

# Drug Class Review on Skeletal Muscle Relaxants



## Update #3: Preliminary Scan Report #4

September 2010

**The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. 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.**

Roger Chou, MD  
Kim Peterson, MS

Oregon Evidence-based Practice Center and  
Drug Effectiveness Review Project  
Mark Helfand, MD, MPH, Director  
Marian S. McDonagh, PharmD, Principal  
Investigator

Scan prepared by Susan Carson, MPH



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## OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Washington State Health Care Authority 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 only to assist with the Washington State Health Care Authority's consideration of allocating resources toward a full update of this topic. 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 Washington State Health Care Authority 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 FDA or Health Canada since the last report. Other important studies could exist.

### Dates of Previous Reports

Original Report: September 2003

Update #1: January 2004

Update #2: May 2005 (searches through November 2004)

### Dates of Previous Update Scans

Update #3 Preliminary Scan #1: February 2007

Update #3 Preliminary Scan #2: March 2008

Update #3 Preliminary Scan #3: June 2009

## 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?

## Study eligibility criteria

### Population

- 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.

### Drugs

- Baclofen
- Carisoprodol
- Chlorzoxazone
- Cyclobenzaprine
- Dantrolene
- Metaxalone
- Methocarbamol
- Orphenadrine
- Tizanidine
- 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.

### 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)
- Non-clinical outcomes such as electromyogram measurements or spring tension measurements were excluded.

The following adverse events were specifically reviewed:

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

### Study types

- Controlled clinical trials to evaluate efficacy

- For adverse events, clinical trials and large, high-quality observational cohort studies were included.
- Case reports and case series were excluded

## **METHODS**

### **Literature Search**

To identify relevant citations, we searched Ovid MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations from May 2009 through August 31, 2010 using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada (<http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/index-eng.php>) websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote X.02) and duplicate citations were removed.

### **Study Selection**

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

## **RESULTS**

### **Overview**

Searches identified 15 citations. Of those, there were 2 new, potentially relevant studies (Appendix A). One publication described 2 placebo-controlled trials of cyclobenzaprine extended release in patients with muscle spasm associated with low back and neck pain (Malanga 2009), and the other compared carisoprodol 250 mg to placebo and carisoprodol 350 mg in patients with low back spasm (Serfer 2010)

Previous scans did not identify any potentially relevant trials.

### **New Drugs**

No new drugs were identified.

### **New Indications**

No new indications were identified.

### **New Safety Alerts**

No new safety alerts were identified.

## Appendix A. Abstracts of potentially relevant new studies of skeletal muscle relaxants (N=2)

Malanga, G. A., G. E. Ruoff, et al. (2009). "Cyclobenzaprine ER for muscle spasm associated with low back and neck pain: two randomized, double-blind, placebo-controlled studies of identical design." Current Medical Research & Opinion **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.

Serfer, G. T., W. J. Wheeler, et al. (2010). "Randomized, double-blind trial of carisoprodol 250 mg compared with placebo and carisoprodol 350 mg for the treatment of low back spasm." Current Medical Research & Opinion **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.