

THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

Is cyclobenzaprine useful for pain?

Cyclobenzaprine is a tricyclic molecule discovered in 1956 that is structurally related to amitriptyline and imipramine. Evaluated first as a possible tranquilizer, it was noted to have atropine-like properties in animals.¹ In Canada, Merck Frosst Research Laboratories envisaged cyclobenzaprine as a centrally active skeletal muscle relaxant.² However, it was soon apparent that despite being sedative and anti-muscarinic, cyclobenzaprine was not useful for spasticity³, nor for rigidity in Parkinson's disease⁴. Health Canada approved cyclobenzaprine for short-term use (< 3 weeks) as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions.⁵ It eventually found a large North American market⁶, but was not licensed in most European countries. This Letter reviews the evidence for benefits and harms of cyclobenzaprine for common pain indications, compared with placebo.

Utilization in BC

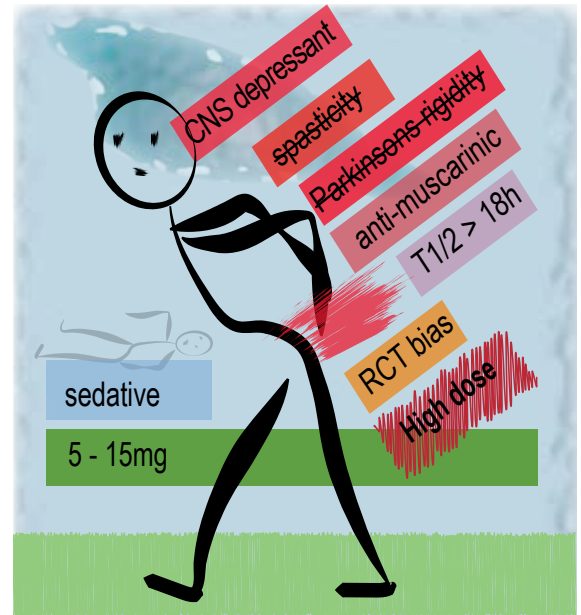
In 2016 over 118,000 British Columbians filled at least one prescription for cyclobenzaprine. Over 71,000 were first time users (within 365 days). Nearly 300,000 total prescriptions were filled, at a mean dose of 17 mg/day, and initial duration of 15 days. Refills had a mean duration of 60 days, and over 8,600 people took it continuously.⁷ Annual expenditures for cyclobenzaprine in BC in 2016 were \$3.9 million, of which PharmaCare paid \$1.5 million. The ingredient cost of one 10 mg tablet is \$0.40.

Pharmacology and Pharmacokinetics

The mean terminal elimination half-life of cyclobenzaprine in healthy volunteers is at least 18 hours (range 8-37 hours)⁸ but may be as long as 30 hours⁵. Plasma concentration can be increased by up to two times in the elderly or in people with mild liver impairment, for whom the monograph recommends dose reductions.⁵

Evidence from RCTs

We identified 46 placebo-controlled RCTs of cyclobenzaprine in muscle spasm/pain of the neck or back or in fibromyalgia and were able to retrieve and assess data from 40.⁹⁻²⁸ Except for 1 trial with duration > 18 days, all were for treatment periods of only 7-14 days.⁹ We judged all



RCTs to have a high risk of bias, due to possible loss of blinding. The majority of trials used subjective, unvalidated, physician-rated assessments of pain and function. All trials were funded by the manufacturers of cyclobenzaprine. Because of this risk of bias, we cannot estimate with confidence the true magnitude of any effects on pain or function.

Most patients do not benefit, but some experience prompt relief

Acute pain (< 30 days)

Eight of 46 RCTs that were retrievable enrolled patients with acute muscle spasm and pain of the neck and/or back. Based on the available evidence, our most optimistic estimate of benefit is a number needed to treat (NNT) of 4-7 over 10-14 days to obtain physician-rated "moderate to marked improvement".^{10,13,17,19,21,24} Cyclobenzaprine's onset of effect occurs within the first 4 days of therapy, but any benefits compared with placebo diminish by the end of the first week, concordant with natural recovery.

Non-acute pain (> 30 days)

Three RCTs enrolled patients with muscle spasm and pain of the neck and/or back that had lasted at least 30 days.^{6,9,12} 20 trials (reported in one publication) used a mixed population with pain of 13-350 days' duration.¹⁸ Our most optimistic estimate of benefit is an NNT of 3-4 over 14 days to obtain physician-rated "moderate to marked improvement." All 23 RCTs in non-acute pain treated patients for only 2 weeks^{6,9,12,18} but only one RCT reported drug effects before the trial ended.



Mailing Address: Therapeutics Initiative
The University of British Columbia
Department of Anesthesiology, Pharmacology & Therapeutics
2176 Health Sciences Mall
Vancouver, BC Canada V6T 1Z3

Tel.: 604 822 0700
Fax: 604 822 0701
E-mail: info@ti.ubc.ca
www.ti.ubc.ca

Compared with placebo, benefits of cyclobenzaprine were observed as early as 7 days for objectively measured parameters (e.g. muscle spasm, local pain, tenderness to palpation, limitation of motion), and these were maintained until the end of the trial at 14 days.¹²

Fibromyalgia

Six placebo-controlled RCTs studied cyclobenzaprine for fibromyalgia, using different definitions of the condition.^{11,14,15,20,22,23} Trial durations varied from 4 to 10 weeks, assessing effects of cyclobenzaprine no earlier than one week. In one 3-month trial, cyclobenzaprine appeared to improve symptoms more than placebo by 1 week for several outcomes, such as patient self-assessments of sleep, pain, and duration of pain and stiffness in the morning.¹¹ Our most optimistic estimate of benefit from cyclobenzaprine is an NNT of 7-8 to obtain moderate to marked or “significant” physician-rated improvement at 3 months.

Dose Response

Six placebo-controlled dose comparison RCTs in patients with pain were identified.^{13,16,17,23} In two RCTs, cyclobenzaprine 5 mg TID was as effective as 10 mg TID, but the lower dose caused less sedation.^{13,16} NNT for substantial pain relief was about 6-7 by day 4.¹³ One double-blind crossover trial in fibromyalgia compared cyclobenzaprine 10 mg daily at bedtime with 10 mg three times daily.²³ The higher dose and frequency caused far more adverse effects with no additional analgesia.²³ One RCT studied four groups: once daily extended-release (ER) 15 mg, once daily ER 30 mg, 10 mg three times daily or placebo.¹⁷ The proportion of patients reporting “good or excellent” responses for medication helpfulness were similar between the 15 mg ER, 30 mg ER and 10 mg three times daily treatment groups.¹⁷

References

- Schwartz MM (Chief Judge). *Merck & Co., Inc. v. Danbury Pharmacal, Inc.*, 694 F. Supp. 1 (D. Del. 1988). U.S. District Court for the District of Delaware; 1988 (<http://law.justia.com/cases/federal/district-courts/FSupp/694/1/1874712/>; accessed June 8, 2017).
- Share NN, McFarlane CS. *Cyclobenzaprine: novel centrally acting skeletal muscle relaxant*. *Neuropharmacology* 1975;14(9):675-84. PMID: 1178121.
- Ashby P; Burke D; Rao S; Jones RF. *Assessment of cyclobenzaprine in the treatment of spasticity*. *J Neurol Neurosurg Psychiatry* 1972;35(5):599-605. PMID: 4563483.
- Campanella G; Roy M; Barbeau A. *Drugs affecting movement disorders*. *Annu Rev Pharmacol Toxicol* 1987; 27:113-136. DOI:10.1146/annurev.pa.27.040187.000553
- Sanis Health Inc. *Cyclobenzaprine Canadian product monograph*. April 2017; https://pdf.hres.ca/dpd_pm/00038944.PDF
- Brown BR Jr, Womble J. *Cyclobenzaprine in intractable pain syndromes with muscle spasm*. *JAMA* 1978; 240(11):1151-2. PMID: 355663.

Harm from cyclobenzaprine

Withdrawals due to adverse events were consistently higher with cyclobenzaprine than placebo. The most commonly reported harms were CNS depressant effects such as drowsiness/fatigue and dizziness, and anti-muscarinic effects such as dry mouth. We estimate the number needed to harm (NNH) at 4-5 over 14 days to cause at least one adverse event, which can be expected after the first dose. This likely underestimates real world harms because individuals at higher risk of experiencing adverse effects were excluded from RCTs. As a result, anti-muscarinic effects, such as impaired visual accommodation, increased dental caries or gum disease, impaired bladder emptying, or constipation are less likely to have been captured in these short term trials. Clinical experience, database studies, and other lines of evidence raise concern that long-term use of anti-muscarinic drugs may cause permanent harm to the brain, such as a higher incidence of subsequent dementia.^{28,29,30}

Discontinuing Cyclobenzaprine

Because of its long elimination half-life, dose tapering should be unnecessary after short term use.^{5,8} We identified no case reports of withdrawal effects.

Conclusions

- In B.C. cyclobenzaprine is prescribed for acute pain at higher doses and for longer durations than necessary, and is frequently prescribed for unapproved long term use.
- There is no compelling evidence that cyclobenzaprine is a muscle-relaxant. Effects on pain or overall function are likely the result of sedation.
- If prescribed, a dose of 5 mg at bedtime should be tried first. Evidence suggests titration based on response and tolerability to a maximum dose of 15 mg/day, for no longer than one week.**

- BC Pharmacare data, courtesy of Greg Carney, TI Pharmacoeconomics Working Group and B.C. Ministry of Health (personal communication).
- US FDA. *Flexeril (cyclobenzaprine HCl) tablets*. NDA 17-821/S-045. https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/017821s0451bl.pdf
- Basmajian JV. Cyclobenzaprine hydrochloride effect of skeletal muscle spasm in the lumbar region and neck: two double-blind controlled clinical and laboratory studies. *Arch Phys Med Rehabil* 1978;59(2):58-63. PMID: 623512.
- Basmajian JV. *Acute back pain and spasm. A controlled multicenter trial of combined analgesic and antispasm agents*. *Spine* 1989;14(4):438-9. PMID: 2524114.
- Bennett RM, Gatter RA, Campbell SM et al. *A comparison of cyclobenzaprine and placebo in the management of fibrositis. A double-blind controlled study*. *Arthritis Rheum* 1988;31(12):1535-42. PMID: 3058130.
- Berzel NA. *Cyclobenzaprine in the treatment of skeletal muscle spasm in osteoarthritis of the cervical and lumbar spine*. *Current Therapeutic Research - Clinical and Experimental* 1977;22(4):462-8.
- 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*. 2003;25(4):1056-73. PMID: 12809957.

For a complete list of references go to: www.ti.ubc.ca/letter105