Although grouped under a single drug class, skeletal muscle relaxants are a heterogeneous group of structurally unrelated medications with variable pharmacologic and safety profiles. Skeletal muscle relaxants are used commonly for the treatment of 2 conditions: spasticity and local musculoskeletal spasms. Approximately 2 million Americans, including more than 300,000 people over 60 years of age, are prescribed muscle relaxants.

Spasticity and spasms are distinct etiologies, and each condition responds differently to certain medications. Spasticity is a disorder of motor neurons that manifests as increased muscle tone and stiffness. Spasms are involuntary localized muscle contractions that arise from acute trauma or muscle strain. Although antispasmodics and antispasticity agents...
generally are not interchangeable, diazepam (Valium) is approved by the Food and Drug Administration (FDA) for both conditions.6,7

In this article, the authors review the etiologies of, and treatment options for, painful spasticity and muscle spasm.

**Skeletal Muscle System**

Table 1 highlights the basic differences between spasticity and spasms, including the etiology, symptoms, causes, and FDA-approved therapies.8

Table 1. Difference Between Spasticity and Spasms

<table>
<thead>
<tr>
<th>Description</th>
<th>Spasticity4,10,13</th>
<th>Spasms3,5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Velocity-dependent increase in muscle tone caused by the increased excitability of the muscle stretch reflex</td>
<td>Involuntary muscle contractions</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>Central</td>
<td>Peripheral&lt;br&gt;Muscle sprain or injury&lt;br&gt;Nerve compression (eg, spinal stenosis)</td>
</tr>
<tr>
<td></td>
<td>Disorder of upper motor neurons</td>
<td></td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Stiffness&lt;br&gt;Hypertonicity&lt;br&gt;Hyperreflexia</td>
<td>Jerks&lt;br&gt;Twitches&lt;br&gt;Cramps</td>
</tr>
<tr>
<td><strong>Causes</strong></td>
<td>Multiple sclerosis&lt;br&gt;Cerebral palsy&lt;br&gt;Spinal cord injury&lt;br&gt;Traumatic brain injury&lt;br&gt;Motor neuron disease&lt;br&gt;Post-stroke syndrome</td>
<td>Musculoskeletal pain&lt;br&gt;Fibromyalgia&lt;br&gt;Sciatica&lt;br&gt;Mechanical low back pain&lt;br&gt;Herniated disk&lt;br&gt;Spinal stenosis&lt;br&gt;Myofascial pain</td>
</tr>
<tr>
<td><strong>FDA-approved agents</strong>a</td>
<td>Botulinum toxinb&lt;br&gt;Baclofen&lt;br&gt;Dantrolene&lt;br&gt;Diazepam&lt;br&gt;Riluzole&lt;br&gt;Tizanidine</td>
<td>Carisoprodol&lt;br&gt;Chlorzoxazone&lt;br&gt;Cyclobenzaprine&lt;br&gt;Metaxalone&lt;br&gt;Methocarbamol&lt;br&gt;Orphenadrine</td>
</tr>
</tbody>
</table>

a See Tables 3 and 4 for more in-depth review of agents.  
b Indication depends on the product.  
c Also approved for prophylaxis and treatment of malignant hyperthermia.  
d Approved for treatment of both spasticity and muscle spasms.  
e Mainly used in patients with amyotrophic lateral sclerosis.

Two types of motor neurons regulate skeletal muscle excitability: upper motor neurons (UMNs), which originate from the cerebral cortex, and lower motor neurons (LMNs), which originate in the spinal cord and brain stem.9-11 UMNs innervate the LMNs in the spinal cord, where they directly innervate skeletal muscles, and in the brain stem (cranial nerves), where they innervate the facial muscles. UMNs can stimulate or inhibit skeletal muscle contraction by direct innervation to LMNs. UMN lesions can result in muscle weakness, spasticity, or both, but LMN lesions may develop into muscle weakness and paralysis.

**How Skeletal Muscle Contracts**

A single α-motor neuron can innervate up to 200 muscle fibers, forming a complex called motor unit (Figure 1, page 44).10 With movement, an action potential originates from the UMN in the motor cortex.9 This action potential depolarizes the motor neuron terminal, resulting in the opening of voltage-gated calcium (Ca2+) channels and the subsequent release of the neurotransmitter acetylcholine (Ach) into the synaptic cleft. In the synaptic cleft, Ach binds to nicotinic cholinergic receptors on the muscle fiber membrane, leading to an influx of sodium (Na+) and a discharge of potassium (K) across the muscle fiber’s membrane, which results in depolarization of the muscle fiber.11 This depolarization opens voltage-gated Ca2+ channels on the sarcoplasmic reticulum (via ryanodine and inositol triphosphate receptors), allowing for Ca2+ influx into the cytoplasm of striated muscle cells.12 The Ca2+ then binds to troponin C,
which exposes myosin-binding sites on actin filaments. A cross-link forms between actin and myosin, leading to muscle contraction. The pumping of Ca²⁺ back into the sarcoplasmic reticulum, using adenosine triphosphate, leads to cessation of contraction.

Neuromuscular System
There are 2 pathways that regulate skeletal muscle excitability and contraction: the monosynaptic and polysynaptic reflex pathways. In the monosynaptic reflex, afferent signals from muscle cells return to the spinal cord, resulting in negative feedback on motor movements. The Golgi tendon, a proprioceptive sensory receptor organ, senses muscle tension and sends an inhibitory signal to the spinal cord. In the polysynaptic reflex, type IA afferent neurons synapse on inhibitory neurons in the dorsal horn and inhibit contraction of the targeted area. For example, if a person touches a hot surface, the brain sends an excitatory signal to stimulate the bicep muscles to contract, allowing for the desired motion, and then sends an inhibitory signal to prevent the triceps from contracting to end the motion.

Spasticity
Spasticity is defined as a velocity-dependent increase in muscle tone caused by the increased excitability of the muscle stretch reflex. Clinical manifestations include muscle stiffness, co-contraction of flexors and extensors, and increased resistance to muscle stretching. The etiology of spasticity is not fully known, but it is thought to be due to excessive stimulation or lack of inhibition of α-motor neurons, leading to increased muscle tone.

Spasticity is associated with increased activity of excitatory neurotransmitters or decreased activity of inhibitory neurotransmitters. Causes of spasticity include multiple sclerosis (MS), cerebral palsy, spinal cord injury, traumatic brain injury, and post-stroke syndrome. Antispasticity medications reduce muscle tone by acting either on the central nervous system (CNS) or directly on skeletal muscles. Agents that work on the CNS include baclofen, tizanidine, gabapentinoids, riluzole, and benzodiazepines, whereas peripheral agents include dantrolene and botulinum toxin. Baclofen is a structural analogue of GABA that binds to GABA₉ receptors, which are coupled to presynaptic and postsynaptic Ca²⁺ and K⁺ channels. Therefore, baclofen acts presynaptically and postsynaptically to inhibit spinal reflexes. Presynaptic activation of GABA₉ receptors results in hyperpolarization and decreased Ca²⁺ influx, which reduces glutamate release, leading to a decrease in α-motor neuron activity. Postsynaptic activation of GABA₉ increases K⁺ conductance in the IA afferent neuron terminals, hyperpolarizing the membrane and enhancing presynaptic inhibition. Baclofen also is thought to inhibit substance P release into the spinal cord, which may reduce pain.

Baclofen is available as an oral medication, as an intrathecal injection, or for use in an intrathecal pump; the latter form is reserved for cases of severe spasticity. Baclofen has been evaluated for other conditions, including cluster headache, intractable hiccups.
and nicotine, cocaine, and alcohol dependence.20-24

Common adverse effects (AEs) include dry mouth and transient sedation that subside with chronic use.17 Withdrawal syndrome has been reported following abrupt stoppage of intrathecal and/or oral baclofen.25,26 Symptoms associated with abrupt withdrawal of baclofen include auditory and visual hallucinations, agitation, delirium, anxiety, fever, tremors, tachycardia, and, potentially, seizures.25,26

**Tizanidine** is a centrally acting \(\alpha_2\) agonist that is structurally similar to clonidine.2,6 Tizanidine inhibits presynaptic release of excitatory neurotransmitters, reducing the excitability of postsynaptic \(\alpha\)-motor neurons.3 In addition, tizanidine can potentiate the actions of glycine.27 Tizanidine has been shown to suppress the polysynaptic reflex and reduce abnormal cocontraction of opposing muscle groups.28 Tizanidine also has been evaluated as an adjunct for prophylaxis of several types of headache, including migraine and tension headache.29

Tizanidine is available as capsules and tablets, which are bioequivalent only when taken on an empty stomach.6 When tizanidine is administered with food, the amount absorbed from the capsule is approximately 80% of that of the tablet. In addition, food increases the plasma concentration of the tablet by 30% and decreases the plasma concentration of the capsule by 20%. Ingesting the contents of the capsule with applesauce results in a 15% to 20% increase in plasma concentration and area under the curve (AUC), compared to ingesting the capsule while fasting.6

Tizanidine is metabolized through CYP1A2, and the inactive metabolites are excreted in the urine (60%) and feces (20%).6 CYP1A2 inhibitors, such as fluvoxamine and ciprofloxacin, can increase plasma levels of tizanidine and the incidence of AEs.30 Studies have shown that concurrent use of oral contraceptives also increased the plasma concentration and hypotensive effects of tizanidine.31

AEs include weakness, dry mouth, increased spasm or tone, hypotension, and mild liver function test (LFT) elevations.6 Withdrawal symptoms, including reflex tachycardia, hypertension, hypertonicity, tremor, and anxiety, have been reported with abrupt discontinuation.32 To minimize withdrawal symptoms, the manufacturer recommends that the dose be tapered slowly (2-4 mg/day), especially in patients receiving high doses (>20 mg/day) for long periods (>9 weeks).6

**Gabapentinoids** are anticonvulsant medications that have shown benefit as antispasticity agents in studies involving patients with spinal cord injuries.2,33-35 Both gabapentin and pregabalin inhibit the \(\alpha_2\delta\) subunit of L-type voltage-gated \(\text{Ca}^{2+}\) channels, which are thought to inhibit glutamate release.36,37 Both agents have demonstrated efficacy in treatment of neuropathic pain and spasticity in patients with MS.35,38

Gabapentin has been shown to have a dose-related efficacy in controlling spasticity at dosages of 1,200 mg to 3,600 mg/day.39 Gabapentin has variable interindividual bioavailability, and it exhibits saturable oral absorption; its bioavailability decreases as the dose increases.5,36 Gabapentin also is
Table 2. Neurotransmitters Involved in the Etiology of Muscle Spasticity and Spasm

- **Gamma-Aminobutyric Acid (GABA)**. GABA, the primary inhibitory neurotransmitter in the nervous system, is released by interneurons within the dorsal and intermediate grey matter of the spinal cord and inhibit IA afferent neurons. Activation of GABA\(_A\) receptors increases chloride (Cl\(^{-}\)) conductance, which hyperpolarizes the cell and inhibits action potential formation. Activation of GABA\(_B\) receptors also can reduce activity of adenylyl cyclase and decrease calcium (Ca\(^{2+}\)) influx into the cell. GABA\(_B\) receptor activation has been shown to inhibit the release of pain mediator substance P.\(^{14}\)

- **Glutamate**. Glutamate, the primary excitatory neurotransmitter, increases Ca\(^{2+}\) influx into the postsynaptic cell. Glutamate is released by IA afferent fibers in the descending corticospinal tract. Glutamate also binds to \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and N-methyl-D-aspartate (NMDA) receptors, which mediate synaptic plasticity.

- **Glycine**. Glycine has both inhibitory and excitatory functions in the CNS. Activation of glycine \(\text{s}\) activates Cl\(^{-}\) channels, as does GABA, which exerts inhibitory effects. Impaired glycine transmission has been linked to autism and hyperekplexia. Glycine is a co-agonist for N-methyl-D-aspartate, which increases neuronal excitation.

- **Acetylcholine (Ach)**. Ach is the primary neurotransmitter responsible for transmitting signals between neurons and muscle fibers. It binds to skeletal muscle nicotinic receptors and increases conductance of sodium (Na\(^{+}\)) and Ca\(^{2+}\), leading to depolarization and muscle contraction.
Common AEs reported during clinical trials included nausea, vomiting, dyspepsia, flatulence, dry mouth, and weight loss.41-44 Riluzole was reported to cause dose-related LFT elevations (3-fold increase in serum alanine transferase), and the manufacturer recommends using caution in patients with hepatic impairment.41,43

**Peripheral Agents**

**Dantrolene** is a hydantoin derivative structurally related to phenytoin that blocks the ryanodine channel, which inhibits Ca²⁺ release from the sarcoplasmic reticulum, thus reducing muscle contraction.12,46 Dantrolene has been approved for “controlling the manifestations of clinical spasticity” that is the result of UMN disorders.46

AEs include skeletal muscle weakness, dyspnea, dysphasia, somnolence, and dose-dependent diarrhea. There have been reports of life-threatening hepatotoxicity.47,48 Dantrolene carries a black box warning of hepatotoxicity associated with high doses (>800 mg/day) and long-term use (3 to 12 months).46 Due to the risk of hepatotoxicity, it is not commonly used in practice for treatment of chronic spasticity and is mainly reserved for acute conditions such as neuroleptic malignant syndrome and malignant hyperthermia.

**Botulinum toxin** (BTX) is produced from *Clostridium botulinum* and is injected locally to inhibit presynaptic release of Ach in the neuromuscular junction, resulting in paralysis of the muscle.49,50 The onset of effect varies depending on the indication but is typically 14 days for spasticity and cervical dystonia—the effect typically lasts approximately 3 months.50 The effect diminishes when motor neurons develop new nerve terminals that start releasing Ach.51 Resistance to the paralytic effect could develop with repeated injections due to development of antibodies against the toxin.52,53 Adverse effects include rash and muscle weakness at the injection site, flu-like symptoms,
and headache.

There are 2 antigenically distinct serotypes of BTX on the market: BTX-A and BTX-B. BTX-A is available as onabotulinumtoxinA (Botox), abobotulinumtoxinA (Dysport), and incobotulinumtoxinA (Xeomin).39,50 The only available BTX-B on the market is rimabotulinumtoxinB (Myobloc). Each agent has different FDA indications. All agents are approved for cervical dystonia; however, BTX-A has been shown to have a longer duration of effect than BTX-B.54 OnabotulinumtoxinA is approved for treatment of upper and lower limb spasticity, whereas abobotulinumtoxinA is approved for upper limb spasticity.55,56

**Muscle Spasms**

A muscle spasm is a sudden involuntary contraction of a muscle group that involves jerking and twitching.1,2,5 Unlike spasticity, which is a disorder of the CNS, muscle spasms arise from a variety of peripheral musculoskeletal conditions, such as mechanical low back pain. Common skeletal muscle conditions that cause spasms include fibromyalgia, myofascial pain syndrome, and mechanical low back or neck pain.1

**Antispasm Agents**

Most of the agents discussed here are FDA approved for adjunctive use to treat muscle spasms and pain associated with acute musculoskeletal conditions (Table 4, page 58). Health data from 2003 to 2004 revealed that cyclobenzaprine (Amrix, Fexmid, others), carisoprodol (Soma, others), and metaxalone (Metaxall, Skelaxin, others) accounted for more than 45% of medications prescribed for acute musculoskeletal pain.3

Although skeletal muscle relaxants are recommended for short-term use in the treatment of musculoskeletal pain, approximately 44.5% of users remain on them for more than a year.3 Due to CNS depression, cyclobenzaprine, metaxalone, orphenadrine (Norflex, others), metocarbamol (Robaxin, others), carisoprodol, and chlorzoxazone (Lorzzone, Parafon Forte DSC, others) are on the American Geriatrics Society’s *Beers List* of inappropriate drugs for elderly patients.5 Despite this, approximately 300,000 annual prescriptions for skeletal muscle relaxants (15%) are issued to patients older than 65 years of age.5,5

**Cyclobenzaprine** has no direct activity on skeletal muscle, and its mechanism in myorelaxation has not been elucidated fully but is thought to be due primarily to its sedative effects.2,15,57 Cyclobenzaprine is highly sedating, which could be beneficial in patients with acute muscle spasms who are also experiencing difficulty sleeping, but the toxicity that comes with its significant anticholinergic risks cannot be overstated.1,15

Cyclobenzaprine is structurally similar to tricyclic antidepressants (TCAs), differing from amitriptyline by only 1 bond in the central ring.58 A meta-analysis evaluating cyclobenzaprine in fibromyalgia patients showed that the medication was superior to placebo; however, it has been shown to be inferior to its chemically related TCA counterparts.59,60

Long-term use beyond 3 weeks is not recommended due to lack of data on efficacy for prolonged use.61 Cyclobenzaprine undergoes hepatic metabolism through CYP3A4, CYP1A2, and CYP2D6 and is mainly excreted in the urine as glucuronide conjugates and, to a lesser extent, as unchanged drug in the feces. Its AE profile is similar to amitriptyline and includes anticholinergic AEs (dry mouth, confusion, urinary retention), fatigue, tachycardia, and cardiac conduction disturbances. It is not recommended in patients with arrhythmias or cardiac conduction abnormalities.

**Methocarbamol** is a centrally acting muscle relaxant that is a carbamate derivative of guaifenesin (Liquibid, Mucinex, others).2,62 Its muscle relaxant mechanism is unknown but is presumed to be due to sedation. In a head-to-head trial comparing methocarbamol to cyclobenzaprine, methocarbamol was associated with less sedation (38% vs 58%), but the percentage of patients who stopped therapy due to AEs was similar for the 2 agents (6% vs 7%, respectively).63 The risk of respiratory depression may be increased when patients also are taking opioids, benzodiazepines, or barbiturates. A unique AE of the medication is brown or green urine discoloration. Muscle coordination abnormalities and grand mal seizures also have been reported.

**Similar to the other agents in this class, carisoprodol** is a centrally acting muscle relaxant from the carbamate class.74 In animal studies, carisoprodol exhibited its muscle relaxant effects by altering interneuronal activity in the spinal cord and the descending reticular formation of the brain.64 It also has been found to have analgesic properties by reducing perception of pain.64

Carisoprodol undergoes extensive hepatic metabolism through CYP2C19 to several metabolites, including meprobamate, which exerts barbiturate-like activity at the GABA₆ receptors.50 Poor CYP2C19 metabolizers (prevalent in 5%-15% of Asians and 3%-5% of Caucasians and African Americans) have experienced up to a 4-fold increase in exposure to carisoprodol and 50% reduction in exposure to meprobamate.66

AEs include drowsiness, headache, vertigo, insomnia, and an increased risk of respiratory depression, especially in patients on concomitant opioids, benzodiazepines, or barbiturates. Compared to cyclobenzaprine, carisoprodol is associated with less frequent...
<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Recommended Dosing</th>
<th>Dose Adjustment for Hepatic/ Renal Impairment</th>
</tr>
</thead>
</table>
| Baclofen[^1-9] (Gablofen, Lioresal, others) | GABA<sub>B</sub> receptor agonist
Inhibits presynaptic and postsynaptic glutamate release | Starting dose: 5 mg orally 3 times daily
Increase by 5 mg per dose every 3 days
MDD: 80 mg | Hepatic: none
Renal: none |
| Tizanidine[^2,6,27-32] (Zanaflex, others) | Structurally similar to clonidine
Centrally acting alpha<sub>2</sub> agonist
Inhibits presynaptic and postsynaptic alpha<sub>2</sub> motor neurons
Could potentiate the actions of glycine | Starting dose: 2-4 mg orally 3 times a day
Titrate to MDD of 36 mg/day in 3 divided doses | Hepatic: avoid use; if used, reduce initial dose during titration
Renal: CrCl <25 mL/min: use with caution |
| Gabapentin[^2,36,39,40] (Neurontin, Gralise, Horizant, others) | Inhibits α<sub>2</sub>δ subunit of L-type voltage-gated Ca<sup>2+</sup> channels, which inhibits glutamate release | Gabapentin IR: 1,200 mg-3,600 mg/day in 3-4 divided doses
Horizant: 600 mg once or twice daily
Gralise: 300 to 800 mg once daily | Hepatic: none
Renal: CrCl >30-59 mL/min: 300 mg/day in 2-3 divided doses
CrCl >15-29 mL/min: 150 mg/day in 1-2 divided doses
CrCl ≤15 mL/min: 75 mg daily |
| Pregabalin[^2,37] (Lyrica) | Inhibits α<sub>2</sub>δ subunit of L-type voltage-gated Ca<sup>2+</sup> channels, which inhibits glutamate release | 75-300 mg/day in 2-3 divided doses | Hepatic: none
Renal: CrCl >30-59 mL/min: 300 mg/day in 2-3 divided doses
CrCl >15-29 mL/min: 150 mg/day in 1-2 divided doses
CrCl ≤15 mL/min: 75 mg daily |
| Diazepam [^2,7] (Diazepam, Intensol, Valium, others) | GABA<sub>A</sub> receptor agonist
Increases chloride conductance, which results in presynaptic inhibition in the spinal cord | Starting dose: 2 mg orally 2-3 times daily or 5 mg at night for nocturnal spasticity
Target dose: 40-60 mg/day in divided doses | Renal: N/A
Hepatic: contraindicated in severe hepatic impairment |
### Table 3. Agents Used for Treatment of Spasticity

<table>
<thead>
<tr>
<th>Unique Adverse Effects</th>
<th>Pharmacokinetics</th>
<th>Drug Interactions</th>
</tr>
</thead>
</table>
| Transient dizziness that usually resolves with continued therapy, withdrawal syndrome with abrupt discontinuation | Metabolism: 15% of the dose undergoes hepatic deamination  
Elimination: 70%-85% of the dose is renally excreted as unchanged drug in urine | CNS depressants                                                                    |
| Hypotension (20% decrease in blood pressure), mild LFT elevations (usually reversible), withdrawal syndrome with abrupt discontinuation | Bioavailability depends on formulation and food:  
- Fasting: capsules and tablets are bioequivalent  
- With meal: capsule has 25% less bioavailability than tablet  
Metabolism: CYP1A2  
Elimination: 60% urine and 20% feces | CNS depressants  
↑ Exposure with  
CYP1A2 inhibitors (eg, fluvoxamine ciprofloxacin, oral contraceptives, verapamil)  
↓ Exposure  
CYP1A2 inducers (eg, tobacco) |
| Peripheral edema, weight gain, cognitive decline and memory loss                       | Nonlinear absorption with high intersubject variability  
Eliminated in the urine as unchanged drug | CNS depressants                                                                    |
| Peripheral edema, weight gain, cognitive decline, and memory loss; better tolerated than gabapentin | Linear absorption  
More predicted PK profile compared to gabapentin  
Eliminated in the urine as unchanged drug | CNS depressants                                                                    |
| Cognitive impairment, potential for dependence or abuse, withdrawal syndrome with abrupt discontinuation | Metabolism: CYP3A4 and 2C19  
Eliminated in the urine as glucuronide conjugates | CNS depressants  
↑ Exposure with CYP3A4 inhibitors (eg, amlodipine, cyclosporine, fluconazole, fluoxetine, isoniazid, ketoconazole, ritonavir, verapamil)  
CYP2C19 inhibitors (eg, celecoxib, chloramphenicol, fluoxetine, fluvoxamine, omeprazole)  
↓ Exposure with CYP3A4 inducers (eg, carbamazepine, glucocorticoids, phenobarbital, phenytoin, rifampin, St. John’s wort)  
CYP2C19 inducers (eg, carbamazepine, norethisterone, rifampin) |
Table 3. Agents Used for Treatment of Spasticity (continued)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Recommended Dosing</th>
<th>Dose Adjustment for Hepatic/ Renal Impairment</th>
</tr>
</thead>
</table>
| Dantrolene2,46-48               | Hydantoin derivative related to phentoin. Blocks the RyR1 channel and inhibits Ca^2+ release from the sarcoplasmic reticulum | Week 1: 25 mg once daily  
Week 2: 25 mg 3 times daily  
Week 3: 50 mg 3 times daily  
Week 4: 100 mg 3 times daily  
MDD: 400 mg  
Discontinue if efficacy is not evident in 45 days | Hepatic: contraindicated in liver disease  
Renal: N/A |
| Riluzole41-45                   | Inhibits voltage-gated Na+ channels on glutaminergic nerve terminals  
Inhibits glutamate release and postsynaptic receptor activation | 50 mg orally twice daily on empty stomach | Hepatic: N/A  
Renal: N/A |
| Botulinum toxin 49-56           | Inhibits presynaptic release of acetylcholine in the neuromuscular junction | Dosing depends on product | — |

CNS, central nervous system; CrCl, creatinine clearance estimate of renal function based on Cockcroft and Gault equation; GABA, gamma-aminobutyric acid; IR, immediate release; LFT, liver function tests; MDD, maximum daily dose; N/A, no information provided by the manufacturer; PK, pharmacokinetic; RYR1, ryanodine receptor 1

The mechanism of action of metaxalone has not been established. It has no direct effect on skeletal muscles or nerve fibers, but CNS depression may be responsible for its effects. When taken with a high-fat meal, the bioavailability and AUC of metaxalone is increased. Metaxalone undergoes hepatic metabolism by CYP1A2, CYP2D6, CYP2E1, and CYP3A4, and its metabolites are excreted through the kidneys. Metaxalone is contraindicated in patients with renal or hepatic impairment.

AEs include dizziness, headache, nervousness, epigastric discomfort, and increased risk for respiratory depression in patients taking opioids, benzodiazepines, and barbiturates. Compared to other agents within the class, metaxalone has a relatively low risk of drowsiness or cognitive defects. Paradoxical muscle cramping has been documented with its use.

Chlorzoxazone was FDA approved in 1958 as an adjunct for relief of discomfort associated with acute musculoskeletal conditions. Data from animal studies showed that it acts primarily at the level of the spinal cord and subcortical areas of the brain, which results in inhibition of multisynaptic reflex arcs involved in muscle spasms. It undergoes hepatic glucuronidation into an inactive metabolite that is excreted in the urine. Chlorzoxazone can cause orange, red, or purple urine discoloration.

AEs include dizziness, somnolence, and occasional overstimulation. Rare cases of idiosyncratic hepatocellular toxicity have been reported. The manufacturer recommends immediate discontinuation if symptoms, including fever, rash, dark urine, or jaundice, develop. Periodic LFT monitoring is recommended for patients on chronic therapy.
Table 3. Agents Used for Treatment of Spasticity

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<tr>
<th>Unique Adverse Effects</th>
<th>Pharmacokinetics</th>
<th>Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-dependent hepatotoxicity, diarrhea</td>
<td>Metabolism: CYP3A4</td>
<td>CNS depressants</td>
</tr>
<tr>
<td></td>
<td>Elimination:</td>
<td>↑ Exposure with CYP3A4 inhibitors (eg,</td>
</tr>
<tr>
<td></td>
<td>-Feces 50%</td>
<td>amiodarone, cyclosporine fluconazole,</td>
</tr>
<tr>
<td></td>
<td>-Urine 25%</td>
<td>fluoxetine, isoniazid, ketoconazole ritonavir,</td>
</tr>
<tr>
<td>Dose-related LFT elevations, decreased lung function, pruritus</td>
<td>Bioavailability decreased when coadministered with food</td>
<td>↓ Exposure with CYP3A4 inducers (eg, carbamazepine, glucocorticoids, phenobarbital, phenytoin, rifampin, St. John’s wort)</td>
</tr>
<tr>
<td>Rash and muscle weakness at the injection site, flu-like symptoms, and headache</td>
<td>Metabolism: CYP1A2</td>
<td>↑ Exposure with CYP1A2 inhibitors (eg, ciprofloxacin, fluvoxamine, oral contraceptives, verapamil)</td>
</tr>
<tr>
<td></td>
<td>Eliminated in the urine 85% as glucuronide metabolites</td>
<td>↓ Exposure with CYP1A2 inducers (eg, tobacco)</td>
</tr>
</tbody>
</table>

Conclusion

Skeletal muscle relaxants represent a diverse pharmacotherapeutic group of medications across several chemical classes that are structurally dissimilar. These agents are effective for spasticity, skeletal muscle spasms, or both. Because of the breadth of pharmacologic mechanisms and variable pharmacokinetics, the drugs have a huge range of AEs and potential drug interactions. Considering that these agents are most often used in the elderly and also as adjuvants for the treatment of chronic pain patients with multiple comorbidities who are likely receiving a polypharmaceutical regimen (including opioids), skeletal muscle drug selection for each patient requires careful attention to these factors.

Authors’ Bios: At the time of this writing, Mena Raouf was a PharmD candidate, 2016, at Albany College of Pharmacy and Health Sciences, with a concentration in nephrology. He is currently a PGY-1 pharmacy resident at Veterans Administration (VA) Tennessee Valley Healthcare System.

Dr. Raouf completed an advanced pharmacy practice rotation in pain management under the mentorship of Dr. Jeffrey Fudin at the Stratton VA Medical Center. He has been involved in developing an automated software platform to assess pre-validated risk for opioid-induced respiratory depression to qualify patients for in-home naloxone.

Jeffrey Fudin, PharmD, DAAPM, FCCP, FASHP, is president and director, Scientific and Clinical Affairs REMITIGATE LLC and a clinical pharmacy specialist at the Stratton VA Medical Center. He is an adjunct associate professor of Pharmacy Practice at Western New England University College of Pharmacy; adjunct associate professor of Pharmacy Practice at Albany College of Pharmacy; adjunct assistant professor of Pharmacy Practice at the University of Connecticut School of Pharmacy. He is a diplomate of the American Academy of Pain Management, a fellow of the American College of Clinical Pharmacy and the American Society of Health-system Pharmacists. Dr. Fudin is a section editor for Pain Medicine, the official journal of AAPM. He is Founder/Chairman of Professionals for Rational Opioid Monitoring & Pharmacotherapy (PROMPT), a group that advocates in favor of safe opioid prescribing by encouraging clinician education, proactive risk stratification, and appropriate therapeutic monitoring.

Dr. Fudin disclosed that his involvement with this article was not part of his official government duties. Practical Pain Management readers will recognize Dr. Fudin as one of the co-developers of the PPM Opioid Calculator.
### Table 4. Agents Used for Treatment of Musculoskeletal Spasms

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Recommended Dosing</th>
<th>Dose Adjustment for Hepatic / Renal Impairment</th>
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<tbody>
<tr>
<td><strong>Cyclobenzaprine</strong>&lt;sup&gt;2,5,8,61&lt;/sup&gt; (Amrix, Fexmid, Flexeril, others)</td>
<td>Structurally similar to amitriptyline; CNS depressant acting primarily at the brain stem level; Reduces excitability of alpha and gamma motor neurons</td>
<td>5 mg orally 3 times daily; May increase to 7.5 mg or 10 mg 3 times daily for 2-3 weeks; May consider initially dosing at bedtime to gauge tolerance; Elderly: 5 mg orally and less frequent dosing</td>
<td>Hepatic: Mild: 5 mg initial dosing and titrate with caution; Moderate-severe: use is not recommended; Renal: N/A</td>
</tr>
<tr>
<td><strong>Methocarbamol</strong>&lt;sup&gt;62,63&lt;/sup&gt; (Robaxin, others)</td>
<td>Carbamate derivative of guaifenesin; Unknown mechanism but is thought to cause myorelaxation via sedation</td>
<td>Initial dose: 1,500-2,000 mg orally 4 times daily for 2-3 days; Maintenance dose: 750-1,000 mg orally 3-4 times daily</td>
<td>Hepatic: N/A; Oral: N/A; Parenteral: use is contraindicated due to presence of propylene glycol in the formulation</td>
</tr>
<tr>
<td><strong>Carisoprodol</strong>&lt;sup&gt;64-68&lt;/sup&gt; (Soma, others)</td>
<td>Interrupts interneuronal activity in the descending reticular formation and spinal cord; Metabolized to meprobamate, which exerts barbiturate-like activity at the GABA&lt;sub&gt;A&lt;/sub&gt; receptors</td>
<td>250-350 mg orally 4 times daily</td>
<td>Hepatic: N/A; use with caution due to extensive hepatic metabolism; Renal: N/A</td>
</tr>
<tr>
<td><strong>Orphenadrine</strong>&lt;sup&gt;69&lt;/sup&gt; (Norflex, others)</td>
<td>Anticholinergic receptor antagonist; H&lt;sub&gt;1&lt;/sub&gt; receptor antagonist; NMDA receptor antagonist; Structurally similar to diphenhydramine</td>
<td>100 mg orally twice daily</td>
<td>Hepatic: N/A; Renal: N/A</td>
</tr>
<tr>
<td><strong>Metaxalone</strong>&lt;sup&gt;71,72&lt;/sup&gt; (Metaxall, Skelaxin, others)</td>
<td>Unknown mechanism but is thought to cause myorelaxation via sedation</td>
<td>800 mg orally 3-4 times daily</td>
<td>Hepatic: N/A; use is contraindicated with severe hepatic impairment; Renal: N/A; use is contraindicated with severe renal impairment</td>
</tr>
<tr>
<td><strong>Chlorzoxazone</strong>&lt;sup&gt;73-75&lt;/sup&gt; (Lorzone, Parafon Forte DSC, others)</td>
<td>Acts primarily on at the spinal cord and subcortical areas of the brain to inhibit multisynaptic reflex arc</td>
<td>Initial dose: 250-500 mg orally 3-4 times daily; MDD: 750 mg orally 3-4 times daily</td>
<td>Hepatic: N/A; Renal: N/A</td>
</tr>
</tbody>
</table>

**CNS**, central nervous system; **CrCl**, creatinine clearance estimate of renal function based on Cockcroft and Gault equation; **LFT**, liver function test; **MDD**, maximum daily dose; **N/A**, no information provided by the manufacturer
<table>
<thead>
<tr>
<th>Adverse Effects and Clinical Pearls</th>
<th>Pharmacokinetics</th>
<th>Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic effects (dizziness, dry mouth, constipation, urinary retention, ocular hypertension), palpitations, sinus tachycardia, cardiac conduction disturbances</td>
<td>Metabolism: CYP12 (major), CYP3A4 and CYP2D6 (minor)</td>
<td>CNS depressants</td>
</tr>
<tr>
<td>Treatment is not recommended beyond 3 weeks; avoid in the elderly; use caution in patients with underlying cardiac conduction problems or arrhythmias; avoid in patients with closed angle glaucoma</td>
<td>Elimination: Urine as glucuronide conjugates (major); feces as unchanged drug (minor)</td>
<td>Serotonergic agents</td>
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<td></td>
<td></td>
<td>↑ Exposure with CYP1A2 inhibitors (eg, ciprofloxacin, fluvoxamine, oral contraceptives, verapamil)</td>
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<tr>
<td></td>
<td></td>
<td>↓ Exposure with CYP1A2 inducers (eg, tobacco)</td>
</tr>
<tr>
<td>Sedation, vertigo, confusion, headache, visual disturbances, amnesia, nausea, and dyspepsia; bradycardia, hypotension, syncope, muscle coordination abnormalities and grand mal seizures; urine discoloration (brown, green)</td>
<td>Metabolism: hepatic dealkylation, hydroxylation, conjugation</td>
<td>CNS depressants</td>
</tr>
<tr>
<td></td>
<td>Elimination: urine</td>
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<tr>
<td>Drowsiness, headache, vertigo, insomnia; psychological dependence, withdrawal syndrome, respiratory depression when used with opioids, benzoizepines, or barbiturates</td>
<td>Metabolism: CYP2C19</td>
<td>↑ Exposure with CYP2C19 inhibitors (eg, celecoxib, chloramphenicol, fluoxetine, fluvoxamine, oral contraceptives)</td>
</tr>
<tr>
<td></td>
<td>Elimination: renal and non-renal routes</td>
<td>↓ Exposure with CYP2C19 inducers (eg, carbamazepine, norethisterone, rifampin)</td>
</tr>
<tr>
<td>Anticholinergic effects (dizziness, dry mouth, constipation, urinary retention, ocular hypertension, palpitations, sinus tachycardia); rare aplastic anemia</td>
<td>Metabolism: Hepatic N-desmethylation and conjugation</td>
<td>CNS depressants</td>
</tr>
<tr>
<td></td>
<td>Elimination: Urine</td>
<td></td>
</tr>
<tr>
<td>Dizziness (less frequent), irritability, nausea, gastrointestinal upset; contraindicated in patients with hepatic impairment</td>
<td>Co-administration with food increases bioavailability</td>
<td>CNS depressants</td>
</tr>
<tr>
<td>Paradoxical muscle cramps and respiratory depression when used with opioids, benzoizepines, or barbiturates; contraindicated in serious liver or renal impairment</td>
<td>Metabolism: • CYP1A2 • CYP2D6 • CYP2E1 • CYP3A4</td>
<td>Increased risk for respiratory depression with opioids, benzoizepines, barbiturates</td>
</tr>
<tr>
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<td>Elimination: urine</td>
<td></td>
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<tr>
<td>Dizziness, sedation, irritability, nausea, and gastrointestinal upset; respiratory depression when used with opioids, benzoizepines, or barbiturates; rare idiosyncratic hepatotoxicity, urine discoloration (orange, red, or purple)</td>
<td>Metabolism: Hepatic glucuronidation</td>
<td>CNS depressants</td>
</tr>
<tr>
<td></td>
<td>Elimination: urine</td>
<td>Increased risk for respiratory depression with opioids, benzoizepines, barbiturates</td>
</tr>
</tbody>
</table>


62. Robaxin (Methocarbamol oral tablets), Westward Pharmaceutical Corp, Eatontown, NJ; 2009.


