

# Overview of Topical Analgesics

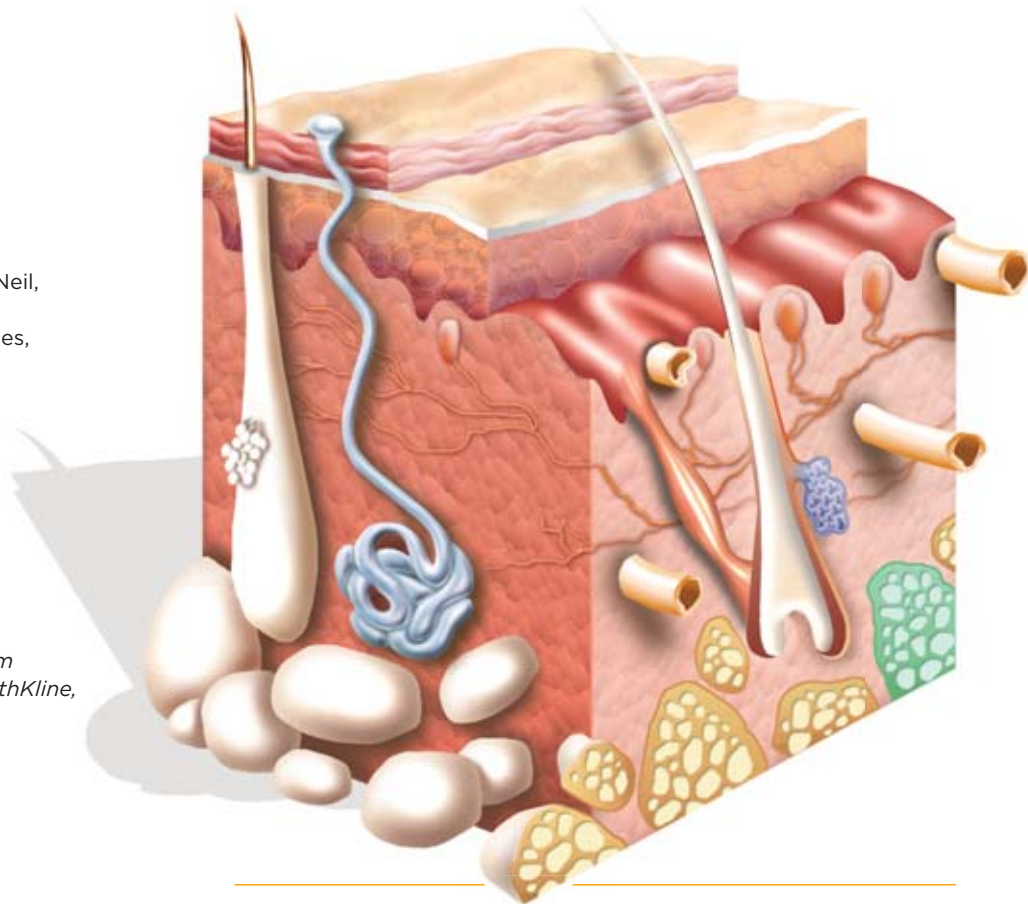
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**SEE COMMENTARY BY  
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ON PAGE 24.**

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The evolving field of pain management has shifted toward more targeted delivery of medications, with a localized effect. The change in prescribing habits has been fueled by the controversies regarding adverse event data for over-the-counter (OTC) and prescription nonsteroidal anti-inflammatory drugs (NSAIDs).

**Table 1. Prescription Transdermal And Topical Formulations**

Transdermal <sup>a</sup>	Topical <sup>b</sup>
Clonidine	Diclofenac gel
Estrogen	Diclofenac patch
Fentanyl	Lidocaine gel
Nicotine	Lidocaine 5% patch
Nitroglycerin	Nonsteroidal anti-inflammatory drugs
Oxybutynin	Tricyclic antidepressant (doxepin)
Scopolamine	
Testosterone	

<sup>a</sup> Therapeutic goal: systemic absorption.

<sup>b</sup> Therapeutic goal: local delivery.

**Table 2. Active Methods for the Delivery of Topical and Transdermal Medications**

Type	Method
Electrical	Electroporation Iontophoresis
Heat	Thermophoresis
Mechanical	Abrasion Microneedle/puncture/perforation Needle-less injection Stretching Suction
Miscellaneous	Laser and photomechanical waves Magnetophoresis Radiofrequency Ultrasound

An updated understanding of the topical alternatives available for common neuropathic and musculoskeletal conditions associated with pain may help to expand a clinician's options for treatment. In comparison with oral agents, topical preparations entail a lower risk for systemic adverse effects. Currently available oral NSAIDs, cyclooxygenase-2 (COX-2) inhibitors, and opioids, although potentially powerful analgesics, may cause morbidity and mortality through their effects on the gastrointestinal tract, heart, kidneys, and other organs and their effects on cognition.<sup>1</sup> Recent management recommendations for the treatment of osteoarthritis published by the American College of Geriatrics cautioned the use of NSAIDs and COX-2 inhibitors, once thought to be first-line for treatment of painful conditions, due to potential adverse end-organ effects. The recommendations support the use of topical analgesics as an option for treatment in older patients.<sup>2</sup> Topical analgesics may be used alone or to supplement an established regimen of oral medication for pain.

### Topical Drug Delivery

Topical analgesics target peripheral tissues when they are directly applied over the painful site.<sup>3</sup> Low to clinically insignificant serum levels follow the application of topical agents, making systemic side effects unlikely. Topical analgesics can be broadly categorized into 3 subgroups: analgesics, counterirritants, and anesthetics.

Pharmacokinetic principles are important in understanding basic mechanisms of action and differentiating among evolving formulations and topical delivery systems. Formulations have been engineered to improve absorption across the main barrier of the skin—the stratum corneum.<sup>4</sup> Penetration enhancers, such as lecithin organogels<sup>5</sup> and polyethylene glycol, have been developed and incorporated in the newer topical compounds to improve the absorption characteristics of the active ingredient. Topical products are available in various creams, gels, lotions, patches, and plasters and are distinguished from commonly used transdermal medication systems, which are placed on the skin for extended periods of time to create sustained systemic serum levels (ie, transdermal fentanyl patches, scopolamine, and various estrogen patch systems; Tables 1 and 2). This article reviews the topical preparations commonly used in the primary care setting, including topical capsaicin, topical lidocaine (lidocaine patch 5%), and NSAIDs.

### CAPSAICIN

Capsaicin is a natural pungent constituent of chili peppers. Capsaicin cream is available OTC in 0.025% and 0.075% concentrations. Capsaicin is presently used biologically in more than 900 patented products, and in the foreseeable future, more available medications and products will include this natural ingredient.<sup>6</sup>

The application of capsaicin was classically thought to lead to the selective activation of vanilloid receptors, desensitization, and/or neurotoxic effects on small-diameter sensory afferents caused by the release of excitatory chemicals, substance P, and glutamate. Research on the vanilloid receptor in the late 1990s led to the cloning and elucidation of a range of transient receptor protein (TRP) channels or thermoreceptors, increasing our understanding of temperature sensation and opening the door to the development of new analgesic compounds.<sup>7</sup> Besides capsaicin, the vanilloid receptor (TRPV1) can be activated by heat, acid, and inflammatory stimuli.<sup>8</sup> Activation may manifest clinically as touch allodynia (the perception of innocuous stimuli as painful) or as hyperalgesia (the exaggerated perception of painful stimuli as still more painful); both phenomena are common signs of neuropathic and inflammatory pain states. Clinically, the use of capsaicin is limited by the need for a sensitization phase, during which the sensation of burning is a major effect of its application. Following repeated application, pharmacologic desensitization—during which the response to capsaicin diminishes because of inhibition at the receptor level—is followed by functional desensitization, in which pain in response to a broad range of stimuli is attenuated.<sup>9</sup> However, many patients are unable to tolerate ongoing therapy-induced pain with repeated dosing of the medication, making it difficult to achieve functional desensitization of the receptors and subsequent analgesia. Also, the continued application of capsaicin is required to maintain desensitization; otherwise, the affected nerve terminals slowly regenerate and regain sensitivity.

Topical capsaicin has been recommended for the treatment of osteoarthritis (OA) of the hand, hip, and knee.<sup>10-12</sup> A meta-analysis of trials of the effectiveness of topical capsaicin indicated that the treatment afforded greater relief of pain than did placebo to patients with diabetic neuropathy (odds ratio [OR], 2.74; 95% confidence interval [CI], 1.73-4.32) or OA (OR, 4.36; 95% CI, 2.77-6.88). In November 2009, an 8% capsaicin patch (Qutenza, NeurogesX) was approved by the FDA for the treatment of neuropathic pain related to postherpetic neuralgia (PHN).

#### **LIDOCAINE PATCH 5%**

In painful peripheral neuropathic conditions (diabetic neuropathy, PHN), plasticity of the nervous system leads to spontaneous firing in peripheral sensory neurons.<sup>12</sup> Sodium channels have an essential role in impulse conduction in normal neural tissue. Voltage-gated sodium channels have been found to be dramatically upregulated in a model of chronic inflammation, lowering the threshold for cutaneous pain.<sup>13,14</sup>

Lidocaine functions as a sodium channel blocker, reducing ectopic impulses in afferent fibers to relieve

**Table 3. Topical Nonsteroidal Anti-inflammatory Drugs for the Treatment of Musculoskeletal Pain**

Formulation	Active Ingredient
Cream	Benzydamine, diclofenac, ibuprofen, salicylic acid
Drops	Diclofenac, ketorolac, flurbiprofen
Foam	Felbinac, ketoprofen
Gel	Diclofenac, <sup>a</sup> eltenac, felbinac, ibuprofen, indomethacin, ketoprofen, piroxicam, salicylic acid
Ointment	Indomethacin
Patch/plaster	Diclofenac, <sup>b</sup> flurbiprofen
Spray	Indomethacin

<sup>a</sup>FDA-approved for pain associated with osteoarthritis affecting the joints of the hands and knees.

<sup>b</sup>FDA-approved for acute pain associated with minor sprains and strains.

pain.<sup>15</sup> The FDA has approved the lidocaine patch 5% (Lidoderm, Endo Pharmaceuticals) for the relief of pain associated with PHN.<sup>16</sup> The local anesthetic in the patch relieves pain, and the patch itself serves as a mechanical barrier that decreases allodynia.<sup>17,18</sup>

In the mid-1990s, a patch formulation of lidocaine 5% was developed and studied in a randomized, double-blind trial of 35 patients with PHN affecting the torso or upper extremities.<sup>19</sup> The treatment group reported a significantly reduced intensity of pain in comparison with the participants in the vehicle-only cohort from 4 to 12 hours after application. Dosing recommendations for the lidocaine patch 5% include 12-hour daily dosing of up to 3 patches.<sup>20</sup> Follow-up studies have demonstrated safety with the application of 3 to 4 patches for 24 hours at a time.

#### **TOPICAL NONSTEROIDAL ANTI-INFLAMMATORY DRUGS**

NSAIDs are commonly prescribed analgesics that function by reversibly inhibiting COX, an enzyme that catalyzes the synthesis of pain-producing prostaglandins (Table 3). Oral NSAIDs account for nearly one-fourth of all reported adverse events<sup>21</sup>; because peak plasma concentrations are much lower with topical NSAIDs (<10% of levels attained with oral NSAIDs;

range, 0.2%-8.0%), these formulations are associated with a lower risk for systemic adverse effects.

A systematic review of 86 trials of topical NSAIDs involving 10,160 patients found treatment efficacy superior to that of placebo for the relief of acute musculoskeletal pain.<sup>22</sup> In addition, the authors of this review concluded that there was a benefit of NSAID therapy for chronic pain; however, a separate review of studies of NSAID treatment for a duration of longer than 2 weeks found no evidence of efficacy superior to that of placebo for OA pain.<sup>23</sup>

A topical 1.5% diclofenac solution (Pennsaid, Covidien) was approved for the treatment of OA of the knee by the FDA in November 2009. Two randomized controlled trials of 248 and 326 patients with OA of the knee found that topical diclofenac was more efficacious than vehicle only, and that significant differences in physical function favored diclofenac.<sup>24,25</sup> A 12-week randomized controlled comparison of topical and oral diclofenac found that the

2 preparations produced equivalent pain relief.<sup>26</sup>

In 2007, the FDA approved 2 topical formulations of diclofenac for the treatment of pain. Topical diclofenac sodium gel (Voltaren Gel, Endo Pharmaceuticals), applied 4 times per day (2 g for upper extremity joints and 4 g for lower extremity joints), was approved for OA pain amenable to topical treatment, such as pain of the knees or hands. In a randomized, double-blind, vehicle-controlled trial, the topical diclofenac gel demonstrated a statistically significant change in mean pain scores in patients with knee and hand OA (12 and 8 weeks, respectively).<sup>27</sup>

The diclofenac epolamine topical patch 1.3% (Flector Patch, King Pharmaceuticals) was approved for the treatment of acute pain associated with strains and sprains. The diclofenac patch (10×14 cm) is applied to the affected area every 12 hours. A study of patients with acute ankle sprain demonstrated reductions in spontaneous pain lasting from 4 hours to 7 days.<sup>28</sup>

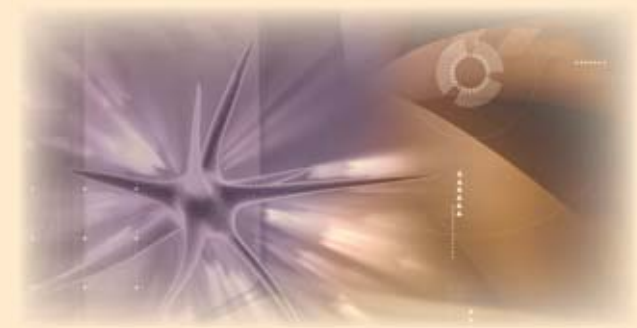
## Commentary

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**S**triking progress has been made over the past decade in the understanding of the pathophysiology of pain, driven in part by advances in the technology of neurochemistry, neuroimaging, and neuropathology. For example, maladaptive neuroplasticity, evidenced by peripheral and central sensitization, has been well established as a contributor to chronic neuropathic pain.<sup>1,2</sup>

Preclinical models have provided important insights into the complex interplay of cellular receptors, neurotransmitters, and inflammatory mediators in the genesis and maintenance of chronic pain. Unfortunately, these insights have not been matched by sufficient improvements in the clinical management of pain. Numerous studies document clinicians' inadequate knowledge of optimal pain management and under-treatment of chronic pain.<sup>3-6</sup>

Compounding the challenge of pain management is the problem that even optimal treatment by experienced pain specialists often yields disappointing results. For example, the leading measure of pain reduction in conditions marked by chronic neuropathic pain, such as diabetic neuropathy or PHN, is the "50/50" rule. This rule recalls that 50% of subjects in a



placebo-controlled clinical trial of a therapeutic agent experience a 50% reduction in pain from baseline.<sup>7</sup> Although most investigators and pharmaceutical manufacturers may be pleased with this result—enough to push a product through the FDA approval process—many clinicians and patients are unsatisfied with the 50/50 standard.<sup>8</sup>

Frustration about the limited efficacy of analgesics is exacerbated by the significant toxicities of these drugs. This is particularly true for oral agents, whose systemic adverse effects frequently limit dosing and effectiveness. For example, tricyclic antidepressants are among the most effective medications for neuropathic pain, as demonstrated by their number needed to treat to achieve a 50% reduction in pain<sup>9</sup>; however, their use is curtailed dramatically by potentially serious anticholinergic toxicities.

These limitations of systemic analgesics create a large unmet need and window of opportunity for topical agents. In addition to their lack of systemic toxicities, topicals relieve patients of the burden of taking



Studies comparing plasma bioavailability with patch application versus that with oral dosing demonstrated minimal systemic bioavailability (0.70%±0.11%), similar to the range reported in other systematic reviews of topical analgesics (range, 0.1%-8.0%),<sup>29</sup> which may be responsible for a reduction in potential risk for systemic end-organ adverse effects seen with the use of oral NSAIDs (ie, gastrointestinal bleeding, cardiac and/or renal impairment).

A recent study examined the use of topical NSAID patch (diclofenac) for the treatment of myofascial trigger points of the shoulder muscles (trapezius). The study found the diclofenac patch to demonstrate greater pain reduction and improvement in cervical range of motion at day 4 and 8 as compared to placebo (menthol patch).<sup>30</sup> The authors suggest the analgesic effect may be related to a non-anti-inflammatory effect of NSAIDs in which the nociceptor response to stimuli is altered.

## COUNTERIRRITANTS AND OTHER OVER-THE-COUNTER AGENTS

A number of OTC preparations are commonly used by patients either singly or in combination with prescription medications. These topical agents include various mixtures of substances, including counterirritants (eg, salicylates and benzyl nicotinate), substances that cause sensations of cold or heat (eg, menthol, camphor), and capsaicin products. In addition, many compounded NSAID and other analgesic topical products are available in a range of concentrations and formulations from specialty companies and pharmacies. Objective clinical data to support the efficacy of these compounded agents are usually lacking. Other potential drawbacks of compounded agents include inconsistent formulation, less regulation by government bodies than is customary for pharmaceutical products, and limited cost coverage by insurance companies and drug plans. Careful

another pill, which often is substantial in conditions such as HIV infection. In this issue, Dr. Stanos reviews the use of topical agents in pain management. Several of these agents, such as the lidocaine patch for PHN, diclofenac gel for OA of the knees and hands, and the diclofenac patch for acute pain associated with strains and sprains, are FDA-approved, based on demonstrated efficacy in double-blind, placebo-controlled trials. Numerous other agents, including clonidine, estrogen, tricyclic antidepressants, and menthol, have been used topically, often in combination preparations supplied by compounding pharmacies. However, reports of their efficacy are predominantly anecdotal.

Extracts of hot chili pepper have been used in folk medicine for analgesia in many societies. A strong rationale exists for the use of topical capsaicin for analgesia, given the central role of the vanilloid receptor in pain processing. Evidence supports the efficacy of topical capsaicin in both diabetic neuropathy and OA. The relatively low potency and limited efficacy of OTC formulations (0.025%-0.075%), discomfort during treatment, and the need for frequent reapplication have limited the utility of capsaicin products. A high-concentration (8%) capsaicin patch (Qutenza, NeurogesX) was recently approved to treat neuropathic pain associated with PHN, based on the results of 2 double-blind, randomized, dose-controlled, multicenter trials.<sup>10</sup>

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selection of patients and guidance by physicians with expertise can help determine the benefit in the use of these agents.

## Conclusion

Overall, evidence-based medicine supports the use of topical analgesics in the treatment of musculoskeletal pain, the pain of OA, and PHN. Recently approved topical NSAIDs (gel and patch formulations) are available for the treatment of pain related to sprains and strains and to OA. In addition, the lidocaine patch 5% is FDA-approved for PHN. More importantly, many of these agents have demonstrated a low level of systemic absorption and therefore entail less risk for systemic toxicity and drug-drug interactions. Clinicians should familiarize themselves with the evolving area of prescription and OTC topical analgesics to enhance their armamentarium for the management of pain.

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