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## Literature Scan: Topical Analgesics

**Date of Review:** November 2015

**Date of Last Review:** March 2013

**Literature Search:** February 2013-October 2015

### **Current Status of PDL Class:**

See **Appendix 1**.

### **Conclusions:**

- Moderate quality evidence supports the use of topical non-steroidal anti-inflammatory drugs (NSAIDs) as safe and effective treatment options for acute musculoskeletal pain over 1 to 2 weeks. However, evidence comparing topical NSAIDs to other topical analgesics is insufficient.
- Insufficient evidence exists to adequately compare efficacy or safety between most topical analgesics. However, there is low to moderate quality evidence that topical 8% capsaicin improves neuropathic pain more than lower concentrations of capsaicin topical products in post-herpetic neuralgia and neuropathic pain in HIV infected patients, though long-term evidence of safety for this product is insufficient.
- Insufficient evidence exists for the use of 5% topical lidocaine patches in the treatment of mixed peripheral neuropathic pain conditions in adults.

### **Recommendations:**

- No changes to the PDL recommended at this time.

### **Previous Conclusions:**

- Evidence does not support a difference in efficacy or safety between topical analgesics.
- Efficacy and safety not established in patients less than 18 years of age.

### **Previous Recommendations:**

- No further review or research needed at this time. No change to the PDL recommended.

### **Methods:**

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using

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the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

### **New Systematic Reviews:**

A review assessed the efficacy and safety of topical NSAIDs in the treatment of acute musculoskeletal pain in adults.<sup>1</sup> Acute musculoskeletal pain was defined as pain lasting less than 3 months in duration and associated with a soft-tissue injury. Eligible studies included RCTs which compared topical NSAIDs with active treatment or similar topical placebo for adults with acute pain from recent injury such as a sprain, strain or overuse typically within previous 24-48 hours.<sup>1</sup> Outcomes measured included participant reported pain reduction of 50% from baseline or similar measure including a participant reported global assessment of treatment as close to 7 days as possible. Adverse events and withdrawals were assessed as secondary outcomes. The review included 61 studies and involved 5311 participants treated with a topical NSAID, 3470 with placebo, and 220 with an oral NSAID. Topical NSAID agents assessed included diclofenac, ibuprofen, ketoprofen, piroxicam, indomethacin, and benzydamine. Overall, the review was limited by heterogeneity of various trials, but all studied formulations except benzydamine demonstrated a significant higher rate of clinical success versus topical placebo.<sup>1</sup> An analysis of 10 studies (n=2050) with topical diclofenac versus placebo found significantly higher clinical success with diclofenac (Risk Ratio [RR] 1.6; 95% CI, 1.5 to 1.7; NNT = 4 ). Of 10 studies, 2 were high quality studies (RR 3.4; 95% CI, 2.7 to 5.5; NNT 2). Two moderate quality studies that compared topical ibuprofen gel versus placebo also found higher rate of clinical success with ibuprofen gel (RR 2.7; 95% CI, 1.7 to 4.2; NNT 4). Five moderate quality studies of topical ketoprofen gel found significantly more (>50%) pain reduction relative to placebo (RR 2.2; 95% CI, 1.7 to 2.8; NNT 3). Other topical NSAIDs studied had a NNT greater than 4 compared to placebo. There were insufficient data to perform a meta-analysis on differences in efficacy between topical NSAIDs and oral NSAIDs. There were insufficient data to compare different formulations of topical NSAIDs, with the exception of piroxicam versus indomethacin.<sup>1</sup> Topical piroxicam may have a higher clinical success rate when compared to topical indomethacin (RR 1.24; 95% CI, 1.1 to 1.4; NNT 13]. There was high quality evidence that showed no significant differences between topical NSAIDs for local adverse events, systemic adverse events, or withdrawals.<sup>1</sup>

A second Cochrane Review assessed the analgesic efficacy and associated adverse events of topical lidocaine formulations for mixed peripheral neuropathic pain in adults.<sup>2</sup> Twelve eligible studies with a total of 508 participants were included in the review. Four different formulations of lidocaine were used in the studies: 5% patch, 5% cream, 5% gel, and 8% spray.<sup>2</sup> Six of the studies involved participants with moderate to severe post-herpetic neuralgia, while the remaining studies included in the review enrolled a mix of various neuropathic pain conditions, including trigeminal neuralgia, post-traumatic neuralgia, phantom limb pain, and diabetic neuropathy. Outcomes measured were 30% or 50% reduction in pain or improvement on a Patient Global Impression of Change (PGIC) scale, as well as withdrawals due to lack of efficacy or adverse events. The majority of studies used a cross-over design, and two used a parallel-group design. The studies were of low quality and at high risk of bias due to small number of participants or incomplete assessment of outcomes.<sup>2</sup> The review found there to be insufficient evidence at this time to support use of topical lidocaine to treat mixed peripheral neuropathic pain.<sup>2</sup>

A third Cochrane Review investigated the efficacy and tolerability of topical (8%) capsaicin patch for chronic neuropathic pain in adults.<sup>3</sup> Six double-blind RCTs with a total of 2073 participants were assessed. Topical 8% capsaicin patch was compared with placebo or another active treatment. Clinical improvement was defined by a 50% pain reduction by a patient reported global impression of change (PGIC) scale at 8 and 12 weeks. PGIC scale scores were categorized as follows: none/slight pain at rest, none/slight pain on movement, pain treatment much/very much improved, or pain treatment very good/excellent.<sup>3</sup> Secondary outcomes included number of patients with withdrawals due to lack of efficacy or adverse events. Four studies of participants with post-herpetic neuralgia

(n=1272) showed significant benefit in PGIC scale scores (pain much/very much improved) for topical 8% capsaicin over placebo (ie, 0.04% capsaicin) control at 8 weeks [RR 1.4; 95% CI, 1.1 to 1.8; NNT 9] and 12 weeks [RR 1.6; 95% CI, 1.2 to 2.0; NNT 7]. Two studies involved participants with HIV and neuropathic pain (n=801). One of the studies (n=307) demonstrated significant pain improvement (much/very much improved) at 12 weeks [RR 2.8; 95% CI, 1.4 to 5.6; NNT 6]. Both studies reported at least 30% pain intensity reduction over weeks 2 to 12 with respect to baseline [RR 1.4; 95% CI, 1.1 to 1.7; NNT 11]. Localized skin reactions such as erythema and burning at the application site were consistently reported but self-limiting. Serious adverse events were uncommon and not statistically significant.<sup>3</sup>

**New Guidelines:**

Veterans Affairs/ Department of Defense Guidelines (VA/DoD)

The Veterans Affairs/ Department of Defense Guidelines state that topical capsaicin can be considered as first line therapy or adjunctive therapy for patients with mild to moderate pain associated with osteoarthritis of the knee [Grade C – Moderate certainty of small net benefit].<sup>4</sup> There was insufficient evidence to recommend for or against the use of topical capsaicin as first line or adjunctive therapy in treatment for the hip [Grade I – Insufficient evidence to assess benefit versus harm].<sup>4</sup>

NICE Guidance – Osteoarthritis – Care and management in adults

The National Institute for Health and Care Excellence (NICE) has maintained its recommendation for consideration of topical NSAIDs ahead of oral NSAIDs, cyclooxygenase 2 (COX-2) inhibitors or opioids as an option for pharmacological management of pain relief in osteoarthritis of the knee or hand.<sup>5</sup> Topical capsaicin was also recommended as an adjunct agent to core treatments for knee or hand osteoarthritis.<sup>5</sup>

NICE Guidance – Neuropathic Pain - Pharmacological management

The National Institute for Health and Care Excellence (NICE) has recommended that capsaicin cream be considered for treatment of localized neuropathic pain (except trigeminal neuralgia) in patients who wish to avoid or who cannot tolerate oral treatments.<sup>6</sup> NICE has also recommended against use of capsaicin patch to treat neuropathic pain when in a non-specialist setting unless instructed by a specialist.<sup>6</sup>

**New FDA Drug Approvals:**

None identified.

**New Formulations/Indications:**

None identified.

**New FDA Safety Alerts:**

No specific safety alerts for topical analgesics have been published. Due to an increase in concerns about the safety of NSAID use during pregnancy, the FDA reviewed the possible risks of miscarriage for various prescription and over-the-counter (OTC) NSAIDs.<sup>7</sup> It was determined that data were too limited to make any new recommendations at this time; however, a Drug Safety Communication was released with a reminder to pregnant women to always consult with their health care professional about the risks and benefits before taking any prescription or OTC medication to treat pain or other conditions.<sup>7</sup>

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## References:

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5. Osteoarthritis. Care and management in adults. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Feb. 36 p. (Clinical guideline; no. 177) Available at: <https://www.nice.org.uk/guidance/cg177/chapter/1-Recommendations>. Accessed on 9 October 2015.
6. Neuropathic pain – pharmacological management. The pharmacological management of neuropathic pain in adults in non-specialist settings. London (UK): National Institute for Health and Care Excellence (NICE); Issued Nov 2013 last modified: Dec 2014. (Clinical guideline; no. 173) Available at: <https://www.nice.org.uk/guidance/cg173>. Accessed on 9 October 2015.
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**Appendix 1: Current Status on Preferred Drug List**

<b>ROUTE</b>	<b>FORMULATION</b>	<b>BRAND</b>	<b>GENERIC</b>	<b>PDL</b>
TOPICAL	CREAM (G)	CAPSAICIN	CAPSAICIN	Y
TOPICAL	CREAM (G)	TRIXAICIN	CAPSAICIN	Y
TOPICAL	CREAM (G)	TRIXAICIN HP	CAPSAICIN	Y
TOPICAL	KIT	QUTENZA	CAPSAICIN/SKIN CLEANSER	N
TOPICAL	GEL (GRAM)	VOLTAREN	DICLOFENAC SODIUM	N
TOPICAL	DROPS	DICLOFENAC SODIUM	DICLOFENAC SODIUM	N
TOPICAL	SOL MD PMP	PENNSAID	DICLOFENAC SODIUM	N
TRANSDERM	PATCH TD12	FLECTOR	DICLOFENAC EPOLAMINE	N
TOPICAL	OINT. (G)	LIDOCAINE	LIDOCAINE	N
TOPICAL	CREAM (G)	LIDOCAINE	LIDOCAINE	N
TOPICAL	ADH. PATCH	LIDOCAINE	LIDOCAINE	N
TOPICAL	ADH. PATCH	LIDODERM	LIDOCAINE	N
TOPICAL	GEL (GRAM)	DICLOFENAC SODIUM	DICLOFENAC SODIUM	N
TOPICAL	GEL (GRAM)	SOLARAZE	DICLOFENAC SODIUM	N
TOPICAL	CREAM (G)	ZIKS	CAPSAICIN/METHYL-SALICYLATE/MENTHOL	N

## Appendix 2: New Clinical Trials

A total of 92 citations were manually reviewed from the literature search. After further review, 91 trials were excluded because of wrong study design (observational), lack of comparator (placebo), outcome studied (non-clinical), or had been previously addressed by a high quality review source within the literature scan. The remaining trial is briefly described in the table below. The abstract is included in Appendix 3.

**Table 1:** Description of Clinical Trial

Study	Comparison	Population	Primary Outcome	Results	Quality*
Casanueva, B.; Rodero, B. et al. 2013 RCT, SC	Topical Capsaicin 0.075% versus standard medical treatment (included non-steroidal anti-inflammatory drugs, major opioids, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, anticonvulsants, or other multidisciplinary therapies)	Fibromyalgia diagnosed by a Rheumatologist, patients age 18 years or older, unresponsive to at least one standard medical treatment agent (n=130)	Improvements in myalgic score, global subjective improvement score, fatigue severity scale, pressure pain threshold, SF36 Pain Score, etc. (Twenty-nine different assessments) through 6 weeks of treatment	Capsaicin treated patients showed significant improvement in 2 of 29 areas: myalgic score (5.21 in capsaicin-treated vs 3.80 in controls, p = 0.02) and "subjective improvement" (16 cases in capsaicin-treated vs 3 cases in the control group, p = 0.001)	Poor (High risk of bias-selection, performance and detection bias, unreasonable definitions for clinical outcomes)

Abbreviations: RCT = Randomized controlled trial; SC = single-center.

\*Quality of each study is ranked as "Good", "Fair" or "Poor" based on DURM Standard Methods for Quality Assessment and Grading the Evidence.

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### Appendix 3: Abstracts of Clinical Trials

**Casanueva, Benigno; Rodero, Baltasar, et al. Short-term efficacy of topical capsaicin therapy in severely affected fibromyalgia patients. *Rheumatology International*. 2013. 33:2665–2670 doi: 10.1007/s00296-012-2490-5**

**ABSTRACT:** The purpose of this study was to evaluate the short-term efficacy of topical capsaicin treatment in patients severely affected by fibromyalgia.

**METHODS:** One hundred and thirty fibromyalgia patients were randomly divided into two groups. The control group, 56 women and 4 men who continued their medical treatment, and the capsaicin group, 70 women who apart from continuing their medical treatment, also underwent topical capsaicin 0.075 % 3 times daily for 6 weeks.

**RESULTS:** At the beginning of the program, there were no significant differences between the two groups in any of the analyzed parameters. At the end of the treatment, there were significant improvements in the capsaicin group in the myalgic score (5.21 vs 3.8,  $p = 0.02$ ) and global subjective improvement (22.8 vs 5 %,  $p = 0.001$ ). Six weeks after the end of the treatment, the experimental group showed significant differences in Visual Analogue Scale of depression (5.63 vs 7.35,  $p = 0.02$ ), Fibromyalgia Impact Questionnaire (67.89 vs 77.7,  $p = 0.02$ ), role limitations due to emotional problems (36.17 vs 17.2,  $p = 0.05$ ), Fatigue Severity Scale (6.2 vs 6.6,  $p = 0.04$ ), myalgic score (3.94 vs 2.66,  $p = 0.02$ ) and pressure pain threshold (79.25 vs 56.71,  $p = 0.004$ ).

**CONCLUSION:** Patients severely affected by fibromyalgia can obtain short-term improvements following topical capsaicin 0.075 % treatment three times daily for 6 weeks.

### Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to October Week 2 2015

- 1 exp Capsaicin/ 6165
- 2 exp Diclofenac/ 4732
- 3 exp Lidocaine/ 10002
- 4 1 or 2 or 3 20734
- 5 exp Administration, Topical/48214
- 6 4 and 5 1938
- 7 limit 6 to (english and humans and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) and last 2 years) 92

## Preferred Drug List (PDL) – Non-Preferred Drugs in Select PDL Classes

**Goal(s):**

- The purpose of this prior authorization policy is to ensure that non-preferred drugs are used appropriately for an OHP-funded condition.

**Initiative:**

- PDL: Preferred Drug List

**Length of Authorization:**

Up to 6 months

**Requires PA:**

- Non-preferred drugs

**Covered Alternatives:**

Preferred alternatives listed at <http://www.orpdl.org/drugs/>

**Note:**

A complete list of PDL classes is available at <http://www.orpdl.org/drugs/>

### Approval Criteria

1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny for medical appropriateness
3. Is this an OHP-funded diagnosis?	<b>Yes:</b> Go to #4.	<b>No:</b> Go to #5.

## Approval Criteria

4. Will the prescriber consider a change to a preferred product?

**Message:**

Preferred products do not generally require a PA. Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.

**Yes:** Inform provider of covered alternatives in class.

**No:** Approve until anticipated formal review by the P&T committee, for 6 months, or for length of the prescription, whichever is less.

5. RPH only: All other indications need to be evaluated as to whether they are a funded diagnosis on the OHP prioritized list.

- If funded and clinic provides supporting literature: Approve until anticipated formal review by the P&T committee, for 6 months, or for length of the prescription, whichever is less.
- If not funded: Deny;not funded by the OHP.

*P&T / DUR Review:* 7/15 (RC), 9/10; 9/09; 5/09  
*Implementation:* 8/1/15; 1/1/11, 9/16/10