Previous Recommendations:

- The evidence does not support any conclusions about the comparative effectiveness between baclofen, tizanidine, or dantrolene for spasticity. All are effective and equivalent to diazepam. Dantrolene is associated with rare serious dose-related hepatotoxicity.
- The evidence does not support any conclusions for the comparative efficacy or safety between skeletal muscle relaxants for musculoskeletal conditions.
- Cyclobenzaprine had the largest body of evidence to support its efficacy compared to placebo.
- Chlorzoxazone is associated with rare serious dose-related hepatotoxicity.
- The evidence does not support any conclusions about the comparative efficacy or adverse effects for different subpopulations of patients such as race, gender, or age.

PA Criteria: A Prior Authorization is in place to support preferred PDL skeletal muscle relaxants and to cover for OHP above the line diagnoses only. A quantity limit restricts carisoprodol products to less than 56 tablets within 90 days unless patient has a terminal illness.

Methods

Three scans were completed by the Oregon Evidence-based Practice Center Drug Effectiveness Review project with a literature search through May 2009. Of those, there were no new, potentially relevant studies. A MEDLINE OVID search was conducted using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials, controlled clinical trials, or meta-analysis from May 2009 (date from last DERP scan) to current. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

New Trials:

A total of 49 citations resulted from initial literature search. After inclusion for further review, 4 potentially relevant randomized trials were identified (Appendix A) and include two trials evaluating cyclobenzaprine ER (Amrix®), one study
comparing tizanidine sublingual and tizanidine oral, and a randomized trial evaluating carisoprodol 250mg in patients with low back pain. These trials are briefly described in table 1.

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Population</th>
<th>Primary Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weill, 2010¹</td>
<td>Pooled analysis of 2 RCT, DB, PC, PG studies</td>
<td>Adults with local muscle spasm associated with neck/low back pain</td>
<td>Patient’s rating of medication helpfulness and physicians’ clinical global assessment of response at day 4</td>
<td>Relief from local pain: CER 15: 74 (58.3%) CER 30: 84 (66.7%) CIR 10: 79 (64.2%) Pl: 60 (46.9%) Physicians’ clinical global assessment: NS for all treatment groups Overall 34.5% attrition</td>
</tr>
<tr>
<td>Vakhapova, 2010²</td>
<td>Tizanidine 8mg SL vs. tizanidine 8mg PO vs. placebo N=16</td>
<td>Adults with Multiple Sclerosis and spasticity requiring treatment</td>
<td>Spasticity as measured by the Ashworth Scale</td>
<td>Spasticity (mean Ashworth scale): TZ SL: 8.31 TZ PO: 9.5 Pla: 11.31 P=0.002; TZ vs. placebo P=0.002; PO vs. placebo P=0.34 SL vs. PO tizanidine NS for all treatment groups in mobility time</td>
</tr>
<tr>
<td>Malanga, 2009³</td>
<td>2 RCT, DB, DD, PC</td>
<td>Adults with muscle spasm of cervical or lumbar origin associated with local pain</td>
<td>Patient’s rating of medication helpfulness and physicians’ clinical global assessment of response at day 4</td>
<td>Study 1105: Patient’s rating of medication helpfulness good to excellent (day 4): CER 30: 38 (58.4%) CER 15: 30 (16.9%) CIR 10: 31 (49.9%) Pl: 21 (32.8%) P=0.007; CER vs. placebo P=0.029; CER vs. placebo P=0.061 CIR vs. placebo Physicians’ clinical global assessment: NS for all treatment groups Study 1106: Patient’s rating of medication helpfulness good to excellent (day 4): CER 30: 45 (67.7%) CER 15: 38 (53.3%) CIR 10: 40 (65.5%) Pl: 25 (39.1%) P=0.018; CER vs. placebo P=0.092; CER vs. placebo P=0.007; CIR vs. placebo Physicians’ clinical global assessment: NS for all treatment groups</td>
</tr>
<tr>
<td>Serfer, 2012⁴</td>
<td>Carisoprodol 250mg QID vs. Carisoprodol 350mg QID vs. placebo (n=806) 1 week</td>
<td>Painful musculoskeletal spasm of the lower back</td>
<td>Patient-rated relief from starting backache and patient rated global impression of change</td>
<td>Patient-rated relief: 250mg: 64.3% 350mg: 66.2% Pla: 52.2% P=0.0001 for 250mg vs. pla P=0.001 for 350mg vs. pla P=NS for 250mg vs. 350mg Global impression of change (mean improvement): 250mg: 3 (1.1%) 350mg: 15 (5.0%) Pla: 10 (3.3%) Discontinuations due to adverse events 250mg: 3 (1.1%) 350mg: 15 (5.0%) Pla: 10 (3.3%)</td>
</tr>
</tbody>
</table>

Table 1: Potentially relevant new trials
New drugs:
None

New formulations/dosage forms:
Cyclobenzaprine Extended Release Oral Capsule (Amrix®) 15mg, 30mg strengths: Approved 2/1/07

New FDA Indications:
None

New FDA safety alerts:

<table>
<thead>
<tr>
<th>SMR</th>
<th>Date</th>
<th>Alert type</th>
<th>Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carisoprodol</td>
<td>9/07</td>
<td>Label Change: Warnings, Precautions and Adverse Reactions</td>
<td>Risk of sedative properties, drug dependence, withdrawal and abuse</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>4/07</td>
<td>Label Change: Contraindications and warnings</td>
<td>When administered with fluvoxamine or ciprofloxacin (CYP1A2 inhibitors), the serum concentration of tizanidine was significantly increased and potentiated its hypotensive and sedative effects</td>
</tr>
<tr>
<td>Metaxalone</td>
<td>10/2008</td>
<td>Precaution</td>
<td>The sedative effects of Skelaxin and other CNS depressants (e.g., alcohol, benzodiazepines, opioids, tricyclic antidepressants) may be additive. Therefore, caution should be exercised with patients who take more than one of these CNS depressants simultaneously</td>
</tr>
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</table>

New Systematic Reviews:
One review from the Cochrane Collaboration (Appendix B) assessed the effectiveness and safety of drugs for the long-term treatment of spasticity in Spinal Cord Injury (SCI) patients. Nine studies were identified, two of these evaluating intrathecal baclofen. One study showed a significant improvement in spasticity as measured by the Ashworth scale in tizanidine compared to placebo (-3.70, SE 0.67; p<0.001) but no differences in activities of daily living. Results from studies for gabapentin, clonidine, diazepam, and baclofen did not provide evidence for clinically significant effectiveness. Overall, there was insufficient evidence to make conclusions for antispastic treatment in SCI patients.

A second review from the Cochrane Collaboration evaluated anti-spasticity agents in patients with Multiple Sclerosis (MS) and again found insufficient evidence for comparative effectiveness conclusions between the medications. Twenty six placebo controlled and thirteen comparative studies were included in this review and only three of the placebo-controlled trials and none of the comparative studies showed a statistically significant difference in the Ashworth scale for spasticity between the drugs. The remaining studies were assessed using unvalidated scores and results of functional assessments were inconclusive.

Recommendations:
1. No further research or review needed.
2. Evaluate comparative costs for any further decisions or changes.
Appendix A: New Trial Abstracts


OBJECTIVE: To assess the efficacy and tolerability of once-daily cyclobenzaprine extended release (CER) 15 and 30 mg in relieving acute muscle spasm. METHODS: This is a pooled analysis of 2 randomized, double-blind, placebo-controlled, parallel-group studies of identical design. Adults with local muscle spasm associated with neck/low back pain were randomized to treatment with once-daily CER 15 (n = 127) or 30 mg (n = 126), cyclobenzaprine immediate release (CIR) 10 mg 3 times daily (n = 123), or placebo (n = 128) for 14 days. Primary outcome measures were the patient's rating of medication helpfulness and physician's clinical global assessment of response to therapy at day 4. RESULTS: Of 504 patients, 330 (65.5%) completed the studies. Significantly greater improvements in patient's rating of medication helpfulness were reported with CER 15 and 30 mg versus placebo at day 4 (P < 0.025). No differences were reported between groups in physician's clinical global assessment. Significantly greater improvements (P < 0.025) were noted in patient-rated secondary measures versus placebo: relief from local pain at days 4 (CER 30 mg) and 8 (CER 15 and 30 mg), global impression of change at days 4 and 8 (CER 30 mg), and restriction of movement at day 4 (CER 30 mg). Improvements with CER 15 and 30 mg on most efficacy measures were similar to CIR. There was less reported daytime drowsiness with CER 15 and 30 mg than with CIR (P < 0.05). Most adverse events (AEs) were mild in intensity. The most common AEs for all groups were dry mouth, constipation, dizziness, headache, and somnolence. The rate of somnolence reported as an AE was lower (P < 0.05) with CER 15 (0.8%) and 30 mg (1.6%) than with CIR (7.3%). CONCLUSION: Once-daily CER was effective in relieving acute muscle spasm based on patient's rating of medication helpfulness at day 4 and was generally well tolerated with a low rate of reported somnolence.


BACKGROUND: Approximately 90% of patients with multiple sclerosis (MS) experience spasticity during their lifetime. Tizanidine HCl is an alpha2 adrenergic agonist indicated for treating spasticity due to MS or spinal cord injury. OBJECTIVES: To compare the clinical efficacy and safety of once-nightly sublingual versus oral tizanidine HCl (8 mg) or placebo in MS patients with spasticity requiring treatment. METHODS: A double-blind, double-dummy, randomized, 3-treatment, 2-way crossover, comparative, placebo-controlled study was conducted in a neuroimmunology clinic of a university-affiliated medical center (December 2005 to March 2006). Enrolled patients received placebo once nightly and were then randomized to receive oral tizanidine HCl following sublingual tizanidine HCl or sublingual tizanidine HCl following oral tizanidine HCl, each arm for 7 days. The patients were evaluated for spasticity (Ashworth scale), mobility, Global Assessments of Disease Severity and Change, and safety parameters, including next-day somnolence (Epworth Sleepiness Scale), fatigue, hypotension, and hepatotoxicity. RESULTS: Sixteen MS patients aged 20 to 65 years with spasticity requiring treatment and Expanded Disability Status Scale score of 6.5 or less were enrolled. There were significant reductions in next-day (12-14 hours after dosing) spasticity following sublingual tizanidine compared with placebo and oral tizanidine, or placebo treatment, and sublingual tizanidine versus placebo treatment. Fatigue, hypotension, or hepatotoxicity levels did not increase. CONCLUSIONS: Overnight sublingual tizanidine provides improvement in next-day spasticity compared with placebo, without increasing next-day somnolence. The Epworth somnolence score improved significantly with sublingual tizanidine treatment. This is contrary to the reported day-dose tizanidine use, in which increased somnolence is the most cited cause for patient dissatisfaction and noncompliance.

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 were reported with CER versus placebo (CER 30 mg, study 1, p = 0.007; CER 15 mg, study 2, p = 0.018) at day 4. Significant improvements with CER 30 mg versus placebo were also seen at day 4 in study 1 for patient-rated global impression of change (p = 0.008), relief of local pain (p = 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.


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 moderate to severe back spasm. MAIN OUTCOME MEASURES: The coprimary efficacy variables were patient-rated relief from starting backache and patient-rated global impression of change assessed on treatment day 3. 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.

Objectives: To assess the effectiveness and safety of baclofen, dantrolene, tizanidine and any other drugs for the treatment of long-term spasticity in SCI patients, as well as the effectiveness and safety of different routes of administration of baclofen. Methods: We searched the Cochrane Injuries Group Specialised Register, CENTRAL, MEDLINE/PubMed, EMBASE, Zetoc, Web of Knowledge, CINAHL and Current Controlled Trials. We also checked the reference lists of relevant papers to identify any further studies. The searches were last conducted in July 2008. All parallel and cross-over randomised controlled trials (RCTs) including spinal cord injury patients complaining of 'severe spasticity'. Studies where less than 50% of patients had a spinal cord injury were excluded. Methodological quality of studies (allocation concealment, blinding, patient's characteristics, inclusion and exclusion criteria, interventions, outcomes, losses to follow up) was independently assessed by two investigators. The heterogeneity among studies did not allow quantitative combination of results. Results: Nine studies met the inclusion criteria. Study designs were: 8 cross-over and 1 parallel-group trial. Two studies (14 SCI patients), showed a significant effect of intrathecal baclofen in reducing spasticity (Ashworth Score and ADL performances), compared to placebo, without any adverse effects. 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 did not provide evidence for clinically significant effectiveness. Conclusion: 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.


Objectives: To assess the absolute and comparative efficacy and tolerability of anti-spasticity agents in MS patients. Methods: We searched the Cochrane MS Group trials register (June 2003), the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 2, 2003), MEDLINE (January 1966 to June 2003), EMBASE (January 1988 to June 2003), bibliographies of relevant articles, personal communication, manual searches of relevant journals and information from drug companies. Double-blind, randomised controlled trials (either placebo-controlled or comparative studies) of at least seven days duration. Two independent reviewers extracted data and the findings of the trials were summarised. Missing data were collected by correspondence with principal investigators. A meta-analysis was not performed due to the inadequacy of outcome measures and methodological problems with the studies reviewed. Results: Twenty-six placebo-controlled studies (using baclofen, dantrolene, tizanidine, botulinum toxin, vigabatrin, prazepam, threonine and cannabinoids) and thirteen comparative studies met the selection criteria and were included in this review. Only fifteen of these studies used the Ashworth scale, of which only three of the eight placebo-controlled trials and none of the seven comparative studies showed a statistically significant difference between test drugs. Spasms, other symptoms and overall impressions were only assessed using unvalidated scores and results of functional assessments were inconclusive. Conclusions: The absolute and comparative efficacy and tolerability of anti-spasticity agents in multiple sclerosis is poorly documented and no recommendations can be made to guide prescribing. The rationale for treating features of the upper motor neurone syndrome must be better understood and sensitive, validated spasticity measures need to be developed.