Topical agents for the management of neuropathic pain

Agentes tópicos para manejo del dolor neuropático

Oscar A. de Leon-Casasola

RESUMEN

Diversas lesiones del sistema nervioso como la diabetes, el trauma, las neoplasias y el herpes zoster pueden causar un dolor crónico y severo denominado "dolor neuropático". Se han utilizado diversos agentes tópicos para el tratamiento del dolor neuropático, aunque no se dispone de evidencia adecuada para su uso. La eficacia de un analgésico tópico, agonista alpha2-adrenérgico, como la clonidina, se estudio en varios ensayos obteniendo una utilidad moderada. Se ha propuesto que la ketamina tópica actúa sobre los receptores opiáceos periféricos, y sobre los canales de sodio y potasio reduciendo el dolor. Los anestésicos locales aplicados tópicamente pueden proporcionar alivio del dolor neuropático reduciendo las descargas ectópicas de los nervios somáticos superficiales. Algunos estudios aleatorizados y controlados con placebo analizaron la administración de diferentes presentaciones tópicas de amitriptilina al 2 por ciento, de ketamina al 1 por ciento y de una combinación de ellas; en pacientes diabéticos con neuropatía periférica (DPN), en neuralgia post-herpética (PHN), o en síndrome regional complejo de dolor (CRPS) II demostrando una adecuada la reducción del dolor. Sustancias como la capsaicina han tenido éxito limitado como analgésicos tópicos en pacientes con dolor neuropático.

Basados en la literatura actualmente disponible, los mejores efectos analgésico en el dolor neuropático se obtienen con el parche de lidocaine al 5 por ciento, con la capsaicina, y con las combinaciones de amitriptyline-ketamine

Palabras clave: amitriptilina, analgésicos, neuralgia post-herpética, ketamina.

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SUMMARY

Nervous system lesions from various etiologies, including diabetes, trauma, malignancy, and herpes zoster infection, can generates chronic and severe pain named "neuropathic pain".

Many topical agents are commonly used for the treatment of neuropathic pain, despite either unavailable or poor quality randomized, controlled trial data. The analgesic effectiveness of a topical alpha2-adrenergic agonist, clonidine, was studied in several trials with moderated utility. It has been proposed that topical ketamine targets both peripheral opioid receptors, and sodium and potassium channels to reduce pain. Topically applied local anesthetics may provide neuropathic pain relief by reducing ectopic discharges in superficial somatic nerves. Some randomized, placebo controlled studies considered the topical administration of 2 per cent amitriptyline, 1 per cent ketamine, and a combination of both in diabetic peripheral neuropathy (DPN), postherpetic neuralgia (PHN), or complex regional pain syndrome (CRPS) type II in different presentations with moderate pain reduction. Counter-irritants, such as capsaicin have had limited success at providing analgesia for patients with neuropathic pain. Based on the currently available literature, the strongest analgesic effects for neuropathic pain tend to be observed with lidocaine patch 5 per cent, capsaicin, and amitriptyline/ketamine combinations

Key words: herpes zoster, neuropathic pain, topical agents, opioid receptors, amitriptyline, ketamine.

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MULTIMODAL APPROACHES TO THE MANAGEMENT OF NEUROPATHIC PAIN: THE ROLE OF TOPICAL ANALGESIA

The pathophysiology of neuropathic pain

Nervous system lesions from various etiologies, including diabetes, trauma, malignancy, and herpes zoster infection, have generated chronic and severe intractable pain or "neuropathic pain" for a portion of patients who have had these diverse conditions (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, a stimulus is applied to the skin, the information is transferred to the central nervous system (CNS) via activation of the sodium channels that convert this mechanical stimulus into an electrical signal. This is called transduction (1). Then, the electrical signal moving through the peripheral nerves to the CNS through is called conduction. 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 will modulate this signal. Thus, if the nociceptive input reaches the higher CNS centers, this will result in the perception of pain that will trigger a neuroendocrine and/or sympathetic response and a skeletal muscle spasm. Thus, transduction can be inhibited by therapies that modulate pain at the periphery as with topical analgesics, while transmissions can be modulated by activation of the descending inhibitory pathways from the CNS and other mechanisms that block the transfer of the signal from the dorsal horn of the spinal cord to the spinothalamic tract that may eventually transmit the nociceptive input to the cerebral cortex and limbic system.

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. Furthermore, 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 (ATP), 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 decrease the threshold for activation of nociceptors. The resulting vasodilation and inflammation sensitizes 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, neuro-modifications 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-dependant physiological pain, neuropathic pain arises spontaneously (1). Three mechanisms are responsible for the pacemaker-like activity that is one of the sources of neuropathic pain. Ectopic activity in peripheral neurons may be mediated by the abnormal expression of sodium channels. Additionally, injured peripheral nerves may undergo localized demyelination and/or develop altered cell bodies. These abnormalities lead to ectopic activity in the dorsal root ganglia, where either peripheral and/or central spontaneous discharges generate electrical activity (2).

Other reversible changes can increase the hypersensitivity of nociceptors, and result in peripheral sensitization (2). For example, peripheral nociceptors may become sensitized when inflammatory signaling molecules trigger the phosphorylation of tetrodotoxin (TTX) resistant sensory-neuron specific sodium ion channel SNS (3). 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 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 (VR-1) and SNS receptors are up-regulated, which also helps to lower the threshold for nociceptor activation (1).

Input from peripheral nociceptors can induce central sensitization, as well (4). 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 aminobutyric acid (GABA) and glycine, in particular. N-methyl-D-aspartate (NMDA) and amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) 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. The loss of cells that inhibit pain transmission promotes disinhibition (1).

Molecular targets for topical analgesia to treat neuropathic pain

Because research conducted in the past 3-5 years has identified many peripheral antagonists and their respective receptors, pharmacotherapies which specifically target mechanisms required for transduction of pain signals to the CNS have been developed. In the acute phase, transduction may be blocked by reducing cyclooxygenase-2 enzyme activity through COX-1 and COX-2 selective inhibitors, to 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 (4). Though, 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 SNS/PN3. These abnormalities all contribute to prolonged nociceptive depolarizations 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. Hence, agents which profoundly reduce neurotransmitter release from nociceptors generating ectopic pulses, such as topical local anesthetics and anticonvulsants, can relieve neuropathic pain (4). 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 adjuncts such as NSAIDs and capsaicin (4). 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-blockers and clonidine. Topical antihistamine may decrease the release of the histamine and serotonin, in order to limit the inflammatory process and hinder vasodilatation. Topical opioids can target the opioid receptors present on nociceptive fibers and mast cells. Binding of opioid receptors can inhibit the release of 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) (5).

Many topical agents are commonly used for the treatment of neuropathic pain, despite either unavailable or poor quality randomized, controlled trial data. The tricyclic antidepressants, amitriptyline and doxepin, and the NMDA antagonists, ketamine, amantadine, dextromethorphan, and orphenadrine have been utilized in an off-label manner to treat neuropathic pain. Among local anesthetics, lidocaine has frequently been used to provide neuropathic pain relief; although in Europe, tetracaine and ropivacaine have also been used. Counter-irritants that target transient receptor potential (TRP) channel proteins are in common use, especially capsaicin. Although originally developed as an

antihypertensive agent, the -2 adrenergic agonist, clonidine, has been applied topically to provide pain relief by interrupting the ectopic pulses generated by sympathetic afferent nerves (3). Tizanidine has been used as well, but with little supporting evidence in the literature. Topical NSAIDs, such as aspirin, indomethacin, diclofenac, and benzydamine, (6) have been used to treat neuropathic pain, although with inconsistent results (7) and likely with a rubefacient mechanism-of-action (8). 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 (3). Pentoxifylline, the tumor necrosis alpha (TNF-α) 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. 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 (9). Likely, the pain relief mechanism also involves the hyperpolarization of nicotinic ganglia by alpha$_2$-adrenergic stimulants (10). The analgesic effectiveness of a topical alpha$_2$-adrenergic agonist, clonidine, was investigated in six patients with chronic pain and hyperalgesia (9). Patches delivering 30 g/cm^2/day (either 7.0 or 10.5 cm2 in size) were applied for a maximum of seven days; ongoing pain was assessed by VAS, 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 (9). Transdermal clonidine was also investigated for relief of pain due to diabetic neuropathy in a study with a two-stage enriched enrollment design (11). The twelve 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 per cent less pain than placebo (95 per cent confidence interval CI: 4-35 per cent 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.(11) 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. (12) Overall, the neuropathy group had a 30 per cent reduction in pain and a 59 per cent reduction among treatment responders, compared to a 55 per cent overall reduction and a 94 per cent reduction for treatment responders among patients with neuralgia. Yet, the difference between the groups was not statistically significant (12).

N-methyl-D-aspartate (NMDA) antagonists

While there is no published literature that supports the use of topical amantadine, dextromethorphan, or orphenadrine for neuropathic pain, case reports (13,14) and studies conducted with healthy volunteers (15,16) 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 a following section. It has been proposed that topical ketamine targets both peripheral opioid receptors, and sodium and potassium channels to reduce pain (13). Also, recent research has suggested that ketamine may alter the "docking station" for vesicles containing neurotransmitters, such as glutamate (Dunteman E. Targeted peripheral analgesics in chronic pain syndromes. Practical Pain Management. July-August 2005, pp 14-19). 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 provide neuropathic pain relief by reducing ectopic discharges in superficial somatic nerves (10). Lidocaine patch 5 per cent 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 per cent lidocaine and 2.5 per cent prilocaine), was investigated in a study of 11 patients with PHN.110 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 (17).

Recent studies have elucidated further mechanisms by which topical lidocaine can induce analgesia. When lidocaine patch 5 per cent 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. Also, the patch provides a barrier against potential sources of mechanical stimulation (i.e. bedclothes) which can provoke allodynia in some patients.

Pharmacokinetic studies conducted with 10 healthy volunteers showed that four lidocaine patches continuously applied for 72 hours and changed every 12 hours yielded steady state plasma concentrations of 225 ng/mL (18). Approximately, the concentration was 8-fold and 25-fold lower than the typical concentration of lidocaine required to produce antiarrhythmic effects or 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 (18). Overall, lidocaine 5 per cent delivered in a patch has a minimal risk of systemic absorption. When used according to the recommended dosing instructions, approximately 3 ± 2 per cent of the lidocaine dose is typically absorbed, resulting in an approximate mean peak blood concentration of 0.13 g/mL. This has tremendous implications for patients that require polypharmacy, such as the elderly, as well as for patients that may not tolerate the doses of oral medications required to achieve adequate analgesia. Improved analgesia may be obtained by a multimodal approach that utilizes several medications with multiple modes of action, taken at lower doses.

Several controlled clinical trials have demonstrated the efficacy of the lidocaine patch 5 per cent for relief of pain from PHN. Most recently, two publications reported a randomized, controlled trial of 96 patients (19) and an open-label, nonrandomized study of 332 participants (20). In the randomized study, following 3 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 = .043) Also, the study documented a 25 per cent improvement in the quality of analgesia for the treatment group from baseline (19). The second effectiveness trial in PHN conducted in 2002 demonstrated that 65.8 per cent of patients had improvements in pain intensity within the first week of therapy, and 77 per cent of patients reported an improvement in their quality of life (P=.0001) (20). At study completion at 28 days, 58 per cent 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, anti-depressants, and opioids. Thus, the study documented the successful use of the patch as an adjuvant to an already-established therapy (20).

The effectiveness, tolerability, and impact on quality of life of lidocaine patch 5 per cent for patients with DPN was studied in a three-week trial conducted by Barbano and colleagues (21). Significant improvements (30 per cent reduction) from baseline in mean daily diary pain ratings were documented by 70 per cent 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 administered lidocaine patch 5 per cent add-on therapy and the placebo group after seven days (P=.0002) (22).

Tricyclic antidepressants (TCAs)

More widely used in Europe, topical tricyclic antidepressants, such as doxepin and amitriptyline, have demonstrated efficacy in a number of neuropathic pain states (23,24). Amitriptyline provides pain relief via multiple pharmacologic mechanisms, including inhibiting norepinephrine and serotonin reuptake, blocking NMDA and 2-adrenergic receptors, and impeding sodium and voltage-gated potassium and calcium channels (25,26). A study of the transdermal delivery of amitriptyline found a dose-dependant analgesic effect that was greater and with longer duration than the corresponding concentration of lidocaine (26). For example, 100 mM of lidocaine induced a maximal analgesic effect of 45.9 ± 4.2 per cent (mean ± SEM number of pinpricks without response) with full recovery at 15 h, while the same concentration of amitriptyline had a maximal analgesic effect of 70.8 ± 15.0 per cent, with complete recovery at 25 h (26). However, when concentrations high enough to produce a local anesthetic block were applied to rats, amitriptyline was found to cause Wallerian degeneration of peripheral nerve fibers (25). 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 mayor as 500 mM induces skin injury in rats (25). In the clinical studies of amitriptyline, ketamine was co-administered in order to minimize the concentrations required for an analgesic effect, and the resulting side effects (27). A randomized, placebo controlled study considered the topical administration of 2 per cent amitriptyline, 1 per cent ketamine, and a combination of both in 92 patients with diabetic peripheral neuropathy (DPN), postherpetic neuralgia (PHN), or complex regional pain syndrome (CRPS) type II (28). Lynch and colleagues found no significant differences in 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 (28). A longer duration study (6 to 12 months) found no systemic absorption and minimal adverse events (29). A recent randomized placebo controlled trial examined a higher dose of topical 4 per cent amitriptyline and 2 per cent ketamine using an enriched enrollment design (30). In phase I of the trial, 52 per cent (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 per cent amitriptyline-2 per cent ketamine, 2 per cent amitriptyline-1 per cent ketamine, or placebo cream for an additional 2 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 (NS), and 4.34 for the control. The difference was significant between the high dose treatment group and the placebo group (P=0.026). The number of patients attaining a 30 per cent reduction in pain intensity was 46 per cent for the higher-dose cream, 26 per cent for the lower-dose cream, and 19 per cent 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 per cent of the participants and those measurable were well below therapeutic levels (30).

Although there is less published data supporting the topical application of doxepin for neuropathic pain, the initial reports have suggested potential benefit. Studies in rat suggest 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 control ($P < 0.05$) (31). Epstein and colleagues also recorded oral numbness for a period of 4 h after rinsing with doxepin among healthy human volunteers, suggesting an anesthetic effect (32). Yet, the authors suggest 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 (33). On average, participants reported a 70 per cent maximum decrease in pain ($P < 0.0001$) and of those who were responsive to treatment, 95 per cent experienced pain relief within 15 min of rinsing with doxepin (33). Also, a case study reported the benefit of topical doxepin for complex regional pain syndrome (34).

Counter-irritants

Counter-irritants, such as capsaicin have had limited success at providing analgesia for patients with neuropathic pain. Topical formulations of capsaicin did not have demonstrated efficacy in controlled trials of patients with HIV-associated neuropathic pain (35) and painful distal polyneuropathy (36), however studies of patients with diabetic peripheral neuropathy (37) and postherpetic neuralgia (38,39) administered 0.075 per cent capsaicin cream reported benefit. A meta-analysis of trials on the effectiveness of topical capsaicin for the treatment of diabetic neuropathy, osteoarthritis, and postherpetic neuralgia showed capsaicin cream provided more pain relief to patients with diabetic neuropathy than placebo. The calculated odds ratio (OR) and corresponding 95 per cent confidence interval (OR=2.74; 95 per cent CI=1.73, 4.32) also favored capsaicin cream.

In addition, a large, eigth-week, double blind trial which compared capsaicin with oral amitriptyline, found equal analgesia for patients with diabetic peripheral neuropathy (40). Seventy-six percent of the patients reported a 40 per cent 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 were limited to application site reactions, such as burning sensations, while the amitriptyline group reported numerous potentially serious systemic adverse Additionally, capsaicin leads to the morphologic degeneration of unmyelinated C-fiber afferent neurons in the epidermis. Furthermore, capsaicin 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.

Infrequently, other counterirritants have been used to provide analgesia for neuropathic pain. For example, another TRP 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 (41). 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 (6).

Conclusions

There is good evidence supporting the use of topical analgesic effects in neuropathic pain, especially in view of the typical low incidence of side effects. Likely, the best approach may be to utilize them as part of a multimodal therapeutic program. Based on the currently available literature, the strongest analgesic effects for neuropathic pain tend to be observed with lidocaine patch 5 per cent, capsaicin, and amitriptyline/ketamine combinations. Combinations of drugs are an attractive alternative, as analgesic approaches which have multiple types of targets often produce an additive or even synergistic effect, or have improved pharmacokinetics. 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 per cent doxepin, and 0.025 per cent capsaicin, than either agent alone (23). Yet, variability in topical preparations can be an issue, as compounding pharmacies often have unique recipes. Continuing research will elucidate how analgesic therapy can best be implemented for patients with neuropathic pain.

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