Special Article

Multimodal Approaches to the Management of Neuropathic Pain: The Role of Topical Analgesia

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Abstract
Because of their localized activity and low systemic absorption, topical analgesics have a favorable safety profile and a low risk for drug-drug interactions. There is a growing body of evidence on the efficacy and safety of these agents in a variety of pain disorders, including the most prevalent neuropathic pain conditions. The molecular basis for the usage of peripheral analgesics in neuropathic pain and the available clinical trial evidence for a wide variety of topical agents are reviewed. J Pain Symptom Manage 2007;33:356–364. © *2007 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

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

Introduction

Neuropathic pain results from heterogeneous disorders and can be extremely challenging to treat. A role for topical analgesics in these conditions is suggested by emerging data concerning the varied mechanisms that may sustain pain. Clinical trial data have provided support for the use of specific topical agents in a number of discrete disorders.

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Accepted for publication: November 28, 2006.

0885-3924/07/$–see front matter
doi:10.1016/j.jpainsymman.2006.11.004

The Pathophysiology of Neuropathic Pain

Nervous system lesions from various etiologies, such as diabetes, trauma, malignancy, and herpes zoster infection, may lead to "neuropathic pain."[1,2] In order to understand how various analgesic techniques may provide pain relief and to suggest the potential target sites for topical analgesia in neuropathic pain, the pathophysiology of neuropathic pain at the peripheral level must be considered, beginning with an understanding of the pain pathway in a healthy individual.

With physiological pain, when a stimulus is applied to the skin, the information is transferred to the central nervous system (CNS) via activation of the sodium channels in nociceptors that convert this mechanical stimulus into an electrical signal. This is called transduction.[1] Conduction refers to movement of

the electrical signal through the peripheral nerves to the CNS. Transmission of the message to the somatic sensory cortex and the limbic system will only occur if there is no activation of the descending pathways that can modulate this signal. If the nociceptive input reaches higher CNS centers, perception of pain may result and this may trigger a neuroendocrine and/or sympathetic response and a skeletal muscle spasm. Transduction can be inhibited by therapies that modulate pain at the periphery—such as topical analgesics. Transmission also can be modulated by activation of the descending inhibitory pathways from the CNS. In addition, other mechanisms that may eventually transmit the nociceptive input to the cerebral cortex and limbic system can block the transfer of the signal from the dorsal horn of the spinal cord to the spinothalamic tract.

At the molecular level, injury stimulates the release of phospholipids, which in turn activates phospholipase A2 to generate prostaglandin A2. Subsequently, this product binds to the primary nociceptive fiber and induces the phosphorylation of sodium channels therein. These events result in the transmission of a signal through the primary afferent neuron (also called the first-order neuron) to the CNS. As prostaglandin continues to be produced, it also binds to sensory fibers and becomes absorbed systemically, resulting in liberation of substance P, release of adenosine triphosphate, and local changes in the pH. Also, inflammatory mediators, such as bradykinin, serotonin, and histamine, are released by damaged cells and tissues near the injury site, and these decrease the threshold for activation of nociceptors.[3] The resulting vasodilation and inflammation sensitize the affected nociceptors to subsequent stimuli and can result in a positive feedback loop (called axon reflex) that begins to recruit afferent pain fibers in close proximity to the initially activated nerve.[1] These injury-induced neuromodifications contribute to peripheral sensitization, which is marked by the release of norepinephrine. When advanced, this phenomenon can be perceived as allodynia or hyperalgesia.

In contrast to activation-dependent physiological pain, neuropathic pain arises without the necessity of an ongoing source of tissue injury.[1] When a peripheral nerve is injured, many mechanisms may be responsible for the pacemaker-like activity that is one of the sources of neuropathic pain. For example, ectopic activity in peripheral neurons may be mediated by the abnormal expression of sodium channels.[4] Injured peripheral nerves also may undergo localized demyelination and/or develop altered cell bodies, abnormalities that may be associated with ectopic activity in the dorsal root ganglia.[2]

Other reversible changes can increase the sensitivity of nociceptors and result in peripheral sensitization.[1] For example, peripheral nociceptors may become sensitized when inflammatory signaling molecules trigger the phosphorylation of tetrodotoxin-resistant sensory neuron-specific (SNS) sodium ion channel.[5] Once these sensitized nerves are activated, they produce a large evoked potential and resultant transmission to the CNS. Consequently, these nociceptors engage at a lower activation threshold for transduction.[1] Also, after inflammation or peripheral axon damage, the expression of receptors and neurotransmitters may be altered. These potentially long-lasting alterations may also contribute to clinical pain hypersensitivity.[1] Gene transcription may be altered in both the dorsal root ganglia and the dorsal horn neurons. In particular, the vanilloid receptor-1 and SNS receptors are upregulated, which also helps to lower the threshold for nociceptor activation.[1]

Input from peripheral nociceptors can induce central sensitization as well (Fig. 1).[1] Nociceptive stimuli may trigger molecular changes in central neurons that result in the enhanced responsiveness of pain transmission neurons. Lower levels of inhibitory transmitters in the neurons of the spinal cord dorsal horn may reduce descending pathway inhibition.[2] This so-called "disinhibition" is promoted by a reduction in the concentrations of γ-aminobutyric acid and glycine, in particular. *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor activation lower the threshold for nerve transduction and produce lasting facilitation of synaptic transmissions.[1] Other more permanent modifications involve altered receptor expression and cell death in the superficial laminae of the dorsal horn, where inhibitory interneurons are concentrated.

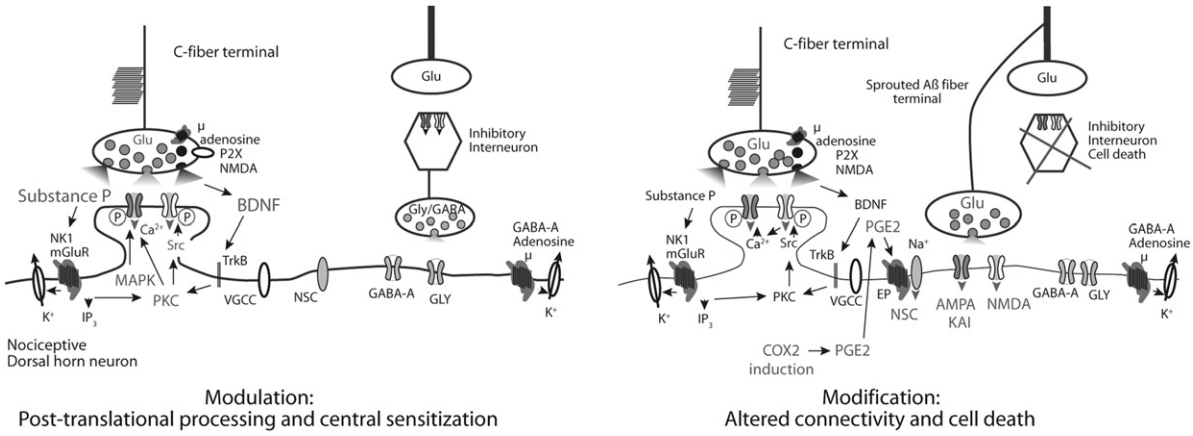

Fig. 1. Molecular and cellular modifications associated with central sensitization. GABA = γ-aminobutyric acid, GLY = glycine, NMDA = *N*-methyl-D-aspartate, AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, BDNF = brain-derived neurotrophic factor, PKC = protein kinase C, NSC = nonspecific cation channels, VGCC = voltage-gated calcium channel, TrkB = tyrosine kinase B receptor, IP_3 = inositol 1,4,5-trisphosphate, NK1 = neurokinin-1, mGluR = mammalian glutamate receptor, EP = prostaglandin E_2 receptor. Adapted from Ref. 1.

The loss of cells that inhibit pain transmission promotes disinhibition.[1]

Molecular Targets for Topical Analgesia to Treat Neuropathic Pain

Research conducted during the past 3–5 years has identified many potential peripheral mechanisms for neuropathic pain, enabling the development of pharmacotherapies that specifically target these mechanisms. For example, transduction may be blocked by reducing cyclooxygenase (COX)-2 enzyme activity through COX-1 and COX-2 selective inhibitors, which limit the production of prostaglandin E2. Prostaglandin-mediated sensitization in the cutaneous terminals of primary afferent nociceptors may be blocked by topical therapies that include aspirin, diclofenac, and indomethacin.[6]

Once abnormal sodium channels are established, other pharmacotherapies may be required to effectively reduce the transduction of pain signals. Sodium channel blockers can inhibit the ectopic activity of sodium channels in both injured peripheral and demyelinated neurons, as well as block the overactivity of sodium channels mediated by modifications such as phosphorylation and the upregulation of specific isoforms such as the tetradotoxin resistant sodium channel. These abnormalities all contribute to prolonged nociceptive depolarization and result in a supralinear increase in neurotransmitter release. Overactive sodium channels tend to remain in a persistently open conformation, which is preferentially bound by sodium channel blockers.[4] Hence, agents that profoundly reduce neurotransmitter release from nociceptors generating ectopic pulses, such as topical local anesthetics and anticonvulsants, may relieve neuropathic pain.[6] Likewise, increased peripheral sensitivity mediated through the release of prostaglandin E2 and substance P at the peripheral level results in spontaneous discharges that may be inhibited by topical drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and capsaicin.[6] Additionally, topical substance P inhibitors and ketamine can reduce the effects of substance P, while sympathetic afferent activation can be modified by the topical administration of a beta-blocker and clonidine. Topical antihistamine may decrease the release of the histamine and serotonin, thereby limiting the inflammatory process and hindering vasodilation. Topical opioids can target the opioid receptors present on nociceptive fibers and mast cells. Binding of opioid receptors can inhibit the release of the calcitonin gene-related peptide (CGRP) and substance P from nerves, thereby preventing the feed-forward mechanism of pain that typically results in

sensitization at the site of injury (primary hyperalgesia).[7]

Empiric Use of Topical Agents

Many topical agents are commonly used for the treatment of neuropathic pain, despite data being either unavailable or from poor quality randomized, controlled trials. The tricyclic antidepressants, amitriptyline and doxepin, and the NMDA antagonists, ketamine, amantadine, dextromethorphan, and orphenadrine, have been used in an off-label manner to treat neuropathic pain. Among local anesthetics, lidocaine has been used frequently to provide neuropathic pain relief; in Europe, tetracaine and ropivacaine have also been used. Counterirritants that target transient receptor potential channel proteins are in common use, especially capsaicin. Although originally developed as an antihypertensive agent, the alpha$_2$-adrenergic agonist, clonidine, has been applied topically to provide pain relief by interrupting the ectopic pulses generated by sympathetic afferent nerves.[5] Tizanidine has been used as well, but with little supporting evidence in the literature. Topical NSAIDs, such as aspirin, indomethacin, diclofenac, and benzydamine,[8] have been used to treat neuropathic pain, although with inconsistent results[9] and likely with a rubefacient mechanism of action.[10] Limited literature involving animal models has reported the use of topically administered opioids, such as morphine, methadone, and loperamide, for peripheral analgesia in neuropathic pain.[5] Pentoxifylline, the tumor necrosis alpha antagonist, has been effective at providing pain relief for some neuropathic conditions when applied topically, although its use for this purpose has not been supported by randomized, controlled trial evidence.

Clinical Trials of Topical Agents

Alpha$_2$-Adrenergic Agonists

Injured peripheral nerves tend to exhibit adrenergic sensitivity; sympathetic agonists may increase the ectopic impulses generated from these types of efferent axons.[11] Sympathetic nerve terminals containing alpha$_2$ receptors are inhibited from releasing norepinephrine upon adrenergic agonist binding, potentially resulting in a reduction in pain and allodynia.[11,12] Likely, the pain relief mechanism also involves the hyperpolarization of nicotinic ganglia by alpha$_2$-adrenergic stimulants.[13] The analgesic effectiveness of a topical alpha$_2$-adrenergic agonist, clonidine, was investigated in six patients with chronic pain and hyperalgesia.[12] Patches delivering 30 μg/cm^2/day (either 7.0 or 10.5 cm^2 in size) were applied for a maximum of seven days; ongoing pain was assessed by a visual analog scale, and hyperalgesia to both mechanical and cold stimuli was tested. Following patch removal, hyperalgesia to mechanical stimuli was greatly reduced or completely eliminated for a minimum of 12 hours. Side effects included local rash, drowsiness, thirstiness, and dry eyes.[12]

Transdermal clonidine was also investigated for relief of pain due to diabetic neuropathy in a study with a two-stage enriched enrollment design.[14] The 12 apparent responders from the initial enrichment phase entered into a double-blind, randomized, one-week treatment period comparing transdermal clonidine to placebo. Although there was little pain intensity difference between the clonidine and placebo groups in the first phase, the participants in the second phase of clonidine treatment reported 20% less pain than placebo (95% confidence interval [CI]: 4%−35% pain reduction; $P = 0.015$). A post hoc analysis suggested that patients who described their pain as sharp and shooting may have a greater likelihood of responding to clonidine.[14]

Similarly, another pilot study of 17 patients with orofacial pain found more benefit of topical clonidine cream for neuralgia-like (lancinating, sharp) pain over neuropathic (burning, aching) pain.[15] Overall, the neuropathy group had a 30% reduction in pain and a 59% reduction among treatment responders, compared to a 55% overall reduction and a 94% reduction for treatment responders among patients with neuralgia. Yet, the difference between the groups was not statistically significant.[15]

NMDA Antagonists

While there is no published literature that supports the use of topical amantadine, dextromethorphan, or orphenadrine for neuropathic

pain, case reports[16,17] and studies conducted with healthy volunteers[18,19] offer preliminary evidence which suggests that further study of ketamine gel/ointment is warranted. Also, several trials have examined a topical ketamine/amitriptyline combination and are discussed in detail in the following section. It has been proposed that topical ketamine targets both peripheral opioid receptors and sodium and potassium channels to reduce pain.[16] Also, recent research has suggested that ketamine may alter the "docking station" for vesicles containing neurotransmitters, such as glutamate.[20] The vesicles travel through the primary afferent neuron and have an effect at the presynaptic level, before binding to the intermediate receptors.

Local Anesthetics

Topically applied local anesthetics may relieve neuropathic pain by reducing ectopic discharges in superficial somatic nerves residing in the area of localized pain.[11] Lidocaine patch 5% is the single local anesthetic formulation that has been well-studied for relief of neuropathic pain in randomized, controlled trials. However, another local anesthetic, EMLA (eutectic mixture of local anesthetics) (2.5% lidocaine and 2.5% prilocaine), was investigated in a study of 11 patients with postherpetic neuralgia (PHN).[21] Although a single application of EMLA did not induce a significant reduction in pain, the repeated daily application of the agent produced a significant reduction in paroxysmal pains and mechanical allodynia/hyperalgesia. Mild erythema was frequently reported and itching was noted in one patient as well.[21]

Recent studies have elucidated further mechanisms by which topical lidocaine can induce analgesia. When lidocaine patch 5% is applied to painful skin, lidocaine avidly binds to abnormal sodium channels that are upregulated within damaged peripheral nerves, thereby suppressing the abnormal spontaneous and evoked activity that can initiate and maintain some neuropathic pain.[22] Also, the patch provides a barrier against potential sources of mechanical stimulation (i.e., bedclothes), which can provoke allodynia in some patients.

A pharmacokinetic study assessed the effects of lidocaine patches 5% applied continuously for 72 hours in 20 healthy volunteers. Ten of the study participants changed patches every 24 hours and 10 participants applied a new patch every 12 hours. Even among the volunteers who changed patches every 12 hours, the steady-state plasma concentrations were 225 ng/mL.[23] These concentrations are approximately eight times and 25 times lower than the typical concentration of lidocaine required to produce antiarrhythmic effects and toxicity, respectively. There were no reports of loss of sensation at the application site, but most patients had mild local erythema. No systemic adverse reactions were judged to be related to the application of the patches.[23] Overall, lidocaine 5% delivered in a patch has a minimal risk of systemic absorption. When used according to the recommended dosing instructions, approximately $3 \pm 2\%$ of the lidocaine dose is typically absorbed, resulting in an approximate mean peak blood concentration of 0.13 μg/mL. This has tremendous implications for patients who require polypharmacy, such as the elderly, as well as for patients who may not tolerate the doses of oral antineuropathic medications required to achieve adequate analgesia. Improved analgesia may be obtained by a multimodal approach that uses several medications with multiple modes of action, albeit at lower doses.

Several controlled clinical trials have demonstrated the efficacy of the lidocaine patch 5% for relief of pain from PHN. Most recently, a publication reported a randomized, controlled trial in 96 patients[24] and an open-label, nonrandomized study in 332 participants.[25] In the randomized study, following three weeks of daily therapy, there was a statistically significant difference between the Neuropathic Pain Scale (NPS) scores reported by the treatment and placebo groups (NPS-10; $P = 0.043$). Moreover, the study documented a 25% improvement in the quality of analgesia for the treatment group from baseline.[24] The second effectiveness trial in PHN conducted in 2002 demonstrated that 65.8% of patients had improvements in pain intensity within the first week of therapy and 77% of patients reported an improvement in their quality of life ($P = 0.0001$).[25] At study completion, after 28 days of therapy, 58% of the patients reported moderate to complete pain relief. The most commonly reported adverse event was a localized rash (14%), typically mild in nature. The

participants in the study were allowed to continue using concomitant systemic analgesics, such as anticonvulsants, antidepressants, and opioids. Thus, the study documented the successful use of the patch as an adjuvant to an already established therapy.[25]

The effectiveness, tolerability, and impact on quality of life of lidocaine patch 5% for patients with diabetic peripheral neuropathy (DPN) was studied in a three-week trial conducted by Barbano et al.[26] Significant improvements (≥30% reduction) from baseline in mean daily-diary pain ratings were documented by 70% of the patients (37/53). Similarly, another trial completed by 40 patients with focal peripheral neuropathic pain syndromes found significant differences in ongoing pain between the group treated with lidocaine patch 5% as add-on therapy and the placebo group after seven days of therapy ($P = 0.0002$).[27] The number needed to treat (NNT) with lidocaine patch 5% for one patient to have a 50% reduction in ongoing pain was calculated to be 4.4 (95% CI, 2.5−17.5), compared to an NNT of 8.4 (95% CI, 3.5−∞) for placebo. The most frequently reported adverse event was mild skin irritation; notably, the frequency did not differ significantly between the treatment and control groups ($\chi^2 = 0.29$; $P = 0.59$). A quantitative review of analgesic therapies for PHN also reported an NNT for lidocaine patch 5%; Hempenstall et al. calculated this to be 2.00 (1.43−3.31).[8]

Tricyclic Antidepressants

Topical tricyclic antidepressants, such as doxepin and amitriptyline, have demonstrated efficacy in a number of neuropathic pain states.[28,29] Amitriptyline provides pain relief via multiple pharmacologic mechanisms, including inhibiting norepinephrine and serotonin reuptake at the presynaptic level, blocking NMDA and alpha$_2$-adrenergic receptors and partially blocking sodium[4] and voltage-gated potassium and calcium channels.[30,31] Transdermal delivery of amitriptyline has resulted in a dose-dependent analgesic effect that was greater and of longer duration than the corresponding concentration of lidocaine in a recent study.[31] For example, 100 mM of lidocaine induced a maximal analgesic effect of 45.9 ± 4.2% (mean ± SEM number of pinpricks without response), with full recovery at 15 hours, while the same concentration of amitriptyline had a maximal analgesic effect of 70.8 ± 15.0%, with complete recovery at 25 hours.[31] However, when concentrations high enough to produce a local anesthetic block were applied, amitriptyline was found to cause Wallerian degeneration of peripheral nerve fibers in rats.[30] Following injury to nerve fibers, this pathologic process results in the progressive degeneration of the axon and its supporting cells. In addition, cutaneous concentrations of amitriptyline >500 mM also resulted in skin injury in these animals.[30]

In the available clinical studies of amitriptyline, ketamine was coadministered in order to minimize the concentrations required to obtain an analgesic effect and the resulting side effects.[32] A randomized, placebo-controlled study evaluated the topical administration of 2% amitriptyline, 1% ketamine, and a combination of both in 92 patients with diabetic peripheral neuropathy, PHN, or complex regional pain syndrome type II.[33] Lynch et al. found no significant differences in the change in pain scores between placebo and the treatment groups. A lack of a systemic effect was indicated by a decrease in pain levels despite minimally detectable plasma concentrations of amitriptyline, ketamine, or their metabolites.[33] Likewise, a longer duration study (6−12 months) found no systemic absorption and minimal adverse events.[34] However, a recent randomized, placebo-controlled trial evaluated a higher dose of topical amitriptyline (4%) and ketamine (2%) using an enriched enrollment design.[35] In phase I of the trial, 52% (129/250) of the participants responded after one week of open treatment with the drug combination. During the randomization phase, 118 participants were randomly assigned to receive 4% amitriptyline−2% ketamine, 2% amitriptyline−1% ketamine, or placebo cream for an additional two weeks. Following three weeks of the treatment phase, the mean average daily pain intensity decreased from 6.5 at baseline to 3.28 for the higher dose cream, 4.08 for the lower dose cream (non-statistical significance, NS), and 4.34 for the control. The difference was significant between the high-dose treatment group and the placebo group ($P = 0.026$). Moreover, the number of patients

attaining a 30% reduction in pain intensity was 46% for the higher dose cream, 26% for the lower dose cream, and 19% for the placebo group ($P = 0.025$ between the high-dose group and control group). Plasma levels of either drug were detected in less than 10% of the participants and those measurable were well below therapeutic levels.[35] These findings suggest that for topical amitriptyline/ketamine combinations to be effective, concentrations of at least 4% and 2%, respectively, should be used.

Although there is less published data supporting the topical application of doxepin for neuropathic pain, the initial reports have suggested potential benefit. Studies in rats imply that topical doxepin acts as a local anesthetic; doxepin applied as a patch at concentrations of 75 mM and 100 mM was significantly more effective than placebo ($P < 0.05$).[36] Epstein et al. also recorded oral numbness for a period of up to two hours after rinsing with doxepin among healthy human volunteers, suggesting an anesthetic effect.[37] Yet, the authors pointed out that the limited duration of numbness/anesthesia cannot account for the extended duration of pain relief observed in patients with mucosal lesions. Another study conducted in 2006 reported an analgesic effect from a topical doxepin rinse (5 mg/mL) in patients with oral mucositis resulting from cancer and cancer therapy.[38] On average, participants reported a 70% maximum decrease in pain ($P < 0.0001$) and of those who were responsive to treatment, 95% experienced pain relief within 15 minutes of rinsing with doxepin.[38] A case study also reported the benefit of topical doxepin in a patient with complex regional pain syndrome.[39]

Counterirritants

Counterirritants, such as capsaicin, have had limited success at providing analgesia for patients with neuropathic pain. Topical formulations of capsaicin did not have a demonstrated efficacy in controlled trials of patients with HIV-associated neuropathic pain[40] and painful distal polyneuropathy.[41] However, studies of patients with diabetic peripheral neuropathy[42] and PHN[43,44] who were treated with 0.075% capsaicin cream reported a benefit. A meta-analysis of trials on the effectiveness of topical capsaicin for the treatment of diabetic neuropathy, osteoarthritis, and PHN showed that capsaicin cream provided more pain relief to patients with diabetic neuropathy than placebo.[45] The calculated odds ratio and corresponding 95% CI (odds ratio = 2.74; 95% CI = 1.73, 4.32) also favored capsaicin cream.

In addition, a large, eight-week, double-blind trial compared capsaicin with oral amitriptyline and found equal analgesia for patients with diabetic peripheral neuropathy.[46] Seventy-six percent of the patients reported a 40% mean decrease in pain intensity, and noticeable improvements in sleep and movement in both treatment groups were observed as well. However, the side effects in the capsaicin group included application site reactions, such as burning sensations, while numerous potentially serious systemic adverse reactions were reported in the amitriptyline group. It is noteworthy that capsaicin leads to the morphologic degeneration of unmyelinated C-fiber afferent neurons in the epidermis.[47] Furthermore, it must be applied for approximately two weeks to a month in order to obtain peak analgesic effect, often making treatment adherence difficult. Yet, capsaicin may be a good choice for topical analgesia, especially in patients who are intolerant or unresponsive to other analgesic therapies.[48]

Infrequently, other counterirritants have been used to provide analgesia for neuropathic pain. For example, the transient receptor potential channel activator, menthol, has had limited use in mixtures or applied as topical peppermint oil. A case report documented the effective use of peppermint oil for relief of pain associated with PHN, with only a minor side effect after two months of treatment.[49] Other counterirritants have not had as much success according to the literature. A quantitative, systematic review reported the ineffective use of several topical NSAIDs for PHN, including benzydamine and diclofenac, but warned that the trial designs may have been inadequate.[8]

Conclusions

There is good evidence supporting the use of topical analgesics in neuropathic pain, especially in view of the typical low incidence of side effects. The best approach may be to use them as part of a multimodal therapeutic

program. Based on the current available literature, the strongest analgesic effects for neuropathic pain tend to be observed with lidocaine patch 5%, capsaicin and amitriptyline/ketamine combinations. Combinations of drugs are an attractive alternative, as multimodal therapies target several receptors, often producing additive or even synergistic effects. For example, a randomized, double-blind, placebo-controlled trial of 200 participants with neuropathic pain reported more rapid analgesia from the topical application of a combination of 3.3% doxepin and 0.025% capsaicin than either agent alone.[28] Yet, variability in topical preparations can be an issue, as compounding pharmacies often have unique recipes. However, it is clear at this point that topical analgesia offers a viable alternative as adjuvant therapy for patients with neuropathic pain.

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