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Month/Year of Review: March 2012
PDL Class: Skeletal Muscle Relaxants

Date of Last Review: May 2005
Source Document: DERP

Current Preferred Agents:
Cyclobenzaprine
Carisoprodol
Baclofen
Methocarbamol
Orphenadrine ER
Carisoprodol/aspirin
Tizanidine

Current Non-Preferred Agents:
Chlorzoxazone
Metaxalone (Skelaxin®)
Dantrolene (Dantrium®)
Cyclobenzaprine ER 24 hr (Amrix®)

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 w 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 1: Potentially relevant new trials

Study	Comparison	Population	Primary Outcome	Results
Weill, 2010[1] Pooled analysis of 2 RCT, DB, PC, PG studies	Cyclobenzaprine ER (CER) 15mg, CER 30mg, Cyclobenzaprine IR (CIR) 10mg TID, or placebo N=330 14 days	Adults with local muscle spasm associated with neck/low back pain	Patient's rating of medication helpfulness and physicians' clinical global assessment of response at day 4	<u>Patient's rating of medication helpfulness good to excellent (day 4):</u> CER 15: 65 (51.2%) CER30: 68 (54%) CIR10: 71 (57.7%) Pl: 46 (35.9%) P<0.025 for both doses of CER vs. placebo NS for both doses of CER vs. CIR 10mg TID <u>Relief from local pain</u> CER 15: 74 (58.3%) CER30: 84 (66.7%) CIR10: 79 (64.2%) Pl: 60 (46.9%) <u>physicians' clinical global assessment</u> NS for all treatment groups Overall 34.5% attrition
Vakhapova, 2010[2] RCT, DB, DD, PC	Tizanidine 8mg SL vs. tizanidine 8mg PO vs. placebo N=16	Adults with Multiple Sclerosis and spasticity requiring treatment	Spasticity as measured by the Ashworth Scale	<u>Spasticity (mean Ashworth scale)</u> TZ SL: 8.31 TZ PO: 9.5 Pla: 11.31 P=0.002; SL vs. placebo P=0.002; PO vs. placebo P=0.34 SL vs. PO tizanidine NS for all treatment groups in mobility time
Malanga, 2009[3] 2 RCT, DB, PC	Cyclobenzaprine ER (CER) 15mg, CER 30mg, Cyclobenzaprine IR (CIR) 10mg TID, or placebo N=504 14 days	Adults with muscle spasm of cervical or lumbar origin associated with local pain	Patient's rating of medication helpfulness and physicians' clinical global assessment of response at day 4	*<u>Study 1105</u>* <u>Patient's rating of medication helpfulness good to excellent (day 4):</u> CER30: 38 (58.4%) CER15: 30 (16.9%) CIR10: 31 (49.9%) Pl: 21 (32.8%) P=0.007; CER30 vs. Placebo P=0.29; CER14 vs. placebo P=0.061 CIR vs. placebo <u>physicians' clinical global assessment</u> NS for all treatment groups *<u>Study 1106</u>* <u>Patient's rating of medication helpfulness good to excellent (day 4):</u> CER30: 30 (48.3%) CER 15: 35 (55.5%) CIR10: 40 (65.5%) Pl: 25 (39.1%) P=0.018; CER15 vs. placebo P=0.092; CER30 vs. placebo P=0.007; CIR vs. placebo <u>physicians' clinical global assessment</u> NS for all treatment groups
Serfer, 2012[4] DB, RCT, PC	Carisoprodol 250mg QID vs. Carisoprodol 350mg QID vs. placebo (n=806) 1 week	Painful musculoskeletal spasm of the lower back	Patient-rated relief from starting backache and patient rated global impression of change	*<u>Patient-rated relief</u>* 250mg: 64.3% 350mg: 66.2% Pla: 52.2% P=0.0001 for 250mg v. pla P<0.001 for 350mg vs. pla P=NS for 250mg vs. 350mg *<u>Global impression of change (mean improvement)</u>* P=0.0046 for 250mg vs. pla P=0.0011 for 350mg vs. pla P=NS for 250mg vs. 350mg *<u>Discontinuations due to adverse events</u>* 250mg: 3 (1.1%) 350mg: 15 (5.0%) Pla: 10 (3.3%)

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:

SMR	Date	Alert type	Focus
Carisoprodol	9/07	Label Change: Warnings, Precautions and Adverse Reactions	Risk of sedative properties, drug dependence, withdrawal and abuse
Tizanidine	4/07	Label Change: Contraindications and warnings	When administered with fluvoxamine or ciprofloxacin (CYP1A2 inhibitors), the serum concentration of tizanidine was significantly increased and potentiated its hypotensive and sedative effects
Metaxalone	10/2008	Precaution	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

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.[5] 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.[5]

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.[6] 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.[6]

Recommendations:
1. No further research or review needed.
2. Evaluate comparative costs for any further decisions or changes.

Appendix A: New Trial Abstracts

1. **Weil AJ, Ruoff GE, Nalamachu S, Altman CA, Xie F, Taylor DR. Efficacy and tolerability of cyclobenzaprine extended release for acute muscle spasm: a pooled analysis. Postgrad Med. 2010 Jul;122(4):158-69.**

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.

2. **Vakhapova V, Auriel E, Karni A. Nightly sublingual tizanidine HCl in multiple sclerosis: clinical efficacy and safety. Clin Neuropharmacol. 2010 May;33(3):151-4.**

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, oral versus 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.

3. **Malanga GA, Ruoff GE, Weil AJ, Altman CA, Xie F, Borenstein DG. Cyclobenzaprine ER for muscle spasm associated with low back and neck pain: two randomized, double-blind, placebo-controlled studies of identical design. Curr Med Res Opin. 2009 May;25(5):1179-96.**

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.

4. **Serfer GT, Wheeler WJ, Sacks HJ. Randomized, double-blind trial of carisoprodol 250 mg compared with placebo and carisoprodol 350 mg for the treatment of low back spasm. Curr Med Res Opin. 2010 Jan;26(1):91-9.**

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. 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.

5. **Taricco M, Adone R, Pagliacci C, Telaro E. Pharmacological interventions for spasticity following spinal cord injury. Cochrane Database of Systematic Reviews 2000, Issue 2. Art. No.: CD001131. DOI: 10.1002/14651858.CD001131.**

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.

6. **Shakespeare D, Boggild M, Young CA. Anti-spasticity agents for multiple sclerosis. Cochrane Database of Systematic Reviews 2003, Issue 4. Art. No.: CD001332. DOI: 10.1002/14651858.CD001332.**

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.