A Supplement to
Family Practice News

CLINICAL UPDATE

Once-Daily Cyclobenzaprine Extended-Release: A Simple Alternative to Control Muscle Spasm

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Acute musculoskeletal spasm is a common, self-limiting condition manifested clinically as localized pain, tenderness, and diminished mobility.[1] Many terms describe this common condition, including lumbar or cervical "sprain" or "strain" and "mechanical back pain."

Painful low back and neck conditions are commonly associated with muscle spasm.

Back and neck pain are among the symptoms most frequently encountered in clinical practice.[2] Low back pain, for example, affects at least 80% of US adults at some point in their lives, is the world's leading cause of occupational disability, and is the most common cause of work absenteeism.[3,4] Approximately 1% of the population is chronically disabled because of back problems, and another 1% of the population is temporarily disabled.[5] A delay in returning to work results in high treatment costs and compensation.[6] In the United States, the direct, annual cost of back problems is $25 billion; another $50 billion is spent in indirect costs related to lost productivity and disability payments.[4]

Back pain is the leading cause of days out of work and activity limitation.[7]

The cause of back pain is not fully understood. One model proposed to explain the evolution and progression of back pain is the spasm-pain-spasm cycle. According to this theory, an initial event (eg, acute injury) produces a muscle spasm, resulting in pain, causing further muscle spasm, and inducing a self-perpetuating cycle[8] (**Figure 1**).

Symptomatic relief and reduced recovery time are important clinical goals and may hasten a return to functioning and prevent progression to a chronic condition.[6] Many treatment options are used to manage back conditions. These range from nonpharmacological (bed rest, massage therapy, exercise, acupuncture) to pharmacological measures (analgesics, skeletal muscle relaxants [SMRs], steroid injections). Nonpharmacological options are often useful but many lack sound scientific evidence; hence, pharmacotherapy is the most frequently recommended and utilized intervention for painful low back conditions.[9,10]

FIGURE 1. Spasm-Pain-Spasm Cycle

Medications are pivotal in breaking the spasm-pain-spasm cycle and enhancing mobilization, thereby promoting healing and enabling patients to return to normal daily activities.[11,12] Amongst the available pharmacological options (acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], SMRs, opioid analgesics), NSAIDs and SMRs are the most widely prescribed agents for the management of acute back pain.[10,13]

Approximately 35% of patients with low back pain are prescribed muscle relaxants by a primary care provider.[14]

Although palliative pain management (acetaminophen, NSAIDs) may be the initial treatment, relief from low back pain is typically facilitated by alleviation of the underlying muscle spasm.[9] SMRs, a cornerstone in the armamentarium for nonspecific low back pain, encompass a wide range of drugs with different indications and mechanisms of action. Muscle relaxants can be divided into two main categories: antispasmodic and antispasticity medications. Antispasmodics, such as cyclobenzaprine, carisoprodol, and metaxalone, are used to decrease muscle spasm associated with painful conditions such as low back pain. SMRs with antispastic properties are used to reduce

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Faculty Disclosure

Dr Ruoff is on the advisory boards of and has participated in a lecture series for Cephalon, Inc., GlaxoSmithKline, and Takeda Pharmaceuticals North America, Inc. He has conducted research for Abbott Laboratories, Cephalon, Inc., GlaxoSmithKline, Merck & Co., Inc., and Takeda Pharmaceuticals North America, Inc.

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Career Focus

Gary E. Ruoff, MD, received his bachelor of science degree in chemistry and biology from St. Peter's College in New Jersey and obtained his medical degree from Stritch School of Medicine at Loyola University. He is board-certified by the American Board of Family Practice and is an active member of the American Academy of Family Physicians and the Michigan State Medical Society. Dr Ruoff is also board-certified by the National Board for Headache Management.

A Clinical Professor of Family Medicine at Michigan State University College of Human Medicine, Dr Ruoff is in private practice at Westside Family Medical Center in Kalamazoo, Michigan, where he serves as medical director and principal investigator of clinical research. He has expertise in musculoskeletal disorders and headache management and served as an investigator in clinical studies with cyclobenzaprine. Dr Ruoff has published numerous articles based on his research and areas of expertise.

Dr Ruoff holds a membership in several organizations, including the American Medical Association, Michigan State Medical Society, Kalamazoo Academy of Medicine, American Academy of Family Physicians, Michigan Academy of Family Physicians, Southwest Michigan Academy of Family Physicians, American Headache Society, and National Headache Association.

spasticity caused by nerve damage, such as occurs with cerebral palsy, multiple sclerosis, and spinal cord injuries.[15]

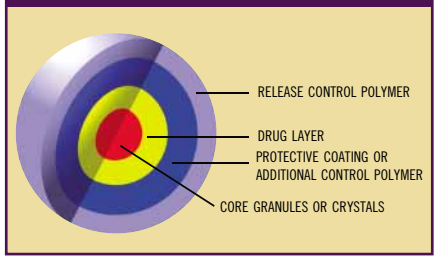
Antispasmodics have been recognized as useful adjuncts to rest and physical therapy in the treatment of muscle spasm associated with acute, painful musculoskeletal conditions. A meta-analysis and a systematic review of randomized clinical studies provide strong evidence that antispasmodics are helpful in treating nonspecific acute low back pain, with most of the benefit seen in the first 1 or 2 weeks of treatment.[16,17] Similarly, current American Pain Society and American College of Physicians practice guidelines present good evidence in support of SMRs for acute relief of low back pain.[18]

Despite their efficacy, the clinical utility of muscle relaxants has been somewhat limited and their role continues to be a source of controversy amongst physicians, mainly because of concerns about tolerability. Cyclobenzaprine, for example, has been commonly associated with sedation, with a reported incidence of 39% in early controlled studies and 16% in a post-marketing surveillance program.[19] Concerns related to abuse liability with prolonged exposure to certain agents (eg, carisoprodol) have also been reported.[9]

Cyclobenzaprine Extended-Release (CER) Capsules

Recently, cyclobenzaprine was made available in an extended-release capsule (*AMRIX*®, Cephalon, Inc., Frazer, PA). Cyclobenzaprine extended-release (CER) is a novel, once-daily SMR employing the Diffucaps® drug delivery technology (Eurand Pharmaceuticals, Inc., Vandalia, OH; **Figure 2**) to provide for a distinct pharmacokinetic profile.[20] The formulation is designed to control the rate of diffusion and subsequent cyclobenzaprine absorption, delivering early systemic exposure while maintaining plasma levels over 24 hours.[21] Most patients take CER 15 mg once daily, with an option to increase up to 30 mg once daily, if necessary.

FIGURE 2. *AMRIX*® Diffucaps® Bead Technology



CER for Acute Muscle Spasm: Evaluating the Evidence

What is the background on the *AMRIX* clinical study program?

The goal behind the development of CER was to provide physicians with a convenient, once-daily treatment alternative for managing muscle spasm associated with acute, painful musculoskeletal conditions.

The primary objectives of the two pivotal studies were to assess the efficacy and tolerability of once-daily CER 15 and 30 mg in patients with muscle spasm associated with acute, painful musculoskeletal conditions.[22]

What were the methodology and patient population for the studies?

The two phase III studies were of identical design and were randomized, double-blind, parallel-group, placebo-controlled, and multicenter in nature. Patients were randomized to one of four treatment arms for 14 days: CER 15 mg once daily, CER 30 mg once daily, cyclobenzaprine immediate-release (CIR) 10 mg three times daily (as a reference drug), or placebo. Patients were instructed to take one capsule between 6 AM and 7 AM, noon and 1 PM, and 6 PM and 7 PM. In the CER groups, the blinded CER capsules were taken as the evening dose (between 6 PM and 7 PM daily).

The patients included in these studies were similar to those in earlier randomized, controlled studies with CIR and other SMRs. Eligible individuals included men and nonpregnant women aged 18 to 75 years with muscle spasm of cervical or lumbar origin associated with local pain, tenderness, limitation of motion, and restrictions in activities of daily living, and a baseline intensity rating of moderate to severe for pain lasting no longer than 7 days.

What were the key outcome measures?

Each study included two primary efficacy assessments recorded at day 4: (1) patient's rating of medication helpfulness, a daily rating of study medication effectiveness, and (2) the physician's clinical global assessment, a composite measure based on the presence of muscle spasm and local pain and limitation in range of motion and activities of daily living.

In addition to the co-primary efficacy measures, secondary efficacy assessments, evaluated at days 4, 8, and 14, included patient-rated relief from local pain due to muscle spasm, global impression of change, restriction of movement, and daytime drowsiness.

Safety and tolerability assessments, including adverse events (AEs), were recorded at each study visit and monitored for 3 weeks after the last dose of study drug.

What were the major efficacy findings?

Primary efficacy measures

In both studies, a higher proportion of patients reported good to excellent ratings for medication helpfulness in both CER groups versus placebo at day 4. Across all ratings, the differences versus placebo were significant in study 1 (30 mg, P=0.007) and study 2 (15 mg, P=0.018). Responses following CIR versus placebo were generally similar to those following CER versus placebo.

Significant improvements in patient's rating of medication helpfulness were observed with CER versus placebo.

There were no statistically significant differences in the distribution of responses at day 4 between CER and placebo groups in either study in the physician's clinical global assessment.

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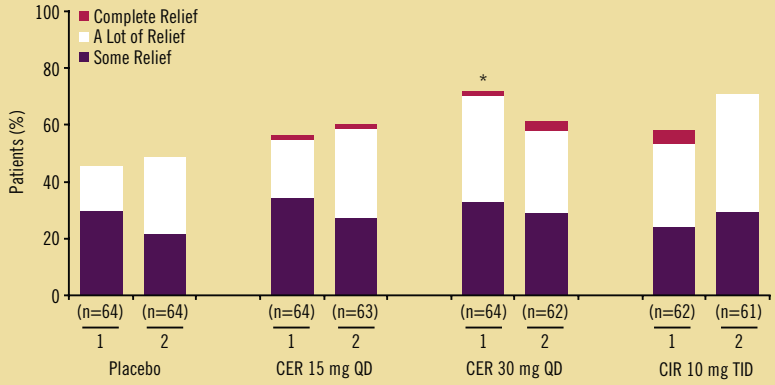
FIGURE 3. Patient's Rating of Relief From Local Pain at Day 4: Studies 1 and 2



*P<0.025 vs placebo.
CER=cyclobenzaprine extended-release; CIR=cyclobenzaprine immediate-release.

Secondary efficacy measures

In study 1, notable improvements with CER 30 mg versus placebo on days 4 and 8 were observed in relief from local pain (day 4, P=0.004; day 8, P=0.010) (**Figure 3**), patient-rated global impression of change (day 4, P=0.008; day 8, P=0.003), and restriction of movement (day 4, P=0.002; day 8, P=0.016). Responses following CIR were generally similar to those following CER for secondary efficacy measures.

CER relieves pain and increases range of motion.

As expected, on day 4, more patients in the CER groups (study 1: 15 mg [48.4%], 30 mg [56.3%]; study 2: 15 mg [42.9%], 30 mg [54.8%]) and CIR group (study 1 [67.7%]; study 2 [68.9%]) reported daytime drowsiness than in the placebo group (study 1 [29.7%]; study 2 [32.8%]). Daytime drowsiness tended to decrease over time and was reported more frequently in the CIR 10 mg three times daily group than in both CER groups at most time points during the study.

What was the observed tolerability profile of CER?

The majority (93%) of AEs in these studies were mild or moderate in intensity. Dry mouth was most frequently reported, with an occurrence of approximately 8.5% in each study (combined incidence for all groups). In both studies, more AEs were reported in the active treatment groups versus placebo. Notably, somnolence occurred more frequently with CIR.

In both studies, more patients discontinued due to AEs with CIR, followed by CER 30 mg, placebo, and CER 15 mg. The most common AE resulting in discontinuation was somnolence (**Figure 4**).

"The most striking finding by far in these studies was the somnolence data; the highest rates were seen in the CIR group. Rates were lower in the CER 30 mg group and were equivalent to placebo in the CER 15 mg group."
– *G. Ruoff, MD*

Fewer patients receiving CER reported AEs or required discontinuation of study medication compared with CIR.

Two serious AEs were reported in study 2: one report of cellulitis (CER 30 mg; considered by the investigator to be unrelated to treatment) and one report of atrial fibrillation (placebo).

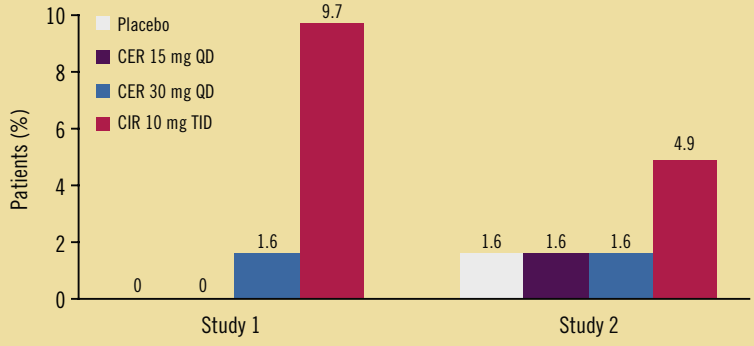
What are the strengths and limitations of these studies?

The phase III clinical studies with CER were robust in design, and the patient population reflected those most likely to utilize and benefit from CER in the general population. The CER dosage strengths were equivalent to the recommended daily dosage of the immediate-release formulation. As anticipated, the efficacy findings observed in these studies of once-daily CER were generally consistent with findings from previous randomized controlled studies of CIR versus placebo.[1,23-31] These earlier studies reported the superiority of CIR treatment versus placebo, as reflected in several assessments, including relief of acute local pain/tenderness, muscle spasm, medication helpfulness, and global improvement.

In the clinical studies, two sources of somnolence data provided for a more complete tolerability picture of CER. Daytime drowsiness was assessed as a daily diary-based secondary efficacy measure, whereas somnolence was assessed as a spontaneously reported AE. Together, they may be regarded as part of the same constellation of AEs, because both are common complaints of patients treated with cyclobenzaprine that may lead to lack of adherence to or discontinuation of therapy.[17,19] Fewer patients treated with CER versus CIR reported somnolence or withdrew from the study because of somnolence. Different effects of CER versus CIR were also apparent on daytime drowsiness (although no formal statistical comparisons were made).

As with any controlled study, important limitations should be considered. Muscle spasm is poorly defined and pain is inherently subjective. Some outcome measures may not have been sensitive enough to detect differences between CER and placebo (eg, physician's clinical global assessment). The majority of outcome measures were based on self-reports, making them subject to recall bias. The clinical studies were not powered to detect differences among active treatments. NSAIDs, topical over-the-counter

FIGURE 4. Incidence of Treatment-Emergent Somnolence



CER=cyclobenzaprine extended-release; CIR=cyclobenzaprine immediate-release.

medications, and physical therapy were allowed as add-on rescue therapy. The studies did not control for consumption, dose, contribution to efficacy, or AEs of concomitant analgesics; therefore, the influence of these agents on the study outcomes is unclear.

What are the important clinical implications of these studies?

As evidenced by the reports of increased improvement across several efficacy measures, CER was more efficacious than placebo and showed similar results to those of CIR for the treatment of muscle spasm associated with acute, painful musculoskeletal conditions. These results suggest that the efficacy of cyclobenzaprine, traditionally dosed up to three times daily, can be achieved through once-daily dosing with CER. CER was generally well tolerated. Rates of somnolence, a clinically important AE, were lower for CER than for CIR.

Family practitioners and general internists play an integral role in the evaluation and treatment of acute and chronic low back pain.[32] Given the typical time constraints primary care physicians have when they evaluate patients, it is imperative that they be well versed in the appropriate management of acute musculoskeletal conditions and the available treatment options. A multimodal treatment approach with pharmacotherapy has been shown to reduce time to recovery and may prevent progression to a chronic, more costly long-term condition.[33] The therapeutic benefit of many effective medications, including CER, can best be achieved when physicians and their patients adhere to the prescribed treatment regimens (as outlined in the prescribing information).[34]

"The full therapeutic benefit can best be realized by adherence to the dosage schedule; therefore, patients may be more compliant with a once-a-day treatment rather than three times per day."

– G. Ruoff, MD

The simple dosing regimen and low rates of somnolence afforded by CER may improve patients' adherence to therapy and thus optimize efficacy in clinical practice.[34]

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