



TITLE: Long-term Use of Cyclobenzaprine for Pain: A Review of the Clinical Effectiveness

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CONTEXT AND POLICY ISSUES

Cyclobenzaprine is an oral prescription medication, indicated for treatment of pain associated with muscle spasm due to acute musculoskeletal conditions.¹ Examples of common painful conditions for which cyclobenzaprine could be used include fibromyalgia,² low back pain,³ and neck pain.⁴

Cyclobenzaprine belongs to a heterogeneous class of medications known as muscle relaxants.^{1,5} More specifically, it is classified as an anti-spasmodic.⁵ It is structurally similar to the tricyclic antidepressants (e.g. amitriptyline), and has similar associated side effects including drowsiness, dizziness and dry mouth; according to the product monograph, these adverse effects occur in 39%, 27%, and 11% of patients, respectively.¹

Owing to its anticholinergic activity and long half-life, cyclobenzaprine is not recommended for use in the elderly.⁵ The *Beers Criteria for Potentially Inappropriate Medication Use in Older Adults* recommend that muscle relaxants including cyclobenzaprine be avoided in the elderly; this is classified as a strong recommendation with a moderate level of evidence.⁶

According to the product monograph, “cyclobenzaprine should be used only for short periods (up to two or three weeks), because adequate evidence of effectiveness for more prolonged use is not available”.¹

RESEARCH QUESTIONS

1. What is the clinical effectiveness of long term cyclobenzaprine for treating pain?
2. What is the clinical effectiveness of long-term cyclobenzaprine as an adjunct to other pain medication?

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3. What is the cost-effectiveness of cyclobenzaprine alone or as an adjunct to other medications for treating pain?
4. What are the evidence-based guidelines for the use of cyclobenzaprine for treating pain?

KEY FINDINGS

The efficacy and safety of cyclobenzaprine has been assessed in randomized controlled trials (RCTs) and systematic reviews of RCTs for fibromyalgia, back pain, neck pain, myofascial pain, and spasticity. Cyclobenzaprine may be more effective in fibromyalgia and back pain than placebo, however available studies are of limited duration, mostly two weeks or less. RCT results have been inconsistent, and they are not without limitations. Comparative studies of cyclobenzaprine vs amitriptyline in fibromyalgia, and vs diazepam, NSAIDs or other muscle relaxants for musculoskeletal pain, have found similar outcomes between groups. There is no evidence of benefit of cyclobenzaprine in neck pain or myofascial pain. An RCT assessing combination therapy with cyclobenzaprine plus an NSAID or cyclobenzaprine alone for neck pain found no evidence of benefit of combination or monotherapy vs placebo. Adverse events including drowsiness, dizziness and dry mouth occur frequently.

There were no economic evaluations or systematic reviews of economic evaluations identified.

Evidence-based practice guidelines lack specific recommendations with respect to use of cyclobenzaprine or other medications, reflecting the lack of quality and quantity of available evidence.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, Ovid Medline, Ovid Embase, The Cochrane Library (2015, Issue 1), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published before January 23, 2015.

Selection Criteria and Methods

A single reviewer screened and selected studies. Titles and abstracts of all citations identified by the electronic database and grey literature searches were reviewed. Full texts of potentially relevant articles were retrieved and assessed for eligibility, based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with pain (chronic non-cancer pain, musculoskeletal pain, neuropathic pain)
Intervention	Long-term cyclobenzaprine use (> 5 days) alone or in combination with other pain medications
Comparator	Short term cyclobenzaprine use (≤5 days) Placebo Pain medication without the use of cyclobenzaprine
Outcomes	Clinical Effectiveness, safety
Study Designs	Health Technology Assessments (HTAs)/Systematic reviews/Meta-analyses, Randomized controlled trials (RCTs), Economic evaluations, Evidence-based guidelines

Exclusion Criteria

Reports not meeting selection criteria as outlined in Table 1, and reports published prior to January 1995 or in languages other than English were excluded. RCTs included within any of the included systematic reviews were also excluded.

Critical Appraisal of Individual Studies

Quality of included studies was assessed using AMSTAR for included systematic reviews,⁷ the Cochrane Collaboration’s tool for assessing risk of bias for included RCTs,⁸ and AGREE II for included practice guidelines.⁹ For each study, a numeric score was not calculated; instead the strengths and limitations were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

The electronic literature search identified 437 citations. After title and abstract screening, 410 citations were excluded, and full-texts of 27 reports were retrieved. An additional 28 reports identified in the grey literature search were also reviewed. Forty-one reports were excluded after full text review, leaving 14 reports meeting eligibility criteria: seven systematic reviews, four RCTs reported in three papers, and four practice guidelines. No economic evaluations were identified. Two systematic reviews assessed cyclobenzaprine for treatment of fibromyalgia,^{10,11} two for back pain,^{12,13} one for spasticity and musculoskeletal conditions,¹⁴ one for myofascial pain,¹⁵ and another for mechanical neck disorders.¹⁶ One of the RCTs assessed cyclobenzaprine for neck pain,¹⁷ another for myofascial pain,¹⁸ and two identically designed RCTs in a single report assessed cyclobenzaprine for neck or back pain.¹⁹ Of the four practice guidelines, two were for treatment of fibromyalgia,^{6,20} one for chronic pain,²¹ and one for low back pain.²²

The study selection process is outlined in a PRISMA flow chart presented in Appendix 1.

Summary of Study Characteristics

A summary of characteristics of individual studies is provided in Appendix 2.

Systematic reviews

There were seven systematic reviews meeting the eligibility criteria. None of the included systematic reviews restricted eligibility to a specific duration of cyclobenzaprine treatment or length of follow-up, however cyclobenzaprine was used for longer than five days for the majority of studies included within each review. Smith 2011 assessed efficacy and safety of antidepressant, anticonvulsant, and muscle relaxant medications (including cyclobenzaprine) for adults with fibromyalgia in a systematic review.¹⁰ They found no studies where cyclobenzaprine was used as adjunct to other pain medications, but reported comparisons of cyclobenzaprine to placebo from three RCTs and cyclobenzaprine to amitriptyline from a single RCT. Although there was insufficient data to perform meta-analysis for efficacy outcomes, pooled analyses of safety outcomes were performed for the comparison of cyclobenzaprine to placebo. Leite 2009 assessed the efficacy and safety of cyclobenzaprine for myofascial pain in a Cochrane systematic review, and included two RCTs. Results were described narratively, as data were not amenable to meta-analysis.¹⁵ Peloso 2007 performed a Cochrane systematic review assessing pharmacotherapy of mechanical neck disorders.¹⁶ The meta-analysis included two RCTs assessing cyclobenzaprine. Chou 2005 was a systematic review assessing efficacy and safety of muscle relaxants, including cyclobenzaprine, in a broad population of patients with spasticity or musculoskeletal conditions.¹⁴ This report included controlled clinical trials and systematic reviews, as well as large high quality cohort studies for safety. Although they had no inclusion criteria with respect to length of follow-up, single dose studies were excluded. Twenty-one placebo-controlled and six active comparator controlled studies were included. Data from included studies was not amenable to pooling in meta-analysis due to methodological and clinical heterogeneity. Results were presented in evidence tables. Tofferi 2004 compared cyclobenzaprine to placebo for fibromyalgia in a systematic review and meta-analysis, including five RCTs, two of which were of crossover and three of parallel design.¹¹ Van Tulder 2003 compared the efficacy and safety of muscle relaxants to placebo, each other, and other analgesics for nonspecific low back pain in a Cochrane systematic review.¹² Five of the included RCTs within this systematic review assessed cyclobenzaprine. Results were described narratively, with insufficient data for meta-analysis. Browning 2001 compared efficacy and safety of cyclobenzaprine vs placebo for the treatment of low back pain a systematic review and meta-analysis.¹³ Fourteen RCTs from 13 publications were included. This study included some RCTs not included by Van Tulder 2003,¹² because this systematic review was not limited to patients without musculoskeletal disorders.¹³

Randomized controlled trials

Four randomized controlled trials in three reports met the eligibility criteria. Alencar 2014 performed an RCT in 45 patients comparing the effectiveness of pharmacological treatment with cyclobenzaprine or tizanidine vs placebo for 3 weeks, in addition to patient education and a self-care management program, for myofascial pain and associated jaw pain on awakening.²³ Khwaja 2010 compared ibuprofen, cyclobenzaprine, or both for 7 days in patients with acute cervical strain (neck pain) due to motor vehicle collisions or falls in 61 patients.¹² Malanga 2009 reported the results of two RCTs with 254 and 250 patients each, assessing the efficacy of cyclobenzaprine extended release 15 mg and 30 mg compared to cyclobenzaprine immediate release 10mg three times daily and placebo for neck or back pain.¹⁹ Although day four outcomes were the primary endpoint of the study, results at 14 days were also reported.

Evidence-based guidelines

Four practice guidelines met eligibility criteria. Guidelines from the Institute for Clinical Systems Improvement for the assessment and management of chronic pain were published in 2013.²¹ This is a “not-for-profit, quality improvement organization based in Bloomington, Minnesota.” Evidence for recommendations was rated using ‘GRADE’ methodology. Additional recent fibromyalgia guidelines including recommendations for its management and diagnosis were published in 2012.²⁰ These guidelines were developed at the request of the Canadian pain society. Recommendations were “graded according to the level of supporting evidence.” “Toward Optimized Practice” Alberta guidelines for management of low back pain published in 2011 aimed “To help Alberta clinicians make evidence-informed decisions about care of patients with nonspecific low back pain.”²² Recommendations in these guidelines are primarily drawn from other previously published guidelines, but evidence was supplemented by a search of more recent literature. Evidence-based guidelines for the treatment of fibromyalgia published in 2004 were funded by the American Pain Society.⁶ These guidelines ranked evidence for treatment efficacy as strong (“positive results from a meta-analysis or consistently positive results from more than 1 randomized controlled trial”), moderate (“positive results from 1 RCT or largely positive results from multiple RCTs or consistently positive results from multiple non-RCT studies”, or weak (“positive results from descriptive and case studies, inconsistent results from RCTs, or both”).

Summary of Critical Appraisal

A summary of the critical appraisal of individual studies is provided in Appendix 3.

All seven included systematic reviews were of acceptable or high quality according to the AMSTAR items. All performed a comprehensive literature search, assessed the quality of included studies, and considered quality of included studies in the formulation of their conclusions. Two of the seven provided an a priori design,^{24,25} and two provided a list of excluded studies.^{25,26} The two systematic reviews in fibromyalgia were of acceptable quality,^{10,11} as were the two systematic reviews in back pain,^{12,13} and the systematic review of treatments for patients with spasticity of any musculoskeletal condition.¹⁴ The Cochrane reviews assessing cyclobenzaprine for myofascial pain¹⁵ and interventions for mechanical neck pain¹⁶ were high quality. Although the included systematic reviews themselves were deemed as being of acceptable to high quality, the quality of the RCTs included within the systematic reviews varied, and this is discussed within the ‘Summary of Findings’ section.

The included randomized controlled trials varied in their risk of bias. The recent RCT reported by Alencar et al. 2014 was deemed to have a high risk of bias.²³ There was a lack of description of randomization, lack of allocation concealment, inadequate blinding of personnel combined with subjective outcome measures, and no sample size calculation was performed. The study of cyclobenzaprine vs ibuprofen or both for neck pain was deemed to have low risk of bias with adequate randomization, allocation concealment and blinding. However, there was no sample size calculation performed.¹⁷ It is possible that the lack of observed differences between groups was due to insufficient power to detect differences. Also, medications were to be taken by patients as needed and the actual frequency of use of medication was not reported. The two randomized controlled trials of identical design reported in Malanga 2009 have an unclear risk of bias. These RCTs in patients with muscle spasm associated with neck or back pain lacked an adequate of description of randomization and allocation concealment methods. Although they were noted to be double-blind, an adequate description of blinding was also lacking.¹⁹

The practice guidelines were all rated as poor to fair quality according to the AGREE II criteria. The 2013 guidelines for the assessment and management of chronic pain were of fair quality.²¹ Although it is noted that a systematic process for searching and selecting the evidence was used, this is not described in detail. The relevant recommendations are non-specific, however this is likely a reflection of the lack of evidence. The 2012 Canadian fibromyalgia guidelines for fibromyalgia were of fair quality.²⁰ Although they had clear scope and purpose, they were lacking in rigour of development with no description of a systematic approach to the selection of evidence, and no description of method for development of recommendations before distribution to panel members for selection. Alberta's 2011 Toward Optimized Practice guidelines for management of low back pain were rated as poor quality.²² The overall objectives and population to which the guidelines were meant to apply were well-described, however these guidelines were also lacking in rigour of development with no description of a systematic approach to the selection of evidence, and no description of methods for development of recommendations. Although it was noted that systematic methods were used to identify more recent evidence, previously published practice guidelines were the source for most of the evidence presented. Competing interests were not declared, and the make-up of the guideline development team was not described. The 2004 guidelines aiming to provide up to date evidence-based guidelines for the treatment of fibromyalgia were rated as poor quality overall, as they were lacking in all domains of the guideline rating tool (scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability, and editorial independence).⁶ Specifically, with respect to rigour of development, although it was noted that a systematic literature search was performed it was not described, nor was the selection criteria for the included studies, or the methods for development of recommendations. Strengths and limitations of included studies were not presented, risks of treatments were not adequately discussed, and an external review was not described.

Summary of Findings

A summary of the results of the individual included studies is provided in Appendix 4.

Clinical Effectiveness

Systematic reviews

Smith 2011¹⁰ performed a systematic review assessing efficacy of medications for treatment of fibromyalgia that included a single RCT that compared cyclobenzaprine to amitriptyline and three RCTs comparing cyclobenzaprine to placebo. All four RCTs were deemed to be of fair quality. The authors concluded from the comparison of cyclobenzaprine (mean dose 20 mg) to amitriptyline that there was no significant difference between the two drugs for pain (reduction of visual analog scores for pain of 33% versus 28%) or other efficacy outcomes, with low-strength of evidence. Strength of evidence incorporates quality, directness, consistency and precision of included studies; a low strength of evidence was defined as "low confidence that the evidence reflects the true effect." (Table 2, page 16) With respect to harms, the RCT comparing cyclobenzaprine to amitriptyline in 184 patients over 6 months found that the occurrence of overall adverse events was similar at 98% vs. 95%, relative risk 1.02 (95% confidence interval [CI], 0.96 to 1.11), with dry mouth, somnolence, dizziness and weight gain being the most frequently reported adverse events. There was a trend towards increased withdrawals due to adverse events with cyclobenzaprine vs amitriptyline at 16% vs. 8%, relative risk 1.90 (95% CI,

0.82 to 4.44). For the comparison of cyclobenzaprine to placebo, efficacy data from the three RCTs could not be pooled due to outcome heterogeneity. Dosing was flexible in all three RCTs and ranged from 10 to 40 mg per day. The largest RCT of 120 patients was the only one to find a significant reduction in pain severity, with a reduction of 28% vs 17% ($P < 0.02$) on visual analogue scale at 12 weeks. Sleep was also improved at 34% vs 18% ($P < 0.02$) at 12 weeks. In this same RCT, physician-rated marked global improvement was significantly more likely in the cyclobenzaprine vs placebo groups, with a relative risk of 2.18 (95% CI: 1.12 to 4.36; $P < 0.012$). For other outcomes including duration of stiffness, fatigue, tender points, muscle tightness, or global pain there was no significant difference at 12 weeks. The two smaller RCTs ($n=40$ and $n=12$) each found no statistically significant differences in pain but trends towards improvement were reported for some outcomes at 6 weeks and 4 weeks respectively. For this comparison, adverse events were not reported consistently in the included RCTs. Pooled data from all three RCTs showed no statistically significant difference in withdrawals due to adverse events between the two groups (95% CI for relative risk, 0.48 to 13.59), however overall occurrence of adverse events was statistically significantly more likely with cyclobenzaprine than with placebo with a relative risk of 1.39 (95% CI 1.14 to 1.76) reported in the largest RCT ($n=120$), as were the individual adverse events of dry mouth and drowsiness.¹⁰

Leite 2009 performed a systematic review of cyclobenzaprine for myofascial pain.¹⁵ Two RCTs were found: one comparing cyclobenzaprine to clonazepam and placebo in a total of 41 patients over three weeks, and another comparing cyclobenzaprine for 15 days to lidocaine infusion in 41 patients. Although cyclobenzaprine was found to have slight improvement in pain intensity compared to clonazepam and placebo, the authors concluded that “There was insufficient evidence to support the use of cyclobenzaprine in the treatment of [myofascial pain]” due to the limited number of patients in which cyclobenzaprine has been studied and the uncertain clinical significance of the results. Compared to lidocaine injection, differences between groups at 30 days were not statistically significant and trended towards improved outcomes with lidocaine. These RCTs were assessed as having low risk of bias in all domains, with the exception of high risk of performance bias in the lidocaine RCT.¹⁵

Peloso 2007¹⁶ was a Cochrane review of cyclobenzaprine for neck pain and found unclear evidence of benefit from two RCTs. One RCT comparing cyclobenzaprine to lysine clonixinate was not relevant, as cyclobenzaprine was used for only four days. The second RCT found that cyclobenzaprine was not superior to placebo for the outcome of global evaluation of muscle spasm at 14 to 18 days in 22 patients.¹⁶

Chou 2005 assessed comparative effectiveness of muscle relaxants in a broad population of patients with spasticity or musculoskeletal conditions.¹⁴ In patients with spasticity, a single RCT comparing cyclobenzaprine to placebo was included. In patients with musculoskeletal conditions, two relevant systematic reviews already included within this report were included,^{11,13} as well as several controlled clinical trials: a single study comparing methocarbamol or placebo to cyclobenzaprine, one comparing cyclobenzaprine to carisoprodol, five trials in four publications compared cyclobenzaprine to diazepam or placebo, and a total of 15 placebo-controlled studies of cyclobenzaprine in 14 publications. When including those studies with an active comparator arm, a total of 21 placebo-controlled studies were included. This comprehensive review concluded that “there is insufficient evidence from other fair quality head-to-head trials to suggest that any other skeletal muscle relaxant is more effective than others in patients with musculoskeletal conditions” and “There is fair-quality evidence from a total of 21 trials (none rated good quality) comparing cyclobenzaprine to placebo (including

head-to-head trials with a placebo arm) that consistently found that cyclobenzaprine is more effective than placebo for various measures of pain relief, muscle spasm, or functional ability in patients with primarily acute back or neck pain.” Detailed evidence tables within provided a detailed summary of results of included studies.¹⁴

Tofferi 2004 included three parallel design and two cross-over randomized controlled trials in a systematic review and meta-analysis comparing cyclobenzaprine to placebo for fibromyalgia.¹¹ Several major flaws within the included RCTs were noted including inadequate description of randomization, failure to identify blinding in all five studies, and large losses to follow-up in four of the five studies. Patients’ global assessment of improvement was statistically significantly superior in the cyclobenzaprine compared to placebo with an OR of 3.0, however assessment of pain on a continuous scale was significantly improved only at week four with a standard mean difference of 0.35, but not at weeks eight and 12.¹¹

Van Tulder 2003 was a systematic review in nonspecific low back pain assessing muscle relaxants.¹² They found “limited evidence” from one low quality RCT in 76 patients pointing towards no difference between cyclobenzaprine vs placebo for muscle spasm in chronic low back pain at 18 days, and also found no significant differences between cyclobenzaprine and diazepam for chronic low back pain in another low quality RCT. A high quality RCT comparing cyclobenzaprine to carisoprodol in acute low back pain also found no significant differences between treatments, whereas a low quality RCT found a statistically significant decrease in muscle spasm with cyclobenzaprine vs NSAIDs after 14 days but no difference in pain or global assessment of efficacy. Two RCTs deemed to be of high quality assessed cyclobenzaprine vs placebo for acute low back pain. A pooled analysis comparing all oral non-benzodiazepine muscle relaxants to placebo did not report results separately for cyclobenzaprine. The two relevant RCTs were described separately. An RCT of 10 days duration in 48 patients found statistically significantly higher number of patients with improvement in pain and spasm, physician’s global evaluation, and activities of daily living with cyclobenzaprine compared with placebo. Another RCT of 14 days duration in 24 patients found statistically significant improvement in pain, daily activities, and global improvement with cyclobenzaprine compared with placebo at day 7 but not at day 14. Effect sizes and their confidence intervals were not reported.¹²

Browning 2001 performed a systematic review and meta-analysis of 14 RCTs from 13 publications comparing cyclobenzaprine to placebo for treatment of back pain.¹³ Although studies were reported overall to be of moderate quality, authors noted major methodological flaws within included RCTs including inadequate description of randomization in nine, and concerns regarding ineffective blinding in 10 studies. Duration of the included studies ranged from 8 to 21 days. Of 10 studies reporting patient or physician reported global improvement in pain at study end, the pooled odds ratio was 4.7 (95% CI 2.7 to 8.1). For continuous variables representing the five domains of back pain (local pain, muscle spasm, tenderness to palpation, range of motion and activities of daily living), cyclobenzaprine was found to be statistically significantly superior to placebo for all comparisons at all three time points assessed, with a statistically significant trend towards decreasing effectiveness over time. Between five and seven studies were pooled for each of these five endpoints. Adverse events overall were more common with cyclobenzaprine compared with placebo, occurring in 53% vs 28% ($P < 0.002$). Drowsiness was the most commonly reported in 20% vs 2% ($P < 0.001$).¹³

Randomized controlled trials

Alencar 2014 randomized a total of 45 patients with myofascial pain and associated jaw pain on awakening to cyclobenzaprine 10 mg daily, tizanidine 4mg daily, or placebo 2 hours before bedtime.²³ Patients received these interventions concomitant with patient education as part of a self-care management program. There were 15 patients in each group. All groups improved from baseline after three weeks, however no significant differences in pain or sleep quality were observed between the three groups. Morning drowsiness was the most commonly reported adverse event, occurring in 13% of placebo, 73% of tizanidine and 53% of cyclobenzaprine group patients.²³

Khwaja 2010 reported the results of an RCT comparing ibuprofen (n=20), cyclobenzaprine (n=21), or both (n=20) in patients with acute cervical strain (neck pain) due to motor vehicle collisions or falls.¹⁷ Outcomes included pain as assessed by visual analogue scale, resumption of normal activities, use of rescue medications, and adverse events. There was no statistically significant difference in any efficacy outcomes. Adverse events were minimal, with four patients out of the total of 41 receiving cyclobenzaprine either alone or in combination reporting dizziness, compared with one of 20 patients receiving ibuprofen alone. The authors conclude that using cyclobenzaprine alone or adding to NSAIDs offers little benefit in this patient population.

Malanga 2009 reports the results of two identically designed RCTs assessing the efficacy of cyclobenzaprine extended release 15 mg and 30 mg once daily compared with immediate release 10mg three times daily or placebo in patients with muscle spasms associated with low back or neck pain.¹⁹ Dropouts were substantial, with 156 of 254 patients completing study #1 and 174 of 250 patients completing study #2. At day 14, although patient's rating of medication helpfulness was statistically significantly superior to placebo for carbamazepine 15mg extended release once daily compared with placebo in study #1, the other study and both 30mg treatment groups were not statistically significantly different than placebo for this or any other efficacy outcomes including physician's global assessment, response vs. nonresponse to treatment, relief from local pain, patients global impression of change, or activities of daily living. With respect to adverse events, in study #1, nine patients in the immediate release cyclobenzaprine group discontinued therapy due to adverse events vs three in the 30mg group, one in the 15mg group, and two in the placebo group. In study #2, five in the immediate release, three in the 30mg and one in each of the other groups discontinued therapy due to adverse events. The extended release cyclobenzaprine products are not currently marketed in Canada. Two serious adverse events were reported in the entire study population and these were thought to be unlikely due to the treatment.¹⁹

Cost-effectiveness

No economic evaluations or systematic reviews of economic evaluations were identified.

Evidence-based Guidelines

Relevant recommendations from the included guidelines are presented in Appendix 5.

The Institute for Clinical Systems Improvement published evidence-based guidelines for the assessment and management of chronic pain in 2013.²¹ These guidelines state that

“Cyclobenzaprine also has modest benefit in patients with fibromyalgia and is used as a standard therapy for muscle pain.” With respect to the use of cyclobenzaprine in neuropathic pain, they cite the systematic review by Tofferi et al.¹¹ Cyclobenzaprine is listed as a drug therapy option for management of muscle pain, however it is noted that recommendations for muscle pain management were made “in the absence of evidence”.²¹

Canadian guidelines for the diagnosis and management of fibromyalgia, endorsed by the Canadian Pain Society and the Canadian Rheumatology Association, were published in 2012.²⁰ Statements within these guidelines relevant to cyclobenzaprine include “Cyclobenzaprine, technically a muscle relaxant, structurally similar to the TCAs, has shown moderate benefit for global improvement with an odds ratio (OR) of 3.0 (95% CI 1.6-5.6).” And that “very low doses of cyclobenzaprine increased restorative sleep, with improvement in fatigue and pain.” Recommendations regarding treatment do not specifically address cyclobenzaprine use.²⁰

Alberta’s 2011 “Toward Optimized Practice” guidelines for the management of low back pain primarily used previously published guidelines as their sources.²² They suggested that for chronic low back pain, muscle relaxants may be appropriate if used selectively and cautiously for pain and muscle spasm. For acute and subacute low back pain, they suggest acetaminophen as first choice and NSAIDs as second choice if medications are necessary, and to “Only consider adding a short course of muscle relaxant (benzodiazepines, cyclobenzaprine, or antispasticity drugs) on its own, or added to NSAIDs, if acetaminophen or NSAIDs have failed to reduce pain.” These guidelines are the only to recommend a specific dosage of cyclobenzaprine. They suggest 10 to 30 mg per day for up to two weeks duration, with the greatest benefit being seen in the first week.²²

Evidence-based guidelines for the treatment of fibromyalgia were published in 2004.¹¹ A review of evidence was performed by 13 methodological experts. These guidelines state that the “strongest evidence for medication efficacy” in fibromyalgia is for cyclobenzaprine and amitriptyline, and that cyclobenzaprine has been effective in RCTs of 6 to 12 weeks duration. This guideline references the systematic review by Tofferi et al included in this report.¹¹

Limitations

Although included systematic reviews were of acceptable to high quality, their ability to draw clear conclusions was limited by the lack of quality and quantity of available RCTs. Included RCTs were often noted to have methodological flaws leading to potential bias, and were generally of small size and short duration. The majority of RCTs included in the systematic reviews were conducted greater than 20 years ago; standards for the conduct and reporting of RCTs have become more rigorous over time, and clinical practice could have changed since most of these RCTs were conducted.

Four recent RCTs of cyclobenzaprine used for different types of pain ranged from low to high risk of bias. Although none showed clear evidence of benefit, these RCTs were all of relatively small size and two of them had no sample size calculation, making them potentially underpowered to detect clinically meaningful differences.

The included clinical practice guidelines were generally lacking in rigour of development. Non-specific recommendations within each of the guidelines with respect to medication use were likely a reflection of the lack of quality and quantity of supporting evidence.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Cyclobenzaprine may be more effective than placebo for symptomatic treatment of fibromyalgia and back pain, but frequently causes side effects including drowsiness, dizziness, and dry mouth. In RCTs comparing cyclobenzaprine to other pharmacologic agents, including benzodiazepines, amitriptyline, and other muscle relaxants, it has not shown to be significantly different. Combination therapy of cyclobenzaprine with NSAIDs was not shown to be superior to cyclobenzaprine alone or placebo for treatment of neck pain. No economic evaluations were identified. Relevant evidence-based clinical practice guidelines include cyclobenzaprine as an option for treatment of symptoms of fibromyalgia, back pain, and muscle pain, but recommendations are non-specific with respect to cyclobenzaprine's dosing, duration, or place in therapy relative to other available treatments.

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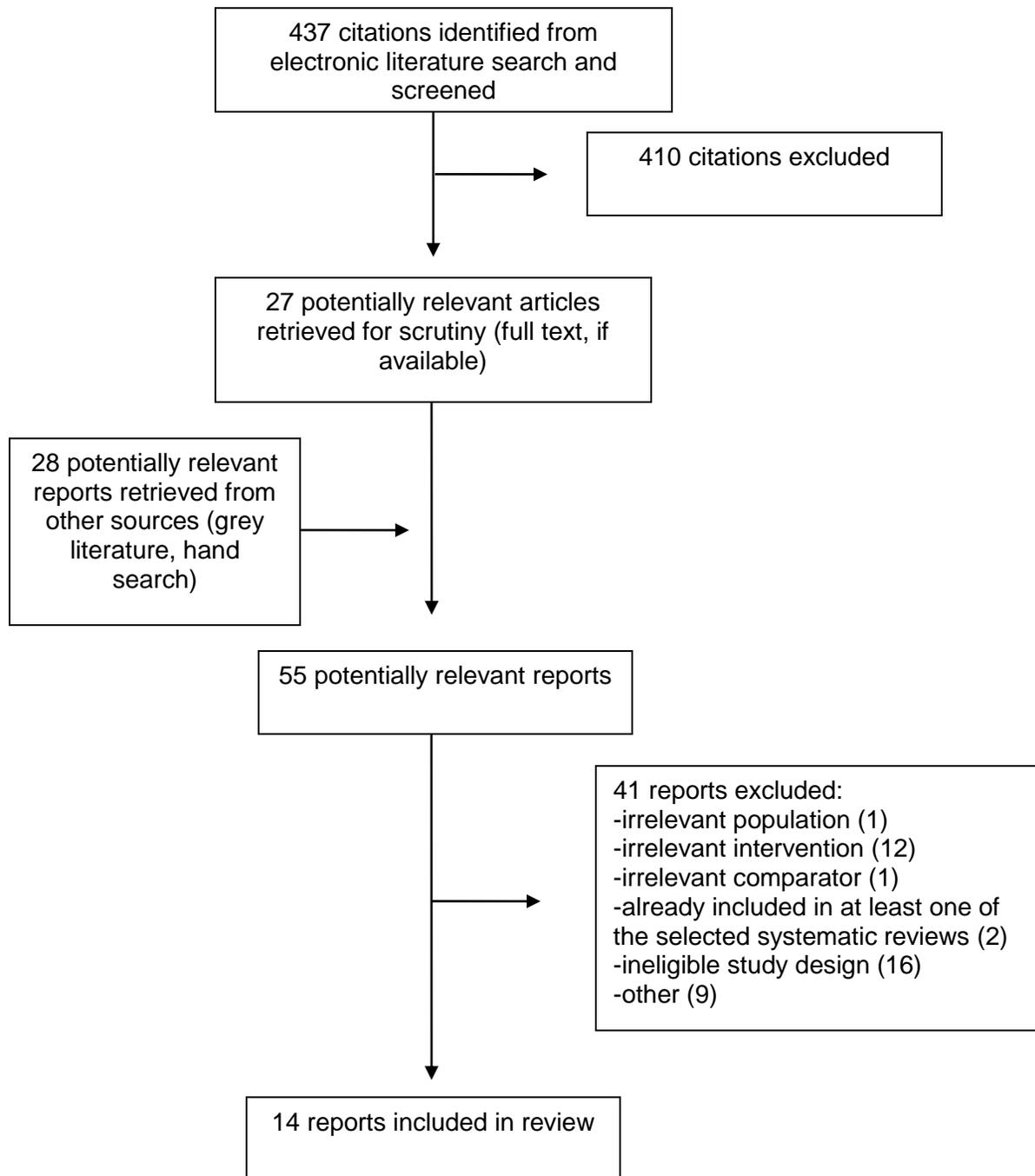
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Appendix 1: Selection of Included Studies



Appendix 2: Summary of Study Characteristics

Characteristics of included systematic reviews					
Author, year, Search date	Method of data synthesis	Population / pain type	Intervention(s)	Comparator(s)	Outcomes
Smith, 2011 ¹⁰ October 2010	Meta-analysis of harms outcomes Insufficient data for meta-analysis of efficacy outcomes	Adults with fibromyalgia	Antidepressants, antiepileptic medications, and muscle relaxants (including cyclobenzaprine)	Placebo, or any of the interventions compared head to head	-Pain (primary outcome), all types of assessments and any time point -Adverse events (overall and specific) -Withdrawal due to adverse events
Leite, 2009 ¹⁵ February 2009	Qualitative summary Insufficient data for meta-analysis	Myofascial pain	Cyclobenzaprine	Placebo, no intervention, physiotherapy, or other control	-Intensity, frequency and duration of pain crises measured using validated scales (primary outcome) -Adverse events -Sleep quality -Quality of life
Peloso, 2007 ¹⁶ December 2006	Qualitative summary Insufficient data for Meta-analysis	Mechanical neck pain	Oral or injectable medications (including cyclobenzaprine)	Any control	-Patient and examiner measured pain -Functional status, work status, -Range of motion -Global perceived effect -Patient satisfaction

Characteristics of included systematic reviews					
Author, year, Search date	Method of data synthesis	Population / pain type	Intervention(s)	Comparator(s)	Outcomes
Chou, 2005 ¹⁴ January 2003	Qualitative summary; evidence tables Insufficient data for meta-analysis	Spasticity and musculoskeletal conditions	Muscle relaxants, including cyclobenzaprine	Any of the interventions compared head to head, to active treatment, or to placebo	-Relief of muscle spasms -Pain -Functional status -Quality of life, -Withdrawal rates -Adverse effects
Tofferi, 2004 ¹¹ November 2000	Meta-analysis and qualitative summary	Fibromyalgia	Cyclobenzaprine	Placebo	-Global improvement -Treatment effects on pain, fatigue, sleep, and tender points
Van Tulder 2003 ¹² October 2001	Qualitative summary Insufficient data for meta-analysis	Non-specific low back pain	Muscle relaxants (benzodiazepines , non-benzodiazepine anti-spasmodics including cyclobenzaprine, and antispasticity medications) alone or in combination with analgesics	Placebo, other muscle relaxants, other analgesics	Pain intensity -Global improvement, -Specific and general functional status -Return to work -Physiologic outcomes
Browning, 2001 ¹³ December 1999	Meta-analysis	Low back pain	Cyclobenzaprine	Any control	-Global improvement -Five domains of back pain

Characteristics of included randomized controlled trials				
Author, year	Population	Intervention	Comparison	Outcome Measures
Alencar, 2014 ²³	Myofascial pain and jaw pain upon awakening	Cyclobenzaprine 10 mg daily, tizanidine 4mg daily (2 hours before bedtime), for 3 weeks	Placebo	-Decrease of pain symptoms evaluated by the modified Severity Symptoms Index and by the pain intensity on a visual analogue scale (primary outcomes). -Change in sleep quality (secondary outcome).
Khwaja, 2010 ¹⁷	Presenting to the emergency department with cervical strain (neck pain)	Cyclobenzaprine 5mg three times daily or cyclobenzaprine plus ibuprofen 800mg three times daily, as needed for up to 7 days	Ibuprofen 800mg three times daily as needed	-Pain as assessed by visual analogue scale -Resumption of normal activities -Use of rescue medications -Adverse events.
Malanga, 2009 ¹⁹	Muscle spasm associated with neck or back pain	Cyclobenzaprine extended release 15mg (study 2) daily or 30 mg daily (study 1), for 14 days	Cyclobenzaprine 10mg three times daily or placebo	-Patients rating of medication helpfulness -Physicians clinical global assessment -Relief from local pain, global impression of change -Activities of daily living -Sleep -Quality of life

Appendix 3: Summary of Critical Appraisal of Included Reports

Summary of strengths and limitations of included studies and guidelines		
Author, publication year, overall assessment of quality/risk of bias	Strengths	Limitations
Systematic reviews:		
Smith, 2011 ¹⁰	<ul style="list-style-type: none"> -List of included and excluded studies provided -Performed a GRADE evaluation of strength of evidence -Comprehensive, well-described literature search 	<ul style="list-style-type: none"> -No a priori design -Limited to English language -Comprehensive search for unpublished studies not performed -Basic characteristics of included studies not provided
Leite, 2009 ¹⁵	<ul style="list-style-type: none"> -A priori design -Comprehensive literature search -Thorough description of methods -Thorough description and quality assessment of included studies -No language or publication status restrictions of eligibility 	<ul style="list-style-type: none"> -Limited evidence available; insufficient quantity for meta-analysis -No list of excluded studies
Peloso, 2007 ¹⁶	<ul style="list-style-type: none"> -A priori design provided -Comprehensive literature search -List of excluded studies provided -No language or publication status restrictions of eligibility -Thorough description of methods 	<ul style="list-style-type: none"> -Limited evidence available; insufficient quantity for meta-analysis
Chou, 2005 ¹⁴	<ul style="list-style-type: none"> -Comprehensive review of a large number of studies -Comprehensive literature search -Evidence tables provided detailed summary of results and level of evidence of all included studies -Searched for unpublished studies 	<ul style="list-style-type: none"> -No a priori design -Study selection by a single reviewer -Difficult to navigate the report due to the large quantity of studies and information and the organization of the report -Limited to English language -Lacking detail re: characteristics of included studies -No list of excluded studies
Tofferi, 2004 ¹¹	<ul style="list-style-type: none"> -Comprehensive literature search 	<ul style="list-style-type: none"> -No a priori design -Study selection not performed

Summary of strengths and limitations of included studies and guidelines		
Author, publication year, overall assessment of quality/risk of bias	Strengths	Limitations
	<ul style="list-style-type: none"> -Study characteristics well-presented -Searched for unpublished studies -Publication bias assessed 	<ul style="list-style-type: none"> in duplicate; data extraction not described -No list of excluded studies -Conflict of interest not declared -Significant flaws in included studies -Lack of full description of outcomes and 95% CIs not presented
Van Tulder, 2003 ¹²	<ul style="list-style-type: none"> -Comprehensive literature search -List of included and excluded studies provided -Searched for unpublished studies -Thorough description of methods 	<ul style="list-style-type: none"> -No a priori design -Results of included studies reported only as significant or non-significant, without 95% confidence intervals -Language restrictions for inclusion -Pooled analysis included all oral non-benzodiazepines, a heterogeneous group of medications -Conflict of interest not declared
Browning, 2001 ¹³	<ul style="list-style-type: none"> -Concise, thorough presentation of study characteristics -Searched for unpublished studies -Publication bias assessed 	<ul style="list-style-type: none"> -No a priori design -Language restrictions for inclusion -Study selection and extraction performed only by a single reviewer -No list of excluded studies -Statistical heterogeneity not adequately explored -Conflict of interest not declared
Randomized controlled trials:		
Alencar, 2014 ²³	<ul style="list-style-type: none"> -Active and placebo control groups 	<ul style="list-style-type: none"> -Lack of description of randomization -Inadequate allocation concealment and blinding, with subjective outcome measures -No sample size calculation
Khwaja, 2010 ¹⁷	<ul style="list-style-type: none"> -Patients and physicians blind to treatment allocation -Adequate description of randomization and allocation concealment 	<ul style="list-style-type: none"> -Small study (20 or 21 patients per group) with no sample size calculation

Summary of strengths and limitations of included studies and guidelines		
Author, publication year, overall assessment of quality/risk of bias	Strengths	Limitations
Malanga, 2009 ¹⁹	<ul style="list-style-type: none"> -Reports the results of two RCTs of identical design -Sample size calculation performed 	<ul style="list-style-type: none"> -Lack of description of randomization or allocation concealment methods -Noted to be double-blind, but blinding not otherwise described
Evidence-based guidelines		
Hooten, 2013 ²¹	<ul style="list-style-type: none"> -Clear scope and purpose (objectives, questions to be addressed, and population to which the guideline is meant to apply) -Competing interests declared -GRADE assessment of level of evidence performed 	<ul style="list-style-type: none"> -Noted that systematic review methods were used, but this was not described in detail -Risks/side effects not explicitly considered -Specific methods of formulating recommendations not described -Non-specific recommendations with respect to pharmacological treatment -No external review
Fitzcharles, 2012 ²⁰	<ul style="list-style-type: none"> -Clear description of objectives, population to which the guidelines apply, and target users of the guidelines -Externally reviewed by experts -Competing interests declared 	<ul style="list-style-type: none"> -No description of systematic methods for selecting evidence -Levels of evidence not defined -Risks/side effects not explicitly considered -Method of drafting recommendations submitted to guideline advisory panel not described
Toward Optimized Practice (Alberta), 2011 ²²	<ul style="list-style-type: none"> -Provides dosing recommendations -Addresses potential harms 	<ul style="list-style-type: none"> -No description of methods used for searching or selecting evidence -No description of methods for formulating recommendations -Strengths and limitations of evidence not provided -Source of information was primarily other guidelines -No list of authors/contributors -Competing interests not declared
Goldenberg, 2004 ⁶	<ul style="list-style-type: none"> -Objectives well described -Key recommendations were easily found within the report 	<ul style="list-style-type: none"> -No description of systematic methods for searching or selecting evidence -Strengths and limitations of evidence not clearly described -No description of methods for

Summary of strengths and limitations of included studies and guidelines		
Author, publication year, overall assessment of quality/risk of bias	Strengths	Limitations
		formulating recommendations -Risks/side effects not explicitly considered -No external review -Lack of consideration to side effects and risks of treatments -No statement of competing interests

Appendix 4: Summary of Results of Included Systematic Reviews and RCTs

Results of included systematic reviews and RCTs				
Author, Year, study design	Intervention/ comparison	# of RCTs, # of patients	Outcome/ Method of data synthesis (if applicable)	Summary of results
Systematic Reviews				
Smith, 2011 ¹⁰	Cyclobenzaprine/ amitriptyline	1 RCT, n=184	Qualitative description	No significant differences for efficacy or safety outcomes (page 76)
	Cyclobenzaprine/ placebo	3 RCTs, n=172	Efficacy outcomes; qualitative description	1 of 3 included studies found statistically significant improvement in some efficacy outcomes at 12 weeks (page 84)
		Overall AEs: 1 RCT n=120 Withdrawal due to AEs: 3 RCTs n=172	Harms outcomes; Meta-analysis	Overall adverse events: RR 1.39 (95% CI 1.14, 1.76); 1 RCT (n=120). Withdrawals due to adverse events: RR 2.56 (95% CI 0.48, 13.59); 3 RCTs (page 84)
Tofferi, 2004 ¹¹	Cyclobenzaprine / placebo	3 RCTs	Patient reported global improvement; Meta-analysis	OR 3.0 (95% CI 1.6, 5.6) (page 11)
		"2-3 RCTs"	Pain on a continuous scale; Meta-analysis	4 weeks: Standard mean difference 0.35, p<0.05 8 and 12 weeks: Not reported, NS, p>0.05 (page 12)
Chou, 2006 ¹⁴	Cyclobenzaprine / diazepam Level of evidence = FAIR	5 RCTs	Efficacy outcomes including pain, spasm, and global response Qualitative synthesis	"2 fair-quality head-to-head trials...found that cyclobenzaprine and diazepam are roughly equivalent for various measures of efficacy but 3 other fair quality trials found that cyclobenzaprine was superior to diazepam for most (2 trials) or some (1 trial) clinical outcomes" (page 76)

Results of included systematic reviews and RCTs				
Author, Year, study design	Intervention/ comparison	# of RCTs, # of patients	Outcome/ Method of data synthesis (if applicable)	Summary of results
	Cyclobenzaprine/ placebo	21 RCTs	Efficacy endpoints Qualitative synthesis	"21 fair-quality trials consistently found cyclobenzaprine to be more effective than placebo for various measures of efficacy (pain relief, muscle spasms, functional status) in patients with musculoskeletal conditions"
Leite, 2009 ¹⁵	Cyclobenzaprine/ clonazepam	1 RCT; 26 patients	Mean change from baseline pain intensity	Mean difference -0.25 (95% CI -0.41, -0.09), P = 0.002
			Side effects	Risk Ratio 1.6 (95% CI 0.71, 3.60)
	Cyclobenzaprine/ placebo	1 RCT; 28 patients	Mean change from baseline pain intensity	Mean difference -0.25 (95% CI, 0.41 to -0.09); P= 0.002
			Side effects	Risk Ratio 3.08 (95% CI 1.02, 9.24)
	Cyclobenzaprine/ lidocaine	1 RCT; 38 patients	Mean global pain	Mean difference 0.90 (95% CI -0.35, 2.15), P= 0.16
			Side effects	Risk ratio 1.39 (95% CI 0.92, 2.10)
Van Tulder, 2003 ¹²	Cyclobenzaprine/ placebo (Chronic low back pain)	1 RCT; 76 patients	Muscle spasm at 18 days	"no difference"
	Cyclobenzaprine/ placebo (acute low back pain)	2 RCTs	Pain, muscle spasm (1 RCT), activities of daily living, physicians global improvement	Statistically significant improvement at 7 days but not 14 days in 1 RCT; statistically significant improvement at 10 days in another RCT
	Cyclobenzaprine/ diazepam (chronic low back pain)	1 RCT	Pain	No significant differences
	Cyclobenzaprine/ carisoprodol (acute low back pain)	1 RCT	Pain	No significant differences

Results of included systematic reviews and RCTs				
Author, Year, study design	Intervention/ comparison	# of RCTs, # of patients	Outcome/ Method of data synthesis (if applicable)	Summary of results
Browning, 2001 ¹³	Cyclobenzaprine/ placebo	10 RCTs, moderate quality overall	Global improvement Meta-analysis	OR 4.7 (95% CI 2.7, 8.1)
		5-7 RCTs for each endpoint	5 domains of back pain (local pain, muscle spasm, tenderness to palpation, range of motion and activities of daily living) Meta-analysis	Statistically significant improvement with cyclobenzaprine vs placebo at all 3 time points (1-4 days, 5-9 days, >9 days); statistically significant trend towards decreasing effectiveness over time (Table 2 and figure 2 page 1618)
		NR	Adverse events	53% cyclobenzaprine vs 28% placebo, p=0.002
Peloso 2007 ¹⁶	Cyclobenzaprine 10mg three times daily/ diazepam 5mg three times daily	1 RCT, n=22	Global evaluation of muscle spasm	No significant difference
Randomized Controlled Trials				
Alencar, 2014 ²³	Cyclobenzaprine 10 mg daily, tizanidine 4mg daily (2 hours before bedtime) vs placebo; in addition to a patient education and self-management program	n=45	-Pain -Sleep quality	No significant differences between groups
Khwaja, 2010 ¹⁷	Cyclobenzaprine/ cyclobenzaprine + ibuprofen/ or ibuprofen	n=61	Change in pain scores over time (main outcome measure)	Mean change in pain score 35, and 43.3, 26 at day 7 Not statistically significantly different.
Malanga, 2009 ¹⁹	Cyclobenzaprine 10mg three times daily/ 15mg extended release	Study 1, n=254 Study 2,	Efficacy results (day 14)	No statistically significant difference for any efficacy endpoints, with the exception of the

Results of included systematic reviews and RCTs				
Author, Year, study design	Intervention/ comparison	# of RCTs, # of patients	Outcome/ Method of data synthesis (if applicable)	Summary of results
	once daily/ 30mg extended release once daily/ placebo	n=250		distribution of responses for patient's rating of medication helpfulness for 15mg daily vs placebo. (page 1191)
95% CI = 95% confidence interval; NS = not significant; RCT = randomized controlled trial; NR= not reported; OR = odds ratio; RR = relative risk				

Appendix 5: Summary of Recommendations from Included Guidelines

Summary of recommendations from included guidelines		
Guideline (author, year, population)	Level of evidence for recommendation	Recommendation
Goldenberg, 2004 ⁶ Fibromyalgia	“Strong Evidence for Efficacy” of cyclobenzaprine as well as amitriptyline	Step 1: involves treatment of comorbidities (e.g. mood disturbances and sleep disorders), followed by: “Step 2: Trial with low-dose tricyclic antidepressant or cyclobenzaprine. Begin cardiovascular fitness exercise program. Refer for cognitive behavior therapy or combine that with exercise.” Step 3: Includes “trials with selective serotonin reuptake inhibitor, serotonin and norepinephrine reuptake inhibitor, or tramadol. Consider combination medication trial or anticonvulsant.” (Page 2393)
Fitzcharles, 2012 ²⁰ Fibromyalgia	Level 1, Grade A Level 5, consensus	“All categories of antidepressant medications including TCAs, SSRIs and SNRIs may be used for treatment of pain and other symptoms in patients with fibromyalgia” “...with choice driven by available evidence for efficacy, physician knowledge, patient characteristics, and attention to side effect profile” (In “Management” section) (Note: cyclobenzaprine is considered as a TCA in this report)
Hooten, 2013 ²¹ Chronic pain	Low quality evidence “In the absence of evidence”	“Pharmacological therapy with FDA indication for fibromyalgia includes pregabalin, duloxetine and milnacipran. Other agents that have been shown to be effective in controlled trials include gabapentin, cyclobenzaprine, tramadol, and tricyclic antidepressants” Regarding muscle pain, drug therapy recommendations include cyclobenzaprine (dose/duration not specified) or tricyclic antidepressants for pain and sleep.
“Toward Optimized Practice”, 2011 ²² Low back pain	Not specified	Chronic low back pain: “Some muscle relaxants (e.g. cyclobenzaprine) may be appropriate in selected patients for symptomatic relief of pain and muscle spasm. Caution must be exercised with managing side effects, particularly drowsiness, and also with patient selection, given the abuse potential for this class of drugs.” (page 17) Acute and subacute low back pain:

		<p>“Prescribe medication, if necessary, for pain relief preferably to be taken at regular intervals. First choice acetaminophen; second choice NSAIDs. Only consider adding a short course of muscle relaxant (benzodiazepines, cyclobenzaprine, or antispasticity drugs) on its own, or added to NSAIDs, if acetaminophen or NSAIDs have failed to reduce pain.” “Drowsiness, dizziness, and dependency are common adverse effects of muscle relaxants.”(page 11).</p> <p>Dosage, for acute pain or flare up of chronic back pain: “10 to 30 mg per day; Greatest benefit seen within one week; therapy up to 2 weeks may be justified.” (page 24. Medication Table, Appendix B)</p>
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