



Cyclobenzaprine extended release for acute low back and neck pain

Low back and neck pain are common clinical complaints that have a substantial social impact and incur considerable direct and indirect costs. Skeletal muscle relaxants (SMRs) are one of a number of therapy options for patients with these conditions. SMRs are effective in relieving acute muscle spasm associated with nonspecific low back or neck pain; however, patient acceptability of SMRs is reduced by frequent dosing (three- to four-times daily) and the occurrence of somnolence and sedation. Cyclobenzaprine immediate release is an SMR that has consistently been shown to be significantly more effective than placebo in the treatment of low back and neck pain. Cyclobenzaprine extended release, approved by the US FDA in February 2007, is a once-daily SMR that retains the clinical efficacy of the immediate-release formulation, but has a reduced frequency of the adverse events of daytime sleepiness and dizziness versus the immediate-release formulation.

KEYWORDS: central muscle relaxants ■ cyclobenzaprine ■ low back pain ■ neck pain ■ neuromuscular agents

Low back pain and neck pain are major public health problems in the USA [1]. In a 3-month prevalence study conducted across the USA, more than 34 million (17%) adults reported low back pain alone, 9 million (4%) reported neck pain alone and 19 million (9%) reported both low back pain and neck pain, resulting in a 3-month combined prevalence of 31% of adults [1]. Studies conducted elsewhere report similar prevalence estimates [2], and it is estimated that approximately 70% of all adults will experience back or neck pain at some point in their lives [1]. Low back pain and neck pain cause discomfort and disability, affecting an individual's capacity to perform routine daily activities and imposing work limitations.

The cost of low back and neck pain is considerable. Studies conducted in the 1990s give estimates of direct costs in the USA ranging from US\$12.2 billion to US\$90.6 billion [3]. The most recent study of direct medical costs in the USA estimated that the incremental cost of spinal problems per patient in 2005 was US\$2580 (95% confidence interval [CI]: US\$2404–2757), giving a total direct cost of US\$85.9 billion (95% CI: US\$80.1–91.8 billion) [4]. Indirect costs in the USA have been estimated as being between US\$7.4 billion (the most recent estimate in 2004) and US\$28.2 billion (in 1996) [3].

Diagnosis of low back & neck pain

Low back and neck pain are generally classified into acute, subacute and chronic pain [5–7]. The

American College of Physicians defines acute and subacute low back pain as pain present for less than 4 weeks and for less than 3 months, respectively [5]. In European guidelines, acute low back pain describes pain that continues for less than 6 weeks, with the term subacute used to describe pain persisting for between 6 weeks and 12 weeks [6,7]. Chronic low back and neck pain persist for longer than 3 months or occur episodically within a 6-month period [5–7]. de Vet *et al.* defined an episode of low back pain as pain in the lower back for more than 24 h, preceded and followed by a period of 1 month or more without low back pain. An episode of care for back pain was defined as a consultation or consultations for low back pain preceded and followed by at least 3 months without a consultation for the same condition. Work absence was defined as a period of work absence due to low back pain, preceded and followed by a period of 1 day or more at work [8].

There are a number of reasons why patients may present with low back pain, and it is important that serious underlying pathologies are investigated and addressed [5,7]. There has been international acceptance of the concept of the 'diagnostic triage', in which low back pain is divided into three categories: nonspecific low back pain, back pain potentially associated with radiculopathy or nerve root compression and back pain associated with serious spinal pathology [5,7]. Different clinical practice guidelines recommend slightly different ways by which

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physicians should assign the most likely cause of back pain, but there is general consensus that a history should be taken and a physical examination performed [7]. The history should allow for the identification of 'red flags' for serious pathologies, such as previous significant trauma, thoracic pain, unexplained weight loss and widespread neurological problems. A physical examination should include straight leg raises in order to identify nerve root pain [7].

It is estimated that 85% of patients with low back and neck pain can be classified as having nonspecific back pain [9]. This review will focus on the pharmacology and efficacy of cyclobenzaprine extended release (ER) in the treatment of nonspecific low back and neck pain.

Overview of the market

A number of clinical practice guidelines provide recommendations for the treatment of acute low back and neck pain [5,7,10–12]. There is variation in the recommendations with regard to which treatments to explore, in what order to try them and for how long agents should

be used [7]. However, there is agreement that patients should be advised to remain active and return to work if possible. If necessary, patients should consider the use of analgesics to aid their return to physical activity, with the majority of guidelines suggesting acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line agents for most patients [7]. Possible second-line agents are the skeletal muscle relaxants (SMRs), a heterogeneous group of agents recommended in many, but not all, of the current clinical practice guidelines [13]. These agents are recommended in the current US and European guidelines for short-course use if treatment with acetaminophen or NSAIDs has been unsuccessful [5,7].

A number of different SMRs are approved in both the USA and Europe for the treatment of muscle spasm (TABLE 1). A Cochrane review of the effect of SMRs as a group suggests that they are more effective than placebo in the treatment of nonspecific low back pain (pooled relative risk [RR] vs placebo for nonbenzodiazepine muscle relaxants 0.80 [95% CI: 0.71–0.89] for pain

Table 1. Muscle relaxants used to treat skeletal muscle spasm.

Agent	Description	Dosing	Ref.
Carisoprodol	Propanediol Metabolized to active form of meprobamate Centrally acting (binds to γ -aminobutyric acid receptors)	250 and 350 mg Three-times daily and at bedtime	[31]
Chlorzoxazone	Centrally acting, derived from benzoxalone	500 mg Three- to four-times daily	[14,32]
Cyclobenzaprine	Closely related to the first-generation tricyclic antidepressants amitriptyline and imipramine Centrally acting	10 mg Three-times daily	[18,25]
Metaxalone	Oxazolidinone Possibly a CNS depressant	800 mg Three- to four-times daily	[33]
Methocarbamol	Related structurally to mephenesin	500 mg Three tablets three- to four-times daily 750 mg Two tablets three- to four-times daily	[34]
Orphenadrine citrate	Derived from the antihistamine diphenhydramine	25 mg (often combined with aspirin and caffeine) One or two tablets three- to four-times daily	[14,35]

relief and 0.49 [95% CI: 0.25–0.95] for global efficacy) [13]. A comparative systematic review found no evidence that a particular SMR had significantly better efficacy than any other SMR for the treatment of musculoskeletal conditions [14]. This presents a difficulty to physicians because there is a lack of high-quality efficacy evidence to guide them in choosing an initial muscle relaxant therapy [14], and current US and European guidelines do not recommend the use of a specific SMR [5,7].

SMRs are generally well-tolerated, but sedation, dizziness and somnolence are frequently observed with the current available agents [15]. For nonbenzodiazepine SMRs versus placebo after 2–4 days of treatment, the pooled RR for all adverse events (AEs) is 1.50 (95% CI: 1.14–1.98) and for CNS AEs it is 2.04 (95% CI: 1.23–3.37), indicating that AEs are significantly more likely in patients taking SMRs than in patients taking placebo [13]. These AEs may interfere with the patient's daily activities to a great enough extent to cause them to discontinue treatment [14]. In addition, certain SMRs have been linked with psychological dependence [14]. These factors may discourage physicians from prescribing such agents. Concerns about AEs and psychological dependence are cited as reasons for the lack of recommendation in those guidelines that do not advocate the use of SMRs [7,13]. In addition, most currently available muscle relaxants need to be taken three- to four-times daily, which may raise concerns about treatment compliance [16].

The unmet needs for muscle relaxant treatment are for less frequent dosing, better tolerability through reduced sedation and a low risk of psychological dependence. Attention to these unmet needs may make muscle relaxant therapy more acceptable to patients and improve compliance with treatment as prescribed.

Introduction to cyclobenzaprine extended-release

Cyclobenzaprine was initially developed as an immediate release (IR) formulation that was first approved for the treatment of muscle spasm in low back and neck pain in 1977 [17]. Cyclobenzaprine ER (Amrix®, Cephalon, Inc., PA, USA) was approved by the US FDA on February 1, 2007, as an adjunct to rest and physical therapy for the relief of muscle spasm. The ER formulation was developed to provide a convenient, once-daily (q.d.) dosing alternative with a unique pharmacokinetic profile.

Chemistry

Cyclobenzaprine is a tricyclic chemical analog of amitriptyline. It is designated chemically as 3-(5*H*-dibenzo[*a,d*]cyclohepten-5-ylidene)-*N,N*-dimethyl-1-propanamine hydrochloride (FIGURE 1).

Pharmacodynamics

The exact mechanism of action of cyclobenzaprine is not fully understood. The drug does not operate at the level of the neuromuscular junction and has no direct effect on skeletal muscle. Animal studies suggest that cyclobenzaprine operates primarily at the level of the brain stem, with some possible overlapping effect at the level of the spinal cord [18]. The overall effect of cyclobenzaprine is to reduce α and γ motor pathway activity, which is probably responsible for the muscle relaxant action of the drug [15]. Cyclobenzaprine may be an antagonist of 5-hydroxytryptamine type 2 receptors, and consequently inhibition may be via serotonergic (rather than noradrenergic) descending neurons [17].

Pharmacokinetics & metabolism

Cyclobenzaprine is typically eliminated slowly from the body (elimination half-life ~32 h) [19]. This might suggest that cyclobenzaprine IR would be ideal for infrequent dosing; however, to avoid AEs – such as somnolence and sedation – that are associated with high peak plasma concentrations, cyclobenzaprine IR is typically administered as 10 mg, three-times daily (t.i.d.) [17,19]. An ER formulation was therefore developed in order to reduce the dosing frequency while maintaining effective and well-tolerated plasma concentrations of cyclobenzaprine. The suggested starting dose for cyclobenzaprine ER is 15 mg q.d. with a maximum dose of 30 mg q.d. It is recommended that treatment is limited to 2–3 weeks [18].

The median time (T_{max}) to maximum plasma concentration (C_{max}) with 30 mg cyclobenzaprine ER was 6–8 h in healthy adults compared with

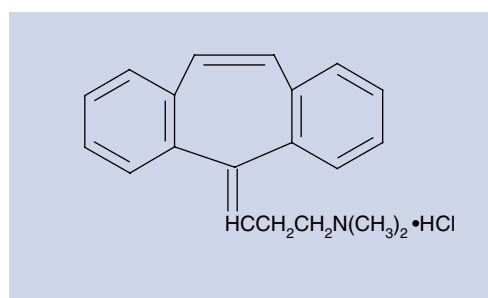


Figure 1. Cyclobenzaprine.

an initial peak at 4 h for 10 mg t.i.d. cyclobenzaprine IR (after the administration of the first daily tablet). The T_{max} for cyclobenzaprine IR t.i.d. was 12 h (FIGURE 2) [19]. The plasma concentrations of cyclobenzaprine ER and IR were similar at 4 h, suggesting no delay in drug delivery with the ER versus the IR formulation [19]. A simulation of the pharmacokinetics of 15 mg cyclobenzaprine ER suggests that a steady-state plasma concentration is achieved by day 7 of treatment. At day 4 of treatment plasma concentrations are approximately 90% of the steady-state level [20].

Total systemic exposure to 30 mg q.d. cyclobenzaprine ER was similar to that of 10 mg t.i.d. cyclobenzaprine IR. The area under the plasma concentration–time curve up to 168 h (AUC_{0-168h}) or up to infinity ($AUC_{0-\infty}$) were 805.4 ng·h/ml, and 837.4 ng·h/ml, respectively, for cyclobenzaprine IR and 715.1 ng·h/ml, and 751.2 ng·h/ml, respectively, for cyclobenzaprine ER. The elimination half-lives of the IR and ER formulations were similar at 30.4 and 32.4 h, respectively [19]. The drug is extensively protein bound in plasma [21]. Plasma clearance is 0.7 l/min following a single dose of cyclobenzaprine ER [18].

Cyclobenzaprine ER is available at two different doses: 15 and 30 mg. A pharmacokinetic comparison of 30 mg q.d. and 15 mg q.d. cyclobenzaprine ER in healthy adults found that the AUC and C_{max} parameters for a single 30 mg dose were approximately double those observed in individuals who received a single 15 mg dose ($AUC_{0-\infty}$: 15 mg q.d. 354.1 ng·h/ml, 30 mg 779.9 ng·h/ml; C_{max} : 15 mg 8.3 ng/ml, 30 mg 19.9 ng/ml). The median T_{max} for both doses was 6 h and the half-lives were similar (15 mg 33.4 h; 30 mg 32.0 h). This suggests that the pharmacokinetics of the ER formulation scales up and down predictably, and is consistent with the known dose proportionality of cyclobenzaprine IR [22].

The effects of food on the pharmacokinetics of cyclobenzaprine ER have been investigated [23]. In the fed state, the AUC increased by approximately 20% and the C_{max} by 36% compared with the fasted values. The ratio of C_{max} in the fed state to that in the fasted state was outside the predefined limit for a food effect. It was thus concluded that a food effect should be assumed for the pharmacokinetics of cyclobenzaprine ER. However, no appreciable differences were noted in the absorption lag time,

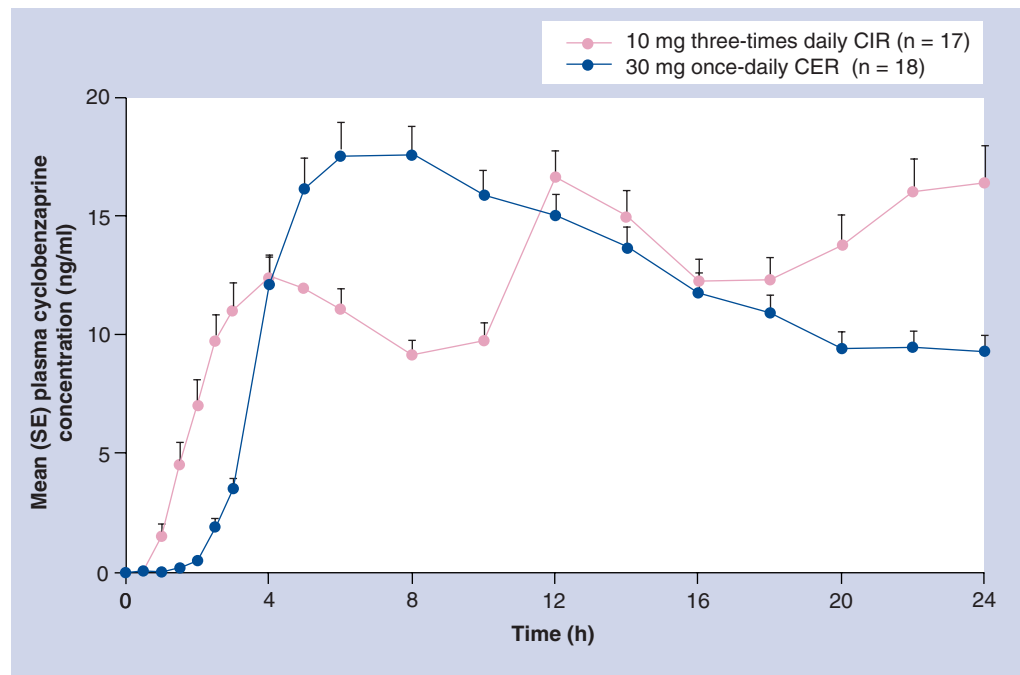


Figure 2. Plasma concentrations of cyclobenzaprine over 24 h after treatment with three doses of 10 mg cyclobenzaprine immediate release or a single dose of 30 mg cyclobenzaprine extended release in individuals aged 18–45 years.

CER: Cyclobenzaprine extended release CIR: Cyclobenzaprine immediate release; SE: Standard error. Figure reproduced with permission from Darwish M, Hellriegel ET, Xie F: Single-dose pharmacokinetics of once-daily cyclobenzaprine extended release 30 mg versus cyclobenzaprine immediate release 10 mg three times daily in healthy young adults: a randomized, open-label, two-period crossover, single-centre study. *Clin. Drug Investig.* 28(12), 793–801 (2008) [19].

T_{max} or elimination half-life, and the shape of the mean plasma cyclobenzaprine concentration–time curve was similar for the fed and fasted states. Furthermore, the tolerability of the drug in fed and fasted volunteers was similar. These results suggest that dose adjustment because of food intake is not necessary [23].

In healthy older volunteers (aged 65–75 years), a comparison of 30 mg q.d. cyclobenzaprine ER and 10 mg t.i.d. cyclobenzaprine IR showed that the systemic exposure was similar in these individuals for the two dose regimens [24]. However, compared with younger individuals, systemic exposure with either the ER or IR formulation was approximately 50% greater in adults aged 65–75 years [22,24]. For treatment with cyclobenzaprine IR in the elderly, the recommendation is to initiate with a 5-mg dose and titrate slowly upwards [25]. The use of cyclobenzaprine ER is not recommended in the elderly [18].

In patients with hepatic impairment (mild-to-moderate Child–Pugh score), the systemic exposure to cyclobenzaprine IR was approximately doubled. The pharmacokinetics of cyclobenzaprine in patients with severe hepatic impairment has not been studied. The use of cyclobenzaprine ER is not recommended in patients with hepatic impairment [18].

Cyclobenzaprine is extensively metabolized, with less than 1% of the oral dose being excreted unchanged [26]; it is primarily excreted as glucuronides by the kidney. To a lesser extent cyclobenzaprine is also *N*-demethylated by cytochrome P450 enzymes 1A2 and 2D6 [27].

Clinical efficacy

The use of cyclobenzaprine in the management of acute low back and neck pain has been widely studied with the IR formulation, making cyclobenzaprine one of the most extensively studied SMRs for this indication [17]. A systematic review of cyclobenzaprine IR studies for a meta-analysis was conducted on articles published up to 1999 [17]; there were 14 studies in low back and neck pain, 11 of which were in the treatment of acute low back and neck pain. The available evidence confirms that the superiority of cyclobenzaprine IR versus placebo in the treatment of musculoskeletal conditions is substantially greater than for the alternative SMRs [14]. The clinical evidence for the IR formulation will be summarized before a consideration of the evidence for the ER formulation. Cyclobenzaprine IR is typically given as three divided doses of 10 mg each per day, although the use of both higher (up to 60 mg) and lower (10 mg) daily doses has been described [17].

More recent data suggest that 5 mg t.i.d. cyclobenzaprine IR, but not lower doses, is significantly more effective than placebo in the treatment of muscle spasm, and is as effective as 10 mg t.i.d. with fewer AEs [28].

Of the 14 studies on the use of cyclobenzaprine IR in low back and neck pain that were included in a meta-analysis [17], ten looked for and reported a global improvement in symptoms at day 10 of treatment and found that the odds ratio of experiencing an improvement with cyclobenzaprine IR versus placebo was 4.7 (95% CI: 2.7–8.1) (FIGURE 3), with 2.7 patients needing to be treated for one patient to experience symptom improvement. The most common method used to determine clinical efficacy in studies of cyclobenzaprine IR versus placebo was a five-point rating scale for muscle spasm, local pain, tenderness, limitation of motion, daily activities and global evaluation. In a combined analysis of these five domains, patients receiving cyclobenzaprine IR reported a moderate improvement versus placebo (combined effect size of 0.44) at the end of treatment (an effect size of 0.5 is considered a moderate improvement). Within the first 1–4 days of treatment, cyclobenzaprine IR gave an average effect size of 0.52 versus placebo, suggesting that the effect of treatment was larger in the first few days of treatment compared with after 1–2 weeks of treatment [17]. Another systematic review

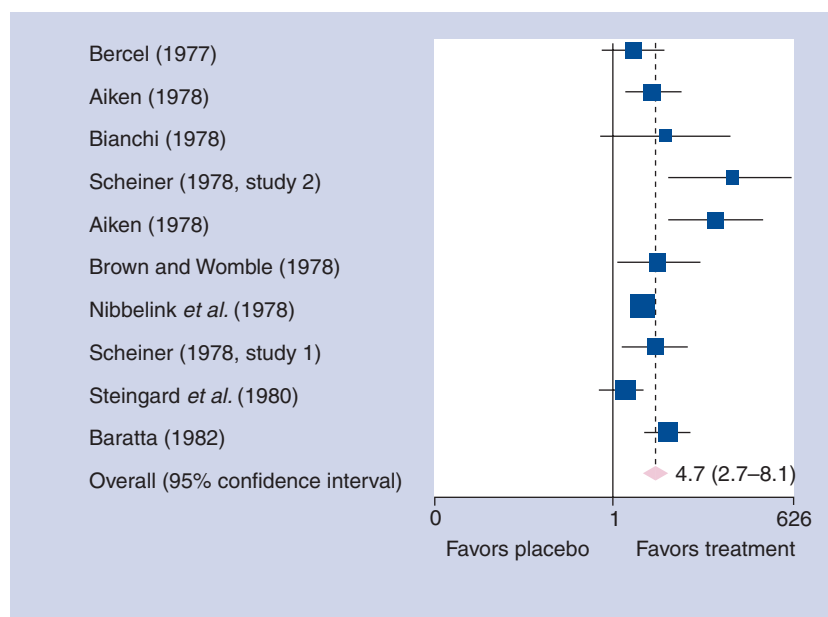


Figure 3. Likelihood of overall improvement in back pain by the end of the study in patients treated with cyclobenzaprine immediate release compared with placebo. Study names refer to articles analyzed by Browning *et al.* [17].

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found that cyclobenzaprine IR was significantly superior to placebo in all or some of these individual domains after 1–2 weeks of treatment in the majority of studies of acute low back or neck pain [14].

In general, there is a lack of direct head-to-head evidence comparing different SMRs against each other [14]. Studies of cyclobenzaprine IR versus methocarbamol in localized muscle spasm and cyclobenzaprine IR versus carisprodol in acute back pain found no significant differences in efficacy between agents. Studies of cyclobenzaprine IR versus diazepam have generally found cyclobenzaprine to have greater efficacy in measurements of pain, muscle spasm, functional status and global evaluations [14].

The efficacy of cyclobenzaprine ER in the treatment of acute low back and neck pain has been examined in two identical, randomized, double-blind, placebo-controlled studies analyzed independently but reported in a single publication [29] (TABLE 2). In both studies, patients were randomized 1:1:1:1 to treatment with placebo, 30 mg q.d. cyclobenzaprine ER, 15 mg q.d. cyclobenzaprine ER, or 10 mg t.i.d. cyclobenzaprine IR. The number of patients included in these studies was more than in most previous clinical studies of SMRs [14], and the end points and statistical techniques are detailed in the published methodology. However, it should be noted that the following results for cyclobenzaprine ER are based on a single publication.

Table 2. Key outcomes of cyclobenzaprine extended release treatment in patients with acute low back or neck pain at day 4.

End point	Treatment (% of patients)				Statistically significant comparisons [#]
	Placebo [*]	30 mg q.d. CER [†]	15 mg q.d. CER [‡]	10 mg t.i.d. CIR [¶]	
Patient's rating of medication helpfulness – good to excellent					
Study 1	32.8	59.4	46.9	49.9	30 mg CER vs placebo p = 0.007
Study 2	39.1	48.3	55.5	65.5	15 mg CER vs placebo p = 0.018
Physician's clinical global assessment – marked or moderate improvement					
Study 1	34.4	42.2	34.4	45.1	
Study 2	37.5	46.8	44.5	54.1	
Relief from local pain – some, a lot or complete relief					
Study 1	45.3	71.9	56.3	58.1	30 mg CER vs placebo p = 0.004
Study 2	48.4	61.3	60.3	70.4	
Patient-rated global impression of change – mild, moderate or marked improvement					
Study 1	67.2	85.9	73.4	74.2	30 mg CER vs placebo p = 0.008
Study 2	65.6	74.2	79.4	90.2	
Restriction in activities of daily living – mild, moderate or marked improvement					
Study 1	54.7	70.3	60.9	67.7	
Study 2	62.5	56.5	71.4	77	
Restriction of movement – some, a lot or complete relief					
Study 1	50	73.4	56.3	59.7	30 mg CER vs placebo p = 0.002
Study 2	43.8	61.3	60.3	68.9	
Daytime drowsiness – no or very little					
Study 1	56.3	43.8	42.2	24.2	30 mg CER vs placebo p < 0.025
Study 2	62.5	49.2	38.7	31.1	30 mg and 15 mg CER vs placebo p < 0.025
Quality of night-time sleep – no or very few sleep disturbances					
Study 1	35.9	57.8	56.3	51.6	
Study 2	53.1	61.3	47.6	65.6	

^{*}Study 1: n = 64; Study 2: n = 64.
[†]Study 1: n = 64; Study 2: n = 62.
[‡]Study 1: n = 64; Study 2: n = 63.
[¶]Study 1: n = 62; Study 2: n = 61.
[#]Only statistically significant comparisons are shown across all ratings; the patient's rating of helpfulness and physician's clinical global assessment were corrected for multiple comparisons.
 CER: Cyclobenzaprine extended release; CIR: Cyclobenzaprine immediate release; q.d.: Once daily; t.i.d.: Three-times daily.
 Data taken from [29].

Compared with those receiving placebo, a significantly higher proportion of patients reported their rating of medication helpfulness (the co-primary study end point) as good or excellent at day 4 of treatment in the 30 mg cyclobenzaprine ER (study 1, $p = 0.007$) and the 15 mg cyclobenzaprine ER groups (study 2, $p = 0.018$) (TABLE 2). In study 2, the patient rating of medication helpfulness for 15 mg cyclobenzaprine ER was also significantly better at day 14 (20.6% vs placebo 15.6%; $p = 0.024$). However, there was no significant difference between the active treatment groups and placebo for the other co-primary end point of the physician's clinical global assessment [29]. Other findings of note at day 4 were a significantly greater improvement with 30 mg cyclobenzaprine ER versus placebo in patient-rated relief from local pain ($p = 0.004$), global impression of change ($p = 0.008$) and restriction of movement ($p = 0.002$) in study 1. These improvements in symptoms at day 4 correspond with a predicted cyclobenzaprine plasma concentration of 90% at the steady-state level [20].

Certain efficacy findings that were significantly improved versus placebo in the 30 mg cyclobenzaprine ER group at day 4 were still significantly improved at day 8 in study 1: patient-rated relief from local pain ($p = 0.010$), global impression of change ($p = 0.003$) and restriction of movement ($p = 0.016$) [29].

Postmarketing surveillance

A postmarketing surveillance study of 7607 patients treated with 10 mg t.i.d.

cyclobenzaprine IR reported that the most common AEs were drowsiness (16%), dry mouth (7%) and dizziness (3%). The incidence of these common AEs was lower in the surveillance program than in the controlled clinical studies for cyclobenzaprine IR (drowsiness: 39%; dry mouth: 27%; dizziness: 11%; $n = 473$). The overall effectiveness of cyclobenzaprine IR reported in postmarketing surveillance was similar to that observed in the double-blind controlled studies [18].

Safety & tolerability

In general, somnolence and sedation associated with the use of muscle relaxants are important AEs that may impair patients' daily activities and lead to reduced adherence to the prescribed treatment regimen or even discontinuation of drug treatment, potentially prolonging muscle spasm and patient discomfort. These AEs have led to calls for caution in the use of these agents [13].

A key aim of the development of cyclobenzaprine ER was the reduction of daytime drowsiness compared with cyclobenzaprine IR. In the two studies described by Malanga *et al.* [29], 42.2–49.2% of patients in the cyclobenzaprine ER groups had no or very little daytime drowsiness compared with 24.2–31.1% of patients in the cyclobenzaprine IR groups and 56.3–62.5% in the placebo groups. In the two studies, no patients in the 15 mg cyclobenzaprine ER or placebo groups discontinued medication because of somnolence or dizziness. In

Table 3. Summary of adverse events reported in more than 4% of patients in any treatment group in each of two identical clinical studies of cyclobenzaprine versus placebo in patients with low back or neck pain.

Adverse event	No. of patients (%)							
	Placebo		30 mg q.d. CER		15 mg q.d. CER		10 mg t.i.d. CIR	
	Study 1 (n = 64)	Study 2 (n = 64)	Study 1 (n = 64)	Study 2 (n = 62)	Study 1 (n = 64)	Study 2 (n = 63)	Study 1 (n = 62)	Study 2 (n = 61)
Dry mouth	2 (3.1)	0	8 (12.5)	9 (14.5)	3 (4.7)	4 (6.3)	9 (14.5)	8 (13.1)
Headache NOS	4 (6.3)	7 (10.9)	0	1 (1.6)	4 (6.3)	3 (4.8)	4 (6.5)	4 (6.6)
Dizziness	0	2 (3.1)	4 (6.3)	4 (6.5)	3 (4.7)	1 (1.6)	4 (6.5)	3 (4.9)
Fatigue	1 (1.6)	–	3 (4.7)	–	3 (4.7)	–	3 (4.8)	–
Dyspepsia	1 (1.6)	–	3 (4.7)	–	0	–	3 (4.8)	–
Somnolence	0	1 (1.6)	1 (1.6)	1 (1.6)	0	1 (1.6)	6 (9.7)	3 (4.9)
Constipation	0	0	2 (3.1)	2 (3.2)	0	1 (1.6)	3 (4.8)	4 (6.6)
Nausea	–	0	–	3 (4.8)	–	2 (3.2)	–	2 (3.3)
Diarrhea NOS	3 (4.7)	–	0	–	1 (1.6)	–	2 (3.2)	–

CER: Cyclobenzaprine extended release; CIR: Cyclobenzaprine immediate release; NOS: Not otherwise specified; q.d.: Once daily; t.i.d.: Three-times daily. Data taken from [29].

study 1 and study 2 combined, 2/126 (1.6%) in the 30 mg cyclobenzaprine ER group discontinued because of somnolence, and 1/126 (0.8%) discontinued because of dizziness. In comparison, 8/123 (6.5%) in the cyclobenzaprine IR group discontinued because of somnolence and 4/123 (3.3%) discontinued because of dizziness. This suggests that the ER formulation is more acceptable to patients.

Adverse events occurring in more than 4% of patients reported with cyclobenzaprine ER and cyclobenzaprine IR from the two 14-day controlled efficacy studies described by Malanga *et al.* [29] are shown in TABLE 3. The frequencies of these common AEs observed for cyclobenzaprine IR are similar to those observed in previous clinical studies [14] and, except for nausea, occurred more frequently in the cyclobenzaprine IR group than in the 15 mg cyclobenzaprine ER group. This may reflect a benefit with the reduced total daily dose of cyclobenzaprine in the 15 mg ER formulation compared with the standard 30 mg IR formulation. Even in the 30 mg cyclobenzaprine ER group, the frequency of somnolence was reduced compared with the cyclobenzaprine IR group [29].

A number of contraindications and warnings for cyclobenzaprine IR and ER are shared with tricyclic antidepressants, such as a contraindication for concomitant use of monoamine oxidase inhibitors, warnings of the possibility of arrhythmias, sinus tachycardia, prolongation of conduction time leading to myocardial infarction, stroke and certain CNS AEs [25,18]. Drug interactions may lead to enhancement of the effects of alcohol, barbiturates and other CNS depressants; blocking of the antihypertensive action of guanethidine and similarly acting compounds; and enhancement of the seizure risk in patients receiving tramadol [18]. Cyclobenzaprine IR should not be used in patients with moderate or severe hepatic impairment; in patients with mild hepatic impairment; and in the elderly, use of cyclobenzaprine IR should be initiated with a 5-mg dose and titrated slowly upwards [25]. The use of cyclobenzaprine ER is not recommended in patients with hepatic impairment or in elderly patients [18].

Unlike carisoprodol [15], cyclobenzaprine has a low potential for substance abuse [30].

Regulatory affairs

Cyclobenzaprine ER is currently approved only in the USA as an adjunct to rest and physical therapy for the relief of muscle spasm associated with acute, painful musculoskeletal conditions. It should be noted that cyclobenzaprine ER is not

included in current US clinical practice guidelines for low back and neck pain [5] as it was approved after the formulation of these guidelines.

Conclusion

Back pain is a common clinical complaint with a substantial social and economic impact. Data suggest that several SMRs are more effective than placebo for the short-term therapy of acute low back and neck pain. However, there is no compelling evidence from head-to-head studies of superior efficacy for a particular SMR compared with other SMRs. In addition, the use of SMRs is often compromised by the AEs of somnolence and sedation and frequency of dosing, which reduce their acceptability to patients.

Cyclobenzaprine is one of the most widely studied SMRs, with a substantial body of evidence for superior efficacy in treating acute low back and neck pain compared with placebo. It is approved for the treatment of muscle spasm as an adjunct to rest and physical therapy. Cyclobenzaprine ER reduces many of the AEs associated with cyclobenzaprine IR by avoiding the sedation and somnolence associated with high peak plasma concentrations of the drug. Compared with the IR formulation, the ER formulation is associated both with fewer AEs and with lower levels of treatment discontinuation because of AEs. Cyclobenzaprine ER also appears to have a lower frequency of AEs than other SMRs, although this would need to be explored in direct head-to-head comparisons. These improvements in tolerability are combined with a long duration of action that allows once-daily dosing and with clinical efficacy comparable to cyclobenzaprine IR. These factors would be expected to improve treatment compliance and persistence and may address the concerns about SMR tolerability expressed in some clinical practice guidelines [7].

Cyclobenzaprine ER retains the well-documented efficacy of cyclobenzaprine IR, being associated with a higher proportion of patients rating their medication helpfulness as good-to-excellent at day 4 of treatment.

Future perspective

The role of SMRs in treating muscle spasm associated with acute low back and neck pain is well established and clinically relevant. With the addition of once-daily cyclobenzaprine ER to the treatment paradigm for acute low back and neck pain, our focus has progressed from efficacy to tolerability, AE reduction and increased patient compliance with treatment.

Within the practice of chronic pain management, one often encounters the patient who has continuous pain without a well-established pathophysiology. Mechanical low back pain has been shown to respond favorably to SMR treatment. Is there a role for SMRs in the treatment of chronic low back pain associated with recurrent muscle spasm? There is definitely a need for clinical studies to assess efficacy in this area. Within the next 2–5 years this may be the opportunity to evaluate the role of SMRs in chronic pain.

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Executive summary

Back pain

- Low back and neck pain are common clinical complaints that are associated with considerable disability and have a substantial economic impact.
- Most cases of low back and neck pain are nonspecific and cannot be attributed to a specific pathology.
- Current US and European guidelines recommend that patients with nonspecific back pain should be encouraged towards physical activity, with analgesia if necessary. First-line agents for analgesia include acetaminophen or nonsteroidal anti-inflammatory drugs. Second-line agents can include skeletal muscle relaxants (SMRs).

Cyclobenzaprine extended release

- Cyclobenzaprine extended release (ER) is an SMR approved as an adjunct to rest and physical therapy for the treatment of muscle spasm associated with acute low back and neck pain.
- Cyclobenzaprine ER is a once-daily agent available as 15 and 30 mg tablets.

Pharmacokinetic properties of cyclobenzaprine ER

- The T_{max} of a single dose of cyclobenzaprine ER is 6–8 h, compared with an initial peak at 4 h for the first dose of cyclobenzaprine immediate release (IR), but plasma concentrations at 4 h are similar. Systemic exposure over 24 h is similar for a single dose of 30 mg cyclobenzaprine ER and the standard cyclobenzaprine IR regimen of 10 mg three-times a day.
- The absorption lag time, T_{max} , shape of the mean plasma concentration–time curve, and tolerability of cyclobenzaprine ER are unaffected by food, suggesting that dose adjustment of cyclobenzaprine ER because of food intake is unnecessary.
- Systemic exposure is increased in patients with hepatic impairment and in elderly individuals. Cyclobenzaprine ER is not recommended in these individuals.

Clinical evidence

- Cyclobenzaprine IR is associated with an improvement in acute low back and neck pain, particularly in the first few days of treatment.
- The clinical efficacy of cyclobenzaprine ER is comparable to that of cyclobenzaprine IR.
- More patients rated medication helpfulness as good to excellent at day 4 of treatment with cyclobenzaprine ER than with placebo (study 1: 30 mg cyclobenzaprine ER 48.9% vs placebo 32.8%, $p = 0.007$; study 2: 15 mg cyclobenzaprine ER 48.3% vs placebo 39.1%, $p = 0.017$).
- The use of cyclobenzaprine ER is associated with fewer adverse events than the use of cyclobenzaprine IR, with fewer discontinuations because of somnolence and dizziness.
- The ER formulation of cyclobenzaprine may be more acceptable to patients than the IR formulation and may improve adherence to treatment as prescribed, leading to improved patient outcomes.

Safety & tolerability

- In postmarketing surveillance of 10 mg three-times a day cyclobenzaprine IR, the most commonly reported adverse events were drowsiness (16%), dry mouth (7%) and dizziness (3%).

Drug interactions

- Cyclobenzaprine should not be taken concomitantly with monoamine oxidase inhibitors. It may enhance the effects of alcohol, barbiturates and other CNS depressants, block the antihypertensive action of guanethidine and similarly acting compounds and enhance the seizure risk in patients receiving tramadol.

Dosage & administration

- Cyclobenzaprine ER is available as a starting dose of 15 mg or a maximum dose of 30 mg, both to be taken once daily with or without food.

Bibliography

Papers of special note have been highlighted as:

- of interest
- of considerable interest

- 1 Strine TW, Hootman JM: US national prevalence and correlates of low back and neck pain among adults. *Arthritis Rheum.* 57(4), 656–665 (2007).
- 2 Webb R, Brammah T, Lunt M, Urwin M, Allison T, Symmons D: Prevalence and predictors of intense, chronic, and disabling neck and back pain in the UK general population. *Spine* 28(11), 1195–1202 (2003).
- 3 Dagenais S, Caro J, Haldeman S: A systematic review of low back pain cost of illness studies in the United States and internationally. *Spine J.* 8(1), 8–20 (2008).
- 4 Martin BI, Deyo RA, Mirza SK *et al.*: Expenditures and health status among adults with back and neck problems. *JAMA* 299(6), 656–664 (2008).
- 5 Chou R, Qaseem A, Snow V *et al.*: Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann. Intern. Med.* 147(7), 478–491 (2007).
 - **A key clinical practice guideline outlining treatment options for patients with both acute and chronic low back pain.**
- 6 Krismer M, van Tulder M: Strategies for prevention and management of musculoskeletal conditions. Low back pain (non-specific). *Best Pract. Res. Clin. Rheumatol.* 21(1), 77–91 (2007).
- 7 van Tulder M, Becker A, Bekkering T *et al.*: Chapter 3. European guidelines for the management of acute nonspecific low back pain in primary care. *Eur. Spine J.* 15(Suppl. 2), S169–S191 (2006).
 - **A key clinical practice guideline outlining treatment options for patients with both acute and chronic low back pain.**
- 8 de Vet HC, Heymans MW, Dunn KM *et al.*: Episodes of low back pain: a proposal for uniform definitions to be used in research. *Spine* 27(21), 2409–2416 (2002).
- 9 van Tulder MW, Assendelft WJ, Koes BW, Bouter LM: Spinal radiographic findings and nonspecific low back pain. A systematic review of observational studies. *Spine* 22(4), 427–434 (1997).
- 10 Arnau JM, Vallano A, Lopez A, Pellise F, Delgado MJ, Prat N: A critical review of guidelines for low back pain treatment. *Eur. Spine J.* 15(5), 543–553 (2006).
- 11 Philadelphia Panel: Philadelphia Panel evidence-based clinical practice guidelines on selected rehabilitation interventions for neck pain. *Phys. Ther.* 81(10), 1701–1717 (2001).
- 12 Childs JD, Cleland JA, Elliott JM *et al.*: Neck pain: Clinical practice guidelines linked to the International Classification of Functioning, Disability, and Health from the Orthopedic Section of the American Physical Therapy Association. *J. Orthop. Sports Phys. Ther.* 38(9), A1–A34 (2008).
- 13 van Tulder MW, Touray T, Furlan AD, Solway S, Bouter LM: Muscle relaxants for non-specific low back pain. *Cochrane Database Syst. Rev.* (2), CD004252 (2003).
 - **Cochrane systematic review examining the evidence for the use of skeletal muscle relaxants (SMRs) in low back pain.**
- 14 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.* 28(2), 140–175 (2004).
 - **A general systematic review of SMRs in multiple musculoskeletal conditions.**
- 15 Beebe FA, Barkin RL, Barkin S: A clinical and pharmacologic review of skeletal muscle relaxants for musculoskeletal conditions. *Am. J. Ther.* 12(2), 151–171 (2005).
 - **Important review examining the evidence for the use of SMRs in muscle spasm and the relationship between muscle spasm and pain.**
- 16 Claxton AJ, Cramer J, Pierce C: A systematic review of the associations between dose regimens and medication compliance. *Clin. Ther.* 23(8), 1296–1310 (2001).
- 17 Browning R, Jackson JL, O'Malley PG: Cyclobenzaprine and back pain: a meta-analysis. *Arch. Intern. Med.* 161(13), 1613–1620 (2001).
 - **A meta-analysis of the clinical evidence for the use of cyclobenzaprine immediate release (IR) in low back and neck pain, with the overall finding of a 4.7-times greater chance of achieving an improvement of symptoms with cyclobenzaprine than with placebo.**
- 18 Amrix® package insert. Cephalon Inc., PA, USA (2008).
- 19 Darwish M, Hellriegel ET, Xie F: Single-dose pharmacokinetics of once-daily cyclobenzaprine extended release 30 mg versus cyclobenzaprine immediate release 10 mg three times daily in healthy young adults: a randomized, open-label, two-period crossover, single-centre study. *Clin. Drug Investig.* 28(12), 793–801 (2008).
 - **Key comparison of the pharmacokinetics of the new extended release (ER) formulation of cyclobenzaprine with the older IR formula; AUC and C_{max} parameters were similar, indicating similar systemic exposure to the drug between the two regimens.**
- 20 Darwish M, Hellriegel E, Weil A: Relationship between the pharmacokinetics and efficacy of once-daily cyclobenzaprine extended-release. *Pain Med.* 10(1), 260–261 (2009).
- 21 Hucker HB, Stauffer SC, Balletto AJ, White SD, Zacchei AG, Arison BH: Physiological disposition and metabolism of cyclobenzaprine in the rat, dog, rhesus monkey, and man. *Drug Metab. Dispos.* 6(6), 659–672 (1978).
- 22 Darwish M, Chang S, Hellriegel ET: A pharmacokinetic comparison of single doses of once-daily cyclobenzaprine extended-release 15 mg and 30 mg: a randomized, double-blind, two-period crossover study in healthy volunteers. *Clin. Ther.* 31(1), 108–114 (2009).
 - **Comparison of ER 15 and 30 mg doses; AUC parameters and C_{max} doubled in healthy volunteers receiving 30 mg dose compared with the 15 mg dose, showing predictable dose scaling of cyclobenzaprine ER.**
- 23 Darwish M, Xie F: Effect of food on the pharmacokinetics of once-daily cyclobenzaprine extended-release 30 mg: a randomized, open-label, crossover, single-centre study. *Clin. Drug Investig.* 29(3), 145–152 (2009).
- 24 Darwish M, Xie F: Comparison of the single-dose pharmacokinetics of once-daily cyclobenzaprine extended-release 30 mg and cyclobenzaprine immediate-release 10 mg three times daily in the elderly: a randomized, open-label, crossover study. *Drugs Aging* 26(2), 95–101 (2009).
- 25 Flexeril® package insert. McNeil Consumer & Specialty Pharmaceuticals, PA, USA (2003).
- 26 Hucker HB, Stauffer SC, Albert KS, Lei BW: Plasma levels and bioavailability of cyclobenzaprine in human subjects. *J. Clin. Pharmacol.* 17(11–12), 719–727 (1977).
- 27 Wang RW, Liu L, Cheng H: Identification of human liver cytochrome P450 isoforms involved in the *in vitro* metabolism of cyclobenzaprine. *Drug Metab. Dispos.* 24(7), 786–791 (1996).
- 28 Borenstein DG, Korn S: Efficacy of a low-dose regimen of cyclobenzaprine hydrochloride in acute skeletal muscle spasm: results of two placebo-controlled trials. *Clin. Ther.* 25(4), 1056–1073 (2003).
- 29 Malanga GA, Ruoff GE, Weil AJ, Altman CA, Xie F, Borenstein DG: Cyclobenzaprine ER for muscle spasm associated with low back and neck pain: two randomized, double-blind, placebo-controlled studies of identical design. *Curr. Med. Res. Opin.* 25(5), 1179–1196 (2009).

- ■ Key clinical efficacy data from two clinical studies of cyclobenzaprine ER in muscle spasm associated with low back and neck pain; significant improvements in patient rating of medication helpfulness for cyclobenzaprine ER versus placebo (30 mg in study 1, $p = 0.007$; 15 mg in study 2, $p = 0.018$).
- 30 Katz WA, Dube J: Cyclobenzaprine in the treatment of acute muscle spasm: review of a decade of clinical experience. *Clin. Ther.* 10(2), 216–228 (1988).
- 31 SOMA® package insert. MedPointe Healthcare, Inc., NJ, USA (2007).
- 32 Parafon Forte® package insert. Ortho-McNeil Pharmaceuticals, Inc., NJ, USA (2009).
- 33 Skelaxin® package insert. King Pharmaceuticals, Inc., TN, USA (2008).
- 34 Robaxin® package insert. Schwarz Pharma AG, Monnheim, Germany (2003).
- 35 Orphengesic package insert. Par Pharmaceutical, Inc., NY, USA (1998).