

Topical Medications in the Treatment of Pain

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Topical medications are delivered through a variety of dosage formulations including creams, ointments, gels, lotions, solutions, pastes, sprays, eye and ear drops, nasal sprays, and transdermal patches.¹ Topical medication administration has been used for decades to effectively prevent and treat a wide variety of medical conditions, with many medications currently under investigation for topical formulation, particularly transdermal use.^{2,3}

There are a number of advantages and disadvantages to medication administration via the topical route, as compared with oral or injectable administration. Advantages include avoidance of hepatic first-pass metabolism, ease of application, less fluctuation in drug levels, achievement of efficacy with a lower total daily dose, simple discontinuation of a medication if needed, ability to be more “site-specific” with drug delivery, improved adherence, and avoidance of significant risks associated with oral or intravenous administration (ie, major drug interactions or infection).⁴ Disadvantages include skin irritation, poor permeability through the skin for some medications, the possibility of allergic reactions, and the fact that topical administration can really only be used for medications that require low plasma concentrations to achieve a therapeutic effect. This article will provide an overview of topical agents available for the management of acute and chronic pain (see Table).

Nonsteroidal Anti-inflammatory Agents

Topical formulations (ie, solution, gel, and transdermal patch) of diclofenac are available for use in the treatment of pain.⁹⁻¹¹ The diclofenac transdermal patch is approved for the treatment of acute musculoskeletal injury (sprains and strains), whereas diclofenac solution and gel are approved for treatment of osteoarthritis of the knee.

Nonsteroidal anti-inflammatory drug (NSAID) therapy, including topical formulations, is associated with several serious safety concerns.¹² All NSAIDs include a boxed warning highlighting the potential for increased risk of cardiovascular events as well as serious, potentially life-threatening gastrointestinal bleeding. Additionally, NSAIDs are contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.⁹⁻¹¹

DICLOFENAC TRANSDERMAL PATCH

The diclofenac transdermal patch (Flector Patch) was the first NSAID approved in a transdermal patch formulation. It has been postulated that diclofenac transdermal exerts its pharmacologic effects through localized accumulation at the application site rather than from systemic absorption.¹³ The bioavailability of diclofenac transdermal is approximately 1% that of oral diclofenac, with an elimination half-life of 12 hours compared with 1.2 to 2 hours with oral diclofenac.⁹ The diclofenac transdermal patch was well tolerated in clinical trials. The most commonly reported adverse events were erythema, pruritis, dermatitis, and blisters. The patch should not be applied to open wounds or broken skin.

Diclofenac transdermal patch has been compared favorably with placebo in the treatment of minor pains and strains in 2 trials.^{14,15} In the first trial, 222 patients were randomized to receive diclofenac or placebo

patch every 12 hours for 14 days for treatment of acute muscular pain. Pain intensity was measured using a visual analog scale on 3 separate clinic visits (days 3, 7, and 14). There was a statistically significant difference in pain intensity in favor of diclofenac on days 3 and 14 ($P=0.036$ and $P=0.048$, respectively). A second trial evaluated the efficacy of diclofenac transdermal patch versus placebo applied once a day for 1 week in 134 patients with an ankle sprain occurring less than 48 hours prior to the study. Diclofenac was statistically superior to placebo in pain relief (pain on movement) at 4 hours after application of the first patch through the 7-day trial. Diclofenac was superior with regard to secondary end points (pain on stretch, pain at rest, pain on pressure) by day 3 of the trial.

There are currently no clinical trials comparing diclofenac transdermal to other NSAIDs, topical or oral, for acute pain conditions. The use of oral analgesics, ibuprofen, or acetaminophen still remains the initial treatment of sprains and strains.

DICLOFENAC TOPICAL SOLUTION, DICLOFENAC GEL

Diclofenac topical solution (Pennsaid) has been shown to be superior to placebo and similar in efficacy to 50 mg 3 times a day oral diclofenac for treatment of osteoarthritis of the knee.^{16,17} Specifically, when compared with oral diclofenac, the topical solution was better tolerated in terms of gastrointestinal adverse events ($P=0.0006$).¹⁶ However, the solution was associated with more local application-site reactions, including dry skin, rash, pruritis, and vesiculobullous rash ($P<0.0001$).

In a 12-week study of 492 patients with osteoarthritis of the knee, diclofenac gel (Voltaren Gel) was superior to a placebo vehicle.¹⁸ Both diclofenac gel and placebo were applied to the affected knee 4 times per day. Diclofenac gel was superior for reduction in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain index (-5 vs -4 decrease from baseline; $P=0.01$) and physical function index (-15 vs -10.9; $P=0.001$). Pain on movement also was significantly improved with diclofenac gel administration (-27.7 vs -20.1 mm; $P<0.002$).

Topical Anesthetics

Lidocaine transdermal (Lidoderm) is indicated for the treatment of postherpetic neuralgia.^{19,20} Current guidelines for the treatment of neuropathic pain recommend topical lidocaine as a third-line therapy in patients who are unable to take oral medications. Synera, the lidocaine/tetracaine combination topical patch, provides local dermal analgesia for superficial venous access and dermatologic procedures (ie, excision, electrodesiccation, and shave biopsy of skin lesions).⁸

LIDOCAINE 5% TRANSDERMAL PATCH

When lidocaine transdermal is applied to the skin,

the dose released results in analgesia, but not complete nerve block.²¹ The patch contains 700 mg of lidocaine; however, only 1% to 5% of the dose is absorbed through the skin with recommended use. The remaining 95% (665 mg) is retained in the patch. The patch is contraindicated in patients with an allergy to amide-type anesthetic agents.

With application of the lidocaine patch, it is important to consider any other local anesthetics the patient may be receiving when calculating total exposure.²¹ Additionally, lidocaine transdermal should be used cautiously in patients receiving class I antiarrhythmic agents (tocainamide, mexilitene) because the effects may be additive and result in toxicity.

The lidocaine transdermal patch has been compared with a placebo patch in post-herpetic neuralgiaPHN.²² In a crossover study of 32 patients, the median time to exit the treatment period (ie, reduction in pain relief score of 2 or more categories on a 6-item Pain Relief Scale for any 2 consecutive days) was 14 days for the lidocaine patch, compared with 3.8 days with placebo ($P \leq 0.001$). Seventy-eight percent of subjects preferred the lidocaine patch to placebo ($P \leq 0.001$). Lidocaine transdermal patches have not been evaluated against other treatments for post-herpetic neuralgia.

The most common side effects reported with lidocaine transdermal include blister, bruising, depigmentation, and application-site burning.²¹ Systemic side effects are uncommon, but may include nervousness, lightheadedness, confusion, euphoria, or cardiac arrest.

Lidocaine transdermal should only be applied to intact skin.²¹ After application of the patch, the patient should be instructed to avoid contact with eyes and to wash hands thoroughly. Because a large amount of lidocaine is retained in the patch even after use, it is important that it be safely discarded. Prior to disposal, the patch should be folded so that the adhesive sticks to itself.

LIDOCAINE 70 MG/TETRACAINE 70 MG TRANSDERMAL PATCH

The combination of lidocaine/tetracaine (Synera) in a patch formulation provides local dermal analgesia through the blocking of sodium channels required for the initiation and conduction of neuronal impulses.⁸ Synera contains a heating component that is meant to enhance local anesthetic delivery. In general, the maximum effect of both agents within the patch is observed within 30 minutes after application; keeping the patch in place for up to 60 minutes did not result in a significant increase in lidocaine or tetracaine levels.

The lidocaine/tetracaine patch is contraindicated in patients with a known hypersensitivity to amide- or ester-type anesthetics or paraaminobenzoic acid.⁸ Similar to Lidoderm, a used lidocaine/tetracaine patch retains a large amount of medication (at least 90%

of the initial amount). Application, storage, and disposal procedures for Synera also are similar; use caution when storing or disposing the product so that children or pets do not inadvertently suffer serious adverse effects. Additionally, consideration should be given to total anesthetic exposure if the patient is on other local anesthetics concomitantly. Side effects also would be similar to those seen with lidocaine transdermal; however, the toxicity associated with coadministered local anesthetics is thought to be at least additive.

The lidocaine/tetracaine patch has been compared to lidocaine/prilocaine cream (EMLA) in 82 adults undergoing a vascular access procedure.²³ Results revealed the patch to be associated with significantly lower median visual analogue scale (VAS) scores at 10 minutes ($P=0.01$), 20 minutes ($P=0.042$), and 30 minutes ($P=0.001$). Lidocaine/tetracaine was associated with more erythema, whereas EMLA cream produced more blanching at specific time points.

Counterirritants

Counterirritants are agents that desensitize individuals to painful stimuli. Capsaicin is a transient receptor potential vanilloid subfamily member 1 (TRPV1) agonist.⁷ It works by initially stimulating the TRPV1 nociceptors in the skin followed by a desensitization of the TRPV1 nociceptor nerve endings. This desensitization of the nerve endings can last for several months providing pain relief to the area. Eventually, nerve fibers are reinnervated and the area may become painful again.

CAPSAICIN 8% TRANSDERMAL PATCH

With the capsaicin patch (Qutenza), the physician should conduct an initial pain assessment and mark the skin to identify the application site.⁷ Prior to applying the patch, a topical anesthetic agent should be applied to the treatment area to lessen pain and discomfort associated with patch application. Physicians should wear nitrile gloves when applying the patch. The patch or patches (up to 4 patches may be applied at once) are left in place for 60 minutes, then removed. A special cleansing gel must be applied to the treated area to eradicate any remaining capsaicin from the skin after removal.

Patients have reported irritation of the airways and eyes during patch application.⁷ There can be an elevation in blood pressure (ie, normally limited to a 10 mm Hg increase with some even higher spikes) that may last up to 2 hours after removal of the patch. This increase in blood pressure is a direct result of the pain associated with capsaicin patch application. Patients with uncontrolled hypertension may be at risk for cardiac events. Topical reactions to the capsaicin patch include erythema, pain, itching, rash, and excoriation. Patients often will require analgesic medications including opioids to control the pain associated with

Table. Topical Agents for Pain⁵⁻⁸

Brand Name	Indication	Dosing and Administration
Nonsteroidal anti-inflammatory agents		
Diclofenac epolamine 1.5% patch (Flector Patch; King Pharmaceuticals)	Acute musculoskeletal pain	Apply one patch bid (every 12 h). Apply only to intact skin.
Diclofenac sodium 1.5% topical solution (Pennsaid; Covidien)	OA of the knee	Apply 40 drops to each painful knee qid. Apply 10 drops at a time either directly to the knee or to the hand to spread evenly on the knee. Allow the area to dry before covering with clothing.
Diclofenac sodium 1% gel (Voltaren Gel; Novartis, Endo Pharmaceuticals)	OA of joints amenable to topical treatment (knees, hands); not evaluated for use on joints of the spine, hip, or shoulder	Lower extremities: apply 4 g qid. Do not apply more than 16 g daily to any one affected joint of the lower extremities. Upper extremities: apply 2 g qid. Do not apply more than 8 g daily to any one affected joint of the upper extremities. Do not shower or bathe for 1 h after application of diclofenac gel. Avoid covering with clothing or gloves for at least 10 min after application.
Local Anesthetics		
Lidocaine 5% patch (Lidoderm; Endo Pharmaceuticals)	PHN	Up to 3 patches only once to the most painful affected area for up to 12 h in a 24-h period. In patients who are debilitated or who have hepatic impairment, smaller doses should be used.
Lidocaine 70 mg/tetracaine 70 mg patch (Synera; Zars Pharma)	Local dermal analgesia for superficial venous access and dermatologic procedures	Venipuncture or cannulation: apply to intact skin for 20-30 min prior to procedure Dermatologic procedures: apply to intact skin for 30 min prior to procedure
Counterirritants		
Capsaicin 8% patch (Qutenza; NeurogesX)	PHN	Apply for 60 min and repeat every 3 mo or as warranted by return of pain. Do not apply more frequently than every 3 mo. Only health care professionals may administer the patch.
Capsaicin 0.025%, 0.075% lotion, cream, gel, patch (Zostrix; HealthCare Products) ^a	Temporary relief of minor aches and pains	Apply 3 to 4 times a day. Used off-label for PHN.

ATC, around-the-clock; **bid**, twice daily; **OA**, osteoarthritis; **PHN**, postherpetic neuralgia; **qid**, 4 times daily

^a Nonprescription product.

Table. Topical Agents for Pain⁵⁻⁸

Brand Name	Indication	Dosing and Administration
Counterirritants (Continued)		
Methylsalicylate 15%, 30% cream and ointment (BenGay; Pfizer, various generics) ^a	Pain due to muscular aches, neuralgia, arthritis, sprains	Apply 3 to 4 times a day as directed. Do not use for longer than 7 d.
Menthol 2.5%, 5% 10%,16% cream, gel, ointment, patch (Icy Hot; Chattem, various generics) ^a	Pain due to muscular aches, neuralgia, arthritis, sprains	Apply 3 to 4 times a day as directed. Do not use for longer than 7 d.
Trolamine salicylate 10% cream, lotion (Aspercreme, Sportscreme; Chattem) ^a	Pain due to muscular aches, neuralgia, arthritis, sprains	Apply 3 to 4 times a day as directed. Do not use for longer than 7 d.
Camphor 11%, menthol 11% (Tiger Balm; Haw Par Healthcare Limited) ^a	Pain due to muscular aches, neuralgia, arthritis, sprains	Apply 3 to 4 times a day as directed. Do not use for longer than 7 d.
Narcotic analgesics		
Fentanyl patch (Duragesic; Janssen, various generics) DURAGESIC-12 (12 mcg/h) DURAGESIC-25 (25 mcg/h) DURAGESIC-50 (50 mcg/h) DURAGESIC-75 (75 mcg/h) DURAGESIC-100 (100 mcg/h)	Persistent, moderate to severe chronic pain that requires continuous, ATC opioid administration for an extended period of time, and cannot be managed by other means	Apply one patch every 72 h. Use ONLY for opioid-tolerant patients.
Buprenorphine patch (Butrans, Purdue Pharma LP) 5 mcg/h 10 mcg/h 20 mcg/h	Moderate to severe chronic pain in patients requiring a continuous, ATC opioid analgesic for an extended period	Apply the patch once every 7 d. 5 mcg/h patch: appropriate for opioid-naïve patients, mild to moderate hepatic impairment, those who require <30 mg oral morphine equivalents daily 10 mcg/h patch: appropriate for those requiring between 30 and 80 mg oral morphine equivalents daily Dose can be titrated after 72 h to a maximum 20 mcg/h patch. Do not exceed one 20 mcg/h patch due to risk for QT prolongation.

ATC, around-the-clock; **bid**, twice daily; **OA**, osteoarthritis; **PHN**, postherpetic neuralgia; **qid**, 4 times daily

^a Nonprescription product.

capsaicin patch application. Ice packs during the procedure and following removal of the patch may be useful.

The capsaicin 8% patch has been compared with a low-dose capsaicin (0.04%) control patch in 402 patients with postherpetic neuralgia.²⁴ The active treatment group (capsaicin 8%) had significant improvement in pain scores during weeks 2 through 12 ($P=0.002$) compared with those in the control group. Patients experienced minor changes in blood pressure and local pain and irritation at the application site. The capsaicin patch has not been compared with other oral or topical therapies for postherpetic neuralgia.

Nonprescription Topical Pain Agents

A number of nonprescription products are available for topical use in the management of muscle pain, sprains, arthritis, and rheumatism. These agents are classified as counterirritants and contain variable concentrations of methyl salicylate, menthol, camphor, or capsaicin (see Table 1).⁵ These products are intended for short-term use in the management of mild pain symptoms; use for longer than 7 days is not recommended.²⁵ Avoid using these agents in combination with a heating pad to prevent skin irritation and burning of the skin. Systemic absorption of methyl salicylate may occur; physicians should thus monitor for signs of toxicity (tinnitus, nausea, vomiting). Increased anticoagulation may occur in patients taking warfarin who use methyl salicylate topically.

Narcotic Analgesics

There are currently 2 FDA-approved opioid transdermal patches for the management of chronic pain. Fentanyl (Duragesic) transdermal patches have been available since 1990 and buprenorphine (Butrans) was approved in July 2010.^{6,26} Both of these agents carry a significant risk for misuse, abuse, and diversion (MAD). MAD is a particular concern in patients with a history of substance abuse or mental illness. The fentanyl patch is a schedule II narcotic, whereas buprenorphine is a schedule III.

The fentanyl patch only should be used in patients who are opioid-dependant and require continuous opioid analgesia for chronic pain. It is contraindicated for use in patients who are NOT opioid tolerant, postoperative pain, other acute pain situations, or for intermittent pain.²⁶

Buprenorphine transdermal patch only should be used in patients requiring long-term chronic pain management.⁶ It is contraindicated in patients with significant respiratory depression or severe bronchial asthma. Buprenorphine should not be used within 2 weeks of monoamine oxidase inhibitors and should not be given to patients with a long QT interval or patients receiving class 1A or 3 antiarrhythmic medications. Buprenorphine can cause severe hypotension.

Patient Care Considerations

Whenever physicians prescribe topical products for pain, it is important to consider the following:^{6,7,9-11,21,26}

- Some transdermal patches contain metallic components and may need to be removed prior to magnetic resonance imaging (MRI).
- Impaired organ function and potential drug allergies may affect choice of agent and dose administered.
- Use of over-the-counter pain relievers in addition to topical prescription products, such as NSAIDs, may increase adverse effects. Physicians should question patients regarding use of nonprescription products.
- Although systemic absorption is limited with topical NSAIDs, it is important to consider potential drug interactions. All NSAIDs can interact with concurrent antihypertensive therapies such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β -blockers, and diuretics, resulting in a diminished antihypertensive/diuretic effect.
- If any NSAIDs are coadministered with anticoagulants, the risk for bleeding may be increased.
- Do not use any product containing salicylate (methyl salicylate, trolamine salicylate) if the patient is taking an anticoagulant such as warfarin.
- Review any other local anesthetic exposure prior to prescribing the lidocaine or lidocaine/tetracaine combination patch in order to avoid serious adverse effects.
- Do not apply transdermal patches to broken or inflamed skin, burns, open wounds, or blisters.
- Transdermal patch exposure to direct heat sources (including saunas, hot tubs, heat lamps, hot baths, or sunbathing) should be avoided; temperature-dependent increases in fentanyl or buprenorphine exposure can lead to overdose and death.
- Because used transdermal products may still contain significant amounts of drug, keep used patches away from children and pets. Fold the patch onto itself prior to disposing.

Summary

Topical medications are available in a variety of dosage formulations and more medications are being investigated to determine if a topical dosage form may be appropriate. Currently, multiple topical medications are available for the treatment of pain including NSAIDs, anesthetics, counterirritants, and narcotic analgesics. These medications have advantages and disadvantages to oral or intravenous administration. The efficacy of these agents has been demonstrated (primarily in placebo-controlled trials); however, their topical route of administration does not eliminate safety concerns. Physicians should be aware of the multiple patient care considerations when prescribing topical agents for pain.

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