CONNECTICUT MEDICAL ASSISTANCE PROGRAM DEPARTMENT OF SOCIAL SERVICES & HEALTH INFORMATION DESIGNS

Connecticut Medical Assistance Program Quarterly Newsletter

The skeletal muscle relaxant (SMR) class is a unique group of medications unlike any other. They are a diverse group of drugs with different mechanisms of action, indications, pharmacokinetics, pharmacodynamics, and side effect profiles. There are 10 medications classified as SMRs: baclofen, dantrolene, carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, orphenadrine, diazepam, and tizanidine. This group can be further differentiated by indication: antispastic agents, antispasmodic agents, and agents that treat both conditions. Connecticut Medical Assistance Program utilization of individual agents during 2020 is listed in table 1.

Spasticity is a malfunction of upper motor neurons which occurs when regions that facilitate and control movement are impaired. Antispastic agents are used to treat disorders stemming from upper motor neuron syndromes such as multiple sclerosis (MS), spinal cord injuries, traumatic brain injury (TBI), and cerebral palsy.[1,2] Antispastic agents exert their effect on the spinal cord or skeletal muscles directly. Spinal motor neuron overstimulation causes stiffness, rigidity, clonus, and issues with movement and walking in patients. Spasticity is commonly measured by the Ashworth scale and if spasticity is found to impact daily life, treatment with medication is warranted. The duration of treatment with SMRs indicated for spasticity can be longer compared to the duration recommended for antispasmodics. Medications indicated to treat spasticity are listed in Figure 1 and Table 2.[3,4]

Antispasmodic agents are indicated to treat acute musculoskeletal pain and spasm originating from peripheral muscle sites.[1] The opioids are not effective SMRs. Common reasons for antispasmodic utilization include injuries to the muscle, tendon or ligaments caused by sports injury, trauma, neck, or low back pain. These agents do not have a direct effect on skeletal muscle but are thought to exert their effect via CNS depression.[5] Prior to using a SMR for acute musculoskeletal pain, non-pharmacologic approaches such as heat and cold therapy, compression, physical therapy, massage, or manipulation are recommmended.[6,7] The American Pain Society recommends the use of acetaminophen (APAP) or non-steroidal anti-inflammatory drugs (NSAIDs) as

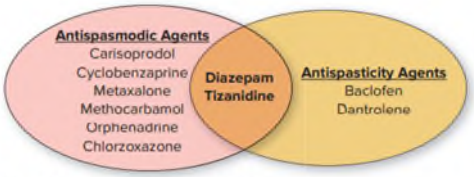

Figure 1 Classification of Skeletal Muscle Relaxants

first line therapy for acute low back pain.[8] APAP, rather than NSAIDs, should be used in patient who have underlying renal or cardiovascular disease. SMRs should be used only when non-pharmacologic and first line analgesic options fail.[8]

A recent Cochrane review found that SMRs used to treat low back pain were more effective than placebo for short term use, but their effectiveness to treat chronic low back pain was not determined.[9] It is recommended to use SMRs for musculoskeletal pain for no more than 2-3 weeks because of the lack of evidence for long term efficacy.[9] Additionally, there is a lack of head to head comparison between the different antispasmodic agents. When considering SMR selection, individual patient specifics such as symptoms, prior and concurrent medications, side effects, cost, patient age, and comorbidities should be considered. Antispasmodic agents are listed in Figure 1 and Table 2.[3,4]

It should be noted that commonly shared side effects among all SMRs (antispastic and antispasmodic agents) include drowsiness and sedation, with a risk of causing altered mental status and falls, especially in older patients. The American Geriatric Society (AGS) Beers criteria for Potentially Inappropriate Medication Use in Older Adults recommends that all SMRs carry a strong warning against use in older adults due to anticholinergic and sedative effects of these medications and the increased risk of falls.[10] Additionally, the National Committee of Quality Assurance (NCQA) Healthcare Effectiveness and Data Information Set (HEDIS) created quality measures for the

Table 1 Connecticut Medical Assistance Program Skeletal Muscle Relaxant Utilization 2020

Drug	RX Count	Total Quantity Dispensed	Unique Recipients	Recipients > 65 years of age
Baclofen	29,953	2,323,830	7,373	184
Dantrolene	148	12,482	24	1
Carisoprodol	3,739	252,503	658	14
Chlorzoxazone	959	74,536	187	3
Cyclobenzaprine	82,360	3,432,853	36,613	479
Metaxalone	1,762	88,806	765	8
Methocarbamol	32,950	1,761,984	16,795	255
Orphenadrine	276	11,188	132	5
Diazepam	22,180	900,279	7,809	104
Tizanidine	16,241	1,091,125	4,927	115

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use of SMRs in the elderly, recommending to avoid their use in this population.[11] High risk medication use in the elderly can be associated with an increase in emergency department (ED) visits, hospitalization and an increase in mortality.[12]

Antispastic Agents

Baclofen[13]

Baclofen is FDA approved to treat upper motor neuron spastic conditions associated with MS or spinal cord injury. While the exact mechanism of action is not completely understood, it does inhibit reflexes at the spinal level, blocks pre and post-synaptic gamma-aminobutyric acid ($GABA_B$) receptors and causes CNS depression, which is thought to reduce the hyperactivity of muscle reflexes and spasm.[14] The effects of baclofen will not be reversed by the benzodiazepine antagonist flumazenil. Baclofen is formulated for oral and intrathecal administration. Oral baclofen is typically dosed 3-4 times a day due to its short half- life. Oral doses typically range from 15-80 mg/day with a recommendation not to exceed 80 mg/day. 60-85% of the drug is eliminated via renal excretion.[15] Dose reduction is recommended in renal impairment, and it is recommended to avoid use in patients with severe renal impairment (ClCr < 30 ml/min) and in patients on dialysis.[15] Baclofen can be delivered intrathecally to treat severe spasticity via an implanted pump and catheter. Baclofen carries a black box warning regarding the abrupt withdrawal of the intrathecal formulation. Patients who receive treatment with intrathecal baclofen for > 2 months and who are abruptly withdrawn (often due to a delivery system malfunction), can experience a hypermetabolic state with hyperpyrexia, muscle rigidity, impaired cognition, and severe rebound spasticity which can lead to rhabdomyolysis and/or multiple organ failure.[16]

Dantrolene[17]

Dantrolene is a postsynaptic muscle relaxant, structurally similar to phenytoin.[5] Dantrolene differs from the other centrally acting antispastic agents due to its direct inhibition of calcium release from skeletal muscle sarcoplasmic reticulum.[5,14] Similar to baclofen, dantrolene is FDA approved to treat spastic conditions associated with stroke, MS, spinal cord injury, and cerebral palsy. It is also the only known and available treatment for malignant hyperthermia, a rare but very serious and life-threatening event that is caused by halogenated anesthetics used during general anesthesia. Dantrolene is available as IV and oral capsule formulations. The oral formulation has a black box warning regarding the risk of hepatoxicity and is contraindicated in patients who have underlying hepatic disorders such as cirrhosis, hepatitis B or C infection. Due to the risk of liver damage, if benefits of dantrolene treatment are not seen within 45 days of starting therapy, it is recommended to discontinue the drug. Dantrolene is typically dosed 3 -4 times a day with a recommended max dose of 100 mg four times a day. CNS depression side effects are evident with dantrolene.

Antispasmodic Agents

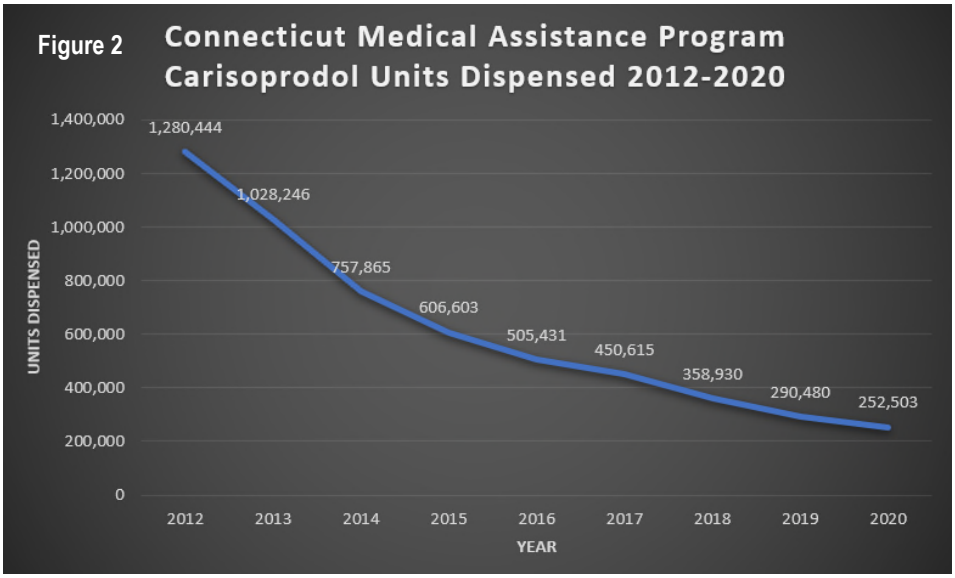
Carisoprodol[18]

Carisoprodol is a schedule IV controlled substance FDA approved to treat acute and painful musculoskeletal disorders for up to three weeks in patients ≥ 16 years of age.[19] The mechanism of carisoprodol is not fully understood but it is thought to exert its effect via CNS depression. Carisoprodol is metabolized to the active metabolite meprobamate, primarily by the hepatic cytochrome P-450 enzyme 2C19.[19] Many variables can affect carisoprodol and meprobamate concentrations, including use of concurrent medications that induce (rifampin) or inhibit (omeprazole) 2C19. The half-life of carisoprodol is 1.7-2 hours, whereas the half-life of meprobamate is approximately 10 hours.[19] The half-life of meprobamate can increase to 48 hours in patients who use carisoprodol long term, increasing the potential for drug accumulation and adverse events.[20] Meprobamate, also a schedule IV controlled substance, was marketed as a tranquilizer during the 1950's under names such as Miltown and Equanil. It remained a popular choice as an antianxiety medication until the benzodiazepines were introduced.[20] Both carisoprodol and meprobamate, similar to the benzodiazepines, potentiate the GABA receptor site.[21] They both carry a risk of abuse, dependence and withdrawal and can act as respiratory depressants.[19] When used concomitantly with opioids and benzodiazepines, the effects on respiratory depression are additive and increase the risk of overdose and death. The "holy trinity" is a street term used to describe the concurrent use of an opioid, benzodiazepine, and carisoprodol to elicit euphoric effects.[21] CNS depression is additive when these three medications are used together, and adverse events are more likely. National emergency room visits associated with carisoprodol doubled from 1994 to 2004 (6,569 to 14,376) and then doubled again by 2009 to approximately 30,000.[20] Carisoprodol was scheduled by the Food and Drug Administration (FDA) as a class IV medication in 2012 and an article by Reeves et al stated "There is no definite gauge or way to predict the impact that classifying carisoprodol as a schedule IV at the Federal level will have on the use of the drug.[20]" In taking a closer look at the Connecticut Medical Assistance data, there has been an 80% decline in quantities dispensed of carisoprodol from 2012 to 2020 in our population (figure 2).

Chlorzoxazone[22]

Chlorzoxazone is a centrally acting SMR indicated for muscle spasm and pain associated with musculoskeletal disorders. Similar to the other SMRs, the mechanism of action of chlorzoxazone is not completely understood but is thought to be associated with the sedative properties of the drug. Chlorzoxazone has no direct effect or relaxation properties on skeletal muscles. Chlorzoxazone is formulated as a

Figure 2 Connecticut Medical Assistance Program Carisoprodol Units Dispensed 2012-2020



500 mg oral tablet and is typically dosed 3-4 times a day. Adverse drug events (ADEs), similar to other SMRs, include CNS depression and sedation. A rare side effect of chlorzoxazone is hepatocellular toxicity. It is recommended to educate patients regarding warning signs of liver malfunction and to monitor liver function tests (LFTs) in patients receiving chlorzoxazone as a long term treatment.

Cyclobenzaprine[23]

Cyclobenzaprine is indicated to treat muscle spasm associated with painful musculoskeletal conditions. It has a chemical structure similar to the tricyclic antidepressant amitriptyline. It is available as 5 and 10 mg immediate release tablets and 15 and 30 mg extended release capsules. It is the only SMR that is considered safe in pregnancy as it is rated FDA Category B. Similar to the other antispasmodics, cyclobenzaprine should not be used for more than 2-3 weeks due to a lack of efficacy with long term use. Cyclobenzaprine is contraindicated in patients taking concurrent monoamine oxidase inhibitors (MAOIs) and in patients in the acute recovery phase of myocardial infarction, and in patients with arrythmias, heart block, conduction disturbances, and congestive heart failure. Due to its tricyclic antidepressant structure, it can prolong the QTc. ADEs associated with cyclobenzaprine include anticholinergic side effects and CNS depression. It is not recommended to use this medication in patients with moderate to severe hepatic impairment or in patients > 65 years of age. Cyclobenzaprine has a half-life of 1 -3 days and two case reports found the potential for cyclobenzaprine induced protracted delirium in the very elderly.[24] Cyclobenzaprine is the most widely used SMR under the CT Medicaid benefit but due to effects such as sedation, anticholinergic ADEs, and QTc prolongation, first line use of cyclobenzaprine should be subsequent to other agents in the class.

Metaxalone[25]

Metaxalone is indicated to treat acute pain associated with musculoskeletal conditions. It does not work directly on skeletal muscles and is thought to exert its effect via CNS depression and sedation. The recommended dose is 800 mg three-four times a day in patients greater than 12 years of age. Metaxalone carries warnings for serotonin syndrome, CNS depression (especially when used concurrently with other CNS depressants) and is contraindicated in severe hepatic and renal disease.

Methocarbamol[26]

Methocarbamol is a derivative of guaifenesin (Mucinex). It is an antispasmodic indicated to treat acute musculoskeletal pain (adjunct to physical therapy). Formulated as 500 mg and 750 mg tablets (as well as IM and IV formulations), methocarbamol is typically administered 3 -4 times a day with a maximum recommended dose of 6-8 gm/day. The half-life of methocarbamol is approximately 1-2 hours and is metabolized by the liver via dealkylation, hydroxylation, and glucuronidation. Methocarbamol (and metaxalone) are thought to cause less sedation compared to the other agents in the class, however, CNS depression can still occur and the risk for abuse potential remains.[27]

Orphenadrine[28]

Orphenadrine, an analog of diphenhydramine, is indicated for acute treatment of painful musculoskeletal conditions. It is formulated as 100 mg tablets that cannot be crushed. Short term use is recommended, and tapering is recommended in patients who are receiving chronic therapy. Anticholinergic side effects can occur with use. It is recommended to use with caution in patients with underlying heart failure, tachycardia, or arrhythmia. Similar to other SMRs, orphenadrine carries an abuse and dependence warning.

Antispastic/Antispasmodic Agents

Diazepam[29]

Diazepam is a schedule IV benzodiazepine indicated as an antispasmodic for the treatment of acute painful musculoskeletal conditions (trauma, back pain) and as an antispastic for the treatment of upper motor neuron disorders (spinal cord injuries, MS). Diazepam has direct effect on GABA and is thought to exert its skeletal muscle relaxant effect through this pathway. The recommended dose for treatment of musculoskeletal spasm is 2-10 mg three to four times a day. Diazepam carries a black box warning regarding the use of concomitant opioids and risk of respiratory depression. This drug should be used with extreme caution in patients with a history alcohol and/or drug abuse. Diazepam, similar to all other SMRs, is a Beers list medication and not recommended for use in patients > 65 years of age unless the risks outweigh the benefits. It is recommended that both carisoprodol and diazepam remain last line choices during SMR selection due to their risk of abuse.[8] Carisoprodol and diazepam are the only SMRs that have a documented risk of addiction in addition to physical dependence.[4]

Tizanidine[30]

Tizanidine is indicated to treat both spastic and spasmodic conditions. It is chemically similar to clonidine and guanfacine. Tizanidine is a centrally acting alpha-2 agonist which impairs the release of excitatory amino acids and increases the presynaptic inhibition of motor neuron pathways.[31] This drug is initially dosed at 1-2 mg three times a day and can be increased by 2-4 mg/dose, leaving 1-4 days between dose increases. Tizanidine has a max dose of 36 mg/day. Tizanidine can cause hypotension due to its central alpha 2 agonist effects. Other ADEs include dry mouth, somnolence, and dizziness. It has been reported that tizanidine can increase hepatic transaminases asymptomatically therefore it is recommended to monitor LFTs. Rebound hypertension can occur when stopping this medication abruptly. Concurrent use with ciprofloxacin or fluvoxamine is contraindicated due to the potentiation of hypotension and bradycardia.[31] It is recommended to use with caution with other central alpha 2 agonists and to consider avoiding use in patients receiving multiple antihypertensives. It is also recommended to monitor renal and hepatic function in patients receiving tizanidine as use has been associated with acute liver toxicity, similar to chlorzoxazone and dantrolene.

The SMRs are a unique class of medications with many differences from chemical structure to mechanism of action, however, they are all known to cause CNS depression, sedation, and should be used cautiously in the elderly. Non-pharmacologic approaches and/or first line analgesics should be considered prior to starting SMR therapy. In the event SMR therapy is warranted, length of treatment should be kept to the shortest time possible in order to avoid toxicity and adverse events. Due to the lack of guidelines and comparative efficacy among the class, agent selection should be considered on a case by case basis using clinical judgement and individual patient specifics. Prior to prescribing or dispensing a SMR, healthcare professionals should work together to evaluate patient risk of substance abuse as these agents have abuse potential.

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Table 2 Skeletal Muscle Relaxants[3,4] (*indicates CT Medicaid preferred agents)				
Medication	**Indication**	**Common Oral Adult Dosing**	**Geriatric Consideration**	**Clinical Pearls**
Antispastic Agents				
Baclofen* (Lioresal)	Spasticity from MS or spinal cord injuries	5 mg TID Max dose: 80 mg/day	Beers criteria: No Use lowest effective dose	Black box warning: Avoid abrupt discontinuation due to risk of withdrawal Renal elimination (60-85%)
Dantrolene (Dantrium)	Chronic spasticity (spinal cord injury, stroke, cerebral palsy, MS) Malignant hyperthermia	Initial: 25 mg daily Maintenance: 25–100 mg up to 4 times daily	Beers criteria: No	Black box warning for hepatotoxicity If no benefit is seen within 45 days, discontinue
Antispasmodic Agents				
Carisoprodol (Soma)	Acute musculoskeletal pain	250–350 mg 3 times a day and at bedtime Max: 1,400 mg daily	Beers criteria: yes	Schedule IV Meprobamate is active metabolite
Chlorzoxazone* (Parafon Forte)	Acute musculoskeletal pain	500 mg 3–4 times daily Max: 750 mg 3–4 times daily	Beers criteria: yes	Rare but serious hepatotoxicity, monitor LFTs
Cyclobenzaprine* (Flexeril)	Acute musculoskeletal pain	IR: 5 mg 3 times daily Max: 10 mg 3 times daily ER: 15 mg daily Max: 30 mg daily	Beers criteria: yes Extended release formulation not recommended	Anticholinergic ADEs Structurally similar to TCAs
Metaxalone (Skelaxin)	Acute musculoskeletal pain	800 mg 3–4 times daily	Beers criteria: yes	Risk of serotonin syndrome Contraindicated in severe hepatic and renal dysfunction
Methocarbamol* (Robaxin)	Acute musculoskeletal pain	Initial: 1,500 mg 4 times daily for 2–3 days Maintenance: 750 mg every 4 hours, 1,500 mg by mouth 3 times daily, or 1,000 mg 4 times daily Max: 4 g daily	Beers criteria: yes	Drug may change color of urine to brown, black, or green
Orphenadrine (Norflex)	Acute musculoskeletal pain	100 mg 2 times daily	Beers criteria: yes	Anticholinergic ADEs Euphorigenic and analgesic properties; must taper in chronic use
Antispastic/Antispasmodic Agents				
Diazepam (Valium)	Acute musculoskeletal pain Spasticity associated with upper motor neuron disorders	2–10 mg 3 to 4 times daily	Beers criteria: yes Elderly: 2–2.5 mg 1–2 times daily; titrate gradually as tolerated	Schedule IV Black box warning regarding increased risk of death when used concurrently with opioids
Tizanidine* (Zanaflex)	Acute musculoskeletal pain Spasticity associated with upper motor neuron disorders	2 mg 3 times daily, titration recommended to increase dose Max dose 36 mg/day	Beers criteria: yes	Alpha-agonist Rebound hypertension when discontinued abruptly