A SUPPLEMENT TO
Clinician Reviews

Once-Daily Cyclobenzaprine Extended-Release for Acute Muscle Spasm

Expanding Pain Management Options for Clinicians and Patients

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Back and neck pain are among the most common reasons patients visit their health care provider.[1-3] At some point during their lifetime, up to 85% of adults will experience back pain[4] and about 67% will experience neck pain.[5] The burden of such pain can be great. Low back pain is a leading cause of physical disability among adults[6] and accounts for an estimated $190 billion in direct medical costs annually.[7]

How these patients are managed varies considerably from provider to provider. An understanding of the various options available, especially the science behind them, may lead to more thoughtful treatment selections. The choice of treatment path is important because it can greatly affect a patient's quality of life.

The presence of nonphysician providers has increased tremendously over the years, making it likely that individuals with back pain will be treated by a nonphysician provider.[8] A recent survey of more than 13,500 nurse practitioners reported that back and neck pain were among the 15 most common health problems they encounter in their practice.[9]

This review seeks to expand physician assistants' and nurse practitioners' understanding of the treatment options available for acute back and neck pain.

MUSCLE SPASM

Muscle spasm is a sudden, painful, and involuntary contraction of muscles that may accompany back and neck pain. An acute event, such as tissue injury, can cause muscle spasm, which results in pain and more

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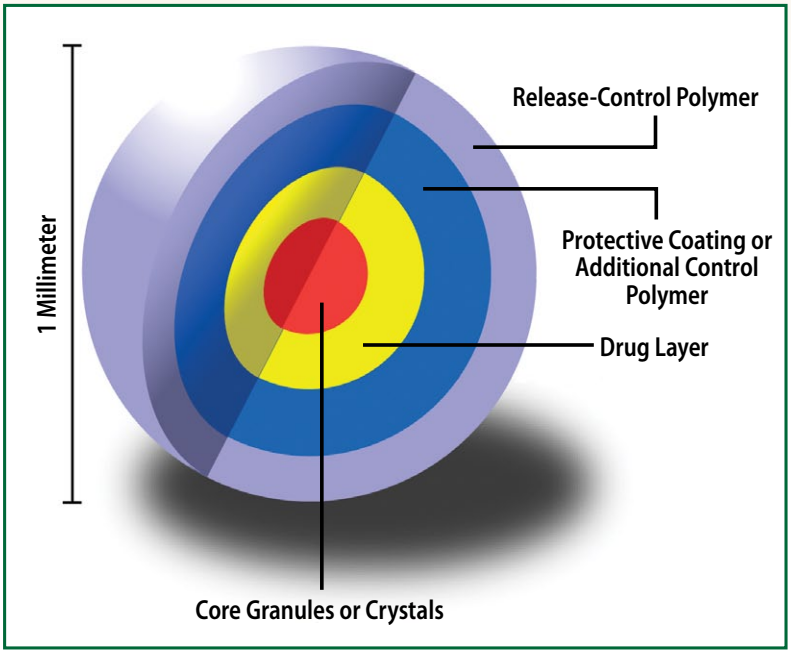
FIGURE 1
Cyclobenzaprine Extended-Release Diffucaps Bead Technology



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muscle spasm, creating a self-perpetuating spasm-pain-spasm cycle.[10] Prompt interruption of this cycle is important because prolonged pain and its sequelae may reduce an individual's ability to function and maintain work productivity.[11]

The development of controlled-release formulations of medications with established efficacy and safety profiles has increased the treatment options available in multiple therapeutic areas. Modifying the technology used to deliver an established medication can substantially alter clinical outcomes. A drug delivery modification that allows once-daily dosing may improve tolerability and patient adherence compared with immediate-release (IR) formulations that are administered multiple times per day.[12-15] Improved adherence may lead to fewer office visits, lower health care costs, and better outcomes.[16-18] This review outlines the unique properties of one treatment option, an extended-release (ER) formulation of cyclobenzaprine, for acute, painful muscle spasm.

TREATMENT OF MUSCLE SPASM

The goals of treating acute, painful muscle spasm are to relieve symptoms and allow patients to return to their normal activities.[19-21] Numerous treatment options are available for the management of back pain. Analgesics, such as acetaminophen and NSAIDs, are often recommended as first-line agents for managing low back pain.[10,22]

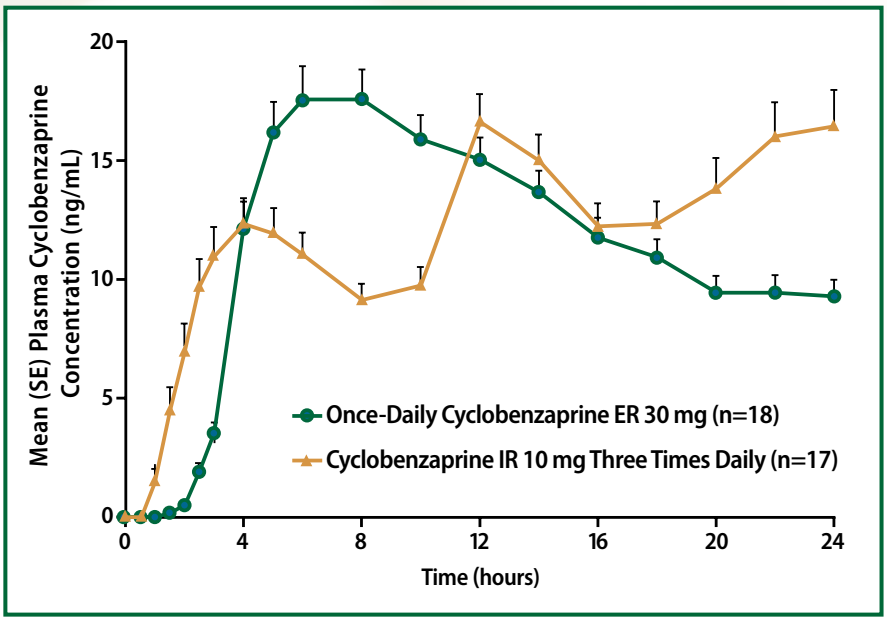
Skeletal muscle relaxants and opioids are also prescribed for back pain.[3,23] These medications can be effective in breaking the spasm-pain-spasm cycle, potentially reducing recovery time, improving physical functioning, and shortening rehabilitation time.[24]

Nonpharmacologic options include heat application, exercise therapy, acupuncture, and massage therapy.[25] While these therapies are commonly used for the management of acute low back pain, evidence supporting their effectiveness is limited.[25]

Some patients may require treatment with skeletal muscle relaxants, alone or in combination with analgesics, to alleviate muscle spasm associated with acute back pain.[26] The skeletal muscle relaxants are a group of structurally unrelated medications that are divided into two categories: (1) *antispasticity agents*, which treat muscle spasticity caused by traumatic neurologic injury, multiple sclerosis, and other conditions, and (2) *antispasmodic agents*, which treat muscular pain or spasm associated with acute, nonspecific musculoskeletal conditions.[27] Cyclobenzaprine is an antispasmodic agent. Skeletal muscle relaxants with antispasmodic properties are thought to relieve acute low back pain by alleviating the underlying muscle spasm.[10] The efficacy of these agents has been shown in controlled clinical studies; however, they are associated with adverse effects, principally somnolence.[22,28]

Cyclobenzaprine is commonly used as an adjunct to rest and physical therapy for the relief of muscle spasm associated with acute, painful musculoskeletal conditions (reviewed in Borenstein and Korn,[21] Browning et al,[29] and Katz and Dube[30]). Cyclobenzaprine IR has been widely studied and its efficacy is well established.[31-39] However, when administered three times daily as indicated, cyclobenzaprine IR is often associated with sedation.[21,29,30] Because of concerns about daytime drowsiness, some prescribers may instruct patients to take

FIGURE 2
Mean (SE) Plasma Cyclobenzaprine Concentration Through 24 Hours in Healthy Young Adults[42]



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cyclobenzaprine IR at bedtime only[40] and not three times daily as indicated. Deviating from the approved dosing regimen may lessen the effectiveness of treatment,[41] resulting in inadequate relief of muscle spasm throughout the day.[21]

CYCLOBENZAPRINE EXTENDED-RELEASE CAPSULE

The cyclobenzaprine ER capsule (*AMRIX*®, Cephalon, Inc., Frazer, PA) was introduced in 2007 for the relief of muscle spasm associated with acute, painful musculoskeletal conditions. This formulation was developed to maximize the clinical benefit of cyclobenzaprine and increase tolerability. Cyclobenzaprine ER employs Diffucaps® drug delivery technology (Eurand, Inc., Vandalia, OH), allowing for once-daily dosing.[42,43] It is the only once-daily skeletal muscle relaxant currently available. The Diffucaps beads contained in each capsule consist of an inert (sugar) core in the center surrounded by a layer of active drug (cyclobenzaprine), a protective coating, and a polymer membrane that controls the rate of cyclobenzaprine release[42-44] (see Figure 1). Each bead measures 1 mm or less in diameter. The capsules are filled with enough beads to provide a 15- or 30-mg dose of cyclobenzaprine.

The Diffucaps technology employed in cyclobenzaprine ER results in a distinct pharmacokinetic profile.[42] The formulation delivers early systemic exposure to cyclobenzaprine, with a plasma concentration at 4 hours that is similar to that observed with cyclobenzaprine IR (see Figure 2).[42] In contrast to the fluctuating peaks and troughs in plasma cyclobenzaprine concentration after administration of the IR formulation three times daily, plasma cyclobenzaprine concentration with the ER formulation is sustained over 24 hours following the administration of a single dose.[42]

CLINICAL STUDIES

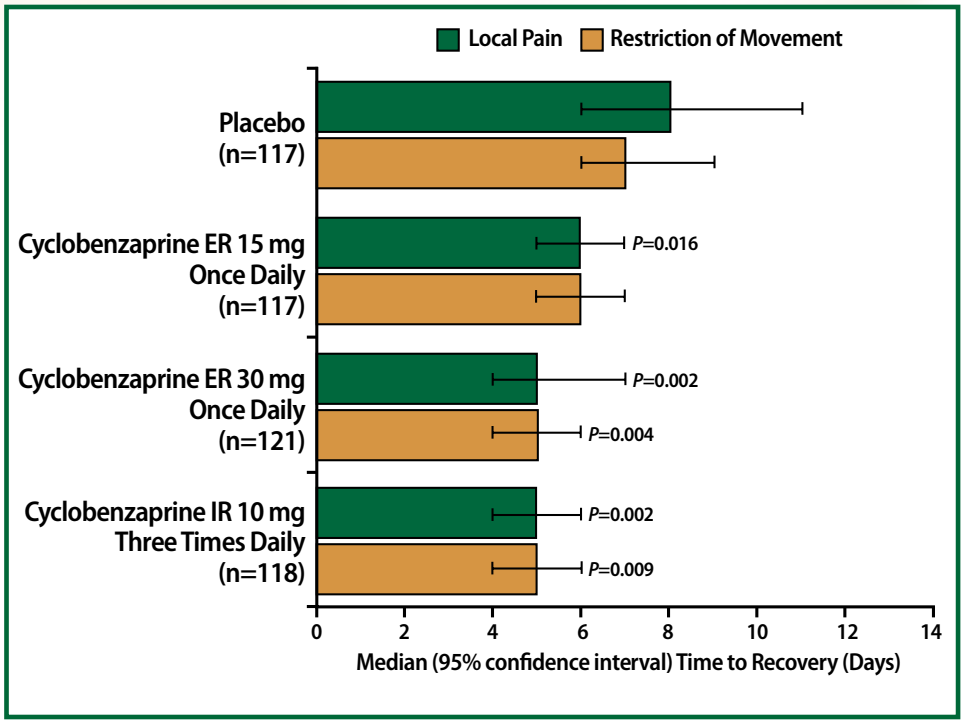
The efficacy and tolerability of once-daily cyclobenzaprine ER 15 and 30 mg were evaluated in two identically designed, randomized, double-blind, parallel-group, placebo-controlled studies with an active comparator arm.[45] Eligible patients were men and nonpregnant women ages 18 to 75 with moderate to severe muscle spasm of cervical or lumbar origin associated with local pain, tenderness, limitation of motion, and restrictions in activities of daily living. Spasm could not be present for more than 7 days before study entry.

Patients were randomly assigned to one of four treatment arms for 14 days: cyclobenzaprine ER 15 or 30 mg once daily, cyclobenzaprine IR 10 mg three times daily, or placebo. All were blinded to the treatment and instructed to take one dose between 6 AM and 7 AM, one between 12 PM and 1 PM, and one between 6 PM and 7 PM each day. The blinded cyclobenzaprine ER capsule was taken as the evening dose.[45]

The primary efficacy measures were patient's rating of medication helpfulness and physician's clinical global assessment at day 4.[45] In both studies, the cyclobenzaprine ER and IR formulations were more effective than placebo in reducing muscle spasm and associated symptoms, as reflected in patients' ratings of medication helpfulness at day 4 and other secondary efficacy measures, such as patient-rated relief from local pain due to muscle spasm and relief from restriction of movement.[45] No statistically significant differences were noted in the distribution of responses across groups in the physician's clinical global assessment.

FIGURE 3

Time to Recovery Based on Patients' Ratings of "A Lot" or "Complete" Relief From Local Pain and Relief From Restriction of Movement[46]



Data extracted from: Landy S, Altman CA, Xie F. Time to recovery in patients with acute painful musculoskeletal conditions treated with extended-release or immediate-release cyclobenzaprine (Figure 2). *Advances in Therapy*© 2011. Reprinted with kind permission from Springer Science+Business Media B.V.[46]

A more detailed assessment of the efficacy outcomes in the two studies was conducted in a post hoc pooled analysis.[46] Time to recovery, defined as the median number of days from the start of the study to patients' first ratings of "a lot" or "complete" relief from local pain or restriction of movement, was calculated for patients who received cyclobenzaprine ER, cyclobenzaprine IR, or placebo. Patients recorded their assessments in a diary each day during the studies. Overall, the median time to recovery was approximately 2 days shorter with the active treatments than with placebo. The median time to patients' first ratings of "a lot" or "complete" relief from local pain was significantly shorter ($P < .025$) with cyclobenzaprine ER 15 mg (6 days), ER 30 mg (5 days), and IR (5 days) compared with placebo (8 days; see Figure 3).[46] The median time to patients' first ratings of "a lot" or "complete" relief from restriction of movement was also significantly shorter ($P < .025$) with cyclobenzaprine ER 30 mg (5 days) and IR (5 days) than with placebo (7 days; see Figure 3).[46]

An earlier analysis of the pooled data from these two studies showed that significantly fewer patients reported some to extreme daytime drowsiness with cyclobenzaprine ER (15-mg capsule, 45.7%; 30-mg capsule, 55.6%) compared with cyclobenzaprine IR (68.3%; $P < .05$; see table, next page).[47]

SAFETY AND TOLERABILITY

Both formulations of cyclobenzaprine were generally well tolerated in the two studies.[47] The majority of adverse events were mild to moderate in intensity. The overall incidence of adverse events was highest with cyclobenzaprine IR (48.8%), followed by cyclobenzaprine ER 30 mg (39.7%) and 15 mg (38.6%), and placebo (28.1%). Dry mouth was the most frequently reported adverse event, occurring in 5.5% of the ER 15-mg group, 13.5% of the ER 30-mg group, 13.8% of the IR group, and 1.6% of the placebo group.

The most common adverse event leading to discontinuation was somnolence (cyclobenzaprine IR, eight patients; cyclobenzaprine ER 30 mg, two patients).[47] A significantly greater proportion of patients who received cyclobenzaprine IR (7.3%) reported somnolence compared with patients who received cyclobenzaprine ER 15 mg (0.8%) and 30 mg (1.6%; $P < .05$ for each dose of ER versus IR; see table).[47]

Two serious adverse events were reported to have occurred after the end of treatment: One patient taking placebo experienced atrial fibrillation, and one taking cyclobenzaprine ER 30 mg experienced cellulitis, which the investigator considered to be unrelated to study medication.[47]

CONCLUSION

The application of Diffucaps technology used in cyclobenzaprine ER has made it possible to develop a formulation

TABLE

Daytime Drowsiness at Day 4 and Somnolence Throughout the Study[47]

Parameter	Cyclobenzaprine			Placebo
	ER 15 mg n=127	ER 30 mg n=126	IR 10 mg n=123	n=128
Daytime drowsiness, n (%)*†				
Some to extreme	58 (45.7)	70 (55.6)	84 (68.3)	40 (31.3)
None to very little	59 (46.5)	51 (40.5)	34 (27.6)	76 (59.4)
Missing	10 (7.9)	5 (4.0)	5 (4.1)	12 (9.4)
Somnolence, n (%)†	1 (0.8)	2 (1.6)	9 (7.3)	0

*$P < .025$ for cyclobenzaprine ER 15 and 30 mg versus placebo.

†$P < .05$ for cyclobenzaprine ER 15 and 30 mg versus cyclobenzaprine IR.
Abbreviations: ER, extended release; IR, immediate release.

Data extracted from: Weil et al. *Postgrad Med.* 2010.[47]

that results in more consistent cyclobenzaprine plasma levels over 24 hours, which in turn allows once-daily administration. In clinical studies, the efficacy of once-daily cyclobenzaprine ER and cyclobenzaprine IR administered three times daily was similar, but patients who received the ER formulation reported less somnolence than those who received the IR formulation.

PERSPECTIVE

Cyclobenzaprine is a widely prescribed medication with a long history of efficacy and safety, but there are barriers to its use. The Diffucaps technology used in cyclobenzaprine ER may help patients and health care providers overcome some of these barriers.

Back and neck pain can have a substantial socioeconomic impact on society and are common reasons patients seek care from health care providers. As part of a treatment plan, a once-daily regimen with cyclobenzaprine ER may offer less sedation and a simplified dosing regimen compared with the three-times-daily dosing of the IR formulation. More comprehensive understanding of the available treatment options will lead to more individualized treatment selection and improved patient outcomes.

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Disclaimer

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