"Spasticity vs Spasms" An Island of Misfit Medications

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In professional practice, numerous medications are disguised as “muscle relaxants”, however just how many actually are true relaxants of peripheral muscle? In this discussion on the overall classes of “muscle relaxants”, we will endeavor to evaluate these medications based on respective mechanisms of action and truly decipher just what actual type of medications the stereotypical “muscle relaxants” actually are. We will also aim to improve patient care by providing a strategic thought process into the appropriate selection of these medications for use in patients with muscle spasticity and/or muscle spasms. At the conclusion of our discussion, we will be able to declare that “the gig is up!” and reveal the true identity of these so-called “muscle relaxants”!

Learning Objectives
Pharmacist
1. Distinguish between “muscle relaxant” treatments for muscle spasticity versus those for muscle spasms.
2. Recognize the unique characteristics of the stereotypical class of “muscle relaxants” in order to improve patient care.
3. Recall the appropriate use and dosage of the stereotypical class of “muscle relaxants” in order to improve patient care.

Pharmacy Technician
1. Recognize the difference between treating muscle spasticity versus treating muscle spasms.
2. Recall the unique characteristics of the stereotypical class of muscle relaxants.
3. Recall the appropriate use and dosage of the stereotypical class of muscle relaxants.

Nurse
1. Distinguish between “muscle relaxant” treatments for muscle spasticity versus those for muscle spasms.
2. Recognize the unique characteristics of the stereotypical class of “muscle relaxants” in order to improve patient care.
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Target Audience
Pharmacists, Pharmacy Technicians, Nurses

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Pharmacy Technician 0798-0000-19-007-L01-T
Nurse 0798-0000-19-007-L01-P

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Pharmacist Learning Objectives

• Distinguish between “muscle relaxant” treatments for muscle spasticity versus those for muscle spasms.
• Recognize the unique characteristics of the stereotypical class of “muscle relaxants” in order to improve patient care.
• Recall the appropriate use and dosage of the stereotypical class of "muscle relaxants" in order to improve patient care.

Pharmacy Technician Learning Objectives

• Recognize the difference between treating muscle spasticity versus treating muscle spasms.
• Recall the unique characteristics of the stereotypical class of muscle relaxants.
• Recall the appropriate use and dosage of the stereotypical class of muscle relaxants.

“Muscle Relaxants”
"It was the best of times, it was the worst of times..."

A TALE OF TWO CITIES
Charles Dickens

“Muscle Relaxants”
"It was the best of times, it was the worst of times..."

A Tale of Two Cities: Spasticity versus Spasm
Stiffness or Twitching Differential Diagnosis

Spasticity vs Spasms

<table>
<thead>
<tr>
<th>Stiffness or Twitching</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Velocity-dependent increase in muscle tone caused by the decreased availability of the muscle stretch reflex.</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>Central disorder of upper motor neurons, Peripheral muscle spasm or nerve compression.</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Stiffness, Twitching</td>
</tr>
<tr>
<td><strong>Causes</strong></td>
<td>MS, Cerebral Palsy, Spinal Cord or Brain Injury, Motor Neuron Disease, or Post-Stroke Syndrome.</td>
</tr>
<tr>
<td><strong>FDA Approved Medications</strong></td>
<td>Botulinum toxin, Baclofen, Dantrolene, Diazepam, Riluzole, Tizanidine, Carisoprodol, Chlorzoxazone, Cyclobenzaprine, Metaxalone, Methocarbamol, Orphenadrine, etc.</td>
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</tbody>
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Pain Management Treatments

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<tbody>
<tr>
<td><strong>Non-Pharmacological</strong></td>
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<tr>
<td><strong>Non-Opioid</strong></td>
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<tr>
<td><strong>Opioids</strong></td>
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<tr>
<td><strong>Adjuvants</strong></td>
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<tr>
<td><strong>Interventional</strong></td>
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<tr>
<td><strong>Surgery</strong></td>
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Adjuvant Therapies

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<tr>
<td><strong>Antidepressants</strong></td>
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<tr>
<td><strong>Alpha-2 Agonists</strong></td>
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<tr>
<td><strong>Muscle Relaxants</strong></td>
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<tr>
<td><strong>Benzodiazepines</strong></td>
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<tr>
<td><strong>Gabapentinoids</strong></td>
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<tr>
<td><strong>Anti-Epileptic Drugs</strong></td>
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<tr>
<td><strong>Antihypertensives</strong></td>
</tr>
<tr>
<td><strong>NMDA Antagonists</strong></td>
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“Muscle Relaxants”

Not recommended for chronic pain, except for acute flare-ups

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<th>Spasticity (Stiffness)</th>
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Dantrolene

- Hydantoin derivative structurally related to phenytoin
- Used for Upper motor neuron disorders & Malignant hyperthermia

**Mechanism of Action**
- Blocks ryanodine channel, which inhibits Ca²⁺ release, thus reducing muscle contraction
- Does NOT interfere with Ca²⁺ entry at the cell surface as with Ca²⁺ Channel Blockers

**Side Effects**
- Skeletal muscle weakness
- Troubled breathing (Dyspnea)
- Troubled swallowing (Dysphasia)
- Somnolence
- Dose-dependent gallstones
- Black Box warning of hepatotoxicity
  - Associated with high doses (>800 mg/day) & long-term use (>3 months)

**Products**
- Dantumax® 25mg & 50mg Capsules
- Generic available as 25mg, 50mg, & 100mg
- Revonto® 20mg Powder for Injection
- Ryanodex® 250mg Powder for Injection

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Island of Misfit “Muscle Relaxants”

**Tizanidine**

- Structural Analog of clonidine
- Blocks Afferent sensory spine neuron firing (Alpha-2 Agonist)
- Central Analgesia (Dorsal Horn receives sensory info from periphery)

**Notable Side Effects**
- Hypotension
  - Weakness & Lack of Energy (Asthenia)
  - More sedation than baclofen; so dose at bedtime
  - Elevated Liver Function Tests (LFTs)

**Products**
- Zanaflex® 2mg, 4mg, 6mg Capsules (generic available)
- Capsule w/ Food = Concentration & Absorption
- Zanaflex® 2mg & 4mg Tablets (generic available)
- Tablet w/ Food > Concentration & Absorption

**Interactions**
- CYP1A2 Inhibitors
  - Major: ciprofloxacin & fluvoxamine
  - Minor: cimetidine, famotidine, verapamil, & ethinyl estradiol
- ACEIs/ARBs → severe hypotension

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"Spasticity vs Spasms" An Island of Misfit Medications
Baclofen

- Structural Analog of Gama-Amino-Butyric Acid (GABA)
- Originally designed to treat epilepsy
- Being studied for alcohol-use disorder

Mechanism of Action
- Activates GABA chloride channel
- Blocks Central Afferent sensory neurons

Notable Side Effects
- Decreased muscle tone (Hypotonia)
- Drowsiness
- Abrupt discontinuation → Withdrawal (Benzo-Like)
- Seizures, tachycardia, hyperthermia, anxiety, hallucinations, etc.

Products
- Baclofen 10mg & 20mg (Generic ONLY)
- Lioresal® Solution for Injection

Carisoprodol

- Structural Analog of amitriptyline
- Synthesized in 1961
- FDA approved in 1977 for ACUTE muscle spasms

Package Insert
- Should be used only for short periods (2-3 weeks)
- Adequate evidence of effectiveness for more prolonged use is NOT available

Products
- Soma® 250mg & 350mg Tablets (generic available)
- Carisoprodol 200mg & Aspirin 325mg (only generic is available)
- Carisoprodol 200mg, Aspirin 325mg, & Codeine 16mg (only generic is available)
Cyclobenzaprine

Notable Side Effects
- Remote cases of Serotonin Syndrome with other serotonergic agents

Metabolism
- CYP3A4, CYP1A2, and to a lesser extent CYP2D6

Products
- ER: Amrix® 15mg & 30mg (brand only as of 2017)
- IR: Flexeril® 5mg & 10mg (generic available)
- IR: Fexmid® 7.5mg (generic available)

Orphenadrine

- Structural (methylated) Analog of diphenhydramine
- In 1947, Parke-Davis® led the development of orphenadrine
  - Prior to amantadine (~1960), anticholinergics were main Parkinson's agents

Mechanisms of Action
- H1 receptor antagonist (stronger than diphenhydramine)
- Anticholinergic (Muscarinic Receptor Antagonist)
- NMDA Antagonist
- NE Reuptake Inhibitor

Methocarbamol

- Structural analog of mephenesin
  - Very窄 Therapeutic Index involving Respiratory Depression at clinical doses
  - Antidote for Strychnine poisoning
  - Used to develop meprobamate (Miltown®) in the 1950's as a barbiturate
  - 1st Blockbuster Psychotropic Medication
  - Carbamate derivative of guaifenesin (Mucinex®, etc.)

Urine Drug Screenings

TCA False Positives

- Cyproheptadine
- Carbamazepine
- Cyclobenzaprine
- Amitriptyline

Orphenadrine

Notable Side Effects
- Antihistamine Sedation Effect
- Anticholinergic Effects (e.g. "Drying")
- Aplastic anemia (Rare)

Products (all generic only)
- Orphenadrine 25mg/Aspirin 385mg/Caffeine 30mg IR Tablets
- Orphenadrine 50mg/Aspirin 770mg/Caffeine 60mg IR Tablets
- Orphenadrine ER 100mg Tablets
- Solutions for Injection
  - Canada → OTC

Methocarbamol Products

- Robaxin® 500mg & 750mg (generic available)
- Robaxin® Solution for Injection
- Methocarbamol 400mg & Aspirin 325mg Tablets (OFF MARKET)
- Canada → OTC
  - Robaxin (methocarbamol)
  - Robax Platinum (+IBU)
  - Robaxacet (+APAP)
  - Robaxisol (+ASA)
Methocarbamol

Metabolism
- Does not produce guaifenesin as a metabolite (carbamate bond not hydrolyzed)
- Phase I hydroxylation and O-demethylation, followed by Phase II conjugation

Notable Side Effect
- Brown/Black/Green Urine

Urine Color
- The yellow coloration of urine results from urobilin that is produced as a product of bilirubin degradation
- Normal urine color: light yellow to golden

Chlorzoxazone

FDA approved in 1958
- Adjunct for relief of discomfort associated with acute musculoskeletal conditions

Kinetics/Metabolism
- Hepatic glucuronidation into an inactive metabolite that is excreted in the urine (Orange/Red/Purple)

Products
- Parafon Forte DSC® & Relax-DS® 500mg (generic available)
- Lorzone® 375mg & 750mg (Brand Only)

Notable Drug Interactions
- Diclofenac, acetaminophen, tramadol, & famotidine

Notable Side Effects
- Rare cases of idiosyncratic hepatocellular toxicity (Monitor LFTs)
- Orange/Red/Purple Urine
FDA approved in 1962
• Adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute painful musculoskeletal conditions

Kinetics/Metabolism
• High Fat meals > bioavailability & AUC
• CYP1A2, CYP2D6, CYP2E1, & CYP3A4

Products
• Skelaxin® 800mg (generic available)
• Metaxalone 400mg (generic only) *Watch for confusion with metolazone (diuretic)

Metaxalone methocarbamol tablet 500mg, 750mg
Robaxin® tablet 500mg, 750mg
carisoprodol tablet 250mg, 500mg
Soma® Tablet 250mg, 350mg
cyclobenzaprine tablet 5mg, 7.5mg, 10mg
Flaxor® tablet 5mg, 7.5mg, 10mg
Amrix® ER Capsule 15mg, 30mg
orphenadrine ER tablet 100mg
metaxalone tablet 400mg, 800mg
Metaxal® 800mg
Skelaxin® 800mg
baclofen tablet 10mg, 20mg
chlorzoxazone tablet 500mg
Lorzone® tablet 375mg, 750mg
Relax-DS® 500mg
tizanidine capsule 2mg, 4mg, 6mg
Zanaflex® capsule 2mg, 4mg, 6mg
tizanidine tablet 2mg, 4mg
Zanaflex® tablet 2mg, 4mg
Dantrium® capsule 25mg, 50mg, 100mg
dantrolene capsule 25mg, 50mg, 100mg

“Muscle Relaxant” Products Available

“Muscle Relaxants” Not recommended for chronic pain, except for acute flare-ups

Spasticity (Spasms)
• tizanidine (Zanaflex®)
• baclofen (Lioresal®)
• Gabapentinoids & Benzos
• orphenadrine (Norflex®)

Musculoskeletal Disorders (Spasms)
• carisoprodol (Soma®)
• cyclobenzaprine (Flexeril®)
• orphenadrine (Norflex®)
• methocarbamol (Robaxin®)
• chlorzoxazone (Parafon Forte DSC®, Lorzone®, Relax-DS®)
• metaxalone (Skelaxin®)

Spasticity vs Spasms” An Island of Misfit Medications

Opioids, Benzos, “Relaxants”, & Hypnotics Overlapping Sedative Side Effects...

Opioid-Sedative Interactions “Name Game”

Drug-Dose Interaction | Proposed Name
--- | ---
Opioid + Benzodiazepine Sedative | “Bozo”
Opioid + “Muscle Relaxant” Sedative | “Relaxoid”
Opioid + Sedative Hypnotic | “Hypoid”
Opioid + One Other Sedative | “Deadly Duo”
Opioid + Two Other Sedatives | “Unholy Trinity”
Opioid + Three Other Sedatives | “Quattro Killer”
Benzodiazepine & Sedative Hypnotic | “Hypo”
Benzodiazepine & “Muscle Relaxant” Sedative | “Relaxoid”

And, they said that no one would notice if I peed in the pool.”

“Spasticity vs Spasms” An Island of Misfit Medications
A Wine Bottle Opener in Every Bag...

Flogging a Dead Horse... ???

Medication Database Sedative Drug-Drug Interaction Reports
- Micromedex®
- Lexicomp®
- Clinical Pharmacology®
- Facts & Comparisons®

oxycodone, alprazolam, carisoprodol, and zolpidem

“Spasticity vs Spasms” An Island of Misfit Medications
Oxycodone, alprazolam, carisoprodol, and zolpidem

Medication Database Interaction Screenings
Facts & Comparisons®


Musculoskeletal Disorders
(Spasms)
carisoprodol (Soma®)
cyclobenzaprine (Flexeril®)
orphenadrine (Norflex®)
methocarbamol (Robaxin®)
chlorzoxazone (Parafon Forte DSC®, Lorzone®, Relax-DS®)
metaxalone (Skelaxin®)

central acting

tizanidine (Zanaflex®)
baclofen (Lioresal®)

Peripheral Acting
dantrolene (Dantrium®)
BOTOX®

Musculoskeletal Disorders
(peripheral)
carisoprodol (Soma®)
cyclobenzaprine (Flexeril®)
orphenadrine (Norflex®)
methocarbamol (Robaxin®)
chlorzoxazone (Parafon Forte DSC®, Lorzone®, Relax-DS®)
metaxalone (Skelaxin®)

“Muscle Relaxants” Not recommended for chronic pain, except for acute flare-ups

Spasticity
(Central)
tizanidine (Zanaflex®)
baclofen (Lioresal®)
Gabapentinoids & Benzos
Galantamine, Donepezil, and Rivastigmine

Peripheral Acting
dantrolene (Dantrium®)
BOTOX®

Musculoskeletal Disorders
(peripheral)
carisoprodol (Soma®)
cyclobenzaprine (Flexeril®)
orphenadrine (Norflex®)
methocarbamol (Robaxin®)
chlorzoxazone (Parafon Forte DSC®, Lorzone®, Relax-DS®)
metaxalone (Skelaxin®)

“Muscle Relaxants” and Chocolate???

Spasticity vs Spasms

Treatment

“Spasticity vs Spasms” An Island of Misfit Medications

All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy.

~ Paracelsus

~10yo → ~1,900 mini milk bars
~10yo → ~800 mini dark bars

www.addictionsurvivors.org

10yo → ~1,900 mini milk bars
10yo → ~800 mini dark bars

“Spasticity vs Spasms” An Island of Misfit Medications