

Cyclobenzaprine and Back Pain

A Meta-analysis

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Background: Back pain is a common problem for which cyclobenzaprine hydrochloride is frequently prescribed.

Objective: To perform a systematic review of cyclobenzaprine's effectiveness in the treatment of back pain.

Methods: We searched MEDLINE, PsycLIT, CINAHL, EMBASE, AIDSLINE, HEALTHSTAR, CANCERLIT, the Cochrane Library, Micromedex, Federal Research in Progress, and the references of reviewed articles, and contacted Merck, Sharpe and Dohme for English-language, randomized, placebo-controlled trials of cyclobenzaprine in adults with back pain. Outcomes included global improvement and 5 specific domains of back pain (local pain, muscle spasm, range of motion, tenderness to palpation, and activities of daily living). Study quality was assessed using the methods of Jadad. Summary outcomes were obtained using a random-effects model.

Results: Patients treated with cyclobenzaprine were nearly 5 times (odds ratio, 4.7; 95% confidence interval, 2.7-8.1) as likely to report symptom improvement by day

14 as were those treated with placebo. Slightly fewer than 3 individuals (2.7; 95% confidence interval, 2.0-4.2) needed treatment for 1 to improve. The magnitude of this improvement was modest, with an effect size of 0.38 to 0.58 in all 5 outcomes (local pain, muscle spasm, tenderness to palpation, range of motion, and activities of daily living). Treatment efficacy for these 5 outcomes was greatest early, in the first few days of treatment, declining after the first week. Patients receiving cyclobenzaprine also experienced more adverse effects, the most common being drowsiness.

Conclusions: Cyclobenzaprine is more effective than placebo in the management of back pain; the effect is modest and comes at the price of greater adverse effects. The effect is greatest in the first 4 days of treatment, suggesting that shorter courses may be better. Studies comparing the relative value of acetaminophen, nonsteroidal anti-inflammatory drugs, and cyclobenzaprine individually and in combination in the treatment of back pain are needed.

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BACK AND NECK pain are common, accounting for 1.8% of all office visits in the United States, approximately 200 000 visits per year.¹ Among adults presenting with a physical complaint, these problems are second only to upper respiratory tract infections as a reason for seeking medical care.²⁻⁴ Since only about a fourth of patients with a physical symptom seek medical attention,⁵ back and neck pain are even more prevalent in the general population. It is estimated that up to half of working adults experience back pain each year,⁶ and 70% of all adults experience it at some time in their life.⁷ Most episodes are self-limited, with 90% of patients recovering to full activity within 1 month.⁸ Even among the 2% with sciatica, more than half improve substantially within 6 weeks and only 5% to 10% eventually require surgery.⁶

Guidelines for treating back pain recommend empirical therapy, with no radiologic evaluation in most patients.⁷⁻¹⁰ The

Agency for Health Care Policy and Research (AHCPR) back pain guidelines,¹¹ released in 1994, suggest that acetaminophen is the safest and most effective medication for acute low back problems and that nonsteroidal anti-inflammatory drugs (NSAIDs), although effective, should be used sparingly since they can cause gastrointestinal irritation, ulceration, and, less commonly, renal or allergic problems. The panel recommended that muscle relaxants not be used, because they were believed to be no more effective than NSAIDs; their use in combination with acetaminophen or NSAIDs had no additional demonstrated benefit; and adverse effects, including drowsiness, are common.

Despite these guidelines, cyclobenzaprine hydrochloride is still commonly used in the management of acute back pain. National Ambulatory Medical Care Survey data from 1995 to 1997 indicate that among 7 million ambulatory visits to primary care physicians for back pain, 13% of the patients received cyclobenzaprine.¹² Be-

MATERIALS AND METHODS

For this review, we searched MEDLINE (January 1966-December 1999), PsycLIT (November 1887-December 1999), CINAHL (1982-1999), EMBASE (January 1974-December 1999), AIDSLINE, HEALTHSTAR, CANCELIT, and Micromedex using the text word and keyword (all languages) *cyclobenzaprine*. An additional search using the Medical Subject Heading terms *dibenzocycloheptenes* and *propylamines* was combined with the following text words: *back pain*, *backache*, *low back pain*, *lumbago*, *acute muscle spasm*, or *muscle spasm*. We used the Cochrane Library, searching the clinical trials registry for randomized trials, and the Cochrane Database of Systematic Reviews for systematic reviews. We searched Federal Research in Progress to identify unpublished literature. We searched the references of reviewed articles for additional articles missed by the computerized database search. We also contacted Merck, Sharpe and Dohme, West Point, Pa.

Studies were screened for inclusion (through review of the abstract or the published article, if the abstract was unclear) based on the following criteria: randomization, placebo control, at least one group receiving cyclobenzaprine, and measurable outcomes reported. Studies evaluating cyclobenzaprine in the treatment of muscle spasticity of central nervous system origin were excluded from this meta-analysis. Authors of abstracts that appeared promising were contacted and asked to provide data.

Included study quality was assessed using a 6-item instrument developed and validated by Jadad et al.¹³ The 6 items in this scale include description of randomization, adequacy of blinding, description of withdrawals and dropouts, appropriateness of statistical analysis, description of inclusion and exclusion criteria, and method for assessing adverse treatment effects. The study quality was assessed independently in duplicate, with substantial inter-rater agreement (κ , 0.79). Disagreements were arbitrated by consensus.

Abstracted data included setting, country of origin, treatment characteristics (dose, duration, and follow-up), demo-

graphics, number of participants enrolled, follow-up losses, adverse effects, and outcomes. Outcomes were extracted as either dichotomous or continuous variables (or both), depending on how they were reported in the studies.

All analyses were done using Stata 6.0 (Stata Corp, College Station, Tex). Assessment for publication bias was done using the methods of Egger et al¹⁴; heterogeneity was assessed visually with Galbraith plots¹⁵ and Q (χ^2) statistics using the methods of Mantel-Haenszel.¹⁶ Although most pooled results were homogeneous, the more conservative random-effects model using the method of DerSimonian and Laird¹⁶ was used to calculate summary odds ratios (ORs), risk differences, and standardized mean differences. Analysis of the continuous outcome involved comparing standardized differences in means between control and treatment groups. Mean outcome scores for the 5 continuous outcomes (local pain, muscle spasm, tenderness to palpation, range of motion, and activities of daily living) were standardized by dividing the means for the placebo and treatment groups in each study by their SD. The differences between these standardized outcome scores, also known as *effect sizes*, were calculated for each study and analyzed. This approach is especially appropriate when studies measure the same concept but use various continuous scales. By standardization, the study results are transformed to a common scale (SD units) that facilitates pooling.

Several measures of the sensitivity of the meta-analysis results to various assumptions were conducted. The sensitivity of the results to the existence of unpublished studies was assessed using a "file drawer" test,¹⁷ conducted by determining how many studies with negative results (OR, 1.0; standardized mean difference, 0), each with variance and size equal to the average found among the included studies, would have to exist to negate our findings. A test for the relative influence of each individual study on the results was determined by sequentially dropping individual studies and calculating summary measures. We explored several sources of heterogeneity, including year of publication, type of syndrome (acute vs chronic back pain), study quality scores, and duration and dose of therapy using metaregression.

cause cyclobenzaprine is frequently used for the management of back pain, we conducted a meta-analysis of the English-language literature to assess the efficacy of this treatment option.

RESULTS

Our literature search produced 315 articles, 20¹⁸⁻³⁷ of which appeared to be potential candidates for inclusion in the analysis. Of these 20, 7 were excluded because 1¹⁹ was non-English, 2^{28,29} were observational studies, 1²⁰ had no independent cyclobenzaprine arm, and 3^{23,26,27} had no placebo arm, leaving 13^{18,21,22,24,25,30-37} that met the inclusion criteria. One of these¹⁸ was an abstract for which the authors provided additional information and data. Another article³⁶ included results from 2 independent trials, producing a final total of 14 studies (**Table 1**).

These 14 randomized controlled trials were of moderate quality, with a mean quality score of 4.3 (95% confidence interval [CI], 3.3-5.3; median, 4.0; range, 1-8). While

all studies were randomized and placebo controlled, there were several specific quality problems (Table 1), including inadequate description of the randomization method in 9,^{18,21,22,25,30-32,35,37} failure to describe the placebo as identical to the active medicine in 10,^{18,21,22,25,30-33,35,37} no description of or excessive withdrawals in 3,^{18,32,37} no intention-to-treat analysis in 11,^{21,22,24,25,30,32-36} inadequate description of the selection or exclusion criteria in 2,^{30,31} and no sample size calculations in all.^{18,21,22,24,25,30-37} None of the studies directly tested patients for the effectiveness of blinding, but all but 3 of the studies^{21,34,37} had significantly greater adverse effects in the treatment than the placebo group, suggesting failure to maintain blinding. One of the studies³¹ had an inadequate discussion of adverse medication effects. Many studies^{18,21,24,30,33-37} either were sponsored by or received editorial support from pharmaceutical companies.

Although some of the trials had treatment arms with other drugs, including diazepam,^{30-32,35,36} diflunisal (Dolobid),²¹ and methocarbamol,²² only cyclobenzaprine and

Table 1. Characteristics of the Included Studies*

Source, y	Location	Syndrome and/or Comments†	Drug Data‡	Length of the Trial, d	Quality Score§	Quality Problems
Larouche et al, ¹⁸ 1999	United States (20 primary care clinics)	Acute back or neck pain and muscle spasm for <14 d; patient-rated outcomes; sponsored by Merck, Sharpe and Dohme; and unpublished data	Cyclobenzaprine, 5 mg TID (n = 242), vs cyclobenzaprine, 10 mg TID (n = 249), vs placebo (n = 246)	14	4	Inadequate description of randomization, placebo not described as identical, inadequate description of withdrawals, and no sample size calculations
Basmajian, ²¹ 1989	Canada (20 primary care clinics)	Acute back pain and muscle spasm for <10 d; physician-rated outcomes; and participation by Merck, Sharpe and Dohme	Cyclobenzaprine, 5 mg BID (n = 43), vs cyclobenzaprine, 5 mg, plus diflunisal, 500 mg, BID (n = 43), vs diflunisal, 500 mg BID (n = 44), vs placebo (n = 45)	10	2	Inadequate description of randomization, placebo not described as identical, no intention-to-treat analysis, method of statistical analysis not stated, and no sample size calculations
Preston et al, ²² 1984	United States and Canada (12 investigators)	Acute back pain and muscle spasm for <14 d; physician-rated outcomes; and sponsored by A. H. Robins Co, Inc.	Cyclobenzaprine, 10 mg TID (n = 87), vs methocarbamol, 1500 mg QID (n = 94), vs placebo (n = 46)	8	4	Inadequate description of randomization, placebo not described as identical, and no intention-to-treat analysis
Baratta, ²⁴ 1982	United States	Acute back pain and muscle spasm; physician-rated outcomes, except for VAS for local pain; and assistance with the statistical analysis provided by Merck, Sharpe and Dohme	Cyclobenzaprine, 10 mg TID to QID (n = 58), vs placebo (n = 59)	10	8	No intention-to-treat analysis and no sample size calculations
Steingard et al, ²⁵ 1980	United States (3 clinics)	Acute back or neck pain and muscle spasm; and outcomes described as observations, but rater not specifically described	Cyclobenzaprine, 10 mg TID (n = 41), vs placebo (n = 42)	21	4	Inadequate description of randomization, placebo not described as identical, no intention-to-treat analysis, and no sample size calculations
Nibbelink et al, ³⁰ 1978	United States (20 clinics)	Acute back or neck pain and muscle spasm; physician-rated outcomes; and sponsored by Merck, Sharpe and Dohme	Cyclobenzaprine, 10 mg TID (n = 434), vs diazepam, 5 mg TID (n = 280), vs placebo (n = 439)	14	3	Inadequate description of randomization, placebo not described as identical, no intention-to-treat analysis, inadequate description of selection or exclusion criteria, and no sample size calculations
Brown and Womble, ³¹ 1978	United States	Chronic back or neck pain for >12 mo and nonphysician rater of outcomes to lessen bias	Cyclobenzaprine, 10 mg TID (n = 16), vs diazepam, 5 mg TID (n = 16), vs placebo (n = 17)	14	1	Inadequate description of randomization, placebo not described as identical, no sample size calculations, method of statistical analysis not stated, inadequate description of selection or exclusion criteria, and inadequate description of adverse effects
Basmajian, ³² 1978	United States	Chronic and subacute back and neck pain for >30 d (study 1 of 2 presented in the article) and physician-rated outcomes	Cyclobenzaprine, 10 mg TID (n = 17), vs diazepam, 5 mg TID (n = 16), vs placebo (n = 19)	18	3	Inadequate description of randomization, placebo not described as identical, inadequate description of withdrawals, no intention-to-treat analysis, and no sample size calculations
Bianchi, ³³ 1978	Italy	Acute back or neck pain and muscle spasm for <14 d; rater of outcomes not described; and sponsored by Merck, Sharpe and Dohme	Cyclobenzaprine, 10 mg TID (n = 24), vs placebo (n = 24)	14	6	Placebo not described as identical, no intention-to-treat analysis, and no sample size calculations
Aiken, ³⁴ 1978	United States	Acute back or neck pain and muscle spasm for <10 d; rater of outcomes not described; and sponsored by Merck, Sharpe and Dohme	Cyclobenzaprine, 10 mg TID (n = 25), vs placebo (n = 25)	14	8	No intention-to-treat analysis and no sample size calculations

(continued)

Table 1. Characteristics of the Included Studies* (cont)

Source, y	Location	Syndrome and/or Comments†	Drug Data‡	Length of the Trial, d	Quality Score§	Quality Problems
Aiken, ³⁵ 1978	United States	Acute back or neck pain and muscle spasm for <30 d; physician-rated outcomes; and sponsored by Merck, Sharpe and Dohme	Cyclobenzaprine, 10 mg TID (n = 37), vs diazepam, 5 mg TID (n = 38), vs placebo (n = 39)	14	4	Inadequate description of randomization, placebo not described as identical, no intention-to-treat analysis, and no sample size calculations
Scheiner, ³⁶ 1978						
Study 1	United States	Acute back or neck pain and muscle spasm for <30 d; physician-rated outcomes; and editorial assistance provided by Merck, Sharpe and Dohme	Cyclobenzaprine, 10 mg TID (n = 34), vs diazepam, 5 mg TID (n = 32), vs placebo (n = 30)	14	8	No intention-to-treat analysis and no sample size calculations
Study 2	United States	Acute back or neck pain and muscle spasm for <30 d; physician-rated outcomes; goniometric measurements also performed; and editorial assistance provided by Merck, Sharpe and Dohme	Cyclobenzaprine, 10 mg TID (n = 24), vs diazepam, 5 mg TID (n = 21), vs placebo (n = 24)	14	8	No intention-to-treat analysis and no sample size calculations
Bercel, ³⁷ 1977	United States	Moderate to severe local neck or back pain and muscle spasm for >30 d in patients with an x-ray file-confirmed diagnosis of osteoarthritis of the cervical or lumbar spine; outcome rater not described; and assistance provided by Merck, Sharpe and Dohme	Cyclobenzaprine, 10 mg TID (n = 27), vs placebo (n = 27)	14	3	Inadequate description of randomization, placebo not described as identical, inadequate description of withdrawals, no intention-to-treat analysis, and no sample size calculations

*TID indicates 3 times daily; BID, 2 times daily; QID, 4 times daily; and VAS, visual analog scale.

†Merck, Sharpe and Dohme is located in West Point, Pa; and A. H. Robins Co, Inc, in Richmond, Va.

‡Cyclobenzaprine was given as cyclobenzaprine hydrochloride.

§The range was from 0 (lowest) to 8 (highest).

placebo data from each trial were abstracted. Cyclobenzaprine was given in 10-mg tablets, except in 2 studies,^{18,21} in which 5-mg tablets were used. The daily dose ranged from 10 to 60 mg, titrated based on the adverse effects, with a median dose of 30 mg/d. One study²¹ used a twice-daily dose of cyclobenzaprine, and the remainder of the studies^{18,22,24,25,30-37} used 3 times daily doses. The study duration averaged 12.3 days, ranging from 7 to 18 days (median, 14 days).

All 14 studies^{18,21,22,24,25,30-37} focused on low back pain in association with muscle spasm, although 5³³⁻³⁷ also included data on cervical or neck pain and muscle spasm. Eleven studies^{18,21,22,24,25,30,33-36} included only acute back pain, with 3^{31,32,37} evaluating chronic low back pain. Exclusion criteria were consistent between the studies: all excluded persons with spasticity or rigidity due to central nervous system pathological features, those with worker's compensation, and those involved in litigation. Patients with glaucoma; urinary retention; urinary tract infection; cardiac, pulmonary, hepatic, hematological, or renal diseases; rheumatoid arthritis; irreversible ankylosis; irreversible contractures; and mental disorders were also excluded. Excluded drugs included tranquilizers, antidepressants, corticosteroids other than oral contraceptives, muscle relaxants, and analgesics. One study³⁷ focused on muscle spasm and pain associated with lumbar and cervical osteoarthritis.

All 14 studies^{18,21,22,24,25,30-37} had extractable data. Thirteen articles^{18,21,24,25,30-37} reported a global measure of symp-

tom improvement. While articles reported this outcome at various time points, only global improvement at the end of the trials was present in a sufficient number of studies to be considered reliable enough for this analysis. Nine^{24,25,30,31,33-37} of these ratings of improvement were physician rated, and 1¹⁸ was patient rated.

Among the 10 studies^{18,24,25,30,31,33-37} reporting global improvement in back pain at the end of the trial, the summary OR for improvement by day 10 was 4.7 (**Figure 1**). There was evidence of heterogeneity between the different studies ($\chi^2_0 = 25.90$; $P = .002$) but no evidence of publication bias (Egger $P = .37$). The pooled risk difference for these studies was 0.37 (95% CI, 0.24-0.50), which calculates to 2.7 (95% CI, 2.0-4.2) individuals needing treatment for 1 to experience symptom improvement.

In addition to a global rating of improvement, data were abstracted for 5 continuous variables: local pain, muscle spasm, tenderness to palpation, range of motion, and activities of daily living. These data were abstracted at 3 points (days 1-4, 5-9, and >9) and were largely patient rated. The results of analysis of each of these 5 continuous variables at each of the 3 points are given in **Table 2** and presented graphically in **Figure 2**. At all 3 points, patients treated with cyclobenzaprine had significantly greater improvement in all 5 variables reported. For 4 of the variables (muscle spasm, tenderness to palpation, range of motion, and activities of daily living), there was a greater difference between the placebo and cyclobenzaprine groups in

the first 3 days of treatment than at either 1 or 2 weeks. In the first few days of treatment, patients had an average effect size of 0.52 (modest), an effect that declined to 0.44 through the end of the trials. To put this into context, an effect size of 0.2 is considered small; 0.5, moderate; and 0.8, large.³⁸ While the differences at the 3 points were not significant, there was statistical evidence of a trend toward decreasing effectiveness over time ($P = .04$). There was no evidence of statistical heterogeneity for any of the continuous points abstracted.

For the global improvement outcome and for the first few days among 4 of the continuous outcomes (local pain, muscle spasm, tenderness to palpation, and range of motion), there was statistical evidence for publication bias (Table 2). Because of this possibility, we conducted a file drawer test to see how many unpublished studies with negative findings would have to be filed away somewhere to negate our findings. We found that there would have to be 947 studies finding no global improvement with the use of cyclobenzaprine and between 201 and 786 studies (Table 2) finding no benefit in our 5 specific back pain measures to negate our results.

A sensitivity analysis was also performed to assess the effects of study quality, year of publication, duration of treatment, type of back pain, and whether Merck, Sharpe and Dohme sponsored the study. There was no effect of any of these on our data. We also explored the effect of dropping individual studies from our meta-analysis, also without significant effect on our summary OR.

Patients treated with cyclobenzaprine were significantly more likely to experience adverse effects (Table 3). Fifty-three percent of the patients receiving cyclobenzaprine experienced at least one adverse effect, compared with 28% receiving placebo. The most common adverse effects included drowsiness, dry mouth, and dizziness.

COMMENT

Our meta-analysis suggests that cyclobenzaprine may be useful in the management of back pain. Patients given cyclobenzaprine were nearly 5 times more likely to improve, and only 3 patients needed to be treated for 1 to improve. In the 5 domains of back pain and disability (local pain, muscle spasm, tenderness to palpation, range of motion, and activities of daily living), the magnitude of improvement was modest, with an average effect size of 0.5. There was evidence of a trend toward decreasing efficacy over time, with the greatest effect in the first few days of treatment. This improvement was accompanied by adverse effects: more than half of the patients experienced at least one, with drowsiness being the most common.

The AHCPR clinical practice guidelines,¹¹ released in 1994, recommend acetaminophen as the first choice for treating back pain. Nonsteroidal anti-inflammatory drugs, while deemed effective, were considered less optimal secondary to adverse effects. The AHCPR further recommended that muscle relaxants not be used. The AHCPR's qualitative review was based on 0 studies specifically examining acetaminophen and back pain, on 4 randomized controlled trials of NSAIDs, and on 12 randomized controlled trials evaluating muscle relaxants, although only 2 evaluated cyclobenzaprine. Our search

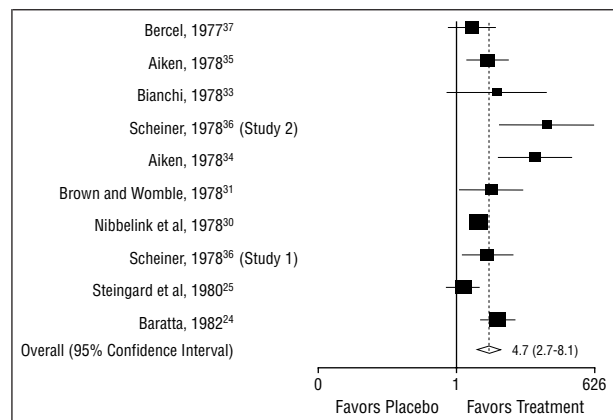


Figure 1. Likelihood of experiencing overall improvement in back pain by the end of the study among patients treated with cyclobenzaprine hydrochloride compared with placebo. Squares represent the sample size; horizontal lines, the respective 95% confidence intervals of the odd ratios.

found 14 randomized placebo-controlled trials of cyclobenzaprine, most (11 of the 14) not indexed in MEDLINE, the search engine the AHCPR panel used.¹¹

Another systematic review³⁹ that looked at muscle relaxants as a class included studies of tizanidine hydrochloride, dantrolene sodium, carisoprodol, methocarbamol, baclofen, orphenadrine citrate, chlormezanone, diazepam, and tetrazepam, although only one study evaluated cyclobenzaprine. Among these 14 trials, 11 found benefit and 3 did not, although only 8 were placebo controlled. The review concluded that there was strong evidence for the benefit of muscle relaxants and that the different types of muscle relaxants were equally effective in treating acute back pain.

There are several other common treatment modalities for acute low back pain. While they are the most commonly used medicine in low back pain, evidence for the effectiveness of NSAIDs is modest. The AHCPR low back pain NSAID recommendations¹¹ are based on 4 randomized placebo-controlled trials⁴⁰⁻⁴³ that looked at diclofenac, piroxicam, naproxen sodium, and diflunisal. Two of these studies^{41,43} were placebo controlled, and 1⁴² compared diflunisal alone with diflunisal in combination with cyclobenzaprine and placebo. The fourth study⁴⁰ compared diclofenac to manipulation, physical therapy, bed rest, back school, and placebo (topical gel). The results were mixed: one⁴³ found NSAIDs superior to placebo at all time points, another⁴¹ found benefit only at day 3 of treatment, and another⁴² found that the combination of an NSAID and cyclobenzaprine helped only at day 4. A recent systematic review³⁹ of back pain treatment retrieved 19 randomized controlled trials evaluating NSAIDs. Eleven studies of acute back pain found no benefit, 7 found benefit, and 1 was unclear. The researchers concluded that while NSAIDs were better than placebo, they might not be better than other analgesic agents.

The AHCPR panel also concluded that the evidence could not support a recommendation for using muscle relaxants in combination with NSAIDs vs using NSAIDs or acetaminophen alone. This is based on one 4-armed study²¹ (n = 175) that compared diflunisal, cyclobenzaprine, diflunisal combined with cyclobenzaprine, and placebo, finding that the combination of dif-

Table 2. Standardized Mean Differences Between Treatment With Placebo and Cyclobenzaprine*

Outcome	Standardized Mean Difference (95% Confidence Interval)	No. of Studies	Heterogeneity (P)†	Publication Bias (P)‡	File Drawer Test§
Local pain, d					
1-4	0.41 (0.29-0.53)	7	.56	.02	786
5-9	0.38 (0.21-0.56)	7	.19	.22	323
>9	0.44 (0.24-0.64)	6	.84	.89	231
Muscle spasm, d					
1-4	0.53 (0.33-0.73)	6	.53	.01	363
5-9	0.46 (0.27-0.66)	6	.72	.49	624
>9	0.45 (0.21-0.69)	6	.61	.20	287
Tenderness to palpation, d					
1-4	0.54 (0.33-0.75)	5	.55	.01	233
5-9	0.46 (0.23-0.69)	6	.21	.12	202
>9	0.45 (0.25-0.65)	6	.67	.70	252
Range of motion, d					
1-4	0.58 (0.38-0.77)	6	.87	.02	431
5-9	0.48 (0.23-0.73)	7	.10	.08	252
>9	0.38 (0.16-0.60)	7	.24	.15	201
Activities of daily living, d					
1-4	0.54 (0.34-0.74)	6	.50	.13	384
5-9	0.44 (0.19-0.69)	7	.10	.16	205
>9	0.49 (0.30-0.69)	7	.53	.85	461

*Cyclobenzaprine was given as cyclobenzaprine hydrochloride.

† χ^2 Test; $P < .10$ indicates heterogeneity of the effect size between studies.

‡Egger test; $P < .10$ indicates bias against small studies with negative findings.

§Rosenthal test; indicates the number of studies with no effect needed to negate the effect found in the analysis for this outcome.

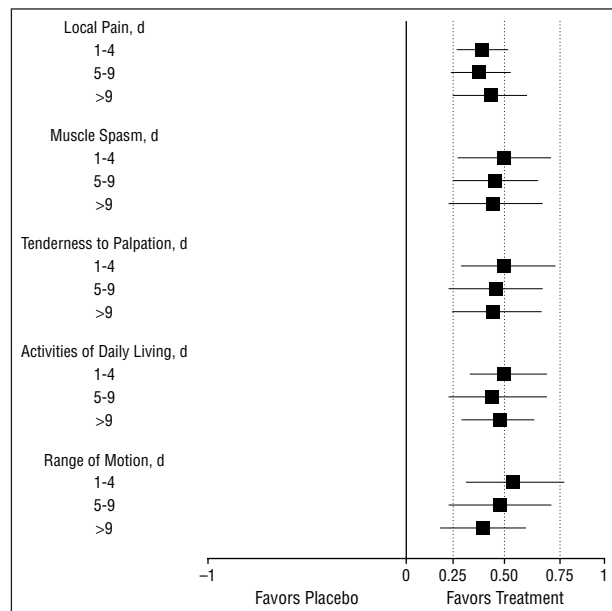


Figure 2. Standardized mean differences in patient response to cyclobenzaprine hydrochloride compared with placebo on 5 different domains of back pain. Squares represent the sample size; horizontal lines, the respective 95% confidence intervals of the effect size.

lunisal and cyclobenzaprine was better at only one point, day 4, compared with either drug alone or placebo. Another small ($n=40$) non-placebo-controlled study²⁰ evaluating the combination of naproxen and cyclobenzaprine vs naproxen alone found the combination to be better than either alone for the relief of muscle spasm and tenderness, with a greater range of motion of the lower back ($P < .05$). Although the available evidence for the use of a combination of muscle relaxants and NSAIDs in the

Table 3. Comparison of Adverse Effects Between Cyclobenzaprine and Placebo*

Adverse Effect	Cyclobenzaprine	Placebo	P
Drowsiness	20	2	<.001
Dry mouth	8	2	.02
Dizziness	7	4	.04
Nausea	2	2	.70
Any	53	28	.002

*Data are given as the percentage of patients. Cyclobenzaprine was given as cyclobenzaprine hydrochloride.

treatment of back pain is limited, it implies a positive role for the combination.

The use of tricyclic antidepressants, which are chemically comparable to cyclobenzaprine, in the management of back pain has been studied, with mixed results. Some studies⁴⁴⁻⁴⁶ found benefit, particularly among patients with comorbid depression,^{47,48} and others⁴⁹⁻⁵¹ found no benefit. A recent meta-analysis⁵² suggested no benefit for the use of tricyclic antidepressants in patients with back pain, although the included studies focused on chronic back pain. Since low back pain has been associated with a higher prevalence of mental disorders and cyclobenzaprine is chemically similar to tricyclic antidepressants, it is possible that the effect found may be a result of treating depression. While most of our studies excluded mental disorders, no study used validated instruments to screen or control for depressive symptoms in its analysis. However, the low doses of cyclobenzaprine used, and the rapidity of improvement in symptoms, argue against a treatment effect mediated by resolution of depressive symptoms.

Other treatment modalities, including acupuncture and chiropractic care, have also been reviewed. A Cochrane Collaboration meta-analysis⁵³ of acupuncture, based on a review of 11 low-quality randomized controlled trials, concluded that there was no evidence that acupuncture was more effective than no treatment, trigger-point injection, or transcutaneous electrical nerve stimulation. Similarly, a systematic review⁵⁴ of the use of chiropractic care, based on 8 low-quality randomized controlled trials, found no convincing evidence of superiority to placebo treatment.

While our results suggest a modest benefit from the use of cyclobenzaprine, there are several important limitations to these findings. First, 10 of the 14 trials had evidence that blinding may not have been effective; patients receiving cyclobenzaprine had more adverse effects than those treated with placebo. The most common adverse effects were sedation, dry mouth, fatigue, and dizziness (Table 3). Inadequate blinding has been believed to be responsible for bias in previous trials suggesting benefit from ascorbic acid⁵⁵ and zinc⁵⁶ for the common cold. Our results may be particularly prone to this bias, since most outcomes are based on physician rather than patient reports of symptom improvement. One of our studies¹⁸ that used patient ratings had results consistent with those based on physician ratings. Another study³⁰ explored the potential biasing effect of higher rates of adverse effects by stratifying patient results by the presence or absence of adverse effects. This study³⁰ found the rate of improvement between both groups to be equal, and concluded that the potential unmasking of treatment group by adverse effects had no impact on patient outcomes.

A second problem was heterogeneity of our dichotomous outcome, global improvement. We explored for the possible sources of this heterogeneity among the trials. Three studies^{31,32,37} explored chronic rather than acute back pain, another³⁷ focused on osteoarthritis, and study quality varied widely among trials. Drug companies also sponsored some studies. None of these factors explained the heterogeneity in our data. While 2^{34,36} of the trials had significantly greater treatment effects than the remaining ones, deleting any single trial had no significant effect on the summary OR, and even when both were simultaneously dropped, there was still evidence for benefit (OR, 2.9; 95% CI, 2.3-3.7). There was no evidence of heterogeneity among any of our continuous outcomes, perhaps because of the remarkable consistency among the trials in reporting on all 5 outcomes (local pain, muscle spasm, tenderness to palpation, range of motion, and activities of daily living) and in using similar scales.

Another problem in our analysis was the presence of publication bias among some of our 5 continuous outcomes. Publication bias looks for evidence that small trials with negative findings may be missing from the analysis, that they have been "filed away" rather than published. Publication bias posits that trials showing effectiveness would probably be published, as would large trials with negative findings. The concern is that there may be small trials that may not be published if they have negative findings, since they would meet considerable editorial obstacles on the issue of being "underpowered." To see what effect such studies could have on our meta-analysis, a file

drawer test was conducted. This asks the following question: how many studies with negative findings would there have to be, filed away somewhere, for the meta-analysis to reach a wrong conclusion? In this analysis, the results are comfortably large. It seems unlikely that several hundred trials with negative findings could exist, filed away somewhere. We searched exhaustively for unpublished studies, including searching the National Institutes of Health's database of funded research and asking pharmaceutical companies. The many studies with negative results needed to negate our findings is not evidence that cyclobenzaprine is effective. This determination should be based on the quality of the underlying trials and on the quality of the meta-analysis. In this case, we found a 5-fold increase in the likelihood of reporting at least modest improvement in symptoms. A large file drawer test result is reassuring that the analysis is not likely to be wrong because of missing small unpublished trials, but is not itself evidence of treatment efficacy.

A fourth problem is that it is impossible to say what the optimum duration of treatment is. In the first 4 days of treatment, patients experienced moderate degrees of improvement. After day 4, the degree of improvement declined from moderate (>0.5 effect size) to small (>0.2 effect size).³⁸ There was evidence of a trend toward declining effectiveness over time. While this suggests that the optimum duration of treatment may be short, on the order of a few days, it is unclear what the optimum treatment duration is, since even at 14 days there was evidence of improvement with treatment.

A final limitation is that, in the real world, clinicians are not limited to just 1 treatment option. National Ambulatory Medical Care Survey data suggest that patients presenting with low back pain are commonly given more than 1 treatment.¹² Often, acetaminophen is combined with an NSAID or a muscle relaxant. Less commonly, patients are given a narcotic for the first few days of pain. To our knowledge, no studies have been done to determine the optimum combination of treatment modalities. Since many of these treatments may be operating on different aspects of back pain, there may be an additive effect. On the other hand, overmedication is a common problem among patients, and more may not be better. Studies to look at back pain management with a combination of common therapies are needed. Some clinicians, well versed with the sedative effects of cyclobenzaprine, prescribe it for the short term as a nighttime medicine. The trials in our analysis all used a 2 or 3 times daily dose. Whether similar benefits will accrue with a single nighttime dose is uncertain.

We conclude that cyclobenzaprine is significantly better at relieving back pain than placebo at all times measured. Patients can expect about a 5-fold increase in the odds of experiencing improvement by 14 days and up to 2 SDs of improvement, a moderate effect size. Clinicians will need to treat 3 patients to improve the symptoms of 1. Adverse effects will be common, experienced in more than half of the patients, with 20% experiencing drowsiness. The treatment effect is greatest early, suggesting that a short course may be preferable, although even at 2 weeks patients given cyclobenzaprine had slightly better results on all 5 domains of back pain. Stud-

ies to determine the optimum combination and duration of treatment in the management of acute back pain are needed.

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