

Considerations for the Appropriate Use of Skeletal Muscle Relaxants for the Management Of Acute Low Back Pain

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INTRODUCTION

For the past three decades, low back pain has consistently been ranked among the top five most common reasons for physician visits in the United States.¹⁻³ However, there is little consensus on a proper diagnosis and optimal treatment strategy for these patients. The three main classifications of low back pain include: nonspecific low back pain, back pain associated with radiculopathy or spinal stenosis, and back pain correlated with another specific spinal cause (i.e., malignancy, infection, or vertebral fracture).¹ Nonspecific low back pain is primarily acute without an identifiable cause and typically resolves in less than four weeks.⁴ However, a significant portion of patients may experience persistent back pain well beyond the acute episode, affecting health care costs and limiting daily activities.⁵

The American Pain Society and the American College of Physicians published guidelines in 2007 for low back pain, recommending acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line treatment for most patients. This recommendation is primarily due to the favorable side-effect profile of these agents compared with other options as opposed to superior efficacy.¹ After failure of a first-line agent, skeletal muscle relaxants, benzodiazepines, and opioids may be initiated based on evidence of temporary additional pain relief.¹

In general, muscle relaxants are controversial alternatives that have efficacy in nonspecific back pain but carry risks of adverse effects and increased cost. Although they are not recommended as primary treatment, 35% of patients are prescribed muscle relaxants for nonspecific low back pain, and 18.5% receive initial muscle relaxant therapy.^{2,6,7} Patients are often prescribed these agents for the treatment of acute back pain, and many experience relief within several weeks of starting therapy.⁸ For example,

patients receiving cyclobenzaprine were more likely to report symptomatic improvement at two weeks compared with placebo (number needed to treat = 3).⁸ Given the frequency of use, the questionable role in the treatment of back pain, and the potential for misuse, it is imperative for clinicians to be aware of the facts regarding commonly used muscle relaxants in the United States.

EVIDENCE FOR THE USE OF SKELETAL MUSCLE RELAXANTS

Recent literature analyzing the prevalence of muscle relaxant use is scarce. Some clinicians would agree that the medications in this class tend to be used more frequently than necessary, but clear data are lacking. IMS Health data from 2003–2004 showed carisoprodol, cyclobenzaprine, and metaxalone accounted for more than 45% of all prescriptions written for the management of musculoskeletal pain.⁹ Dillon et al. sought to define U.S. usage patterns using data from the third National Health and Nutrition Examination Survey (NHANES III).¹⁰ In this cross-sectional prevalence study, the authors concluded that approximately two million U.S. adults used skeletal muscle relaxants. Interestingly, the study found that although two-thirds of patients taking these agents had a recent history of back pain, the prevalence of these medications was only 4% among all participants who reported a history of back pain in the previous year (95% CI, 2.9%–5.2%). In addition, the study showed that 44.5% of users took muscle relaxants for more than a year (95% CI, 35.7%–53.3%). This finding is of concern because each agent is recommended only for short-term use and has yet to be studied in chronic management. Sociodemographic analysis of the data shows users' median age was 42.3 years (95% CI, 38.1–47.8), and 16% were more than 60 years old.¹⁰ While the findings in this study offer some data on muscle relaxant use, it is important to remember that the NHANES III survey presents information from 1988 to 1994.

A systematic review indicated that skeletal muscle relaxants were effective in the short-term relief of acute low back pain when compared with placebo.⁶ However, these agents were associated with a 50% increased risk of adverse events (AEs) with a relative risk of 1.50 (95% CI, 1.14–1.98).⁶ Specifically, central nervous system (CNS) adverse events had a stronger association with skeletal muscle relaxant use, with a relative risk of 2.04 (95% CI, 1.23–3.37).⁶ In addition to sedation, patients may experience headaches, blurred vision, and dependency with the use of these agents.

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Considerations for the Use of Skeletal Muscle Relaxants for Acute Low Back Pain

There are very few high-quality studies comparing the efficacy of skeletal muscle relaxants.⁶ Only one high-quality head-to-head study shows superiority of carisoprodol to diazepam.¹¹ Additionally, no studies have been conducted to evaluate skeletal muscle relaxants compared with first-line treatments (e.g., acetaminophen or NSAIDs). Therefore, if a skeletal muscle relaxant is needed, an appropriate selection should be based on individual factors including duration and severity of symptoms, prior response to medications, potential side effects, desired benefits, comorbid conditions, and cost.^{5,6}

One element of selecting the correct treatment involves ensuring that the agent is used in appropriate populations. The Beers Criteria for Potentially Inappropriate Medication Use in Older Adults is a collection of recommendations from health care providers on medications with potential AE risks that outweigh most benefits for use. Because they cause CNS depression, several skeletal muscle relaxants are on the Beers list, including carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, and orphenadrine.¹² These agents are poorly tolerated in patients more than 65 years old due to anticholinergic AEs, sedation, and risk for falls and fractures.¹² Despite this risk, approximately 15% (300,000) of annual prescriptions for skeletal muscle relaxants are given to patients over the age of 65.¹⁰ In a nationwide case-control study in the Medicare Advantage population, the use of skeletal muscle relaxants was associated with a 40% increase in fracture risk (adjusted odds ratio [OR] = 1.40; 95% CI, 1.15–1.72, $P < 0.001$).¹³ Furthermore, the risk increased with the concomitant use of long-acting benzodiazepines (adjusted OR = 2.66; 95% CI, 1.94–3.65).¹³ Although this study was retrospective, the results support the classification of these agents on the Beers list.

Billups et al. conducted a pre-post cohort analysis to compare the incidence of physical injury in patients before and after the initiation of a skeletal muscle relaxant. Although retrospective in design and with limitations, this study showed a small, statistically significant increase in injury including fractures, contusions, lacerations, and falls within the first 60 days of initiation of a skeletal muscle relaxant.¹⁴ These results do not imply that use should be avoided in all geriatric patients but suggest clinicians should be cautious, personalize therapy, and assure that the benefits outweigh the risks of side effects.

When considering the overuse of these medications, it is important to understand the consequences and possible dangers to the public. The Substance Abuse and Mental Health Services Administration and the U.S. Department of Health and Human Services released national estimates of drug-related visits to hospital emergency departments (EDs) based on data from the Drug Abuse Warning Network (DAWN), a public health surveillance system of non-federal hospitals operating 24-hour EDs. Participating hospitals retrospectively review cases involving all types of drug use, including illegal, prescription, and over-the-counter medications. Estimates are made each calendar year, allowing for comparisons between years that show changes in prevalence among the different classes of medications.

In the 2011 DAWN update, 33.9% of the ED visits from anxiolytics, including benzodiazepines, were associated with nonmedical use of prescription drugs.¹⁵ Even though the prevalence is lower than other agents such as analgesics,

skeletal muscle relaxants are still a major concern in the U.S. In 2011, an estimated 53,000 ED visits were caused by muscle relaxant misuse or abuse, and 18% of these cases involved concomitant alcohol consumption.¹⁵ Carisoprodol was the most common skeletal muscle relaxant misused, with 25,528 cases, followed by cyclobenzaprine with 11,551 cases, contributing 2.1% and 0.9%, respectively, of all visits involving nonmedical use of pharmaceuticals.¹⁵ When investigating rates of suicide attempts, muscle relaxants were the primary agent in 4.8% of cases.¹⁵ Cyclobenzaprine was the most common agent (2.5%), followed by carisoprodol (1.0%). Since 2004, there has been an 84% increase in skeletal muscle relaxant involvement in suicide attempts, with cyclobenzaprine accounting for more than half of such visits.¹⁵

In an effort to investigate the potential shift in abuse or misuse of agents after carisoprodol was reclassified as a controlled substance, a search was conducted on skeletal muscle relaxant exposures reported to the Florida Poison Information Center Network from 2009 to 2012. Data extracted included intentional abuse or misuse of carisoprodol, cyclobenzaprine, and a combination of other muscle relaxants. The frequency of carisoprodol exposure in 2012 after its reclassification as a controlled substance was 75 cases, compared with an average of 132 cases annually between 2009 and 2011.¹⁶ Interestingly, the frequency of cyclobenzaprine exposure decreased to 27 cases in 2012 compared with an average of 36 cases annually between 2009 and 2011.¹⁶ Data on other muscle relaxant exposures showed variation among years without a clear increase in abuse or misuse after carisoprodol became a controlled substance.¹⁶ Additional analysis must be done to assess the impact of the reclassification of carisoprodol on the frequency of misuse and abuse of other, noncontrolled skeletal muscle relaxants.

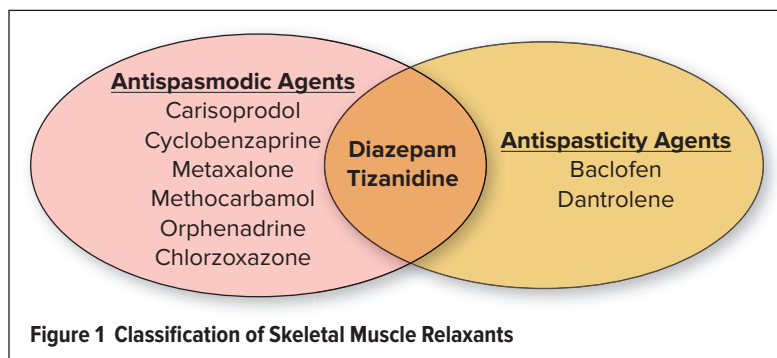
CLASS OVERVIEW

Skeletal muscle relaxants include a variety of structurally unrelated compounds that can be classified into two main categories: antispasticity and antispasmodic medications. These agents have different indications, mechanisms of action, and side-effect profiles. Understanding these differences can improve selection of an appropriate agent to optimize patient-specific therapy.

Antispasticity agents work on the spinal cord or directly on the skeletal muscles to improve muscle hypertonicity and involuntary spasms. Spasticity is defined as the increased muscle tone or stiffness that leads to undesirable and uncontrolled movements.¹ These medications are used for spastic conditions such as cerebral palsy, multiple sclerosis, and spinal cord injuries. A common antispasticity agent used in practice is baclofen. Dantrolene is also an antispasticity agent, but it should not be used for low back pain because its efficacy has not been proven for musculoskeletal conditions. In addition, dantrolene has a boxed warning associated with the potential for fatal hepatotoxicity.¹⁷

Antispasmodics decrease muscle spasms through alterations of CNS conduction. They are divided into benzodiazepines, which inhibit transmission on the postsynaptic γ -aminobutyric acid (GABA) neurons, and nonbenzodiazepine agents, which act at the brain stem and spinal cord.¹ Benzodiazepines (e.g., diazepam) are used as sedatives, anxiolytics, and anticonvulsants,

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and have been shown to have efficacy in the acute management of low back pain.⁶ Other antispasmodics commonly prescribed for the reduction of muscle spasms include: carisoprodol, cyclobenzaprine, metaxalone, and methocarbamol.

In general, antispasticity agents and antispasmodics are not interchangeable and should not be substituted for one another. However, some muscle relaxants, such as tizanidine and diazepam, carry indications approved by the Food and Drug Administration (FDA) for both conditions (Figure 1). Limited evidence exists for comparing one agent with another, so selecting an optimal agent relies on important patient-specific factors such as risks for side effects, potential drug interactions with concomitant therapies, and total cost.⁶

Indications, dosages, precautions, and other characteristics of skeletal muscle relaxants are summarized in Table 1.

Antispasticity Agents

Baclofen

Baclofen is a centrally acting skeletal muscle relaxant that is structurally similar to γ -aminobutyric acid (GABA), differing only in the presence of an additional phenylchloride group. Baclofen acts on the presynaptic GABA_A site, decreasing synaptic transmission on the spinal cord. It has FDA-labeled indications for muscle spasms and spasticity related to CNS lesions, mainly multiple sclerosis and spinal cord lesions.¹⁸ Although it is equivalent to other antispasticity agents, it has a decreased occurrence of CNS depression.

Dosing regimens vary by indication, but generally are initiated at 5 mg three times daily, and can be titrated by 5 mg per dose every three days. The effective range is 40 mg to 80 mg in divided doses given three or four times daily. Peak blood concentrations following administration occur in three to four hours.¹⁸ About 15% of the drug is metabolized in the liver by deamination, and the drug is primarily excreted (70% to 85%) by the kidneys.¹⁸

There are no recommended dosing adjustments for hepatic or renal dysfunction; however, due to the extensive renal elimination, recent literature suggests a dose reduction should be considered in patients with renal impairment.¹⁹ In a pharmacokinetic analysis comparing 21 patients with normal and impaired renal function, oral baclofen 5 mg clearance was reduced by about 34%, 49%, and 64% in patients with mild, moderate, and severe chronic kidney disease, respectively.¹⁹ As the estimated glomerular filtration rate (eGFR) decreased, baclofen elimination decreased. This allowed for increased serum concentrations and potentially increased AE risks. Based on these results,

33%, 50%, and 66% dose reductions should be considered in patients with mild (creatinine clearance [CrCl] of 50 mL/min or more), moderate (CrCl of 30 mL/min or more), and severe (CrCl of less than 30 mL/min) renal dysfunction, respectively.¹⁹ The drug is effectively removed by hemodialysis in the case of excessive accumulation or overdose.

Oral baclofen carries a boxed warning regarding abrupt discontinuation, which may cause confusion, hallucinations, seizures, and exacerbations of spastic conditions due to precipitation of withdrawal.¹⁸ A gradual reduction in dose over several weeks is recommended when discontinuing baclofen.¹⁸ Common AEs include weakness, dizziness, drowsiness, vertigo, and insomnia.¹⁸

Dantrolene

Dantrolene is a skeletal muscle relaxant structurally related to phenytoin. It has a unique peripheral mechanism of action, differing from the centrally acting agents. Dantrolene interferes with the release of calcium ions from the sarcoplasmic reticulum in the skeletal muscle cell. This disruption slows the contraction cycles of muscle cells occurring in malignant hyperthermia, making dantrolene an ideal agent for the treatment of this condition.²⁰ This agent is FDA-approved for the treatment of spasticity of upper neuronal disorders, including spinal cord injury, multiple sclerosis, and cerebral palsy.²⁰

Oral dantrolene carries a boxed warning regarding the risk of hepatotoxicity with chronic use^{17,20} and should not be used in the treatment of low back pain.¹⁷

Antispasmodic Agents

Metaxalone

Metaxalone is a CNS depressant used for acute musculoskeletal spasmic pain. Although commonly classified as a muscle relaxant, metaxalone does not act directly on skeletal muscle. While its mechanism is not fully understood, its antispasmodic effects are attributed to its sedative properties. Metaxalone is indicated only as adjunct treatment to physical therapy for acute musculoskeletal pain.²¹ The recommended dosing regimen is 800 mg given three to four times daily.²¹ The onset of action can be seen within an hour, and patients will experience effects for up to six hours. Meals higher in fat appear to increase bioavailability, so metaxalone should be taken with food.

Metaxalone undergoes hepatic metabolism through the cytochrome P450 (CYP) isoenzymes 1A2, 2D6, 2E1, and 3A4, and metabolites are excreted in the urine.²¹ Other medications used concomitantly must be taken into consideration due to the hepatic metabolism by numerous CYP enzymes. Common reported AEs include dizziness, drowsiness, nausea, and vomiting. Rare but serious AEs include hemolytic anemia, leukopenia, and jaundice. Metaxalone is contraindicated in severe hepatic and renal dysfunction; liver function tests should be monitored with therapy from baseline in mild-to-moderate liver dysfunction.²¹

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Table 1 Skeletal Muscle Relaxants

Medication	Indication	Common Dosage	Metabolism	Dose Adjustments
Antispasticity Agents				
Baclofen (Lioresal)	Spasticity	5 mg 3 times daily Max: 80 mg daily	Hepatic (15%)	None
Dantrolene (Dantrium)	Spasticity, malignant hyperthermia	Initial: 25 mg daily Maintenance: 25–100 mg up to 4 times daily	Hepatic (extensive)	None
Antispasmodic Agents				
Carisoprodol (Soma)	Acute musculoskeletal pain	250–350 mg 3 times a day and at bedtime Max: 1,400 mg daily	Hepatic (2C19) Active metabolite: meprobamate	Liver disease: Use lower initial dose and increase gradually as needed/ tolerated
Chlorzoxazone (Parafon Forte DSC)	Acute musculoskeletal pain	500 mg 3–4 times daily Max: 750 mg 3–4 times daily	Hepatic (glucuronidation)	None
Cyclobenzaprine (Amrix)	Acute musculoskeletal pain	IR: 5 mg 3 times daily Max: 10 mg 3 times daily ER: 15 mg daily Max: 30 mg daily	Hepatic (CYP3A4, 1A2)	Renal, none; hepatic, use with caution
Metaxalone (Skelaxin)	Acute musculoskeletal pain	800 mg 3–4 times daily	Hepatic (CYP1A2, 2D6, 2E1, 3A4)	Contraindicated in severe hepatic and renal dysfunction
Methocarbamol (Robaxin)	Acute musculoskeletal pain	Initial: 1,500 mg 4 times daily for 2–3 days Maintenance: 750 mg every 4 hours, 1,500 mg by mouth 3 times daily, or 1,000 mg 4 times daily Max: 4 g daily	Conjugation, dealkylation, and hydroxylation	None
Orphenadrine (Norflex)	Acute musculoskeletal pain	100 mg 2 times daily	Hepatic (extensive)	None
Antispasticity and Antispasmodic Agents				
Diazepam (Valium)	Relief of skeletal muscle spasm	2–10 mg 3 to 4 times daily	Hepatic (2C19, 3A4)	Renal, none; hepatic, decrease by 50%
Tizanidine (Zanaflex)	Spasticity	Initial: 4 mg up to 3 times daily; may titrate to optimal effect in 2–4 mg increments as needed to a max of 3 doses in 24 hours	Hepatic (1A2)	Renal, use with caution if CrCl < 25 mL/min; hepatic, avoid use in severe impairment

CNS = central nervous system; CrCl = creatinine clearance rate; ER = extended release; IR = immediate release; LFT = liver function test; Max = maximum

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Table 1 Skeletal Muscle Relaxants (continued)				
Medication	Beers Criteria	Special Precautions	Adverse Effects	Clinical Pearls
Antispasticity Agents				
Baclofen (Lioresal)	No	Geriatric: 5 mg 2–3 times daily; use lowest effective dose	CNS depression	Boxed warning: Avoid abrupt discontinuation due to risk of withdrawal
Dantrolene (Dantrium)	No	May cause sun sensitivity	Major hepatic impairment including fatal hepatitis, CNS depression, difficulty swallowing	Boxed warning: risk for hepatotoxicity with chronic use; routine use not recommended
Antispasmodic Agents				
Carisoprodol (Soma)	Yes	Has been subject to abuse, dependence, withdrawal, misuse, and criminal diversion	Drowsiness, dizziness, headaches, somnolence, seizure	Schedule IV Active metabolite with barbiturate effects; some evidence suggests sedation is primary mechanism of action without direct effects on skeletal muscle. Limit use to 2–3 weeks.
Chlorzoxazone (Parafon Forte DSC)	Yes	Idiosyncratic and unpredictable hepatotoxicity (rare but serious)	CNS depression	Periodic LFTs recommended during chronic use
Cyclobenzaprine (Amrix)	Yes	Caution with elderly and hepatic impairment	Anticholinergic effects, CNS depression, rare arrhythmias	Structure similar to tricyclic antidepressants. Do not use longer than 2–3 weeks; do not use within 14 days of monoamine oxidase inhibitors.
Metaxalone (Skelaxin)	Yes	Monitor liver function in mild-to-moderate hepatic dysfunction	CNS depression, nausea, vomiting; rare: jaundice, hemolytic anemia, elevated LFTs	Mechanism associated with sedative properties; take with food
Methocarbamol (Robaxin)	Yes	Geriatrics, liver, and renal impairment: Use lower initial doses and increase gradually as needed/tolerated	Dizziness, headache, lightheadedness	Mechanism associated with CNS depression; drug may change color of urine to brown, black, or green
Orphenadrine (Norflex)	Yes	Caution in patients with heart failure (palpitations, tachycardia); do not crush	Anticholinergic effects	Euphorigenic and analgesic properties; must taper in chronic use
Antispasticity and Antispasmodic Agents				
Diazepam (Valium)	Yes	Elderly: 2–2.5 mg 1–2 times daily; titrate gradually as tolerated	Drowsiness, fatigue, and ataxia	Schedule IV Avoid abrupt discontinuation after extended therapy
Tizanidine (Zanaflex)	No	Elderly: use with caution due to decreased clearance	Somnolence, xerostomia, and weakness	Concomitant use with other psychotropics may cause additive sedation; monitor liver function; avoid rapid discontinuation
CNS = central nervous system; CrCl = creatinine clearance rate; ER = extended release; IR = immediate release; LFT = liver function test; Max = maximum				

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Methocarbamol

Methocarbamol is an oral and parenteral centrally acting muscle relaxant indicated as an adjunct to physical therapy for the relief of acute musculoskeletal pain. Similar to many medications in this class, the exact mechanism of action is unknown, but its effects may be due to general CNS depression. It is available in 500-mg and 750-mg tablets; the initial recommended dose is 1,500 mg four times daily for two to three days for the treatment of acute musculoskeletal pain.²² Maintenance therapy is recommended at a decreased dose of 4 g to 4.5 g divided into three to six doses daily.

After oral administration, methocarbamol is quickly and completely absorbed. It is extensively metabolized by dealkylation and hydroxylation, and conjugation may be involved as well. Virtually all metabolites and remaining unchanged methocarbamol are excreted in the urine. The most common AEs are lightheadedness, dizziness, and drowsiness. There are insufficient data on its efficacy; however, it can be helpful in patients who cannot tolerate the stronger sedative effects of other muscle relaxants.²²

Orphenadrine

Orphenadrine citrate is an analog of diphenhydramine that is used for the treatment of muscle spasm associated with acute painful musculoskeletal conditions. It indirectly alleviates muscle pain through central atropine-like effects, and has some euphorogenic and analgesic properties. It comes in 100-mg extended-release tablets that cannot be crushed. It is recommended for short-term use, and must be tapered slowly if use becomes chronic.²³

Orphenadrine undergoes extensive hepatic metabolism through the CYP450 enzyme system, but it is a minor substrate and weak inhibitor, which limits concern about drug interactions. Peak effects are typically seen within two to four hours and can last up to six hours. Since patients may experience cardiovascular side effects such as palpitations and tachycardia, caution must be taken for patients with heart failure, tachycardia, or cardiac arrhythmias. Due to anticholinergic side effects, use in the elderly is generally not recommended. Common AEs include constipation, urinary retention, and confusion.²³

Chlorzoxazone

Chlorzoxazone is indicated for the symptomatic treatment of muscle spasms and pain associated with acute musculoskeletal conditions. It acts on the spinal cord and subcortical areas of the brain to inhibit polysynaptic reflex arcs involved in causing and maintaining skeletal muscle spasms. It comes in 375-mg, 500-mg, and 750-mg scored tablets; the recommended dosage is 500 mg three to four times daily, but a clinician may increase the dosage up to 750 mg three to four times daily if needed.²⁴ Peak effects can be seen within an hour and last up to six hours.

Similar to other agents in this class, chlorzoxazone can cause CNS side effects, such as dizziness, drowsiness, and lightheadedness, and use in the elderly population is generally not recommended. A rare but serious reported AE is idiosyncratic and unpredictable hepatocellular toxicity. If symptoms such as fever, rash, dark urine, or jaundice develop, discontinue the medication immediately. Periodic liver function tests are recommended, especially during chronic use.²⁴

Carisoprodol

Carisoprodol is an oral, centrally acting skeletal muscle relaxant indicated for the acute treatment of musculoskeletal pain. The exact mechanism of action remains unknown, but it is associated with altered neuronal communication at the reticular formation and spinal cord, causing CNS depression and a reduction in pain perception.²⁵ Some evidence suggests that sedation is the primary mechanism of action without directly affecting the skeletal muscle.²⁶ It is available in 250-mg and 350-mg tablets; administration is recommended three times daily and at bedtime.²⁵ It has only been proven efficacious in the treatment of acute low back pain, which limits its duration to two or three weeks. The onset of action is approximately 30 minutes and its effects can last for four to six hours.²⁵

Caution must be taken in patients with renal or hepatic dysfunction, as there is insufficient evidence of proper dosing in these populations. The most common AEs of CNS depression include dizziness, drowsiness, and headache, which can be increased with extended use and overuse. Carisoprodol is on the Beers list because the risks of side effects outweigh the potential benefits of treatment.¹²

Carisoprodol is extensively metabolized by CYP2C19, particularly to meprobamate, which has both sedative and anxiolytic properties.²⁵ Since conversion to the active metabolite is done predominantly by CYP2C19, there are concerns regarding genetic polymorphisms affecting serum drug concentrations. Reports have shown a fourfold increase in carisoprodol exposure and a 50% reduced meprobamate exposure in individuals with polymorphisms compared to normal metabolizers.²⁵ Hoiseith et al. sought to investigate the role of genetics in mortality related to carisoprodol toxicity. In this study, the variant alleles for the enzymes were not associated with an increased risk for mortality.²⁷

There are limited data comparing carisoprodol to other skeletal muscle relaxants. Boyles et al. conducted a randomized, double-blind trial of carisoprodol versus diazepam and found carisoprodol led to increased overall improvement in pain scores with respect to muscle stiffness, activity, and relief.¹¹ Rollings et al. conducted a high-quality study with carisoprodol and cyclobenzaprine and found no statistically significant differences in overall pain scores.²⁸

The abuse potential of carisoprodol is derived from its capability to modulate GABA_A function, and the active metabolite, meprobamate, can exacerbate this effect.²⁹ Meprobamate is a Schedule IV controlled substance, introduced as an anxiolytic agent during the 1950s, with a mechanism of action similar to barbiturates. The half-life of meprobamate is approximately 10 hours but can escalate to 48 hours in chronic use.³⁰ When it is used long-term, many patients may experience enhanced CNS depression due to the accumulation of the metabolites. Elderly patients and those with renal insufficiency are at a higher risk for this effect. Chronic users of carisoprodol have an increased likelihood of experiencing withdrawal symptoms following abrupt discontinuation. Symptoms of withdrawal include anxiety, insomnia, irritability, tremors, muscle twitching, and ataxia, which may be exacerbated with the metabolite accumulation.^{29,31}

According to the Drug Enforcement Agency (DEA), drug-induced seizures from carisoprodol increased from 3,988 in

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2008 to more than 5,000 in 2010: more than lorazepam and methylphenidate, which have a common association with abuse. Diversion has become more prevalent among legitimate medical practices and community pharmacies, with tactics ranging from “doctor shopping” to forged prescriptions. Reports of carisoprodol abuse grew more frequent as it came to be seen as an easily accessible sedative that can augment or alter the effects of other drugs. Carisoprodol use has been reported among patients to increase the sedating effects of benzodiazepines or alcohol, prevent jitteriness during cocaine consumption, and help calm individuals after cocaine use.³⁰ Carisoprodol can also be taken with other drugs to produce synergistic effects of extreme relaxation and euphoria.³⁰

In 1996, the DEA suggested reclassifying carisoprodol as a controlled substance in response to increasing case reports of effects similar to its meprobamate metabolite, which has been classified as a controlled substance in the U.S. since 1970. The FDA’s Drug Advisory Committee concluded that there was insufficient evidence to support the change at that time.³² Between 1994 and 2004, DAWN data showed that carisoprodol-related ED visits more than doubled, with an estimated 14,736 visits in 2004. In 2009, the frequency of ED visits doubled again, with 29,980 cases of nonmedical carisoprodol use.¹⁵ The 2009 Monitoring the Future national survey reported that carisoprodol abuse was seen in 1.4% of high school seniors, a frequency higher than lorazepam and clonazepam.³⁰

A survey of 40 individuals who had been taking carisoprodol for at least three months showed that half had a history of substance abuse. Of these 20 individuals, 40% admitted taking more than prescribed, 30% admitted taking it for effects other than prescribed, 10% admitted taking it to augment effects of other drugs, and 5% admitted taking it to counteract other drug effects.³³ The same survey assessed 100 physicians’ knowledge of carisoprodol and found that 95% knew meprobamate was a controlled substance but only 18% were aware that meprobamate was the active metabolite of carisoprodol.³³

Due to the accumulating evidence, on January 11, 2012, carisoprodol became a Schedule IV medication under the Controlled Substances Act of 1970.

Cyclobenzaprine

Cyclobenzaprine is structurally similar to tricyclic antidepressants such as amitriptyline and nortriptyline. Its mechanism of action as a muscle relaxant is not fully understood, but it is thought to act on the supraspinal area of the brain stem as an α_2 agonist at descending noradrenergic neurons.³⁴ Evidence shows that cyclobenzaprine also has some serotonergic antagonism at the 5-HT₂ receptor, which may contribute to its antispasmodic properties.³⁵ It is FDA-approved for the relief of spasms associated with acute musculoskeletal conditions unrelated to CNS disease. Patients can experience alleviation of acute musculoskeletal pain and increased mobility.³⁴ It is often used off-label for fibromyalgia, but has not been proven efficacious for treatment longer than one month.³⁶

Cyclobenzaprine is available as 5-mg and 10-mg immediate-release tablets and 15-mg and 30-mg extended-release tablets.^{34,37} The current recommended dosing regimen starts at 5 mg three times daily (10 mg at bedtime for fibromyalgia), and can be titrated to a maximum dose of 10 mg three times

daily.³⁴ The initial dose of the extended-release formulation, Amrix (Cephalon), is 15 mg once daily but may be titrated to a maximum of 30 mg daily.³⁷ Both formulations are recommended for use for up to three weeks due to a lack of evidence for benefits of chronic use.³⁸ In comparisons of safety and efficacy of immediate-release versus extended-release formulations, patients experienced similar relief from local pain and restriction of movement.^{39,40} The only difference was a lower incidence of somnolence in the extended-release formulation.^{39,40}

The most common side effects patients may experience include dizziness and drowsiness. Due to the activity at cholinergic receptors, cyclobenzaprine can cause anticholinergic effects such as dry mouth, blurred vision, constipation, and urinary retention. Similar to tricyclic antidepressants, cardiac arrhythmias including QTc prolongation are possible, and use may not be preferred in patients who have a history of arrhythmias or who are concurrently taking medications that also may prolong QTc.^{34,37}

Cyclobenzaprine is metabolized primarily by CYP3A4 and CYP1A2. The half-life ranges from eight to 36 hours and is heavily patient-specific. Caution should be taken with use in the elderly due to a relatively long half-life and elevated drug concentrations that can greatly increase the risk of drug-related AEs.⁴¹ This increased risk in the elderly is mostly due to decreased hepatic metabolism that can lead to average steady-state plasma concentrations more than 1.7 times greater than the concentrations in younger adults.^{34,41}

Antispasmodic and Antispasticity Agents

Tizanidine

Tizanidine is a centrally acting α_2 -adrenergic agonist approved for the management of spasticity. It is thought that the drug exerts its effects through an increase in the presynaptic inhibition of motor neurons with no direct effect on skeletal muscle fibers.⁴² Tizanidine is available as 2-mg and 4-mg tablets and as 2-mg, 4-mg, and 6-mg capsules. It is important to note that the capsules and tablets are bioequivalent under fasting conditions, but not when taken with meals. The quantity absorbed from the capsule under fed conditions is approximately 80% compared to the tablet formulation. The initial dosing recommendation is 4 mg given up to three times daily at six- to eight-hour intervals.⁴² The manufacturer gives this recommendation, despite the lack of efficacy in studies with doses less than 8 mg, due to concerns with dose-dependent AEs. The dose can be increased in 2-mg to 4-mg increments to achieve optimal effect, and the total daily dose should not exceed 36 mg.⁴²

The most common side effects include dry mouth, somnolence, asthenia, and dizziness. Asymptomatic hepatic aminotransaminase elevations have been noted in patients taking tizanidine, so monitoring of liver enzymes is warranted as deemed necessary by the clinician. Abrupt discontinuation may induce a hyperadrenergic syndrome that can include reflex tachycardia and hypertension, tremor, anxiety, and hypertonicity.⁴² A recent case report showed that abrupt discontinuation of tizanidine given concomitantly with baclofen led to the development of delirium, extrapyramidal symptoms, and autonomic dysfunction in a patient with impaired renal function.⁴³ This case highlights the risks of using more than one muscle relaxant that can lead to increased CNS depression.

Considerations for the Use of Skeletal Muscle Relaxants for Acute Low Back Pain

Due to hepatic metabolism through the CYP1A2 pathway, concentrations of tizanidine are increased with concomitant administration of inhibitors of this cytochrome P450 such as ciprofloxacin, fluvoxamine, cimetidine, famotidine, antiarrhythmics, and oral contraceptives. Interaction with antiarrhythmics warrants special attention: A recent study showed that prolonged use of tizanidine can induce QT prolongation, especially in patients predisposed to arrhythmias and patients with impaired drug elimination.⁴⁴ The manufacturer recommends that treatment with tizanidine should be reserved for those activities and times when relief of spasticity is most important.⁴²

Diazepam

Diazepam is a benzodiazepine used for its muscle relaxant activity in addition to its anxiolytic, antiepileptic, and hypnotic effects.⁴⁵ It is believed that the drug plays a role in the increase in GABA-mediated presynaptic inhibition at spinal and supraspinal sites. This suggests that diazepam might be of value for spinal spasticity but not for cerebral spasticity.

Diazepam is a controlled substance that is available in 2-mg, 5-mg, and 10-mg tablets as well as solution for injection and oral administration. Per the manufacturer's recommendation, the oral dose for relief of skeletal muscle spasm is 2 mg to 10 mg three to four times daily.⁴⁵ Starting the drug at a low dose and slowly titrating to a maximum daily dose of 30 mg is recommended due to concerns about side effects. The most common AEs include drowsiness, fatigue, and ataxia.

Fairly few articles have been published in recent years looking at diazepam's effects in the treatment of spasms.⁴⁵ A systematic review conducted by van Tulder et al. highlighted studies that showed diazepam to be inferior to carisoprodol in improving functional status in patients with low back pain and to exhibit no improvement over tizanidine after seven days of administration.⁶

When considering the use of diazepam, it is important to note that older adults have increased sensitivity to benzodiazepines and slower metabolism of long-acting agents. Per the Beers Criteria, benzodiazepines should generally be avoided in the elderly because of an increased risk of cognitive impairment, delirium, falls, and fractures.¹² Their use may be appropriate for seizure disorders, benzodiazepine withdrawal, alcohol withdrawal, severe general anxiety disorder, and end-of-life care.¹² Routine use for the treatment of low back pain should be minimal based on this criteria and increased risks.

CONCLUSION

Skeletal muscle relaxants are effective agents used for the management of acute nonspecific low back pain. However, the risk of adverse drug events raises concern for their safety in routine use. In the past decade, the overuse of some agents has grown drastically, with an increased incidence of adverse effects. In addition to sedation, patients may experience headache, dizziness, blurred vision, nausea, and vomiting.

The potential for abuse and dependency seen with carisoprodol resulted in its reclassification as a controlled substance in 2012 by the DEA. Ideally, this agent should be used with caution due to lack of efficacy, abuse potential, and risk for active metabolite accumulation.

The medications in this class are commonly used to treat acute musculoskeletal back pain, but they are often taken in higher quantities and for longer durations than recommended. Since evidence supports their use only for acute low back pain, they should be used temporarily for pain relief. This also prevents the extended masking of any underlying condition causing the back pain.

There are no set guidelines as to which agents are preferred; therefore, clinical judgment with proper understanding of the drug characteristics and patient-specific parameters should guide appropriate drug selection.⁶ Health care providers must use their judgment to weigh the pros and cons of prescribing a muscle relaxant while tailoring therapy to the individual needs of each patient. As evidence improves, recommendations can be modified, allowing patients to achieve safe and effective relief of their acute low back pain.

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