Skeletal Muscle Relaxants
Drug Class Review

12:20.04 Centrally Acting Skeletal Muscle Relaxants

Baclofen (Lioresal®, others)
FDA Approved 1982
Carisoprodol (Soma®, others)
FDA Approved 1959
Carisoprodol/Aspirin (Soma Compound®, others)
FDA Approved 1983
Carisoprodol/Aspirin/Codeine (Soma Compound with Codeine®, others)
FDA Approved 1983
Chlorzoxazone (Parafon Forte®, Lorzone®, others)
FDA Approved 1958
Cyclobenzaprine (Flexeril®, others)
FDA Approved 1977
Dantrolene (Dantrium®, others)
FDA Approved 1974
Metaxalone (Skelaxin®, others)
FDA Approved 1962
Methocarbamol (Robaxin®, others)
FDA Approved 1957
Orphenadrine (Norflex®, others)
FDA Approved 1959
Orphenadrine/Aspirin/Caffeine (Orphenadrine Compound®)
FDA Approved 1996
Tizanidine (Zanaflex®, others)
Approved 1996

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Table of Contents

Executive Summary....3
Introduction....5
Disease Overview....6
Table 1. Comparison of the Skeletal Muscle Relaxants16-20....7
Place in Therapy – Guidelines....11
Table 2. Summary of Current Clinical Practice Guidelines for Skeletal Muscle Relaxants....11
Pharmacology....12
Pharmacokinetics....13
Table 3. Pharmacokinetics of the Skeletal Muscle Relaxants[16,17,34]....14
Methods....16
Special Populations....16
Table 4: Dosing Recommendations for Use of Skeletal Muscle Relaxants in Special Populations [17,20,35,37,38]....17
Safety....19
*Table 5 Safety of the Skeletal Muscle Relaxants** [5,16,20,34,38,68,75]....20
Withdrawal Reactions....22
Agent Specific Information....22
Adherence....24
Potential for Abuse....24
Drug Interactions....25
Table 6. Drug Interactions with the Skeletal Muscle Relaxants....26
Clinical Evidence....27
Summary....30
References....32
Appendix I: Comparative Efficacy for Skeletal Muscle Relaxants: Systematic Review[9]....36
Appendix II: Comparative Safety of Skeletal Muscle Relaxants – Systematic Review[9]....37
Appendix III: Clinical Evidence for Skeletal Muscle Relaxants: Systematic Review[81]....38
Appendix IV: Clinical Evidence for Skeletal Muscle Relaxants: Anti-spasticity Agents in Children[73,74]....40

Executive Summary

Introduction:
Pain is the most common reason people enter the health care system. The presence of low back pain remains among the top 5 reasons for primary physician visits. Three of the skeletal muscle relaxants, carisoprodol, cyclobenzaprine and metaxalone comprise 45% of all prescriptions for lower back pain.

This heterogeneous group of agents are useful in the treatment of musculoskeletal disorders associated with spasticity resulting from upper motor neuron disorders or in the treatment of peripheral musculoskeletal disorders associated with muscle pain or spasm.

No clinical practice guideline suggests using a skeletal muscle relaxant as first-line therapy for the treatment of pain or spasm. These agents are indicated as adjunct or alternative therapy after first or second line therapies have failed. Virtually every guideline points out the adverse effect profile (including abuse potential) of these agents and suggests caution in patient selection.

For the treatment of spasticity baclofen is considered a first line agent with dantrolene and tizanidine generally recommended second line.

Clinical Efficacy:
There are few comparative trials. Many initial clinical trials were published in in the 1960's to 1970's and were of poor quality. Trials often did not define the use of concomitant medications, pre-study treatment, many were not double-blind, and among other issues, the term muscle-spasm was not well defined. The data supporting many of these agents is weak. Data supporting the use of combination products is rare.

Efficacy appears to decline over time particularly for muscle pain and spasm. No data clearly demonstrated an advantage over non-steroidal anti-inflammatory drugs or when used in combination with them. The agents with the least clinical evidence supporting their use include chlorzoxazone, methocarbamol, dantrolene and baclofen for pain and spasm. Carisoprodol and cyclobenzaprine offer more evidence supporting their use for muscle pain and spasm. Only tizanidine, dantrolene and baclofen have evidence supporting their use in spasticity.

Adverse Drug Reactions:
In general, these agents are associated with significant side effects. Anticholinergic symptoms including sedation, somnolence and dry mouth occur commonly. All the antispasmodics are considered potentially unsafe for use in the elderly according to the most current Beers criteria list. Hepatotoxicity is problematic for some medications while abuse potential and withdrawal reactions are noted with others.

Summary:
Evidence does seem to support the efficacy of cyclobenzaprine and carisoprodol for the treatment of muscle pain and spasm. Overall, these agents have limited evidence supporting their short-term use with virtually no data suggesting any agent offers long-term benefits. They are not considered first-line therapy in the indications for which they have approval and most carry the

risk potential for significant adverse events and/or abuse potential. These agents should be used judiciously with careful consideration of patient-related variable in their selection and careful monitoring of these agents in use.

Introduction

The most common reason people enter the health care system is the presence of pain.[2-4] Low back pain remains among the top 5 reasons primary physician office visits.[5] Musculoskeletal disorders are responsible for 20% of outpatient visits in the US yearly (>315 million).[6] Most acute musculoskeletal pain is non-specific, and resolve within 4 weeks. When pain extends beyond 3 months it significantly affects quality of life and health care utilization and costs.[5] The direct medical costs associated with back pain in 1990 exceeded $24 billion.[1] Skeletal muscle relaxants constitute 18.5% of prescriptions written for musculoskeletal pain making them the most common drug class prescribed for musculoskeletal disorders.[7] Three of the agents carisoprodol, cyclobenzaprine and metaxalone comprise 45% of all prescriptions for lower back pain.[5] According to data from Symphony Health Solutions four of the skeletal muscle relaxants are among the top 200 medications dispensed in 2014. Cyclobenzaprine is #35 with 27.5 million prescriptions, tizanidine is #107 with 8.6 million prescriptions, carisoprodol is #122 with 7.9 million prescriptions and methocarbamol is #150 with 6 million prescriptions dispensed in 2014.[8]

Skeletal muscle relaxants include a heterogeneous mix of agents with differing structures and generally undefined mechanism of action. These agents are typically classified as antispasticity (baclofen, dantrolene) or antispasmodic agents (carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, and orphenadrine. Antispasticity agents have activity in upper motor syndromes (e.g. multiple sclerosis, cerebral palsy, traumatic brain injury, spinal cord injury and post-stroke syndrome) while the antispasmodics are used for peripheral muscle pain and spasm. Tizanidine demonstrates both activities. [7,9]

Antispasmodic skeletal muscle relaxants are generally considered second-line or adjunct therapy for musculoskeletal pain when initial therapy fails. They are commonly used to treat fibromyalgia, low back or neck pain, tension headaches, myofascial pain and muscle spasm where they reduce muscle pain and improve functional status.[7] None of the agents acts via direct effect on muscle fibers. It is presumed their activity occurs secondary to their sedative properties. The antispasmodic skeletal muscle relaxants are on the Beers criteria list for potentially inappropriate use in the elderly, yet 15% of prescriptions for these agents are written for this population.[5]

The anti-spasticity skeletal muscle relaxants act directly on skeletal muscles or more commonly at the level of the spinal cord or brainstem.[11] They reduce muscle tone, stiffness, exaggerated tendon reflexes, involuntary movements and spasms in a diverse variety of conditions, including multiple sclerosis, cerebral palsy, spinal cord injuries, traumatic brain injury and post-stroke syndrome.[5,11] Spasticity can be painful and disabling with significant effects on health status.[10]

In general, these agents are associated with significant side effects. Anticholinergic symptoms including sedation, somnolence and dry mouth occur commonly. Lower dose formulations of carisoprodol and cyclobenzaprine were developed in an effort to combat drug intolerability.

Disease Overview

The heterogeneous group of agents, the skeletal muscle relaxants are useful in the treatment of musculoskeletal disorders associated with spasticity resulting from upper motor neuron disorders or in the treatment of peripheral musculoskeletal disorders associated with muscle pain or spasm.

Spasticity

Spasticity is a motor disorder affecting 12 million people worldwide, in which upper motor neuron lesions result in continuous, increased tonic stretch reflexes.[11,12] According to the American Association of Neurological Surgeons, 60% of patients with multiple sclerosis and 65-78% of patients with spinal cord injuries are affected.[12] The overall effects on upper and lower motor neuron signaling is referred to as the motor neuron syndrome, which is common in patients with multiple sclerosis, cerebral palsy, traumatic brain injury, spinal cord injury, amyotrophic lateral sclerosis, progressive bulbar palsy, pseudobulbar palsy, primary lateral sclerosis and post-stroke syndrome.[11] Common symptoms associated with the upper motor neuron syndrome include exaggerated reflexes, autonomic hyperreflexia, dystonia, contractures, paresis, lack of dexterity, fatigability and spasticity. Often speech, gait and movement are affected which negatively affects health status and quality of life. [10,9,11,13]

Spasms Associated with Musculoskeletal Pain

Involuntary contractions of a muscle or muscle group (spasms) most commonly result from an acute partial muscle tear (strain) or partial or complete ligament rupture (sprain). It is believed that an initial muscle spasm causes pain leading to further contractions and resulting in a perpetuating cycle.[1] A known cause for the pain and spasms is not found in the majority of cases.[1] Therapy is aimed at interrupting the cycle of spasm-pain-spasm, which occurs in mechanical neck or back pain, fibromyalgia, tension headache and myofascial pain syndrome. Treatment includes pharmacologic and non-pharmacologic modalities aimed to bring pain relief, mobilization and a return to normal functioning. Pain resolves within 2 months for 90% of patients. If left untreated acute pain may become chronic in 10-15% of patients resulting in additional pain and discomfort.[1,14,15]

A comparison of the skeletal muscle relaxants is presented in **Table 1**.

Table 1. Comparison of the Skeletal Muscle Relaxants16-20

Characteristics	Dosage Forms	Labeled/Recommended Use	Dose Range	Contraindications	Generic Availability
Single Agents for Spasticity					
Baclofen	Oral Tablet: Lioresal® 10 mg, 20 mg Topical Cream: EnovaRX-Baclofen® KIT 1%, 2% Intrathecal Solution: Gablofen®: 50 mcg/mL (1 mL); Lioresal®: 0.05 mg/mL (1 mL);	Management of reversible spasticity associated with multiple sclerosis or spinal cord lesions	Tablet: 5mg 3x daily; may increase by 5 mg per dose every 3 days until optimal response is reached. • Usual dosage range: 40 to 80 mg daily • Do not exceed 80 mg daily Pediatric: ≥4 months <2 years: 10 to 20 mg in divided doses every 8 hours (max 40 mg/day) 2 to 7 years: 20 to 40 mg in divided doses every 8 hours (max 60 mg/day) ≥8 years and adolescents: 30-40 mg in divided doses every 8 hours (max 60-80 mg/day)	Hypersensitivity	Yes
Dantrolene	Oral Capsule: Dantrium® 25mg, 50mg, 100mg	Treatment of spasticity associated with upper motor neuron disorders	25 mg once daily for 7 days; increase to 25 mg 3x daily for 7 days, increase to 50 mg 3x daily for 7 days, and then increase to 100 mg 3x daily; some patients may require 100 mg 4x daily Maximum dose: 400 mg daily Pediatric: 0.5 mg/kg/dose once daily for 7 days; increase to 0.5 mg/kg/dose 3x daily for 7 days, increase to 1 mg/kg/dose 3x daily for 7 days, and then increase to 2 mg/kg/dose 3x daily; some patients may require 2 mg/kg/dose 4x daily Maximum dose: 400 mg daily	Active hepatic disease (e.g. hepatitis, cirrhosis); should not be used when spasticity is used to maintain posture/balance during locomotion or to obtain/maintain increased function	Yes

Tizanidine	Oral Tablet: Zanaflex® 2mg, 4mg Oral Capsule: Zanaflex® 2mg, 4mg, 6mg Note: Tablet and capsule are bioequivalent only under fasting conditions.	Treatment of spasticity. Because of the short duration of effect, treatment should be reserved for those daily activities and times when relief of spasticity is most important.	Initial: 2mg every 6 or 8 hours MAX: 3 doses/24hr Maintenance: Increase 2 to 4mg every 1 to 4 days (MAX: 36 mg/day, 16 mg per dose) Doses < 8 mg do not have established efficacy Pediatric: Not recommended	Hypersensitivity: do not use with fluvoxamine or ciprofloxacin (CYP1A2 inhibitors) which significantly increase tizanidine exposure	Yes
Single Agents for Musculoskeletal Spasm					
Carisoprodol	Oral tablet: Soma® 250mg, 350mg	Treatment of muscle spasm associated with acute musculoskeletal pain Recommended for short-term use (2-3 weeks) only	250mg-350mg 3x daily and at bedtime Pediatric: Children ≥16 years: Refer to adult dosing	Hypersensitivity to carisoprodol or carbamates; history of acute intermittent porphyria	Yes
Chlorzoxazone	Oral Tablet: Lorzone® 375mg, 750mg; Parafon Forte® 500mg	Treatment of muscle spasm and pain associated with acute musculoskeletal conditions	500mg 3-4x daily, may increase up to 750mg 3-4x daily Pediatric: 125-500 mg 3 to 4x daily or 20mg/kg in divided doses. May be crushed.	Hypersensitivity	Lorzone®: No Parafon Forte®: Yes
Cyclobenzaprine	Oral Tablet: Fexmid® 7.5 mg; Flexeril® 5 mg, 7.5 mg, 10 mg Oral Capsule, Extended Release: Amrix® 15 mg, 30 mg Oral Suspension: Tabradol FusePaq® 1 mg/mL Transdermal Cream: Active-Cyclobenzaprine® KIT 5%; EnovaRX-Cyclobenzaprine® KIT 20 mg/gm	Treatment of muscle spasm associated with acute, musculoskeletal pain. Recommended for short-term use (2-3 weeks) only	Tablet: 5mg 3x daily; may increase up to 10mg 3x daily Capsule: 15mg once daily, up to 30mg once daily Pediatric: Children ≥15 years: Refer to adult dosing	Do not use during or within 14 days of MAO inhibitors; hyperthyroidism; congestive heart failure; arrhythmias; heart block or conduction disturbances; acute recovery phase of myocardial infarction	Oral Tablet: Yes Oral Capsule, Solution, Topical Cream: No

Metaxalone	Oral Tablet: Skelaxin® 400mg, 800mg	Treatment of muscle spasm associated with acute, musculoskeletal pain	800 mg 3-4x daily Pediatric: Children >12 years: refer to adult dosing	Hypersensitivity to metaxalone; significantly impaired hepatic or renal function; history of drug-induced hemolytic anemias or other anemias	Yes
Methocarbamol	Oral Tablet: Robaxin® 500mg, 750mg Intramuscular (IM) injection: Robaxin® 1,000 mg/10ml	Adjunctive treatment of muscle spasm associated with acute, painful musculoskeletal conditions	Tablet: 1.5 gm 4x daily for 2-3 days (up to 8 gm per day for severe conditions), then decrease dose (4-4.5 gm in 3-6 divided doses daily). IM solution: Initial: 1 gm; may repeat every 8 hours if oral administration not possible; Maximum dose: 3 gm/day for no more than 3 consecutive days. If condition persists, may repeat course of therapy after a drug-free interval of 48 hours Pediatric: Children ≥16 years: Refer to adult dosing	Hypersensitivity	Yes
Orphenadrine	Injection Solution: Norflex® 30mg/ml Oral Tablet, Extended Release: Orphenadrine® 100mg Products contain sulfite	Treatment of muscle spasm associated with acute painful musculoskeletal conditions Long-term efficacy is not established	Tablet: 100 mg twice a day IM, IV: 60 mg every 12 hours, change to oral for maintenance therapy Pediatric: Not indicated	Hypersensitivity; glaucoma; GI obstruction, stenosing peptic ulcer; prostatic hypertrophy, bladder neck obstruction; cardiospasm; myasthenia gravis	Yes
Combination Products for Musculoskeletal Spasm					
Carisoprodol/Aspirin	Oral Tablet: Carisoprodol/Aspirin 200 mg/325 mg	Treatment of muscle spasm associated with acute, musculoskeletal pain. Recommended for short-term use (2-3 weeks) only	1-2 tablets 4x daily for 2-3 weeks Maximum dose: 8 tablets per 24 hours Pediatric: Children ≥16 years: Refer to adult dosing	Hypersensitivity to a carbamate; serious gastrointestinal complications due to aspirin use; aspirin-induced asthma; acute intermittent porphyria; allergy to aspirin or other pain reliever/fever reducer	Yes

Characteristics	Dosage Forms	Labeled/Recommended Use	Dose Range	Contraindications	Generic Availability
Carisoprodol/Aspirin /Codeine	Oral Tablet: Carisoprodol/Aspirin/ Codeine 200mg/325mg/16mg	Treatment of muscle spasm associated with acute, musculoskeletal pain. Recommended for short-term use (2-3 weeks) only	1-2 tablets 4 times daily (maximum 8 tablets per 24 hours; treatment should be temporary (2-3 weeks) Pediatric: No indication	Hypersensitivity to a carbamate; serious gastrointestinal complications due to aspirin use; aspirin-induced asthma; acute intermittent porphyria; allergy to aspirin or other pain reliever/fever reducer; hypersensitivity to codeine; respiratory depression in the absence of resuscitative equipment; acute or severe bronchial asthma or hypercarbia; presence or suspicion of paralytic ileus	Yes
Orphenadrine /Aspirin/Caffeine	Oral Tablet: Orphenadrine Compound 25mg/385mg/30mg, Orphenadrine Compound DS 50mg/770mg/60mg	Treatment of muscle spasm associated with acute painful musculoskeletal conditions	1-2 tablets 3-4x daily Pediatric: No indication	Hypersensitivity to any component of the formulation; glaucoma; pyloric obstruction; duodenal obstruction; achalasia; prostatic hyperplasia; bladder obstruction; myasthenia gravis	Yes

Key- IM - Intramuscular, IV - Intravenous

Place in Therapy – Guidelines

A review of the current clinical practice recommendations is presented in **Table 2**. No guideline suggests a skeletal muscle relaxant as first-line therapy for the treatment of pain or spasm. These agents are indicated as adjunct or alternative therapy after first or second line therapy has failed. Virtually every guideline points out the adverse effect profile (including abuse potential) of these agents and suggests caution in patient selection.[4,21-26]

For the treatment of spasticity baclofen is considered a first line agent with dantrolene and tizanidine generally recommended second line. Long-term therapy with baclofen is acceptable. Disparity is noted among some guidelines with similar, yet differing populations. In non-progressive brain disorders baclofen is recommended first-line in children, may be continued long-term and implantable pumps are acceptable while in the treatment of children and adolescents with cerebral palsy tizanidine is preferred, the authors citing insufficient evidence for baclofen or dantrolene.[27-30]

Table 2. Summary of Current Clinical Practice Guidelines for Skeletal Muscle Relaxants

Guideline	Recommendation
Muscle Spasm Associated with Acute Musculoskeletal Pain and Symptoms of Spinal Cord Lesions	
Assessment and Management of Chronic Pain [21]	Skeletal muscle relaxants as **adjunct therapy** to analgesics may be effective for short-term therapy of muscle spasms related to chronic pain. Carisoprodol presents the risk of dependence due to its central action properties. Cyclobenzaprine can be beneficial in treating symptoms of fibromyalgia when used in doses of 10 mg to 40 mg daily. Baclofen may be considered for the treatment of neuropathy.
Diagnosis and Treatment of Low Back Pain [22]	Skeletal muscle relaxants are indicated **after first-line therapy** with acetaminophen or a non-steroidal anti-inflammatory drugs fail. Baclofen and dantrolene lack sufficient proof of efficacy based on evidence available in the treatment of back pain. Short-term use for acute back pain with other skeletal muscle relaxants (carisoprodol, chlorzoxazone) is appropriate for short-term use for acute back pain. However, all skeletal muscle relaxants carry risks of central nervous system adverse effects and there is little evidence to suggest that they differ in effectiveness. A risk-benefit analysis should be done when prescribing these medications.
Cervical and Thoracic Spine Disorders, in: Occupational Medicine Practice Guidelines [23]	For acute cervical and thoracic pain, skeletal muscle relaxants are considered **second-line therapy** for moderate to severe pain inadequately controlled by non-steroidal anti-inflammatory drugs. Evidence is insufficient to support the use of skeletal muscle relaxants in mild to moderate cervicothoracic pain and these drugs should be avoided in subacute and chronic cervicothoracic pain. Consider central nervous system adverse events when prescribing for daytime use and the risk of abuse/dependency. Differences between agents were not discussed.
Guideline for the Evidence-Informed Primary Care Management of Low Back Pain [24]	For the treatment of acute low back pain or exacerbation of chronic low back or spine pain, cyclobenzaprine should be used as add-on therapy to a first or second-line pain medication. Dosing should be 10 mg to 30 mg daily for a duration less than two weeks.

Shoulder Disorders, in: Occupational Medicine Practice Guidelines [25]	All recommendations lack evidence. Muscle relaxants may be used **second-line** for acute and subacute, moderate to severe shoulder pain from muscle spasm unrelieved by non-steroidal anti-inflammatory drugs, acetaminophen or other conservative measures. Agents may be used for pain from shoulder dislocation or instability but is not recommended for post-operative pain. May be used to control pain from labral tears. May be used peri-operatively for pain from adhesive capsulitis. Not recommended for myofascial or trigger point pain. Consider central nervous system adverse events when prescribing for daytime use and the risk of abuse.
Evidence-Based Management of Acute Musculoskeletal Pain[4]	Skeletal muscle relaxants are **not recommended** for the treatment of acute pain as the adverse event profile outweighs any benefit they afford. For the treatment of low back pain there is little evidence to support the superiority of muscle relaxants over placebo or their comparative efficacy to non-steroidal anti-inflammatory agents. Drowsiness, dizziness and dependency are common adverse events.
Traumatic Brain Injury Medical Treatment Guidelines [26]	Most useful for acute musculoskeletal injury or exacerbation of injury. Carisoprodol should not be used because the opioid meprobamate is a metabolite.
Spasticity Associated with Multiple Sclerosis	
Multiple Sclerosis [27]	Skeletal muscle relaxants, as well as other drug classes, may be used to treat spasticity in patients with MS. Baclofen should considered a **first-line** treatment option. In cases of inadequate relief or dose limiting side effects therapy may be switched to gabapentin or it may be added to baclofen therapy. Dantrolene and tizanidine may be considered second-line if the patient fails/cannot tolerate baclofen therapy.
Spasticity Associated with Upper Motor Neuron Lesion Disorders	
Spasticity in Children and Young People with Non-Progressive Brain Disorders, NICE Guideline [28]	If spasticity causes pain, discomfort, muscle spasms, or functional disability, **initiate** a low dose of oral baclofen. Dosing should be increased over 4-6 weeks until therapeutic dose is reached. Add diazepam if therapeutic goal is not achieved. Baclofen treatment may be used **long-term** for maintenance effect. Intrathecal baclofen via continuous infusion pump may be considered if non-invasive therapy has not reduced spasticity, dystonia and there continues to be difficulties with pain, spasm, posture, function or self-care.
Pharmacologic Treatment of Spasticity in Children and Adolescents with Cerebral Palsy[29]	Tizanidine **may be considered** for use in children with cystic fibrosis to treat spasticity. Evidence is lacking for improving motor function. Dantrolene and oral baclofen lack sufficient evidence for use. Evidence is insufficient to support the use of intrathecal baclofen to treat spasticity in children.
European Federation of Neurological Societies (EFNS) Guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis [30]	**If physical therapy treatment is not successful, oral baclofen is appropriate second-line treatment to treat spasticity associated with ALS.**

Pharmacology

These agents represent different chemical classes and mechanisms of action. Cyclobenzaprine is structurally similar to the tricyclic antidepressants. Dantrolene shares structural similarity to phenytoin. Orphenadrine is a derivative of diphenhydramine. Chlorzoxazone is a benzoxazolone

derivative. Carisoprodol is metabolized to meprobamate. Methocarbamol is structurally related to mephenesin. Tizanidine is related to clonidine as an imidazole derivative[9,11]

The action of the anti-spasticity agents (baclofen, dantrolene and tizanidine) counters the exaggerated stretch reflex in the muscles resulting from upper motor neuron complex problems. These agents act directly to decrease rigidity. Baclofen antagonizes $GABA_B$ both pre- and post-synaptically to inhibit monosynaptic and polysynaptic neuronal impulses.[11] Dantrolene acts peripherally on sarcoplasmic reticulum to interfere with the release of calcium in skeletal muscle limiting contractions by slowing the contraction cycle.[9] Tizanidine inhibits presynaptic motor neuron activity via central α-2 adrenergic activity.[9,11]

None of the antispasmodic agents (carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol and orphenadrine) has well documented effects on peripheral muscle fibers. It is believed their activity to reduce muscle spasm and pain is the result of their central nervous system sedative properties.[9,18,19]

Pharmacokinetics

Pharmacokinetic properties of the skeletal muscle relaxants are presented in **Table 3.**

Carisoprodol is metabolized to an active metabolite, meprobamate. Although carisoprodol is not indicated for long-term use, extended durations of therapy are not uncommon. In the setting of chronic use, the half-life of meprobamate increases from 10 hours to 48 hours, increasing the potential for adverse events.

Tizanidine tablets and capsules are bioequivalent (mg-for-mg) in the fasted state. When the oral capsule is administered with a high-fat meal the Cmax is significantly reduced and the Tmax is significantly delayed. These changes exceed the FDA limits on bioequivalence, thus when administered with meals the tablet and capsule are not bioequivalent although no differences in safety were noted.[31] Caution should be used when changing a patient's dosage form or the dosing schedule with respect to meals. Non-bioequivalence was also noted when a 6 mg capsule was administered intact or sprinkled over applesauce. Higher AUC and Cmax levels were found with the sprinkled vs. intact capsule.[32]

Bioequivalence between cyclobenzaprine immediate release and extended release formulations was documented from administering a single dose of the extended release formulation or three doses of the immediate release formulation 24 hour dosing to elderly volunteers. Systemic exposure over 24 hours produced similar AUC, Cmax and $T_{1/2}$ values.[33] This investigator performed an identical study in younger adults and found the elderly in comparison to the younger subjects had similar Cmax and T_{max} but a 50% increased systemic exposure due to longer elimination half-life. [33] It is not recommended to use the extended release dosage form in the elderly.[82]

Table 3. Pharmacokinetics of the Skeletal Muscle Relaxants[16,17,34]

Characteristics	Bioavailability	Time to Peak Concentration	Onset & Duration of Action	Metabolism	Half Life	Excretion
Anti-Spasticity Agents						
Baclofen	100%	2 hours	Onset: 3 to 4 days Duration: Not determined. Effect decreases with continuous therapy	Hepatic (15%) via deamination	2.5 to 4 hours	Renal (70-80%) as unchanged drug or metabolites. Fecal (20-30%)
Dantrolene	35-70%	5 hours	Onset: May take up to 1 week Duration: Not determined	Hepatic via hydroxylation, N-reduction, and acetylation	8.7 hours	Renal
Tizanidine	40%	Tablet/Capsule: 1.5 hours	Tablet/Capsule: Onset: 1-2 hours: Duration: 3-6 hours Effects of Food: Tablets: ↑ exposure Capsules: ↓ exposure	Hepatic (95%) via CYP1A2 to metabolites of unknown activity	2.5 hours (metabolites 20-40 hours)	Urine: 60% Feces: 20%
Anti-Spasmodic Agents						
Carisoprodol	Not established	1.5 to 2 hours	Onset: 30 minutes Duration: 4 to 6 hours	Hepatic via CYP2C19 to 2 inactive and 1 active metabolite (meprobamate) Meprobamate: Half-life of 10 hours increases to 48 hours with chronic use.	Carisoprodol: 2 hours Meprobamate: 8 to 10 hours	Renal, primary as metabolites
Chlorzoxazone	100%	1 to 2 hours	Onset: 1 hours Duration: 3 to 4 hours	Hepatic via glucuronidation to inactive 6-hydroxychlorzoxazone	1.1 hours	Renal as glucuronide
Cyclobenzaprine	33-55%	Tablet: 3.8 to 4 hours Capsule: 15 mg: 8.1 ± 2.9 hours 30 mg: 7.1 ± 1.6 hours	Tablet: Onset: Within 1 hour Duration: 8 to 12 hours Capsule: Onset: Within 1 hour Duration: 24 hours • Food ↑ Cmax 35% Food ↑ AUC 20%	Hepatic via CYP3A4, CYP1A2, and CYP2D6.	Tablet: 8 to 37 hours Capsule: ~32 hours Age > 65 years ~ 50 hours	Renal (51%) primarily as glucuronides. Less than 1% is unchanged.

Methocarbamol	Not established, but rapidly and extensively absorbed	Tablet: 1 to 2 hours IM solution: 1 hour	Tablet: Onset: 30 minutes Duration: up to 8 hours IM solution: Onset: < 30 minutes Duration: 8 to 24 hours	Hepatic via dealkylation, conjugation, and hydroxylation	1 to 2 hours	Renal: 10-15% of excreted dug is unchanged Fecal: Small amounts
Metaxalone	Not established High fat meals increase bioavailability	3 hours	Onset: 1 hour Duration: 4 to 6 hours	Hepatic metabolism (CYP1A2, 2D6, 2E1, 3A4)	2 to 4 hours	Renal elimination as unidentified metabolites
Orphenadrine	95%	Tablet: 2 to 4 hours IM solution: 1 hour	Tablet: Onset: Within 1 hour Duration: 8 hours IM solution: Onset: Within 1 hour Duration: 12 hours	Hepatic metabolism to 8 known metabolites.	14 hours	Renal: 60%
Combination Antispasmodic Product						
Carisoprodol/Aspirin	See Carisoprodol Aspirin: Variable	See Carisoprodol Aspirin: 1 hour	See Carisoprodol Aspirin: Onset: 15 to 30 minutes Duration: 4 to 6 hours	See Carisoprodol Aspirin: Hepatic via esterase hydrolysis. A small amount is metabolized by erythrocytes to salicylic acid.	See Carisoprodol Aspirin: 20 to 60 minutes Salicylic acid: 2 to 12 hours depending on dose	See Carisoprodol Aspirin: Renal
Carisoprodol/Aspirin/Codeine	See Carisoprodol/ Aspirin Codeine: About 90%	See Carisoprodol/Aspirin Codeine: 1 hour	See Carisoprodol/Aspirin Codeine: Onset: 15 to 30 minutes Duration: 4 to 6 hours	See Carisoprodol/Aspirin Codeine: Hepatic via CYP2D6, CYP3A4, and UDP-glucuronosyltransferase 2B7 and 2B4	See Carisoprodol/Aspirin Codeine: 3 hours	See Carisoprodol/Aspirin Codeine: Renal
Orphenadrine/Aspirin/Caffeine	See Orphenadrine Aspirin: Variable Caffeine: 99%	See Orphenadrine Aspirin: 1 hour Caffeine: 0.5 to 0.6 hours	See Orphenadrine Aspirin: Onset 15 to 30 minutes Duration: 4 to 6 hours Caffeine: Onset: 15 to 45 minutes Duration:	See Orphenadrine Aspirin: Hepatic via esterase hydrolysis. A small amount is metabolized by erythrocytes to salicylic acid. Caffeine: Hepatic	See Orphenadrine Aspirin: 20 to 60 minutes Salicylic acid: 2 to 12 hours depending on dose Caffeine: 3 to 7 hours	See Orphenadrine Aspirin: Renal Caffeine: Renal, where only 1% of drug is unchanged

Methods

A literature search was conducted to identify articles addressing the safety and efficacy of the skeletal muscle relaxants, searching the MEDLINE database, EMBASE, the Cochrane Library and reference lists of review articles. For the clinical efficacy section, only comparative clinical trials published in English and indexed on MEDLINE prior to January 2016, evaluating efficacy of the skeletal muscle relaxants with improvement of symptoms as the endpoint are included. Trials evaluating the skeletal muscle relaxants as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included.

Special Populations

A summary of information concerning the use of the skeletal muscle relaxants in special populations is presented in **Table 4.** The American Geriatric Society Beers Criteria list defining "potentially inappropriate" medications for use in the elderly includes the anti-spasmodic agents carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol and orphenedrine.[35] The strong recommendation, based on moderate evidence, considers these agents to offer an unfavorable risk/benefit profile in the elderly as the agents are poorly tolerated due to their strong anticholinergic activity, sedation, increased risk for fractures and a paucity of information confirming clinical efficacy at doses tolerated in the geriatric population.[35,36]

Pediatric dosing of the anti-spasticity agents is defined for baclofen and dantrolene and of the anti-spasmodic agents for chlorzoxazone alone.

Codeine containing products carry a black box warning cautioning that some children may exhibit CYP2D6 polymorphism and rapidly metabolize codeine to morphine, which has resulted in deaths.

Table 4: Dosing Recommendations for Use of Skeletal Muscle Relaxants in Special Populations [17,20,35,37,38]

	Renal	Hepatic	Pediatric	Pregnancy Category	Lactation	Geriatric
Anti-spasticity Agents						
Baclofen	Eliminated unchanged: CrCL 50-80 mL/min: Dosage reduction of 33% CrCl 30-50 mL/min: Dosage reduction of 50% CrCl < 30 mL/min: Dosage reduction of 66% Dialysis: Start with lower doses and increase slowly	Metabolism 15% No adjustment recommended	Oral: Age 2 to 7 years: 10 to 15 mg/day in 2 to 3 divided doses, orally. Increase by no more than 5 to 15 mg/day every 3 days Max dose: 40 mg/day in 3 to 4 divided doses. Age > 8 years: 10 to 15 mg/day in 2 to 3 divided doses, orally. Increase by 5 to 15 mg/day every 3 days Max dose: 60 mg/day in 3 to 4 divided doses. Intrathecal: Test dose: 25 to 50 mcg given intrathecally over > 1 minute. Increase dose by 25 mcg every 24 hours. Endpoint is a 4- to 8-hour positive clinical response (chronic infusion pump candidates respond to a single bolus dose < 100 mcg/2mL) 24-hour post-implant titration: Increase slowly by 5%-15% once daily until response is obtained. Post-implant maintenance: Increase by 5-20 % (max) or decrease by 10-20% as needed.	C	Oral administration: Distributes to milk Intrathecal administration: No data	Elderly patients with cerebral lesions are more likely to have side effects than younger patients. Elderly patients are more sensitive to CNS side effects and initiating therapy with lower doses is recommended.
Dantrolene	Normal dosing	Contraindicated with hepatitis or cirrhosis Use caution with active liver disease or dysfunction	Age < 5 years: Not established Age > 5 years: Titrate dose every 7 days beginning with 0.5 mg/kg QD → 0.5 mg/kg TID → 1 mg/kg TID → 2 mg/kg TID May be used QID Max dose: 100 mg QID If increased dose affords no additional benefit, return to lower dose.	C	Potential for infant risk is possible	Dose with caution
Tizanidine	Use with caution CrCl < 25 ml/min clearance ↓50%	Extensively metabolized Use with caution; avoid use in severe impairment	Not established	C	No information: Use only if benefit exceeds risk	Clearance is reduced four-fold Use with caution
Anti-Spasmodic Agents						
Carisoprodol	Use with caution due to renal elimination	Use with caution: Active metabolite is meprobamate Initiate therapy with lower dose and increase as tolerated	Age < 16 years: Not established	C	Breast-milk concentrations are 4-fold >maternal plasma	Not established Beers criteria

Chlorzoxazone	Normal dosing	Initiate therapy with lower doses and increase as tolerated	Dose (age not defined): 125-500 mg 3 or 4x a day or 20 mg/kg/day in divided doses.	C	Data inadequate or inconclusive	Not established Beers criteria
Cyclobenzaprine	Normal dosing	Mild: Use immediate release only, begin with mg and titrate slowly as needed. Moderate/Severe: Not recommended	Age < 15 years: Not established	B	Potential for infant risk is possible	Use immediate release only. Initiate therapy with 5 mg and titrate slowly as needed Beers criteria
Methocarbamol	Hemodialysis: Clearance reduced 40%; elimination $T_{1/2}$ unchanged	In alcoholic cirrhosis total clearance ↓ 70% and plasma protein binding ↓ ~ 20% compared to normal subjects	Age < 16 years: No information	C	Unknown	Elimination $T_{1/2}$ slightly prolonged, fraction bound slightly increased compared to younger subjects Beers criteria
Metaxalone	Use with caution; avoid use in severe renal dysfunction	Use with caution; avoid use in severe hepatic dysfunction; monitor liver function with mild to moderate impairment	Age < 12 years: No information	N not assigned	No information: Use only if benefit exceeds risk	Bioavailability increases with age and is enhanced when taken in fasted vs. fed state compared to younger subjects Beers criteria
Orphenadrine	No information: Use with caution	No information, extensive hepatic metabolism	Age < 18 years: Not established	C	No information: Use only if benefit exceeds risk	No adjustment recommended Beers criteria
Carisoprodol /Aspirin	Use with caution due to renal elimination	Use with caution due to hepatic metabolism	Age < 16 years: Not established	C	Concentrations > 4x maternal plasma concentration	Not established
Carisoprodol /Aspirin /Codeine	Use with caution: due to renal elimination	Use with caution: due to hepatic metabolism	Age < 16 years: Not established Codeine: In children who a ultra-rapid metabolizers or codeine due to CYD2D6 polymorphism, DEATHS due to respiratory depression have occurred following tonsillectomy or adenoidectomy	C	Concentrations > 4x maternal plasma concentration	Not established
Orphenadrine/Aspirin/Caffeine	No information: Use with caution	No information	Age < 18 years: Not established	C	Aspirin and caffeine cross into milk. May be used short-term with close monitoring of the infant	No adjustment recommended

Safety

A retrospective, case-controlled study in the Medicare advantage population found the risk of fracture associated with the use of a skeletal muscle relaxant to be 40% with an adjusted odds ratio of 1.40 (95% CI 1.15 to 1.72, $p<0.001$).[5] Injury was associated with the use of skeletal muscle relaxants as demonstrated in a pre- post-cohort analysis revealing the use of skeletal muscle relaxants increased the incidence of fractures, contusions, lacerations and falls.[36]

The 2011 Drug Abuse Warning Network (DAWN) documented the use of skeletal muscle relaxants resulted in 53,000 abuse or misuse emergency department visits.[39] Alcohol was as concomitant substance in 18% of cases. Carisoprodol was the most common implicated skeletal muscle relaxant (48%) followed by cyclobenzaprine (22%). The use of skeletal muscle relaxants in suicide attempts increased by 84% from 2004 to 2009.[39] Skeletal muscle relaxants were the single agent involved in 4.8% of all suicide attempts. Cyclobenzaprine and carisoprodol were the most commonly used skeletal muscle relaxants. Emergency department visits secondary to the non-medical use of carisoprodol doubled between 2004 to 2009, with over 29,000 visits reported.[39] In 2009, 1.4% of high school seniors reported they abused carisoprodol.[34]

Libby et al reviewed of 56 cases of skeletal muscle relaxant exposure in 1990. Ingested agents included cyclobenzaprine, methocarbamol, carisoprodol, chlorzoxazone and baclofen. The drugs were used for intentional suicide (46.4%), accidental ingestion (37.5%) and intentional misuse (8.9%). In 1/3 of cases additional substances were involved and the severity of the clinical effects was greater. No deaths occurred and the authors consider morbidity and mortality with these agents to be low but increased with co-administration of other substances.[40]

The most common adverse event associated with all these medications is sedation. These agents should be used cautiously when operating machinery or while driving.[16,18-20]

General safety data for the skeletal muscle relaxants may be found in Table 6.

Table 5 Safety of the Skeletal Muscle Relaxants* [5,16,20,34,38,68,75]

	Frequency	Cardiovascular	Central Nervous System	Endocrine & Metabolic	Gastrointestinal	Hepatic	Neuromuscular Skeletal	Other
Anti-Spasticity Agents								
Baclofen	>10%		Confusion headache, insomnia		Nausea			Urinary frequency >10% Withdrawal symptoms with abrupt discontinuation: • Oral: Confusion, hallucinations, seizures. Taper over a few weeks. • Intrathecal Additionally, high fever, exaggerated rebound spasticity, muscle rigidity and rarely rhabdomyolysis, multiple organ-system failure, and death. • **Boxed warning**: Do not discontinue abruptly
	1-10%	Hypotension			Constipation			
Dantrolene	>10%	Heart failure, AV block, tachycardia	Somnolence		Nausea, diarrhea, dysphagia	Hepatotoxiciy <1%; mortality = 10%	Muscle weakness	Flushing >10% Respiratory failure 1-10% **Boxed warning**: hepatotoxic risk with any dose but higher doses > lower doses, chronic > acute use, women, age >35 years
	1-10%		Difficulty speaking, dizziness, headache	Hyperkalemia				
Tizanidine	>10%		Asthenia Dizziness Somnolence		Xerostomia			Abrupt withdrawal may result in tachycardia, tremor, anxiety, hypertension and increased tonicity. UTI; infection; flu; urinary frequency; pharyngitis; rhinitis; fever in 1-10%
	1-10%	Vasodilation, postural hypotension, syncope, arrhythmia via QT prolongation	Blurred vision, nervousness, migraine, anxiety, depression, hallucinosis, psychotic-like symptoms	Rash, sweating	Constipation, Vomiting	Asymptomatic LFT abnormalities SGPT/ALT↑, rarely, death from liver failure	Dyskinesia, speech disorder, myasthenia, back pain	
Carisoprodol	>10%		Drowsiness, somnolence					Active metabolite is a CNS depressant (meprobamate) Withdrawal symptoms may occur when chronic use stopped (e.g. anxiety, insomnia, irritability, tremor, muscle twitching, ataxia), rarely a first dose idiosyncratic reaction (extreme weakness, transient quadriplegia, dizziness, ataxia, temporary loss of vision, confusion, dysarthria)
	1-10%		Dizziness, headache, seizure					

	Frequency	Cardiovascular	Central Nervous System	Endocrine & Metabolic	Gastrointestinal	Hepatic	Neuromuscular Skeletal	Other
Chlorzoxazone	Frequency not reported		Drowsiness, dizziness, lightheadedness malaise, or over-stimulation		Gastrointestinal bleeding	Rare, serious, unpredictable hepatocellular reactions		Allergic-type skin rashes, petechiae, or ecchymosis
Cyclobenzaprine	>10%		Dizziness, somnolence		Xerostomia			ER formulation less somnolence Fatigue, blurred vision, urinary retention 1-10%
	1-10%	Rare arrhythmias, QTc prolongation	Asthenia, dizziness, headache, nervousness		Constipation, indigestion, nausea,			
Methocarbamol	Frequency not reported	Bradycardia, flushing, hypotension, syncope, thrombophlebitis	Amnesia, confusion, diplopia, dizziness or lightheadedness drowsiness, insomnia, mild muscular incoordination, nystagmus, sedation, seizures (including grand mal), vertigo		Dyspepsia, jaundice (including cholestatic jaundice), nausea and vomiting			Fever, headache, hypersensitivity reactions, blurred vision, nasal congestion, metallic taste, angioneurotic edema, leukopenia
Metaxalone	Frequency not reported		Drowsiness, dizziness, headache, nervousness, “irritability”		Nausea, vomiting, gastrointestinal upset	Jaundice		Leukopenia, hemolytic anemia, hypersensitivity reaction, rash with or without pruritus
Orphenadrine	Frequency not reported	Tachycardia, palpitation	Headache, dizziness, hallucinations, agitation, tremor		Xerostomia, nausea, vomiting, constipation, gastric irritation		Muscle weakness	Urinary hesitancy, retention, blurred vision, ↑ IOP, very rare aplastic anemia, hypersensitivity, pruritus, urticarial
Carisoprodol + Aspirin	Frequency not reported	Hypotension	Sedation		Gastrointestinal perforation or hemorrhage,		Seizure	Anaphalactoid reaction
Carisoprodol + Aspirin + Codeine	Frequency not reported	Hypotension	Sedation, respiratory depression		Gastrointestinal perforation or hemorrhage			Anaphalactoid reaction Black box warning concerning rapid metabolism of codeine to morphine in children
Orphenadrine+ Aspirin + Caffeine	>10%	Syncope	Light-headedness, dizziness		GI hemorrhage (rare)			

*Adverse effects are obtained from package inserts and are not meant to be comparative or all-inclusive. IOP = intraocular pressure, NR = not reported

Withdrawal Reactions

Baclofen, orphenadrine and tizanidine therapy should not be stopped abruptly. A slow discontinue by taper is recommended for patients receiving higher doses and long-term therapy.[16,18-20] Baclofen withdrawal has produced hallucinations and seizures.[18-20]

Agent Specific Information

Anti-spasticity Agents

Dantrolene – The FDA added a black box warning to the dantrolene package insert for significant hepatotoxic potential.[79] Cases have occurred at various doses with higher incidence at larger doses. Toxicity has occurred with short or long course therapy, most commonly between the 3rd to 12th months and presents both with and without symptoms. The risk appears higher for women, at ages over 35 years and in combination with other potentially hepatotoxic agents. Liver function tests must be monitored frequently during use. The lowest effective dose is recommended and discontinuation if improvement is not noted after 45 days.[9,79]

Tizanidine – Chemically related to clonidine, withdrawal reactions (e.g. hypertension, tachycardia, hypertonia, tremor or anxiety) may occur and are more likely when higher doses (i.e. 20 to 36 mg/day) were used for 9 weeks or longer.[38] The manufacture recommends decreasing the dose by 2-4 mg/day particularly in those at risk of a withdrawal reactions.[41] In clinical trials, liver function test elevations up to 10x the upper limit of normal have been reported, rarely. Post-marketing surveillance information reveals that hepatotoxicity and death may result. Aminotransferase levels should be monitored at baseline, 1, 3, 6 months and periodically thereafter.[41] The drug is best avoided in patients with impaired hepatic function. In two reported deaths, the patients were taking other potentially hepatotoxic agents. The most common reasons for discontinuing tizanidine therapy were asthenia, dry mouth, somnolence, dizziness or increased spasm or tone.[41]

Anti-Spasmodic Agents

Carisoprodol

Of the three metabolites resulting from carisoprodol, meprobamate is clinically active and with chronic use the half-life is extended to 48 hours[42]. A review of 104 cases of impaired driving in which either carisoprodol or meprobamate in the blood reveals that impairment can occur at any concentration. In 21 cases carisoprodol was the only substance identified associated with impaired driving. The authors found that impairment was especially significant when the combined concentration of carisoprodol and meprobamate exceeded > 10 mg/L, a concentration within the therapeutic range.[43] Serious toxicity occurred at doses > 12 gm or at lower dosages when combined with other agents.[44] Carisoprodol overdose has resulted in stupor, coma, shock, respiratory depression and death.[45] Carisoprodol was approved by the FDA in 1959, before safety and efficacy documentation was instituted by Kefauver-Harris Amendment (1962).

A lower dose of carisoprodol was developed and assessed for sustained efficacy with a lower risk of adverse events. Two clinical trials evaluated carisoprodol 350 mg with 250 mg in low back spasm. Over 800 patients received carisoprodol with another ~550 receiving placebo. Carisoprodol performed better than placebo and the 350 mg and 250 mg demonstrated equivalence in efficacy measures. Less than 1% of patients receiving the 250 mg dose reported

drowsiness and no patient discontinued the medication due to drowsiness.[46,47]

Cyclobenzaprine

Due to structural similarity with tricyclic antidepressants which have significant cardiovascular and neurotoxicity risk, a 5-year retrospective review of cyclobenzaprine ingestions reported to 5 regional poison control centers was performed, identifying 402 pure cyclobenzaprine exposures.[48] The ingested doses ranged from 5 to 1000 mg with an age range of 7 months to 77 years.[48] Exposures of < 100 mg were managed with gastrointestinal decontamination and supportive care. Commonly reported symptoms included lethargy, sinus tachycardia, hyper- and hypotension, agitation and tachycardia. No life threatening arrhythmias or deaths occurred although a significant number of larger ingestions required ICU care.[48] Other safety issues include seizures when taken concomitantly with tramadol, death by drowning in a combination exposure with ethanol, multiple-drug ingestion deaths, Torsades de Pointes with concomitant droperidol and fluoxetine, psychotic events, delirium and the more commonly reported anticholinergic and sedative effects.[44] New DAWN (drug abuse warning network) Emergency Department data documented an increase in emergency department visits associated with cyclobenzaprine from 6,183 in 2004 to 12,411 in 2010, a statistically significant increase of 101%.[49]

A lower dosage of cyclobenzaprine was developed to see if a lower dose was equally effective with fewer adverse effects. Cyclobenzaprine doses of 5 mg and 10 mg were compared in the treatment of acute muscle spasm. The two doses demonstrated equivalent efficacy while the 5 mg dose was associated with reduced sedation. Dry mouth was less common with a 5 mg vs. 10 mg dose ($p<0.023$).[50] Discontinuation rates were higher with cyclobenzaprine 10 mg vs. 5 mg ($p=0.05$).[50] Discontinuations due to somnolence averaged 5% with 10 mg doses of cyclobenzaprine and 2.5% with cyclobenzaprine 5 mg. The authors concluded that the efficacy of cyclobenzaprine 5 mg was independent of sedation. Cyclobenzaprine 10 mg offered an advantage only in a more rapid onset of action (<24 hours vs. 24-48 hours).[50]

Metaxalone

A study by the North Carolina Medical Examiner's office identified 61 post-mortem autopsy cases from 2002 to 2014 in which metaxalone was found during investigation of cause and manner of death. Serum concentrations were (<1.0 - 8.6 mg/L) in non-contributory cases (53.4%), 4.4 mg/L in cases of multiple drug ingestions (44%), and in the one death with only metaxalone identified, the serum concentration was 63 mg/L. The serum concentration was at or below therapeutic concentrations in 34% of cases.[51] Other deaths have been attributable to metaxalone.[52-54] Serotonin syndrome has been reported in cases of metaxalone overdosage.[55,56] From 2000 to 2006 Texas Poison Control Centers identified 142 cases involving metaxalone ingestion. The most common adverse effects were, drowsiness (27.9%), tachycardia (6.6%), agitation (6.6%), nausea (4.9%), dizziness (4.9%), slurred speech (4.9%), and tremor (4.9%).[57] Management in a health care facility was required more often for patients receiving greater than versus less than 2400 mg (100% vs. 18.2%).[57] This same group looked at pediatric ingestions from 2000-2007 and identified 148 children aged 0-5 years with metaxalone ingestion. All events were considered mild and none required hospitalization. The most common adverse effects were drowsiness (11%), vomiting (3%), agitation (2%), rash (1%), tachycardia (%1), and ataxia (1%).[57,58]

Adherence

A retrospective review assessed adherence to tizanidine, baclofen or dantrolene in 2cyclobenzaprin0 subjects with stroke, spinal cord injury, cerebral palsy, multiple sclerosis or traumatic brain injury. Adherence was poor with a continuous medication possession ratio of 0.1 to 0.5, indicating approximately 50% adherence to therapy. Baclofen performed best with 20.5% adherence compared with 9.1% adherence with tizanidine. The odds of adherence with tizanidine was 37% lower than with baclofen.[59]

Potential for Abuse

Carisoprodol

The National Institute for Drug Abuse identified carisoprodol as a drug of abuse in 1987.[60] Currently it is ranked 54 of 234 abused drugs.[60] Four cases of meprobamate dependence in patients receiving carisoprodol were documented in 1993. The subjects exhibited tolerance, drug seeking behaviors, received prescriptions from multiple prescribers, forged prescriptions and used a veterinary supply distributor to obtain carisoprodol. Toxic reactions were consistent with meprobamate effects including withdrawal reactions.[60]

Carisoprodol is metabolized to meprobamate. Although meprobamate is classified by the FDA as a schedule IV medication, carisoprodol was initially approved without restriction. Eighteen states concerned with the potential for abuse and toxicity designated carisoprodol a controlled substance. The DEA followed suit and beginning January 12, 2012 carisoprodol was designated a schedule IV medication. [61]

As far back as 1999, well before the agent was scheduled as a controlled substance, patients with a history of substance abuse were using carisoprodol in a manner different than prescribed. Of 20 patients, 40% used larger doses than prescribed, 30% did not use it for skeletal muscle relaxation, 10% desired the additive effects achieved in combination with another agent and 5% used it to counteract another medication's effects.[34] Bramness et al accessed and crossed The Norwegian Prescription Database with the Norwegian Road Accident Registry to determine the incidence ratio associated with the use of carisoprodol in Norway. A prescription for carisoprodol was associated with an increase automobile accident incidence ratio of 3.7 (95% CI; 2.9-4.8).[62] Drug seizures sent for analysis to the National Forensic Laboratory Information System consistently report carisoprodol in the top 25 most commonly identified drugs.[45] Cases of carisoprodol dependence date back to 1978, with multiple instances documented in the literature.[63-66] In 1998, carisoprodol was ranked 18th out of 123 substances mentioned in substance abuse literature.[44] Prolonged use of carisoprodol is associated with abuse, tolerance and dependence.[38,67] The incidence of drug-induced seizures increased from 3988 to more than 5000 from 2008 to 2010 according to the DEA.[5] Since carisoprodol was scheduled as a controlled substance in 2012, the Florida Poison Information Center Network documented a decline in carisoprodol exposures. Comparing 2009 to 2012 the number of exposures fell from 132 to 75 cases.[5] The Florida Department of Law Enforcement found Florida deaths related to carisoprodol/meprobamate also decreased in 2012. Deaths in 2011 were 478 while in 2012 there were 326. Although this number declined it remained higher than the 2012 rate of deaths attributable to heroin, fentanyl and oxymorphone.[45] Patients with a past history of addiction or those receiving other medications with abuse potential (e.g. opiates, benzodiazepines, illicit drugs) were most likely to abuse carisoprodol. Withdrawal reactions have been reported.

Carisoprodol should be used with caution in patients with a history of substance abuse or receiving other CNS depressants.[38]

The package insert for Soma Compound with Codeine states, clinical use has rarely been associated with dependence with no abstinence signs observed. They report that high doses of carisoprodol in dogs did not result in withdrawal symptoms while a dose 5x the recommended dose resulted in mild symptoms. No cases of delirium or convulsions were noted. Note is made that dependence on codeine is possible.[68]

Cyclobenzaprine

The effects of other CNS depressants are augmented with cyclobenzaprine. Doses from 10 to 60 mg have been taken orally or nasally to induce euphoria and relaxation. The DEA suggests that cyclobenzaprine is abused or misused based upon the number of case mentions by the American Association of Poison Control Centers, the statistically significant increase in emergency room visits associated with cyclobenzaprine use and the increase in reports involving cyclosporine to forensic laboratories.[49]

Tizanidine

Abuse potential was not evaluated in clinical studies. Animal trials document withdrawal effects.[41] A review of a German pharmacovigilance database found no evidence supporting tizanidine abuse but note their finding may reflect underreporting.[69]

Orphenadrine

Therapeutic doses may result in mood elevating effects.[70] Orphenadrine abuse was documented in 1975.[71]

Drug Interactions

Drug interactions with the skeletal muscle relaxants are presented in **Table 6**. Additive CNS depression occurs when these agents are used in combination with other CNS depressants.

Table 6. Drug Interactions with the Skeletal Muscle Relaxants

	Interacting Medications	Effects
Anti-Spasticity Agents		
Baclofen	CNS Depressants Morphine with intrathecal baclofen	Additive CNS/respiratory effects Hypotension and dyspnea
Dantrolene	CNS Depressants Methotrexate Calcium Channel Blockers Carbamazepine	Additive CNS/respiratory effects Increased methotrexate concentrations and toxicity Cardiovascular collapse and hyperkalemia Increased carbamazepine concentration and potential toxicity
Tizanidine	Fluvoxamine, Ciprofloxacin CYP1A2 inhibitors Antihypertensives Acetaminophen Alcohol CNS depressants Oral contraceptives	Increase Cmax 7-10x; AUC 10-33x Reduced tizanidine clearance Additive hypotensive effects Delayed Tmax by 16 minutes Increases Cmax 15% and AUC 20% Additive effects Reduce plasma clearance 50%
Antispasmodic Agents		
Carisoprodol	CNS Depressants Centrally acting skeletal muscle relaxants Morphine, oxycodone, oxymorphone	Additive CNS/respiratory effects Additive respiratory depression Increased risk of paralytic ileus
Chlorzoxazone	CNS Depressants Morphine, oxycodone	Additive CNS/respiratory effects Increased risk of paralytic ileus
Cyclobenzaprine	CNS Depressants QTc prolonging medications Serotonergic medications Morphine, oxycodone	Additive CNS/respiratory effects Additive QT prolongation Serotonin syndrome Increased risk of paralytic ileus
Methocarbamol	CNS Depressants Morphine, oxycodone	Additive CNS/respiratory effects Increases neuromuscular blocking activity
Metaxolone	CNS Depressants Morphine, oxycodone	Additive CNS/respiratory effects Increases neuromuscular blocking activity
Orphenadrine	CNS Depressants Morphine, Oxycodone Donepezil Phenothiazines	Additive CNS/respiratory effects Increased risk of paralytic ileus Lowered seizure threshold Decreased concentration and effectiveness, increased anticholinergic effects
Aspirin containing products	NSAIDs, corticosteroids, anticoagulants Methotrexate ACE inhibitors Valproic acid Diuretics Meglitinides, sulfonylureas Beta-blockers	Increase bleeding or gastrointestinal ulceration Methotrexate toxicity (leukopenia, thrombocytopenia, anemia, nephrotoxicity, mucosal ulcerations) Decrease anti-hypertensive effectiveness May increase effects of valproic acid May decrease effectiveness of diuretic Hypoglycemic effects may be increased May impair hypotensive effects
Codeine	Opioid antagonists, CNS depressants,	Increased CNS/respiratory depression

containing products	central acting muscle relaxants, benzodiazepines, loxapine	
	Donepezil	Lowered seizure threshold
	Drugs eliminated by CYP2D6 enzymes (e.g. bupropion, paroxetine, clozapine)	Elevated substrate concentration

Clinical Evidence

The skeletal muscle relaxants have come to market over the last 57 years. The newest single entity is tizanidine, which was approved for use by the FDA in 1996. Carisoprodol, chlorzoxazone, metaxolone, methocarbamol and orphenadrine were FDA approved before the enactment of the Kefauver-Harris Amendment (1962), which required manufacturers to document the safety and efficacy of medications. These medications became DESI- (drug efficacy study implementation) drugs.

Most clinical studies were done prior to the establishment of clinical trial quality standards.[80] Most studies documented positive outcomes raising the question of publication bias. Many trials did not identify the randomization method or account for data or patients lost during the trial. In performing trials in which outcomes include subjective measures the concealment of treatment allocation was not defined. Compliance, which reflects tolerability, was not adequately assessed in most trials. Little information was provided to define the randomization method increasing the possibility of low quality, inappropriate randomization methods. Many used non-validated outcome measures while pharmaceutical manufacturers supported others. Patient populations were not homogenous and the use of co-interventions was not stratified. Many of the trials were published prior to the development of standards for performing clinical trials. Most evidence suggests the efficacy of the anti-spasmodic medications declines over time.[72,80]

Systematic Reviews

No data was found addressing comparative safety or efficacy of the combination products.

Spasticity and Musculoskeletal disorders

A systematic review was published by Chou et al, in 2004 evaluated the comparative efficacy and safety of the different muscle relaxants. Due to limitations including trial methodology, statistical analysis and bias, meta-analysis was not possible. The authors summarize the available data from 101 randomized trials. Overall, the trials were of poor to fair quality and adverse event reporting was poor.[9] Outcomes measures included relief of pain or spasms, functional status and quality of life measures. Adverse events, particularly somnolence, fatigue, dizziness, dry mouth, weakness, hepatic injury, abuse and addiction were compared. The authors reported withdrawal rates as a measure of drug tolerability and ineffectiveness since the differences in adverse event reporting did not allow for pooling of data. Most trials were published before 1990 and exhibited multiple methodological flaws (e.g. high heterogeneity, non-validated outcome measures, non-standardized reporting of results and poor trial design or statistical analysis).

Regarding the anti-spasticity agents (baclofen, dantrolene and tizanidine), tizanidine and baclofen perform similarly in fair-rated antispasticity trials in predominantly multiple sclerosis

populations. Outcome measures which improved with treatment included spasms, functional status and patient preference. Dantrolene, tizanidine and baclofen perform comparably to diazepam and superior to placebo in trials treating spasticity but comparison among the skeletal muscle relaxant agents was not possible. There was insufficient information concerning other skeletal muscle relaxants (e.g. carisoprodol, chlorzoxazone, cyclobenzaprine, metaxolone, methocarbamol, orphenadrine) in the treatment of spasticity.[9]

With respect to adverse events in the setting of spasticity, tizanidine was associated with higher rates of dry mouth while baclofen was associated with more muscle weakness. Withdrawals due to adverse events were similar among trials suggesting equal tolerability. Dantrolene is associated with serious hepatotoxicity. Reversible, asymptomatic, rarely serious or fatal hepatotoxicity has occurred with tizanidine and chlorzoxazone.[9]

Regarding the anti-spasmodic agents (carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol and orphenadrine), half of the fair-rated trials found cyclobenzaprine and diazepam at least equivalent in improving a number of outcome measures (e.g. pain, spasm, global response) while the remaining trials demonstrated superiority with cyclobenzaprine in various measures in the treatment of musculoskeletal pain and/or spasm. Carisoprodol was shown to improve some non-validated outcome measures of efficacy over diazepam. There is very little data in order to directly compare the skeletal muscle relaxants in the setting of musculoskeletal conditions. Cyclobenzaprine consistently performed better than placebo. Limited data suggest carisoprodol, orphenadrine and tizanidine perform better than placebo and there is insufficient information concerning the efficacy of other skeletal muscle relaxants (e.g. methocarbamol, metaxalone, dantrolene, chlorzoxazone or baclofen) in this setting.[9]

With respect to adverse events in the setting of muscle pain and spasm, there is insufficient evidence to compare adverse events associated with the use of skeletal muscle relaxants in the treatment of musculoskeletal conditions and no data compared abuse or dependence potential.[9]

Muscle Relaxants for Non-specific Low-back Pain

A systematic review was published by van Tulder et al, evaluating the use of skeletal muscle relaxants for non-specific low back pain.[81] Thirty trials were identified. Seventy seven percent were high quality studies of which 80% evaluated acute low back pain. The medications used in the trials included benzodiazepines (n=4), non-benzodiazepines (n=11), anti-spasticity muscle relaxants (n=2). All agents were compared to placebo. For the short-term treatment of acute low-back pain, all muscle relaxants performed better than placebo. At 2 to 4 days, non-benzodiazepines produced more pain relief (pooled relative risk 0.80 (95% CI: 0.71 to 0.89) and superior overall global efficacy 0.49 (95% confidence interval: 0.25 to 0.95). Adverse events were significantly more common with skeletal muscle relaxants, with a relative risk of 1.50 (95% confidence interval; 1.14 to 1.98). Central nervous system adverse effects occurred most commonly with a relative risk of 2.04 (95% confidence interval; 1.23 to 3.37). No differences were noted among the various agents in terms of either efficacy of safety.[81]

Use in Children

A Cochrane review of baclofen in the treatment of spasticity in children with cerebral palsy reported improvement in spasticity, ease of care and comfort.[73] Meta-analysis was not

performed. Trials were small size, with significant bias, questionable methodology and statistical analysis. The same group of investigators performed three of the six trials. Spasticity was reduced in 4 trials (2 with statistical analysis issues), and 1 long- and 1 short-term trial documented improvements in comfort and ease of care. Three serious adverse events were reported, 2 relating to device failure and 1 patient developed seizures.[73]

A non-randomized, retrospective review of 30 children with cerebral palsy treated with botulinum toxin type A found that the addition of tizanidine was superior to the addition of baclofen in reducing gastrocnemius spasticity.[74]

Summary

In the setting of non-specific low back pain, pooled data including all skeletal muscle relaxants found they all agents performed better than placebo and offered more rapid pain relief. Central nervous system adverse effects were more common with the skeletal muscle relaxants and no differences in efficacy or adverse events was noted between agents.

In children, oral tizanidine was superior to oral baclofen when added to botulinum toxin for treating gastrocnemius spasticity and associated with fewer adverse events. In children with cerebral palsy and spasticity, 4 of 5 baclofen trials demonstrated a reduction in spasticity.

All the antispasmodic agents are on the 2015 Beers criteria list and considered potentially inappropriate for use in the elderly. Only the antispasmodic agents baclofen, dantrolene and tizanidine are not included on the current list.

Due to the limited quality of the clinical trials, lack of substantial head-to-head data and diversity in adverse event profiles, it may be useful to consider the agents individually.

Antispasticity Agents

Baclofen – The side effect profile includes sedation, dizziness, weakness, hypotension, nausea, respiratory depression and constipation. Abrupt withdrawal may result in hallucinations or seizures. Caution is required when using in renal or hepatic impairment. Baclofen is dosed 3 times daily. In most antispasticity trials, baclofen was found comparable to tizanidine in demonstrating efficacy while muscle weakness is more common than other agents. Insufficient evidence is available to confirm its efficacy in the treatment of musculoskeletal pain and spasm.

Dantrolene carries a black-box warning concerning symptomatic hepatitis, which may be fatal. Dantrolene is dosed 3 times daily. Efficacy in antispasticity trials is less well documented with dantrolene. In some studies dantrolene demonstrated equal efficacy to tizanidine and baclofen. The most significant adverse event is hepatotoxicity, which is more serious than with baclofen or tizanidine. Insufficient evidence is available to confirm its efficacy in the treatment of musculoskeletal pain and spasm.

Tizanidine is approved for the treatment of spasticity. It is not approved for use as an antispasmodic although clinical evidence demonstrates efficacy for this indication. Therapeutic effects require the use of multiples of tablets or capsules at each dose. Tizanidine capsules and tablets are only bioavailable in fasted states. Common adverse events include somnolence, dry mouth, hypotension and weakness. Because of the risk for hepatotoxicity, LFTs should be monitored at baseline, 1, 3, and 6 months. Tizanidine is titrated upward balancing a clinical response with side-effects tolerability resulting in each dose requiring multiple tablets or capsules. Abrupt withdrawal may result in withdrawal symptoms. Caution is required when using in renal or hepatic impairment. In most antispasticity trials, tizanidine was found comparable to tizanidine in demonstrating efficacy while dry mouth was more common than with other agents. Limited data suggest tizanidine is superior to placebo in the treatment of muscle pain and spasm.

Antispasmodic Agents

Cyclobenzaprine is modestly superior to placebo in treating back pain but with adverse events. For symptom improvement at 2 weeks the number needed to treat is 3 with greatest effects found at day 4. The side effect profile includes anticholinergic effects (e.g. drowsiness, urinary retention, dry mouth, constipation), which may limit its use. Use should be avoided in the presence of arrhythmias, congestive heart failure, heart block or recent myocardial infarction. Side effects are more significant in the elderly. Cyclobenzaprine is dosed 3 times daily with the oral tablet or once daily with the extended release capsule. Cyclobenzaprine was found equivalent to diazepam in the treatment of muscle pain and spasm. Fifty percent of trials demonstrated overall superiority while 50% demonstrated efficacy in some but not all outcome measures. Cyclobenzaprine consistently performed superior to placebo. Insufficient evidence is available to confirm its efficacy in the treatment of muscle spasticity.

Carisoprodol was approved before the FDA required clinical efficacy and safety trials. The drug is metabolized to meprobamate, an active metabolite, which may have an extended half-life with chronic dosing (for which it does not have an indication). Adverse events include drowsiness, psychological and physical dependence. Abrupt discontinuation may result in withdrawal symptoms. Carisoprodol is dosed 4 times daily. Carisoprodol demonstrated efficacy compared with diazepam for some non-validated outcome measures in the treatment of muscle pain and spasm. Limited data suggests carisoprodol is superior to placebo in the treatment of muscle pain and spasm. Insufficient evidence is available to confirm its efficacy in the treatment of muscle spasticity.

Chlorzoxazone offers less sedation and less abuse potential than other agents. The most common adverse events are drowsiness and dizziness. Caution is required when using in hepatic impairment. Chlorzoxazone is dosed 3 or 4 times daily. Insufficient evidence is available to confirm its efficacy in the treatment of muscle spasticity or musculoskeletal pain and spasm.

Metaxalone clinical data was published in the 1960's and do not meet high-quality trial standards. Hypersensitivity reactions have been reported with its use. It is purported to be less sedating than other skeletal muscle relaxants however it may cause drowsiness and dizziness as well as headache, nausea, vomiting, nervousness and gastrointestinal upset. Caution is required when using in renal or hepatic impairment. Metaxalone is dosed 4 times daily. Insufficient evidence is available to confirm its efficacy in the treatment of muscle spasticity or musculoskeletal pain and spasm.

Methocarbamol has little clinical evidence supporting its use. The most common adverse events are drowsiness, dizziness and lightheadedness. Methocarbamol is dosed 3 times daily. Insufficient evidence is available to confirm its efficacy in the treatment of muscle spasticity or musculoskeletal pain and spasm. Insufficient evidence is available to confirm its efficacy in the treatment of muscle spasticity or muscle pain and spasm.

Orphenadrine use is associated with higher anticholinergic effects than diphenhydramine including dry mouth, drowsiness and urinary retention. Adverse events may be more troublesome in the elderly. This agent has been abused for mood elevating and euphoric effects. Orphenadrine is dosed twice daily and as the combination orphenadrine/aspirin/caffeine at 3 to 4

times daily. Limited data suggest orphenadrine is superior to placebo in the treatment of muscle pain and spasm. Insufficient evidence is available to confirm its efficacy in the treatment of muscle spasticity.

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Appendix I: Comparative Efficacy for Skeletal Muscle Relaxants: Systematic Review[9]

Reference Trial	N	Comparators	Level of Evidence	Efficacy
Chou[9]	55 trials	**Spasticity** Tizanidine vs Baclofen Tizanidine or Baclofen or Dantrolene vs Diazepam Dantrolene vs Tizanidine Dantrolene vs other SKELETAL MUSCLE RELAXANTs Tizanidine, Baclofen, Dantrolene vs Placebo	 Fair Fair Poor Poor Fair	**Spasms, Functional Status, Patient Preference** • Tizanidine = Baclofen **Efficacy** • Diazepam = Tizanidine • Diazepam = Baclofen • Diazepam = Dantrolene • Dantrolene > Placebo • Tizanidine > Placebo • Baclofen > Placebo
	46 trials	**Musculoskeletal Conditions** Cyclobenzaprine vs Diazepam Carisoprodol vs Diazepam Cyclobenzaprine, carisoprodol, orphenadrine or tizanidine vs Placebo Other agents vs Placebo	 Fair Poor Fair Poor	**Pain, Spasm, Global Response** • Cyclobenzaprine = Diazepam (2 head to head, 1 meta-analysis) • Cyclobenzaprine > Diazepam (2 trials and some efficacy measures in a third) **Efficacy** • Carisoprodol > Diazepam • **Pain Relief, Muscle Spasms, Functional Status** • Cyclobenzaprine > Placebo **Pain Relief, Muscle Spasms, Functional Status (less robust finding)** • Carisoprodol > Placebo • Orphenadrine > Placebo • Tizanidine > Placebo **Limited/inconsistent evidence** Methocarbamol, Metaxalone, Dantrolene, Chlorzoxazone, Baclofen vs Placebo

Appendix II: Comparative Safety of Skeletal Muscle Relaxants – Systematic Review[9]

Reference Trial	N	Comparators	Level of Evidence	Safety
Chou	55 trials	**Spasticity** Tizanidine vs Baclofen Hepatotoxicity with Dantrolene or Tizanidine Other SKELETAL MUSCLE RELAXANTs	 Fair Fair Poor	**Overall Tolerability (based upon withdrawal rates)** • Tizanidine = Baclofen **Dry Mouth** • Tizanidine > Baclofen **Weakness** • Baclofen > Tizanidine **Hepatotoxicity** • Dantrolene associated with serious hepatotoxicity • Tizanidine associated with asymptomatic, reversible, rarely serious hepatotoxicity Limited/insufficient evidence
	46 trials	**Musculoskeletal Conditions** Available data	Poor Fair	Limited/insufficient evidence to compare agents head-to-head No pattern of superiority in placebo controlled trials was observed No evidence answers questions concerning abuse or addiction risk **Hepatotoxicity** • **Tizanidine and chlorzoxazone associated with usually reversible, rarely serious or fatal hepatotoxicity**

Appendix III: Clinical Evidence for Skeletal Muscle Relaxants: Systematic Review[81]

Reference Trial	N	Population	Treatment	Outcome	Safety
van Tulder MW et al, 2003	80	N=1	Single dose IV orphenadrine vs placebo in acute low back pain	**Pain and Spasm** • Orphenadrine > PBO	Adverse events: Pooled studies (n=8; 724 people) SMR > PBO Total adverse events [RR (95% CI)] • 1.5 (1.14-1.98) Adverse CNS events • 2.04 (1.23-3.37) PBO > SMR Adverse GI events • 0.95 (0.29-3.19) Most common adverse events • Drowsiness • Dizziness • Nausea
	294	N=4	Short-term oral therapy for acute low back pain and spasm (orphenadrine, tizanidine and cyclobenzaprine)	SMRs > PBO [RR (95% confidence interval)] **Pain intensity** • 2-4 days (4 trials) 0.80 (0.71-0.89) • 5-7 days (3 trials) 0.58 (0.45-0.76) **Global efficacy** • 2-4 days (4 trials) 0.49 (0.25-0.95) • 5-7 days (4 trials) 0.68 (0.41-1.13) **Pooled physical outcome data** • 2-4 days (3 trials) 0.76 (0.66-0.88) • 5-7 days (3 trials) 0.55 (0.40-0.77)	
	267	N=1	Tizanidine vs placebo in acute low back pain and spasm	Tizanidine = PBO in pain relief and global efficacy at day 3 and 7	
	220	N=2	Short-term oral therapy for acute low back pain and spasm (dantrolene and baclofen)	Short-term pain relief @ 4 days • SMR > PBO Reduction in muscle spasm @ 4 days • SMR > PBO Overall improvement at 10 days (1 trial) • Baclofen > PBO	
	96	N=2	Short-term oral therapy for acute low back pain and spasm (cyclobenzaprine and carisoprodol)	SMR > PBO • pain intensity, global efficacy and muscle spasm @ 7 & 14 days (cyclobenzaprine) • pain intensity @ 4 days (carisoprodol)	

Reference Trial	N	Population	Treatment	Outcome	Safety
	560	N=3	Short-term treatment of acute low back pain and spasm with tizanidine + analgesics	Pain relief & spasm reduction at 3-4 and 7-8 days • Tizanidine/analgesic > PBO + analgesic or NSAID Global efficacy • Orphenadrine/ACTM = PBO + ACTM	
	50	N=1	Short-term treatment of acute low back pain and spasm with orphenadrine + ACTM	Disability days • Orphenadrine/ACTM > PBO + ACTM (statistically significant)	

Appendix IV: Clinical Evidence for Skeletal Muscle Relaxants: Anti-spasticity Agents in Children[73,74]

Referernce Trial	N	Population	Treatment	Outcome	Safety
Dai et al, 2008 Non-randomized, retrospective	30	Children with cerebral palsy with gastrocnemius spasticity	All children received botulinum toxin Adjuvant therapy (3 months) Tizanidine (oral) • 0.3-0.5 mg/kg/day in 4 divided doses Baclofen (oral) • 10-15 mg/kg/day in 3 divided doses Max: 40 mg/day < 8 year Max: 60 mg/day > 8 years	Tizanidine (n=17) Baclofen (n=13) Gross Motor Functional Measurement • Tizanidine > baclofen • 76.63 ± 5.88 vs 68.17 ± 1.99; p<0.001 Caregiver Questionnaire Form • Tizanidine > baclofen • 70.23 ± 4.76 vs 66.59 ± 3.53; p=0.03 • Caregiver Questionnaire Form (improvement over botulinum toxin) • Baclofen > botulinum • Improvement of 2.24 ± 0.56	Adverse Events Tizanidine < baclofen Common baclofen AEs • Anorexia • Abdominal pain
Hasnat et al, 2014	139	Children with cerebral palsy and spasticity (5 short-term and 1 long-term trial, meta-analysis not possible)	Most non-placebo controlled, inadequate patient and investigator blinding Baclofen doses ranged from 10-100 mcg 4-baclofen via lumbar puncture 1-baclofen via implantable pump	Spasticity • Reduced in 4 trials (2/4 with questionable statistical analysis) • Insufficient results in 1 trial Comfort, ease of care, quality of life parameters Improved in 1 short- and 1 long-term study	Adverse Events 80 reports in 17 children Serious but not life-threatening (n=3) • 1 – seizures • 2 – device related