Choosing a Skeletal Muscle Relaxant

SHARON SEE, PharmD, BCPS, and REGINA GINZBURG, PharmD
St. John's University College of Pharmacy and Allied Health Professions, Jamaica, New York

Skeletal muscle relaxants are widely used in treating musculoskeletal conditions. However, evidence of their effectiveness consists mainly of studies with poor methodologic design. In addition, these drugs have not been proven to be superior to acetaminophen or nonsteroidal anti-inflammatory drugs for low back pain. Systematic reviews and meta-analyses support using skeletal muscle relaxants for short-term relief of acute low back pain when nonsteroidal anti-inflammatory drugs or acetaminophen are not effective or tolerated. Comparison studies have not shown one skeletal muscle relaxant to be superior to another. Cyclobenzaprine is the most heavily studied and has been shown to be effective for various musculoskeletal conditions. The sedative properties of tizanidine and cyclobenzaprine may benefit patients with insomnia caused by severe muscle spasms. Methocarbamol and metaxalone are less sedating, although effectiveness evidence is limited. Adverse effects, particularly dizziness and drowsiness, are consistently reported with all skeletal muscle relaxants. The potential adverse effects should be communicated clearly to the patient. Because of limited comparable effectiveness data, choice of agent should be based on side-effect profile, patient preference, abuse potential, and possible drug interactions. (*Am Fam Physician*. 2008;78(3):365-370. Copyright © 2008 American Academy of Family Physicians.)

Skeletal muscle relaxants are often prescribed for musculoskeletal conditions including low back pain, neck pain, fibromyalgia, tension headaches, and myofascial pain syndrome. The goals of treatment include managing muscle pain and improving functional status so the patient can return to work or resume previous activities.

Skeletal muscle relaxants are divided into two categories: antispastic (for conditions such as cerebral palsy and multiple sclerosis) and antispasmodic agents (for musculoskeletal conditions). Antispastic agents (e.g., baclofen [Lioresal], dantrolene [Dantrium]) should not be prescribed for musculoskeletal conditions because there is sparse evidence to support their use. Rather, an antispasmodic agent may be more appropriate *(Table 1)*.[1-9]

Among antispasmodic agents, carisoprodol (Soma), cyclobenzaprine (Flexeril), metaxalone (Skelaxin), and methocarbamol (Robaxin) were among the top 200 drugs dispensed in the United States in 2006.[10,11] Despite their popularity, skeletal muscle relaxants should not be the primary drug class of choice for musculoskeletal conditions. The American Pain Society and the American College of Physicians recommend using acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line agents for acute low back pain and reserving skeletal muscle relaxants as an alternative treatment option.[12] This recommendation is based on available literature, which shows skeletal muscle relaxants are better than placebo, but not more effective than NSAIDs in patients with acute back pain. Similar recommendations exist in treating tension headaches.[13] A meta-analysis evaluating the use of cyclobenzaprine showed that, although this drug was better than placebo for the treatment of fibromyalgia, it was considered inferior to antidepressants.[14] Additionally, recent guidelines on fibromyalgia recommend using a comprehensive approach that utilizes tramadol (Ultram), antidepressants, and/or a heated pool (with or without exercise).[15]

Prescription rates for nonspecific back pain revealed that skeletal muscle relaxants accounted for 18.5 percent of prescriptions compared with 16.3 percent for NSAIDs and 10 percent for cyclooxygenase-2 inhibitors.[16] Because of the high rate of prescribing skeletal

Table 1. Skeletal Muscle Relaxants (Antispasmodic Agents)

Drug	*Recommended dosage*	*Most common adverse effects*
Carisoprodol (Soma)[1]	350 mg four times daily Not recommended for children younger than 12 years	Dizziness, drowsiness, headache Rare idiosyncratic reactions (mental status changes, transient quadriplegia, and temporary loss of vision) after first dose; may require hospitalization Allergy-type reactions may occur after the first to fourth dose; may be mild (e.g., cutaneous rash) or more severe (e.g., asthma attack, angioneurotic edema, hypotension, or anaphylactic shock); antihistamines, epinephrine, or corticosteroids may be needed
Chlorzoxazone (Parafon Forte)[2]	Adults: 250 to 750 mg three to four times daily Children: 125 to 500 mg three to four times daily; or 20 mg per kg daily in three or four divided doses	Dizziness, drowsiness Red or orange urine GI irritation and rare GI bleeding Hepatoxicity (rare); discontinue with elevated liver function test
Cyclobenzaprine (Flexeril)[3]	5 mg three times daily; may increase to 10 mg three times daily	Anticholinergic effect (drowsiness, dry mouth, urinary retention, increased intraocular pressure) Rare but serious adverse effects are arrhythmias, seizures, myocardial infarction
Diazepam (Valium)[4]	Adults: 2 to 10 mg three to four times daily Children: 0.12 to 0.80 mg per kg daily in three or four divided doses	Dizziness, drowsiness, confusion Abuse potential
Metaxalone (Skelaxin)[5]	800 mg three to four times daily Not recommended in children younger than 12 years	Drowsiness, dizziness, headache, nervousness Leukopenia or hemolytic anemia (rare) Liver function test elevation (rare) Nausea, vomiting, and diarrhea (rare) Paradoxical muscle cramps
Methocarbamol (Robaxin)[6]	1,500 mg four times daily for first two to three days, followed by 750 mg four times daily	Black, brown, or green urine possible Mental status impairment Possible exacerbation of myasthenia gravis symptoms
Orphenadrine (Norflex)[7]	100 mg twice daily Combination products are dosed three to four times daily	Anticholinergic effect (drowsiness, dry mouth, urinary retention, increased intraocular pressure) Aplastic anemia (rare) GI irritation Confusion, tachycardia, hypersensitivity reaction (with high doses)
Tizanidine (Zanaflex)[8,9]	4 mg initially; may increase by 2 to 4 mg every six to eight hours until relief Do not exceed 36 mg daily	Dose-related hypotension, sedation, and dry mouth Hepatotoxicity; monitor liver function tests at baseline and one, three, and six months Withdrawal and rebound hypertension may occur in patients discontinuing therapy after receiving high doses for long period of time; tapering is recommended

NOTE: *The table contains only selected highlights about these medications. All of these drugs may cause increased drowsiness with central nervous system depressants. Caution is advised when prescribing skeletal muscle relaxants in older patients.*

CYP = cytochrome P; FDA = U.S. Food and Drug Administration; GI = gastrointestinal.

Comments	*Monthly cost**
Physical or psychological dependence may occur; withdrawal symptoms may occur with discontinuation Possible respiratory depression when combined with benzodiazepines, barbiturates, codeine or its derivatives, or other muscle relaxants Contraindicated in acute intermittent porphyria FDA pregnancy category C	$72 to $100 (generic) $590 (brand)
Avoid use in patients with hepatic impairment Possible respiratory depression when combined with benzodiazepines, barbiturates, codeine or its derivatives, or other muscle relaxants FDA pregnancy category C	15 to 77 (generic) 180 (brand)
Most studied skeletal muscle relaxant Long elimination half-life 5-mg dose as effective as 10-mg, with fewer adverse effects Avoid in older patients and in patients with glaucoma Possible drug interaction with CYP450 inhibitors Seizures reported with concomitant use of tramadol (Ultram); combination should be avoided in patients with medical conditions that may induce seizures Contraindicated in patients with arrhythmias, recent myocardial infarction, or congestive heart failure FDA pregnancy category B	120 to 140 (generic) 157 (brand)
Also an antispastic agent Long elimination half-life; avoid in older patients and in patients with hepatic impairment Possible drug interaction with CYP450 inhibitors Complete blood count and liver function tests indicated for prolonged use FDA pregnancy category D; avoid especially in the first trimester	11 to 23 (generic) 184 (brand)
Use with caution in patients with liver failure Possible respiratory depression when combined with benzodiazepines, barbiturates, codeine or its derivatives, or other muscle relaxants Less dizziness and drowsiness than other skeletal muscle relaxants FDA pregnancy category C	275; generic not available
Possible respiratory depression when combined with benzodiazepines, barbiturates, codeine or its derivatives, or other muscle relaxants FDA pregnancy category C; reports of fetal abnormalities	15 to 58 (generic) 176 (brand)
Long elimination half-life Reduced dosages in older patients Avoid in patients with glaucoma, cardiospasm, or myasthenia gravis Decreases effect of phenothiazines (e.g., chlorpromazine [Thorazine†], promethazine [Phenergan]) FDA pregnancy category C	110 to 140 (generic) 162 (brand)
Also antispastic agent Do not use with CYP1A2 inhibitors, ciprofloxacin (Cipro) or fluvoxamine (Luvox CR) Caution with CYP1A2 inhibitors, central nervous system depressants, or alcohol Decreased effectiveness with oral contraceptives FDA pregnancy category C	329 (generic) 437 (brand)

**—For the recommended adult dosage. Estimated cost to the pharmacist based on average wholesale prices (rounded to the nearest dollar) in* Red Book. *Montvale, N.J.: Medical Economics Data, 2007. Cost to the patient will be higher, depending on prescription filling fee.*

†—Brand not available in the United States.

Information from references 1 through 9.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Skeletal muscle relaxants are not considered first-line therapy for musculoskeletal conditions.	C	12, 13, 15
Skeletal muscle relaxants may be used as adjunctive therapy for acute low back pain.	B	17, 18
Antispasmodic agents should be used short-term (two weeks) for acute low back pain.	C	17, 18
There is no clear evidence that one skeletal muscle relaxant is superior to another for musculoskeletal spasms.	B	17, 18
Choice of skeletal muscle relaxant should be based on individual drug characteristics and patient situation.	C	32

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see http://www.aafp.org/afpsort.xml.

muscle relaxants, an understanding of the risks and benefits of this class of drugs is vital. This article presents evidence regarding the use of antispasmodic skeletal muscle relaxants for various musculoskeletal conditions, and appropriate drug selection if a skeletal muscle relaxant is required. Highlights of contraindications, adverse effects, and drug interactions for these drugs are listed in *Table 1*.[1-9]

Evidence of Effectiveness

Many of the studies evaluating the effectiveness of skeletal muscle relaxants are hampered by poor methodologic design, including incomplete reporting of compliance, improper or no mention of allocation concealment, not utilizing intention-to-treat methods, and inadequate randomization.[17,18] Nonetheless, skeletal muscle relaxants have been evaluated in systematic reviews and meta-analyses.

BACK AND NECK PAIN

Some evidence appears to support nonbenzodiazepine skeletal muscle relaxants, such as carisoprodol, cyclobenzaprine, orphenadrine (Norflex), and tizanidine (Zanaflex), for acute low back pain.[17,18] These agents have been shown to be moderately effective for short-term relief (two weeks) compared with placebo.[17,18] Randomized controlled trials involving metaxalone have not been conducted since the 1970s. One fair-quality study showed no difference between metaxalone and placebo.[19] Limited evidence exists to support the use of skeletal muscle relaxants in chronic low back pain.[17,20] Benzodiazepines have been effective for short-term use compared with placebo, but the basis of this recommendation stemmed from trials involving tetrazepam, which is not available in the United States.[21,22]

Cyclobenzaprine has been the most heavily studied drug, with consistently proven effectiveness.[17,18] It was shown to improve pain, muscle spasm, functional status, and global evaluation versus diazepam (Valium) in two fair-quality studies.[23,24] Conversely, two other fair- and poor-quality studies did not reveal any significant difference between cyclobenzaprine and diazepam.[25,26] One meta-analysis evaluated 14 studies comparing cyclobenzaprine with placebo for back and neck pain.[27] The trials included were of less than 14 days' duration. Cyclobenzaprine was found to be moderately more effective than placebo, but had more central nervous system adverse effects. The authors also described several limitations of the meta-analysis including inadequate blinding, heterogeneity among studies, and the presence of publication bias.[27] Overall, studies appear to be consistent, with cyclobenzaprine having greatest benefit within the first few days of treatment rather than at one or two weeks.[18,27]

Skeletal muscle relaxants have also been studied as adjunctive therapy to analgesics in treating acute low back pain. In one open-label study (20 patients), the addition of cyclobenzaprine to naproxen (Naprosyn) resulted in a statistically significant decrease in muscle spasm and tenderness compared with naproxen alone.[28] A Cochrane review analyzed three high-quality trials (560 total patients) that showed tizanidine plus analgesics was more effective in providing pain relief and decreasing muscle spasm than analgesics alone.[17] Conversely, one low-quality open-label study (867 patients) comparing cyclobenzaprine alone (5 mg three times daily) versus combination with ibuprofen (Motrin; either 400 or 800 mg three times daily) showed that, although all groups improved at seven days, there was no statistical difference in outcomes among the groups.[29] Nonetheless, the use of combination therapy has been supported in quickening recovery,[17] with minimal overall risk of adverse effects (relative risk [RR] = 1.34; 95% confidence interval [CI], 0.67 to 2.67].[20]

FIBROMYALGIA

Cyclobenzaprine has also been studied in treating fibromyalgia. A meta-analysis of five trials ranging from six to 24 weeks' duration included a total of 312 patients with fibromyalgia. The authors reported that, although cyclobenzaprine moderately improved sleep and pain, the long-term benefits were unknown. This meta-analysis was limited by a high drop-out rate, short trial duration, few studies having an intention-to-treat design, and inadequate blinding.[14]

COMPARISON DATA

Strong data comparing skeletal muscle relaxants to each other are scarce. A systematic review evaluated 46 trials (head-to-head and placebo-controlled) comprising mostly of studies on low back pain or neck syndromes. The placebo-controlled trials included 17 on cyclobenzaprine, six on tizanidine, four on carisoprodol, and four on orphenadrine, and were mostly conducted more than 15 years ago. The average patient enrollment was less than 150 patients (range 12 to 400 patients). In general, all of the drugs were shown to have some benefit.[18] The limitations of published comparison trials include using unvalidated scales to measure outcomes, involving small numbers of participants, and often not reporting adverse effects of studied medications. One fair-quality study showed carisoprodol was better than diazepam at improving muscle spasm and global and functional status in patients with low back pain.[30] Another fair-quality study comparing tizanidine with chlorzoxazone (Parafon Forte) for back spasms did not show any significant difference.[31]

A different systematic review did include some studies which were considered to be high quality.[17] These studies revealed no difference in outcomes (e.g., muscle spasms, muscle pain, tension, tenderness, functional status) among cyclobenzaprine versus carisoprodol; chlorzoxazone versus tizanidine; or diazepam versus tizanidine.[17]

Place in Therapy

Although the evidence for effectiveness of skeletal muscle relaxants in musculoskeletal conditions is limited, strong evidence does exist in terms of toxicity. In acute low back pain trials, skeletal muscle relaxants increased overall adverse effects (RR = 1.50; 95% CI, 1.14 to 1.98) and central nervous system adverse effects (RR = 2.04; 95% CI, 1.23 to 3.37) such as dizziness and drowsiness.[17] Because of the weak evidence for comparable effectiveness, selection of an agent should be based on side-effect profile, patient preference, abuse potential, drug interaction potential, and other characteristics of the individual drugs.[32] Skeletal muscle relaxants are indicated for short-term use; therefore, multiple modalities (e.g., physical therapy, adjunctive analgesics) may be warranted to prevent chronic use of these medications.

Selection of a skeletal muscle relaxant should be individualized to the patient. If there are tender spots over the muscle or trigger points on physical examination, a skeletal muscle relaxant is a reasonable adjunct to analgesic treatment of low back pain. Skeletal muscle relaxants may also be used as an alternative to NSAIDs in patients who are at risk of gastrointestinal or renal complications.

Patients with low back pain or fibromyalgia may benefit from treatment with cyclobenzaprine. Recent evidence showed similar effectiveness at half of its manufacturer recommended dose (5 mg), but with fewer adverse effects.[33] It may optimally be used in younger patients with limited or no medical conditions. Higher doses of cyclobenzaprine or tizanidine would be appropriate to promote sedation in cases of more severe discomfort or perceived muscular spasm. Although there appears to be insufficient data on metaxalone and methocarbamol, these may be useful in patients who cannot tolerate the sedative properties of cyclobenzaprine or tizanidine. Of note, methocarbamol costs substantially less than metaxalone.

Carisoprodol is metabolized to meprobamate (a class III controlled substance) and has been shown to produce psychological and physical dependence.[34] Carisoprodol and diazepam should be reserved for last-line therapy because of their abuse potential and lack of superiority to other skeletal muscle relaxants. Although all skeletal muscle relaxants should be used with caution in older patients, diazepam especially should be avoided in older patients or in patients with significant cognitive or hepatic impairment.

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The Authors

SHARON SEE, PharmD, BCPS, is an associate clinical professor at St. John's University College of Pharmacy and Allied Health Professions in Jamaica, NY, and a faculty member at the Beth Israel Residency Program in Urban Family Practice in New York, NY. She received her doctor of pharmacy degree from Rutgers University College of Pharmacy in New Brunswick, NJ, and completed an inpatient family medicine pharmacy specialty residency at Deaconess Hospital and the St. Louis College of Pharmacy in St. Louis, Mo.

REGINA GINZBURG, PharmD, is an assistant clinical professor at St. John's University College of Pharmacy and Allied Health Professions and a faculty member at the Beth Israel Residency Program in Urban Family Practice. She received her doctor of pharmacy degree from St. John's University College of Pharmacy and Allied Health Professions, and completed a general practice residency at Albert Einstein Medical Center in Philadelphia, Pa.

Address correspondence to Sharon See, PharmD, BCPS, St. John's University College of Pharmacy and Allied Health Professions, 8000 Utopia Parkway, Jamaica, NY 11439 (e-mail: sees@stjohns.edu). Reprints are not available from the authors.

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