

## *Skeletal Muscle Relaxants Class Review*

### I. Overview

Skeletal muscle relaxants are classified by their pharmacologic properties as either antispasticity or antispasmodic agents. The antispasticity agents are used to reduce spasticity that interferes with function or daily living activities, such as in cerebral palsy, multiple sclerosis and spinal cord injuries.<sup>1</sup> The antispasmodic agents are primarily indicated as adjuncts to rest, physical therapy and other measures for the relief of discomfort associated with acute, painful musculoskeletal disorders.<sup>2</sup>

The mechanism of action of these agents is not well understood. Antispasticity drugs, such as baclofen and tizanidine act centrally on the spinal cord or brain stem and inhibit neuronal transmission.<sup>2,3</sup> Baclofen is an analog of gamma aminobutyric acid (GABA) and is thought to act by stimulating this inhibitory neurotransmitter. Tizanidine is classified as an alpha-2-adrenergic agonist and it is believed to act by increasing presynaptic inhibition of spinal motor neurons. Dantrolene directly acts on the skeletal muscle by inhibition of the release of calcium from the sarcoplasmic reticulum, which inhibits muscle contraction.

Skeletal muscle relaxants with antispastic properties are used to relieve musculoskeletal pain. Agents that fall into this category include carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, and methocarbamol. These agents are central nervous system (CNS) depressants and exert their effects either at the spinal cord or cerebral level. Well-controlled clinical studies have not conclusively demonstrated whether relief of musculoskeletal pain by carisoprodol, chlorzoxazone, metaxalone, or methocarbamol results from skeletal muscle relaxant effects, sedative effects or a placebo effect of the drug.<sup>3</sup> Cyclobenzaprine is structurally related to the tricyclic antidepressants. Orphenadrine may be slightly different than the other musculoskeletal agents because it is believed to decrease skeletal muscle spasm through atropine-like effects directly on the cerebral motor neurons. Orphenadrine may also have analgesic properties that may add to its therapeutic effects.<sup>2,3</sup> This review encompasses all oral dosage forms and strengths.

**Table 1. Oral Skeletal Muscle Relaxants Included in this Review**<sup>2-4</sup>

Generic Name	Formulation (AHFS)	Example Brand Name (s)
<b>Musculoskeletal Agents</b>		
Carisoprodol	350 mg tablet	Soma <sup>®*</sup>
Carisoprodol, ASA	200 mg with 325 mg ASA	Soma Compound <sup>®*</sup>
Carisoprodol, ASA, codeine	200 mg with 325 mg ASA and 16 mg codeine	Soma Compound with Codeine <sup>®*</sup>
Chlorphenesin	400 mg tablet	Maolate <sup>®</sup>
Chlorzoxazone	250 mg and 500 mg tablet	Parafon Forte DSC <sup>®*</sup>
Cyclobenzaprine	5 mg and 10 mg* tablet	Flexeril <sup>®*</sup>
Metaxalone	400 mg and 800 mg tablet	Skelaxin <sup>®</sup>
Methocarbamol	500 mg and 750 mg tablet	Robaxin <sup>®*</sup>
Methocarbamol, ASA	400 mg with 325 mg ASA	Robaxisal <sup>®*</sup>
Orphenadrine citrate	100 mg extended-release tablet	Norflex <sup>®*</sup>
Orphenadrine, ASA, caffeine	25 mg with 385 mg ASA and 30 mg caffeine; 50 mg with 770 mg ASA and 60 mg caffeine	Norgesic <sup>®*</sup> , Norgesic Forte <sup>®*</sup>
<b>Antispasticity Agents</b>		
Baclofen	10 mg and 20 mg tablet	Lioresal <sup>®*</sup>
Dantrolene	15 mg, 50 mg, 100 mg capsule	Dantrium <sup>®</sup>
Tizanidine	2 mg and 4 mg capsule and tablet	Zanaflex <sup>®*</sup>

ASA=aspirin

## II. Indications

**Table 2. Indications for Skeletal Muscle Relaxants<sup>2,5</sup>**

	Muscle Spasticity	Adjunct to rest, physical therapy and other measures for the relief of discomforts associated with acute, painful musculoskeletal disorders	Tetanus	Other
Baclofen	yes			
Carisoprodol		yes		
Chlorzoxazone		yes		
Cyclobenzaprine		yes		
Dantrolene	yes			malignant hyperthermia
Metaxalone		yes		
Methocarbamol		yes	yes	
Orphenadrine		yes		
Tizanidine	yes			

## III. Pharmacokinetics

**Table 3. Pharmacokinetic Parameters of the Oral Skeletal Muscle Relaxants<sup>5</sup>**

	C <sub>max</sub>	Half-Life	Bioavailability (%)	Protein Binding (%)	Metabolism	Excretion
Baclofen	2-3 hours	2.5-4 hours	100 %	30%	Hepatic (deamination) (15% of dose)	Urine and feces (85% as unchanged drug)
Carisoprodol	4 hours	8 hours	--	--	Hepatic	Urine as metabolites
Chlorzoxazone	1-2 hours	1 hour	100%	--	Hepatic - glucuronidation	Urine (75%) as metabolites
Cyclobenzaprine	4 hours	18 hours	33%-55%	93%	Hepatic - oxidation and conjugation to inactive metabolite; undergoes enterohepatic circulation	Urine (mainly as inactive metabolites)
Dantrolene	5 hours	9 hours	70%	--	Hepatic - hydroxylation, N-reduction, and acetylation to less active metabolites	Urine (20%) as unchanged drug and active metabolites
Metaxalone	2 hours	2-3 hours	100%	--	Hepatic	Urine (as metabolites)

	Cmax	Half-Life	Bioavailability (%)	Protein Binding (%)	Metabolism	Excretion
Methocarbamol	1-2 hours	0.9-2 hours	100%	--	Hepatic - dealkylation & hydroxylation	Urine (10-15% as unchanged drug and 50% as metabolites)
Orphenadrine citrate	2-4 hours	14 hours	95%	--	Hepatic	Urine, mostly as metabolites
Tizanidine	2.5 hours	2 hours	40%	30%	Hepatic 95% metabolized to inact.metabolites	Urine- 60 % and 20% Feces

Cmax =time to reach maximum concentration

#### IV. Drug Interactions<sup>5</sup>

As all agents are considered central nervous system depressants, additive effects can be seen when combined with other CNS depressants. Examples include alcohol, benzodiazepines, antidepressants, and opioid analgesics.

Cyclobenzaprine is structurally related to tricyclic antidepressants and shares a similar drug interaction profile. Concomitant use of cyclobenzaprine with monoamine oxidase inhibitors may result in serotonin syndrome – hyperpyretic crisis, seizures, and death. Therefore, this medication is contraindicated in patients receiving MAO inhibitors and should not be used within 14 days following discontinuance of these drugs. The risk of seizures may also be enhanced when cyclobenzaprine is used concurrently with tramadol. Cyclobenzaprine may also antagonize the hypotensive effects of some antihypertensive agents.

Concomitant use of dantrolene with estrogen may cause hepatotoxicity. Myocardial depression has also been reported when administering intravenous dantrolene with verapamil.

Orphenadrine is an analogue of diphenhydramine with anticholinergic properties. Concurrent use of orphenadrine with phenothiazines may reduce oral absorption of these agents, antagonize the antipsychotic effect, and enhance anticholinergic side effects.

Tizanidine in combination with antihypertensive agents may lead to additive hypotensive effects. It should not be used in combination with other alpha 2 agonists such as clonidine. Oral contraceptives may also decrease the plasma clearance of tizanidine.

#### V. Adverse Drug Events<sup>5</sup>

As a class, all skeletal muscle relaxants carry some risk of drowsiness and dizziness. Other shared adverse drug reactions may include vertigo, nausea, vomiting, and impaired vision.

Blood dyscrasias such as thrombocytopenia, leucopenia, and aplastic anemia have been reported with dantrolene, metaxolone, methocarbamol, and tizanidine.

Carisoprodol has been reported to produce rare cardiovascular side effects including tachycardia, postural hypotension, and facial flushing.

Chlorzoxazone has been associated with rare, but fatal hepatocellular toxicity.

Cyclobenzaprine has anticholinergic properties and should therefore be used with caution in patients with a history of urinary retention, angle-closure glaucoma, and benign prostate hypertrophy (BPH).

Rare but serious non-fatal hepatotoxicity has been reported with dantrolene.

### Carisoprodol Abuse

Federal, state and local sources of information indicate that carisoprodol abuse is increasing, widespread and significant.<sup>6</sup> Carisoprodol is metabolized to meprobamate, pharmacologically similar to barbiturates and designated Schedule IV by federal law. In some states, including Alabama, carisoprodol is also classified as Schedule IV. Carisoprodol is abused typically by poly-drug abusers (e.g., benzodiazepines and narcotic analgesics), however several reports indicate that carisoprodol can be the sole drug of abuse. Based on drug mentions during emergency department visits during the year 2000, carisoprodol was ranked 14 on the list of 20 most abused mood-altering substances in the US. Furthermore, carisoprodol was ranked as being more often abused than oxycodone. Carisoprodol has been used to prolong the duration and to increase the effects of alcohol or narcotics and “to take the edge off” the jittery feeling associated with cocaine abuse. When used in combination with tramadol, carisoprodol produces profound relaxation and euphoria.

## VI. Dosing and Administration<sup>5</sup>

**Table 4. Usual Dosage Regimen for Skeletal Muscle Relaxants**

Generic	Adult Oral Dose	Maximum Dose
Baclofen	5 mg TID; dose may be increased by 5 mg/dose every 3 days up to 80 mg/day	80 mg/day
Carisoprodol	350 mg TID and QHS	--
Chlorzoxazone	250-750 mg TID-QID	--
Cyclobenzaprine	5mg-10 mg TID	60 mg
Dantrolene	<b>Spasticity</b> 100 g TID ; should be titrated by 25 mg/week; if no response by 45 days, discontinue use  <b>Malignant hyperthermia</b> post crisis: 4-8mg/kg/day in 4 divided doses for 1-3 days then titrate to effect	400 mg
Metaxalone	<b>Spasticity</b> 800 mg TID-QID	
Methocarbamol	<b>Acute</b> up to 1500 mg QID  <b>Maintenance</b> 750mg every 4 hours or 1500 mg TID	6-8 grams
Orphenadrine	100 mg BID	--
Tizanidine	Initial 4 mg dose every 6-8 hours  Increase dose 2 mg-4 mg daily up to 8 mg TID-QID	36 mg/day

## VII. Special Precautions

Baclofen, carisoprodol, methocarbamol (IV only), and tizanidine should be used with caution in patients with renal impairment.

Carisoprodol, chlorzoxazone, cyclobenzaprine, dantrolene, metaxolone, and tizanidine should all be used with caution or avoided in patients with liver dysfunction.

Safety in children less than 12 years-old has not been established for the majority of agents.

Dantrolene should be used with caution in patients with chronic obstructive pulmonary disease and/or impaired cardiac function . It is also contraindicated in patients with amyotrophic lateral sclerosis.

Baclofen and methocarbamol should be used with caution in patients with seizure disorders.

## VIII. Effectiveness

Although skeletal muscle relaxants have been available for many years, most clinical studies are fairly dated and of poor quality. Additionally, there are limited head-to-head comparisons among the skeletal muscle relaxants for the treatment of musculoskeletal pain or spasticity. Trials that have been conducted have utilized a very small study sample and are conducted over a brief time period (usually 7 days). The majority of comparative trials which have been conducted between agents within the same class (carisoprodol vs. cyclobenzaprine, chlorzoxazone vs. tizanidine) have been performed in patients with multiple sclerosis or low back pain.

In general, the available evidence suggests no difference or very marginal differences amongst these agents with regard to efficacy. The best available comparative evidence suggests that tizanidine is roughly equivalent in efficacy to baclofen in patients with spasticity, and that cyclobenzaprine is roughly equivalent to the benzodiazepines (primarily diazepam) for the treatment of musculoskeletal conditions.

Although the adverse effect profile of these agents may vary, there is also insufficient evidence to clearly distinguish any one product as offering advantages with regard to overall safety. Of note however is the fact that dantrolene, tizanidine and chlorzoxazone have all been associated with rare but serious hepatotoxicity, and carisoprodol has been associated with numerous case reports of abuse and addiction.

## IX. Cost

**Table 5. Cost Per Unit of Oral Skeletal Muscle Relaxants**

Generic Name	Formulation	Example Brand Name	Brand	Generic
<b>Musculoskeletal Agents</b>				
Carisoprodol*	350 mg tablet	<i>Soma</i> <sup>®</sup>		
Carisoprodol, ASA*	200 mg with 325 mg ASA	<i>Soma Compound</i> <sup>®</sup>		
Carisoprodol, ASA, codeine*	200 mg with 325 mg ASA and 16 mg codeine	<i>Soma Compound with Codeine</i> <sup>®</sup>		
Chlorzoxazone*	500 mg tablet	<i>Parafon Forte DSC</i> <sup>®</sup>		
Cyclobenzaprine*	5 mg* and 10 mg* tablet	<i>Flexeril</i> <sup>®</sup>		
Metaxalone	800 mg tablet	<i>Skelaxin</i> <sup>®</sup>		
Methocarbamol*	500 mg and 750 mg tablet	<i>Robaxin</i> <sup>®</sup>		
Methocarbamol, ASA	400 mg with 325 ASA	<i>Robaxisal</i> <sup>®</sup>		
Orphenadrine citrate*	100 mg extended-release tablet	<i>Norflex</i> <sup>®</sup>		
Orphenadrine, ASA, caffeine*	25 mg with 385 mg ASA and 30 mg caffeine; 50 mg with 770 ASA and 60 mg caffeine	<i>Norgesic</i> <sup>®</sup> , <i>Norgesic Forte</i> <sup>®</sup>		
<b>Antispasticity Agents</b>				
Baclofen*	10 mg and 20 mg tablet	<i>Lioresal</i> <sup>®</sup>		
Dantrolene*	15 mg, 50 mg, 100 mg capsule	<i>Dantrium</i> <sup>®</sup>		
Tizanidine*	2 mg and 4 mg capsule and tablet	<i>Zanaflex</i> <sup>®</sup>		

\*Generic available; ASA=aspirin    \*\* Brand-name Lioresal tabs no longer manufactured in the U.S.

## X. Conclusions

Skeletal muscle relaxants are most commonly prescribed to treat conditions that include spasticity (due to neurological conditions) and musculoskeletal conditions (which result in muscle spasms [e.g., mechanical low back or neck pain]). The exact mechanism of action of these agents—relaxation of muscles or sedation—has been questioned and the potential for carisoprodol abuse has been worrisome. The majority of literature that has been recently published evaluates tizanidine; otherwise minimal literature has been published recently comparing or evaluating these agents as adjuncts in treating musculoskeletal conditions. According to the available information, no specific agent from this class has been documented to produce a greater therapeutic effect than another agent. There are no long term studies on the safety and efficacy of these agents for musculoskeletal conditions.

Therefore, all brand products within the skeletal muscle class are comparable to each other and the generics in the class and offer no significant clinical advantage over other alternatives in general use.

## XI. Recommendations

All multi-source brand name products should remain ‘non-covered’ products requiring generic substitution. For the single-source branded agent – Skelaxin, step therapy is recommended to insure failure of at least two generic SMR’s before approval of this agent is granted.

## References

1. van Tulder MW, Touray T, Furlan AD, et al. Muscle relaxants for nonspecific low back pain: a systematic review within the framework of the Cochrane Collaboration. *Spine* 2003;28(17):1978-92.
2. Kastrup EK, Ed. *Drug Facts and Comparisons*. Facts and Comparisons. St. Louis. 2005.
3. McEvoy GK, Ed. *American Hospital Formulary Service, AHFS Drug information*. American Society of Health-System Pharmacists. Bethesda. 2005.
4. *Electronic Orange Book*. Available at:<http://www.fda.gov/cder/ob/>. Accessed August 18, 2005
5. *Micromedex® Healthcare Series*: Thomson Micromedex, Greenwood Village, Colorado (Edition 2005).
6. Johnson-Rochee M, ed. *In the Spotlight: Carisoprodol*. On-Line With Industry. Winter 2002/2003;02(1):3-6. Available <http://www.deadivision.usdoj.gov/>.
7. Beard S, Hunn A, Wight J. Treatments of spasticity and pain in multiple sclerosis: a systematic review. *Health Technol Assess* 2003;7(40). Available <http://www.hta.nhsweb.nhs.uk/fullmono/mon740.pdf>. Accessed September 15, 2005.

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