Special Article

Topical Agents for the Management of Musculoskeletal Pain

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Abstract
The recent recognition of the magnitude of cardiovascular risk of both nonselective nonsteroidal anti-inflammatory drugs and COX-2 selective inhibitors, in addition to the persistent concerns about the use of opioids, has brought increased attention to nonsystemic, topical analgesics. These agents have a favorable safety profile and there is increasing evidence indicating their efficacy for a variety of pain disorders. The use of topical analgesics in the treatment of the most prevalent musculoskeletal pain syndromes is described, with a focus on mechanisms for drug delivery and clinical trials data. J Pain Symptom Manage 2007;33:342–355. © *2007 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words
Counterirritants, local anesthetics, musculoskeletal pain, topical analgesics

Introduction

Musculoskeletal pain encompasses a wide spectrum of disorders from simple ligamentous injuries (e.g., ankle sprains) to intra-articular disorders (e.g., osteoarthritis and rheumatoid arthritis), muscle pain syndromes (e.g., myofascial pain and fibromyalgia), and various spine-related neck and low back conditions (e.g., disc degeneration, disc herniation, facet arthropathies, and spondylosis). These disorders are highly prevalent and exact a huge toll in terms of individual quality of life and cost to society. Topical analgesics may provide a safe and effective therapeutic approach for some musculoskeletal pains.

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Epidemiology

Low back pain (LBP) and osteoarthritis are the most common musculoskeletal disorders. LBP creates a significant burden on society due to its high prevalence (17.6% within the U.S. work force)[1] and consequent economic impact (estimated to exceed $50 billion).[2] LBP is the most reported musculoskeletal pain[3] and as many as 84% of adults will experience LBP in their lifetime.[4] When chronic, the complex pathophysiology, often involving both musculoskeletal and neuropathic components, may cause the management of LBP to be notoriously challenging.

Osteoarthritis affects more than 20 million Americans between the ages of 25 years and 75 years[5] and is predicted to become the

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fourth leading cause of disability by the year 2020, worldwide.[3] Over the course of the disease progression, joints undergo degeneration of articular cartilage, osteophyte formation, and subchondral bone sclerosis.[5] Nerve fibers localize densely within bone, and chronic pain is thought to arise from sensitized nociceptors that become exposed due to the erosion of articular cartilage.[6]

Numerous other musculoskeletal pains are prevalent. Ankle sprain alone has an incidence of 52.7 per 10,000, according to a study conducted in the United Kingdom.[7] Bone pain may result from metastatic cancer, orthopedic surgery, and traumatic injuries—potentially affecting many people. Although the majority of these injuries are benign and self-limiting, many patients may experience intermittent or more persistent pain and/or loss of function, both of which adversely affect a patient's general quality of life.[8]

The Biology of Pain: Pathologic vs. Physiologic Pain

In a healthy individual, *pain* may be defined as a complex sensory experience associated with actual or potential tissue damage.[9] Injury in the periphery induces keratinocytes and blood vessels in the dermis to release excitatory factors, such as prostaglandins, substance P (SP), and calcitonin gene-related peptide, which bind to receptors on nociceptive fibers and cause depolarization. These unspecialized, peripheral nerve fibers—C and Aδ polymodal nociceptors—can be stimulated by noxious thermal, chemical, and mechanical inputs. They transmit signals from the periphery via the dorsal horn to higher cerebral structures.[10] Generally, the intensity, localization, and timing of the initiating stimuli are reflected in the level of the neuronal signal.[11] In contrast, with inflamed tissue, an external stimulus is not required to generate signal transduction and transmission to the dorsal horn. This hypersensitivity, seen in diseases like osteoarthritis, can be inhibited by a number of different pharmacologic agents, such as nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and cannabinoids.[11]

Topical Drug Delivery

Controversy regarding postmarketing adverse event (AE) data and a re-examination of coxib and traditional NSAID safety studies ignited intense debate within both popular and medical media starting from the end of 2004 and still ongoing currently.[12] Certainly, the debates brought the issue of pharmacotherapy safety to the forefront, and consequently may have positively affected the prescribing habits of clinicians. Hence, health care providers and the pharmaceutical industry are currently reassessing the potential analgesic and additional safety advantages of one of the oldest routes of delivery, topical application.[13] Potentially, topical agents can achieve a similar efficacy to oral formulations without the associated systemic side effects. Some evidence has shown that topically delivered agents can accumulate to therapeutic concentrations within the local tissues to which they have been applied while maintaining low serum levels. Potentially, lowering the systemic levels of medications reduces the associated risk of organ or tissue toxicity; a more complete list of the benefits and limitations of dermal and transdermal delivery systems[14–32] are listed in Table 1.

Topical agents comprise a growing part of the over-the-counter analgesic market, as well as a smaller evolving niche market of compounding pharmacies in the United States and Europe. Topical medications for pain accounted for 6.1% of the U.S. analgesic market in 2000.[33] Yet, an email survey in 2002 conducted by the American Society of Regional Anesthesia and Pain Medicine indicated that only 27% of clinicians prescribe compounded topical analgesics, despite the perception that $43 \pm 3\%$ of treated patients respond favorably to topical agents, with an average of $47 \pm 3\%$ pain relief and few side effects.[34]

Topical vs. Transdermal

The terms "topical" and "transdermal" are sometimes used interchangeably, although important differences need to be considered. Both delivery methods must transverse the stratum corneum—the major barrier to delivering treatment.[6] Transdermal methods deliver medication through percutaneous absorption, with the goal of achieving

Table 1
Benefits and Limitations of Analgesia by Cutaneous Delivery

Benefits	Limitations
• First pass metabolism and other variables associated with the gastrointestinal tract (such as pH and gastric emptying time) are avoided.[15–17] • Reduced side effects, and the minimization of drug concentration peaks and troughs in the blood.[17,18] • Ease of dose termination in the event of untoward side effects. • Delivery can be sustained and controlled over a prolonged period.[19,20] • Direct access to the target site.[13,14] • Convenient and painless administration.[15,16] • Improved patient acceptance and adherence to therapy.[21–23] • Ease of use may reduce overall health treatment costs.[24] • Provides a viable solution for treatment when oral dosing is not feasible (i.e., in unconscious or nauseated patients.)[17]	• Diffusion across the stratum corneum only occurs for molecules <500 Da.[25] • Topical agents must have both aqueous and lipid solubility.[26] • Both intra- and interindividual variability in the permeability of skin, as well as differences between healthy and diseased skin, causes variable efficacy.[27,28] • Skin enzymes can cause metabolism before cutaneous absorption, reducing the potency of the drug.[29] • Localized skin irritation, such as erythema, can be common.[30–32]

Adapted from Ref. 14.

therapeutic systemic levels of active drug comparable to oral medications. Transdermal pharmacotherapies can be, and often are, administered distal to the site of injury (i.e., sustained release nicotine and clonidine patches and long-acting fentanyl delivery systems), and typically deliver therapy over an extended period of time after a slow onset of action. In contrast, topical agents use cutaneous delivery to specifically target the site of application. The sites of action for topical agents are the soft tissues and peripheral nerves underlying the site of application.[13] Serum levels generally remain relatively low, and consequently, systemic side effects or drug-drug interactions are more unlikely.[13]

The vehicle in which the active ingredient(s) are delivered can affect the skin penetration depth and absorption rate into the epidermis.[13] The penetration of topical modalities is limited by the stratum corneum—a dense layer of flattened keratinocytes that shelters the live epidermis (Fig. 1).[6,14] Once past this relatively impermeable barrier, analgesics may access the unmyelinated C-fibers and encounter the predominant keratinocytes and melanocytes of the epidermal layer. Below the epidermis, the dermal layer also contains nociceptive fibers, along with fibroblasts, connective tissue, blood vessels, hair follicles, and glands. Collectively, the nerves present in the epidermis and dermis are referred to as the cutaneous nociceptors.[6]

Animal models have suggested that the variability in transcutaneous absorption rates between topical agents is likely derived from their ability to negotiate the superficial skin.[35] Ideally, a topical agent will have a low molecular weight (<500 Da)[14] and have both hydrophobic features in order to transverse the stratum corneum and hydrophilic characteristics to penetrate the predominantly aqueous epidermis.[35,36] Furthermore, ex vivo studies of human skin tissue indicate that nonphysiological pHs of the vehicle can reduce the skin penetration of an agent, while occlusion of the skin surface can have a beneficial impact on drug delivery.[36]

Several delivery agents have been engineered to increase the bioavailability of topically delivered analgesics. For example, lecithin organogels are biocompatible jelly-like phases, composed primarily of hydrated phospholipids and organic liquid, which have been used to deliver NSAIDs and other treatments for muscle spasm, cancer, and bruxism.[37] Also, lecithin, pluronic gel, and isopropyl palmitate (called pluronic lecithin organogel-PLO) have been combined to create a colloidal gel used to topically deliver NSAIDs.[38] Additionally, polyethylene glycol and limonene[39] have been used as topical penetration enhancers, increasing the absorption rate of NSAIDs by up to 75-fold.[36] Dating back as far as a century ago, the delivery of topical therapeutics was ameliorated by nonpharmacologic methods, such as iontophoresis.[14] This method uses a low-level current to enhance the permeability of a topically applied agent. Finally, patch preparations and "plasters" incorporate adhesive cloth disposable systems and may offer additional benefit to more traditional topical creams, gels, or solutions, given their potential to deliver medication at a continuous rate.[40]

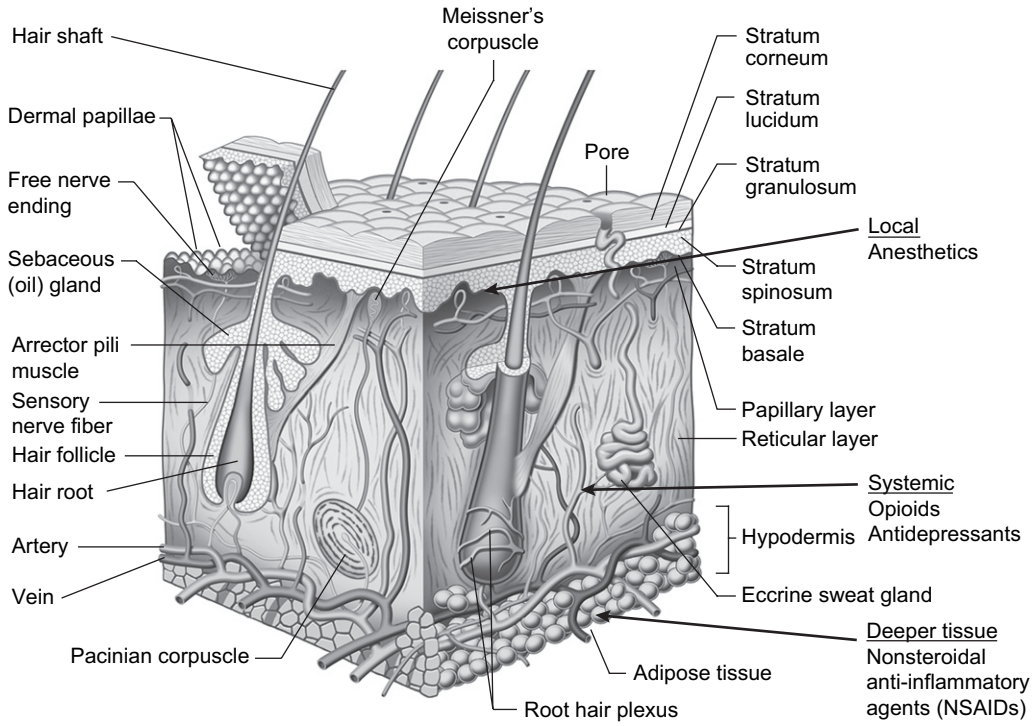

Fig. 1. Anatomy and physiology of the skin with the potential targets or sites of action of selected analgesics. Adapted from Ref. 14.

Although analgesics have been the most thoroughly studied in controlled trials of all types of agents delivered topically, anesthetics and counterirritants can be administered topically as well. In fact, some of the oldest topical medicines may have been counterirritants—mild or moderate noxious agents that suppress the perception of pain.[13] Anesthetic agents have evolved considerably for the treatment of musculoskeletal pain, too. Some examples of commercially available products and pharmacy-compounded agents are listed in Table 2.

Topical Treatment Options: Clinical Trial Evidence

Nonsteroidal Anti-Inflammatory Drugs

Topical NSAIDs have been more widely used and studied in Europe than in the United States. Research primarily conducted in Europe has suggested several potential peripheral mechanisms of analgesic activity, including the inhibition of prostaglandin synthesis, the lipoxygenase pathway, and excitatory amino acids, as well as modulation of G-protein mediated signal transduction.[13] A large variety of topical formulations of NSAIDs are available commercially, including the agents listed in Table 3.[35]

Pharmacokinetic data suggest that topically applied NSAIDs can result in enhanced local

Table 2
Examples of Topical Agents for the Treatment of Musculoskeletal Pain and Prescribing Considerations

	Commercially Available Products	Pharmacy-Compounded Preparations
Examples	Capsaicin 2.5% lidocaine/ 2.5% prilocaine Lidocaine patch 5% Doxepin	Alpha-2 agonists Anticonvulsants Local anesthetics NMDA antagonists NSAIDs Opioids TCAs
Considerations	• Consistency of preparation • Established safety and efficacy (FDA approval)	• Potential variability of preparation • Lack of controlled trials

Table 3
Topical NSAIDs

Formulation	Active Ingredient
Ointment	Indomethacin
Cream	Diclofenac, ibuprofen, benzydamine, salicylic acid
Spray	Indomethacin
Patch/plaster	Diclofenac, flurbiprofen
Gel	Piroxicam, diclofenac, felbinac, ketoprofen, indomethacin, ibuprofen, salicylic acid, eltenac
Drops	Ketorolac, flurbiprofen, suprofen, diclofenac
Foam	Ketoprofen, felbinac

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concentrations without significant toxic systemic levels. Heyneman et al. summarized both single- and multiple-dose NSAID absorption studies.[36] Collectively, the studies indicated that following topical administration of NSAIDs, peak plasma levels were less than 10% of the concentrations obtained from oral dosing (range, 0.2%–8.0%). As the total systemic absorption from topical application is only 3%–5% of the oral route, systemic toxicity from topical NSAIDs are correspondingly rare. Also, the length of time before C_{max} is achieved following topical application ranged from 2.2 to 23 hours, approximately 10 times longer than the time required for the equivalent oral dose. Topical NSAIDs achieve steady-state generally within 2–5 days of repeated application.[36]

Penetration studies also indicate that topically applied NSAIDs reach therapeutic concentrations below the site of application.[36] A two-way crossover design assessed the levels of subcutaneous absorption and muscle absorption of 800 mg of oral ibuprofen or 16 g of 5% ibuprofen gel administered to the thigh.[41] Microdialysis probes inserted 25–30 mm into the muscle found average values of 63.5 ± 90.3 ng h mL^{-1} and 213.4 ± 117.2 ng h mL^{-1} of ibuprofen for the topical and oral routes, respectively. The ibuprofen concentrations in the dermis were 22.5-fold greater when delivered topically; the mean values of ibuprofen in the subcutaneous tissue were 731.2 ± 605.0 ng h mL^{-1} and 176.6 ± 122.9 ng h mL^{-1} for the topical and oral routes, respectively.[41]

Another study of 100 patients considered the ketoprofen concentrations in the intra-articular tissues following a single application of a 30 mg plaster, multiple applications of plasters over a five-day period, or a 50 mg oral dose.[42] The median C_{max} values for topical and oral administration were 568.9 ng/g and 85.7 ng/g in the cartilage, respectively (a 6.8-fold difference). In contrast, the plasma values were 18.7 ng/ml for topically administered ketoprofen and 2,595.3 ng/ml for the oral route. Overall, when applied topically, the ketoprofen levels were 30-fold greater in the cartilage than in the plasma.[42]

Relative to any other topically administered drug, the largest amount of clinical evidence has been accumulated for NSAIDs.[13] A meta-analysis by Moore et al. considered 86 randomized, placebo-controlled trials of NSAIDs for treatment of pain conditions; 10,160 patients were included.[43] The effectiveness measure nearest to one week following the start of treatment for acute conditions, such as soft tissue trauma, sprains, and strains, and the two-week measure for chronic pain conditions, such as osteoarthritis and tendonitis, were used in the meta-analysis. Overall, the number needed to treat (NNT) was 3.9 for acute pain conditions, more specifically: 2.6 for ketoprofen, 3.0 for felbinac, 3.5 for ibuprofen, and 4.2 for piroxicam (benzydamine and indomethacin had efficacies comparable to placebo). For chronic pain conditions, the NNT was 3.1 and ranged between 2.7 and 3.8. Furthermore, for all pain conditions studied, topical NSAIDs rarely induced local skin reactions (3.6%) and more rarely had any adverse systemic effects (<0.5%).[43] Similarly, a smaller meta-analysis of 26 double-blind, placebo-controlled trials by Mason et al., found that topical NSAID treatment was safe and effective for acute pain, following one week of application.[44]

Another meta-analysis of randomized, controlled trials by Lin et al. assessed the efficacy of topical NSAIDs relative to placebo or oral formulations for the treatment of osteoarthritis.[45] Compared to placebo, a positive treatment effect was observed only during Weeks 1 and 2 of treatment; reported pooled treatment effect sizes for pain relief were 0.41 (95% confidence interval [CI], 0.16–0.66) and 0.40 (95% CI, 0.15–0.65) for each week, respectively. In contrast, even in the first week, topical NSAIDs were found inferior to oral versions for improving pain and function, and topical agents induced more local side

effects as well. The authors concluded that no trial evidence has supported the benefit of NSAIDs over placebo for treating osteoarthritis after two weeks of application, and even suggested that the current practice guidelines on osteoarthritis that advocate the use of topical NSAIDs[46–48] should be revised.[45] However, two recent, randomized, controlled trials of a topical diclofenac solution for the treatment of pain from knee osteoarthritis reported benefit following four and 12 weeks of application.[49,50] Measured by Western Ontario and McMaster Universities Osteoarthritis Index scores, the study group had a 42.9% decrease in pain relative to baseline following four weeks, and a 45.7% decrease after 12 weeks, compared to a respective 26.9% and 33.3% decrease in pain by the vehicle-control groups. Measurements of physical function, stiffness, and pain on walking indicated similar benefit of the topical diclofenac over placebo in both studies. Likely due to the skin penetration enhancer, dimethyl sulfoxide, 30 of the 84 patients in the four-week study group and 68 of 164 patients in the 12-week study group reported skin irritation (typically dryness), leading to the discontinuation of five patients in each of the treatment groups.[49,50]

Various novel NSAID patches or plasters have been developed, conferring a more constant delivery of a standardized dose of analgesic (although individual skin variability affects the actual amount absorbed). A study by Galer et al. used a multicenter, randomized, parallel design to assess the efficacy of a topical diclofenac patch for treatment of pain from sports-related soft tissue injuries, such as sprains, strains, or contusions.[51] A diclofenac epolamine 1.3% or placebo patch was applied twice daily on 222 patients for two weeks. The study group achieved statistically significant pain intensity differences from placebo during clinic visits on Day 3 ($P = 0.036$) and Day 14 ($P \leq 0.044$) following treatment initiation, but not on Day 7. Forty percent of participants given placebo reported AEs, while 34% of study group patients reported side effects.[51] A similar study comparing a diclofenac patch to placebo for patients with traumatic blunt soft tissue injury found that the analgesic conferred a significantly beneficial effect over placebo ($P < 0.0001$), as measured by tenderness produced by pressure.[52] Also, the time required to reach pain resolution at the site of injury was significantly shorter for the study group ($P < 0.0001$). The study and control groups experienced a similar frequency of AEs, most commonly local cutaneous reactions.[52] Finally, a placebo-controlled study of patients with pain due to ankle sprain assessed the analgesia achieved by the application of a 100 mg topical ketoprofen patch over a two-week period.[8] There were significantly fewer observations of spontaneous pain for the study group compared to the control group during all visits (Days 3–4, Day 7 ± 1, and Day 14 ± 2). Most notably, there was a 49.9 ± 20.2 mm (−73%) decrease in pain from baseline at Day 7 ± 1 for patients given the ketoprofen patch, compared to a 37.6 ± 24.3 mm (−57%) decrease among the patients given a placebo patch. The intergroup difference in pain relief was significant ($P = 0.0007$), but the difference in AEs was not. Thirty-one percent of the study group and 24% of the control group experienced AEs.[8]

Nitroglycerin (NTG)

Topically applied NTG has been studied for localized treatment of musculoskeletal pain. NTG may be converted to an anti-inflammatory agent—nitric oxide (NO)—that is released endogenously by activated macrophages.[53] Treatment-generated NO may modulate the inflammatory process, as well as produce analgesia through mechanisms directed at nociceptors, similar to the activity of cholinergic drugs.[53] For example, acetylcholine is a cholinergic agent that can induce analgesia by stimulating the release of NO, leading to an elevation of 3′5′ cyclic guanidine monophosphate concentration in nociceptors.

A randomized, double-blind, placebo-controlled trial evaluated a 5 mg NTG patch for relief of shoulder pain when applied daily over a three-day period. While no change in pain intensity was observed in the control group, after 48 hours the NTG group reported a significant decrease in pain intensity from baseline, on a 0–10 analog scale (2 ± 0.3; $P < 0.003$). Two of 10 patients in the treatment group experienced headache.[53] Paoloni et al. examined the use of topical NO for the treatment of chronic extensor tendinosis in a randomized, placebo-controlled trial. Compared to the placebo group, patients in the NO

group reported significantly reduced elbow pain while active at two weeks ($P < 0.05$), reduced extensor tenderness at six and 12 weeks ($P < 0.05$), and an increase in wrist extensor strength at 24 weeks ($P < 0.05$).[54]

Local Anesthetics

Topical anesthetics likely provide pain relief by reducing ectopic discharges from superficial somatic nerves.[13] A number of mechanisms that contribute to peripheral sensitization may be decreased by topical anesthetics.[55] Experiments that have used complete Freund's adjuvant to induce inflammation have shown a correlation between the upregulation of tetrodotoxin-resistant, voltage-gated sodium channels and an inflammatory state.[56,57] As sodium channels play a fundamental role in the excitability of neurons, alterations in their expression levels or function can lead to the neuronal hyperexcitability observed in many types of chronic pain conditions.[58] Additionally, pharmacotherapies which block sodium channels have been shown to provide effective analgesia for the management of some types of chronic pain.[58]

The lidocaine patch 5% likely reduces the ectopic transmission of pain signals to the dorsal horn of the spinal cord by inhibiting abnormal sodium channels in dermal nociceptors residing in the area of the localized pain.[59] The current basic mechanistic understanding of osteoarthritis suggests that pain is the result of a chronic inflammatory state in intra-articular joints. Blocking upregulated sodium channels in inflamed tissues from inducing aberrant transmissions may provide analgesia.[60] A two-week pilot study tested the ability of the lidocaine patch 5% to provide analgesia for 20 patients with knee osteoarthritis. At the completion of the trial, statistically significant improvements were observed for all Western Ontario and McMaster Universities subscale scores of pain, as well as the composite index ($P < 0.01$). Also, 84% of the patients reported the achievement of moderate-to-complete global pain relief, while 90% of the patients had no observed erythema. However, due to the lack of controls and small sample size, further randomized, controlled trials were recommended.[59]

Another open-label study used the Neuropathic Pain Scale to assess the analgesia achieved by the application of the lidocaine patch 5% for 100 patients with knee osteoarthritis.[61] All four composite measures were significantly improved ($P < 0.001$) following two weeks of treatment. No treatment-related AEs were reported in the group given lidocaine patch 5% monotherapy.[61]

Finally, an open-label study of 137 patients with knee osteoarthritis considered the use of the lidocaine patch 5% as add-on therapy to a stable analgesic regimen (e.g., acetaminophen, NSAIDs, COX-2 inhibitors, tramadol, opioids).[62] Following two weeks of treatment once daily with the lidocaine patch 5%, average pain intensity scores decreased by 29% (4.2 ± 2.2) compared to baseline scores (5.9 ± 1.5; $P < 0.001$). Also, Brief Pain Inventory measurements of pain interference on quality of life decreased from 37.2 ± 13.7 at baseline to 23.5 ± 15.1 at Week 2 ($P < 0.001$). Fourteen patients experienced treatment-related side effects that included headache ($n = 4$), dermatitis ($n = 3$), and taste disturbance ($n = 2$). Although there were no serious AEs reported, five patients discontinued treatment.[62]

Open-label trial evidence has suggested that the lidocaine patch 5% may be beneficial for patients experiencing LBP as well. A six-week, nonrandomized trial conducted by Gimbel et al. considered the patch's effectiveness for acute/subacute (<3 months, $n = 21$), short-term chronic (3–12 months, $n = 33$), or long-term chronic (>12 months, $n = 77$) LBP.[63] Compared to baseline, significant reductions in pain intensity were reported by patients within all three categories, at both two and six weeks ($P \leq 0.007$). Overall, 25 patients reported treatment-related AEs; 20 of those AEs were mild-to-moderate in severity.[63] A similarly designed study of 71 patients also found significant improvement measured by the Neuropathic Pain Scale composite at Weeks 2 and 6 ($P < 0.001$).[1] Eleven patients reported dermal side effects, while five patients reported systemic side effects (dizziness and nausea).[1]

Topical Counterirritants

Counterirritants, such as capsaicin, camphor, menthol, and garlic, are a category of analgesics that excite and subsequently desensitize nociceptive sensory neurons.[64] Although many of the members of this group have had a long history of common medical use, it was

not until recently that their molecular mechanisms of action were elucidated. All of these pungent plant derivatives act on the recently elucidated transient receptor potential (TRP) superfamily, a group of structurally similar ion channels, such as TRPV1 (also called vanilloid receptor subtype 1), TRPV3, TRPM8, and TRPA1.[65] The superfamily is activated by capsaicin, camphor, menthol, and garlic, respectively[64] (Fig. 2). These thermosensitive receptors detect a wide range of temperatures ranging from noxious heat to extreme cold, as well as other stimuli, including acidic pH, lipids, changes in extracellular osmolarity and/or pressure, and depletion of intracellular Ca^{2+} stores (Fig. 3).[6,66] These proteins are expressed in primary sensory neurons as well as other tissues. Upon the activation of TRP receptors, the release of calcitonin gene-related peptide, SP, and other inflammatory neurotransmitters are induced; hence, producing local irritation and inflammation.[67] This can lead to two types of desensitization: 1) acute or "pharmacologic" desensitization characterized by a diminished response during a constant agonist application, and 2) over a longer period, tachyphylaxis or "functional" desensitization characterized by a reduction in response after many stimulations.[64]

As early as the 19th century, the selective effects of capsaicin on sensory nerve fibers were recognized.[6] The spicy ingredient in chili peppers has been used to relieve neuropathic pain, uremic pruritus, and bladder overactivity, as well as for providing analgesia.[68] Currently, nonprescription creams, lotions, and patches containing 0.025%–0.075% capsaicin by weight for treatment of musculoskeletal and neuropathic pains are available.[69] When applied topically, capsaicin has a biphasic pharmacologic effect on sensory neurons. The first phase is characterized by the excitation and activation of TRPV1, while the second phase produces analgesia from the depletion of pronociceptive transmitters, including SP.[70] There is significant pain, burning, itching, and cutaneous vasodilatation experienced upon initial application due to excitation and sensitization of cutaneous C- and A-fiber nociceptors; however, the repeated application of capsaicin leads to the persistent desensitization of nociceptors during Phase 2.[71]

A systematic review of topical capsaicin for the relief of musculoskeletal pain pooled the results of three double-blind, placebo-controlled trials, summing up to 368 patients in total.[72] After four weeks of treatment with capsaicin 0.025% or plaster, the mean response rate (the percentage of patients with at least 50% pain relief) was 38% (range, 34%–42%), while the placebo response rate was 25% (range, 17%–37%). The NNT was 8.1 and approximately one-third of the patients experienced local, treatment-related AEs.[72] An older meta-analysis also reported that capsaicin cream provided better pain relief for osteoarthritis than placebo (odds ratio = 4.36; 95% CI = 2.77-6.88).[73] However, products with low concentrations of capsaicin require multiple applications to provoke the desensitization of nerves,[68] and often contaminate the patient's personal surroundings (bed, contact lenses, etc.).[6] Those hindrances, along with the side effect of burning and pain upon application, reduce patient adherence and concomitantly, the efficacy of the treatment.[6,68] Yet due to the reversible desensitization of nociceptive C-fibers and lack of

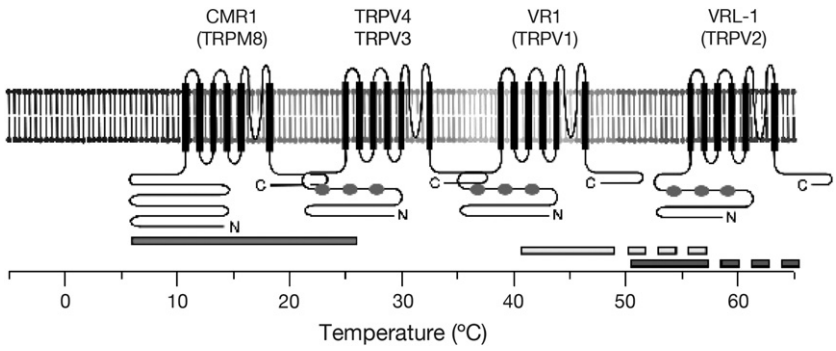

Fig. 2. TRP family receptors and their thermosensitivity (adapted from Ref. 69).

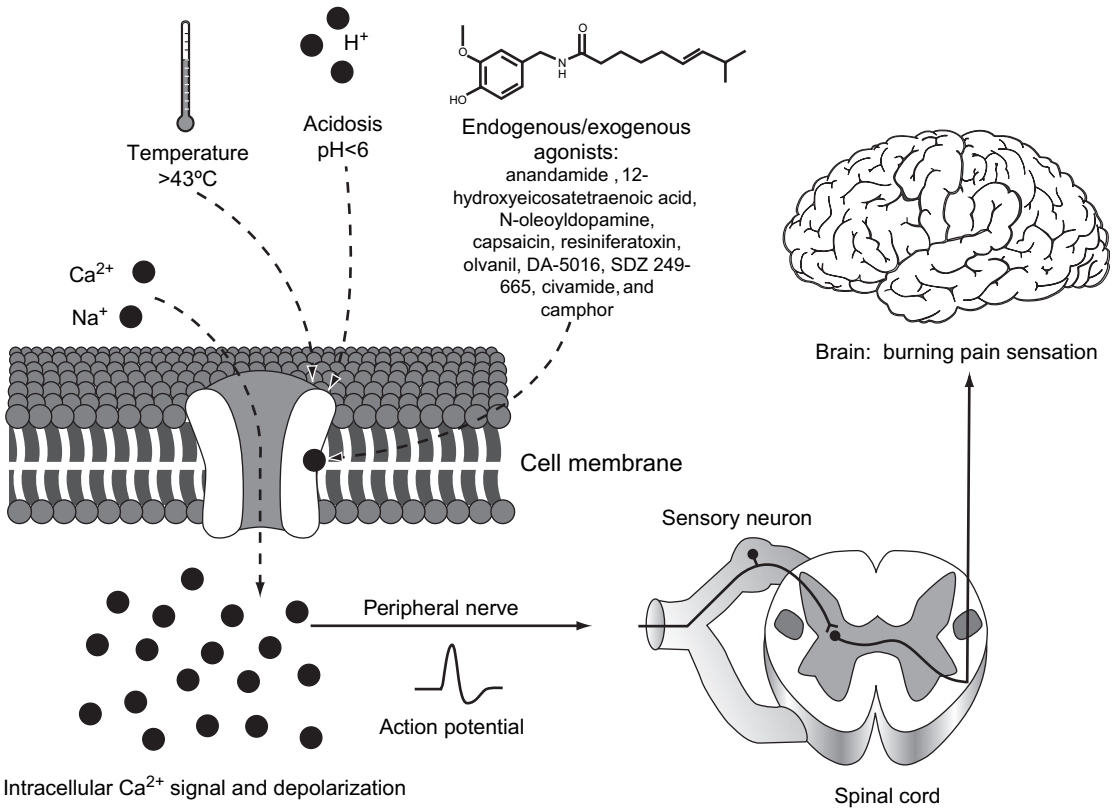

Fig. 3. Acute activation of the TRPV1 receptor leads to local intracellular calcium signals and the sensation of heat or burning pain. TRPV-transient receptor potential vanilloid. Reprinted with permission from Ref. 6.

systemic side effects, topical capsaicin was recommended by the European League Against Rheumatism (EULAR) in 2003 for the treatment of knee osteoarthritis.[47]

The potent analog of capsaicin, resiniferatoxin (RTX), is an extract from the resin of the *Euphorbia* cactus.[6] RTX induces a slower depolarization and influx of Ca^{2+} into C-fibers[74] and induces less pain upon application.[68] Despite some promising clinical trial results for treating detrusor hyperreflexia and bladder hyperreflexia,[68] RTX has not been approved for use within the United States.

Camphor is derived from the wood of the camphor laurel tree (*Cinnamomum camphora*) and historically, the sweet-smelling compound has had many medicinal uses, including as a decongestant, cough suppressant, and antipruritic agent.[64] Over-the-counter camphor-containing balms have also been used to provide analgesia. Recent research has implicated three receptors in camphor's mechanism of action, TRPV3, the capsaicin receptor—TRPV1, and the garlic receptor—TRPA1.[64]

The analgesic capacity of the compounds in garlic (allicin and diallyl disulfide) have not been well-explored, although they have been often used to treat hypertension, high blood cholesterol, and thrombosis.[67] Allicin and diallyl disulfide both bear a structural resemblance to the components in mustard plants which induce pain and inflammation—isothiocyanates. Likewise, recent research has indicated that mustard and garlic depolarize sensory neurons specifically through activation of the TRPA1 receptor to elicit inflammatory pain.[67,75]

In contrast, menthol—the component that confers mint smell and flavor to the *Mentha* species—is often included in eutectic formulations of local anesthetic agents.[76] Anecdotally, menthol induces tingling and cooling sensations when applied topically. Menthol generates analgesia through its Ca^{2+} channel blocking activity. In addition to binding TRPM8,[65,69] menthol binds κ-opioid receptors, and possibly engenders analgesia through both mechanisms.[76] Animal studies have

demonstrated that menthol can confer analgesia following both noxious thermal and chemical stimuli.[76] Furthermore, similar to other terpenes, menthol is an effective topical permeation enhancer for water-soluble drugs, such as the antidepressant, imipramine.[77]

Another type of counterirritant is topical rubefacients containing salicylates. Although, it has been postulated that analgesia is conferred by a mode different than that of NSAIDs, as yet, salicylates have an unidentified mechanism of action.[78] Despite this, salicylates are often found in many topical preparations. Randomized, clinical trial data describing the efficacy of salicylates for pain relief have been systematically reviewed by Mason et al.[78] Only three double-blind, placebo-controlled trials have been published that consider the use of topical salicylates for the treatment of acute musculoskeletal pain. The study groups exhibited significantly better pain reductions than placebo (relative benefit = 3.6, 95% CI, 2.4−5.6; NNT = 2.1, range, 1.7−2.8). Although the long-term efficacy data and the reporting of AEs were poor for chronic musculoskeletal pain, the information from six double blind, placebo-controlled trials indicated a relative benefit over control of 1.5 (range, 1.3−1.9; NNT 5.3, range, 3.6−10.2).[78]

Other counterirritants often found in over-the-counter analgesic preparations include marsh tea, peppermint oil, and poison ivy. A randomized, controlled trial explored the use of a topical homeopathic gel that included the ingredients, *Symphytum officinale* (comfrey), *Rhus toxicodendron* (poison ivy), and *Ledum palustre* (marsh tea) for the management of knee osteoarthritis pain.[79] The 86 patients that completed the trial in the homeopathy group reported a reduction in pain of 16.5 mm by visual analogue scale, compared to an 8.1 mm pain reduction by the 86 patients in the piroxicam group. The difference between the treatment groups was 8.4 mm (95% CI, 0.8−15.9). Twelve patients within the homeopathy group and 16 patients within the NSAID group experienced an AE, causing five and nine patients, respectively, to withdraw from the study.[79]

Other Agents

Heat wraps are a popular therapy for back pain, and the treatment has been recommended by practice guidelines in both the United States and the United Kingdom for management of acute LBP.[80] A randomized, single-blind clinical trial compared a group of 113 patients treated with a 40°C heat wrap for 8 hours per day to patients given one of the two most common oral, nonprescription drugs in the United States: acetaminophen (4,000 mg/day; $n = 113$) or ibuprofen (1,200 mg/day; $n = 106$).[80] Significantly better mean pain relief was obtained by the heat-wrap therapy group on Day 1, and then again by Days 3−4 (extended mean pain relief = 2.61, compared to 1.68 for ibuprofen, $P = 0.0001$ and 1.95 for acetaminophen, $P = 0.0009$). Furthermore, lateral trunk mobility and disability significantly improved for the heat-wrap therapy group relative to the comparators.[80] Another randomized, controlled trial also found better functional outcomes for patients treated with low-level heat wraps than for the control group.[81] Combining heat wraps with directional, preference-based exercise further reduced disability scores after a week of treatment to nearly half those of either therapy alone.[81]

For thousands of years, medicinal leeches have been used for the treatment of various diseases, and more recently have offered a novel option for the treatment of venous congestion in plastic surgery[82,83] and in chronic musculoskeletal disorders.[84] Leeches, *Hirudo medicinalis*, purportedly have biologically active, anti-inflammatory and anticoagulant mediators within their saliva.[85] In a recent study, 24 patients with osteoarthritis of the knee were locally administered four to six leeches for approximately 70 minutes, and compared with 27 patients treated with a 28-day regimen of topical diclofenac gel (300 mg, twice a day).[84] The mean reduction in pain observed within the leech therapy group was 53.5 ± 13.7 at baseline and 19.3 ± 12.2 at Day 7. Compared with the diclofenac group (51.5 ± 16.8 at baseline and 42.4 ± 19.27 at Day 7), there was a significant between-group difference (−23.9; CI, −32.8 to −15.1; $P < 0.001$). However, 17 of the 24 patients administered leeches experienced local itching, while none of the patients given topical NSAIDs reported pruritus.[84]

Although the evidence-based literature indicates that systemic opioids are effective at

providing analgesia for a variety of painful conditions, topical preparations of opioids have not been well-explored, with the exception of some studies of relief from painful skin ulcers.[86,87] Potentially, the local application of opioids could minimize systemic side effects, such as sedation, respiratory depression, and nausea.[88] A 2005 study followed three patients administered topical morphine in PLO gel for relief of chronic arthritis pain.[89] A satisfactory level of pain control was reported, although likely due to the systemic absorption of the opioid, as indicated by urinalysis results.[89] Furthermore, an animal study indicated potential synergy between topical lidocaine and topical opioids.[88] Possibly, combining different drug classes to create a topical preparation that targets multiple peripheral sites may enhance the analgesia obtained. Preliminary results in an animal model suggest that combining topical morphine with topical cannabinoid may improve the antinociceptive effects that are achieved, while reducing central nervous system exposure to opioid.[90] Other precursory results suggest that topical cannabinoid preparations may buffer emerging pain signals at peripheral sites via CB_1 receptors, while avoiding the dysphoric side effects and abuse potential of central-acting cannabinoid agents.[91] This promising research could lead to the development of another agent in the armamentarium of topical analgesics.

Conclusion

Recent research has significantly evolved our understanding of the diverse mechanisms by which topical preparations induce analgesia. Many topical agents have significantly less systemic AEs than oral pharmacotherapies, while providing effective pain relief. In particular, topical NSAIDs have demonstrated benefit for treating pain from acute and chronic musculoskeletal conditions, while topical lidocaine has provided effective peripheral analgesia for localized pain associated with joint and low back ailments. Also, clinicians should become familiar with over-the-counter topical preparations for analgesia, as they are often used and can contain ingredients with analgesic mechanisms supported by evidence in the literature. Furthermore, maintaining an understanding of topical delivery systems, as new ones are developed and others optimized, will be important to providing continuing best practice for patients requiring diverse, multimodal options for managing their pain.

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