 1, p = 0.007; CER 15 mg, study 2, p = 0.018) at day 4.
0.004), and restriction of movement (p = 0.002). Neither study reported differences between study groups on the physician's clinical global assessment. Improvements with CER were comparable to that of CIR. In both studies, daytime drowsiness was reported more frequently in active treatment groups than in the placebo group; however, reports of drowsiness decreased over time in all groups. In general, daytime drowsiness was reported more frequently in CIR groups than in CER groups. More adverse events were reported in the active treatment groups versus placebo and were similar in the CER and CIR groups, except somnolence, which occurred more frequently with CIR.

CONCLUSIONS: Once-daily CER 15 mg (study 2) and CER 30 mg (study 1) were effective in treating muscle spasm associated with painful musculoskeletal conditions after 4 days of treatment. Differences between CER and placebo groups did not reach statistical significance on all efficacy measures, and the protocols were not powered to detect differences between active treatment arms. CER was generally safe and well tolerated, with low rates of somnolence.


Muscle spasm and hypertonia limit mobility in children with spastic cerebral palsy. This double-blind, placebo-controlled, randomized controlled clinical trial studies the clinical efficacy of a low dose of diazepam in enhancing movement in children with spastic cerebral palsy. One hundred and eighty children fulfilled the criteria and were randomly allocated to receive one of two doses of diazepam or placebo at bedtime; 173 completed the study. There was a significant reduction of hypertonia, improvement in the range of passive movement, and an increase in spontaneous movement in the children who received diazepam. There was no report of daytime drowsiness. In developing countries, where cost factors often determine choice of drug, diazepam is a cheap and effective way of relieving spasm and stiffness, optimizing physical therapy and facilitating movement in children with spasticity.


BACKGROUND: Carisoprodol, a centrally active skeletal muscle relaxant, is widely used for the treatment of acute, painful musculoskeletal disorders. When administered at a dose of 350 mg four times daily, carisoprodol demonstrated significant clinical benefit in its early clinical development trials; however, some unfavorable side effects, such as drowsiness and dizziness, were reported. Recently, research was conducted to determine if a lower dose of carisoprodol would retain efficacy but improve tolerability compared to the higher 350-mg dose. OBJECTIVE: The purpose of this multicenter study was to compare the efficacy and safety of carisoprodol 250-mg tablets four times daily to 350-mg tablets four times daily and to placebo in patients with acute, painful musculoskeletal spasm of the lower back. RESEARCH DESIGN AND METHODS: In this 1-week double-blind, placebo-controlled, parallel-group multicenter trial, patients 18 to 65 years of age with moderate to severe back spasm were randomly assigned to treatment with
carisoprodol 250-mg tablets (n = 264), 350-mg tablets (n = 273), or matching placebo tablets (n = 269) three times daily and at bedtime. RESULTS: The carisoprodol 250-mg regimen was significantly more effective than placebo as assessed by both patient-rated relief from starting backache (p = 0.0001) and patient-rated global impression of change (p = 0.0046). There were no significant differences between the 250-mg and 350-mg dosages for the coprimary efficacy endpoints, and patients improved with or without sedation. Fewer than 1% of patients in the carisoprodol 250-mg group discontinued prematurely because of treatment-emergent adverse events, and no patient discontinued because of drowsiness. CONCLUSIONS: When administered three times daily and at bedtime, carisoprodol 250 mg was as effective as 350 mg three times daily and at bedtime with a lower incidence of adverse events and fewer discontinuations of therapy due to adverse events. Patients improved whether or not they reported sedation as an adverse event.

Systematic Reviews (N=1)


The aim of this paper was to assess the effectiveness and safety of baclofen, dantrolene, tizanidine and any other drugs for the treatment of long-term spasticity in spinal cord injury (SCI) patients, as well as the effectiveness and safety of different routes of administration of baclofen. A systematic review of randomised controlled trials (RCTs), within the Cochrane Collaboration Injuries Group, was carried out. The Cochrane Injuries Group Specialised Register, the Cochrane Controlled Trials Register, MEDLINE, EMBASE and CINAHL were searched up to July 2006 without language restriction. Drug companies and experts active in the area were also contacted to find other relevant studies. Two investigators independently identified relevant studies, extracted data and assessed methodological quality of studies resolving disagreement by consensus. Nine out of 55 studies met the inclusion criteria. The heterogeneity among studies did not allow quantitative combination of RESULTS: Study designs were: 8 crossover, 1 parallel-group trial. Two studies (14 SCI patients) showed a significant effect of intrathecal baclofen in reducing spasticity (Ashworth score and activities of daily living [ADL] performances), compared to placebo, without any adverse effect. The study comparing tizanidine to placebo (118 SCI patients) showed a significant effect of tizanidine in improving Ashworth score but not in ADL performances. The tizanidine group reported significant rates of adverse effects (drowsiness, xerostomia). For the other drugs (gabapentin, clonidine, diazepam, amytal and oral baclofen) the results do not provide evidence for a clinical significant effectiveness. This systematic review indicates that there is insufficient evidence to assist clinicians in a rational approach to antispastic treatment for SCI. Further research is urgently needed to improve the scientific basis of patient care. [References: 66]