TOPICAL ANALGESICS: A REVIEW OF RECENT CLINICAL TRIALS AND THEIR APPLICATION TO CLINICAL PRACTICE

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ABSTRACT

Topical analgesics can play an important role in the therapeutic armamentarium for pain management. The mechanism of action of topical analgesics is largely within the peripheral nervous system. However, recent clinical investigations suggest that the effect of topical analgesics on peripheral processing of pain transmission may lead to the dampening of central pain mechanisms as well. Thus, indirectly, topical analgesics may act to relieve the discomfort associated with central, as well as peripheral, pain states. This article summarizes recent studies of the use of topical analgesics in varied chronic pain conditions. Much of the recent clinical research on topical analgesics has been conducted using the topical lidocaine patch 5%.


Despite ongoing research and therapeutic advances, most physicians who treat pain recognize that significant challenges remain. Regardless of the source or pathophysiology of the individual pain experience, patients often gain only partial relief. Systemic analgesic regimens, such as nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, opiates, and alpha-adrenergic receptor antagonists, play a significant role. However, these regimens are often limited by tolerability issues associated with their use. Given these limitations, topical analgesics are being investigated as an additional option in the management of chronic pain.

Because topical analgesics exert their pharmacologic activity at the site of pain, they are associated with minimal systemic absorption and provide a targeted means of delivering analgesia, without systemic adverse effects. They can be used regularly and consistently over time with no significant systemic accumulation, minimizing risks of adverse effects and drug-drug interactions more likely to occur with systemic analgesics. This is a distinct advantage, particularly in older patients, who are more likely to be taking systemic medications concomitantly with pain management therapies. In contrast, transdermal systems, such as the fentanyl patch, exert their activity through systemic drug absorption and therefore can be applied at any site on the body to which patches can adhere. The variations between topical and transdermal application systems are summarized in Table 1.

The topical lidocaine patch, the first drug approved by the US Food and Drug Administration (FDA) with an indication for postherpetic neuralgia (PHN), provides an effective treatment option with minimal adverse effects. The topical lidocaine patch 5% is a pliable 10 x 14-cm patch that can be affixed directly to the affected areas. Multiple patches may be
used to treat multiple painful sites, or the patch may be trimmed to fit the shape of different body sites. The current approved dosing is that up to 3 patches may be applied to intact skin for up to 12 hours within a 24-hour period. In a recent pharmacokinetic study in which 4 patches were applied to the back of healthy volunteers for 24 hours for 3 consecutive days, systemic levels were well below those associated with either treatment for cardiac arrhythmias or toxicity; mean maximum concentration (C_max) at steady state with lidocaine patches applied daily was 186 ng/mL, and with lidocaine patches applied twice daily was 225 ng/mL. Areas under the curve were reported at 3550 ng·h/mL (daily dosing) and 4506 ng·h/mL (twice daily dosing).

The efficacy of the lidocaine patch 5% has been demonstrated in 3 randomized vehicle-controlled trials. Moreover, clinical trials show no statistical difference in adverse effects between the lidocaine patch 5% and a vehicle patch (no active drug). The most common adverse event reported with the topical lidocaine patch 5% is transient minor local irritation of the skin. Data from a clinical trial by Rowbotham et al, in which patients were treated with vehicle patches, suggest that patches also provide a mechanical barrier to the stimuli that can cause allodynia in patients with neuropathic pain.

The lidocaine patch is currently FDA approved for use in PHN, based on findings from several randomized, controlled clinical trials. A study conducted at the University of California, San Francisco Clinical Pain Center reported the lidocaine patch significantly reduced pain over a 12-hour period in 35 patients aged 50 years to 90 years with allodynia and a mean duration of PHN of 4 years (Figure 1). The lidocaine patch was superior to observation only (P < .0001) and vehicle patches containing no medication (P = .033). The vehicle patch was also superior to observation only (P = .001), suggesting that placing a barrier on the skin may be useful for patients with allodynia.

Quantitative sensory testing demonstrated a slight reduction in heat sensitivity and a significant reduction in cold sensitivity for patients wearing the lidocaine patch. The highest blood lidocaine levels measured were 0.1 µg/mL (approximately one tenth of the level in

<table>
<thead>
<tr>
<th>Table 1: Topical vs Transdermal Patch Delivery Systems</th>
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<tr>
<td><strong>Topical (Lidocaine Patch 5%)</strong></td>
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<tr>
<td>- Peripheral tissue activity</td>
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<tr>
<td>- Applied directly over painful site</td>
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<tr>
<td>- Insignificant serum levels</td>
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<tr>
<td>- Systemic side effects unlikely</td>
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<tr>
<td><strong>Transdermal (Fentanyl Patch)</strong></td>
</tr>
<tr>
<td>- Systemic activity</td>
</tr>
<tr>
<td>- Applied away from painful site</td>
</tr>
<tr>
<td>- Serum levels necessary for effect</td>
</tr>
<tr>
<td>- Systemic adverse effects</td>
</tr>
</tbody>
</table>

![Figure 1. Change in Pain Intensity with Lidocaine Patch 5% in 35 Patients with Postherpetic Neuralgia](image-url)

VAS = visual analog scale.
* P = .0001 to .021 vs observational only; † P = .016 and P = .041 vs observational only;
‡ P < .001 to P = .038 vs vehicle from 4–12 h.
Adapted with permission from Rowbotham et al. Pain. 1996;65:39-44.
patients taking antiarrhythmic agents). Patches were well tolerated on the allodynic skin, with the most frequent adverse effect being a mild, temporary rash; no systemic adverse effects were reported.

In a study conducted by Galer et al, patients who had previously responded to the lidocaine patch were randomly assigned to receive either a lidocaine patch or a vehicle patch, with the time to exit serving as the primary outcome measure. Subjects were enrolled in a 2-treatment period, vehicle-controlled, cross-over study. Subjects were allowed to exit either treatment period if they experienced inadequate pain relief (i.e., if their pain relief score decreased by 2 or more categories on a 6-item Pain Relief Scale for any 2 consecutive days). The median time to exit with the lidocaine patch phase was greater than the 14-day duration of the study, whereas the vehicle patch exit time was 3.8 days ($P < .001$). At study completion, 25 of the 32 subjects (78.1%) preferred the lidocaine patch treatment phase compared with 3 of the 32 patients (9.4%) preferring the placebo patch phase ($P < .001$). No statistical difference was noted between the active treatment and the placebo treatment regarding adverse effects.

Although the lidocaine patch is indicated only for PHN, several open-label pilot studies have been undertaken to evaluate its safety and efficacy in patients with painful conditions other than PHN. Some of these studies do have limitations; some were prospective, and 3 were multicenter. All of these studies have generated interesting clinical findings that are now under further investigation in randomized, controlled clinical trials.

The first was an open-label study of 16 patients with refractory neuropathic pain: postthoracotomy pain, complex regional pain syndrome, postamputation pain, diabetic neuropathy, meralgia paresthetica, neuroma pain, or postmastectomy pain. The term refractory was used to describe patients who experienced inadequate relief and/or intolerable adverse effects with opiates, antidepressants, anticonvulsants, or antiarrhythmic agents before the study period. Of the 16 patients enrolled in the study, 15 experienced notable pain relief from the patch without any significant adverse effects. These preliminary findings have prompted additional investigation into the potential use of the lidocaine patch in patients with diabetic neuropathy, low back pain, and osteoarthritis.

The patch’s efficacy in pain states of nonperipheral origin was further evaluated in an open-label, prospective study of 56 patients with diabetic neuropathy, with or without allodynia. Up to 4 lidocaine patches were applied daily (18 hours on, 6 hours off) to the areas of maximal peripheral neuropathic pain. Patients were permitted to continue their current analgesic medication, with no change in dosing, throughout the study. Treatment with the lidocaine patch resulted in significant improvements from baseline to week 3 in worst and average pain and pain relief ($P < .0001$); least pain ($P < .001$); and pain right now ($P < .05$), as measured by the Brief Pain Inventory (BPI). The patch was helpful in reducing pain and was also beneficial in allowing patients to sleep more comfortably. Use of the patch resulted in statistically significant reductions in BPI composite scores for pain interference with quality of life, and Beck Depression Inventory scores. Patients with and without allodynia reported benefits.

A multicenter pilot study investigated the use of the lidocaine patch in combination with gabapentin.

Figure 2. Mean Change in BPI Pain Intensity Using Lidocaine Patch 5% with Gabapentin

![Graph showing mean change in BPI pain intensity using lidocaine patch 5% with gabapentin.](image)

BPI = Brief Pain Inventory.

* $P < .0001$; † $P = .0008$; ‡ $P = .0003$.

Scores for pain relief were normalized to a scale of 0–10.

Adapted from Gimbel et al.
for chronic pain. The study was designed as a rational polypharmacy approach to treating conditions perpetuated by both peripheral and central nervous system pain processes by combining agents that target both processes. In this study, 107 patients (PHN, n = 11; diabetic neuralgia, n = 49; low back pain, n = 47) were treated with up to 4 lidocaine patches applied over a 24-hour period for 2 weeks. Addition of the patch to regimens containing gabapentin was found to significantly reduce pain interference with quality of life for most measures in the small group of patients with PHN and for all measures in patients with low back pain or painful diabetic neuralgia (P < .05 for all; Figure 2). The most frequently reported treatment-related adverse events were somnolence, paresthesia, and dermatitis (n = 2).

Additional multicenter pilot studies of the lidocaine patch 5% used as monotherapy in low back pain and osteoarthritis have yielded positive results. In the low back pain study, 131 patients were assigned to 3 groups: acute and subacute pain, short-term chronic pain, and long-term chronic pain. Patients maintained their current analgesic regimens without dosage adjustment; up to 4 lidocaine patches were applied every 24 hours for 2 weeks to the area of maximal peripheral pain. All patients demonstrated a statistically significant reduction in pain with application of the lidocaine patch (Figure 3) and significant improvement in all quality-of-life domains (P < .0001). In osteoarthritis, the lidocaine patch has been studied either as monotherapy (n = 32) or add-on therapy (n = 135) for usual treatments in a 2-week, multicenter, prospective, open-label investigation; outcomes were positive (Figure 4). These studies suggest a peripheral analgesic that is FDA approved for a neuropathic pain state may be efficacious for pain conditions not considered to be related to neuropathic mechanisms. The results of these pilot studies suggest there may be an overlap between nociceptive and neuropathic pain states and have warranted additional investigation in randomized clinical trials currently in progress.
**Eutectic Mixture of Local Anesthetics**

The lidocaine patch produces an analgesic effect without causing a local anesthetic effect; however, the use of EMLA® cream (eutectic mixture of local anesthetics; 2.5% lidocaine/2.5% prilocaine) may result in a clearly demonstrable anesthetic effect on the application site and is particularly effective in acutely painful procedures, such as venipuncture and biopsy. EM LA is not currently commercially available but was originally FDA approved to reduce phlebotomy-associated pain in the pediatric population. Controlled studies using EM LA cream for acute pain associated with venipuncture, intramuscular saline injections, spinal needle insertion, excisional biopsy, or curettage with electrosurgery have demonstrated pain reduction within 60 minutes. Reports of its efficacy for the treatment of PHN have been inconsistent. Some studies have reported positive results with the use of EM LA cream and other topical analgesics in nonneuropathic pain states, such as low back pain, osteoarthritis, chronic myofascial pain, acute soft-tissue injury pain, and postoperative pain (Table 2).

Local anesthetics, such as those found in the lidocaine patch or EM LA, appear to diminish ectopic discharges within the sensory afferents by blocking the expression of mRNA for certain voltage-gated sodium ions in sodium channels so that central nervous system hyperexcitability and any associated augmentation or facilitation of pain is reduced and the pain cycle is interrupted. Application of the lidocaine patch also shields allodynic skin from direct mechanical stimulation, thereby reducing allodynia and hyperalgesic pain. Unlike EM LA cream, which produces a local anesthetic effect by numbing the skin, the lidocaine patch 5% has no effect on dermal sensation and is, therefore, inappropriate for the pretreatment of procedural pain, such as that associated with venipuncture.

**TOPICAL OPIATES**

Evidence from a recent study by Galeotti et al suggests a mechanism of analgesia for menthol, a common ingredient in over-the-counter preparations, may actually be the activation of kappa-opiate receptors. In a more recently published study of topical mor-

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**Table 2. Comparison of 2 Topical Peripheral Analgesics**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Proposed Mechanism of Action</th>
<th>Uses*</th>
<th>Efficacy</th>
<th>Tolerability</th>
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<tbody>
<tr>
<td>EMLA® cream</td>
<td>Inhibits the neuronal membrane ion fluxes</td>
<td>PHN</td>
<td>Effective for acute procedural pain</td>
<td>Anesthetic well tolerated, but compounding may raise issues regarding delivery and systemic toxicities</td>
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<td></td>
<td></td>
<td>Acute pain associated with venipuncture, intramuscular saline injections, spinal needle insertion, excisional biopsy, and curettage with electrosurgery</td>
<td>Conflicting reports in PHN, same results as placebo in controlled PHN trial</td>
<td>Requires occlusive dressing that may cause abrasions</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(+) analgesia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(+) anesthetic effect</td>
<td></td>
</tr>
<tr>
<td>Lidocaine patch 5%</td>
<td>Diminishes ectopic discharges within peripheral sensory afferents</td>
<td>PHN</td>
<td>Significantly better than placebo</td>
<td>Well tolerated, even with extended dosing</td>
</tr>
<tr>
<td></td>
<td>Reduces allodynia, hyperalgesia</td>
<td>Polyneuropathies</td>
<td>Improves pain-related quality-of-life indicators</td>
<td>Minimal erythema reported</td>
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<tr>
<td></td>
<td></td>
<td>Acute soft-tissue injuries</td>
<td>(+) analgesia</td>
<td></td>
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<td></td>
<td></td>
<td>Low back pain</td>
<td>(-) anesthetic effect</td>
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<td></td>
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<td>Postsurgical pain</td>
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<td></td>
<td></td>
<td>Radiographic evidence of osteoarthritis</td>
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* Approved/unapproved uses.
EMLA = eutectic mixture of local anesthetics; PHN = postherpetic neuralgia.
Adapted with permission from Clinical advances in pain management: targeted peripheral analgesics.
Topical anesthetics may be effective in reducing pain and improving function in patients with a variety of neuropathic and nonneuropathic pain states, either when used alone or in combination with systemic agents. Topical opiates may be effective in treating cutaneous cancer-related pain. Although these topical agents are believed to work peripherally, the exact mechanism of their effect must be more clearly defined.

**REFERENCES**