Formulary Drug Listing Decisions

SKELETAL MUSCLE RELAXANTS

Indications

The management of discomfort ± acute muscle spasm associated with painful musculoskeletal (MSK) conditions (cylcobenzaprine, methocarbamol, and orphenadrine).

The treatment of spasticity associated with spinal cord injuries and neuron disorders (baclofen, dantrolene, and tizanidine).

DAC Recommendation

The DAC recommended that: (i) orphenadrine and cyclobenzaprine be listed in the 25WS formulary ONLY; (ii) baclofen be listed in the 03WS formulary ONLY; and (iii) dantrolene, methocarbamol, and tizanidine NOT BE LISTED in any WSIB formularies.

The WSIB Decision

Based on the DAC's recommendations, the WSIB has decided to: (i) **LIST** cyclobenzaprine and orphenadrine in the initial musculoskeletal (25WS) formulary; (ii) **LIST** baclofen in the CNS-Brain injury (03WS) formulary; and (iii) **NOT LIST** dantrolene, methocarbamol, or tizanidine in any formulary at this time.

Formulary Status

Cyclobenzaprine and orphenadrine are listed in the 25WS formulary ONLY. Baclofen is listed in the 03WS formulary ONLY. New requests for these drugs outside these formularies WILL NOT be approved. Dantrolene, methocarbamol, and tizanidine ARE NOT listed in any WSIB formularies.

Recommendation Highlights

- Skeletal muscle relaxants (SMRs) are a heterogeneous group of drugs used to treat muscle spasm, pain associated with acute MSK conditions and spasticity associated with spinal cord injuries and neuron disorders.
- Cyclobenzaprine, orphenadrine, and tizanidine have demonstrated significant short-term symptomatic relief and overall improvement of acute low back pain compared to placebo. Long-term data are unavailable. Concerns exist in the medical literature regarding their potential for central nervous system (CNS) adverse events and drug interactions.
- Tizanidine does not provide any therapeutic benefit compared to cyclobenzaprine or orphenadrine in the treatment of acute back pain; however, tizanidine is associated with liver and cardiac side effects, an increased risk of abuse and a significantly higher cost.
- Baclofen has fair to strong evidence of efficacy in muscle spasm and spasticity associated with upper motor neuron syndrome (based mainly on trials in multiple sclerosis). Rigorous evidence in other musculoskeletal conditions are lacking.
- There is limited evidence for the use of methocarbamol or dantrolene in the treatment of acute back pain or spasticity. Both drugs are associated with CNS side effects and potential drug interactions.
- Overall, systematic reviews indicate that most SMR trials have several methodological shortcomings including poor quality, poorly designed and described methods, short duration and heterogeneity of outcome measures.
- Relatively few comparative trials involving SMRs are available, making it difficult to assess whether important differences exist between agents.

Drug Profile

Products available in Canada:

Baclofen *(e.g., Lioresal®, various generic)*

Cyclobenzaprine *(e.g., various generic)*

Dantrolene *(e.g., Dantrium®)*

Methocarbamol *(e.g., Robaxin®, Robaxacet®)*

Orphenadrine *(e.g., Norflex™, various generic)*

Tizanidine *(e.g., Zanaflex™, various generic)*

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- Few pharmacoeconomic studies have evaluated the cost-effectiveness of SMRs; those available have major methodological limitations.
- **The DAC concluded that an independent review of the clinical efficacy, safety, and cost-effectiveness of SMRs in the treatment of acute muscle spasms and painful musculoskeletal conditions demonstrated variable evidence by drug class.** Consequently, the DAC recommended that (i) cyclobenzaprine and orphenadrine be listed in the 25WS formulary as they present the best quality evidence; (ii) baclofen be listed in the 03WS formulary for the treatment of spasticity due to CNS-related injury/illness; and (iii) dantrolene, methocarbamol, and tizanidine not be listed in any formularies as these agents do not provide any therapeutic advantage and pose additional risks.

DETAILED DISCUSSION

Background

The term skeletal muscle relaxants (SMRs) refers to a heterogeneous group of drugs used to treat muscle spasm and pain associated with acute musculoskeletal (MSK) conditions and spasticity associated with spinal cord injuries and neuron disorders (e.g., cerebral palsy, multiple sclerosis, paraplegia, etc.). Although SMRs are indicated for the short-term treatment of these symptoms/disorders, they are often prescribed for long-term use. Concerns have arisen in the medical literature surrounding the lack of evidence for their long-term use and their potential for serious adverse events and drug interactions.

Summary of Committee Considerations

The DAC considered an external, independent review of the clinical efficacy, safety, and cost-effectiveness of SMRs in the treatment of acute or chronic MSK conditions or traumatic nervous system diseases. The report included systematic reviews of randomized controlled trials (RCTs). Eight systematic reviews evaluating acute low back pain (2), nonprogressive neurologic disease (2), spasticity and MSK conditions (1), sciatica (1), mechanical neck disorders (1), and fibromyalgia (1) were included in the report. The SMRs investigated were baclofen, cyclobenzaprine, dantrolene, methocarbamol, orphenadrine, and tizanidine.

Baclofen is indicated in the treatment of spasticity from multiple sclerosis and spinal cord injury/disease. There is fair to strong evidence that baclofen is effective in alleviating muscle spasm (non-specific back pain) and spasticity (mainly in multiple sclerosis). Although balcofen has only been compared to placebo in lower back pain, head-to-head studies evaluating its use in relief of spasticity suggest that it is equivalent to tizanidine. Long-term efficacy and safety data are lacking. Baclofen's efficacy in other MSK conditions (e.g., non-progressive neurological diseases, spasticity following spinal cord injury, and mechanical neck disorders) remains unproven in rigorous trials of adequate duration. Baclofen is associated with an elevated risk of abuse, central nervous

system (CNS) adverse events, and exacerbation of psychiatric illnesses. Withdrawal reactions can occur upon abrupt discontinuation.

Cyclobenzaprine is indicated for the short-term treatment of muscle spasm associated with acute MSK conditions. Two systematic reviews concluded that there is strong evidence for significant symptomatic relief and overall improvement with short-term cyclobenzaprine use in acute low back pain (ALBP). There is fair to good quality evidence that it is effective in treating acute neck pain compared to placebo. Although fair quality evidence demonstrates improved global functioning and sleep in fibromyalgia patients, no improvement in fatigue or tender points has been observed. Furthermore, these studies are limited by their high drop-out rates and short duration. Cyclobenzaprine has not been evaluated in the treatment of spasticity or spinal cord injuries/diseases. Multiple adverse events have been reported, including cardiac arrhythmias, urinary retention, dry mouth, sedation, and impairment of physical and mental abilities. Additive sedation can occur when taken with other sedating drugs.

Dantrolene is indicated for controlling symptoms of chronic spasticity from neurological conditions. Although there is moderate to good evidence that dantrolene reduces muscle spasm in ALBP compared to placebo, the generalizability of these results is limited by the short duration of the trials (4-10 days). The evidence for the use of dantrolene in the treatment of spasticity associated with MSK conditions is also limited and inconsistent, calling into question its role in the treatment of these conditions. Although there are no well-designed RCTs comparing dantrolene and baclofen, dantrolene appears to be associated with more severe adverse events. Side effects most commonly reported include drowsiness, weakness, malaise, fatigue, and diarrhea. Fatal and nonfatal cases of hepatitis have also been reported. Dantrolene is contraindicated in individuals with a history of compromised pulmonary function. It should also be used with caution in individuals with a history of myocardial disease.

Methocarbamol is indicated as an adjunct in the relief of discomforts associated with acute, painful MSK conditions. There is limited evidence for the use of methocarbamol in muscle spasm or spasticity. Two placebo-controlled trials produced inconsistent results and were rated as being of poor quality. Methocarbamol's efficacy in other MSK conditions has not been investigated in rigorous RCTs. Drowsiness, dizziness, and lightheadedness are the most frequently reported side effects. Blurred vision, headache, fever, and nausea may also occur.

Orphenadrine is indicated in acute skeletal muscle spasm. A systematic review concluded that orphenadrine is effective in the treatment of ALBP. Fair evidence demonstrates that orphenadrine is effective in general acute MSK conditions (e.g., neck pain). Its long-term efficacy and safety have not been established. Orphenadrine's efficacy in other MSK conditions has not been investigated in any rigorous RCTs. The most commonly reported side effects include dry mouth, urinary hesitancy or retention, blurred vision, mydriasis, drowsiness, headache, tachycardia, palpitations, and GI disturbances. Orphenadrine can impair an individual's ability to engage in potentially hazardous activities, such as operating machinery or driving motor vehicles.

Tizanidine is indicated for the management of spasticity. Similarly to cyclobenzaprine and orphenadrine, systematic reviews have demonstrated strong evidence for significant relief and overall short-term improvement in ALBP with tizanidine and fair evidence that it is more effective than placebo in MSK conditions, such as acute neck pain. Cyclobenzaprine has been best studied and has produced the most consistent evidence, however. Although there is fair evidence for the use of tizanidine compared to placebo in the treatment of spasticity (primarily in multiple sclerosis), it appears to be roughly equivalent to baclofen. A single, low quality study failed to demonstrate any difference in overall improvement for tizanidine compared to placebo in the treatment of sciatica. The most frequently reported side effects appear to be dose-related and include dry mouth, somnolence, asthenia, and dizziness. Tizanidine can also produce hypotension and has been associated with reports of QT prolongation. Liver injury has been reported (regular monitoring of aminotransferase levels is recommended).

Rebound can occur upon sudden withdrawal. Reports of abuse and dependence exist, especially with concurrent use of opioids, benzodiazepines, and hypnotics.

Overall, systematic reviews have concluded that most SMR studies have *numerous methodological shortcomings, are of short duration, and provide limited evidence for their efficacy.* Where efficacy has been observed, the magnitude of benefit has generally been modest to moderate. Furthermore, all SMRs are associated with frequent adverse events that may limit their usefulness; many are associated with rare but serious side effects. Cautious use is recommended.

Guidelines were reviewed to establish best practices. In general, the short-term use of SMRs (e.g., cyclobenzaprine) is recommended in the treatment of acute or subacute back pain, when first-and second-line agents (i.e., acetaminophen and nonsteroidal anti-inflammatory drugs, respectively) have failed to produce sufficient relief. Long-term use is not recommended due to lack of evidence and concerns regarding possible CNS side effects and dependence.

The Ontario Drug Benefit Program does not list most SMRs. Diazepam is listed as a psychoactive agent. Dantrolene and baclofen are listed for the treatment of spasticity due to neurological illness (e.g., cerebral palsy, spinal cord injury, etc.).

Based on the published and unpublished evidence, the DAC concluded that there was no compelling evidence demonstrating efficacy or safety for the long-term use of any SMRs. Evidence is available for the short-term use of cyclobenzaprine, orphenadrine, and tizanidine in the treatment of acute MSK conditions and for the use of baclofen and dantrolene in spasticity in neurological illness. However, multiple notable safety concerns exist with tizanidine and dantrolene. Hence, the DAC recommended that: (i) cyclobenzaprine and orphenadrine be listed on the 25WS (initial Musculoskeletal) formulary only; (ii) baclofen be listed on the 03WS (CNS - Brain Injury) formulary only; and (iii) dantrolene, methocarbamol, and tizanidine not be listed on any formularies.

Revised: January 29, 2013