Making Sense of Topical Pain Relief Options: Comparing Topical Analgesics in Efficacy and Safety

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Context: In patients with musculoskeletal (MSK) conditions, pain is the leading contributor to disability and significantly limits mobility and dexterity. This narrative review describes the efficacy and safety of topical analgesics in common use today.

Evidence Acquisition: Secondary literature gained via a literature search using PubMed.gov and the Cochrane library were used.

Study Design: Recent literature (2000-2023) on several major classes of topical analgesics and topical delivery systems were reviewed to provide strength of recommendation taxonomy (SORT) levels. A total of 86 articles were reviewed.

Level of Evidence: Level 2.

Results: Topical nonsteroidal anti-inflammatory drugs (NSAIDs) and cabbage leaf wraps (CLW) appear to be best suited for multiple types of acute MSK pain, and topical nitroglycerin is helpful when used specifically for rotator cuff pain in patients seeking relief while performing activities of daily living and willing to treat for long periods of time. For compounded topical formulations, it may be better to offer single agent creams based on patient preferences. Little data support the use of cryotherapy. Traumeel could be a promising natural analgesic that compares with diclofenac. Topical lidocaine appears best suited for postherpetic neuropathic pain. O24 is a reasonable alternative with a low risk profile to treat pain in patients with fibromyalgia syndrome.

Conclusion: Choice of topical agents should be guided by current evidence accounting for type of pain, medication side effects, patient comorbidities, as well as patient preference, convenience, and cost.

Strength-of-Recommendation Taxonomy (SORT): Of the topical analgesics and modalities reviewed, SORT level A evidence was found for topical NSAID use in decreasing MSK pain, topical lidocaine for postherpetic neuralgia, and nitroglycerin patches for treating rotator cuff pain if used for prolonged periods of time. Alternative treatments such as CLW and Traumeel show promising results (SORT level B).

Keywords: complementary medicine; compounded topical agents; cryotherapy; lidocaine; nitroglycerin; nonsteroidal anti-inflammatory drugs; topical analgesic

Approximately 1.7 billion people suffer from musculoskeletal (MSK) conditions worldwide. MSK pain is the leading contributor to disability, significantly limiting mobility and dexterity.[15] The global pain management market, including oral formulations of acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) and topical pain analgesics, is valued at US$70 to US$80 billion per year and continues to grow.[56] Topical analgesic use dates back to antiquity and provides targeted treatment at the site of pain generation and injury.[56] Although oral medications are commonly used as

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The authors report no potential conflicts of interest in the development and publication of this article.
DOI: 10.1177/19417381241280593

initial therapy, many patients could be treated with topical analgesics with potentially less risk of side effects. This narrative review appraises recent literature on several major classes of topical analgesics to provide SORT levels.[22]

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

NSAIDs are used commonly to treat both acute and chronic MSK conditions in athletes.[52] Oral formulations of NSAIDs have been recommended for osteoarthritis (OA) pain, soft tissue injuries, pain associated with rheumatologic diseases, and other medical conditions associated with MSK pain.[52,86] NSAIDs exert their effect through the inhibition of cyclooxygenase 1 (COX1) and cyclooxygenase 2 (COX2), which account for the majority of their anti-inflammatory and analgesic properties.[52] Although oral NSAIDs are effective analgesics, and are available over-the-counter (OTC), they are associated with multiple safety concerns, including an increased risk of gastrointestinal toxicity, renal toxicity, and cardiovascular events.[52]

Systemic absorption occurs with both oral and topical NSAIDs, but topical NSAID formulations produce only 2% to 8% of the peak serum concentration of oral NSAIDs.[52] Because of this, topical NSAIDs are associated with a lower risk of serious adverse effects.[52,71,76,86] Whereas topical NSAIDs are considered safe overall, they are not completely benign as adverse skin effects such as localized rash, itching, burning, skin redness, and dryness can occur up to 40% of the time.[38,86] In addition, they are relatively contraindicated in patients with rash-affected areas and contraindicated in patients with allergies to NSAIDs.[72] However, given their beneficial systemic safety profile and proven pain relieving effects, topical NSAIDs are an attractive first-line therapy for painful MSK conditions in athletes and are strongly recommended for patients aged 75 years and older.[66]

Topical NSAIDs exist in multiple formulations, including gels, sprays, creams, and patches.[19] They are applied directly to the affected area and must penetrate both the epidermis and dermis to obtain their desired effect on soft tissue/connective tissue.[52,76] Sites of the body with a thicker layer of epidermis, ie, palm of hands or soles of feet, are more difficult to penetrate as compared with the skin of the appendages or trunk, which have a thinner epidermis and larger body surface area.[52] For relief of joint symptoms, topical anti-inflammatories can either penetrate directly through the articular lining or enter the dermal capillaries and be deposited into the synovial fluid from the blood.[52] When determining rate of diffusion through the skin, significant variability exists as multiple factors–including sex, age, hydration status, skin temperature, obesity, and site of application–affect skin penetration.[52] For example, the physical properties of ketoprofen allow for excellent transdermal delivery and local concentrations are higher than plasma concentration.[4] Topical formulations of ibuprofen and celecoxib successfully introduced these NSAIDs into synovial fluid at concentrations similar to those observed in circulation.[4]

A Cochrane systematic review of randomized, double-blind, active, or placebo-controlled trials in adults with acute pain resulting from strains, sprains, and sports/overuse injuries compared topical NSAIDs in the form of a gel, spray, or cream with a topical placebo.[19] The review found that topical NSAIDs provide good levels of pain relief for acute MSK conditions, such as OA, sprains, and strains,[19,38,45] compared with topical placebo, with gel formulations of diclofenac, ibuprofen, and ketoprofen being the most effective, especially during short-term (2 week) use.[19,45,66] Previous systematic reviews have shown topical NSAIDs to be more effective than placebo and equally effective as oral NSAIDS for reducing pain and improving function in patients with OA but not other chronic painful conditions.[17,61,77,86] Topical diclofenac, specifically patches, and topical ketoprofen were most effective for pain relief.[71,81,86] However, for back and neck pain, diclofenac alone showed efficacy comparable with that of a placebo, suggesting it is a poor choice for treating pain in these areas.[63]

Still, for athletes in general, topical NSAIDs may provide pain relief for numerous acute and chronic MSK conditions. Nudo et al[59] showed topical medications were significantly better at reducing pain compared with oral medications and placebo in injured athletes. Guidelines in Asia recently changed to recommend topical NSAIDs as first-line early treatment of OA of the hand and knee.[66,72,84] Systematic reviews have shown comparable efficacy between topical and oral NSAIDs.[4] Their superior side effect profile as compared with oral NSAIDs and their ease of use makes them an ideal first-line option for treating pain in this patient population. Sports medicine providers who care for athletes should be aware of these topical options and be familiar with their use.

A total of 21 articles, including 2 Cochrane Reviews, 5 meta-analysis, and 1 multicenter randomized controlled trial [RCT], on NSAIDs were reviewed. Based on the available evidence, their strength-of-recommendation taxonomy (SORT) level is A.

LIDOCAINE

Lidocaine is an amide anesthetic and an antiarrhythmic that functions systemically or locally depending on the route of delivery and formulation.[31] It was first synthesized in the 1940s and is used commonly in the injectable form to provide local analgesia. Anesthetic properties result from disruption of pain sensory transduction via blockage of voltage-gated sodium channels in sensory neurons. Topical preparations of lidocaine are available in gel, cream, spray, or patch, as a prescription or OTC, and are commonly used to manage acute and chronic pain.

Local absorption of lidocaine depends on the area of application, skin thickness, drug concentration, and local soft tissue vascularity. For example, mucosal surfaces absorb topical lidocaine at a higher rate.[7] The maximum penetration of topical lidocaine ranges from 8 to 10 mm.[79] Risk of systemic exposure of topical lidocaine is low but is increased by compounding

doses, overuse or abuse, use on acutely inflamed or damaged skin, or occluding the site of application. Side effects include dizziness, drowsiness, muscle twitch, seizure, respiratory distress, loss of consciousness, and cardiac arrest.[7]

Topical lidocaine is approved by the United States (US) Food and Drug Administration (FDA) for treatment of postherpetic neuralgia as multiple studies have demonstrated the effectiveness of it use.[8,9,24,48,68,69] There is limited evidence specific to topical lidocaine use in athletes, although its safety profile and ease of application make it an attractive option. There is some evidence supporting its use in lower back pain,[37] knee OA,[41] and shoulder impingement.[65] Anecdotally, topical lidocaine in athletes can be used for a variety of acute and subacute pathologies including muscle, joint, and nerve pain; however, data on its efficacy in such uses are limited. It is important to discuss appropriate use to avoid overdose and to monitor for potential side effects.

A total of 11 articles on lidocaine were reviewed. Based on the available evidence, the SORT level for use of topical lidocaine for postherpetic neuralgia is A, and for lower back, knee OA, and shoulder impingement pain, the level is C.

NITROGLYCERIN

Nitroglycerin is a nitrate that increases nitric oxide (NO) in vascular smooth muscle, increasing cyclic guanosine monophosphate(cGMP), thereby inducing smooth muscle relaxation and increasing blood flow. NO has also demonstrated a role in fibroblast proliferation, collagen synthesis, and contraction of collagen lattices.[26] A high output isoform of NO, is involved in macrophage activity and is upregulated in tendinopathy.[26,50] These components are critical in the healing process specifically related to tendinopathies. As NO increases these components, logical deduction would support NO accelerating the healing process and therefore reducing the time of inflammation and injury related pain.

A systematic review performed by Challoumas et al[13] provides good evidence for the effectiveness of using nitroglycerin patches for 12 to 24 weeks to treat tendinopathies. At 12 weeks, patients treated with nitroglycerin patches demonstrated greater rotator cuff force, less pain at rest, and less pain at night compared with the placebo group. At 24 weeks, patients treated with nitroglycerin patches had less pain at rest, at night, with range of motion, and with activity compared with the placebo group. In addition, they had a significantly higher chance of being asymptomatic with activities of daily living. Patients in the nitroglycerin group continued to demonstrate greater rotator cuff force, had greater range of motion, and fewer signs of impingement. This systematic review did not show a significant difference in improvement if the nitroglycerin patches were used for <8 weeks.[13]

A meta-analysis looked at the use of topical nitroglycerin in adults with a diagnosed tendinopathy and the presence of acute, subacute, or chronic pain.[27] Pain relief in the acute phase with topical nitroglycerin versus corticosteroid injections (control group) did not show a significant difference, but the results favored the corticosteroids. When topical nitroglycerin was compared with a placebo, there was no significant difference. There was limited evidence as to the effectiveness of topical nitroglycerin improving pain at rest and pain during sleep hours. The most prominent finding of topical nitroglycerin was the suggestion of significant pain reduction in performing activities of daily living in the chronic pain subgroup.[27]

An RCT compared 40 patients with noninsertional Achilles tendinopathy receiving physical therapy of eccentric stretching versus physical therapy with transdermal nitroglycerin.[39] Both groups were permitted to take Tylenol for nitroglycerin-induced headaches, but no other analgesics. Both groups had similar pain and disability scores before treatment, and both groups experienced significant pain reduction after treatment. However, after 6 months of treatment, there was no significant difference between the groups for pain or disability.[39] Several patients underwent open decompression at the end of the 6-month period, and histological samples were obtained. Examination failed to show any difference in neovascularization, fibroblast activity, collagen synthesis, or endothelial nitric oxide synthase/inducible nitric oxide synthase expression between the 2 groups.[39]

Although previous studies have shown benefit as a sole treatment in reducing pain in chronic tendinopathies, a recent randomized double-blind placebo-controlled trial by Kirwan et al.[40] found that adding NTG for up to 24 weeks to a 12-week eccentric exercise program for Achilles tendinopathy did not improve pain when compared to placebo added to a 12-week eccentric exercise program.

Although there are some data that support the use of topical nitroglycerin in MSK pain, its efficacy appears to be limited to patients with rotator cuff pain when performing their activities of daily living.

Six articles on nitroglycerin, including 1 systematic review, were reviewed. Based on available evidence, the SORT level is A for rotator cuff pain but requires nitroglycerin application for prolonged periods of time.

CRYOTHERAPY

Cryotherapy has been a longstanding treatment for acute MSK injuries and postoperative pain control. Cold can be applied directly to an injured area or via total body immersion, depending on the goals of treatment. The goal of localized treatment is to reduce tissue temperature at the injured site and slow neuronal conduction of afferent pain fibers. A decrease in the inflammatory cascade leads to reduced edema and pain from a blunted central nervous system pain registration. Total body immersion theoretically reduces soreness and pain via promotion of venous return with resultant clearance of lactic acid. Despite a multitude of cryotherapy modalities offered, there is little evidence to support any specific form of cryotherapy. Likewise, treatment protocols vary widely without

strong evidence to support duration of treatment recommendations. Recent studies have reported only modest efficacy for cryotherapy in the treatment of acute MSK injuries. Adie et al[1] reported in a Cochrane Database review of cryotherapy after knee replacement the potential benefits of cryotherapy were too small to justify its use. They cited a need for well-designed randomized studies to improve the quality of evidence for routine usage. In a systematic review, Klintberg and Larsson[42] concluded that cryotherapy is well tolerated by patients, but more rigorous studies that include timing, temperature reporting, usage frequency, and dosage (time used per patient) are needed. Thienpont reported an RCT comparing advanced cryotherapy devices versus cold packs in postoperative total knee arthroplasty patients.[74] They found no difference in patient reported visual analog scale (VAS), pain reporting, or narcotic consumption during the first 5 postoperative days after knee arthroplasty. Recently, several authors have studied the efficacy of local evaporative cooling techniques versus traditional topical ice treatment. Park et al[60] reported on the use of cryotherapy for acute ankle fractures. They concluded evaporative coolants and ice packs showed comparable efficacy in both edema and pain control in their patient population, with no adverse effects reported in either group.[1] Mumith et al[57] reported an evaporative cooling system (Physiocool) was superior to chilled water circulation (Cryocuff, DJO) for improving ROM and decreasing pain during the first 48 hours after knee arthroplasty procedures. These authors found evaporative cooling to be more cost effective and easier to administer, theoretically increasing patient compliance. Rohner-Spengler et al[67] studied compression therapy versus elevation and ice in the care of patients with acute hindfoot and ankle injuries. They concluded that multilayer-compression-therapy controlled edema more effectively than ice and elevation in the immediate postoperative care of these patients. In a systematic review, MacAuley[49] proposed that ice applied to soft tissue injuries at 10 minute intervals was the most effective in reducing pain with the fewest side effects. In a random, double-blinded trial, Bleakley et al[10] demonstrated that intermittent application of ice to soft tissue injuries enhanced the therapeutic effects while significantly reducing pain compared with the standard 20-minute application protocol. Although studies do not overwhelmingly support cryotherapy for MSK pain reduction, it is well tolerated by patients. Standard icing techniques are low cost and readily available and are often included in a multimodal pain treatment program.

Eight articles on cryotherapy, including 1 Cochrane Review and 1 meta-analysis, were reviewed. Based on available evidence, the SORT level is C.

COMPLEMENTARY AND ALTERNATIVE TOPICAL MEDICINE

Complementary and alternative medicine approaches to traditional analgesics have been used for centuries and, with expanding interest in natural (herbal) medicine, are becoming more common today. Although many such compounds are applied topically, studies are limited or nonexistent and often the recommendations for topical use are extrapolated from studies performed using oral formulations. Of the studies specifically evaluating topical forms, most have low numbers of subjects, are heavily biased, or are case reports. However, recent studies in alternative topical analgesics such as cannabinoids, capsaicin, xiaotong tiegao, camphor spray with essential oils, Traumeel, and cabbage leaf wraps (CLW) do show promising initial results as natural analgesic options. With any herbal or alternative compound where manufacturing is less regulated and credible certification for purity has not been sought, the risk of contamination must be considered. A total of 19 articles on complementary and alternative medicines, 15 articles related to cannabinoids that included 2 systematic reviews and 1 meta-analysis, were reviewed.

Cannabinoids

Cannabinoids are produced naturally in the body and act on the cannabinoid receptors in the central nervous system. Preliminary studies appear to support the use of cannabinoids for the treatment of chronic pain, but most data are based on oral forms and have had mixed results. Biochemically, Wen et al[80] demonstrated antinociceptive activity and elucidated that transient receptor potential vanilloid 1 (TRPV1) and cannabinoid receptor subtype 2 (CB2R) are receptors that produce antinociceptive effects, suggesting that cannabidiol (CBD) may be a viable option in topical pain management. Palmitoylethanolamid (PEA) is a cannabinoid compound and lipid messenger that is thought to suppress inflammation by reducing proinflammatory enzymes. Although oral forms have been associated with significant pain reduction compared with placebo, studies on topical PEA are limited.[3] One of the earlier studies on topical medical cannabis (TMC) demonstrated benefit in 3 case reports with patients suffering from pyoderma gangrenosum.[51] All 3 patients experienced onset of analgesia within 3 to 5 minutes of application. Two patients experienced statistically significant pain reduction with routine and regular use of PEA. All 3 patients had a pain reduction that was clinically significant. Patients on opiates before initiation of PEA therapy had a statistically significant reduction in their use of opiates after routine and regular use of PEA. Although this small study of 3 patients is promising, it must be noted that the TMC was applied to skin that lacked epithelial coverage.[51] Two recent studies in patients with intact skin have shown positive benefits. Topical dermal CBD was studied recently in the treatment of myofascial pain related to temporomandibular disorders. CBD was applied to the masseter muscles twice a day for 14 days and had positive results in the reduction of myofascial pain.[33] Bruni et al[11] showed promising results using terpenes as CBD and tetrahydrocannabinol penetration enhancers to aid in transdermal administration. Both these studies involved intact skin, overcoming a limiting factor in the case studies involving PEA.

In a study by Hall et al,[35] there was a significant improvement in self-reported pain levels and pain-related disability among

elite athletes using topical cannabidiol; 50% of the respondents reported minor adverse effects, mostly commonly skin dryness and skin rash that resolved rapidly.[35] In 2 case reports by Eskander et al,[23] hemp-derived CBD in a transdermal cream provided significant pain relief for patients with acute and chronic back pain associated with a lumbar compression fracture and postsurgical resection of a meningioma. A cross-sectional study by Frane et al[25] showed significant improvement in pain and physical function in OA when using topical cannabidiol but less effective with autoimmune arthritis. In a small study, Xu et al[82] demonstrated that transdermal CBD oil can achieve significant pain improvement in patients with peripheral neuropathy.

However, other studies have shown less favorable results. Preclinical animal studies provided low-quality evidence for peripherally administered cannabinoids to provide regional antinociceptive effects. Haffar et al[34] demonstrated that augmenting multimodal analgesia with topical CBD after a total knee amputation did not reduce pain, opioid consumption, or improve sleep scores; suggesting the local effects of topical CBD are not beneficial for providing additional pain relief after TKA.

Miller et al[55] demonstrated that commercial CBD products show "inconsistent labeling, vary largely from their label claims should they make them, and show lot-to-lot variability, making dosing unpredictable." In general, new clinical trials that standardize formulation and application methods are needed to demonstrate outcomes are reliable, unbiased, safe, and are solely from CBD pharmacology.[55]

The SORT level for both cannabinoid compounds is C.

Natural Herbs and Oils

Xiaotong Tiegao

Natural herbs and oils applied topically are a popular choice for many patients with arthritis and fibromyalgia syndrome (FMS) seeking pain relief. Duan et al[20] compared Tibetan herbal xiaotong tiegao (XTT) patches and capsaicin cream by applying it to the skin of rats over an inflamed anterior tibialis muscle and then performing pain behavioral tests with evaluation of plasma extravasation and electrophysiological recordings of afferent nerve fibers. Both topical agents showed significantly reduced pain with increased weightbearing capacity on the affected hind limb, and both analgesics agents showed plasma extravasation in the affected skin.[20] In electrophysiological recordings, XTT selectively activated C-fibers, decreasing the afferent spontaneous firing rate in the nerve innervating the inflamed muscle; XTT did not selectively activate A-fibers.[20] XTT might be appropriate to use on patients with arthritis and FMS pain but studies on humans are lacking.

Based on available evidence, the SORT level is C.

O24

O24 is a camphor (3.1%) spray with a mixture of 6 essential oils. Ko et al[43] performed a literature review for published RCTs on topical therapies for FMS pain and describe a double-blinded placebo-controlled trial in outpatient clinics treating 153 FMS patients with O24 vs placebo for 1 month. Of the main outcomes measured, improvements were noted in the VAS pain rating, Jamar grip strength, average tender point threshold, and the Lanier scale with topical O24 over placebo.[43] O24 may be an effective alternative for symptom control in patients with FMS.

Based on available evidence, the SORT level for O24 is B for patients with FMS, but whether this can be extrapolated to other conditions is unknown.

Traumeel

Traumeel, available in topical ointment, gel, and injectable formulations, is a proprietary combination of plant extracts (predominantly *Arnica montana* root) and calcium sulfide used for treating inflammation and pain caused by MSK injuries. Grech et al[32] and González de Vega et al[30] both showed topical Traumeel to be comparable with diclofenac gel; however, both studies were funded by the manufacturer of Traumeel.

Based on available evidence, Traumeel can be considered in patients with MSK injuries; the SORT level is B.

Cabbage Leaf Wraps

The use of CLW for pain control can be traced back to the early Romans, and their use has since been incorporated into folk medicine throughout Europe. CLW are used today in many parts of the world to decrease pain from breast engorgement during lactation, and they have also been explored for MSK pain relief. CLW contain sulfur compounds that increase skin penetration by anti-inflammatory compounds such as flavonoids.[85] Lauche et al[46] looked at CLW for the treatment of OA of the knee in 81 patients. The study compared 4 weeks of treatment for stage II and stage III OA of the knee with CLW, topical pain gel (TPG) consisting of 10 mg diclofenac per gram, and usual care (UC). The primary outcome showed that patients using CLW reported significantly less pain at 4 weeks compared with those in the UC group; there was no significant difference in pain relief at 4 weeks between those in the CWL group and the TPG group.[46] The study also had 7 secondary outcomes that were evaluated at 4 weeks and 12 weeks. When the CLW group was compared with the UC group, significant positive effects were found in functional disability, quality of life, physical function, and pressure pain sensitivity. Effects were also found in functional disability after 4 weeks and quality of life after 12 weeks in the CWL group compared with the TPG group.[46] With patients being satisfied in both active treatment groups, CLW was superior to UC and CLW was at least equivalent to TPG. In an open-labeled RCT, Chobpenthai et al[14] showed that CLW are as efficacious as a cooling gel pad. Application of CLW with ice to the knee in men may promote a reduction of swelling (by accelerating absorption of knee exudates) if applied during the acute stage of the knee injury.[21]

Based on available evidence, CLW can be used in patients with knee pain secondary to OA; the SORT level is B.

COMPOUNDED TOPICAL AGENTS

Compounded topical agents have become increasingly popular recently. A cross-sectional study performed by McPherson et al[54] showed that patients were highly satisfied with the pain relief provided by compounded prescription topical creams when obtained through compounded pharmacies and were satisfied with out-of-pocket costs. With their ready availability and high costs, it is important to understand their efficacy. In an effort to review costs, the Department of Defense initiated a study on compounded topical agents at Walter Reed Hospital.[12] Patients with localized pain and an average pain score ≥4 were included in the study. The patients were given formulations that are used frequently in the marketplace with concentrations in the mid-to-high range and were selected based on accepted systemic indications for neuropathic and nociceptive pain. Those with neuropathic pain received a compound containing 10% ketamine, 6% gabapentin, 0.2% clonidine, and 2% lidocaine. Patients with nociceptive pain were given a compound that contained 10% ketoprofen, 2% baclofen, 2% cyclobenzaprine, and 2% lidocaine. Patients with a mixed pain disorder were given a compound containing 10% ketamine, 6% gabapentin, 3% diclofenac, 2% baclofen, 2% cyclobenzaprine, and 2% lidocaine. The randomized control study failed to demonstrate a significant benefit for the 3 compounded creams versus placebo or approved topical pain creams for the various pain conditions, at both 1-month follow-up and 3-month follow-up.[12] A study published in the *Annals of Internal Medicine* showed that there is no meaningful difference between compounded creams and a placebo in the treatment of chronic pain.[12]

Guidelines published by the National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division further state that there is limited evidence to support the use of compounded topical pain creams to pain in the general adult population.[70] With these data, it may be more appropriate to prescribe a simple topical pain cream and avoid the high cost of compounded topical analgesics. However, compounded agents are still an option for select patients who prefer convenience over cost.

Based on available evidence, the SORT is level B for the compounds mentioned in the study.

COUNTERIRRITANTS

Counterirritants, also called rubefacients, including capsaicin, menthol, camphor, and salicylate, work by causing irritation, vasodilation, and inflammation at one area, with the goal of decreasing pain at another.[53] Their primary affect is through the modulation and desensitization of afferent nerves to the skin, which improves pain in the surrounding soft tissues and joints. They are often added to emollients and transport molecules to enhance cutaneous absorption. Most have good safety profile, although caution should be used with salicylates as toxicity can occur.[5,16] A total of 16 articles for counterirritants, including 2 meta-analyses of capsaicin, were reviewed.

Capsaicin

Capsaicin is a capsaicinoid chemical irritant found in chili peppers that has been studied and recommended for analgesic uses. It binds TRPV1 - a receptor on type C afferent fibers - and increases the release of substance P. Initial application leads to burning sensation, but repeated use leads to analgesia due to substance P depletion and a reversible loss of C fibers.[2,6,28] This can have a direct effect on joint pain due to the large amount of nociceptive fibers in the synovium and articular cartilage.[6,28] Numerous studies have demonstrated an improvement in symptoms of knee OA over placebo. In a meta-analysis of randomized controlled studies, topical capsaicin was compared with topical NSAIDs for pain relief in OA.[62] At 4 weeks of use, data indicated both NSAIDs and capsaicin were superior to placebo and there was no significant difference when capsaicin and NSAIDs were compared with each other. However, the meta-analysis had a wide confidence interval for capsaicin, probably due to limited and poor-quality evidence.[62] NSAIDs are generally favored by National Institute for Health and Care Excellence[58] and the American College of Rheumatology in general, but capsaicin is conditionally recommended for knee OA by the American College of Rheumatology.[44] Its use should be guided by patient preference, costs, and individual response. Due to its mechanism of action, capsaicin may be of particular benefit to patients with neuropathic pain,[29,36,64,73] and it is worth noting that 15% of patients with knee pain report neuropathic-like symptoms.

Based on available evidence, the SORT level for capsaicin use to treat knee OA is B.

Menthol

Menthol is a volatile oil from the plant genus *Mentha*, which includes mint, peppermint, and spearmint plants.[47] Menthol acts on the transient receptor potential melastatin-8 (TRPM8) and, similar to capsaicin, may desensitize afferent fibers.[47] The TRPM8 receptor senses cold, giving the cooling sensation noted with menthol.[47,78] Whereas menthol causes localized vasodilation at the application site, the TRPM8 receptor activation leads to decreased blood flow to the extremities, similar to icing. The combination of menthol and ice additively decreases arterial blood flow.[75] Although menthol has less data supporting its role in pain relief for MSK injuries than capsaicin, the cooling effect in combination with icing may play a role in decreasing inflammation.

Based on available evidence, menthol can be offered to patients with pain secondary to MSK injuries; the SORT level is C.

Camphor

Camphor is derived from the wood of camphor laurel trees, but can also be found in several other plants or be derived synthetically.[83] Camphor activates TRPV3, leading to desensitization of sensory nerves.[83] It can also activate TRPV1, like capsaicin, but is not as effective.[83] Camphor can have a cooling effect like menthol, but its affect is not as robust and studies proving its efficacy are lacking.

Table 1. Topical analgesics and modalities: summation of findings

Type	Indications	SORT A	Remarks
NSAIDs	Acute MSK pain OA		Diclofenac, ibuprofen, ketoprofen
Lidocaine	Postherpetic neuralgia		
Nitroglycerin	Rotator cuff injuries		Patches, requires long duration of treatment
Type	**Indications**	**SORT B**	**Remarks**
024	FMS		Uncertain whether applicable to other MSK conditions
Traumeel	MSK injuries		Manufacturer-sponsored study
CLW	Knee OA		Study showed efficacy = topical diclofenac
Compounded agents	Neuropathic pain MSK pain Mixed pain disorder		Separate agents equally efficacious
Capsaicin	Knee OA, neuropathic component		15% of OA knee pain is neuropathic-like
Salicylates	MSK injuries		Level B evidence against effectiveness with warning of potential toxicity
Type	**Indications**	**SORT C**	**Remarks**
Lidocaine	Lower back pain Knee OA Shoulder impingement		
Cryotherapy	Acute fractures Soft tissue injuries		Low risk profile and cost, readily available Intermittent intervals may be better
Cannabinoids	Pyoderma gangrenosum - lacked epithelial cover		Evidence limited to case reports
Natural herb/oil (XTT)	Arthritis FMS		No human studies
Menthol	MSK injuries		
Camphor	MSK injuries		Suspected to be less effective than menthol

CLW, cabbage leaf wraps; FMS, fibromyalgia syndrome; MSK, musculoskeletal; OA, osteoarthritis; XTT, Xiaotong tiegao.

Based on available evidence, camphor may not be a reasonable or effective alternative in patients with MSK pain; the SORT level is C.

Salicylates

Salicylates, such as methyl salicylate, trolamine salicylate, and oil of wintergreen (liquid methylsalicylate) are counterirritants thought to work through sensory nerve modulation and localized inflammation.[5] A Cochrane review failed to show any benefit from topical salicylates for acute or chronic conditions, thus limiting their use for MSK conditions.[18] In addition, toxicity complications are a potential risk.[5,16]

Based on available evidence, topical salicylates are not an effective alternative for patients with MSK pain; the strength of recommendation against their use is level B.

RESULTS

Studies of topicanalgesics are limited in quality. However, the use of several agents and modalities is supported (Table 1), and

most topical analgesics have low risk profiles. Data broadly demonstrate the effectiveness of topical NSAIDs for MSK pain with a SORT level of A. Topical lidocaine is best suited for postherpetic neuropathic pain (SORT A) but less so for MSK pain (SORT C). With a SORT Level of A, topical nitroglycerin can also be used for patients with rotator cuff pain who are looking for relief while performing activities of daily living and are willing to treat for long periods of time. CLW are a safe option for relief of MSK pain, with data demonstrating their efficacy. Few data support the use of cryotherapy, but its risk profile is especially low and availability is high. O24 is a reasonable alternative with a low-risk profile to treat pain in patients with FMS. Traumeel could be a promising natural analgesic that compares with diclofenac; however, independent studies are needed. Data do not support prescribing compounded agents; instead, single agent creams provide the same relief at a lower cost. Capsaicin is an appropriate option for the neuropathic component of MSK pain, whereas topical salicylates do not appear to be effective in reducing MSK pain and have a potentially worrisome risk profile.

LIMITATIONS

All modalities reviewed, with the exception of NSAIDs, were limited in the number of published studies, and 1 modality (Traumeel) had a study sponsored by the manufacturer. Most modalities reviewed did not have meta-analyses or systematic reviews, with NSAIDs and cryotherapy being the only 2 with Cochrane reviews and meta-analyses. NSAIDs, cryotherapy, and topical nitroglycerin each had systematic reviews, which were described in this review. Although the studies in this article used well-known, validated clinical pain scales, pain in and of itself is a subjective assessment; however, this is not just a limitation to this article but to all studies involving pain assessment. Finally, due to the paucity of studies for most topics and their varied statistical approaches, this narrative review was unable to perform a statistical comparison between modalities.

CONCLUSION

Of the topical analgesics and modalities reviewed, SORT level A evidence was found for topical NSAID use decreasing MSK pain, topical lidocaine for postherpetic neuralgia, and nitroglycerin patches for treating rotator cuff pain if used for prolonged periods of time. Alternative treatments such as CLW and Traumeel show promising results and have SORT levels of B. In general, choice of topical agent should be guided by current evidence showing their efficacy and should account for type of pain, medication side effects, and patient comorbidities, as well as by additional consideration for patient preference, convenience, and cost.

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