A Randomized, Double-Blind, Placebo-Controlled Trial of Naproxen With or Without Orphenadrine or Methocarbamol for Acute Low Back Pain

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Study objective: In US emergency departments (EDs), patients with low back pain are often treated with nonsteroidal anti-inflammatory drugs and muscle relaxants. We compare functional outcomes among patients randomized to a 1-week course of naproxen + placebo versus naproxen + orphenadrine or naproxen + methocarbamol.

Methods: This was a randomized, double-blind, comparative effectiveness trial conducted in 2 urban EDs. Patients presenting with acute, nontraumatic, nonradicular low back pain were enrolled. The primary outcome was improvement on the Roland-Morris Disability Questionnaire (RMDQ) between ED discharge and 1 week later. All patients were given 14 tablets of naproxen 500 mg, to be used twice a day, as needed for low back pain. Additionally, patients were randomized to receive a 1-week supply of orphenadrine 100 mg, to be used twice a day as needed, methocarbamol 750 mg, to be used as 1 or 2 tablets 3 times per day as needed, or placebo. All patients received a standardized 10-minute low back pain educational session before discharge.

Results: Two hundred forty patients were randomized. Baseline demographic characteristics were comparable. The mean RMDQ score of patients randomized to naproxen + placebo improved by 10.9 points (95% confidence interval [CI] 8.9 to 12.9). The mean RMDQ score of patients randomized to naproxen + orphenadrine improved by 9.4 points (95% CI 7.4 to 11.5). The mean RMDQ score of patients randomized to naproxen + methocarbamol improved by 8.1 points (95% CI 6.1 to 10.1). None of the between-group differences surpassed our threshold for clinical significance. Adverse events were reported by 17% (95% CI 10% to 28%) of placebo patients, 9% (95% CI 4% to 19%) of orphenadrine patients, and 19% (95% CI 11% to 29%) of methocarbamol patients.

Conclusion: Among ED patients with acute, nontraumatic, nonradicular low back pain, combining naproxen with either orphenadrine or methocarbamol did not improve functional outcomes compared with naproxen + placebo. [Ann Emerg Med. 2017;–:1-9.]

Please see page XX for the Editor's Capsule Summary of this article.

0196-0644/$-see front matter
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https://doi.org/10.1016/j.annemergmed.2017.09.031

INTRODUCTION

Background

Low back pain causes 2.4% of visits to US emergency departments (EDs), resulting in 2.6 million visits annually.1 In general, outcomes for these patients are unfavorable. One week after ED discharge, 70% of patients report persistent back-pain-related functional impairment and 69% report analgesic use within the previous 24 hours.2 Among the subset of ED patients who present with acute, new-onset low back pain, outcomes are generally better; most will recover, although 10% to 20% of this group reports moderate or severe low back pain 3 months later and 30% report persistent low back pain–related functional impairment.3,4

Importance

It is not clear which medications should be prescribed for acute low back pain. Nonsteroidal anti-inflammatory drugs are more efficacious than placebo in regard to low back pain relief, global improvement, and requirement of analgesic medication5 but are insufficient treatment for as many as half of all ED patients with low back pain, who continue to experience discomfort after ED discharge despite use of nonsteroidal anti-inflammatory drugs. Treatment of low back pain with multiple concurrent medications is common in the ED; emergency physicians often prescribe skeletal muscle relaxants or opioids in combination with nonsteroidal anti-inflammatory drugs.1 However, combining oxycodone and acetaminophen,
diazepam, or cyclobenzapr ine (a skeletal muscle relaxant) with a nonsteroidal anti-inflammatory drug does not improve outcomes. It remains uncertain whether adding other skeletal muscle relaxants to nonsteroidal anti-inflammatory drugs improves low back pain outcomes.

Two specific skeletal muscle relaxants, orphenadrine and methocarbamol, are used in more than 250,000 US ED visits for low back pain annually, although scant evidence exists to determine the appropriateness of this approach. Orphenadrine is a centrally acting medication with prominent anticholinergic and antihistaminic properties. The mechanism of action is not understood. Efficacy in low back pain may be related to nonspecific analgesic properties. The mechanism of action of methocarbamol has also not been established. Its efficacy is thought to be related to central nervous system effects rather than direct effects on skeletal muscles.

Goals of This Investigation
Given the poor pain and functional outcomes that persist beyond an ED visit for acute low back pain, we conducted a clinical trial to determine whether combining either orphenadrine or methocarbamol with a nonsteroidal anti-inflammatory drug is more effective than nonsteroidal anti-inflammatory drug monotherapy for the treatment of acute, nontraumatic, nonradicular low back pain. We specifically evaluated the following 2 hypotheses: that the combination of naproxen+orphenadrine provides greater relief of low back pain than naproxen+placebo 1 week and 3 months after an ED visit, as measured by the Roland-Morris Disability Questionnaire (RMDQ); and that the combination of naproxen+methocarbamol provides greater relief of low back pain than naproxen+placebo 1 week and 3 months after an ED visit, as measured by the RMDQ.

MATERIALS AND METHODS

Study Design and Setting
This was a randomized, double-blind, comparative effectiveness study, in which we enrolled ED patients with musculoskeletal low back pain at discharge and followed them by telephone 7 days and 3 months later. Every patient received standard-of-care therapy, consisting of naproxen and a brief low back pain educational session. Patients were then randomized to orphenadrine, methocarbamol, or placebo.

The Albert Einstein College of Medicine Institutional Review Board reviewed and approved this study. Written consent to participate was obtained for all study participants. Enrollment commenced in March 2016 and continued for 11 months.

We report this trial in accordance with Consolidated Standards of Reporting Trials standards.

This study was performed in the 2 academic EDs of Montefiore Medical Center (Bronx, NY), with a combined annual census of 180,000 adult visits. Salaried, full-time, bilingual (English and Spanish), technician-level research associates staffed the EDs 18 to 24 hours per day, 7 days per week during the study period.

Selection of Participants
Our goal was to include a broad representation of patients with musculoskeletal back pain who would potentially respond to the investigational medications. The presence or absence of palpable spasm of the paraspinal muscles was not used as an entry criterion because the clinical significance and reliability of this finding are uncertain. Patients were included if they were aged 18 years and no older than 69 years and presented to one of the participating EDs primarily for management of low back pain, defined as pain originating between the lower border of the scapulae and the upper gluteal folds. At the conclusion of the ED visit, the patient was required to have received a diagnosis consistent with nontraumatic, nonradicular, musculoskeletal low back pain and was to be discharged home. To participate, patients were required to have a baseline score of greater than 5 on the RMDQ (Appendix E1, available online at http://www.annemergmed.com). Patients were excluded from

Editor’s Capsule Summary

What is already known on this topic
Muscle relaxants are sometimes prescribed for acute low back pain.

What question this study addressed
When added to nonsteroidal anti-inflammatory drugs, do muscle relaxants improve functional outcomes for acute low back pain?

What this study adds to our knowledge
In this well-powered, 3-arm, controlled trial of 240 adults, outcomes were similar at 7 days regardless of whether patients received a nonsteroidal anti-inflammatory drug with placebo, orphenadrine, or methocarbamol.

How this is relevant to clinical practice
On average, supplementing nonsteroidal anti-inflammatory drugs with orphenadrine or methocarbamol does not improve functional outcomes in patients with acute low back pain.
participation if they reported radicular pain below the gluteal folds, pain duration greater than 2 weeks, a baseline back pain frequency of at least once per month or substantial direct trauma to the back within the previous month. Patients were also excluded from participation if they would not be available for follow-up; for pregnancy or breast feeding; for a chronic pain syndrome defined as use of any analgesic medication daily or near daily; or for allergy, intolerance, or contraindication to the investigational medications.

Interventions

Study participants were randomized in a 1:1:1 ratio to orphenadrine, methocarbamol, or placebo. Participants in the orphenadrine arm were instructed to use naproxen 500-mg tablets twice per day+orphenadrine 100 mg twice per day. Participants in the methocarbamol arm were instructed to use naproxen 500-mg tablets twice per day+methocarbamol 750 mg as 1 or 2 tablets 3 times per day; thus, they could receive as much as 1,500 mg of methocarbamol 3 times per day. Patients randomized to placebo were randomly assigned to 2 different sets of dosing instructions to match the different dosing regimens of the active arms; half of the participants were instructed to use the investigational capsule twice per day, whereas the other half were instructed to use it as 1 or 2 capsules 3 times per day.

We incorporated a flexible dosing plan in the methocarbamol arm in an effort to maximize effectiveness while minimizing adverse effects. In this study arm, patients were instructed to use 1 or 2 pills of the methocarbamol every 8 hours. If one tablet of the methocarbamol afforded sufficient relief, there was no need for the patient to use the second tablet. However, if the patient had not experienced sufficient relief within 30 minutes of using one investigational medication tablet, he or she was instructed to use the second tablet. We chose this method of administration because optimal dosing of methocarbamol has not been established. We believe the dosing regimen we chose was sufficient to determine effectiveness while not exposing patients to unnecessary risk.8-10 Orphenadrine is manufactured in only 100-mg extended-release tablets and therefore was not amenable to flexible dosing. All study patients were given 14 naproxen tablets, a 7-day supply, and a sufficient number of investigational tablets to last 7 days.

The research pharmacist performed randomization in blocks of 6 based on a sequence generated at http://randomization.com. Each block of 6 contained 2 orphenadrine assignments, 2 methocarbamol assignments, 1 placebo assignment dosed as 1 capsule twice daily (to mirror orphenadrine dosing), and 1 placebo assignment dosed as 1 to 2 capsules 3 times daily (to mirror methocarbamol dosing). Therefore, although patients did not know whether they had been assigned to active medication or placebo, they may have deduced to which medication they were not assigned. This did not threaten the internal validity of the study because patients did not know whether they received active medication or placebo.

Naproxen was not masked. Orphenadrine, methocarbamol, and placebo were masked by placing tablets into identical capsules, which were packed with scant amounts of lactose and sealed. This masking occurred in a secure location inaccessible to ED personnel. Study participants were presented with 2 bottles of medication. The first bottle, containing the naproxen, was labeled in a typical manner. The second bottle, containing orphenadrine, methocarbamol, or placebo, was labeled as investigational medication. Patients were instructed to use the second bottle of investigational medication only as needed for moderate or severe low back pain.

Research personnel provided each patient with a 10-minute educational intervention. This was based on the National Institute for Arthritis and Musculoskeletal Disease’s Handout on Health: Back Pain information Web page (available at http://www.niams.nih.gov/Health_Info/Back_Pain/default.asp). Research personnel reviewed each section of the information sheet with the patient and elicited questions.

Methods of Measurement

The RMDQ (Appendix E1, available online at http://www.annemergmed.com) is a 24-item, low back pain, functional scale recommended for use in low back pain research.11 Its yes/no format is amenable to telephone follow-up. Higher scores signify greater low back–related functional impairment. The baseline questions referred to the period immediately before ED presentation (“Before you came to the ER today, were you able to...”), whereas the 1-week and 3-month follow-up questions referred to the 24 hours preceding the follow-up telephone calls.

Study participants described their back pain with the descriptors “severe,” “moderate,” “mild,” or “none” on an ordinal pain scale. Although not validated, this measure has been used frequently in ED-based low back pain studies.2-4,12

Study participants were asked to answer the question, “Did you require any medication to treat your low back pain?”

Study participants were asked to describe the frequency of their low back pain, using the descriptors “always,”
Low back pain symptomatology is quite variable. Some patients experience no pain unless they move a certain way. Others experience a constant low level of pain. This question helps determine the symptomatic burden of the low back pain in the patient’s daily life. Satisfaction was measured by response to this question: “The next time you go to the ED with low back pain, do you want to receive the same combination of medications?” This question, often used in ED-based acute pain research, allows patients to weigh for themselves the relative efficacy versus tolerability of the investigational medications.

**Outcome Measures**

The primary outcome was improvement in the RMDQ score between ED discharge and 1-week follow-up.
The following secondary outcomes were assessed 1 week after ED discharge: severity of low back pain during the previous 24 hours, the frequency of low back pain during the previous 24 hours, requirement of medication for low back pain during the previous 24 hours, satisfaction with treatment, numbers of days until able to return to usual activities, frequency of follow-up visits to health care providers, and frequency of new symptoms attributable to the investigational medications. Adverse medication effects were elicited with an open-ended question. All study participants were also asked about 3 specific adverse medication effects: drowsiness, dizziness, and stomach irritation. Study participants were asked to rate the severity of these latter 3 symptoms as none, a little, or a lot.

The following secondary outcomes were assessed 3 months after ED discharge: score on the RMDQ, and severity of low back pain during the previous week, using the 4-item ordinal scale described above.

The research associates, who were blinded to assignment, collected all of the data, using structured interviews.

### Primary Data Analysis

An intention-to-treat analysis was performed in which all randomized patients with available follow-up data were included regardless of whether they actually used the investigational medication. The primary outcome was a comparison of the change in RMDQ score between baseline and 1 week. Results are reported as means with 95% confidence interval (CI). Between-group differences are reported with 95% CI. Dichotomous outcomes are reported as n/N (%). Between-group differences (absolute risk reduction) are reported with 95% CI. Continuous outcomes are reported as means with SD or medians with interquartile range. We performed a subgroup analysis of the primary outcomes among patients who used the investigational medication at least twice. SPSS (version 21; SPSS Inc, Chicago, IL) was used for all analyses.

We based our sample size calculation assumptions on a recently completed low back pain clinical trial and a widely accepted minimum clinically important improvement of 5 points on the RMDQ. Using a standard $\alpha$ of .05 and a $\beta$ of .20, we determined the need for 50 subjects in each arm. To account for protocol violations and patients lost to follow-up, and to ensure sufficient power for the intention-to-treat analysis (in previous work, up to one third of enrolled patients did not use the investigational medication), we enrolled 80 patients in each arm.

### RESULTS

#### Characteristics of Study Subjects

During the accrual period, 1,473 patients with low back pain were approached for participation and 240 eligible
patients were randomized (Figure 1). Baseline characteristics were comparable between the groups (Table 1).

**Main Results**

One week after the ED visit, patients randomized to placebo improved by a mean of 10.9 RMDQ points (95% CI 8.9 to 12.9), whereas orphenadrine patients improved by 9.4 (95% CI 7.4 to 11.5) and methocarbamol patients improved by 8.1 (95% CI 6.1 to 10.1) (Figure 2). The difference between orphenadrine and placebo was 1.5 RMDQ points (95% CI –1.4 to 4.3), whereas the difference between placebo and methocarbamol was 2.8 (95% CI 0 to 5.7). Secondary outcomes were similar among the groups (Table 2).

A majority of patients used naproxen at least once per day (Table 3). Use of the investigational medication was slightly less robust. We examined outcomes among participants who used the investigational medication “sometimes,” “daily,” or “several times daily.” In this subgroup analysis, placebo patients reported 1-week RMDQ improvement of 11.3 points (95% CI 9.2 to 13.5), orphenadrine 9.1 points (95% CI 6.8 to 11.4), and methocarbamol 8.2 points (95% CI 5.9 to 10.6).

More than 80% of study participants did not visit another health care provider within 1 week of ED discharge (Table 3). Among those who did visit one, participants reported follow-up visits to primary care, repeated ED visit, and complementary or alternative practitioners.

Adverse events were relatively uncommon and comparable among the groups (Table E1, available online at http://www.annemergmed.com). Other than the symptoms reported in Table 4, only nausea was reported by more than 2 participants. Nausea was reported by 3 methocarbamol patients and 1 placebo patient. There were no serious or unexpected adverse events.

By 3 months after the ED visit, most patients had recovered completely, although one quarter of the sample reported RMDQ scores greater than 8, indicating

![Figure 2](https://via.placeholder.com/150)

**Figure 2.** Spaghetti plot of RMDQ scores over time. A, Naproxen + placebo arm. B, Orphenadrine arm. C, Methocarbamol arm.
substantial functional impairment (Tables E2 and E3, available online at http://www.annemergmed.com). There were no differences in 3-month pain or functional outcomes among the groups.

LIMITATIONS
Our work has a number of limitations (Table E4, available online at http://www.annemergmed.com). First, this was a study of effectiveness rather than efficacy, meaning that we tested the utility of the investigational medications in a real-world scenario. It is possible that orphenadrine and methocarbamol would have alleviated back pain if study participants were mandated to receive these medications on a regular schedule for several days. Second, studies of this type are susceptible to selection bias. Some of the bias we know about: because patients with chronic low back pain were excluded, the results of this study are not applicable to those with chronic low back pain. However, we do not know whether potentially eligible patients who were screened were different from potentially eligible patients who were missed. Similarly, we do not know whether the 52 patients who refused to participate were different from those who were enrolled. Third, the measurement instruments we used for secondary outcome assessment have not been validated. Therefore, we do not know whether they truly captured the patients’ experience. Fourth, we conducted this study in one urban health care system serving a socioeconomically depressed population. Because back pain outcomes may be associated with socioeconomic variables, our results can be generalized most appropriately to EDs that serve similar disadvantaged patient populations.

DISCUSSION
In this randomized, double-blind, comparative effectiveness study, adding skeletal muscle relaxants to naproxen did not improve functional and pain outcomes among patients with acute, nontraumatic, nonradicular low back pain during the previous 24 h (%): mild or none: 50 (66) vs 52 (67) vs 49 (61), moderate or severe: 26 (34) vs 26 (33) vs 31 (39), missing: 3 2 1.

Frequency of low back pain during the previous 24 h (%): never or rarely: 36 (47) vs 40 (51) vs 32 (40), sometimes: 26 (34) vs 22 (28) vs 23 (29), frequently or always: 14 (18) vs 16 (21) vs 25 (31), missing: 3 2 1.

Use of medication for low back pain during the 24 h before 1-wk follow-up (%): none: 34 (45) vs 38 (49) vs 30 (38), yes: 42 (55) vs 40 (51) vs 50 (63), missing: 3 2 1.

Same medications during subsequent episode of low back pain (%): yes: 51 (68) vs 53 (68) vs 51 (65), no: 17 (23) vs 20 (26) vs 16 (21), not sure: 7 (9) vs 5 (6) vs 11 (14), missing: 4 2 3.

Median days until usual activities (IQR): 4 (2 to 7) vs 3 (2 to >7) vs 4 (2 to >8), 0.2 (0.7 to 1.0) vs 0.3 (0.6 to 1.1) vs 0.1 (0.8 to 1.0), missing: 3 2 1.

* Never/rarely vs sometimes/frequently/always.
† Yes vs no/not sure.
‡ 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?” (Appendix E2, available online at http://www.annemergmed.com)
§ Patients who had not yet recovered at the 1-week telephone call were categorized as greater than 7 days.

Table 2. One-week outcomes among study participants who completed 1-week follow-up.
Many of these patients with acute low back pain had improved by the 1-week follow-up, although more than one third reported persistent moderate or severe low back pain. At 3 months, 45% of our cohort reported low back-related functional impairment.

Orphenadrine and methocarbamol are used in more than 250,000 US ED visits for low back pain annually. Among patients with acute low back pain or muscle spasm, monotherapy with methocarbamol has been shown to be superior to placebo in regard to both pain and functionality (Table E5, available online at http://www.annemergmed.com).10,14 We are not aware of other randomized studies in which methocarbamol has been combined with a nonsteroidal anti-inflammatory drug. Orphenadrine has demonstrated superiority to placebo among patients with acute low back pain, although it was not superior to monotherapy with aspirin (Table E6, available online at http://www.annemergmed.com).15-18 We are not aware of other low back pain studies in which orphenadrine was combined with a nonsteroidal anti-inflammatory drug.

Overall, 1-week and 3-month outcomes in this study revealed that most patients experience normalization of low back pain–related functional impairment, although a subset of patients continue to experience both pain and functional impairment. Ideally, patients at higher risk of poor outcome should be targeted for close follow-up, with the goal of preventing the transition from acute to chronic pain. However, it remains difficult to predict which ED patients with acute low back pain are at risk of poor outcomes.19

Our data contribute to a growing body of literature suggesting that, in general, combinations of medications do not improve low back pain. We have demonstrated previously that adding cyclobenzaprine, oxycodone and acetaminophen, diazepam, or corticosteroids12 to naproxen is unlikely to benefit the patient presenting with acute low back pain.3,4 It is also true that acetaminophen is of no benefit for patients with nonradicular low back pain.14 Complementary therapies, including acupuncture,20 yoga,21 and massage22 may be offered but have been inadequately studied to determine efficacy in an acute low back pain population. Spinal manipulation is unlikely to benefit ED patients with acute low back pain who are given a prescription for an analgesic medication.23 Physical therapy too is unlikely to benefit patients in an acute time frame.23 Emergency physicians should counsel their patients that passage of time will bring improvement and eventual relief to most individuals.

Participation in this study did not commence until an individual was ready for discharge from the ED. Therefore, we do not know whether these skeletal muscle relaxants, when administered acutely in the ED, increase the likelihood of discharge among patients who arrive with marked functional impairment due to low back pain.

### Table 3. Use of investigational medication and health care resources within 1 week of ED discharge.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Naproxen + Placebo, No. (%)</th>
<th>Naproxen + Orphenadrine, No. (%)</th>
<th>Naproxen + Methocarbamol, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency of naproxen use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than once/day</td>
<td>50 (67)</td>
<td>48 (62)</td>
<td>41 (53)</td>
</tr>
<tr>
<td>Once/day</td>
<td>19 (25)</td>
<td>19 (24)</td>
<td>19 (24)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>5 (7)</td>
<td>5 (6)</td>
<td>10 (13)</td>
</tr>
<tr>
<td>Only once</td>
<td>1 (1)</td>
<td>4 (5)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Never</td>
<td>0</td>
<td>2 (3)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td><strong>Frequency of placebo/orphenadrine/methocarbamol use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than once/day</td>
<td>38 (51)</td>
<td>36 (46)</td>
<td>34 (44)</td>
</tr>
<tr>
<td>Once/day</td>
<td>22 (29)</td>
<td>21 (27)</td>
<td>23 (29)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>9 (12)</td>
<td>9 (12)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Only once</td>
<td>4 (5)</td>
<td>4 (5)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Never</td>
<td>2 (3)</td>
<td>8 (10)</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td><strong>Health care resources used</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No visit to any clinician</td>
<td>67 (88)</td>
<td>66 (85)</td>
<td>65 (81)</td>
</tr>
<tr>
<td>Subsequent ED visit</td>
<td>1 (1)</td>
<td>2 (3)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Primary care</td>
<td>5 (7)</td>
<td>4 (5)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>MD specialist*</td>
<td>1 (1)</td>
<td>2 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Complementary therapy†</td>
<td>2 (3)</td>
<td>5 (6)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*Orthopedist, pain management.
†Chiropractic, massage, physical therapy.
pain. Also, we excluded from participation patients with chronic or frequent episodic low back pain. Therefore, the role of these medications for these patients is unknown.

In conclusion, neither orphenadrine nor methocarbamol confers any additional analgesic or functional effectiveness when added to naproxen for the treatment of nonradicular, nontraumatic, acute low back pain.

Supervising editor: Steven M. Green, MD

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Author contributions: BWF and EJG conceived the study. BWF, DC, MD, AN, SP, and DW reviewed the literature in preparation for the trial. BWF, DC, CS, and EJG designed the trial. BWF, EJ, and CS supervised the conduct of the trial and data collection. BWF, DC, EJ, AN, SP, and DW managed the data. BWF, DC, MD, SP, and DW analyzed the data. BWF, DC, and AN drafted the article, and all authors contributed substantially to its revision. BWF takes responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and (2) Drafting the work or revising it critically for important intellectual content; and (3) Final approval of the version to be published; and (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding and support: By Annals policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist. This publication was supported in part by the Harold and Muriel Block Institute for Clinical and Translational Research at Einstein and Montefiore grant (UL1TR001073).

Publication dates: Received for publication August 12, 2017. Revision received September 15, 2017. Accepted for publication September 19, 2017.

Trial registration number: NCT02665286

REFERENCES

APPENDIX E1

RMDQ for low back pain

1. During the last 24 h, I have stayed home most of the time because of my back pain: No, 0 Yes, 1
2. During the last 24 h, I changed position frequently to try to get my back comfortable: No, 0 Yes, 1
3. During the last 24 h, I walked more slowly than usual because of my back: No, 0 Yes, 1
4. During the last 24 h, I have not been doing any jobs that I usually do around the house because of my back pain: No, 0 Yes, 1
5. During the last 24 h, I used a handrail to get upstairs because of my back pain: No, 0 Yes, 1
6. During the last 24 h, I lay down to rest more often because of my back pain: No, 0 Yes, 1
7. During the last 24 h, I have had to hold on to something to get out of an easy chair because of my back pain: No, 0 Yes, 1
8. During the last 24 h, I have tried to get other people to do things for me because of my back pain: No, 0 Yes, 1
9. During the last 24 h, I got dressed more slowly than usual because of my back pain: No, 0 Yes, 1
10. During the last 24 h, I stood up for only short periods because of my back pain: No, 0 Yes, 1
11. During the last 24 h, I tried not to bend or kneel because of my back pain: No, 0 Yes, 1
12. During the last 24 h, I found it difficult to get out of a chair because of my back pain: No, 0 Yes, 1
13. During the last 24 h, my back was painful almost all of the time: No, 0 Yes, 1
14. During the last 24 h, I found it difficult to turn over in bed because of my back pain: No, 0 Yes, 1
15. During the last 24 h, my appetite was not very good because of my back pain: No, 0 Yes, 1
16. During the last 24 h, I have had trouble putting on my socks (or stockings) because of the pain in my back or leg: No, 0 Yes, 1
17. During the last 24 h, I could walk only short distances because of my back pain: No, 0 Yes, 1
18. During the last 24 h, I slept less well because of my back: No, 0 Yes, 1
19. During the last 24 h, I got dressed with the help of someone else because of my back pain: No, 0 Yes, 1
20. During the last 24 h, I sat down for most of the day because of my back: No, 0 Yes, 1
21. During the last 24 h, I avoided heavy jobs around the house because of my back pain: No, 0 Yes, 1
22. During the last 24 h, I was more irritable and bad tempered with people than usual because of my back pain: No, 0 Yes, 1
23. During the last 24 h, I went upstairs more slowly than usual because of my back pain: No, 0 Yes, 1
24. During the last 24 h, I stayed in bed most of the time because of my back pain: No, 0 Yes, 1

Table E1. Adverse medication effects.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Naproxen + Placebo, No. (%)</th>
<th>Naproxen + Orphenadrine, No. (%)</th>
<th>Naproxen + Methocarbamol, No. (%)</th>
<th>Difference Between Orphenadrine vs Placebo, % (95% CI)</th>
<th>Difference Between Methocarbamol vs Placebo, % (95% CI)</th>
<th>Difference Between Orphenadrine vs Methocarbamol, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>n = 79 (83)</td>
<td>n = 80 (91)</td>
<td>n = 81 (81)</td>
<td>8 (−3 to 19)</td>
<td>1 (−11 to 14)</td>
<td>9 (−2 to 20)</td>
</tr>
<tr>
<td>No</td>
<td>62 (83)</td>
<td>67 (91)</td>
<td>61 (81)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13 (17)</td>
<td>7 (9)</td>
<td>14 (19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drowsy*</td>
<td></td>
<td></td>
<td></td>
<td>4 (−5 to 13)†</td>
<td>11 (0 to 21)†</td>
<td>7 (−5 to 18)†</td>
</tr>
<tr>
<td>No</td>
<td>43 (57)</td>
<td>41 (55)</td>
<td>38 (51)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A little</td>
<td>27 (36)</td>
<td>25 (34)</td>
<td>24 (32)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A lot</td>
<td>5 (7)</td>
<td>8 (11)</td>
<td>13 (17)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizzy*</td>
<td></td>
<td></td>
<td></td>
<td>1 (−4 to 7)†</td>
<td>3 (−4 to 9)†</td>
<td>1 (−6 to 8)†</td>
</tr>
<tr>
<td>No</td>
<td>63 (84)</td>
<td>59 (80)</td>
<td>61 (81)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A little</td>
<td>10 (13)</td>
<td>12 (16)</td>
<td>10 (13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A lot</td>
<td>2 (3)</td>
<td>3 (4)</td>
<td>4 (5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach irritation*</td>
<td></td>
<td></td>
<td></td>
<td>3 (−2 to 8)†</td>
<td>4 (−2 to 10)†</td>
<td>1 (−6 to 8)†</td>
</tr>
<tr>
<td>No</td>
<td>63 (84)</td>
<td>65 (88)</td>
<td>65 (87)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A little</td>
<td>11 (15)</td>
<td>6 (8)</td>
<td>6 (8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A lot</td>
<td>1 (1)</td>
<td>3 (4)</td>
<td>4 (5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*At the 7-day follow-up, study participants were asked specifically whether they experienced dizziness, drowsiness, and stomach irritation. They were asked to choose among the following options: "no," "a little," and "a lot."
†No” and “a little” vs “a lot.”

Naproxen With or Without Orphenadrine or Methocarbamol for Acute Low Back Pain

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9.e1 Annals of Emergency Medicine

Volume ■, NO. ■ : ■ 2017
APPENDIX E2

Stated reason why patients would not want to receive the same medication combination

One week after ED discharge, patients were asked whether they would want to receive the same medication combination during a subsequent visit to the ED for low back pain. Those who said “no” or “not sure” were asked why.

**Naproxen + placebo**
- Because I’m still in pain.
- Didn’t help much.
- Didn’t really work.
- I am in severe pain.
- I think I got placebo. The medication is not working. I’m still in pain.
- I want stronger meds. It helped more.
- Medication did not work for me. I took Aleve and felt better.
- Medication is not working well for me.
- Medications are too strong.
- No me ayuda con el dolor. (Didn’t help me with this pain.) Not enough relief.
- Not helping for long enough.
- Not sure if there could be a different option.
- Not working; I am still in pain.
- Not working much.
- I believe the back pain went away on its own. I only took the medication twice, and when I took the medication it didn’t help as much as I thought it would.
- I want to take something a little stronger.
- Really didn’t help.
- Sleepy and drowsiness.
- The medication did not make me feel better.
- The naproxen worked. I read the side effects of study med and decided not to take it.
- I did not like the side effects: drowsiness and sleep.
- Too drowsy.
- **Naproxen + orphenadrine**
  - I didn’t like how it made me feel and didn’t help much.
  - Too drowsy and [I] itch.
  - It got me way too sleepy and I didn’t like the feeling. I could not focus.
  - Because I felt sleepy and also palpitations and shortness of breath.
  - Because the medication did not help me. The medication did not work and I’m still [in] severe pain.
  - Because the medication did not help me with my back pain.
  - Because the medication did not work well. (I’m still with mild pain.)
  - Didn’t help as much.
  - Didn’t help much.
  - Does not help.
  - I need stronger meds.
  - Vomiting after second day.
  - I just did not want to take experimental meds.
  - Medication didn’t work for me.
  - Medications did not work for me.
  - Normally Aleve works for me.
  - Not taking pain away.
  - Not work[ing].
  - Uncomfortable taking the muscle relaxer due to not being FDA [Food and Drug Administration] approved for this condition.
  - I do not like taking pills so only took when needed.
  - Something a little stronger.
  - Still in pain.
  - It was not helping.
  - The medications didn’t work. I had to come back to the ED 3 days later. I was still in pain. I was taking the naproxen 2x a day and study med 2x a day. It didn’t help.

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**Table E2. Three-month outcomes.**

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Naproxen + Placebo (n = 79)</th>
<th>Naproxen + Orphenadrine (n = 80)</th>
<th>Naproxen + Methocarbamol (n = 81)</th>
<th>Difference Between Orphenadrine and Placebo, % (95% CI)</th>
<th>Difference Between Methocarbamol and Placebo, % (95% CI)</th>
<th>Difference Between Orphenadrine and Methocarbamol, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median RMDQ (IQR)*</td>
<td>0 (0 to 4)</td>
<td>0 (0 to 13)</td>
<td>0 (0 to 8)</td>
<td>1.8 (-0.7 to 4.2)</td>
<td>1.1 (-3.3 to 3.5)</td>
<td>0.7 (-2.0 to 3.3)</td>
</tr>
<tr>
<td>Missing</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>2 (-11 to 15)</td>
<td>2 (-11 to 16)</td>
<td>4 (-9 to 17)</td>
</tr>
<tr>
<td>Worst low back pain during previous 72 h, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild/none</td>
<td>55 (81)</td>
<td>58 (83)</td>
<td>55 (79)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate/severe</td>
<td>13 (19)</td>
<td>12 (17)</td>
<td>15 (21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>11</td>
<td>10</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| *The RMDQ is a 24-item instrument measuring low back pain-related functional impairment. On this instrument, 0 represents no low back pain-related functional impairment and 24 represents maximum functional impairment.

†Mean difference (95% CI).
The medication affected my stomach. 
Still in pain. The medication does not work. It did not help with the pain. The medication makes me feel sleepy.

**Naproxen + methocarbamol**
I did not think it was necessary to take those medications. After I got medicated in the emergency [ED] the pain got better.
Because I do not know if there is something better. 
Because I don’t want to receive a placebo medication. 
Because I’m still in pain. I would like a medication [to] take away my back pain.
Because my doctor change[d] my medications. 
Because the medication did not help me and also I don’t have any muscles spasm.
Because the medication did not work. I took another medication: Motrin and Tylenol.
Because the medication does not work. [I] still have pain.
Didn’t take away the pain 100%. 
Drowsy. 
It relaxes me; does not take away pain. 

It’s not helping me at all. 
Made me very nauseous and dizzy. 
Naproxen does not help with the pain and also the muscle relaxer medication does not improve the pain. 
No, the medication makes me drowsy. 
Not helping. 
Not helping the pain, just making me sleepy. 
Patient only took Naproxen; didn’t feel comfortable with the study medication.
PCP [primary care physician] told me it was not good. Stomach pain. 
The medication didn’t help and I had to go back to the ER. The medication didn’t help. 
Did not take study medication. Taking tramadol and diazepam. 
I drive for a living and I’ve been working and I was unable to take the medication during my shift. 
I still have the pain. I do not like the medication. I think I got the placebo medication. It’s not working. 
I still have the low back pain. The medication does not help.

<table>
<thead>
<tr>
<th>RMDQ Score</th>
<th>Placebo, No. (%)</th>
<th>Orphenadrine, No. (%)</th>
<th>Methocarbamol, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>39 (57)</td>
<td>37 (54)</td>
<td>38 (54)</td>
</tr>
<tr>
<td>1</td>
<td>4 (6)</td>
<td>4 (6)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>2</td>
<td>5 (7)</td>
<td>3 (4)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>3</td>
<td>3 (4)</td>
<td>0</td>
<td>2 (3)</td>
</tr>
<tr>
<td>4</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
<td>2 (3)</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>7</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>8</td>
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<td>3 (4)</td>
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<tr>
<td>9</td>
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<td>1 (1)</td>
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<tr>
<td>10</td>
<td>0</td>
<td>1 (1)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
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<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>14</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>15</td>
<td>3 (4)</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>17</td>
<td>1 (1)</td>
<td>2 (3)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>18</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>19</td>
<td>0</td>
<td>3 (4)</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>1 (1)</td>
<td>2 (3)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>21</td>
<td>1 (1)</td>
<td>2 (3)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>22</td>
<td>1 (1)</td>
<td>1 (1)</td>
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<tr>
<td>23</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>
**Table E5. Clinical studies of methocarbamol for musculoskeletal pain.**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Setting, Population, N</th>
<th>Methocarbamol Dosing</th>
<th>Comparator</th>
<th>Acute Outcomes</th>
<th>Longer-Term Outcomes</th>
<th>Adverse Medication Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tisdale, 1975</td>
<td>Outpatient, muscle spasm caused by trauma or inflammation, &lt;14 days, N=180</td>
<td>2,000 mg every 6 h</td>
<td>Placebo</td>
<td>48-h improvement in pain, functional impairment, and daily activities &gt;placebo</td>
<td>7- to 9-day improvement in pain, functional limitations, daily activities, desire to receive same medication again</td>
<td>11% report nuisance adverse effects</td>
</tr>
<tr>
<td>Emrich, 2015</td>
<td>Acute back pain, N=202</td>
<td>1,500 mg every 8 h</td>
<td>Placebo</td>
<td>44% vs 18% achieved pain relief</td>
<td>Not reported</td>
<td>5% reported nuisance adverse effects</td>
</tr>
</tbody>
</table>

---

**Table E4. An assessment of blinding.**

<table>
<thead>
<tr>
<th>Response</th>
<th>Naproxen + Placebo, No. (%) (n=79)</th>
<th>Naproxen + Orphenadrine, No. (%) (n=80)</th>
<th>Naproxen + Methocarbamol, No. (%) (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I think I was given placebo</td>
<td>9 (12)</td>
<td>10 (13)</td>
<td>11 (14)</td>
</tr>
<tr>
<td>I think I was given a muscle relaxer</td>
<td>35 (47)</td>
<td>40 (51)</td>
<td>31 (40)</td>
</tr>
<tr>
<td>I'm not sure</td>
<td>31 (41)</td>
<td>28 (36)</td>
<td>36 (46)</td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

*As part of the 1-week follow-up telephone call, study participants were asked, “Do you think you were given the real muscle relaxer or placebo?” Responses are tabulated.*
Table E6. Clinical studies of orphenadrine for musculoskeletal pain.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Setting, Population, N</th>
<th>Orphenadrine Dosing</th>
<th>Comparator</th>
<th>Acute Outcomes</th>
<th>Adverse Effects of Orphenadrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hingorani, 1966</td>
<td>Inpatient, acute or acute-on-chronic lumbar pain, 99</td>
<td>Orphenadrine 70 mg + paracetamol 900 mg TID</td>
<td>Aspirin 100 mg TID</td>
<td>No difference in pain improvement. Fewer patients in orphenadrine group required additional medication.</td>
<td>Self-limited adverse effects in 12%</td>
</tr>
<tr>
<td>Tervo, 1976</td>
<td>Orthopedics/trauma clinic, acute lumbago, 50</td>
<td>Orphenadrine 70 mg + paracetamol 900 mg TID</td>
<td>Paracetamol 900 mg TID</td>
<td>7–10 days: Fewer days of disability</td>
<td>Orphenadrine/APAP: 1 patient with nausea, 1 patient difficulties with accommodation</td>
</tr>
<tr>
<td>Gold, 1978</td>
<td>Outpatient, acute low back pain, 60</td>
<td>100 mg BID</td>
<td>Phenobarbital 32 mg BID Placebo</td>
<td>Reduced pain at 48 h &gt;-comparators</td>
<td>Self-limited adverse effects in 25%</td>
</tr>
<tr>
<td>Klinger, 1988</td>
<td>Military low back pain clinic, 60 mg IV low back pain, spasms, limited ROM, 80</td>
<td>Orphenadrine 60 mg IV</td>
<td>Placebo</td>
<td>Substantially greater relief of pain and range of motion</td>
<td>Mild to moderate in intensity and resolved without sequelae</td>
</tr>
</tbody>
</table>