Original Investigation

Naproxen With Cyclobenzaprine, Oxycodone/Acetaminophen, or Placebo for Treating Acute Low Back Pain
A Randomized Clinical Trial

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IMPORTANCE Low back pain (LBP) is responsible for more than 2.5 million visits to US emergency departments (EDs) annually. These patients are usually treated with nonsteroidal anti-inflammatory drugs, acetaminophen, opioids, or skeletal muscle relaxants, often in combination.

OBJECTIVE To compare functional outcomes and pain at 1 week and 3 months after an ED visit for acute LBP among patients randomized to a 10-day course of (1) naproxen + placebo; (2) naproxen + cyclobenzaprine; or (3) naproxen + oxycodone/acetaminophen.

DESIGN, SETTING, AND PARTICIPANTS This randomized, double-blind, 3-group study was conducted at one urban ED in the Bronx, New York City. Patients who presented with nontraumatic, nonradicular LBP of 2 weeks' duration or less were eligible for enrollment upon ED discharge if they had a score greater than 5 on the Roland-Morris Disability Questionnaire (RMDQ). The RMDQ is a 24-item questionnaire commonly used to measure LBP and related functional impairment on which 0 indicates no functional impairment and 24 indicates maximum impairment. Beginning in April 2012, a total of 2588 patients were approached for enrollment. Of the 323 deemed eligible for participation, 107 were randomized to receive placebo and 108 each to cyclobenzaprine and to oxycodone/acetaminophen. Follow-up was completed in December 2014.

INTERVENTIONS All participants were given 20 tablets of naproxen, 500 mg, to be taken twice a day. They were randomized to receive either 60 tablets of placebo; cyclobenzaprine, 5 mg; or oxycodone, 5 mg/acetaminophen, 325 mg. Participants were instructed to take 1 or 2 of these tablets every 8 hours, as needed for LBP. They also received a standardized 10-minute LBP educational session prior to discharge.

MAIN OUTCOMES AND MEASURES The primary outcome was improvement in RMDQ between ED discharge and 1 week later.

RESULTS Demographic characteristics were comparable among the 3 groups. At baseline, median RMDQ score in the placebo group was 20 (interquartile range [IQR],17-21), in the cyclobenzaprine group 19 (IQR,17-21), and in the oxycodone/acetaminophen group 20 (IQR,17-22). At 1-week follow-up, the mean RMDQ improvement was 9.8 in the placebo group, 10.1 in the cyclobenzaprine group, and 11.1 in the oxycodone/acetaminophen group. Between-group difference in mean RMDQ improvement for cyclobenzaprine vs placebo was 0.3 (98.3% CI, −2.6 to 3.2; $P = .77$), for oxycodone/acetaminophen vs placebo, 1.3 (98.3% CI, −1.5 to 4.1; $P = .28$), and for oxycodone/acetaminophen vs cyclobenzaprine, 0.9 (98.3% CI, −2.1 to 3.9; $P = .45$).

CONCLUSIONS AND RELEVANCE Among patients with acute, nontraumatic, nonradicular LBP presenting to the ED, adding cyclobenzaprine or oxycodone/acetaminophen to naproxen alone did not improve functional outcomes or pain at 1-week follow-up. These findings do not support use of these additional medications in this setting.

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Low back pain is responsible for 2.4% of visits to US emergency departments (EDs) resulting in 2.7 million visits annually.[1] Pain outcomes for these patients are generally poor.[2] One week after an ED visit in an unselected low back pain (LBP) population, 70% of patients reported persistent back pain-related functional impairment and 69% reported continued analgesic use.[2] Three months later, 48% reported functional impairment and 46% reported persistent analgesic use, including 19% who required opioids.[2]

A variety of evidence-based medications are available to treat LBP.[3] Nonsteroidal anti-inflammatory drugs (NSAIDs) are more efficacious than placebo.[4] Skeletal muscle relaxants are effective for short-term pain relief and global efficacy.[5] Opioids are commonly used for moderate or severe acute LBP,[6] although high-quality evidence supporting this practice is lacking.

Treatment of LBP with multiple concurrent medications is common in the ED setting.[7] In a study using data from a national sample gathered in 2002-2006, emergency physicians often prescribed NSAIDs, skeletal muscle relaxants, and opioids in combination, that is, 26% of patients received an NSAID combined with a skeletal muscle relaxant and another 26% received an NSAID combined with an opioid.[7] Sixteen percent of patients received all 3 classes of medication.[7] Several clinical trials have compared NSAIDS + skeletal muscle relaxants to monotherapy with just one of these agents.[8-12] These trials have reported heterogeneous results. The combination of opioids + NSAIDS has been insufficiently evaluated experimentally in patients with acute LBP.[13]

Given the pain and functional impairment that persists beyond an ED visit for musculoskeletal LBP and the heterogeneity in clinical care, we conducted a randomized clinical trial (RCT) to determine whether a 10-day course of muscle relaxants or opioids combined with NSAIDs is more effective than NSAID monotherapy for the treatment of nontraumatic nonradicular low back pain.

Methods

Overview

In this RCT, patients were enrolled during an ED visit for LBP, dispensed a 10-day supply of medication, and contacted by telephone at 7-day and 3-month follow-up. The Albert Einstein College of Medicine institutional review board provided ethical oversight. All participants provided written informed consent. The study protocol is available online (Supplement 1).

Study Setting

We conducted this study in the ED of Montefiore Medical Center, an urban teaching hospital with more than 100 000 adult visits annually. Salaried, trained, fluently bilingual (English and Spanish) research associates staffed the ED 16 to 24 hours per day, 7 days per week during the accrual period.

Participant Selection

Patients were considered for inclusion if they were adults aged 21 to 64 years who presented to the ED primarily for management of acute LBP, defined as pain originating between the lower border of the scapulae and the upper gluteal folds, and received a diagnosis consistent with nontraumatic nonradicular, musculoskeletal LBP. Patients were required to have functionally impairing back pain, which we defined as a score of greater than 5 on the Roland-Morris Disability Questionnaire (RMDQ).[14] The RMDQ is a 24-item questionnaire commonly used to measure LBP and related functional impairment (0 indicates no impairment; 24 indicates maximum impairment). Patients were excluded for radicular pain, which we defined as pain radiating below the gluteal folds, direct trauma to the back within the previous month, pain duration for more than 2 weeks, or recent history of greater than 1 LBP episode per month. We also excluded patients who were pregnant or lactating, unavailable for follow-up, with allergy or contraindication to the investigational medications, or had chronic opioid use currently or in the past. Patients could only be enrolled once.

Interventions

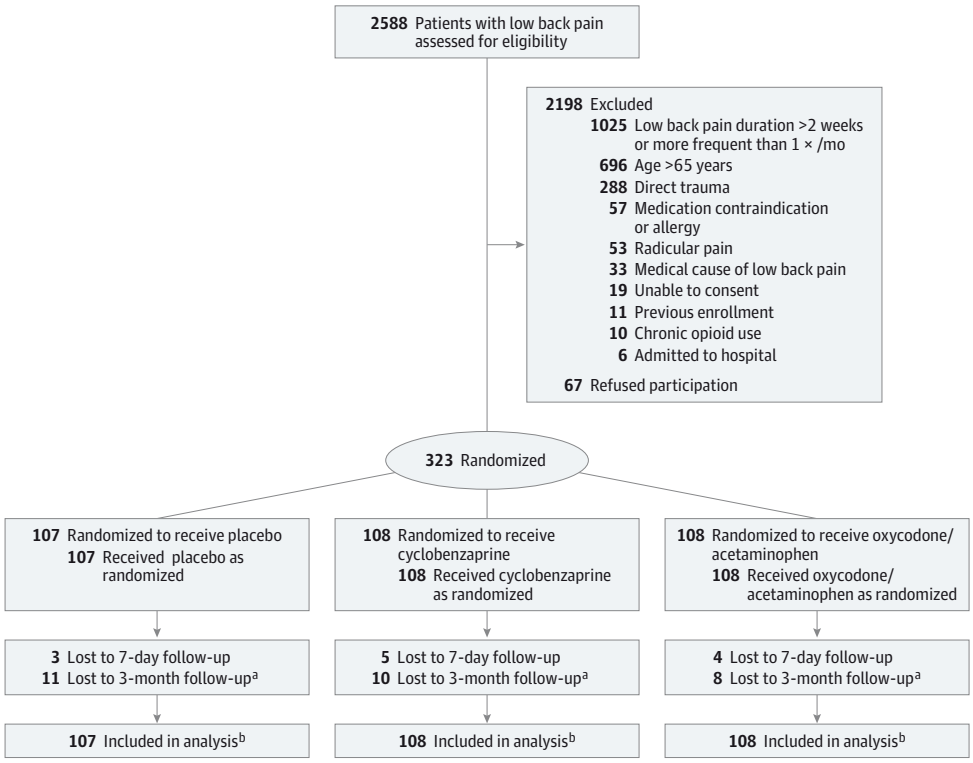
All patients received naproxen, twenty 500-mg tablets, taken as 1 every 12 hours. All patients also received 60 tablets of one of the following investigational medications, to be taken as 1 or 2 tablets every 8 hours: (1) placebo; (2) cyclobenzaprine, 5 mg; or (3) oxycodone, 5 mg/acetaminophen, 325 mg. In an effort to maximize effectiveness while minimizing adverse effects, patients were instructed to take 1 or 2 tablets of their randomly assigned medication, as needed, every 8 hours. If one tablet afforded sufficient relief, there was no need to take the second tablet. However, patients who had not experienced sufficient relief within 30 minutes of taking the first tablet were instructed to take the second. We dispensed 60 capsules of the investigational medication to every patient, enough to last 10 days if the patient took 2 tablets every 8 hours.

Research personnel provided each patient with a 10-minute educational intervention based on information from the National Library of Medicine.[15] Research personnel reviewed the topic with the patient in English or Spanish and answered questions. Each participant was informed that carefully chosen exercises and stretches may help alleviate pain and prevent future occurrences and that hot or cold packs, physical therapy, massage therapy, and acupuncture help some patients.

Randomization and Blinding

The pharmacist performed a stratified randomization in blocks of 6 based on 2 sequences using a randomization plan generator.[16] Patients were stratified based on results of the baseline RMDQ. The pharmacist masked the medication by placing cyclobenzaprine, oxycodone/acetaminophen, or placebo into identical unmarked capsules, which were then packed with small amounts of lactose and sealed. The pharmacist created research packets, each with 2 vials of medication, one containing naproxen and the other containing the masked investigational medication. Research packets were dispensed to study participants by research personnel.

Figure. Flow of Patients Through Acute Low Back Pain Trial



[a] Participants lost to follow-up were those we were unable to contact by telephone or mail.

[b] Multiple imputation was used to account for missing data.

Outcome Measures

The primary outcome for this study was improvement on the RMDQ between ED discharge and the 7-day telephone follow-up. A 5-point improvement on this scale is generally considered a clinically significant improvement.[14]

We assessed a number of exploratory outcomes at 1 week and 3 months after ED discharge. One week after ED discharge, we determined participants' worst LBP during the previous 24 hours, using a 4-item ordinal scale (severe, moderate, mild, or none); the frequency of any analgesic or LBP medication use during the previous 24 hours; the frequency of LBP during the previous 24 hours using a 5-item scale (not at all, rarely, sometimes, usually, always); satisfaction with treatment, as measured by response to the question "The next time you have back pain, do you want to take the same medications you've been taking this past week"; following ED discharge, the day on which the participant was able to return to work and resume all usual activities; and the frequency of visits to any clinician. Three months after ED discharge, we determined participants' worst LBP during the previous 72 hours, using the same ordinal scale as previously described; the frequency of LBP during the previous 72 hours using the previous scale; the frequency of use of any LBP medication during the previous 72 hours; and the frequency of opioid use. We assessed the actual RMDQ score at 1-week and 3-month follow-up as prespecified secondary outcomes; however, these were not described explicitly in the protocol (Supplement 1).

Adverse events were ascertained by asking patients to report any symptoms from the medications. We specifically asked participants to describe whether or not the medications irritated their stomach or made them tired or dizzy. For these latter 3 symptoms, participants were asked to also use the descriptions "a lot," "a little," or "none."

Sample Size Calculation

We assumed a mean (SD) change in RMDQ between baseline and 1 week of 5.6 (10.0)[2] and a minimum clinically important difference on the RMDQ of 5.0.[17] We incorporated a 2-tailed α of .02 to adjust for 3 pairwise comparisons and a β of .20. To account for the possibility of a nonparametric analysis, we added a 15% surplus and an additional 10% to account for those who were lost to follow-up, resulting in the need for 323 patients.

Analysis

An intention-to-treat analysis was performed. A secondary prespecified analysis, not described in the original protocol, included only those patients who reported taking the assigned investigational medication more than once. The analysis of the primary outcome consisted of 3 pairwise comparisons of the change in RMDQ between baseline at ED discharge and 1 week

Table 1. Baseline Characteristics

Variable	No. (%)[a]		
	Naproxen + Placebo (n = 107)	Naproxen + Cyclobenzaprine (n = 108)	Naproxen + Oxycodone/ Acetaminophen (n = 108)
Age, mean (SD), y	39 (11)	38 (11)	39 (11)
Sex			
Men	54 (50)	63 (58)	48 (44)
Women	53 (50)	45 (42)	60 (56)
Educational level[b]			
Did not graduate from high school	25 (24)	30 (28)	35 (33)
Some college	60 (57)	50 (47)	43 (41)
Graduated from college	21 (20)	27 (25)	28 (26)
RMDQ score at time of ED discharge[c]			
Median (IQR)	20 (17-21)	19 (17-21)	20 (17-22)
Mean (SD)	18.7 (4.0)	18.4 (4.1)	18.9 (3.7)
Duration of LBP prior to ED presentation, median (IQR), h	48 (24-96)	48 (18-96)	72 (33-139)
Previous episodes of LBP			
Never	47 (44)	49 (45)	51 (47)
A few times	44 (41)	52 (48)	46 (43)
≥1/y	16 (15)	7 (7)	11 (10)
On-the-job injury[d]	24/106 (23)	36/107 (34)	31/106 (29)
Depression screen positive[d,e]	8/106 (8)	2/108 (2)	5/108 (5)

Abbreviations: ED, emergency department; IQR, interquartile range; LBP, low back pain; RMDQ, Roland Morris Disability Questionnaire.

[a] Data are reported as No (%) unless otherwise indicated.

[b] Missing data for 4 participants.

[c] The RMDQ is a 24-item instrument measuring low back pain–related functional impairment (0 indicates no functional impairment; 24 indicates maximum functional impairment).

[d] Denominators differ because of missing data.

[e] Patients were asked 2 screening questions from the Patient Health Questionnaire: "Before your back pain began, how often were you bothered by little pleasure or interest in doing things?" and "Before your back pain began, how often were you bothered by feeling down, depressed, or hopeless?" Patients who responded to either question "More than half the days" or "Nearly every day" were considered screen positive.

later, reported with 98.3% CI. The significance threshold for the primary outcome was .02. Exploratory outcomes were not adjusted for multiple comparisons. These are reported as between-group differences with 95% CIs or difference between medians with 95% CIs. The number needed to treat (NNT) is presented with a 95% CI when naproxen + active medication resulted in a statistically significant improvement in outcome compared with naproxen + placebo. The number needed to harm (NNH) is presented with a 95% CI when naproxen + active medication resulted in a statistically significant increase in adverse events compared with naproxen + placebo. Multiple imputation was performed to account for missing data. IBM SPSS Statistics, version 21 was used for all analyses.

Results

During a 30-month period beginning in April 2012, a total of 323 patients were enrolled (**Figure**). Follow-up was completed in December 2014. Baseline characteristics were not different between the 3 groups (**Table 1**). Baseline scores on the RMDQ were high in all 3 study groups, indicating substantial functional impairment at baseline.

Primary Outcome

At 1-week follow-up, patients randomized to receive naproxen + placebo improved by a mean of 9.8 (98.3% CI, 7.9 to 11.7) on the RMDQ, those randomized to naproxen + cyclobenzaprine improved by 10.1 (98.3% CI, 7.9 to 12.3), and those randomized to naproxen + oxycodone/acetaminophen improved by 11.1 (98.3% CI, 9.0 to 13.2). Between group differences in mean RMDQ improvement were as follows: cyclobenzaprine vs placebo was 0.3 (98.3% CI, −2.6 to 3.2; $P = .77$), oxycodone/acetaminophen vs placebo was 1.3 (98.3% CI, −1.5 to 4.1; $P = .28$), and oxycodone/acetaminophen vs cyclobenzaprine was 0.9 (98.3% CI, −2.1 to 3.9; $P = .45$).

Exploratory Outcomes

At 1-week follow-up, regardless of study group, more than 50% of patients still required medication for LBP, and as shown in **Table 2**, many patients reported moderate or severe, and frequent pain. Despite these generally poor outcomes, more than two-thirds of patients reported that they would want to receive the same medications during a subsequent ED visit for acute LBP.

More than 75% of participants randomized to receive naproxen used it daily and nearly two-thirds used it twice daily (**Table 3**). Fewer participants used the cyclobenzaprine, oxycodone/acetaminophen, or placebo regularly; only one-third of patients used the medication they were randomized to receive more than once daily and nearly 40% used this medication intermittently, only once, or not at all (Table 3). Use of additional health care resources was infrequent in the 3 study groups. Most participants did not visit their primary care clinician or a complementary/alternative medicine practitioner prior to the 1-week follow-up (Table 3).

Table 2. One-Week Outcomes Among All Study Participants[a]

Outcome Variable	Naproxen + Placebo (n = 107)	Naproxen + Cyclobenzaprine (n = 108)	Naproxen + Oxycodone/ Acetaminophen (n = 108)	Difference, % (95% CI)		
				Cyclobenzaprine vs Placebo	Oxycodone/ Acetaminophen vs Placebo	Cyclobenzaprine vs Oxycodone/ Acetaminophen
Primary Outcome						
Improvement in RMDQ between ED visit and 1-week follow-up, mean (98.3% CI)[b]	9.8 (7.9 to 11.7)	10.1 (7.9 to 12.3)	11.1 (9.0 to 13.2)	0.3 (−2.6 to 3.2)[c]	1.3 (−1.5 to 4.1)[c]	0.9 (−2.1 to 3.9)[c]
Exploratory Outcomes						
RMDQ[b]						
Mean (95% CI) score	8.9 (7.3 to 10.5)	8.2 (6.2 to 9.4)	7.8 (6.6 to 9.8)	0.7 (−1.6 to 3.0)	1.1 (−1.1 to 3.4)	0.4 (−1.2 to 2.7)
Median (IQR) score	7 (0 to 18)	4 (0 to 16)	5 (0 to 15)			
Worst LBP during previous 24 h, No. (%)						
Mild/none	58 (54)	65 (60)	70 (65)	6 (−7 to 19)	11 (−2 to 24)	5 (−8 to 18)
Moderate/severe	49 (46)	43 (40)	38 (35)			
Frequency of LBP during previous 24 h, No. (%)						
Never/rarely	46 (43)	52 (48)	52 (48)	6 (−7 to 18)[d]	6 (−6 to 19)[d]	1 (−11 to 13)[d]
Sometimes	25 (23)	25 (23)	25 (23)			
Frequently/always	37 (35)	31 (29)	30 (28)			
Use of medication for LBP during the 24 h prior to one week follow-up, No. (%)						
No medications	39 (36)	46 (43)	49 (45)	6 (−7 to 19)	9 (−4 to 22)	3 (−10 to 16)
Took medications	68 (64)	62 (57)	59 (55)			
Desires same medications during subsequent episode of LBP, No. (%)[e]						
Yes	72 (67)	81 (75)	79 (73)	8 (−4 to 20)	6 (−6 to 18)	2 (−10 to 14)
No	26 (24)	18 (17)	22 (20)			
Not sure	9 (8)	9 (8)	7 (6)			
No. of days, median (IQR)						
Return to usual activities[f]	5 (2 to >7)	4 (3 to >7)	4 (3 to >7)	0 (0 to 1)	0 (0 to 1)	0 (0 to 0)
Return to work[g]	3 (2 to 4)	3 (2 to 4)	2 (1 to 4)	0 (−1 to 1)	0 (0 to 1)	0 (0 to 1)

Abbreviations: ED, emergency department; IQR, interquartile range; LBP, low back pain; RMDQ, Roland-Morris Disability Questionnaire.

[a] These data include imputed values for 12 patients lost to follow-up at 1-week follow-up. Multiple imputation models included the following variables: age, sex, investigational medication, and baseline RMDQ. Values were rounded to the nearest integer.

[b] The RMDQ is a 24-item instrument measuring low back pain–related functional impairment (0 indicates no functional impairment; 24 indicates maximum functional impairment).

[c] Between-group difference for mean improvement on RMDQ.

[d] Never/rarely/sometimes vs frequently/always.

[e] Participants were asked "The next time you have back pain, do you want to take the same medications you've been taking this past week?" Yes, no, or not sure.

[f] Patients who had not yet recovered at the time of the 1-week follow-up phone call were categorized as requiring more than 7 days before returning to usual activities.

[g] Data include 273 employed participants; 50 participants (15.5% of study population) were unemployed.

Table 3. Use of Investigational Medication and Health Care Resources Within 1 Week of ED Discharge

Outcome	No. (%) [95% CI]		
	Naproxen + Placebo	Naproxen + Cyclobenzaprine	Naproxen + Oxycodone/ Acetaminophen
Frequency of naproxen use			
No. of patients	101	103	104
>1/d	72 (72) [62-79]	67 (65) [55-74]	56 (54) [44-63]
1/d	13 (13) [8-21]	21 (20) [14-29]	26 (25) [18-34]
Sometimes	5 (5) [2-11]	5 (5) [2-11]	10 (10) [5-17]
Only once	6 (6) [3-13]	4 (4) [1-10]	7 (7) [3-13]
Never	5 (5) [2-11]	6 (6) [2-12]	5 (5) [2-11]
Frequency of placebo, cyclobenzaprine, or oxycodone/acetaminophen use			
No. of patients	104	102	102
>1/d	34 (33) [24-42]	32 (31) [23-41]	33 (32) [24-42]
1/d	32 (31) [23-40]	39 (38) [29-48]	21 (21) [14-30]
Sometimes	14 (14) [8-21]	13 (13) [7-21]	17 (17) [11-25]
Only once	8 (8) [4-15]	6 (6) [2-13]	10 (10) [5-17]
Never	16 (15) [10-24]	12 (12) [7-20]	21 (21) [14-30]
Health care resources used			
No. of patients	104	103	103
No visits to any clinician	90 (87) [79-92]	87 (85) [76-90]	89 (86) [78-92]
Subsequent ED visit	3 (3) [1-9]	1 (1) [0-6]	3 (3) [1-9]
Primary care visit	7 (7) [3-13]	11 (11) [6-18]	6 (6) [2-12]
Visit to specialist physician[a]	2 (2) [0-7]	0 (0) [0-4]	1 (1) [0-6]
Complementary therapy visit[b]	4 (4) [1-10]	3 (3) [1-9]	6 (6) [2-12]

Abbreviation: ED, emergency department.

[a] Includes a neurologist or orthopedic clinician.

[b] Includes a chiropractor or physical therapist.

Table 4. Adverse Medication Effects[a]

Adverse Event	No. (%)			Difference, % (95% CI)		
	Naproxen + Placebo (n = 107)	Naproxen + Cyclobenzaprine (n = 108)	Naproxen + Oxycodone/ Acetaminophen (n = 108)	Cyclobenzaprine vs Placebo	Oxycodone/ Acetaminophen vs Placebo	Cyclobenzaprine vs Oxycodone/ Acetaminophen
Any adverse event	22 (21)	36 (33)	43 (40)	13 (1 to 25)	19 (7 to 31)	6 (−6 to 19)
Drowsiness[b]	4 (4)	7 (7)	16 (15)	3 (−3 to 9)	11 (4 to 19)	8 (0 to 16)
Dizziness[b]	3 (3)	3 (3)	16 (15)	0 (−4 to 4)	12 (5 to 19)	12 (5 to 19)
Stomach irritation[b]	5 (5)	7 (6)	7 (6)	2 (−4 to 8)	2 (−3 to 7)	0 (−6 to 7)
Nausea or vomiting	6 (6)	4 (4)	19 (18)	2 (−4 to 8)	12 (4 to 20)	14 (6 to 22)

[a] These data include imputed values for 12 patients lost to follow-up at 1 week. Multiple imputation models included the following variables: age, sex, investigational medication, and baseline Roland-Morris Disability Questionnaire.

[b] At the 7-day follow-up, study participants were asked specifically whether or not they experienced dizziness, drowsiness, and stomach irritation. They were asked to choose among the following options: "no," "a little," or "a lot." Values reported in this table indicate answers from participants whose symptoms were experienced a lot.

Adverse effects were more likely among patients randomized to receive oxycodone/acetaminophen than to placebo (difference, 19% [7% to 31%]; **Table 4**; number needed to harm, 5.3 [95% CI, 3 to 14]), and among patients randomized to receive cyclobenzaprine vs placebo (difference, 13% [1% to 25%]; Table 4; number needed to harm, 7.8 [95% CI, 4 to 129]). Other than the adverse effects listed in Table 4, none occurred in more than 3 participants in any study group.

Among the patients who used the cyclobenzaprine, oxycodone/acetaminophen, or placebo investigational medication more than once, there was no significant difference in the primary outcome (eTable 1 in Supplement 2). Patients randomized to oxycodone/acetaminophen were more likely than those randomized to placebo to report pain levels of mild or none (difference, 18% [95% CI, 3% to 33%]; number needed to treat, 6 [95% CI, 3 to 37]).

Three months after the ED visit, most patients had recovered, although nearly one-fourth in each study group still reported moderate or severe LBP and use of medication for LBP (**Table 5**). Opioid use for treating LBP was reported by 2.3% (95% CI, 0.8 to 5.3%) of participants.

Additional data for the exploratory outcomes of pain intensity at one week follow-up and resumption of usual activities at three month follow-up are reported in eTable 2 in Supplement 2.

Table 5. Three-Month Outcomes[a]

Outcome Variable	Naproxen + Placebo (n = 107)	Naproxen + Cyclobenzaprine (n = 108)	Naproxen + Oxycodone/ Acetaminophen (n = 108)	Difference, % (95% CI)		
				Cyclobenzaprine vs Placebo	Oxycodone/ Acetaminophen vs Placebo	Cyclobenzaprine vs Oxycodone/ Acetaminophen
RMDQ[b]						
Mean (95% CI) score	3.8 (2.6 to 5.1)	4.5 (3.0 to 5.9)	4.6 (3.2 to 6.1)	0.6 (−1.3 to 2.6)	0.8 (−1.1 to 2.7)	0.2 (−1.9 to 2.2)
Median (IQR) score	0 (0 to 3)	0 (0 to 5)	0 (0 to 8)			
	No. (%)					
Worst LBP during previous 72 h						
Mild/none	79 (74)	81 (75)	87 (81)	1 (−11 to 13)	7 (−4 to 18)	6 (−6 to 17)
Moderate/severe	28 (26)	27 (25)	21 (19)			
Frequency of LBP during previous 72 h						
Never/rarely	78 (73)	80 (74)	79 (73)	7 (−3 to 16)[c]	1 (−9 to 11)[c]	6 (−4 to 15)[c]
Sometimes	10 (9)	16 (15)	11 (10)			
Frequently/always	19 (18)	12 (11)	18 (17)			
Use of medication for LBP within 72 h						
No meds	79 (74)	82 (76)	88 (81)	2 (−10 to 14)	8 (−3 to 19)	6 (−5 to 16)
Took meds	28 (26)	26 (24)	20 (19)			
Opioid use within 72 h	3 (3)	1 (1)	2 (2)	2 (−2 to 5)	1 (−3 to 5)	1 (−2 to 4)

Abbreviations: IQR, interquartile range; LBP, low back pain; RMDQ, Roland Morris Disability Questionnaire.

[a] These data include imputed values for 29 patients lost to follow-up at 3-month follow-up. Multiple imputation models included the following variables: age, sex, investigational medication, baseline RMDQ, 7-d RMDQ.

[b] The RMDQ is a 24-item instrument measuring low back pain–related functional impairment; 0 indicates no functional impairment; 24 indicates maximum functional impairment.

[c] Differences were based on never/rarely/sometimes responses vs frequently/always.

Discussion

In this RCT studying ED patients with acute, nontraumatic, nonradicular musculoskeletal LBP, neither naproxen combined with oxycodone/acetaminophen nor naproxen combined with cyclobenzaprine provided better pain relief or better improvement in functional outcomes than naproxen combined with placebo. Measures of pain, functional impairment, and use of health care resources were not different between the study groups at 7 days or at 3 months after the ED visit. Regardless of allocation, nearly two-thirds of patients demonstrated clinically significant improvement in LBP and function 1 week later. However, 40% of the cohort reported moderate or severe pain, half reported functionally impairing LBP, and nearly 60% were still using medication for their LBP 1 week later. By 3-month follow-up, nearly one-fourth of the cohort reported moderate or severe pain and use of medications for LBP. Three months after the ED visit, regardless of study group, opioid use for LBP was uncommon, with fewer than 3% of patients reporting use of an opioid within the previous 72 hours.

Our results are similar to other studies of NSAIDs combined with cyclobenzaprine[8,10,11,18] conducted in a variety of settings, including an ED and primary care and specialty clinics. Despite the fact that both NSAIDS and cyclobenzaprine are efficacious when administered as monotherapy,[5,19] the bulk of the data, including the findings in this study, suggest combination therapy is not better than monotherapy.

We were unable to find high-quality published data that evaluated the efficacy of opioids combined with NSAIDs for acute LBP. Available data do not support the superiority of opioids over NSAIDs.[19] In this study, oxycodone/acetaminophen + naproxen was not better than placebo + naproxen. We identified a difference in pain outcomes among participants who took oxycodone/acetaminophen more than once when compared with those who took placebo more than once. However, this was one of multiple exploratory comparisons. Furthermore, the magnitude of benefit was modest, with a number needed to treat of nearly 6 for moderate or severe pain, which is balanced by a number needed to harm of nearly 5. Although we cannot exclude the possibility of a modest benefit of the opioid combination in a select subgroup of patients, our data do not support providing oxycodone/acetaminophen in addition to naproxen for all ED patients with acute LBP.

Many ED patients had already taken NSAIDs for LBP before arriving to the ED. Some patients may have taken insufficient doses at incorrect intervals and could be helped by optimization of their NSAID regimen. However, for patients who have already optimized their NSAID regimen, there are no additional evidence-based medical therapies available. Our results show that that adding cyclobenzaprine or oxycodone/acetaminophen to naproxen does not improve pain at 7-day or 3-month follow-up. It is also true that corticosteroids[20] and acetaminophen[21] are not beneficial for patients with nonradicular LBP. Benzodiazepines are sometimes used to treat LBP, although whether they are effective is unclear.[22] Remaining active leads to better outcomes than bed rest.[23] Complementary therapies, including acupuncture,[24] yoga,[25] and massage,[26] have been inadequately studied in an acute LBP population. Data on exer-

cise therapy for acute LBP is conflicting.[27] Spinal manipulation is unlikely to benefit ED patients with acute LBP whose symptoms are well-managed medically.[28] Emergency physicians should inform their patients that passage of time is likely to bring improvement and eventual relief to most patients.

Our results are consistent with other reports of outcomes after acute-onset LBP.[29-34] In general, most patients with acute-onset LBP report persistent symptoms 1 week later. By 3 months, however, most symptoms have improved. Risk factors for poor long-term LBP outcomes consist of complicated LBP histories and radicular symptoms.[35] In our study, we selected patients at low risk of poor outcome by excluding those with chronic LBP, radicular symptoms, or chronic use of opioids. Despite selecting for these low-risk patients, more than 20% of our cohort, regardless of study group, reported poor outcomes at 3 months after the ED visit.

We aimed to maximize medication use by instructing patients to choose whether to take 1 or 2 tablets of the investigational medication at each dosing, thereby giving the patient the ability to titrate efficacy against adverse effects. Infrequent use of the study medication is both a limitation and strength of this study—it is possible that standing doses of oxycodone/acetaminophen or cyclobenzaprine may have treated the pain and functional impairment more effectively. However, we chose this study design because it more closely reflects the reality of clinical practice.

We dispensed 60 tablets of oxycodone/acetaminophen to one-third of study participants—a substantial number of opioid tablets—with the goal of not limiting potential benefit because of insufficient dosing. This liberal approach to opioids is at odds with recent clinical practice guidelines.[36] Current recommendations state that when treating LBP, the lowest possible dose of opioids should be prescribed for the shortest amount of time. During the last 2 decades, there has been increasing focus on achieving adequate pain control, with the goal of quick and effective relief of pain.[37] However, permissive use of opioids may be harmful. Using correlative data, others have linked prescriptions for opioids to overdose deaths and use of opioids in general to worse LBP outcomes.[36] Our study provides evidence against the use of opioids for acute LBP because of lack of benefit and increased frequency of adverse effects. However, opioids were not associated with higher rates of functional impairment, more frequent visits to the ED, or an increased propensity for continued opioid use.

Our study has limitations. First, this study was conducted in an urban ED that served a socioeconomically depressed population. Because back pain outcomes may be associated with socioeconomic variables such as access to treatment, our results can most appropriately be generalized to EDs that serve similar patient populations.

Second, we reported a large number of related outcomes. This approach may lead to uncertainty with regard to interpretation of the data when some of the outcomes result in a statistically significant benefit and others do not. In this study, we saw no difference in outcomes between those randomized to receive naproxen + placebo vs those randomized to receive naproxen + oxycodone/acetaminophen. However, among patients who used the investigational medication more than once, fewer patients who used oxycodone/acetaminophen reported moderate or severe pain. These latter findings must be interpreted cautiously because of the large number of analyses we performed.

Third, we did not evaluate the adequacy of patient blinding. Thus, we do not know whether patients' assumptions about the investigational medication they were receiving influenced their self-reports of pain and functional outcomes. Fourth, we did not determine whether participants were using NSAIDs at the time of enrollment, thus limiting this study's generalizability.

Conclusions

Among patients with acute, nontraumatic, nonradicular LBP presenting to an ED, adding cyclobenzaprine or oxycodone/acetaminophen to naproxen alone did not improve functional outcomes or pain at 7 days. These findings do not support the use of these additional medications in this setting.

ARTICLE INFORMATION

Author Contributions: Dr Friedman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Friedman, Davitt, Solorzano, Esses, Bijur, Gallagher.
Acquisition, analysis, or interpretation of data: Friedman, Dym, Holden, Esses, Bijur, Gallagher.
Drafting of the manuscript: Friedman.
Critical revision of the manuscript for important intellectual content: Friedman, Dym, Davitt, Holden, Solorzano, Esses, Bijur, Gallagher.
Statistical analysis: Friedman, Bijur.
Study supervision: Friedman.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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