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Methocarbamol and Orphenadrine for  
Acute, Non-traumatic, Non-radicular Low Back Pain:  
A Randomized, Placebo Controlled, 3-armed Study

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## Specific Aims

Low back pain (LBP) causes 2.4% of visits to US emergency departments (ED) resulting in 2.7 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) Three months after the emergency visit, 48% of ED LBP patients report functional impairment, 42% report moderate or severe pain, and 46% report persistent analgesic use. (2)

It is not clear which medications should be prescribed for acute LBP. Non-steroidal anti-inflammatory drugs (NSAID) are more efficacious than placebo with regard to LBP relief, global improvement, and requirement of analgesic medication (3) but are insufficient treatment for as many as ½ of ED patients, who continue to suffer despite use of NSAIDs. Treatment of LBP with multiple concurrent medications is common in the ED--emergency physicians often prescribe skeletal muscle relaxants or opioids in combination with NSAIDs.(4) However, work recently completed has revealed that combining cyclobenzaprine, a skeletal muscle relaxant, or oxycodone/acetaminophen with an NSAID does not improve outcomes.(5) It remains uncertain if adding other skeletal muscle relaxants to NSAIDs improves LBP outcomes.

Two specific skeletal muscle relaxants, orphenadrine and methocarbamol, are each used in more than 250,000 U.S. ED visits for LBP annually, although scant evidence exists to determine the appropriateness of this approach.(6) Orphenadrine is centrally acting with prominent anti-cholinergic and anti-histaminic properties. Mechanism of action is not understood. Efficacy in low back pain may be related to non-specific analgesic properties. Mechanism of action of methocarbamol has also not been established. Its efficacy is thought to be related to CNS effects rather than direct effects on skeletal muscles.

Given the poor pain and functional outcomes that persist beyond an ED visit for acute LBP, we propose a clinical trial to determine whether combining either orphenadrine or methocarbamol with an NSAID is more effective than NSAID monotherapy for the treatment of acute, non-traumatic, non-radicular low back pain. Specifically, we will evaluate the following two hypotheses:

- 1) A daily regimen of naproxen + orphenadrine will provide greater relief of LBP than naproxen + placebo one week after an ED visit, as measured by the Roland Morris Disability Questionnaire
- 2) A daily regimen of naproxen + methocarbamol will provide greater relief of LBP than naproxen + placebo one week after an ED visit, as measured by the Roland Morris Disability Questionnaire

## Overview.

This will be a single center, double-blind, comparative effectiveness study, in which we enroll patients during an ED visit for musculoskeletal LBP and follow them by telephone seven days and three months later. Every patient will receive standard-of-care therapy, consisting of naproxen and a low back pain education session. Patients will be randomized to orphenadrine, methocarbamol, or placebo.

## Subject selection:

Our goal is to include in this study a broad representation of patients with musculoskeletal back pain who are likely to respond to the investigational medications and who would not be considered candidates for spinal surgery or targeted epidural intervention. We hope for a widely generalizable study and therefore will not require diagnoses to be contingent on advanced imaging studies. Though we could ensure a more homogeneous study population by requiring imaging, we do not believe this is clinically useful and it will not facilitate dissemination and utilization of the study results. The presence or absence of palpable spasm of the paraspinal muscles will be recorded but not used as an entry criterion because the clinical significance and reliability of this finding is uncertain.(7)

## Inclusion criteria:

- Present to ED primary for management of LBP, defined as pain originating between the lower border of the scapulae and the upper gluteal folds. Flank pain, that is pain originating from tissues lateral to the paraspinal muscles, will not be included.
- Absence of non-musculoskeletal etiology of low back, such as urinary tract infection, ovarian cysts, or influenza like illness. The primary clinical diagnosis, at the conclusion of the ED visit, must be a diagnosis consistent with non-traumatic, non-radicular, musculoskeletal LBP.
- Patient is to be discharged home. Patients admitted to the hospital are more likely to be treated with parenteral medication and therefore are not appropriate for this study.
- Age 18-69 Enrollment will be limited to adults younger than 70 years because of the increased risk of adverse medication effects in the elderly.
- Non-radicular pain: pain cannot radiate below the gluteal folds in a radicular pattern. Patients with non-radicular pain extending below the gluteal folds will not be excluded
- Pain duration  $\leq 2$  weeks (336 hours). Patients with more than two weeks of pain are at increased risk of poor pain and functional outcomes.(2)
- Prior to the acute attack of LBP, back pain cannot have occurred once per month or more frequently. Patients with more frequent back pain are at increased risk of poor pain and functional outcomes.(2)
- Non-traumatic LBP: no substantial and direct trauma to the back within the previous month
- Functionally impairing back pain: A baseline score of  $> 5$  on the Roland-Morris Disability Questionnaire (Appendix)

## Exclusion criteria:

- Not available for follow-up
- Pregnant or breast-feeding
- Chronic pain syndrome defined as use of any analgesic medication on a daily or near-daily basis
- Allergic to or intolerant of investigational medications
- Contra-indications to non-steroidal anti-inflammatory drugs: 1) history of hypersensitivity to NSAIDs or aspirin or patients in whom NSAIDs or aspirin have induced allergic manifestations such as asthma, nasal polyps, rhinitis, or urticarial 2) active or history of peptic ulcer disease, chronic dyspepsia, or active or history of gastrointestinal bleed 3) Severe heart failure (NYHA 2 or worse) 4) hypertension (JNC7 stage 2 or worse) 5) Chronic kidney disease 3 or worse 6) Current use of anti-coagulants, bleeding with tooth brushing, easy bruisability 7) Hepatitis 8) Alcoholism

-Contra-indications to orphenadrine: 1) Glaucoma, Prostatic hypertrophy, Myasthenia gravis, Pyloric or duodenal obstruction

-Contra-indications to methocarbamol: 1) Myasthenia gravis, Chronic kidney disease 3 or worse

#### Study arms:

- A. The orphenadrine arm: Naproxen 500mg, orally twice per day + orphenadrine 100mg, orally twice per day
- B. The methocarbamol arm: Naproxen 500mg tablets, orally twice per day + methocarbamol 750mg, orally as 1 or 2 tabs, thrice per day
- C. The control arm: Naproxen 500mg tablets taken twice per day + placebo. Placebo dose will be either 1 capsule orally twice per day or 1 or 2 capsules orally, thrice per day

In an effort to maximize effectiveness while minimizing side effects, patients will be instructed to take one or two pills of the methocarbamol every 8 hours. If one tablet of the methocarbamol affords sufficient relief then there will be no need for the patient to take the second tablet. However, if the patient has not experienced sufficient relief within 30 minutes of taking one investigational medication tablet, they will be instructed to take the second tablet. Orphenadrine is only manufactured in 100mg extended release tablets and is therefore not amenable to flexible dosing. All study patients will be given 14 naproxen tablets, a seven day supply, and a sufficient number of investigational tablets to last 7 days. Optimal dosing of methocarbamol has not been established. We believe the dosing regimen we chose is sufficient to determine efficacy while not exposing patients to unnecessary risk.(8-10)

#### Outcome measures

1. Roland Morris LBP Disability Questionnaire (RMDQ)--Reproduced in the Appendix. This 24-item LBP functional scale is recommended for use in LBP research.(11) Its yes/ no format is amenable to telephone follow-up. We have used it successfully to obtain post-ED follow-up in five previous LBP studies involving more than 1500 patients.
2. Ordinal pain scale (“severe”, “moderate”, “mild”, or “none”). Study participants will be asked to describe their worst back pain in the previous 24 hours.
3. Medication requirements: “Did you require any medication to treat your low back pain in the previous 24 hours?”
4. Low back pain frequency: “Over the last 24 hours, how often were you in pain? Not at all, Rarely, Sometimes, Usually, Always”. Low back pain symptomatology is quite variable. Some patients may experience no pain unless they move a certain way. Others may experience a constant low level of pain. This question will help determine the burdensomeness of the LBP in the patient’s daily life.
5. Satisfaction, as measured by response to this question: The next time you go to the ER with low back pain, do you want to get the same combination of medications?

#### Baseline measures

1. Roland Morris LBP disability questionnaire
2. Patient Health Questionnaire depression module, the PHQ 9, will be assessed at the baseline visit.
3. 5-item Cassandra questionnaire. These five questions, based on psychological variables, predict poor outcomes in an emergency room population.(12) (Reproduced in the Appendix)
4. Perceived risk of not recovering. Pain outcomes may be influenced by expectations. After providing an educational intervention, we will ask study participants to estimate how long they believe they will continue to suffer from pain.

## 5. StarT Back LBP questionnaire

### Primary outcome

The change in Roland Morris scale between the baseline ED visit and the one week follow-up (Roland-Morris<sub>baseline</sub> - Roland-Morris<sub>1week</sub>). The baseline questions will refer to the time period immediately prior to ED presentation (Before you came to the ER today, were you able to.....)..

### Secondary outcomes

The following outcomes will be assessed one week after ED discharge

1. Day post ED discharge able to return to all usual activities
2. Satisfaction with treatment
3. Number of visits to any healthcare provider.
4. Worst LBP over the previous 24 hours, using a four point ordinal scale: severe, moderate, mild, or none and a 0 – 10 verbal integer scale
5. Use of any analgesic or LBP medication within the previous 24 hours.
6. Frequency of low back pain using the five point Likert scale: Not at all, Rarely, Sometimes, Usually, Always
7. Absolute RMDQ score

The following outcomes will be assessed three months after ED discharge

1. Roland Morris Disability Questionnaire
2. Worst LBP over the previous week, using a four point ordinal scale: severe, moderate, mild, or none and a 0 – 10 verbal integer scale
3. Frequency of low back pain over the previous week using the five point Likert scale: Not at all, Rarely, Sometimes, Usually, Always
4. Number of days with LBP since ED discharge
5. Use of any analgesic or LBP medication within the previous 7 days.
6. Number of visits to any healthcare provider.
7. Satisfaction with medication and with the current state of the LBP

### Adverse events

The following adverse medication effects will be assessed at the one week follow-up.

- CNS side effects including drowsiness and dizziness
- GI side effects including dyspepsia, nausea, and bleeding
- All other side effects

### Randomization and blinding

The pharmacist will perform randomization in blocks of 6 based on a sequence generated at <http://randomization.com>. Every block of six will contain two orphenadrine assignments, two methocarbamol assignments, one placebo assignment dosed as 1 capsule twice daily (to mirror orphenadrine dosing), and one placebo assignment dosed as 1-2 capsules thrice daily (to mirror methocarbamol dosing). Therefore, though patients will not know whether they have been assigned to active medication or placebo, they may deduce to which medication they were not assigned. This does not threaten the internal validity of the study because patients will not know whether or not they received active medication.

Naproxen will not be masked. Orphenadrine, methocarbamol, and placebo will be masked by placing tablets into identical capsules, which will be packed with scant amounts of lactose and sealed. This masking will take place in a secure location inaccessible to ED personnel. Patients will be presented with two vials of medication. The vial containing the naproxen will be labeled in a typical manner. The second vial, containing orphenadrine, methocarbamol, or placebo will be labeled as investigational medication. Patients will be instructed to the investigational medication only as needed for moderate or severe LBP.

#### Details of protocol

Prior to discharge from the ED and after the patient's pain has been controlled, the attending emergency physician will refer appropriate patients to study personnel for screening. Eligible patients would have already received different and various medications in the ED for their pain (potentially including naproxen) prior to being approached for study participation. This decision is up to the attending physician and is not related to participation in the study. Patients will be screened and consented. Research associates will ascertain baseline socio-demographic information, low back pain history, and baseline variables discussed above. A urine pregnancy test will be performed. Research personnel will provide each patient with a 15-minute educational intervention. This will be based on NIAMS's Handout on Health: Back Pain information webpage (available at [http://www.niams.nih.gov/Health\\_Info/Back\\_Pain/default.asp](http://www.niams.nih.gov/Health_Info/Back_Pain/default.asp)) Research personnel will review each section of the information sheet with the patient and elicit questions. Patients will be discharged with two medical vials, one containing naproxen and one containing placebo, orphenadrine, or methocarbamol. Patients will be cautioned not to take off protocol LBP medications without first consulting with a healthcare provider. Patients will be cautioned not to drink alcohol or use other centrally-acting substances while using study medications. Patients will be cautioned not to drive after taking the study medications. Follow-up phone calls will be conducted one week and three months after ED discharge. Follow-up will be attempted daily until successful. For patients difficult to contact, express courier or home visit will be used to obtain follow-up information.

Analysis. An intention-to-treat analysis will be performed. The primary outcome will be a comparison of the change in RMDQ between baseline and one week. Results will be reported as means with 95%CI. A t-test for independent samples will be used to determine statistically significant differences between placebo and each of the active medications. Secondary outcomes will be reported as rates with 95%CI. A per protocol efficacy analysis will be conducted among those patients who use the investigational medication at least once.

#### Sample size calculation

We based assumptions on a recently completed RCT of LBP treatment. The mean improvement in RMDQ among those who receive naproxen alone was 10.2. The standard deviation was 8.9. A widely accepted minimum clinically important improvement of 5 points on the RMDQ would require those randomized to active medication to demonstrate a mean improvement of 15.2 on the RMDQ. Using a standard alpha of 0.05 and a beta of 0.20, we determined the need for 50 subjects in each arm. To account for protocol violations and patients lost-to-follow-up (typical lost-to-follow-up rate is 5%) and to ensure sufficient power for the per protocol analysis (in our previous ED-based LBP studies, up to 1/3 of enrolled patients have not used the medication more than once), we intend to enroll 80 patients in each arm.

Data Safety Monitoring Committee. This committee will be headed by Dr. XXX and include XXX. The committee will meet every month with the PI to 1) monitor adverse events and develop strategies to minimize these; and, 2) monitor recruitment and enrollment. There will not be an interim analysis.

Naproxen plus orphenadrine or methocarbamol for LBP. An RCT. Version 012716

Registration. The study will be registered at <http://www.clinicaltrials.gov>.

Consent. Study personnel will obtain informed consent once the patient's pain has been controlled and the patient is ready for discharge from the ED.

#### Risks/Benefits

Non-steroidals are used in 50% of more than 2.5 million annual US ED visits for LBP. Skeletal muscle relaxants are used in 43% of these visits. Regardless of results, this study will have a national impact. Study subjects will benefit by receiving a medication that is likely to improve their acute LBP. In addition to breach of confidentiality, which is unlikely, and inconvenience to the subject, which will undoubtedly occur, it is likely that subjects will experience adverse medication effects. For the most part, these are nuisance events. Skeletal muscle relaxants such as orphenadrine and methocarbamol are generally well tolerated but can cause substantial drowsiness and when combined with alcohol or other centrally acting substances may be lethal. Non-steroidals can cause life-threatening gastro-intestinal bleeding, but this is unlikely in patients screened for gastro-intestinal illness who will take the medication for one week only.

#### Data Storage & Confidentiality

Data will be stored and maintained in REDCap. Data analysis will occur on password-protected computers. Consent documents will be maintained in locked research cabinets. Only study personnel will have access to the data and consent documents.

## References

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Appendix 1. Roland Morris low back pain disability questionnaire

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

## Appendix 2. Cassandra questions

### **Five item Cassandra Instrument**

In the past month, how often were you distressed by:

1. Feeling everything is an effort

Not at all<sup>0</sup> A little bit<sup>1</sup> Moderately<sup>2</sup> Quite a bit<sup>3</sup> Extremely<sup>4</sup> Don't know

2. Trouble getting your breath

Not at all<sup>0</sup> A little bit<sup>1</sup> Moderately<sup>2</sup> Quite a bit<sup>3</sup> Extremely<sup>4</sup> Don't know

3. Hot or cold spells

Not at all<sup>0</sup> A little bit<sup>1</sup> Moderately<sup>2</sup> Quite a bit<sup>3</sup> Extremely<sup>4</sup> Don't know

4. Numbness or tingling in parts of your body

Not at all<sup>0</sup> A little bit<sup>1</sup> Moderately<sup>2</sup> Quite a bit<sup>3</sup> Extremely<sup>4</sup> Don't know

5. Pain in your heart or chest

Not at all<sup>0</sup> A little bit<sup>1</sup> Moderately<sup>2</sup> Quite a bit<sup>3</sup> Extremely<sup>4</sup> Don't know