

**RCT**  
**Potential PURL Review Form**  
**PURL Jam Version**  
Version #11 October 29, 2009

**PURLs Surveillance System**  
**Family Physicians Inquiries Network**

**SECTION 1: Identifying Information for Nominated Potential PURL**  
**[to be completed by PURLs Project Manager]**

- 1. Citation** Friedman BW, Dym AA, Davitt M, Holden L, Solorzano C, Esses D, Bijur PE, Gallagher EJ. Naproxen With Cyclobenzaprine, Oxycodone/Acetaminophen, or Placebo for Treating Acute Low Back Pain: A Randomized Clinical Trial. JAMA. 2015 Oct 20;314(15):1572-80. doi: 10.1001/jama.2015.13043.
- 2. Hypertext link to PDF of full article** <http://www.ncbi.nlm.nih.gov/pubmed/26501533>
- 3. First date published study available to readers** 10/20/15
- 4. PubMed ID** 26501533
- 5. Nominated By** Jim Stevermer Other:
- 6. Institutional Affiliation of Nominator** University of Missouri Other:
- 7. Date Nominated** 11/14/15
- 8. Identified Through** Other Other: TOC
- 9. PURLS Editor Reviewing Nominated Potential PURL** Kate Rowland Other:
- 10. Nomination Decision Date** 11/24/15
- 11. Potential PURL Review Form (PPRF) Type** RCT
- 12. Other comments, materials or discussion**
- 13. Assigned Potential PURL Reviewer**
- 14. Reviewer Affiliation** University of Chicago Other:
- 15. Date Review Due** 02/04/16
- 16. Abstract** **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/acetaminophengroup. 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.

17. Pending  
PURL Review  
Date

**SECTION 2: Critical Appraisal of Validity**

**[to be completed by the Potential PURL Reviewer]**

**[to be revised by the Pending PURL Reviewer if needed]**

- |  |  |
|--|--|
| <b>1. Number of patients starting each arm of the study?</b>   | 107 started on naproxen plus placebo; 108 started on Naproxen plus Cyclobenzaprine and 108 started on Naproxen plus oxycodone/acetaminophen combo  |
| <b>2. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)?</b> | Setting was an urban ER in the Bronx. Inclusion criteria: adults ages 21 to 64 coming into an ER for treatment of acute low back pain defined as pain under the scapula to the upper gluteal folds havnig received a diagnosis of nontraumatic, nonradicular musculoskeletal back pain. Pain had to be functionally impairing which was defined as a score of 5 or greater on the Roland-Morris Disability Questionnaire (RMDQ).<br>Exclusion criteria: radicular pain, direct trauma to the back within the last month, pain lasting >2 weeks, >1 episode of back pain in a month, pregnanct, lactating, allergic to the intervention meds and chronic opioid use |
| <b>3. Intervention(s) being investigated?</b>  | combinations of : Naproxen plus placebo vs. Naproxen plus cyclobenzaprine vs. naproxen plus oxycodone/acetaminophen for the relief of pain and improvement in function   |
| <b>4. Comparison treatment(s), placebo, or nothing?</b>  | as #3  |
| <b>5. Length of follow up? Note specified end points e.g. death, cure,</b>                               | 1 week after d/c from ER and 3 months after d/c from ER  |

etc.

**6.** What outcome measures are used? List all that assess effectiveness.

improvement in Roland-Morris Disability Questionnaire (RMDQ) which is a 24 item questionnaire that measures functional impairment and low back pain, between ER d/c and 1 week later.

**7.** What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CI, p-values, etc.

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).

**8.** What are the adverse effects of intervention compared with no intervention?

Drowsiness, dizziness, stomach irritation and N/V were reported among all three groups but highest among the oxycodone-acetaminophen group

**9.** Study addresses an appropriate and clearly focused question - **select one**

- Well covered
- Adequately addressed
- Poorly addressed
- Not applicable

Comments:

**10.** Random allocation to comparison groups

- Well covered
- Adequately addressed
- Poorly addressed
- Not applicable

Comments:

**11.** Concealed allocation to comparison groups

- Well covered
- Adequately addressed
- Poorly addressed
- Not applicable

Comments:

**12.** Subjects and investigators kept "blind" to comparison group allocation

- Well covered
- Adequately addressed
- Poorly addressed
- Not applicable

Comments:

**12.** Comparison groups are similar at the start of the trial

- Well covered
- Adequately addressed
- Poorly addressed
- Not applicable

Comments:

**14.** Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential source of bias.

- Well covered
- Adequately addressed
- Poorly addressed
- Not applicable

Comments:

15. Were all relevant outcomes measured in a standardized, valid, and reliable way?
- Well covered  
 Adequately addressed  
 Poorly addressed  
 Not applicable

Comments:

16. Are patient oriented outcomes included? If yes, what are they?
- Yes, pain and functional impairment

17. What percent dropped out, and were lost to follow up? Could this bias the results? How?
- 7.6% were lost to followup in the Naproxen/placebo group; 7.2% were lost to followup in the Naproxen/cyclobenzaprine group and 9% were lost to followup in the Naproxen/oxycodone-acetaminophen group

18. Was there an intention-to-treat analysis? If not, could this bias the results? How?
- yes

19. If a multi-site study, are results comparable for all sites?
- n/a

20. Is the funding for the trial a potential source of bias? If yes, what measures were taken to insure scientific integrity?
- source not listed

21. To which patients might the findings apply? Include patients in the study and other patients to whom the findings may be generalized.
- any patient with nontraumatic, nonradicular acute low back pain

22. In what care settings might the findings apply, or not apply?
- any primary care or ER setting

23. To which clinicians or policy makers might the findings be relevant?
- any primary care or ER physicians

**SECTION 3: Review of Secondary Literature**  
**[to be completed by the Potential PURL Reviewer]**  
**[to be revised by the Pending PURL Reviewer as needed]**

**Citation Instructions**

For UpTo Date citations, use style modified from [http://www.uptodate.com/home/help/faq/using\\_UTD/index.html#cite](http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite) & AMA style. Always use Basow DS as editor & current year as publication year.

EXAMPLE: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: <http://www.uptodate.com>. {Insert dated modified if given.} Accessed February 12, 2009. {whatever date PPRF reviewer did their search.}

For DynaMed, use the following style:  
 Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at: <http://www.DynamicMedical.com>. Last updated February 4, 2009. {Insert dated modified if given.} Accessed June 5, 2009.{search date}

1. DynaMed excerpts Addition of cyclobenzaprine or oxycodone/acetaminophen to naproxen does not improve pain in patients with acute nontraumatic, nonradicular low back pain (level 1 [likely reliable] evidence)
2. DynaMed citation/access date Title. Acute Low Back Pain Author. Fatima Stanford In: DynaMed [database online]. Available at: [www.DynamicMedical.com](http://www.DynamicMedical.com) Last updated: November 2015. Accessed Jan 2016
3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences) addition of cyclobenzaprine or oxycodone/acetaminophen to naproxen does not improve pain in patients with acute nontraumatic, nonradicular low back pain (level 1 [likely reliable] evidence)
4. UpToDate excerpts The combination of a muscle relaxant and an NSAID provided the most effective symptom relief at one week in an observational study of over 200 patients seen for their first episode of back pain [35]. Subsequent randomized trial results have been mixed: a trial that compared the use of cyclobenzaprine alone or in combination with ibuprofen (1200 mg or 2400 mg daily dose) found similar outcomes for the treatment groups [36], as did a trial comparing naproxen alone (500 mg twice daily) with naproxen plus cyclobenzaprine [37], while a trial comparing aceclofenac 100 mg twice daily with or without addition of tizanidine 2 mg twice daily found improved pain relief and decreased functional impairment with combination therapy [38].
5. UpToDate citation/access date Always use Basow DS as editor & current year as publication year. Title. Treatment of acute low back pain Author. Knight et al In: UpToDate [database online]. Available at: <http://www.uptodate.com>. Last updated: Nov 7, 2015. Accessed Jan 2016
6. Bottom line recommendation or summary of evidence from UpToDate Evidence is mixed whether a naproxen plus muscle relaxant is effective (1-2 sentences)
7. PEPID PCP excerpts [www.pepidonline.com](http://www.pepidonline.com) username: fpinauthor pw: pepidpcp
- Four interventions w/ adequate data:
    - Analgesics:
      - Less pain than placebo in chronic back pain over 10 weeks
    - Herbal medicine:
      - Less pain than placebo in acute back pain over one week
    - Muscle relaxants:
      - Less pain than placebo in acute back pain over one week
    - NSAIDs:
      - Less pain than placebo in both acute and chronic pain over average of six week
8. PEPID citation/access data Author. Title. In: PEPID [database online]. Available at: <http://www.pepidonline.com>. Last updated: June 2014. Accessed Jan 2015
9. PEPID content updating
1. Do you recommend that PEPID get updated on this topic?
- Yes, there is important evidence or recommendations that are missing
- No, this topic is current, accurate and up to date.
- If yes, which PEPID Topic, Title(s):
2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon (EB) that should be updated on the basis of the review?
- Yes, there is important evidence or recommendations that are missing
- No, this topic is current, accurate and up to date.
- If yes, which Evidence Based Inquiry (HelpDesk Answer or Clinical Inquiry), Title(s):
10. Other excerpts (USPSTF; other guidelines; etc.)
11. Citations for other excerpts

12. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)

**SECTION 4: Conclusions**  
**[to be completed by the Potential PURL Reviewer]**  
**[to be revised by the Pending PURL Reviewer as needed]**

**1. Validity:** How well does the study minimize sources of internal bias and maximize internal validity?

Give one number on a scale of 1 to 7  
(1=extremely well; 4=neutral; 7=extremely poorly)  
1 2 3 4 5 6 7

**2.** If 4.1 was coded as 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?

**3. Relevance:** Are the results of this study generalizable to and relevant to the health care needs of patients cared for by “full scope” family physicians?

Give one number on a scale of 1 to 7  
(1=extremely well; 4=neutral; 7=extremely poorly)  
1 2 3 4 5 6 7

**4.** If 4.3 was coded as 4, 5, 6, or 7, please provide an explanation.

**5. Practice changing potential:** If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice?

Give one number on a scale of 1 to 7  
(1=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice)  
1 2 3 4 5 6 7

**6.** If 4.5 was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

**7. Applicability to a Family Medical Care Setting:**

Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, educating or counseling a patient; or creating a system for implementing an

Give one number on a scale of 1 to 7  
(1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care setting)  
1 2 3 4 5 6 7

intervention?

8. If you coded 4.7 as a 4, 5, 6 or 7, please explain.

**9. Immediacy of**

**Implementation:** Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug or other essentials available on the market?

10. If you coded 4.9 as 4, 5, 6, or 7, please explain why.

**11. Clinical meaningful outcomes or patient oriented outcomes:**

Are the outcomes measured in the study clinically meaningful or patient oriented?

12. If you coded 4.11 as a 4, 5, 6, or 7 please explain why.

13. In your opinion, is this a Pending PURL?

Criteria for a Pending PURL:

- Valid: Strong internal scientific validity; the findings appears to be true.
- Relevant: Relevant to the practice of family medicine
- Practice changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.
- Applicability in medical setting:
- Immediacy of implementation

14. Comments on your response in 4.13

Give one number on a scale of 1 to 7

(1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied)

1 2 3 4 5 6 7

Give one number on a scale of 1 to 7

(1=definitely clinically meaningful or patient oriented; 4=uncertain; 7=definitely not clinically meaningful or patient oriented)

1 2 3 4 5 6 7

Give one number on a scale of 1 to 7

(1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL)

1 2 3 4 5 6 7