Ibuprofen plus metaxolone, tizandine, or baclofen for low back pain. A randomized trial

Specific Aims

Up to ½ of emergency department (ED) patients with acute, new onset low back pain (LBP) report persistent moderate or severe pain one week after the ED visit.(1, 2) Skeletal muscle relaxants (SMR) are commonly used to treat LBP though evidence supporting efficacy is generally lower quality. We have demonstrated previously that two commonly used SMRs, cyclobenzaprine(1) and diazepam(2), when combined with an NSAID, do not improve LBP outcomes more than NSAIDs used alone. This proposal seeks to determine whether there is any benefit from other commonly used SMRs.

The first SMR to be included in this study is baclofen. The precise mechanism of action of baclofen is unknown. Baclofen inhibits monosynaptic and polysynaptic reflexes at the spinal level, although actions at supraspinal sites may contribute to its clinical effect. Baclofen is an analog of the neurotransmitter GABA, but it is uncertain whether GABA is involved in its clinical effects. In a randomized, placebo controlled study, 200 patients with acute LBP were randomized to baclofen or placebo.(3) Patients randomized to baclofen reported modestly better outcomes four and ten days later.

The second investigational SMR is tizanidine. Tizanidine is a centrally acting alpha-2-adrenergic agonist. It reduces muscle spasticity by increasing presynaptic inhibition of motor neurons. In a randomized, placebo controlled trial, 112 patients with acute LBP were randomized to tizanidine. In this study, patients randomized to tizanidine tended to use less aspirin.(4) In an RCT of tizanidine + ibuprofen versus ibuprofen alone, the combination of medications outperformed ibuprofen monotherapy on some pain outcomes.(5)

The third investigational SMR is metaxalone, a CNS depressant whose mechanism of action is not yet understood. In a randomized study of 228 patients with acute symptoms, patients randomized to metaxolone reported improved performance of daily activities than patients who received placebo.(6) Results were similar in two other RCTS of metaxolone versus placebo, each of which enrolled 100 patients.(7)

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 a muscle relaxant with an NSAID is more effective than NSAID monotherapy for the treatment of acute, non-traumatic, non-radicular low back pain. NSAIDs are provided to all patients because these medications are considered standard-of-care therapy for LBP. We will test the following three hypotheses:

1) A daily regimen of ibuprofen + metaxolone will provide greater relief of LBP than ibuprofen + placebo one week after an ED visit, as measured by the Roland Morris Disability Questionnaire
2) A daily regimen of ibuprofen + tizanidine will provide greater relief of LBP than ibuprofen + placebo one week after an ED visit, as measured by the Roland Morris Disability Questionnaire
3) A daily regimen of ibuprofen + baclofen will provide greater relief of LBP than ibuprofen + placebo one week after an ED visit, as measured by the Roland Morris Disability Questionnaire

Overview.
This will be a double-blind, comparative effectiveness study, in which we enroll patients during an ED visit for musculoskeletal LBP and follow them by telephone two and seven days and three months later. Every patient will receive standard-of-care therapy, consisting of ibuprofen and a low back pain education session. Patients will be randomized to metaxolone, tizanidine, baclofen, 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. 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.(8)

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.
- Musculoskeletal etiology of low back. Patients with non-musculoskeletal etiologies such as urinary tract infection, ovarian cysts, or influenza like illness will be excluded. 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 18-64 Enrollment will be limited to adults younger than 65 years because of the increased risk of adverse medication effects in the elderly.
-Non-radicular pain. Patients will be excluded if the pain radiates below the gluteal folds in a radicular pattern.
-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.(9)
-Prior to the acute attack of LBP, back pain cannot occur more frequently than once per month. Patients with more frequent back pain are at increased risk of poor pain and functional outcomes.(9)
-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 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) uncontrolled blood pressure (>160/100) 5) GFR <60ml/min 6) Current use of anti-coagulants 7) cirrhosis or liver enzymes 2xULN

8) Alcoholism 9) MI/ stroke/ unstable angina within the previous 3 months 10) high dose diuretics or ace inhibitors
-Contra-indications to muscle relaxants: 1) Concurrent use of centrally acting opioids; 2) GFR <60 ml.min; 3) Abnormal LFTs 4) Use of any of the following medications: fluvoxamine, flouroquinolones, amiodarone, mexiletine, propafenone, verapamil, cimetidine, famotidine, acyclovir, ticlopidine, oral contraceptive pills

Study arms.

A. The metaxolone arm: Ibuprofen 600mg+ metaxolone 400-800mg, orally, every 8 hours
B. The tizanidine arm: Ibuprofen 600mg+ tizanidine 2-4mg, orally, every 8 hours
C. The baclofen arm: Ibuprofen 600mg+ baclofen 10- 20mg, orally, every 8 hours
D. The control arm: Ibuprofen 600mg + placebo, orally, every 8 hours

In an effort to maximize effectiveness while minimizing side effects, patients will be instructed to take one ibuprofen plus one or two muscle relaxant pills every 8 hours. If one tablet of the muscle relaxant affords sufficient relief then there will be no need for the patient to take the second muscle relaxant tablet. However, if the patient has not experienced sufficient relief within 60 minutes of taking one investigational medication tablet, they will be instructed to take the second tablet. All study patients will be given a seven day supply of ibuprofen and the muscle relaxant.

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.(10) 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: “What medications did you use 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 will be assessed at the baseline visit.
3. 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.
4. 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 $_{baseline}$ - Roland-Morris $_{1week}$). 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 48 hours and 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
8. Frequency of adverse events including
    - -CNS side effects (drowsiness and dizziness)
    - -GI side effects (dyspepsia, nausea, and bleeding)
    - -CV side effects (chest pain, shortness of breath, edema)
    - -renal side effects (fluid retention, development of hypertension as defined by JNC-7 or worsening of blood pressure)
    - -All other side effects

The following will be assessed 3 months after ED discharge

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

Randomization and blinding

The pharmacist will perform randomization in blocks of 8 based on a sequence generated at http://randomization.com. Ibuprofen will not be masked. Metaxolone, tizanidine, baclofen, 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 bottles of medication tablets. The bottle containing the ibuprofen will be labeled in a typical manner. The second vial, containing the muscle relaxant or placebo will be labeled as investigational medication. Patients will be instructed to take 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 NSAIDs) prior to being approached for study participation. 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) Research personnel will review each section of the information sheet with the patient and elicit questions. Patients will be discharged with two medication vials, one containing ibuprofen and one containing metaxolone, tizanidine, baclofen, or placebo. 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. Patients will be instructed to dispose of unused medication by mixing with an unpalatable substance such as coffee grounds and sealing in a plastic bag. Patients will be encouraged to follow-up with their primary care physician. Follow-up phone calls will be conducted 48 hours, 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 among all patients for whom primary outcome data is available. 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.(1) The mean improvement in RMDQ among those who receive an NSAID 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 (total n= 320)

Data Safety Monitoring Committee. This committee will be headed by Dr. Polly Bijur, PhD, an epidemiologist and include Dr. Esses, MD, the director of the Moses ED. 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.

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. The attending physician will assess the patient's

capacity to consent to participate in this study. Because pain may compromise cognition and judgment, the principal investigator or his designee will assess the capacity of the patient to provide ethically and legally adequate informed consent and will document this in the research record.

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. All study subjects receive ibuprofen and thus are likely to benefit. In addition, those who receive active drug may have greater benefit as they will receive a medication that will possibly improve their acute LBP. In addition to breach of confidentiality, which is unlikely, and inconvenience to the subject, which will undoubtedly occur, some subjects will possibly experience adverse medication effects. For the most part, these are minor events. Skeletal muscle relaxants such as tizanidine, metaxalone and baclofen 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-threating gastro-intestinal bleeding, but this is unlikely in patients screened for gastro-intestinal illness who will take the medication for one week only. Non-steroidals increase cardiovascular and and risk of renal injury and may worsen blood pressure control

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