

Class Update: Skeletal Muscle Relaxants

Date of Review: March 2017

Date of Last Review: November 2014

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Update:

The purpose of this class review is to evaluate new evidence for the safety and efficacy of muscle relaxants in treating chronic neurologic conditions associated with spasticity, or in chronic or acute musculoskeletal conditions with or without muscle spasms.

Research Questions:

1. What is the comparative efficacy and effectiveness of skeletal muscle relaxants for 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 harms of skeletal muscle relaxants in neurologic conditions with spasticity or musculoskeletal conditions?
3. Are there certain sub-populations in which skeletal muscle relaxants may be beneficial or cause more harm?

Conclusions:

- There is no new evidence regarding the use of skeletal muscle relaxants in neurological conditions associated with spasticity.
- Moderate quality evidence shows tizanidine, cyclobenzaprine, and baclofen are more efficacious than placebo for short-term (5 to 7 days) pain relief of acute low back pain (LBP).¹
- One high quality study showed that tizanidine, baclofen and cyclobenzaprine are more effective than placebo in reducing pain associated with acute LBP.²
- Three high quality studies revealed carisoprodol is no more effective than placebo in alleviating pain associated with acute LBP.²
- There is insufficient evidence to evaluate the effectiveness of skeletal muscle relaxants in chronic LBP.^{1,2}
- Moderate quality evidence demonstrates that patients experience more adverse effects with skeletal muscle relaxants compared to placebo.¹
- There is no new evidence regarding use of skeletal muscle relaxants in specific populations.

Recommendations:

- No PDL changes recommended after evaluation of costs in the executive session.
- Revise PA criteria to limit duration of skeletal muscle relaxant therapy to 3 months due to limited evidence demonstrating their efficacy beyond 5-7 days and to prevent concomitant use of opioids with carisoprodol.

Previous Conclusions and 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.
- 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 the patient has a terminal illness.

Background:

Skeletal muscle relaxants can be classified into 2 main categories: antispasticity and antispasmodic medications. The antispasticity agents include baclofen and dantrolene. Although the precise mechanism of action of baclofen is unknown, it is postulated baclofen inhibits synaptic reflexes at the spinal cord level.³ Baclofen is Food and Drug Administration (FDA) approved to alleviate signs and symptoms of spasticity resulting from multiple sclerosis (MS) or spinal cord injuries; particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity.³ It is not indicated for the treatment of skeletal muscle spasm due to rheumatic diseases.³ The efficacy of baclofen in stroke, cerebral palsy and Parkinson's disease has not been established.³ In contrast, dantrolene causes skeletal muscle relaxation through a direct effect on skeletal muscle, most likely due to interfering with calcium release from the sarcoplasmic reticulum.⁴ Dantrolene is FDA approved to control the manifestations of clinical spasticity resulting from upper neuron disorders due to spinal cord injury, cerebral palsy, or MS.⁴ Similar to baclofen, dantrolene is not indicated for treatment of skeletal muscle spasm due to rheumatic disorders.⁴ Dantrolene can cause fatal hepatotoxicity and the manufacturer has issued a black box warning notifying prescribers of this serious adverse effect.⁴

Antispasmodic muscle relaxants include carisoprodol, cyclobenzaprine, chlorzoxazone, metaxalone, methocarbamol, and orphenadrine. Cyclobenzaprine is structurally related to the tricyclic antidepressants (TCAs) and causes anticholinergic side effects similar to TCAs. Carisoprodol is metabolized to meprobamate, a drug that is primarily used to treat anxiety. The antispasmodics decrease muscle spasm by altering central nervous system (CNS) conduction resulting in reduced pain perception. Most patients will also experience sedation as a result of the drugs' effects on CNS physiology. Tizanidine, a centrally acting alpha agonist, is a unique agent in this class because it alleviates both spasms and spasticity. It has a short duration of effect, so it should be used at times when relief of spasticity is most important.⁵ In general, antispasticity and antispasmodic agents are not interchangeable and should not be substituted for each other.⁶ **Table 1** outlines the FDA approved indications, dosing, and adverse effects of the skeletal muscle relaxants. The current list of preferred skeletal muscle relaxants is included in **Appendix 1**.

The evidence for effectiveness of the skeletal muscle relaxants is sparse. A 2000 Cochrane review assessed the effectiveness and safety of muscle relaxants for the long-term treatment of spasticity in spinal cord injury (SCI) patients.⁷ Overall, there was insufficient evidence to make conclusions for antispastic treatment in SCI patients.⁷ Another Cochrane review published in 2003 evaluated anti-spasticity agents in patients with MS and again found insufficient evidence for comparative effectiveness between these medications.⁸ An additional 2003 Cochrane review evaluated the effectiveness of skeletal muscle relaxants in the

treatment of nonspecific low back pain.⁹ Eleven short term, placebo controlled, randomized trials of nonbenzodiazepene muscle relaxants were included in this systematic review. The authors concluded there is moderate quality evidence that cyclobenzaprine, carisoprodol, orphenadrine and tizanidine are all more effective than placebo for reducing pain intensity in patients with acute low back pain (Relative Risk (RR) 0.80, 95% Confidence Interval (CI) 0.71 – 0.89).⁹ At the time of this review there were no comparative trials between muscle relaxants and nonsteroidal anti-inflammatory agents (NSAIDs). Of note, adverse effects including drowsiness, headache, blurred vision, nausea, and vomiting, were significantly more prevalent in patients taking muscle relaxants compared to placebo (RR 1.50, 95% CI: 1.14-1.98).⁹ Central nervous adverse effects such as dizziness and drowsiness occurred more frequently than other side effects (RR 2.04, 95% CIL 1.23-3.37).⁹ Although skeletal muscle relaxants are somewhat effective in the short term management of nonspecific low back pain, their adverse effects require that they be used with caution.⁹ This assessment is reinforced by the 2012 American Geriatrics Society (AGS) Beers Criteria update for potentially inappropriate medication use in older adults.¹⁰ For this update, an interdisciplinary panel of AGS reviewers completed a systematic review and graded the evidence using the Cochrane scoring system to evaluate risk of bias.¹¹ Moderate quality evidence revealed that skeletal muscle relaxants are poorly tolerated by older adults due to anticholinergic and sedating adverse effects and should be avoided in the elderly.¹⁰ Furthermore, there is insufficient evidence to support the effectiveness of muscle relaxants at doses tolerated by older adults.¹⁰ When the 2015 update to the Beers criteria was published, no additional evidence was found to modify the 2012 recommendations for avoiding skeletal muscle relaxants in older adults.¹²

The third National Health and Nutrition Examination Survey (NHANES III) examined prevalence of patterns for prescription muscle relaxant use from 1988 through 1994.¹³ This survey reported approximately two million U.S. adults used skeletal muscle relaxants for pain. Eight five percent patients used muscle relaxants for back pain or muscle disorders. The Oregon Health Evidence Review Commission (HERC) issued coverage guidance for pharmacological interventions in lower back pain in 2012.¹⁴ The HERC guidance supported the use of skeletal muscle relaxants for treatment of acute back pain but not for chronic back pain. Until July 2016, not all types of back pain were funded conditions for Oregon Health Plan (OHP) patients. Due to new evidence, changes to the Prioritized List of Health Services were implemented July 1, 2016 to expand coverage for most back conditions. These changes also included recommendations to limit opiates to short term utilization and cautioned against long term opiate prescriptions.¹⁵ Furthermore, nonpharmacologic therapies such as acupuncture, chiropractic and physical therapy are now recommended over surgery and narcotics.¹⁵ A complete list of funded and nonfunded painful back conditions is listed in **Table 2**.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

In the 2016 Agency for Healthcare Research and Quality (AHRQ) report focusing on noninvasive treatments for back pain, a total of 156 publications were reviewed including pharmacologic and nonpharmacologic treatments.¹ Pharmacologic interventions included acetaminophen, NSAIDs, opioids, benzodiazepines,

corticosteroids, antidepressants, antiepileptics, and skeletal muscle relaxants. Seventeen studies evaluated skeletal muscle relaxants versus placebo (n = 12), skeletal muscle relaxants versus an active medication (n = 2), and comparisons between skeletal muscle relaxants (n = 3).¹ Treatment duration for these trials was short term, ranging from 4 to 21 days. Most of the patients enrolled in the trials had non-specific LBP with at least moderate intensity pain at baseline (>5 on a 10 point rating scale).¹ Primary outcomes included reduction in pain intensity and improvements in back specific function. Pharmacological interventions in these trials included: tizanidine (number of trials = 7), cyclobenzaprine (n = 4), oral and IV orphenadrine (n = 3, 1, respectively), carisoprodol (n = 2), chlorzoxazone (n = 1), dantrolene (n = 1), and baclofen (n = 1).¹ Moderate quality evidence showed tizanidine, cyclobenzaprine, and baclofen were more effective than placebo for short-term pain relief over 5 to 7 days (RR 1.72, 95% CI 1.32 -2.22).¹ Low quality evidence found no difference in efficacy between carisoprodol versus cyclobenzaprine and tizanidine versus chlorzoxazone for acute LBP.¹ There was insufficient evidence to evaluate the efficacy of muscle skeletal relaxants versus placebo in management of chronic LBP.¹ In 8 trials, skeletal muscle relaxants were associated with increased risk of any adverse events compared to placebo (RR 1.50, 95% CI 1.14 – 1.98) as well as increased risk of central nervous system events such as sedation (RR 2.04, 95% CI 1.23 – 3.37).¹

A 2016 systematic review was funded by the Australian Medical Research Council and GlaxoSmithKline to evaluate the efficacy and tolerability of skeletal muscle relaxants in the management of adults with LBP.² The reviewers searched for RCTs from 1972 through October 2015. Fifteen studies including 3362 participants met inclusion criteria. Six of the studies evaluated medications available in the United States; cyclobenzaprine, tizanidine, and carisoprodol, the rest of the studies included medications only available in Europe. The reviewers rated the quality of these studies as moderate to high.² The trials were short term (4-7 days) in adults with acute LBP. No evidence was found to evaluate skeletal muscle relaxant use in chronic LBP.² Three studies compared carisoprodol to placebo, 1 trial compared tizanidine to ibuprofen, 1 trial compared tizanidine to placebo, and 1 trial compared carisoprodol to cyclobenzaprine. The primary outcome was changes in pain intensity. The pain outcomes were converted to 0-100 scale (0: no pain - 100: worst possible pain) and were reported as mean differences (MD). Changes in MD by 10 points were considered minimally significant and by 20 points considered clinically significant.² Tizanidine was more effective than placebo in reducing pain intensity (MD = -25, 95% CI -37.1 to -13.1).² There was no significance in effectiveness noted between tizanidine and ibuprofen (MD = -4, 95% CI -18.8 to 10.8).⁶ In a head-to-head trial comparing carisoprodol and cyclobenzaprine, no differences were noted in alleviating pain (MD = -5.0, 95% CI -15.7 to 5.7).² The 3 placebo controlled carisoprodol trials also showed no significant differences in efficacy between drug and placebo (MD = -8.7, 95% CI -12.2 to -5.2; MD = -14, 95% CI -29.3 to 1.3; MD -4.2, 95% CI -7.0 to -.05).² Adverse events such as nausea, dizziness, and headaches were similar for muscle relaxants compared to placebo (n = 6 trial; 16% vs 14.1%; p = 0.5).² Of the 3 skeletal muscle relaxants included in this systematic review, tizanidine was more effective than placebo in reducing pain associated with acute LBP. Carisoprodol showed no benefit in efficacy when compared to placebo and no differences were noted between carisoprodol and cyclobenzaprine in alleviating pain.

In the 2015 CADTH review on long-term use of cyclobenzaprine, seven systematic reviews, four RCTs, and four practice guidelines were evaluated.¹⁶ In the meta-analysis, the study population included patients with fibromyalgia (n = 2), myofascial pain (a chronic condition that affects the connective tissues or muscles; n = 1), mechanical neck disorders (n = 1), and back pain (n = 2). For the RCTs, there was one for neck pain, one for myofascial pain, and two for neck or back pain. For the four practice guidelines, two included fibromyalgia, one for chronic pain, and one for low back pain. There was insufficient evidence to determine if one skeletal muscle relaxant provided more pain relief than the others.¹⁶ Another systematic review for non-specific LBP showed no difference in pain relief between cyclobenzaprine and carisoprodol and a low quality RCT showed a significant decrease in muscle spasm for cyclobenzaprine over NSAID use within two weeks.¹⁶ There was a 2011 guideline that recommended skeletal muscle relaxants in addition to NSAIDs or monotherapy when first-line agents (NSAIDs and acetaminophen) has not reduced the pain, but only up to two weeks.¹⁶ CADTH was unable to extract information on dosing, duration, and place in therapy based on the available literature.

New Guidelines:**American College of Physicians (ACP) Clinical Practice Guideline for Noninvasive Treatments of Back Pain**

In early 2017, updated ACP guidelines were published in the Annals of Internal Medicine. The most recent publication provides treatment guidance for acute, subacute, and chronic low back pain.¹⁷ Nonpharmacologic treatment with heat, massage, acupuncture or spinal manipulation are recommended as first line therapies. If pharmacologic therapy is warranted, NSAIDs or skeletal muscle relaxants are the treatments of choice for acute low back pain for short term use based on moderate quality evidence. Skeletal muscle relaxants are not recommended for management of chronic low back pain due to low quality evidence that showed no differences in any outcome between different muscle relaxants for treatment of chronic back pain. The adverse effects associated with muscle relaxants included sedation, drowsiness, and dizziness. Moderate quality evidence from 8 RCTs showed that muscle relaxants have an increased risk of central nervous effects compared to placebo (RR 2.04; 95% CI 1.14 to 1.98).¹⁷

Table 1. Skeletal muscle relaxants indications and adverse drug reactions^{5,18}

Oral Medications	FDA indications	Oral Dosing	Adverse drug reactions (common)
Antispasticity Agents			
Baclofen	Spasticity from multiple sclerosis and spinal cord injuries	Initial 5 mg 3 times a day May increase by 5 mg every 3 days Do not exceed 20 mg 4 times daily (80 mg daily)	Drowsiness/Dizziness Nausea Weakness/Fatigue Confusion Hypotension Urinary Frequency
Dantrolene	Chronic spasticity due to spinal cord injury, cerebral palsy or multiple sclerosis	Initial 25 mg daily for 7 days Increase to 25 mg 3 times daily for 7 days, increase to 50 mg 3 times daily for 7 days, and then increase to 100 mg 3 times daily May increase to 100 mg 4 times daily Do not exceed 400 mg daily	Drowsiness/Dizziness Weakness Fatigue Diarrhea Hepatotoxicity- Black Box Warning Dysphagia Nausea Urinary Retention
Antispasmodic Agents			
Cyclobenzaprine	Muscle spasm associated with acute, painful musculoskeletal conditions. Do not use longer than 2-3 weeks	Tablet, immediate release: 5 mg 3 times daily; may increase up to 10 mg 3 times daily if needed. Not recommended in moderate to severe hepatic impairment	Drowsiness/Dizziness Blurred Vision Xerostomia
Carisoprodol	Relief of discomfort associated with acute musculoskeletal pain. Do not use longer than 2-3 weeks	250-350 mg 3 times daily at bedtime	Drowsiness/Dizziness Headache
Chlorzoxazone	Relief of discomfort associated with acute musculoskeletal pain.	250-500 mg 3 or 4 times daily, may increase to 750 mg 3 or 4 times daily. Consider dose reductions as symptoms improve	Drowsiness/Dizziness Urine Discoloration Paradoxical CNS stimulation Hepatic Toxicity
Metaxalone	Relief of discomfort associated with acute musculoskeletal pain	800 mg 3 to 4 times daily	Drowsiness/Dizziness Skin rash Nausea Vomiting Hemolytic Anemia Jaundice
Methocarbamol	Relief of discomfort associated with acute musculoskeletal pain.	1.5 grams 4 times daily for 2-3 days (up to 8 grams/day may be given in severe conditions), then decrease to 4-4.5 grams/day in 3-6 divided doses	Drowsiness/Dizziness Skin rash GI upset Jaundice Blurred Vision
Orphenadrine	Relief of discomfort associated with acute musculoskeletal pain.	100 mg twice daily	Drowsiness/Dizziness Tachycardia Blurred Vision Urinary retention
Combination Antispasticity and Antispasmodic Agents			
Tizanidine	Management of spasticity	Initial 2 mg up to 3 times daily (every 6 or 8 hours) as needed. May titrate to optimal effect in 2-4 mg increments per dose (with a minimum of 1-4 days between dose increases). Do not exceed 36 mg daily; single doses >16 mg have not been studied	Drowsiness/Dizziness Hypotension Hepatic Injury Xerostomia Bradycardia Weakness Hallucinations

Table 2: Funded and unfunded conditions of the back

Funded	Unfunded
Line 351: conditions of the back and spine with urgent surgical indications Line 407: Conditions of the back and spine	Line 532: conditions of the back and spine without urgent surgical conditions Line 562: Spastic dysphonia Line 611: Sprains and strains of adjacent muscles and joints, minor Line 663: Musculoskeletal conditions with no or minimally effective treatments or no treatment necessary

Randomized Controlled Trials:

A total of 74 citations were manually reviewed from the literature search. After manual review, 73 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining 1 trial is briefly described in the table below. The full abstract is included in **Appendix 3**.

Table 2: Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Friedman et al. ¹⁹ RCT, DB, ITT, 3 group N = 323	Naproxen 500 mg BID + placebo x 10 days Vs Naproxen 500 mg BID + cyclobenzaprine 5 mg 1-2 tablets q8h prn x 10 days Vs Naproxen 500 mg BID + oxycodone 5 mg/acetaminophen 325 mg daily 1-2 tables q8h prn x 10 days	Age: 21-64 years old with Nontraumatic, nonradicular LBP of 2 weeks duration or less	Improvement in RMDQ between ED discharge and 1 week later	Pain and Disability Improvement: ¹⁹ Naproxen + placebo improved by a mean of 9.8 ; 98.3% CI: 7.9-11.7) Naproxen + cyclobenzaprine improved by a mean of 10.1; 98.3% CI: 9.0-13.2) Naproxen + oxycodone/acetaminophen improved by a mean of 11.1; 98.3% CI: 9.0-13.2) Between group differences in mean RMDQ improvement were as follows: ¹⁹ Cyclobenzaprine vs placebo = 0.3 (98.3% CI, -2.6 to 3.2; P = .77) Oxycodone/acetaminophen vs placebo = 1.3 (98.3% CI, -1.5 to 4.1; P = .28) Oxycodone/acetaminophen vs cyclobenzaprine = 0.9 (98.3% CI, -2.1 to 3.9; P = .45). Authors Conclusions: Adding cyclobenzaprine or oxycodone/acetaminophen to naproxen alone did not improve functional outcomes or pain at 7 days ¹⁹

Abbreviations: ED= Emergency Department, ITT= Intention to Treat, LBP = Low Back Pain, RCT = Randomized Clinical Trial; DB = Double Blinded; BID = twice daily dosing; RMDQ = Roland Morris Disability Questionnaire; n = sample size.

References:

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	BACLOFEN	BACLOFEN	Y
ORAL	TABLET	CYCLOBENZAPRINE HCL	CYCLOBENZAPRINE HCL	Y
ORAL	TABLET	TIZANIDINE HCL	TIZANIDINE HCL	Y
ORAL	TABLET	ZANAFLEX	TIZANIDINE HCL	Y
ORAL	CAP ER 24H	AMRIX	CYCLOBENZAPRINE HCL	N
ORAL	CAPSULE	DANTRIUM	DANTROLENE SODIUM	N
ORAL	CAPSULE	DANTROLENE SODIUM	DANTROLENE SODIUM	N
ORAL	CAPSULE	TIZANIDINE HCL	TIZANIDINE HCL	N
ORAL	CAPSULE	ZANAFLEX	TIZANIDINE HCL	N
ORAL	TABLET	CARISOPRODOL	CARISOPRODOL	N
ORAL	TABLET	CARISOPRODOL COMPOUND	CARISOPRODOL/ASPIRIN	N
ORAL	TABLET	CARISOPRODOL-ASPIRIN	CARISOPRODOL/ASPIRIN	N
ORAL	TABLET	CHLORZOXAZONE	CHLORZOXAZONE	N
ORAL	TABLET	CYCLOBENZAPRINE HCL	CYCLOBENZAPRINE HCL	N
ORAL	TABLET	FEXMID	CYCLOBENZAPRINE HCL	N
ORAL	TABLET	LORZONE	CHLORZOXAZONE	N
ORAL	TABLET	METAXALONE	METAXALONE	N
ORAL	TABLET	METHOCARBAMOL	METHOCARBAMOL	N
ORAL	TABLET	PARAFON FORTE DSC	CHLORZOXAZONE	N
ORAL	TABLET	ROBAXIN	METHOCARBAMOL	N
ORAL	TABLET	ROBAXIN-750	METHOCARBAMOL	N
ORAL	TABLET	SKELAXIN	METAXALONE	N
ORAL	TABLET	SOMA	CARISOPRODOL	N
ORAL	TABLET ER	ORPHENADRINE CITRATE	ORPHENADRINE CITRATE	N
ORAL	TABLET	CARISOPRODOL COMPOUND-CODEINE	CODEINE/CARISOPRODOL/ASPIRIN	N
ORAL	TABLET	CARISOPRODOL-ASPIRIN-CODEINE	CODEINE/CARISOPRODOL/ASPIRIN	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to January Week 4 2017

1. *Baclofen.mp. or exp Baclofen/ 4198*
2. *carisoprodol.mp. or exp Carisoprodol/ 146*
3. *chlorzoxazone.mp. or exp Chlorzoxazone/ 584*
4. *cyclobenzaprine.mp. 143*
5. *dantrolene.mp. or exp Dantrolene/ 1248*
6. *Muscle Relaxants, Central/ or metaxalone.mp. 24*
7. *methocarbamol.mp. or exp Methocarbamol/ 69*
8. *orphenadrine.mp. or exp Orphenadrine/ 153*
9. *tizanidine.mp. 325*
10. *muscle relaxants*
10. *muscle spasticity 7063*
11. *back pain 32049*
11. *1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 7484*
13. *10 or 12 3521*
14. *exp Pain/ 369683*
15. *13 or 14 388524*
16. *11 and 15 2747*
17. *limit 16 to (clinical study or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews), English, humans, 2013- current: 74*

Appendix 3: Abstracts of Clinical Trials

Naproxen with cyclobenzaprine, oxycodone/acetaminophen, or placebo for treating acute low back pain

Importance: Low back pain (LBP) is responsible for more than 2.5 million visits to US emergency departments (EDs) annually. These patients are usually treated with nonsteroidal anti-inflammatory drugs, acetaminophen, opioids, or skeletal muscle relaxants, often in combination.

Objective: To compare functional outcomes and pain at 1 week and 3 months after an ED visit for acute LBP among patients randomized to a 10-day course of (1) naproxen + placebo; (2) naproxen + cyclobenzaprine; or (3) naproxen + oxycodone/acetaminophen.

Design, Setting, and Participants: This randomized, double-blind, 3-group study was conducted at one urban ED in the Bronx, New York City. Patients who presented with nontraumatic, nonradicular LBP of 2 weeks' duration or less were eligible for enrollment upon ED discharge if they had a score greater than 5 on the Roland-Morris Disability Questionnaire (RMDQ). The RMDQ is a 24-item questionnaire commonly used to measure LBP and related functional impairment on which 0 indicates no functional impairment and 24 indicates maximum impairment. Beginning in April 2012, a total of 2588 patients were approached for enrollment. Of the 323 deemed eligible for participation, 107 were randomized to receive placebo and 108 each to cyclobenzaprine and to oxycodone/acetaminophen. Follow-up was completed in December 2014.

Interventions: All participants were given 20 tablets of naproxen, 500 mg, to be taken twice a day. They were randomized to receive either 60 tablets of placebo; cyclobenzaprine, 5 mg; or oxycodone, 5 mg/acetaminophen, 325 mg. Participants were instructed to take 1 or 2 of these tablets every 8 hours, as needed for LBP. They also received a standardized 10-minute LBP educational session prior to discharge.

Main Outcomes and Measures: The primary outcome was improvement in RMDQ between ED discharge and 1 week later.

Results: Demographic characteristics were comparable among the 3 groups. At baseline, median RMDQ score in the placebo group was 20 (interquartile range [IQR], 17-21), in the cyclobenzaprine group 19 (IQR,17-21), and in the oxycodone/acetaminophen group 20 (IQR,17-22). At 1-week follow-up, the mean RMDQ improvement was 9.8 in the placebo group, 10.1 in the cyclobenzaprine group, and 11.1 in the oxycodone/acetaminophen group. Between-group difference in mean RMDQ improvement for cyclobenzaprine vs placebo was 0.3 (98.3% CI, -2.6 to 3.2; P = .77), for oxycodone/acetaminophen vs placebo, 1.3 (98.3% CI, -1.5 to 4.1; P = .28), and for oxycodone/acetaminophen vs cyclobenzaprine, 0.9 (98.3% CI, -2.1 to 3.9; P = .45).

Conclusions and Relevance: Among patients with acute, nontraumatic, nonradicular LBP presenting to the ED, adding cyclobenzaprine or oxycodone/acetaminophen to naproxen alone did not improve functional outcomes or pain at 1-week follow-up. These findings do not support use of these additional medications in this setting.

Appendix 4: Prior Authorization Criteria

Skeletal Muscle Relaxants

Goal(s):

- Cover non-preferred drugs only for funded conditions.
- Restrict carisoprodol to short-term use due to lack of long-term studies to assess safety or efficacy and high potential for abuse.

Length of Authorization:

Up to 3-6 months

Requires PA:

- Non-preferred agents

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis funded by the Oregon Health Plan?	Yes: Go to #3	No: Pass to RPh. Deny; not funded by the OHP
3. Will the prescriber consider a change to a preferred product? Message: <ul style="list-style-type: none"> • Preferred products do not require PA • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee. 	Yes: Inform prescriber of covered alternatives in class	No: Go to #4
4. Is drug requested carisoprodol?	Yes: Go to #5	No: Approve for up to 3 months
5. Does the patient have a history of opioid use within the past 30 days?	Yes: Deny; medical appropriateness	No: Go to #6

Approval Criteria		
<p>6. Does total quantity of carisoprodol exceed 56 tablets in 90 days?</p> <p>From claims, document product, dose, directions, and amount used during last 90 days.</p>	Yes: Go to #7	No: Approve for up to 3 months
<p>7. Does patient have a terminal illness (e.g. metastatic cancer, end stage Parkinson’s disease, ALS)?</p>	Yes: Approve for 6 months.	No: Pass to RPh. Go to #8
<p>8. Pharmacist’s statement:</p> <ul style="list-style-type: none"> • Carisoprodol cannot be approved for long term usage. • Patients are limited to 56 tablets in a 90 day period. • It is recommended that the patient undergo a “taper” of the carisoprodol product of which a supply may be authorized for this to occur. • The amount and length of taper depends upon the patient’s condition. Does the patient meet one or more of the following: <ul style="list-style-type: none"> ○ >65 years of age; or ○ renal failure; or ○ hepatic failure; or ○ take > 1400 mg per day? 	<p>Yes: Document reason and approve long taper:</p> <ul style="list-style-type: none"> • Authorize 18 tablets • Reduce dose over 9 days • 350 mg TID X 3 days, then • 350 mg BID X 3 days, then • 350 mg daily x 3 days then evaluate 	<p>No: Approve short taper:</p> <ul style="list-style-type: none"> • Authorize 10 tablets • Reduce dose over 4 days • 350 mg TID x 1 day, then • 350 mg BID x 2 days, then • 350 mg daily x1 day, then evaluate

P&T Review: 5/17 (DM) 3/17; 11/14; 9/09; 2/06; 2/04; 11/01; 2/01; 9/00; 5/00; 2/00
Implementation: 1/1/15, 1/1/14, 1/1/10, 11/18/04