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Drug Class Update: Topical Analgesics and Anesthetics

Date of Review: August 2020

Date of Last Review: (analgesics) July 2018 (DERP), January 2016; (anesthetics) none
Dates of Literature Search: 11/01/15–03/17/2020

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update: The purpose of this class update is to evaluate new evidence for the safety and effectiveness of topical analgesics in relieving acute and neuropathic pain. In addition, the safety and effectiveness of topical anesthetics in relieving acute pain prior to procedures and venous catheter insertion will be reviewed.

Research Questions:
1. What is the comparative efficacy and effectiveness of topical analgesics (diclofenac, capsaicin, salicylates and lidocaine) for acute and chronic pain?
2. What are the comparative harms of topical analgesics (diclofenac, capsaicin, salicylates, and lidocaine) for acute and chronic pain?
3. Are there subgroups of patients based on demographics, socioeconomic status, other medications, comorbidities, or pregnancy for which there are differences in the benefits and harms of topical analgesics (diclofenac, capsaicin, salicylates, and lidocaine) for acute and chronic pain?
4. What is the comparative efficacy and effectiveness of topical anesthetics (lidocaine, tetracaine, and prilocaine) when used prior to procedures or venous catheter insertion?
5. What are the comparative harms of topical anesthetics (lidocaine, tetracaine, and prilocaine) when used prior to procedures or venous catheter insertion?
6. Are there subgroups of patients based on demographics, socioeconomic status, other medications, comorbidities, or pregnancy for which there are differences in the benefits and harms of topical anesthetics (lidocaine, tetracaine, and prilocaine)?

Conclusions:
Topical Analgesics
- Five recently published systematic reviews were identified for this class update. Four reviews focused on efficacy and safety of topical diclofenac, capsaicin, lidocaine, and salicylate in acute and chronic pain management for adults.[1-4] One systematic review evaluated safety of topical non-steroidal anti-inflammatory drugs (NSAIDs) used for pain associated with osteoarthritis (OA).[5] One recently published guideline included recommendations for use of topical analgesics in OA.[6]
- A 2016 Cochrane review evaluated safety and efficacy of topical non-steroidal anti-inflammatory drugs (NSAIDs) for chronic musculoskeletal pain in adults.[1] In a pooled analysis of studies lasting 6 to 12 weeks, topical diclofenac was more effective than placebo for 50% pain reduction in chronic pain (Risk Ratio

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[RR] 1.2, 95% Confidence Interval [CI] 1.1 to 1.3, Number Needed to Treat [NNT] 10; moderate-quality evidence).[1] A few trials compared a topical NSAID to an oral NSAID in patients with knee OA, but overall they showed similar efficacy (low-quality evidence).[1] There was an increase in local adverse events (mostly mild skin reactions) with topical diclofenac compared with placebo or oral NSAIDs (RR=1.8, 95% CI 1.5 to 2.2, Number Needed to Harm [NNH] 16; moderate quality evidence).[1]

- A 2017 Cochrane review examined safety and efficacy of high-concentration (8%) topical capsaicin for chronic neuropathic pain in adults.[2] In a pooled analysis of 4 trials, more participants with postherpetic neuralgia (PHN) reported having improved pain relief greater than 50% with high-concentration capsaicin compared to low-concentration (0.04%) capsaicin at 8 to 12 weeks (RR 1.44, 95% CI 1.12 to 1.86, NNT 9; moderate quality evidence).[2] Two pooled studies evaluated pain relief in patients with human immunodeficiency virus (HIV)-neuropathy and reported average pain intensity reductions of at least 30% over baseline with capsaicin 8% compared to capsaicin 0.04% (active control) over 2 to 12 weeks (RR 1.35, 95% CI 1.09 to 1.68, NNT 11; very low quality evidence).[2] One study in patients with diabetic peripheral neuropathy (DPN) and another study in participants with persistent pain following inguinal herniorrhaphy did not show a difference between capsaicin and placebo for pain reduction (very low quality evidence).[2] Adverse event withdrawals did not differ between groups, based on small numbers of events (moderate quality evidence).[2]
- A 2017 Cochrane review pooled data from 13 systematic reviews to evaluate the safety and efficacy of topical analgesics (NSAIDs, salicylate rubefacients, capsaicin, and lidocaine) for treatment of acute and chronic pain in adults.[3] The review found superior efficacy of 3 diclofenac formulations compared to placebo in reducing acute pain when used for 1 week, based on moderate quality evidence: Flector® plaster (RR 1.5, 95% CI 1.4 to 1.7, NNT 5), Voltaren Emulgel™ (RR 3.8, 95% CI 2.7 to 5.5, NNT 2) and other types of diclofenac plaster (RR 1.6, 95% CI 1.4 to 1.8, NNT 4).[3] In chronic musculoskeletal pain, the review found topical diclofenac gel and plaster reduced pain compared to placebo for durations less than 6 weeks based on moderate to high-quality evidence (RR 1.9, 95% CI 1.5 to 2.3, NNT 5) and for durations greater than 6 weeks (RR 1.2, 95% CI 1.1 to 1.3, NNT 10).[3] The review found topical capsaicin 8% was efficacious in reducing pain due to PHN compared to placebo based on moderate-quality evidence (RR 1.3, 95% CI 1.0 to 1.7, NNT 11).[3] Efficacy of topical salicylate, low-concentration (0.04%) capsaicin, and lidocaine was not well supported by evidence, and lacked evidence of effect in reducing pain associated with acute or chronic pain conditions.[3]
- The safety assessment from the 2017 Cochrane review on topical analgesics reported systemic or local adverse event (AE) rates with topical NSAIDs (4.3%) did not differ from topical placebo (4.6%) in patients with acute pain (RR 0.98, 95% CI 0.8 to 1.2; high quality evidence).[3] More local adverse events occurred with topical diclofenac (14%) than placebo (8%) in chronic pain conditions (RR 1.8, 95% CI 1.5 to 2.2, NNH 16; moderate-quality evidence).[3] Local pain with topical high-concentration capsaicin occurred more frequently (10%) than with placebo (4%) in patients with neuropathic pain (RR 2.4, 95% CI 1.4 to 4.1, NNH 16; moderate quality evidence).[3] Local AEs with topical capsaicin 0.04% (63%) were higher than topical placebo (24%) in people with chronic pain (RR 2.6, 95% CI 2.1 to 3.3, NNH 3; high quality evidence).[3]
- A 2019 Cochrane review evaluated the safety and efficacy of topical NSAIDs in relieving acute musculoskeletal pain in adults.[4] Ten studies (n=2050) compared topical diclofenac formulations with placebo.[4] In the pooled analysis, the proportion of participants experiencing successful treatment (50% pain reduction) with topical diclofenac was 74% compared to 47% of placebo-treated participants (RR 1.6, 95% CI 1.5 to 1.7, NNT 4).[4] Fifteen studies (n=3271) provided adequate data to analyze local AE with diclofenac. Similar AE rates were reported by 3.1% of patients who used topical diclofenac compared with 4.3% of patients who received placebo (RR 0.78, 95% CI 0.56 to 1.1).[4]
- A 2019 systematic review assessed the safety of topical NSAIDs in the management of OA in an analysis of randomized, placebo-controlled trials.[5] Eight studies with low risk of bias compared topical diclofenac with placebo were included in the meta-analysis.[5] Overall, there were more AEs with topical diclofenac compared with placebo (Odds Ratio [OR] 1.30, 95% CI 1.10 to 1.53; high quality evidence).[5] Study withdrawals due to AEs were also higher with topical diclofenac compared with placebo (OR 2.00, 95% CI 1.27 to 3.14; high quality evidence).[5]

- The American College of Rheumatology/Arthritis Foundation (ACR/AF) 2019 guideline on the management of OA of hand, hip, and knee updated their 2012 recommendations.[6] Topical NSAIDs are strongly recommended for patients with knee OA and conditionally recommended for patients with hand OA.[6] Topical low-concentration (0.04%) capsaicin is conditionally recommended for patients with knee OA and conditionally recommended against use in patients with hand OA.[6] Insufficient data exists to make recommendations about the use of topical lidocaine preparations in OA.[6]
- No new evidence was identified to assess differences in benefits and harms for topical analgesics in specific subgroups of patients based on demographics, socioeconomic status, comorbidities, or pregnancy.

Topical Anesthetics

- A 2012 Cochrane systematic review examined the evidence from 6 randomized controlled trials (RCTs) involving 343 participants with leg ulcer pain using an eutectic mixture of local anesthetics (EMLA) cream compared to a placebo cream prior to ulcer debridement.[7] Participants who received EMLA had lower pain ratings based on the 0 to 100 mm visual analog scale (VAS) (mean difference [MD] -20.65 mm, 95% CI -12.19 to -29.11, $p < 0.00001$; moderate quality evidence) during ulcer debridement.[7] No significant differences between groups in burning or itching were observed.[7]
- A 2017 Cochrane review focused on safety and efficacy of topical anesthetics for pain control during repair of dermal laceration.[8] There was insufficient evidence to compare efficacy of topical anesthetics versus infiltrated local anesthesia.[8] The second objective, to compare the efficacy of various single-component or multi-component topical anesthetic agents for repair of dermal lacerations, found no significant differences between formulations, but the available data had high risk of bias.[8] The overall low-quality of the evidence for this review was due to limitations in design and implementation, imprecision of results, and high probability of publication bias (selective reporting of data).[8] Additional well-designed RCTs with low risk of bias are necessary before definitive conclusions regarding comparative safety and efficacy of topical anesthetics for pain control during dermal laceration repair can be reached.[8]
- There is insufficient evidence to assess differences in benefits and harms for topical anesthetics in specific subgroups of patients based on demographics, socioeconomic status, or comorbidities.

Recommendations:

- Rename the topical analgesic class as “topical pain medications” and add topical anesthetics to this new PDL class.
- Given the insufficient comparative evidence for safety and efficacy, designate at least 1 topical anesthetic with an indication for a funded condition on the Health Evidence Review Commission (HERC) prioritized list as preferred agents in the topical pain medications class on the Practitioner-Managed Prescription Drug Plan (PMPDP) based on drug costs in the executive session.
- After executive session, the P and T Committee recommended making lidocaine-prilocaine, viscous lidocaine, lidocaine cream, lidocaine solution, and lidocaine jelly with applicator preferred. All other products will be designated as non-preferred on the PDL.

Summary of Prior Reviews and Current Policy:

A literature scan focused on safety and efficacy of topical analgesics was presented to the Pharmacy and Therapeutics (P and T) Committee at the January 2016 meeting. The scan found moderate-quality evidence supporting the short-term use of topical NSAIDs as safe and effective treatment options for acute musculoskeletal pain. The comparative safety and efficacy of topical capsaicin and lidocaine in managing neuropathic pain were summarized in a Drug Effectiveness Review Project (DERP) summary report presented to the P and T Committee at the July 2018 meeting. The strength of evidence for most outcomes within the report was low or insufficient, as data came from single studies and were imprecise.[9] In July 2018, the P and T Committee approved a quantity limit of 3 topical lidocaine patches per day to ensure safe use. Prior authorization (PA) Criteria for the lidocaine patch are included in **Appendix 4.** Preferred topical

analgesics on the PMPDP include capsaicin cream and diclofenac drops. Non-preferred medications include diclofenac patch, diclofenac gel, capsaicin patch, lidocaine cream, lidocaine patch, and diclofenac/capsicum oleoresin. **Appendix 1** includes a list of the topical analgesics included on the preferred drug list (PDL)

Approximately 50 Oregon Health Plan (OHP) fee-for-service (FFS) patients had claims for topical analgesics in the first quarter of 2020. Most of the claims for preferred medications in the topical analgesic class were for capsaicin (30%) Most of the approved claims for nonpreferred medications were for diclofenac gel (48%) and lidocaine patches (20%).

Topical anesthetics (lidocaine, prilocaine, tetracaine, and benzocaine) have not been reviewed by the P and T Committee and the medications in this class do not currently have PDL status. As there are similar drugs in the topical analgesic and topical anesthetic classifications, both medication classes are included in this update.

Background:

Topical Analgesics

Commonly used topical analgesics applied to intact skin include salicylate rubefacients, capsaicin, lidocaine, and diclofenac. Indications for topical analgesics include pain relief for acute conditions such as sprains or strains and management of chronic pain associated with neuralgia or osteoarthritis (OA).[10] Management of OA with topical diclofenac is supported by moderate quality evidence, but there is less robust evidence for capsaicin and salicylates.[11] Salicylates are related pharmacologically to aspirin and NSAIDs, but when used topically their principal action is as counter-irritants.[12] Counter-irritation of the sensory nerve endings alters or offsets pain in the underlying muscle or joints that are served by the same nerves.[12] Topical salicylates are approved for temporary relief of minor aches and pains of muscle and joints associated with OA, sprains, and strains. However, a 2014 Cochrane review concluded available evidence does not support the use of topical rubefacients containing salicylates for acute injuries or chronic conditions.[13] The low quality of evidence means that uncertainty remains regarding the efficacy of salicylate-containing rubefacients in relieving acute and chronic pain.[13]

Topical application of capsaicin results in desensitization of the sensory axons and inhibition of pain transmission.[12] Topical capsaicin creams and patches are available in formulations ranging from 0.025% to 0.1% and are indicated for temporary relief of minor aches and pain of muscles and joints. The 2014 Veterans Administration/Department of Defense (VA/DoD) OA guidelines recommend topical capsaicin as an alternative to topical NSAIDs for knee OA.[11] The VA/DoD recommendations are based on moderate quality evidence that a small net benefit has been observed with topical capsaicin in knee OA.[11] There is insufficient evidence for pain relief with capsaicin in hip OA.[11] The National Institute for Health and Clinical Excellence (NICE) guidelines for OA management also include topical capsaicin as a possible adjunct to treatments for knee or hand OA.[14] The 2013 NICE guidance for treatment of neuropathic pain in adults suggests capsaicin cream for people with localized postherpetic neuralgia (PHN) who wish to avoid, or who cannot tolerate, oral treatments.[15]

The high-concentration (8%) capsaicin patch is approved by the Food and Drug Administration (FDA) to treat PHN.[16] In 2012, the FDA denied application of an expanded indication for neurpathic pain from HIV for the 8% capsaicin patch.[16] The 8% patch, which remains on skin for 60 minutes and is readministered no more frequently than 3 months, can only be administered by a health care professional. Patients must be pretreated with a topical anesthetic and monitored for adverse effects at least 2 hours after administration. The treatment setting needs to be well ventilated due to vaporization of capsaicin, as cough due to inhalation of capsaicin vapors is a hazard for both healthcare professionals and patients.[12] To date, no guidelines recommend the use of high-concentration capsaicin for initial management of PHN.

Topical lidocaine dampens peripheral nociceptor sensitization and decreases central nervous system hyperexcitability which prevents transmission of pain signals.[12] The topical lidocaine 5% patch is FDA-approved for relief of pain associated with PHN and requires a prescription. The 4% over-the-counter patch is approved for temporary relief of minor localized pain. Lidocaine does not cross intact skin well, and when applied as a patch, the amount of lidocaine that penetrates is enough to cause analgesia, but not anesthesia.[17] Canadian Pain Society guidelines recommend topical lidocaine as a fourth-line agent for management of PHN.[18]

Topical NSAIDs penetrate the skin and underlying tissues where they inhibit cyclooxygenase (COX) enzymes, thus reducing pain and inflammation.[12] The rationale behind topical application is based on the ability of NSAIDs to inhibit COX enzymes locally, with minimum systemic uptake.[12] Their use is therefore limited to conditions where the pain is superficial and localized, such as in joints and skeletal muscle.[12] Guidance from a 2014 NICE publication recommends topical NSAIDs for patients with mild to moderate OA of the knee or hand, particularly in patients with few affected joints and/or a history of sensitivity to oral NSAIDs.[14] The NICE guidelines also state that topical NSAIDs should be considered before oral therapies and salicylate rubefacients should not be considered for treating OA.[14] Diclofenac is the only topical NSAID available in the United States (U.S). Clinical trials of topical formulations of diclofenac have shown significantly superior efficacy compared to placebo and similar efficacy to oral NSAIDs in reducing pain associated with acute injuries.[19] A comparative summary of topical analgesics is provided in **Table 1**.

Table 1.Topical Analgesic Preparations[20,21]

Topical Agent	Mechanism of Action	FDA Approved Indications	Comments
Diclofenac Patch, Cream, Gel and Solution (1% to 2%)	COX-2 inhibition	-Acute pain due to strains, sprains and contusions -OA Pain	-Bears same FDA-mandated warnings regarding gastrointestinal, cardiovascular, and hepatic risks as oral NSAIDs -Minimal systemic absorption
Trolamine Salicylate 10% cream	Counterirritant: desensitizes pain receptors	Acute Musculoskeletal Pain	-No trial data demonstrating efficacy in OA. -Excessive use or ingestion is associated with toxicity. -Available over-the-counter
Capsaicin Cream, Gel, Liquid, Patch and Lotion (0.025% to 0.1%)	Counterirritant: desensitizes pain receptors	-OA Pain -Musculoskeletal Pain	-Application site pain and burning early in treatment have been reported -Local irritation may be intolerable -Concerns about whether desensitization of nerve fibers is reversible -Available over-the counter
Capsaicin 8% Patch	Counterirritant: desensitizes pain receptors	Postherpetic Neuralgia	-Must be administered by a healthcare professional under close supervision -Requires pre-treatment with a local anesthetic and patient post-application monitoring for up to 2 hours -Treatment may be repeated every 3 months -May apply up to 4 simultaneus patches
Lidocaine 5% Patch	Blocks neuronal impulses	Postherpetic Neuralgia	-Application site reactions have been reported -May apply up to 3 simultaneus patches

Lidocaine Cream, Ointment, Gel and Patch (2% to 4%)	Blocks neuronal impulses	Acute Pain	Available over-the-counter
Abbreviations: COX-2= Cycloxygenase-2; FDA=Food and Drug Administration, NSAID=Non-steroidal anti-inflammatory drug; OA=osteoarthritis			

Topical Anesthetics

Topical anesthetics (lidocaine, benzocaine, prilocaine, and tetracaine) are approved for use in alleviating pain associated with hemorrhoids, sore throat, dermal irritation (i.e., pruritic eczemas, insect bites, sunburns, and abrasions of the skin), mouth and gum irritation, acute pain relief prior to procedural repair or prior to venous catheter insertion.[20,21] According to the Oregon HERC prioritized list, the following conditions are not funded: minor burns (line 605), uncomplicated hemorrhoids (line 621), and contact dermatitis (line 533).[22] This review will focus on use of topical anesthetics in funded conditions including peri-procedural local anesthesia and intravenous (IV) cannulation.

A laceration is a deep cut or tear in the skin or soft tissue often caused by blunt trauma, incision by a sharp object, or mammalian bite.[8] Anesthetics interrupt the transmission of electrical impulses along nerves by inactivating sodium channels.[8] Local anesthetics including lidocaine and bupivacaine injection are used for peri-procedural pain management of laceration repair.[8] Topical anesthetics may be used in children or patients who cannot tolerate injections.[8] Topical anesthetics such as lidocaine, tetracaine, or prilocaine may be combined with a vasoconstrictor such as epinephrine or cocaine. The addition of the vasoconstrictor prevents systemic absorption of the topical anesthetic. Commonly used options include: EMLA cream (2.5% lidocaine/2.5% prilocaine), lidocaine/tetracaine 7%/7% patch or cream, and lidocaine 4% cream. Some commercially available topical anesthetics become effective in 30 minutes, however, the combination of lidocaine/prilocaine may have a delayed onset of 60 minutes.[23]

The largest safety concern with topical anesthetics has been the risk of methemoglobinemia, particularly when there is prolonged use of larger than recommended doses.[24] Prescribing guidance recommends an EMLA dose should be limited to 1 to 2 g of cream per 10 cm^2 to infants older than 3 months, and weighing at least 5 kilograms to avoid toxicity.[24] Similar age and weight-based dosage regimens are recommended to avoid toxicity with other topical anesthetics.[24] **Table 2** summarizes information about the various topical anesthetics that are approved for use in HERC funded conditions.

Table 2. Common Topical Anesthetic Preparations[20,21]

Agent	Dose	Onset of Action (minutes)	Duration of Action (minutes)	Comments
Liposomal lidocaine (LMX_4)	LMX_4 (liposomal lidocaine 4%) ▪ Age <4 years: 1 gram applied to appropriate site (6.25 cm^2 of skin). ▪ Age ≥4 years: 1 to 2.5 gram applied to appropriate site (6.25 cm^2 of skin). Supplied as 5 g, 15 g, and 30 g tube	30	60 to 120	Available over-the-counter May cause methemoglobinemia with excessive application or in patients with predisposition to methemoglobinemia (e.g., glucose-6-phosphate dehydrogenase (G6PD) deficiency or taking methemoglobin-inducing medication).

Self-heating lidocaine and tetracaine patch (Synera) and topical cream (Pliaglis)	Lidocaine 7% and Tetracaine 7% ▪ Apply one patch to intact skin for 20 to 30 minutes and promptly remove. After one failed attempt, one additional patch may be applied in children. Simultaneous application of more than one patch is not recommended in children ≤12 years Supplied as 50 cm^2 patch or 30 g and 100 mg tubes of cream	20 to 30	90	Prolonged application of the patch to intact skin or application to broken skin or mucous membranes may result in serious local anesthetic toxicity. Methemoglobinemia has been reported with use of local anesthetics; increased risk in patients with G6PD deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites and other drugs associated with methemoglobinemia.
Lidocaine-prilocaine (eutectic mixture of local anesthetics [EMLA], Lidopril, Prilovix) cream	Lidocaine 2.5% and Prilocaine 2.5% Adult Dose: 2 grams/10cm^2 of skin Pediatric dosing is based on patient weight. Supplied as 5 g and 30 g tube.	60	60 to 120	Infants under 3 months of age should monitored for methemoglobinemia before, during and after topical application of lidocaine-prilocaine. Methemoglobinemia has been reported with use of local anesthetics; increased risk in patients with G6PD deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites and other drugs associated with methemoglobinemia.

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. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, 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 the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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:

Topical Analgesics

Cochrane: Topical Non-steroidal Anti-Inflammatory Drugs for Chronic Musculoskeletal Pain in Adults

A 2016 Cochrane review updated a previous 2012 evaluation of topical NSAIDs for chronic musculoskeletal pain in adults.[1] New evidence published through February 2016 was included in the update. Randomized, double-blind, active or placebo-controlled trials in which treatments were administered to adults with moderate intensity musculoskeletal pain of at least 3 months duration met inclusion critiera.[1] The primary outcome was clinical success, defined as at least a 50% reduction in pain.[1] Secondary outcomes included adverse events and trial withdrawals due to adverse events or lack of efficacy. Five new studies were included in the update, which expanded the total number of studies to 39. Diclofenac and ketoprofen were the only two topical NSAIDs with good quality and longer duration studies, mostly in people aged over 40 years with painful knee arthritis.[1] Oral NSAIDs that served as active comparators included diclofenac, celecoxib, and ibuprofen; however most of the trials compared a topical NSAID to placebo. For pooled analyses, studies were generally of moderate or high methodological quality, although some trials were at risk of bias due to short duration and small population size.[1]

In a pooled analysis of studies lasting 6 to 12 weeks, topical diclofenac was modestly more effective than placebo for 50% pain reduction (RR 1.2, 95% CI 1.1 to 1.3, NNT 10, 6 trials, moderate quality evidence).[1] Four studies of 6 to 12 weeks duration demonstrated topical ketoprofen gel was modestly more successful in reducing OA knee pain compared to placebo (OR 1.22, 95% CI 1.03 to 1.45, NNT 7; moderate-quality evidence).[1] A few trials compared a topical NSAID to an oral NSAID in patients with knee OA, but overall they showed similar efficacy (low-quality evidence).[1]

Nineteen studies reported information on local adverse events with topical diclofenac and ketoprofen.[1] There was an increase in local adverse events (mostly mild skin reactions) with topical diclofenac compared with placebo or oral NSAIDs (RR 1.8, 95% CI 1.5 to 2.2, NNH 16, 15 studies; moderate-quality evidence). Reporting of systemic adverse events (such as gastrointestinal upset) was poor, but where reported there was no difference between topical NSAID and placebo (very low quality evidence).[1] Serious adverse events were infrequent and not different between topical NSAIDs and placebo (very low-quality evidence).[1]

Cochrane: Topical Capsaicin (High Concentration) For Chronic Neuropathic Pain in Adults

A 2017 Cochrane review updated a 2013 summary of high concentration (8%) topical capsaicin patch for chronic neuropathic pain in adults.[2] Databases were searched through June 2016 for this update. Two new studies (n=415) met inclusion criteria, bringing the total number of studies to 8, which involved a total of 2,488 participants.[2] Participants had pain due to PHN, HIV-neuropathy, DPN, and persistent pain after inguinal herniorrhaphy.[2] The duration of application of the high-concentration topical capsaicin patch varied between 30 and 90 minutes, with most participants treated for 60 minutes.[2] Efficacy outcomes reflecting moderate (improved) to substantial (very much improved) pain relief after a single drug application were based from the Patient Global Impression of Change (PGIC) at specific timepoints, usually 8 and 12 weeks.[2] Other outcomes included average pain scores over weeks 2 to 12, the number of participants with pain intensity reduction of at least 30% or at least 50% over baseline, and information on adverse events and study withdrawals. Two studies used a placebo control and six used low dose (0.04%) topical capsaicin as an active control to help maintain blinding.[2] Efficacy outcomes were inconsistently reported, resulting in analyses for most outcomes being based on incomplete data.[16] Five trials were judged to have low or unclear risk of bias, and one study was judged to have a high risk of bias.[2]

Four studies (n=1272) evaluated people with PHN.[2] At both 8 and 12 weeks about 10% more participants reported much improved or very much improved pain relief greater than 50% with high-concentration (8%) capsaicin compared to low-concentration (0.04%) capsaicin (RR 1.44, 95% CI 1.12 to 1.86, NNT 9; moderate-quality evidence).[2] More participants (about 10%) had average 8-week and 12-week pain intensity reductions over baseline of at least 30% (RR 1.42, 95% CI 1.10 to 1.84, NNT 10) and at least 50% (RR 1.55, 955 CI 1.20 to 1.99, NNT 12) with capsaicin than control (very low-quality evidence).[2]

Two studies (n=801) evaluated people with painful HIV-neuropathy. One study reported the proportion of participants who were much improved or very much improved at 12 weeks (27% with high-concentration capsaicin and 10% with active control).[2] For both studies, more participants had average pain intensity reductions over baseline of at least 30% with capsaicin than control over 2 to 12 weeks (RR 1.35, 95% CI 1.09 to 1.68, NNT 11, very low-quality evidence).[2] One very low quality study (n=369) reported on patients with DPN and noted more participants were much or very much improved with 30% pain reduction at 8 and 12 weeks, but the results were not statistically significant (RR 1.2, 95% CI 0.92 to 1.6).[2] One small study of 46 participants with persistent pain following inguinal herniorrhaphy did not show a difference between capsaicin and placebo for pain reduction (very low-quality evidence).[2] The quality of the evidence was downgraded due to sparse data, imprecision, possible effects of imputation methods, and susceptibility to publication bias.[2]

Local adverse events were common, but not consistently reported. Serious adverse events were no more common with capsaicin 8%(3.5%) than capsaicin 0.04% (3.2%).[2] Adverse event withdrawals did not differ between groups, but lack of study withdrawals due to lack of efficacy were somewhat more common with control than active treatment, based on small numbers of events (six to eight studies, 21 to 67 events; moderate-quality evidence, downgraded due to few events).[2] No deaths were judged to be related to study medication.[2]

Cochrane: Topical Analgesics for Acute and Chronic Pain in Adults

A 2017 Cochrane review analyzed 13 systematic reviews evaluating analgesic efficacy and associated adverse events of topical analgesics (NSAIDs, salicylate rubefacients, capsaicin, and lidocaine) for the treatment of acute and chronic pain in adults.[3] Systematic reviews in acute and chronic pain published to February 2017 were included in the review.[3] The primary outcome was at least 50% pain relief (participant-reported) at an appropriate duration. Withdrawals due to lack of efficacy or adverse events, systemic and local adverse events, and serious adverse events were also assessed. Pain relief in 3 distinct clinical conditions were considered for this review: 1) acute musculoskeletal conditions (sprains, strains, or muscle pain), 2) OA, rheumatoid arthritis, or other chronic musculoskeletal conditions, and 3) neuropathic pain. The 13 Cochrane reviews (206 studies with around 30,700 participants) assessed the efficacy and harms from a range of topical analgesics for management of acute and chronic pain conditions.[3] Most reviews concentrated on evidence comparing topical analgesic to topical placebo products; comparisons between topical and oral analgesics were rare.[3] Management of acute pain with topical therapy was evaluated in 4 systematic reviews.[12] Twelve reviews addressed management of chronic pain with topical agents.[12] All 13 reviews met AMSTAR criteria.[3]

In acute musculoskeletal pain with assessment at about 7 days, therapies included topical diclofenac, piroxicam, and ketoprofen.[3] Evidence was moderate- to high-quality for the acute pain conditions treated for 1 week.[3] Three topical formulations of diclofenac were compared to placebo and showed superior efficacy in reducing pain: Flector® plaster (RR 1.5, 95% CI 1.4 to 1.7, NNT 5) , Voltaren Emulgel™ (RR 3.8, 95% CI 2.7 to 5.5, NNT 2) and other types of diclofenac plaster (RR 1.6, 95% CI 1.4 to 1.8, NNT 4).[3] In chronic musculoskeletal pain (mainly hand and knee OA), NSAID therapies included topical diclofenac and ketoprofen for 6 to 12 weeks.[12] Evidence was analyzed as moderate to high-quality for the chronic pain assessments.[3] Various formulations of diclofenac reduced pain compared to placebo for durations less than 6 weeks (RR 1.9, 95% CI 1.5 to 2.3, NNT 5) and for durations greater than 6 weeks (RR 1.2, 95% CI 1.1 to 1.3, NNT 10).[3] In PHN, topical high-concentration capsaicin had moderate-quality evidence of efficacy in reducing pain compared to placebo (RR 1.3, 95% CI 1.0 to 1.7, NNT 11).[3]

Evidence of efficacy for topical salicylate in acute and chronic pain was low quality.[3] There were quality and potential bias issues, and the available data did not show good evidence of effect, or showed no effect. Evidence of efficacy for low-concentration capsaicin (0.075%) and topical lidocaine in treatment of neuropathic pain was very low quality and typically limited to single studies or comparisons with sparse data.[3] Few analyses were possible due to poor reporting and only a single study with 58 participants provided relevant data for topical lidocaine efficacy.[3] Insufficient evidence was noted for topical capsaicin 0.04% in

PHN.[3] There were 124 participants in two studies.[3] Pooled analysis found no difference in efficacy between capsaicin and placebo.[3] No specific GRADE assessment was made for the 2 trials.[3]

In acute pain, systemic or local AE rates with topical NSAIDs (4.3%) were no greater than with topical placebo (4.6%) (RR 0.98, 95% CI 0.8 to 1.2, 42 studies, 6740 participants; high quality evidence).[3] Moderate-quality evidence indicated there were more local AEs in chronic pain conditions with topical diclofenac (14%) than placebo (8%) (RR 1.8, 95% CI 1.5 to 2.2, NNH 16).[3] Local pain with topical capsaicin 8% was more frequent (10%) than with placebo (4%) for neuropathic pain (RR 2.4, 95% CI 1.4 to 4.1, NNH 16; moderate-quality evidence).[3] In chronic pain, local AEs with topical capsaicin 0.04% (63%) were higher than topical placebo (24%) (RR 2.6, 95% CI 2.1 to 3.3, 5 studies, 557 participants, NNH 3; high-quality evidence).[3]

In chronic pain conditions, study withdrawals due to lack of efficacy were lower with topical diclofenac (6%) than placebo (9%) (RR=0.6, 95% CI 0.5 to 0.8, 11 studies, 3455 participants, moderate-quality evidence), and topical salicylate (2% vs 7% for placebo, RR 0.4, 95% CI 0.2 to 0.9, 5 studies, 501 participants, very low-quality evidence).[3] Study withdrawal due to an adverse event for treatment of chronic pain were higher with low-concentration topical capsaicin (15%) than placebo (3%) (RR 5.0, 95% CI 5.7 to 14, 4 studies, 477 participants, NNH 8; very low-quality evidence), topical salicylate (5% vs 1% for placebo, RR 4.2, 95% CI 1.5 to 12, 7 studies, 735 participants, NNH 26; very low-quality evidence), and topical diclofenac (5% vs 4% for placebo, RR 1.6, 95% CI 1.1 to 2.1, 12 studies, 3552 participants, NNH 51; very low-quality evidence).[3]

In summary, there is good evidence that formulations of topical diclofenac are useful in acute pain conditions such as sprains or strains.[3] In chronic musculoskeletal conditions with assessments over 6 to 12 weeks, topical diclofenac had limited efficacy in hand and knee OA, as did topical high-concentration capsaicin in management of PHN.[3] Efficacy of topical salicylate, low-concentration capsaicin, and lidocaine are not well supported by evidence, and have limited evidence of effect in reducing pain associated with acute or chronic pain conditions.[3]

<u>Cochrane: Topical Non-steroidal Anti-Inflammatory Drugs for Acute Musculoskeletal Pain in Adults</u>

A 2019 Cochrane review updated a 2010 systematic review focused on evaluating the safety and efficacy of topical NSAIDs in relieving acute pain in adults.[4] Literature was searched through February 2015 with a focus on use of NSAIDS in acute musculoskeletal pain. Formulations of topical diclofenac, ibuprofen, ketoprofen, piroxicam, and indomethacin were studied. Criteria included randomized, controlled, double-blind studies comparing topical NSAIDs with placebo (inert carrier) or other active treatment for acute pain, with at least 10 participants per treatment arm and outcomes assessed at a minimum of 3 days).[4] Most studies enrolled participants who had sprains, strains, and contusions, usually as a result of sports injuries, but there was a wide range of when treatment was started from time of injury, from within a few hours to days.[4] Other studies enrolled participants with overuse-type injuries, such as tendinitis and acute low back pain, where pain had been present for days or weeks, but less than 3 months.[4] Fourteen new studies met inclusion criteria.[4] Most of the new trials compared diclofenac formulations with placebo. The primary outcome was clinical success, defined as either at least a 50% reduction in pain or an equivalent measure, such as a very good or excellent global assessment of treatment, or none to slight pain on rest or movement, measured on a categorical scale.[4] Numbers of participants with AEs and withdrawals due to AEs were analyzed as secondary outcomes. A total of 58 studies were included in the meta-analysis.[4] Most of the trials were of low to moderate risk of bias. Twenty-seven studies were at high risk of bias due to small population size (less than 50 participants in the treatment arm).[4]

Ten studies (n=2050) compared diclofenac with placebo.[4] The proportion of participants experiencing successful treatment with topical diclofenac was 74% compared to 47% of placebo treated participants (RR 1.6 95% CI 1.5 to 1.7, NNT 4).[4] Fifteen studies (n=3271) provided adequate data to analyze local AEs with

diclofenac. Similar AE rates were reported by 3.1% of patients who used topical diclofenac compared with 4.3% of patients who were in the placebo arm (RR 0.78, 95% CI 0.56 to 1.1).[4]

Thirty-six studies (n=5576) contributed data on systemic adverse events for all topical NSAIDs. There was no statistically significant difference between treatment groups in the proportion of patients who experienced an adverse event (topical NSAIDs 3.1% vs. placebo 3.5%, RR 0.96, 95% CI 0.73 to 1.3).[4] Forty-two studies (n=6405) reported adverse event withdrawal data. There was no statistically significant difference between treatment groups with respect to withdrawals due to AEs (topical NSAIDs 0.98% vs. placebo 0.99%, RR 1.0, 95% CI 0.64 to 1.6).[4]

Safety of Topical Non-steroidal Anti-Inflammatory Drugs in Osteoarthritis

A 2019 systematic review assessed the safety of topical NSAIDs in the management of OA in a meta-analysis of placebo-controlled RCTs.[5] A comprehensive literature search was undertaken through August 2017.[5] The primary outcomes were overall severe and serious AEs, as well as the following organ-related AEs: GI, vascular, cardiac, nervous system, skin and subcutaneous tissue, musculoskeletal, and connective tissue. Twenty-five RCTs were included in the qualitative synthesis and 19 were included in the meta-analysis: 8 RCTs of diclofenac, 4 RCTs of ketoprofen, 3 RCTs of ibuprofen, and 1 RCT each on eltenac, piroxicam, nimesulide and S-flurbiprofen.[5] Most of the trials included patients with knee OA; only two trials were conducted in patients with hand OA, and one study included patients with lumbar OA.[5] Trial durations varied between 1 and 12 weeks. All topical NSAIDs were assessed as high-quality for each outcome based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[5]

Eight studies with low risk of bias compared topical diclofenac with placebo.[5] Overall, there was a significant increase in total AEs with topical diclofenac compared with placebo (OR 1.30, 95% CI 1.10 to 1.53; high-quality evidence).[5] The rate of study withdrawals due to AEs was statistically significantly higher with topical diclofenac compared with placebo (OR 2.00, 95% CI 1.27 to 3.14; high-quality evidence).[5] High-quality evidence showed there was no statistically significant difference in odds for severe (OR 1.19, 95% CI 0.68 to 2.07) or serious AEs (OR 0.94, 95% CI 0.26 to 3.42), or for specific organ-related AEs, in patients treated with diclofenac compared with those who received placebo.[5] In particular, topical diclofenac was not associated with increased GI toxicity compared to placebo (OR 1.11, 95% CI 0.75 to 1.64; high-quality evidence).[5]

The use of topical NSAIDs was associated with a nearly 50% increase in study withdrawal due to an AE compared with placebo (OR 1.49, 95% CI 1.15 to 1.92; high-quality evidence).[5] Overall, more AEs (OR 1.16, 95% CI 1.04 to 1.29; high-quality evidence) were observed with topical NSAIDs compared with placebo.[5] Similar outcomes were found with topical diclofenac compared with placebo, largely driven by an increase in skin and subcutaneous tissue disorders (OR 1.73, 95% CI 0.96 to 3.10), but the difference was not statistically significant.[5]

Topical Anesthetics

Cochrane: Topical Agents for Pain in Venous Leg Ulcers

A 2012 Cochrane systematic review examined the evidence of EMLA cream prior to ulcer debridement from 6 placebo-controlled RCTs involving 343 participants with leg ulcer pain.[7] Participants who received EMLA cream had statistically significantly lower pain ratings on a 0 to 100 mm visual analog scale (VAS) (mean difference, -20.65 mm; 95% CI -12.19 to -29.11 mm; $p < 0.00001$) during ulcer debridement.[7] No statistically significant between group differences in burning or itching were observed.[7] Overall quality of evidence from these studies was rated as moderate.[7] All 6 RCTs were sponsored by Astra Zeneca.

Cochrane: Topical Anesthetics for Pain Control During Repair of Dermal Laceration

A 2017 Cochrane review updated a previously published 2011 report focused on the safety and efficacy of topical anesthetics for pain control during repair of dermal laceration.[8] The following objectives were analyzed: whether benefits of non-invasive topical anesthetic application occur at the expense of decreased analgesic efficacy, a comparison of the efficacy of various single-component or multi-component topical anesthetic agents for repair of dermal laceration, and to determine the clinical necessity for topical application of cocaine used as a therapeutic anesthetic.[8] The literature search was conducted through December 2016. Randomized controlled trials that evaluated the efficacy and safety of topical anesthetics for repair of dermal laceration in adult and pediatric patients were included. Topical anesthetics included bupivacaine, lidocaine, EMLA, lidocaine-epinephrine-tetracaine (LET), prilocaine, and tetracaine.[8] Two new studies were identified, which resulted in a final analysis of 25 RCTs involving 3,278 participants.[8] Most trials were at high risk of bias due to inadequate blinding, unclear concealment of allocation, and small sample sizes.[8] Local anesthetic efficacy during procedures such as wound repair was assessed by the patient's self-report of pain intensity during the intervention.[8] Acceptable tools for quantifying pain intensity included the VAS, the numerical rating scale, and a verbal rating scale.[8]

There was insufficient evidence to compare efficacy of topical anesthetics versus infiltrated local anesthesia.[8] The second objective, to compare the efficacy of various single-component or multi-component topical anesthetic agents for repair of dermal lacerations, found no significant differences between formulations, but the available data had high risk of bias.[8] For the final objective, researchers found that several cocaine-free topical anesthetics provided effective analgesic efficacy.[8] However, data regarding the efficacy of each topical agent are based mostly on single comparisons in trials with unclear or high risk of bias.[8]

The overall quality of the evidence according to the GRADE system is low, owing to limitations in design and implementation, imprecision of results, and high probability of publication bias (selective reporting of data).[8] Additional well-designed RCTs with low risk of bias are necessary before definitive conclusions can be reached.[8]

After review, 8 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria),[25-29] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[30-32]

New Guidelines:

American College of Rheumatology/Arthritis Foundation

The ACR/AF 2019 guideline on management of hand, hip, and knee OA updated their 2012 recommendations.[6] This guideline used the GRADE methodology to rate the quality of the available evidence and to develop recommendations.[6] An interprofessional voting panel included rheumatologists, an internist, physical and occupational therapists, and patients.[6] Literature published through August 2018 was used in the evidence review. Pertinent recommendations for topical analgesics are summarized in the three statements below:

- Topical NSAIDs are strongly recommended for patients with knee OA and conditionally recommended for patients with hand OA.[6]

In keeping with the principle that medications with the least systemic exposure (i.e., local therapy) are preferable, topical NSAIDs should be considered prior to use of oral NSAIDs. Practical considerations (e.g., frequent hand washing) and the lack of direct evidence of efficacy in the hand lead to a conditional recommendation for use of topical NSAIDs in hand OA.[6] In hip OA, the depth of the joint beneath the skin surface suggests that topical NSAIDs are unlikely to confer benefit, and thus, the voting panel did not examine use in hip OA.[6]

- Topical capsaicin is conditionally recommended for patients with knee OA and conditionally recommended *against* in patients with hand OA.[6]

Topical capsaicin is conditionally recommended for treatment of knee OA due to small effect sizes and wide confidence intervals in the available literature.[6] Topical capsaicin in hand OA is not recommended because of a lack of direct evidence to support use, as well as increased risk of contamination of the eye when

applied to the hand.[6] In hip OA, the depth of the joint beneath the skin surface suggests that topical capsaicin is unlikely to have a meaningful effect, and thus, the voting panel did not examine use of topical capsaicin in hip OA.[6]

- Insufficient data exists to make recommendations about the use of topical lidocaine preparations in OA.[6]

New Formulations or Indications:

- In March 2019, Flector® (diclofenac epolamine) topical system received an expanded indication for treatment of acute pain due to minor strains, sprains, and contusions in adults and pediatric patients 6 years of age and older.[33] Prior to this change, the Flector® labeling did not state if use in pediatric patients was appropriate.

- In February 2020, the FDA approved Voltaren® (diclofenac) 1% topical gel to be available over-the-counter (OTC) through the FDA's prescription-to-OTC switch process.[34] This process is usually initiated by the manufacturer of the prescription drug. For a drug to switch to nonprescription status, the manufacturer must show that consumers can understand how to use the drug safely and effectively without the supervision of a healthcare professional.[34] The OTC product will be called Voltaren Arthritis Pain and is indicated for the temporary relief of OA pain.[34]

New FDA Safety Alerts:

Table 3. Description of new FDA Safety Alerts[35]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Benzocaine	Anbesol, Orabase, Orajel, Baby Orajel, Hurricaine, and Topex	May 2018	Warnings and Contraindications	Over-the-counter (OTC) oral drug products containing benzocaine should not be used to treat infants and children younger than 2 years. Benzocaine oral drug products should only be used in adults and children 2 years and older if they contain certain warnings on the drug label. These products carry serious risks and provide little to no benefits for treating oral pain, including sore gums in infants due to teething. Due to the significant safety risk of methemoglobinemia, manufacturers are urged to stop marketing OTC oral drug products for treating teething in infants and children younger than 2 years.
Topical Lidocaine and Topical Lidocaine in combination with Prilocaine or Tetracaine	Lidoderm, Oraquix, Pliaglis, Synera, Xylocaine, Zingo	November 2018	Warnings and Precautions	Risk of Methemoglobinemia added to Prescribing Information Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with G6PD deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary

				compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. Signs and symptoms of methemoglobinemia may occur immediately or may be delayed some hours after exposure, and are characterized by a cyanotic skin discoloration and abnormal coloration of the blood. Methemoglobin levels may continue to rise; therefore, immediate treatment is required to avert more serious central nervous system and cardiovascular adverse effects, including seizures, coma, arrhythmias, and death. Discontinue lidocaine patch 5% and any other oxidizing agents. Depending on the severity of the symptoms, patients may respond to supportive care, i.e., oxygen therapy, hydration. More severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen.

Randomized Controlled Trials:

A total of 23 citations were manually reviewed from the initial literature search. After further review, 22 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 4. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Diwan et al[36] OL,RCT n=20	1. Transdermal diclofenac 200 mg patch x 1 for 24 hours 2. Diclofenac SR 100 mg BID x 2 doses over 24 hours	Adults aged 20-50 years with chronic periodontitis requiring flap operation	Pain as assessed by a VAS with 6 points (no pain, slight, mild, moderate, severe, horrible) and PIS with 5 points (no pain, very mild pain, mild pain, moderate pain, severe pain) were used to assess the pain 24 hours post-procedure	Minimum / Maximum / Mean / P-value VAS-Transdermal 0.0 / 1.0 / 0.6±0.51 / 0.48 VAS -Oral 0.0 / 1.0 / 0.8±0.42 PIS-Transdermal 0.0 / 2.0 / 1.2±0.63 / 0.16 PIS- Oral 0.0 / 2.0 / 1.6±0.8 There was no statistically significant difference in pain reduction between transdermal patch group and oral diclofenac group for either VAS or PIS assessments

<table>
<tr>
<td>Cozzi et al[37]

MC, RCT

n=356</td>
<td>1. Warm lidocaine and tetracaine patch 30 minutes before needle procedure

2. Lidocaine and prilocaine (EMLA) cream 60 minutes before needle procedure</td>
<td>Pediatric patients aged 3 to 10 years who needed venipuncture or IV cannulation</td>
<td>The primary outcome of this study was the success rate in performing venipuncture or intravenous cannulation at the first attempt.

Secondary outcomes included the procedural pain score, which was self-reported by children.</td>
<td>Main Study Outcomes
<table>
<tr><th>Outcome</th><th>Lidocaine/ Tetracaine Patch</th><th>EMLA</th><th>RR (95% CI) and p-value</th></tr>
<tr><td>Procedural Success [n (%)]</td><td>158 (92.4%)</td><td>142 (85.0%)</td><td>1.09 (1.01 to 1.17) p=0.03 NNT=14</td></tr>
<tr><td>Pain Score > 4 [n (%)]</td><td>18 (10.5%)</td><td>15 (9.0%)</td><td>1.17 (0.61 to 2.24) p=0.65</td></tr>
</table>
Warm lidocaine and tetracaine patch and EMLA cream provided equally useful pain relief</td>
</tr>
<tr>
<td colspan="5">Abbreviations: BID = twice daily; CI = confidence interval; EMLA = eutectic mixture of local anesthetics; IV = intravenous; MC = multi-center; mg = milligram; n = number; NNT = number needed to treat; OL=open-label; PIS = pain intensity scale; RCT = randomized clinical trial; RR = relative risk; SR = sustained release; VAS = visual analog scale</td>
</tr>
</table>

References:

1. Derry S, Conaghan P, Da Silva JA, Wiffen PJ, Moore RA. Topical NSAIDs for chronic musculoskeletal pain in adults. *Cochrane Database Syst Rev.* 2016;4:Cd007400.
2. Derry S, Sven-Rice A, Cole P, Tan T, Moore RA. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. *Cochrane Database Syst Rev.* 2013(2):Cd007393.
3. Derry S, Wiffen PJ, Kalso EA, et al. Topical analgesics for acute and chronic pain in adults - an overview of Cochrane Reviews. *The Cochrane database of systematic reviews.* 2017;5(5):CD008609-CD008609.
4. Massey T, Derry S, Moore RA, McQuay HJ. Topical NSAIDs for acute pain in adults. *Cochrane Database Syst Rev.* (6):CD007402.
5. Honvo G, Leclercq V, Geerinck A, et al. Safety of Topical Non-steroidal Anti-Inflammatory Drugs in Osteoarthritis: Outcomes of a Systematic Review and Meta-Analysis.
6. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis care & research.* 2020;72(2):149-162.
7. Briggs M, Nelson EA, Martyn-St James M. Topical agents or dressings for pain in venous leg ulcers. *Cochrane Database Syst Rev.* 2012(11).
8. Tayeb BO, Eidelman A, Eidelman CL, McNicol ED, Carr DB. Topical anaesthetics for pain control during repair of dermal laceration. *The Cochrane database of systematic reviews.* 2017;2(2):CD005364-CD005364.
9. Crabtree E, Holmes R, Selph S, Fulton M, Liebow S, McDonagh M. Neuropathic Pain. Final Report prepared by the Pacific Northwest Evidence-based Practice Center for the Drug Effectiveness Review Project. Oregon Health & Science University, Portland, Oregon, February 2018.
10. Moore RA, Tramer MR, Carroll D, Wiffen PJ, McQuay HJ. Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. *Bmj.*316(7128):333-338.

11. VA/DoD Clinical Practice Guideline for Non-Surgical Management of Hip and Knee Osteoarthritis. 2014. https://www.healthquality.va.gov/guidelines/CD/OA/OASUM6FIA.pdf. Accessed May 1, 2020.
12. Derry S, Wiffen PJ, Kalso EA, et al. Topical analgesics for acute and chronic pain in adults - an overview of Cochrane Reviews. [Review].
13. Derry S, Matthews PR, Wiffen PJ, Moore RA. Salicylate-containing rubefacients for acute and chronic musculoskeletal pain in adults. *Cochrane Database Syst Rev.* 2014(11):Cd007403.
14. National Institute for Health and Care Excellence. Osteoarthritis: care and management. February 12, 2014. https://www.nice.org.uk/guidance/cg177/resources/osteoarthritis-care-and-management-pdf-35109757272517. Accessed April 27, 2020.
15. National Center of Care and Excellence. Guidance for Treatent of Neuropathic Pain in Adults. . https://www.nice.org.uk/guidance/cg173. Accessed May 1, 2020.
16. Derry S, Rice AS, Cole P, Tan T, Moore RA. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. [Review].
17. Derry S, Wiffen PJ, Moore RA, Quinlan J. Topical lidocaine for neuropathic pain in adults. *Cochrane Database Syst Rev.* (7):CD010958.
18. Mu A, Weinberg E, Moulin DE, Clarke H. Pharmacologic management of chronic neuropathic pain: Review of the Canadian Pain Society consensus statement. [Review].
19. Altman RD, Barthel HR. Topical therapies for osteoarthritis. *Drugs.* 2011;71(10):1259-1279.
20. Lexicomp Online [internet database]. Wolters Kluwer Health, Hudson, Ohio, USA. Available at http://online.lexi.com. Accessed May 18, 2020.
21. Micromedex [internet database]. Truven Health Analytics, Greenwood Village, Colorado, USA. Available at http://www.micromedexsolutions.com. Accessed May 1, 2020.
22. Health Evidence Review Commission. Searchable Prioritized List, Guideline Notes, Multisector Interventions and Services Recommended for Non-Coverage. Accessed May 12, 2020.
23. Steward DJ. Eutectic mixture of local anesthetics (EMLA): What is it? What does it do? *The Journal of pediatrics.* 1993;122(5, Part 2):S21-S23.
24. Ali S, McGrath T, Drendel AL. An Evidence-Based Approach to Minimizing Acute Procedural Pain in the Emergency Department and Beyond. *Pediatr Emerg Care.* 2016;32(1):36-42; quiz 43-34.
25. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. [Review].
26. Deng ZH, Zeng C, Yang Y, et al. Topical diclofenac therapy for osteoarthritis: a meta-analysis of randomized controlled trials. *Clin Rheumatol.* 2016;35(5):1253-1261.
27. van Nooten F, Treur M, Pantiri K, Stoker M, Charokopou M. Capsaicin 8% Patch Versus Oral Neuropathic Pain Medications for the Treatment of Painful Diabetic Peripheral Neuropathy: A Systematic Literature Review and Network Meta-analysis. [Review].
28. Mason L, Moore RA, Derry S, Edwards JE, McQuay HJ. Systematic review of topical capsaicin for the treatment of chronic pain. *Bmj*.328(7446):991.
29. Taddio A, Gurguis MG, Koren G. Lidocaine-prilocaine cream versus tetracaine gel for procedural pain in children. *Ann Pharmacother*.36(4):687-692.
30. Enthoven WT, Roelofs PD, Deyo RA, van Tulder MW, Koes BW. Non-steroidal anti-inflammatory drugs for chronic low back pain. [Review].
31. Foster JP, Taylor C, Spence K. Topical anaesthesia for needle-related pain in newborn infants. *Cochrane Database Syst Rev*.2:CD010331.

32. Shahid S, Florez ID, Mbuagbaw L. Efficacy and Safety of EMLA Cream for Pain Control Due to Venipuncture in Infants: A Meta-analysis. *Pediatrics.* 2019;143(1):01.
33. Flector ® (diclofenac epolamine) topical system Prescribing Information. New York, NY; Pfizer, Inc. March 2019.
34. Food and Drug Administration News Release. FDA Approves Three Drugs for Nonprescription Use Through Rx-to-OTC Switch Process. https://www.fda.gov/news-events/press-announcements/fda-approves-three-drugs-nonprescription-use-through-rx-otc-switch-process. Accessed May 20, 2020.
35. Food and Drug Administration. Drug Safety Labeling Changes (SLC). https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/. Accessed May 13, 2020.
36. Diwan V, Srinivasa TS, Ramreddy KY, Agrawal V, Nagdeve S, Parvez H. A comparative evaluation of transdermal diclofenac patch with oral diclofenac sodium as an analgesic drug following periodontal flap surgery: A randomized controlled clinical study. *Indian Journal of Dental Research.*30(1):57-60.
37. Cozzi G, Borrometi F, Benini F, et al. First-time success with needle procedures was higher with a warm lidocaine and tetracaine patch than an eutectic mixture of lidocaine and prilocaine cream. *Acta Paediatrica.*106(5):773-778.

Appendix 1: Current Preferred Drug List

Topical Analgesics

Generic	Brand	Form	Route	PDL
capsaicin	ARTHRITIS PAIN RELIEVING	CREAM (G)	TOPICAL	Y
capsaicin	CAPSAICIN	CREAM (G)	TOPICAL	Y
capsaicin	CAPSAICIN-HP	CREAM (G)	TOPICAL	Y
capsaicin	HIGH POTENCY CAPSAICIN	CREAM (G)	TOPICAL	Y
capsaicin	CAPSAICIN	LOTION	TOPICAL	N
capsaicin	ZOSTRIX	STICK (EA)	TOPICAL	N
capsaicin/me-salicylate/menth	ZIKS	CREAM (G)	TOPICAL	N
capsaicin/skin cleanser	QUTENZA	KIT	TOPICAL	N
diclofenac epolamine	DICLOFENAC EPOLAMINE	PATCH TD12	TRANSDERM	N
diclofenac epolamine	FLECTOR	PATCH TD12	TRANSDERM	N
diclofenac epolamine	LICART	PATCH TD24	TRANSDERM	N
diclofenac sodium	DICLOFENAC SODIUM	DROPS	TOPICAL	N
diclofenac sodium	KLOFENSAID II	DROPS	TOPICAL	N
diclofenac sodium	DICLOFENAC SODIUM	GEL (GRAM)	TOPICAL	N
diclofenac sodium	VOLTAREN	GEL (GRAM)	TOPICAL	N
diclofenac sodium	PENNSAID	SOL MD PMP	TOPICAL	N
diclofenac sodium	PENNSAID	SOLN PK(G)	TOPICAL	N

diclofenac/kinesiology tape	XRYLIX	KIT	TOPICAL	N
lidocaine	LIDOCAINE	ADH. PATCH	TOPICAL	N
lidocaine	LIDODERM	ADH. PATCH	TOPICAL	N
lidocaine	ZTLIDO	ADH. PATCH	TOPICAL	N
lidocaine	LIDOCAINE	OINT. (G)	TOPICAL	N
lidocaine/kinesiology tape	LIDOPURE PATCH	COMBO. PKG	TOPICAL	N
cocaine HCl	COCAINE HCL	SOLUTION	TOPICAL	
diclofenac/capsicum oleoresin	DERMACINRX LEXITRAL	CMB SOL CR	TOPICAL	
diclofenac/capsicum oleoresin	DICLOFEX DC	CMB SOL CR	TOPICAL	
hydrocortisone/pramoxine	EPIFOAM	FOAM	TOPICAL	
lidocaine HCl	LIDOCAINE HCL	CREAM (G)	TOPICAL	
lidocaine HCl	LIDOTRAL	CREAM (G)	TOPICAL	
lidocaine HCl	GLYDO	JEL/PF APP	MUCOUS MEM	
lidocaine HCl	LIDOCAINE HCL	JEL/PF APP	MUCOUS MEM	
lidocaine HCl	LIDOCAINE HCL	JELLY(ML)	MUCOUS MEM	
lidocaine HCl	LIDOZION	LOTION	TOPICAL	
lidocaine HCl	LIDOCAINE HCL	SOLUTION	MUCOUS MEM	
lidocaine HCl	LIDOCAINE HCL VISCOUS	SOLUTION	MUCOUS MEM	
lidocaine HCl	LIDOCAINE HCL	SOLUTION	TOPICAL	
lidocaine HCl	PRE-ATTACHED LTA KIT	SOLUTION	TOPICAL	
lidocaine/dimethicone	DERMACINRX ZRM PAK	KIT PAT-CR	TOPICAL	
lidocaine/emollient cmb no.102	DERMACINRX PHN PAK	KIT PAT-CR	TOPICAL	
lidocaine/hydrocortisone ac	LIDOCAINE-HYDROCORTISONE	CREAM (G)	TOPICAL	
lidocaine/priloc/lidocaine HCl	PRIZOTRAL	CREAM (G)	TOPICAL	
lidocaine/priloc/lidocaine HCl	PRIZOTRAL-II	CREAM (G)	TOPICAL	
lidocaine/prilocaine	LIDOCAINE-PRILOCAINE	CREAM (G)	TOPICAL	
lidocaine/prilocaine	APRIZIO PAK	KIT	TOPICAL	
lidocaine/prilocaine	DERMACINRX EMPRICAINE	KIT	TOPICAL	
lidocaine/prilocaine	DERMACINRX PRIZOPAK	KIT	TOPICAL	
lidocaine/prilocaine	EMPRICAINE-II	KIT	TOPICAL	
lidocaine/prilocaine	LIDOCAINE-PRILOCAINE	KIT	TOPICAL	
lidocaine/prilocaine	PRILO PATCH	KIT PAT-CR	TOPICAL	
lidocaine/prilocaine/silicone	NUVAKAAN	KIT	TOPICAL	
lidocaine/prilocaine/silicone	NUVAKAAN-II	KIT	TOPICAL	
lidocaine/silicone, adhesive	ZILACAINE PATCH	COMBO. PKG	TOPICAL	
lidocaine/tetracaine	PLIAGLIS	CREAM (G)	TOPICAL	
lidocaine/tetracaine	SYNERA	M.HT PATCH	TOPICAL	

Appendix 2: Abstracts of Comparative Clinical Trials

1. **A comparative evaluation of transdermal diclofenac patch with oral diclofenac sodium as an analgesic drug following periodontal flap surgery: A randomized controlled clinical study.**[36]

Diwan V, Srinivasa TS, Ramreddy KY, Agrawal V, Nagdeve S, Parvez H

BACKGROUND: Pain is an inevitable outcome of any periodontal surgery. Controlling postoperative pain is of utmost importance so as to increase patient compliance. The present study aims to compare the degree of postoperative analgesia with the use of oral diclofenac sodium and transdermal diclofenac patch following periodontal flap surgery in patients with chronic periodontitis.

MATERIALS AND METHODS: A total of 20 patients requiring full mouth flap surgery were selected for this study. Flap surgery was performed quadrant-wise and transdermal diclofenac patch was applied on the right arm following surgery of one of the quadrants and 100 mg oral diclofenac sodium twice daily was prescribed following surgery of the subsequent quadrant. The postoperative pain was recorded on visual analog scale and pain intensity scale 24 h after the surgery.

RESULTS: Both the statistical and clinical observation showed that diclofenac sodium administered transdermally has equal efficacy as compared to drug administered orally.

CONCLUSION: The study concludes that the diclofenac administered transdermally has equal potency in relieving postoperative pain as compared to orally administered diclofenac sodium following modified flap surgery. Transdermal patch has an added advantage of better patient compliance as it does not cause gastric disturbance.

2. **First-time success with needle procedures was higher with a warm lidocaine and tetracaine patch than an eutectic mixture of lidocaine and prilocaine cream.**[37]

Cozzi, G., Borrometi F, Benini F, et al.

Aim: More than 50% of children report apian during venipuncture or intravenous cannulation and using local anesthetics before needle procedures can lead to different success rates. This study examined how many needle procedures were successful at the first attempt when children received either a warm lidocaine and tetracaine patch or an eutectic mixture of lidocaine and prilocaine (EMLA) cream.

Methods: We conducted this multicenter randomized controlled trial at three tertiary-level children's hospitals in Italy in 2015. Children aged three to 10 years were enrolled in an emergency department, pediatric day hospital and pediatric ward and randomly allocated to receive a warm lidocaine and tetracaine patch or EMLA cream. The primary outcome was the success rate at the first attempt.

Results: The analysis included 172 children who received a warm lidocaine and tetracaine patch and 167 who received an EMLA cream. The needle procedure was successful at the first attempt in 158 children (92.4%) who received the warm patch and in 142 children (85.0%) who received the cream ($p = 0.03$). The pain scores were similar in both groups.

Conclusion: This study showed that the first-time needle procedure success was 7.4% higher in children receiving a warm lidocaine and tetracaine patch than EMLA cream.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to March Week 1 2020, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations March 17, 2020.

1.	Benzocaine/	1145
2.	Pramoxine.mp	60
3.	Prilocaine/or Lidocaine, Prilocaine Combinations	2140
4.	Tetracaine	2601
5.	Capsaicin	10309
6.	Diclofenac	7748
7.	Capsicum/	3216
8.	Methyl salicylate.mp	1102
9.	Lidocaine	24233
10.	Cocaine	23944
11.	Analgesics	48017
12.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	96185
13.	Administration, Topical	38069
14.	12 and 13	2122
15.	Acute pain/ or Pain/	133987
16.	14 and 15	431
17.	limit 16 to (english language and humans and yr="2016 -Current" and (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial protocol or clinical trial or comparative study or controlled clinical trial or guideline or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))	23

Lidocaine Patch

Goal(s):

- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:

- 90 days to 12 months (criteria specific)

Requires PA:

- Lidocaine Patch

Covered Alternatives

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (refer to Table 1 for examples).	**Yes:** Go to # 3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Is this a request for renewal of a previously approved prior authorization for lidocaine patch?	**Yes**: Go to **Renewal Criteria**	**No**: Go to # 4
4. Is the prescription for Lidoderm patch greater than 3 patches/day?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 90 days

Renewal Criteria		
1. Does the patient have documented improvement from lidocaine patch?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny for medical appropriateness.

Table 1. OHP Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

Condition	Lidocaine Patch
Funded	Evidence Supports Use
Diabetic Neuropathy	X
Postherpetic Neuropathy	X
Painful Polyneuropathy	X
Spinal Cord Injury Pain	
Chemotherapy Induced Neuropathy	
Non-funded	
Fibromyalgia	

P&T Review: *8/2020 (DM); 7/18 (DM); 3/17*
Implementation: *4/1/17*