
**Potential PURL Review Form: Meta-analysis**

**SECTION 1: IDENTIFYING INFORMATION**

1. **Citation**

2. **Hypertext link to PDF of full article**
   [http://dx.doi.org/10.1002/14651858.CD007402.pub2](http://dx.doi.org/10.1002/14651858.CD007402.pub2)

3. **First date published study available to readers**
   July 16, 2010

4. **PubMed ID**
   20556778

5. **Nominated By**
   Jim Stevermer

6. **Institutional Affiliation of Nominator**
   University of Missouri

7. **Date Nominated**
   July 14, 2010

8. **Identified Through**
   InfoPOEMs

9. **PURLS Editor Reviewing Nominated Potential PURL**
   Bernard Ewigman

10. **Nomination Decision Date**
    July 16, 2010

11. **Potential PURL Review Form (PPRF) Type**
    Meta-analysis

12. **Other comments, materials or discussion**

13. **Assigned Potential PURL Reviewer**
    Nina Rogers

14. **Reviewer Affiliation**
    University of Chicago

15. **Date Review Due**
    August 12, 2010

16. **Abstract**

**BACKGROUND:** Use of topical NSAIDs to treat acute musculoskeletal conditions is widely accepted in some parts of the world, but not in others. Their main attraction is their potential to provide pain relief without associated systemic adverse events.

**OBJECTIVES:** To review the evidence from randomised, double-blind, controlled trials on the efficacy and safety of topically applied NSAIDs in acute pain.

**SEARCH STRATEGY:** We searched MEDLINE, EMBASE, The Cochrane Library, and our own in-house database to December 2009. We sought unpublished studies by asking personal contacts and searching on-line clinical trial registers and manufacturers’ web sites.

**SELECTION CRITERIA:** We included randomised, double-blind, active or placebo (inert carrier)-controlled trials in which treatments were administered to adult patients with acute pain resulting from strains, sprains, or sports or overuse-type injuries (twisted ankle, for instance). There had to be at least 10 participants in each treatment arm, with application of treatment at least once daily.

**DATA COLLECTION AND ANALYSIS:** Two review authors independently assessed trial quality and validity, and extracted data. Numbers of participants achieving each outcome were used to calculate relative risk and numbers needed to treat (NNT) or harm (NNH) compared to placebo or other active treatment.

**MAIN RESULTS:** Forty-seven studies were included; most compared topical NSAIDs in the form of a gel, spray, or cream with a similar placebo, with 3455 participants in the overall analysis of efficacy. For all topical NSAIDs combined, compared with placebo, the number needed to treat to benefit (NNT) for clinical success, equivalent to 50% pain relief, was 4.5 (3.9 to 5.3) for treatment periods of 6 to 14 days. Topical diclofenac, ibuprofen, ketoprofen, and piroxicam were of
similar efficacy, but indomethacin and benzydamine were not significantly better than placebo. Local skin reactions were generally mild and transient, and did not differ from placebo. There were very few systemic adverse events or withdrawals due to adverse events. There were insufficient data to reliably compare individual topical NSAIDs with each other or the same oral NSAID. **AUTHORS’ CONCLUSIONS:** Topical NSAIDs can provide good levels of pain relief, without the systemic adverse events associated with oral NSAIDs, when used to treat acute musculoskeletal conditions.

17. Pending PURL Review

**SECTION 2: CRITICAL APPRAISAL OF VALIDITY**

1. What types of studies are included in this review? Randomized controlled trials
2. What is the key question addressed by this review? Summarize the main conclusions and any strengths or weaknesses.
3. Study addresses an appropriate and clearly focused question - **select one**
   4. A description of the methodology used is included.
   5. The literature search is sufficiently rigorous to identify all the relevant studies.
   6. Study quality is assessed and taken into account.
   7. There are enough similarities between selected studies to make combining them reasonable.
   8. Are patient-oriented outcomes included? If yes, what are they?
   9. Are adverse effects addressed? If so, how would they affect recommendations?
10. Is funding a potential source of bias? If yes, what measures (if any) were taken to insure scientific integrity?
11. To which patients might the findings apply? Include patients in the meta-analysis and other patients to whom the findings may be generalized.

Are topical NSAIDs effective and safe for acute pain? Topical NSAIDs can provide good levels of pain relief without adverse systemic events when used to treat acute musculoskeletal conditions. The strengths of this study are high-quality evidence and many subjects. The weaknesses include limited reporting of randomization among the studies, occasional vague definition of success, some small sample sizes leading to possible chance variation, and no comparison between topical and oral NSAIDs.

Well covered

Yes. Pain improvement, nausea, and stomach upset were the outcomes.

Yes, however this study would not change recommendations.

The study was funded by the United Kingdom Pain Research Funds, the NHS Cochrane Collaboration Programme Grant Scheme, and the NIHR Biomedical Research Centre Programme. These sources provided no input into the study and therefore would not bias the study.

The findings would apply to any patient with acute musculoskeletal injury in the last 24-48 hours who is older than 16 years.
12. In what care settings might the findings apply, or not apply? These findings might apply to the emergency department, urgent care, and primary care offices, and sporting events.

13. To which clinicians or policy makers might the findings be relevant? Emergency and primary care physicians and trainers or physical therapists might find these findings relevant.

SECTION 3: REVIEW OF SECONDARY LITERATURE

1. DynaMed excerpts

2. DynaMed citation/access date

3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)
   Oral NSAIDs are cheaper than topical, safe and effective. Topical NSAIDs are safe and effective for acute pain at one week. Non-prescription low dose NSAIDs when used for a short amount of time are not associated with an increased risk of adverse CV events.

4. UpToDate excerpts

5. UpToDate citation/access date


6. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)
   Topical NSAIDs may be beneficial, but they may potentiate adverse effects of other forms of NSAIDs.

7. PEPID PCP excerpts
   www.pepidonline.com username: fpinauthor pw: pepidpcp

8. PEPID citation/access data

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

      If yes, which PEPID Topic, Title(s):
      NSAIDs

   2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon (_enabled) that should be updated on the basis of the review?
      No, this topic is current, accurate and up to date.

10. Other excerpts (USPSTF; other guidelines; etc.)
   The Agency for Health care Research and Policy, the American College of Sports Medicine, the National Academy of Sports Medicine, and the American Osteopathic Academy of Sports Medicine have no
mention of topical preparations of NSAIDs.

11. Citations for other excerpts

Revisions to Hepatic Effects section of prescribing information regarding potential for elevation in liver function tests during treatment with products containing diclofenac sodium

- Product affected: diclofenac sodium topical gel 1% (Voltaren gel)
- Postmarketing surveillance reported cases of severe hepatic reactions (including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure), including some fatalities or liver transplants
- Transaminases should be measured periodically with long-term diclofenac therapy (within 4-8 weeks of initiation based on clinical trial data and postmarketing experiences)


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

There is no information about topical NSAIDs. There may be some adverse hepatic effects of diclofenac sodium gel after 4 weeks.

SECTION 4: CONCLUSIONS

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)

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)

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)

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 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 intervention? 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)

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? 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)

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? 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)

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? Give one number on a scale of 1 to 7 (1=definitely a Pending PURL; 4=uncertain; 7=definitely not 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**

There is a need for comparison with oral NSAIDs (standard of care).

The benefit of topical NSAIDs has its place, but will not replace oral NSAIDs.
### SECTION 5: EDITORIAL DECISIONS

1. **FPIN PURLs editorial decision (select one)**
   - Pending PURL Review—Schedule for Review

2. **Follow-up issues for pending PURL Reviewer**

3. **FPIN PURLS Editor making decision**
   - Kate Rowland

4. **Date of decision**
   - August 19, 2010, by Umang Sharma

5. **Brief summary of decision**
   - We thought there was some important information lacking: what are the risks of oral NSAIDs just used over 1-2 weeks? Can topical and oral NSAIDs be used together? How many patients in these studies were also on oral NSAIDs? Are they safe to use together?