PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #340
SKELETAL MUSCLE RELAXANTS
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Background Skeletal muscle relaxants (SMRs) are a heterogeneous class of medications used for the management of spasticity or muscle spasms. This *Fast Fact* reviews their role in palliative care.

Pharmacology SMRs are known CNS depressants. Dizziness, drowsiness, confusion, and an increased risk of injury are consistently reported adverse effects, especially in ages ≥ 65 (1-3). Most SMRs are predominantly metabolized by the liver, except for baclofen (only 15% hepatic metabolism). Therefore, SMRs require extra caution and dose reduction in patients with cirrhosis (4).

Mechanism of Action Though their mechanism of action is largely unknown, many experts believe it largely stems from their sedative effects. There are two general types of muscle relaxants:

- Antispasticity agents: these aim to reduce muscle hypertonicity and involuntary jerks associated with neurological disorders like multiple sclerosis (MS) or cerebral palsy (CP). Baclofen is the most commonly prescribed agent in this class (4).
- Antispasmodic agents: these aim to treat striated muscle spasms from peripheral musculoskeletal conditions like low back pain (4). Cyclobenzaprine and methocarbamol are examples (4). Most experts recommend limiting their use to 2-4 weeks because of the associated CNS risks.

Clinical Evidence The most compelling evidence for muscle relaxants is for MS (5). Placebo-controlled trials have shown a similar reduction in daily muscle spasms and clonus in MS patients receiving baclofen or tizanidine (6-8). To date, no head to head trials have adequately compared their effectiveness in controlling MS-related muscle spasms with botulinum injections. For other conditions:

- There is no published evidence firmly establishing the efficacy or safety of SMRs compared with opioids, acetaminophen, or NSAIDs. It is also unknown if SMRs have an opioid-sparing effect.
- For acute back pain, carisoprodol, cyclobenzaprine, and tizanidine have been shown to be moderately effective for short term relief (2 weeks) compared with placebo (1,5).
- For musculoskeletal back pain lasting > 2 weeks, a 2003 systematic review of placebo controlled trials found insufficient evidence to support skeletal muscle relaxants as effective agents (6).
- There is no compelling evidence that one skeletal muscle relaxant is more effective than another.
- For cancer patients, use of baclofen and diazepam has been described as adjuvants for cancer-related spasticity or muscle spasms, although controlled evidence supporting such use is lacking (9).

Patient Selection When assessing patients, first determine whether you are treating spasticity or peripheral muscle spasm. Spasticity is a state of increased muscular tone with exaggeration of tendon reflexes most commonly associated with conditions like MS, traumatic brain injury, and CP (2,4). In contrast, muscle spasm is a sudden involuntary contraction of one or more muscle groups and is typically associated with a muscle strain, fibromyalgia, or mechanical low back pain (2,4). Avoid muscle relaxants in elderly patients or patients with preexisting cognitive impairment who may be at high risk for delirium. For patients <65 with insomnia related to muscle spasms, cyclobenzaprine, tizanidine, and diazepam are the most sedating SMRs while methocarbamol and metaxalone are least sedating.

Pediatric Use: Although mostly off-label, SMRs are commonly prescribed as anti-spasticity agents for children with hypertonicity from conditions such as CP. Baclofen has the most established pediatric dosing: start 5 mg BID or TID; max daily dose is 40 mg in ages 2-7 and 60 mg for ages 8-17. Caution in children with seizure disorders as baclofen can lower the seizure threshold.

Cost As a class, skeletal muscle relaxants are fairly affordable. Diazepam is the least expensive with a usual cost of $0.22/tablet; tizanidine is the most expensive at about $1.22/tablet. For comparison, immediate release morphine sulfate is usually about $0.43/tablet.

Summary Outside their role as anti-spasticity agents, the risks of adverse effects from SMRs is high and may outweigh benefits. When prescribed as anti-spasmodic agents for common conditions such as

low back pain or fibromyalgia, SMRs should be limited to short term use (e.g. 2-4 weeks), with a prescription only being renewed after an in-person reassessment. The choice of a SMR should be based on its adverse-effect profile and tolerability (2). See the table below (4).

Medication	**T 1/2 Hours**	**Starting Dose**	**Special Considerations**
Anti-spasticity Agents			
Baclofen	5	5 mg TID	Lowers seizure threshold. Can increase Alk Phos and AST. Available intrathecally. Adult max dose 80 mg/day. Reduce dose when CrCl <80 mL/min. Also prescribed for alcohol use disorder and hiccoughs (10). FDA approved ages ≥ 12.
Anti-spasmodic Agents			
Cyclo-benzaprine	18	5 mg TID	Structurally akin to tricyclic antidepressants; caution when cardiac issues present as patients are at risk for anticholineric effects like orthostasis, and QTc prolongation. Adult max daily dose 30 mg. FDA approved ages 15 and above.
Carisoprodol	8	250 mg QID	Metabolized to meprobamate which has significant abuse potential. Max adult daily dose 1400 mg.
Metaxalone	9	800 mg TID	Caution in liver failure. Max daily adult dose 2400 mg.
Metho-carbamol	1-2	750 mg QID	May cause brownish/green urine discoloration. Consider 1500 mg QID as a loading dose for 2-3 days. FDA approved ages 16 and above.
Combination Agents			
Diazepam	48	2-10 mg TID	Significant abuse potential.
Tizanidine	20-40	4 mg TID	Hypotension, asthenia, dry-mouth may result. Contra-indicated with ciprofloxaxin and other CYP A12 inhibitors. Dose reduce when CrCl <25 mL/min. Max daily dose 36 mg.

References:

1. van Tulder MW, Touray T, Furlan AD, et al. Muscle relaxants for nonspecific low back pain: a systematic review within the framework of the cochrane collaboration. Spine. 2003;28(17): 1978-1992.
2. See S, Ginzburg R. Choosing a skeletal muscle relaxant. Am Fam Physician. 2008 Aug 1;78(3): 365-70.
3. Spence MM, Shin PJ, et al. Risk of injury associated with skeletal muscle relaxant use in older adults. The Annals of Pharamcotherapy.2013:47:993-8.
4. See S, Ginzburg R. Skeletal muscle relaxants. Pharmacotherapy. 2008 Feb;28(2):207-13.
5. Chou R, Peterson K, Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. J Pain Symptom Manage. 2004;28(2):140–175.
6. Brar SP, Smith MB, et al. Evaluation of treatment protocols on minimal to moderate spasticity in multiple sclerosis. Arch Phys Med Rehabil. 1991 Mar;72(3):186-9.
7. Smith C, Birnbaum G, et al. Tizanidine treatment of spascticity caused by multiple sclerosis: results of a double-blind, placebo-controlled trial. US Tizanidine Study Group. Neurology 1994; 44(11 Supp 9): S34-42;discussion S42-3.
8. Hoogstraten MC, van der Ploeg RJ, vd Burg W, Vreeling A, van Marle S, Minderhoud JM. Tizanidine versus baclofen in the treatment of spasticity in multiple sclerosis patients. Acta Neurol Scand. 1988 Mar;77(3):224-30.
9. Fromm GH. Baclofen as an adjuvant analgesic. J Pain Symptom Manage. 1994;9:500–509.

10. Addolorato G, Leggio L, Ferrulli A, Cardone S, et al. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. Lancet. 2007 Dec 8;370(9603):1915-22.

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