

Drug Class Review on Skeletal Muscle Relaxants



Update #3: Preliminary Scan Report

February 2007

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Roger Chou, MD
Kimberly Peterson, MS

Update report prepared by Tracy Dana, MLS

Oregon Evidence-based Practice Center
Oregon Health & Science University
Mark Helfand, MD, MPH, Director



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OBJECTIVE:

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update:

May 2005 (searches through November 2004)

SCOPE AND KEY QUESTIONS:

The scope of the review and key questions were originally developed and refined by the Oregon Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, pain care specialists, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative efficacy of different muscle relaxants in reducing symptoms and improving functional outcomes in patients with a chronic neurologic condition associated with spasticity, or a chronic or acute musculoskeletal condition with or without muscle spasms?
2. What are the comparative incidence and nature of adverse effects (including addiction and abuse) of different muscle relaxants in patients with a chronic neurologic condition associated with spasticity, or a chronic or acute musculoskeletal condition with or without muscle spasms?
3. Are there subpopulations of patients for which one muscle relaxant is more effective or associated with fewer adverse effects?

Several aspects of the key questions deserve comment:

Population. The population included in this review is adult or pediatric patients with spasticity or a musculoskeletal condition. We defined spasticity as muscle spasms associated with an upper motor neuron syndrome. Musculoskeletal conditions were defined as peripheral conditions resulting in muscle or soft tissue pain or spasms. We included patients with nocturnal leg cramps. We excluded obstetric and dialysis patients. We also excluded patients with restless legs syndrome or nocturnal myoclonus.

Drugs. We included the following oral drugs classified as skeletal muscle relaxants: baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, dantrolene, metaxalone, methocarbamol, orphenadrine, and tizanidine. Benzodiazepenes were not considered primary drugs in this report. However, diazepam, clonazepam, and clorazepate were reviewed when they were compared in head-to-head studies with any of the skeletal muscle relaxants listed above. Other medications used for spasticity but considered to be in another drug class, such as gabapentin (a neuroleptic) and clonidine (an antihypertensive), were also only reviewed when they were directly compared to an included skeletal muscle relaxant. Quinine was only included if it was compared to a skeletal muscle relaxant.

The dose of skeletal muscle relaxants used in trials may affect either the efficacy or adverse event profile. One clinical trial¹ of cyclobenzaprine, for example, found equivalent efficacy at 10 and 20 mg tid, but increased adverse events with the higher dose. A study on dantrolene also found a ‘ceiling’ effect at doses of 200 mg daily, with no increased efficacy but more side effects above that dose.² Most trials titrated skeletal muscle relaxants to the maximum tolerated dose or a pre-specified ceiling dose, but there are no standardized methods of titration and determining target doses.

Outcomes. The main efficacy measures were relief of muscle spasms or pain, functional status, quality of life, withdrawal rates, and adverse effects (including sedation, addiction, and abuse). We excluded non-clinical outcomes such as electromyogram measurements or spring tension measurements. There is no single accepted standard on how to measure the included outcomes. Clinical trials of skeletal muscle relaxants have often used different scales to measure important clinical outcomes such as spasticity, pain, or muscle strength.³ Many trials have used unvalidated or poorly described methods of outcome assessment. Studies that use the same scale often report results differently (for example, mean raw scores after treatment, mean improvement from baseline, or number of patients “improved”). All of these factors make comparisons across trials difficult.

Spasticity is an especially difficult outcome to measure objectively. The most widely used standardized scales to measure spasticity in patients with upper motor neuron syndromes are the Ashworth⁴ and modified Ashworth⁵ scales. In these scales, the assessor tests the resistance to passive movement around a joint and grades it on a scale of 0 (no increase in tone) to 4 (limb rigid in flexion or extension). The modified Ashworth scale adds a “1+” rating between the 1 and 2 ratings of the Ashworth scale. For both of these scales, the scores are usually added for four lower and four upper limb joints, for a total possible score of 0-32, though scoring methods can vary. Some experts have pointed out that resistance to passive movement may measure tone better than it does spasticity and that the Ashworth scale and other ‘objective’ measures of spasticity may not correlate well with patient symptoms or functional ability.⁶ Other areas of uncertainty regard the significance of the 1+ rating in the modified Ashworth scale and how a non-continuous ordinal variable should be statistically analyzed.⁷ An important advantage of the Ashworth scale is that it is a consistent way to measure spasticity or tone across studies, and has been found to have moderate reproducibility.⁷ Other measures of spasticity include the pendulum test, muscle spasm counts, and patient assessment of spasticity severity on a variety of numerical (e.g., 1-3, 1-4, 0-4) or categorical (e.g., none, mild, moderate, severe) scales. The best technique may be to perform both objective and subjective assessments of spasticity, but validated subjective assessment techniques of spasticity are lacking.

Muscle strength is usually assessed with the time-honored British Medical Research Council Scale, which is based on the observation of resistance provided by voluntary muscle activity and used in everyday clinical practice.⁸ An assessor grades each muscle or muscle group

independently on a scale of 0 (no observed muscle activation) to 5 (full strength). This scale was originally devised to test the strength of polio survivors. Data are not available regarding its reliability and validity in assessing spastic and weak patients.

Most studies measure pain using either visual analogue or categorical pain scales. Visual analogue scales (VAS) consist of a line on a piece of paper labeled 0 at one end, indicating no pain, and a maximum number (commonly 100) at the other, indicating excruciating pain. Patients designate their current pain level on the line. An advantage of VAS is that they provide a continuous range of values for relative severity. A disadvantage is that the meaning of a pain score for any individual patient depends on the patient's subjective experience of pain. This poses a challenge in objectively comparing different patients' scores, or even different scores from the same patient. Categorical pain scales, on the other hand, consist of several pain category options from which a patient must choose (e.g., no pain, mild, moderate, or severe). A disadvantage of categorical scales is that patients must choose between categories that may not accurately describe their pain. The best approach may be to utilize both methods.⁹ Pain control (improvement in pain) and pain relief (resolution of pain) are also measured using visual analogue and categorical scales.

Studies can evaluate functional status using either disease-specific or non-specific scales. These scales measure how well an individual functions physically, socially, cognitively, and psychologically. Disease-specific scales tend to be more sensitive to changes in status for that particular condition, but non-specific scales allow for some comparisons of functional status between conditions. The most commonly used disease-specific measure of functional and disability status in patients with multiple sclerosis, for example, is the Kurtzke Extended Disability Status Scale (EDSS).¹⁰ The EDSS measures both disability and impairment, combining the results of a neurological examination and functional assessments of eight domains into an overall score of 0-10 (in increments of 0.5). The overall score of the EDSS is heavily weighted toward ambulation and the inter-rater reliability has been found to be moderate.¹⁰ Disease-specific scales are also available for fibromyalgia,^{11, 12} low back pain, cerebral palsy, and other musculoskeletal and spastic conditions.

Scales that are not disease-specific include the Medical Outcomes Study Short Form-36 (SF-36), Short Form-12 (SF-12), or another multi-question assessment. Another approach to measuring function is to focus on how well the medication helps resolve problems in daily living that patients with spasticity or musculoskeletal conditions commonly face, such as getting enough sleep or staying focused on the job. Some studies also report effects on mood and the preference for one medication over another.

The following adverse events were specifically reviewed: somnolence or fatigue, dizziness, dry mouth, weakness, abuse, and addiction. We also paid special attention to reports of serious hepatic injury.¹³ The subcommittee considered these the most common and potentially troubling adverse events in clinical practice. We recorded rates of these adverse events as well as rates of discontinuation of treatment due to a particular adverse effect. In some studies, only "serious" adverse events or adverse events "thought related to treatment medication" are reported. Many studies do not define these terms. We recorded any information about abuse and addiction, and rates of death and hospitalization when available.

Withdrawal rates. Because of inconsistent reporting of outcomes, withdrawal rates may be a more reliable surrogate measure for either clinical efficacy or adverse events in studies of skeletal muscle relaxants. High withdrawal rates probably indicate some combination of poor tolerability and ineffectiveness. An important subset is *withdrawal due to any adverse event* (those who discontinue specifically because of adverse effects).

Study types. We included controlled clinical trials to evaluate efficacy. The validity of controlled trials depends on how they are designed. Randomized, properly blinded clinical trials are considered the highest level of evidence for assessing efficacy.¹⁴ Clinical trials that are not randomized or blinded or that have other methodologic flaws are less reliable. These are also discussed in our report with references to specific flaws in study design and data analysis.

Trials comparing one skeletal muscle relaxant to another provided direct evidence of comparative efficacy and adverse event rates. Trials comparing skeletal muscle relaxants to other active medications or placebos provided indirect comparative data.

To evaluate adverse event rates, we included clinical trials and large, high-quality observational cohort studies. Clinical trials are often not designed to assess adverse events, and may select patients at low risk for adverse events (in order to minimize dropout rates) or utilize methodology inadequate for assessing adverse events. Observational studies designed to assess adverse event rates may include broader populations, carry out observations over a longer time, utilize higher quality methodologic techniques for assessing adverse events, or examine larger sample sizes. We did not systematically review case reports and case series in which the proportion of patients suffering an adverse event could not be calculated.

METHODS

Literature Search

To identify relevant citations, we searched MEDLINE (December 2004 to January 2007), the Cochrane Central Register of Controlled Trials (through December 2006) and the Cochrane Database of Systematic Reviews (through December 2006). We used terms for included drugs and limiting to English-language trials conducted on humans. We combined terms for spasticity, conditions associated with spasticity, and musculoskeletal disorders with included skeletal muscle relaxants. We searched FDA and Health Canada websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 9.0).

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

We identified 144 potentially relevant citations. Of those, there are 4 new, potentially relevant studies (Appendix A), including one systematic review.

New Drugs

No new drugs were identified.

New Indications

No new indications were identified.

New Safety Alerts

No new MedWatch or Health Canada safety alerts were identified.

REFERENCES

1. Santandrea S, Montrone F, Sarzi-Puttini P, Boccassini L, Caruso I. A double-blind crossover study of two cyclobenzaprine regimens in primary fibromyalgia syndrome. *Journal of International Medical Research*. 1993;21(2):74-80. E
2. Meyler WJ, Bakker H, Kok JJ, Agoston S, Wesseling H. The effect of dantrolene sodium in relation to blood levels in spastic patients after prolonged administration. *Journal of Neurology, Neurosurgery & Psychiatry*. 1981;44(4):334-339.
3. Shakespeare DT, Boggild M, Young C. Anti-spasticity agents for multiple sclerosis.[update of Cochrane Database Syst Rev. 2001;(4):CD001332; PMID: 11687107]. *Cochrane Database of Systematic Reviews*. 2003;4.
4. Ashworth B. Preliminary trial of carisoprodal in multiple sclerosis. *Practitioner*. 1964;192:540-542.
5. Bohannon RW, Smith MB. Inter rater reliability of a modified Ashworth Scale of muscle spasticity. *Physical Therapy*. 1987;67:206-207.
6. Landau WM. Tizanidine and spasticity. *Neurology*. 1995;45(12):2295-2296.
7. Pandyan AD, Johnson GR, Price CI, Curless RH, Barnes MP, Rodgers H. A review of the properties and limitations of the Ashworth and modified Ashworth Scales as measures of spasticity. *Clinical Rehabilitation*. 1999;13(5):373-383.
8. Nance PW. Tizanidine: An alpha2-agonist imidazoline with antispasticity effects. *Today's Therapeutic Trends*. 1997;15(1):11-25.
9. McQuay HJ. Opioid use in chronic pain. *Bandolier*. 2002;<http://www.jr2.ox.ac.uk/bandolier/booth/painpag/wisdom/S31.html>.
10. Sharrack B, Hughes RAC. Clinical scales for multiple sclerosis. *Journal of the Neurological Sciences*. 1996;135:1-9.
11. Simms RW, Felson DT, Goldenberg DL. Development of preliminary criteria for response to treatment in fibromyalgia syndrome. *Journal of Rheumatology*. 1991;18(10):1558-1563.
12. Mannerkorpi K, Ekdahl C. Assessment of functional limitation and disability in patients with fibromyalgia. *Scandinavian Journal of Rheumatology*. 1997;26(1):4-13.
13. Chan CH. Dantrolene sodium and hepatic injury. *Neurology*. 1990;40(9):1427-1432.
14. Anonymous. *Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews CRD Report Number 4 (2nd edition)*. York, UK: NHS Centre for Reviews and Dissemination; 2001. 4 (2nd edition).

Appendix A. Potentially relevant new studies

1. Childers, M. K., D. Borenstein, et al. (2005). "Low-dose cyclobenzaprine versus combination therapy with ibuprofen for acute neck or back pain with muscle spasm: a randomized trial." *Current Medical Research & Opinion* 21(9): 1485-93.

OBJECTIVE: This prospective, randomized, open-label, multicenter, community-based study was conducted to compare cyclobenzaprine 5 mg three times daily (TID) orally (CYC5) given for 7 days as monotherapy or in combination with ibuprofen 400 mg TID (CYC5/IBU400) or 800 mg TID (CYC5/IBU800) in adults with acute neck or back pain with muscle spasm. **STUDY DESIGN:** Eligible patients were 18-65 years old, had cervical or thoracolumbar pain and spasm for ≤ 14 days, and, aside from the prescribed study medications, discontinued treatment with all analgesics, anti-inflammatory agents, and skeletal muscle relaxants during the study period. Randomization was 1:1:1 to the three treatment groups. Treatment outcome was assessed after 3 and 7 days of therapy using five patient-rated scales: spasm, pain, patient global impression of change (PGIC), medication helpfulness, and Oswestry Disability Index (ODI). **RESULTS:** A total of 867 patients provided postbaseline data and were included in the intent-to-treat population (CYC5, $n = 288$; CYC5/IBU400, $n = 286$; CYC5/IBU800, $n = 293$). All three treatment groups demonstrated significant improvements from baseline in PGIC, spasm, pain, ODI, and medication helpfulness ($p < 0.001$ for all comparisons) after 3 and 7 days of therapy. There were no significant differences in mean PGIC among groups after 3 days of therapy ($p = 0.65$ for treatment effect) or after 7 days of therapy (primary endpoint; $p = 0.41$). A PGIC responder analysis of changes from baseline showed that 88% and 93% of patients reported at least mild improvement after 3 and 7 days of therapy, respectively. All three treatments were well tolerated, with no significant differences between treatments regarding the number of adverse events (AEs) reported or number of patients reporting AEs. The most common AEs in all groups were fatigue, somnolence, dizziness, sedation, and nausea. Limitations of this study include an unblinded design and possible introduction of bias into efficacy and safety results by use of a voluntary telephone reporting system. **CONCLUSIONS:** This randomized, community-based clinical trial demonstrated that combination therapy with cyclobenzaprine 5 mg TID plus ibuprofen was not superior to cyclobenzaprine 5 mg TID alone in adult patients with acute neck and back pain with muscle spasm. All treatments were well tolerated.

2. Ketenci, A., E. Ozcan, et al. (2005). "Assessment of efficacy and psychomotor performances of thicolchicoside and tizanidine in patients with acute low back pain." *International Journal of Clinical Practice* 59(7): 764-70.

Objectives of this study were to assess efficacy and effects on psychomotor performances of thicolchicoside (TCC) and tizanidine (TZ) compared to placebo. Patients complaining of acute low back pain (LBP) associated with muscle spasm were enrolled in this randomised, double-blind clinical trial, comparing the effects of oral TCC, TZ and placebo on psychomotor performances assessed by a visual analogue scale of tiredness, drowsiness, dizziness and alertness and by psychometric tests after 2 and 5-7 days of treatment. The efficacy assessments, both TCC and TZ, were more effective than placebo

in improving pain at rest, hand-to-floor distance, Schober test and decreased paracetamol consumption. There were significant differences among the treatment groups in favour of TCC compared to TZ in visual analog scale-parameters. TZ-induced reduction of psychomotor performances of the patients was confirmed by psychometric tests, which showed significant differences among groups. This study showed that TCC is at least as effective as TZ in the treatment of acute LBP, while it appears devoid of any sedative effect in contrast to TZ.

3. Mathew, A., M. C. Mathew, et al. (2005). "The efficacy of diazepam in enhancing motor function in children with spastic cerebral palsy." *Journal of Tropical Pediatrics* 51(2): 109-13.

Muscle spasm and hypertonia limit mobility in children with spastic cerebral palsy. This double-blind, placebo-controlled, randomized controlled clinical trial studies the clinical efficacy of a low dose of diazepam in enhancing movement in children with spastic cerebral palsy. One hundred and eighty children fulfilled the criteria and were randomly allocated to receive one of two doses of diazepam or placebo at bedtime; 173 completed the study. There was a significant reduction of hypertonia, improvement in the range of passive movement, and an increase in spontaneous movement in the children who received diazepam. There was no report of daytime drowsiness. In developing countries, where cost factors often determine choice of drug, diazepam is a cheap and effective way of relieving spasm and stiffness, optimizing physical therapy and facilitating movement in children with spasticity.

- 4.. Taricco, M., M. C. Pagliacci, et al. (2006). "Pharmacological interventions for spasticity following spinal cord injury: results of a Cochrane systematic review." *Europa Medicophysica* 42(1): 5-15.

The aim of this paper was to assess the effectiveness and safety of baclofen, dantrolene, tizanidine and any other drugs for the treatment of long-term spasticity in spinal cord injury (SCI) patients, as well as the effectiveness and safety of different routes of administration of baclofen. A systematic review of randomised controlled trials (RCTs), within the Cochrane Collaboration Injuries Group, was carried out. The Cochrane Injuries Group Specialised Register, the Cochrane Controlled Trials Register, MEDLINE, EMBASE and CINAHL were searched up to July 2006 without language restriction. Drug companies and experts active in the area were also contacted to find other relevant studies. Two investigators independently identified relevant studies, extracted data and assessed methodological quality of studies resolving disagreement by consensus. Nine out of 55 studies met the inclusion criteria. The heterogeneity among studies did not allow quantitative combination of RESULTS: Study designs were: 8 crossover, 1 parallel-group trial. Two studies (14 SCI patients) showed a significant effect of intrathecal baclofen in reducing spasticity (Ashworth score and activities of daily living [ADL] performances), compared to placebo, without any adverse effect. The study comparing tizanidine to placebo (118 SCI patients) showed a significant effect of tizanidine in improving Ashworth score but not in ADL performances. The tizanidine group reported significant rates of adverse effects (drowsiness, xerostomia). For the other drugs (gabapentine, clonidine, diazepam, amytral and oral baclofen) the results do not provide evidence for a clinical significant effectiveness. This systematic review indicates

that there is insufficient evidence to assist clinicians in a rational approach to antispastic treatment for SCI. Further research is urgently needed to improve the scientific basis of patient care. [References: 66]