Topical analgesics for neuropathic pain: Preclinical exploration, clinical validation, future development

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Abstract

Topical analgesics applied locally to skin or to specialized compartments modify pain by actions on sensory nerve endings and/or adjacent cellular elements. With this approach, there are low systemic drug levels, good tolerability and few drug interactions, and combination with oral formulations is feasible. The goal of this review is to provide an overview of the potential for topical analgesics to contribute to improved management of neuropathic pain. Mechanistic and preclinical studies indicate much potential for development of novel topical analgesics for neuropathic pain. In humans, two topical analgesics are approved for use in post-herpetic neuralgia (lidocaine 5% medicated plaster, capsaicin 8% patch), and there is evidence for efficacy in other neuropathic pain conditions. Comparative trials indicate similar efficacy between topical and oral analgesics. Not all individuals respond to topical analgesics, and there is interest in determining factors (patient factors, sensory characteristics) which might predict responsiveness to topical analgesics. There is a growing number of controlled trials and case reports of investigational agents (vasodilators, glutamate receptor antagonists, α2-adrenoreceptor agonists, antidepressants, centrally acting drugs), including combinations of several agents, indicating these produce pain relief in neuropathic pain. There is interest in compounding topical analgesics for neuropathic pain, but several challenges remain for this approach. Topical analgesics have the potential to be a valuable additional approach for the management of neuropathic pain.

1. Introduction

Epidemiological estimates of neuropathic pain indicate a prevalence of 1%–2% based on specific causes, but 6%–8% based on reports of symptoms in the general population (Smith and Torrance, 2012). Several major classes of analgesics are available for the management of neuropathic pain, antidepressants, anticonvulsants, opioids and adjuvant analgesics (Attal et al., 2010; Dworkin et al., 2010; Finnerup et al., 2010), but systemic analgesics are limited by partial efficacy and adverse effects (Tölle, 2010). One means of addressing this is to use combinations that recruit different mechanisms of action (Backonja et al., 2006; Vorobeychik et al., 2011). If synergy or additivity occurs, there could be analgesic-sparing (reduced doses) and fewer adverse effects, but the approach may continue to be limited by adverse effects. Topical analgesics (e.g. creams, gels, patches) are formulated for local delivery to the skin, with effects on pain resulting from actions on sensory nerve endings and adjacent tissue following dermal penetration of the drug. This leads to low systemic drug levels and fewer systemic adverse effects compared to oral analgesics, and safety is one reason for considerable interest in the development of novel topical analgesics (Cairns, 2009). Another reason is the growing understanding of molecular mechanisms involved in pain signalling.
within the peripheral compartment, leading to exploration of novel targets. Topical analgesics also are amenable to rational multidrug therapy because this approach can produce additional analgesia and analgesic-sparing effects without increasing the side effect burden. Thus, topical analgesics can be given as an add-on to oral analgesics or as combinations of different topical agents.

There is a considerable preclinical literature demonstrating that drugs applied locally to the peripheral compartment alleviate sensory hypersensitivity pain responses (behaviours, mechanical allodynia, thermal and mechanical hyperalgesia). In addition, there is a growing clinical literature demonstrating that topical analgesics provide pain relief in a variety of neuropathic pain conditions, providing proof-of-concept validation for the approach. This literature includes randomized-controlled trials, comparative studies and add-on trials with oral analgesics. There is also a growing number of case studies that indicate topical analgesics can produce good outcomes in conditions previously not well managed by other approaches. The purpose of the current review is to provide an overview of the growing potential for topical analgesics to contribute to improved management of neuropathic pain by considering mechanistic issues related to the peripheral compartment, preclinical exploration of peripherally applied analgesics in relevant pain models, findings in clinical studies and issues related to the further development of topical analgesics for neuropathic pain. Two other recent reviews, focusing on topical analgesics for acute and chronic pain (Argoff, 2013) and use of compounded medications for neuropathic pain (Zur, 2013), have recently been published.

2. Mechanisms of neuropathic pain

2.1 Definitions and aetiology

The International Association for the Study of Pain has adopted the definition of neuropathic pain as ‘pain arising as a direct consequence of a lesion or disease affecting the somatosensory system’ (Treede et al., 2008). This supersedes the previous definition of ‘pain initiated or caused by a primary lesion or dysfunction in the nervous system’, and has been subject to debate (Jensen et al., 2011). In some contexts, neuropathic pain may represent a spectrum, with pain having greater or lesser neuropathic contributions (Bennett et al., 2006). Neuropathic pain can arise from: (1) local lesions to the peripheral nervous system [e.g. post-traumatic neuralgia, post-herpetic neuralgia (PHN)], (2) generalized lesions of the peripheral nervous system [e.g. painful diabetic neuropathy (PDN), human immunodeficiency virus (HIV) neuropathy, drug- or toxin-induced neuropathy], (3) lesions within the central nervous system (e.g. spinal cord injury, multiple sclerosis, stroke), (4) complex disorders [e.g. complex regional pain syndrome (CRPS)], and (5) mixed-pain syndromes (e.g. chronic low back pain, radiculopathy) (Baron, 2010). Clinical manifestations of neuropathic pain include spontaneous symptoms (e.g. paresthesia, superficial pain, paroxysmal pain), negative sensory symptoms (e.g. hypoesthesia, hypoalgesia, thermohypoesthesia) and positive sensory symptoms (e.g. mechanical dynamic or static allodynia, mechanical punctate hyperalgesia, heat and cold allodynia) (Baron, 2010). Symptoms expressed (neuropathic pain phenotype) have been proposed to reflect particular aspects of neuronal mechanisms involved; sensory nerve damage produces negative symptoms, peripheral sensitization increases pain sensitivity, and ectopic activity generates spontaneous pain and central sensitization amplifies pain and reduces sensory thresholds (von Hehn et al., 2012).

2.2 Models and mechanisms

In recent decades, a variety of animal models for neuropathic pain have been developed. These include injury to peripheral nerves (transection, ligation, constriction, cuffing, partial ligation, neuritis, laser injury), central pain models (weight drop, compression, chemical injury, photochemical lesions), disease models (e.g. diabetes), chemotherapy-induced neuropathy models (platinum compounds), cancer models and vascular injury models (Jaggi et al., 2011).
Mechanisms involved in neuropathic pain occur at many levels of the pain signalling neuraxis, and include peripheral sensitization, central sensitization in the dorsal spinal cord and changes in cortical and subcortical regions. Neuronal mechanisms and neuroplasticity received initial attention for explaining sensory changes following nerve injury, but glia (microglia, astrocytes) are now known to be activated following nerve injury, to modulate synaptic function and neuronal excitability, and contribute to the development and maintenance of neuropathic pain. Several comprehensive reviews outlining mechanisms involved in neuropathic pain are available (Scholz and Woolf, 2007; Costigan et al., 2009; McMahon and Malcangio, 2009; Milligan and Watkins, 2009; von Hehn et al., 2012).

2.3 Peripheral nerve fibre plasticity

Sensory afferents provide the organism with information about its environment and serve several functions. Signalling occurs via Aβ, Aδ and C fibres which differ in their electrophysiological properties, morphology, site of termination in the spinal cord, molecular expression of functional molecules and sensory perceptions encoded (Albrecht and Rice, 2010; Gold and Gebhart, 2010). Sensory afferents innervate, or interact with, the dermis, glands, vasculature and immune cells, and the peripheral nervous system plays an important neuro-immuno-endocrine role (Roosterman et al., 2006; Chiu et al., 2012). Following nerve injury, peripheral aspects of sensory nerves undergo changes that result in amplification of the signal entering the spinal cord. Many drugs applied topically to treat neuropathic pain are considered to act on ion channels, receptors and other targets on these peripheral nerves, but it is now clear that additional actions on adjacent cellular elements and tissues also occur (section 3).

Several peripheral neuropathic pain conditions are associated with a loss of small fibre sensory afferents. Thus, skin biopsy methods have demonstrated loss of epidermal small fibre innervation in several forms of peripheral neuropathic pain (Ebenzer et al., 2007; Albrecht and Rice, 2010). The seeming paradoxical association of loss of epidermal nerve fibres with neuropathic pain may result from remaining innervation becoming hypersensitive (irritable nociceptor hypothesis) or deafferented neurons within the spinal cord exhibiting increased spontaneous activity (deafferentation hypothesis) (Albrecht and Rice, 2010). Some studies suggest that reduced epidermal innervation might predict neuropathic pain intensity (Polydefkis et al., 2002; Sorensen et al., 2006). However, with herpes zoster, while more severe sensory abnormalities were associated with lower epidermal innervation, sensory responses recovered within 6 months but there was no recovery in innervation at that time (Petersen et al., 2010). Furthermore, there is not a simple relationship between epidermal innervation density and clinical symptoms of pain or patterns of function in neuropathic pain (Kharkar et al., 2012; Schley et al., 2012).

In addition to denervation neuropathies, where there is loss of epidermal nerve fibres, there also appear to be painful syndromes associated with increased nociceptor density. Examples of these conditions include vulvodynia, burning mouth syndrome, interstitial cystitis, rectal hypersensitivity, gastro-oesophageal reflux diseases, inflammatory and irritable bowel disorders, post-surgical breast pain and allergic rhinitis (Anand and Bley, 2011). These conditions do not meet the definition of neuropathic pain as resulting from a lesion or disease affecting the somatosensory system (Treede et al., 2008), but proliferation, sprouting and aberrant innervation may be involved (Anand and Bley, 2011). There are case studies indicating some of these proposed hyperinnervation conditions also respond to topical analgesics (section 4.4).

2.4 Peripheral tissue plasticity

Skin cells provide physical and trophic support for nerve endings, and participate in homeostasis, barrier functions and wound repair; they are also part of an integrated neuro-immuno-cutaneous system and contribute to peripheral sensory signalling (Lumpkin and Caterina, 2007; Boulais and Misery, 2008; Dussor et al., 2009). Keratinocytes are the main cell type in the dermis and epidermis, proliferate from a basal cell layer at the dermal junction, undergo coordinated differentiation and migration and form a stratified epithelium. Several observations support a role for keratinocytes in sensory transduction and signalling. Thus, (1) keratinocytes secrete mediators that can activate or inhibit sensory neuron function [e.g. nerve growth factor (NGF), adenosine 5′-triphosphate (ATP), β-endorphin, interleukins, endothelin-1, calcitonin gene-related peptide (CGRP)], and (2) keratinocytes express channels and receptors involved in signalling and modulating pain [transient receptor potential vanilloid-1 (TRPV1), TRPV3, TRPV4 channels; several P2X and P2Y receptors; cannabinoid (CB)2, neurokinin-1 and CGRP receptors] (Lumpkin and Caterina, 2007; Dussor et al., 2009; Smith, 2009). Melanocytes (produce melatonin in response to ultra
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3. Preclinical studies and peripheral mechanisms of drug action

Primary sensory afferent neurons are the initial generators of noxious input and convey this information to the spinal cord. Attenuating signalling by local delivery of drugs to the peripheral compartment, with actions on sensory neurons and adjacent structures, is a rational therapeutic approach and one that is increasingly being validated by clinical studies. Many voltage- and ligand-gated ion channels and receptors on sensory neurons are implicated in such signalling, and there is considerable interest in further exploring this compartment and developing novel topical analgesics. This section will provide an overview of drug targets being explored in the preclinical literature for neuropathic pain, and consider mechanisms of action of agents that are approved for human use or are being used as investigational topical analgesics.

3.1 Sodium channel blockers

Nociceptors respond to stimuli by generating and propagating action potentials which depend on voltage-gated Na⁺ channels. Nine pore-forming α-subunits for Na⁺ channels (Na,1.1–1.9), with differing kinetics and voltage-dependent properties, have been identified; functional properties reflect expression of α-subunits, as well as influences of β-subunits and proteins mediating phosphorylation or trafficking of the α-subunits to the cell membrane (Dib-Hajj et al., 2009, 2010). Na,1.3, Na,1.7, Na,1.8 and Na,1.9, which are expressed on sensory afferent nerves and exhibit plasticity following injury and inflammation, have received particular attention in relation to pain (Dib-Hajj et al., 2009, 2010). Most functional and expression studies have involved dorsal root ganglion (DRG) cell bodies which are amenable to electrophysiological and molecular analysis, but Na, 1.6–1.9 channels have now been identified on epidermal nerve terminals (Persson et al., 2010). Na,1.7 channels have received particular attention since identification of gain- and loss-of-function genetic mutations that result in clinical conditions with marked changes in pain expression (Dib-Hajj et al., 2009, 2010). Na,1.8 channels have also received attention, as expression was regarded as selective for small diameter sensory afferent neurons (the basis of Na,1.8-Cre conditional knockout technology); however, this channel has now been identified in large diameter myelinated afferents and some conclusions regarding this channel may need to be revised (Shields et al., 2012). Development of Na⁺ channel subtype selective antagonists has been an attractive drug development goal, but selectivity has been difficult to achieve due to homology between subunits (Gold, 2008).

Topical lidocaine, as medicated plaster or patch, is a topical analgesic currently approved for use for PHN in the United States and several European countries (section 4.1). Its proposed mechanism of action is via non-selective block of Na⁺ channels on sensory afferents at the site of application, resulting in reduced ectopic discharge and reduced signal propagation (Gammaitoni et al., 2003). However, in healthy human volunteers, lidocaine medicated plaster (LMP) produces partial and variable effects on various sensory thresholds as determined by quantitative sensory testing (QST) (Lam et al., 2011; Krumova et al., 2012).
In clinical populations with PHN, topical LMP is effective in nociceptor-deprived skin, and clinical responses to lidocaine are not predicted by epidermal nerve fibre density or QST (Wasner et al., 2005; Herrmann et al., 2006). These observations suggest that Na+ channel block on nerve endings may not entirely account for topical lidocaine actions. Systemic actions are unlikely, as kinetic studies indicate minimal absorption (Gammaitoni et al., 2003); there are, however, suggestions that ultra-low doses of lidocaine produce analgesia by central actions (Xiao and Bennett, 2008). Actions of lidocaine on nerve endings at deeper somatic sites and on resident cells within the skin may contribute to efficacy (Herrmann et al., 2006). Keratinocytes release chemokines and cytokines, undergo plasticity following injury, and engage in keratinocyte-neuron and keratinocyte-keratinocyte signalling, and actions on such cells could contribute to its local effects. Local anaesthetics exhibit a range of anti-inflammatory actions on immune and other cells (Cassuto et al., 2006), and these could contribute to the clinical efficacy of LMP when inflammation is involved. Lidocaine also activates TRPV1 and TRPA1 channels (Leffler et al., 2008, 2011), and such actions may contribute to topical analgesia by lidocaine. Application of LMP for 42 days leads to a reduced epidermal nerve fibre density (Wehrfritz et al., 2011), an effect also seen with capsaicin (section 3.2). Given that there can be a loss of epidermal nerve fibres in several forms of neuropathic pain (section 2.3), the seeming paradox of both the condition itself and the treatment resulting in reduction in epidermal nerve fibres requires further understanding.

### 3.2 Capsaicin and TRP channels

The cloning of the TRPV1 channel in 1997, together with recognition of its presence on small diameter sensory nociceptors and responsiveness to heat, protons, endogenous agents and capsaicin (pungent ingredient in chilli peppers), opened up a new era of understanding peripheral sensory signalling (Lumpkin and Caterina, 2007; Szallasi et al., 2007). The TRPV1 channel is one member of a family of channels that includes TRPV2, TRPV3, TRPV4, TRPM8 and TRPA1; these respond to different temperatures, pressure and osmolality, exogenous compounds in the diet and environment, and several endogenous mediators, and are receiving considerable attention as potential novel analgesic targets (Premkumar and Abooj, 2013).

TRPV1 is a six-transmembrane-spanning protein, functions as a non-selective cation channel with a high Ca2+ permeability, is expressed on peripheral terminals of small diameter nociceptors, and functions as a polymodal receptor leading to sensory nerve activation (Lumpkin and Caterina, 2007; Szallasi et al., 2007). Inflammatory mediators potentiate actions by phosphorylation via protein kinases A and C, while other kinases and phosphatases mediate desensitization and tachyphylaxis (Szallasi et al., 2007; Premkumar and Abooj, 2013). Capsaicin, a TRPV1 agonist, is available as a topical analgesic cream in low concentrations (0.025%–0.075%), and as a patch formulation at a higher concentration (8%) (section 4.2). Initially, the effect of capsaicin on TRPV1 receptors leads to depolarization, activation and sensitization of nerve endings and results in localized burning sensations; repeated application or a high concentration produce analgesia due to desensitization and functionalization (Anand and Bley, 2011). In healthy volunteers, degeneration of nerve terminals within the epidermis occurs following repeated application of 0.075% capsaicin for 3 weeks (Nolano et al., 1999) and acute application of the high concentration patch (Malmberg et al., 2004; Kennedy et al., 2010); reinnervation occurs over time (6 weeks cream, 12–24 weeks patch). Given that there can be a loss of epidermal nerve fibres in several forms of neuropathic pain (section 2.3), the seeming paradox of both the condition itself and the treatment resulting in reduction in epidermal nerve fibres requires further understanding.

### 3.3 Opioids

Multiple opioid receptors (ORs) (μ, δ or δ-ORs, κ- or κ-ORs) are present on sensory nerve endings and respond to endogenous opioids derived from immune cells as well as to opioids that are delivered exogenously (Stein et al., 2009). ORs are expressed in small, medium and large diameter DRGs, and are transported to peripheral nerve terminals where they are coupled to Gi and Go proteins that respectively inhibit adenyl cyclase and modulate ion channels, particularly Ca2+ and Na+ channels. There are reports of both up-regulation and down-regulation of mRNA and/or protein for multiple ORs in DRGs following various forms of nerve injury (Obara et al., 2009; Stein et al., 2009).

The functionality of peripheral ORs following nerve injury has been examined by systemic delivery of a peripherally restricted opioid agonist (loperamide) and by local intraplantar (i.pl.) delivery of selective OR agonists. Systemic loperamide reversed mechanical allodynia following L5 spinal nerve ligation, an action blocked by systemic methylnaltrexone (peripherally acting antagonist), and by i.pl. methylnaltrexone and...
CTAP (selective MOR antagonist) (Guan et al., 2008), confirming a peripheral action when administered systematically. In addition, i.pl. loperamide reversed mechanical allodynia and thermal hyperalgesia following spinal nerve ligation (Guan et al., 2008; Chung et al., 2012). Following chronic constriction injury, i.pl. administration of MOR, DOR and KOR agonists led to reduction in tactile allodynia and thermal hyperalgesia which was reversed by respective antagonists, but did not change responses in the contralateral paw indicating local peripheral actions (Obara et al., 2009). Doses required for MOR and KOR agonists to produce analgesia in neuropathy were much higher than that in a model of inflammation, while DOR agonists were effective in similar doses in both models (Obara et al., 2009). Such preclinical results suggest that selective peripheral administration of opioids for neuropathic pain, especially DOR agonists, may be useful to consider for further exploration.

Peripheral opioid analgesia is prominent following inflammation, and there is a clinical literature on analgesia resulting from intra-articular administration of morphine following arthroscopic procedures (Kalser et al., 2002; Stein et al., 2009). Given that neuropathic pain can involve elements of inflammation and immune and glial cell involvement, topical opioids might be amenable to exploration in such conditions. Topical opioids have been explored to some extent in palliative care settings but there is a need for more systematic studies (LeBon et al., 2009).

### 3.4 Cannabinoids

CB1 receptors are expressed on sensory nerve endings in the periphery, in the dorsal spinal cord, and in supraspinal brain regions important for pain signalling. While systemic administration of agonists suppresses pain responses in inflammatory and neuropathic pain models, the potential for systemic CB1 receptor agonists to be analgesics in humans is limited by their psychoactive properties (Walker and Hohmann, 2005). However, there is potential for CB1 agonists to suppress pain following peripheral actions, as CB1 receptors are present in DRG cells and transported to the periphery, while local peripheral administration of CB1 agonists suppresses pain responses (Walker and Hohmann, 2005). More recently, additional methods have been used to explore the contribution of peripheral sites to CB1 agonist actions. Thus, conditional deletion of CB1 receptors in sensory neurons shows reduced effects of systemic and peripheral administration of WIN 55,212-2 (CB1 and CB2 agonist) in inflammation, and of systemic WIN 55,212-2 following nerve injury (Agarwal et al., 2007). Furthermore, systemic administration of a peripherally restricted CB1 agonist (AZ111713908) produced analgesia in inflammatory and neuropathic pain models with its action reduced in CB1 receptor knockout mice (Yu et al., 2010).

CB2 receptors are expressed on immune cells in the periphery and on glial cells in the central nervous system (Guindon and Hohmann, 2008; Anand et al., 2009). CB2 receptors are not normally detected in DRGs, but, following nerve injury, they are observed on central and peripheral aspects of sensory neurons, and CB2 mRNA in DRGs is up-regulated (Wotherspoon et al., 2005; Hsieh et al., 2011). There is also evidence for CB2 receptors in human primary sensory afferents in injured fibres in skin and in synovium (Anand et al., 2008). Local i.pl. administration of CB2 agonists in rodents produces pain suppression in inflammatory and nerve injury models (Gutierrez et al., 2007; Guindon and Hohmann, 2008). CB2 agonists inhibit release of inflammatory mediators (cytokines, growth factors) from immune cells, and this could reduce sensitization of afferents in inflammatory and neuropathic pain (Guindon and Hohmann, 2008; Anand et al., 2009). The CB2 agonist AM1241 can promote release of β-endorphin from keratinocytes to mediate peripheral antinociception (Ibramin et al., 2005), but other CB2 agents do not involve opioid mechanisms (Hsieh et al., 2011).

In humans, topical administration of the CB HU210 (CB1 and CB2 agonist) was demonstrated to reduce pain in human volunteers following intradermal capsaicin (Rukwied et al., 2003), suggesting the usefulness of exploring the peripheral compartment for delivery of cannabinoids. Whether localized topical delivery of cannabinoids will be useful for chronic pain management remains to be determined. It is important to note that cannabinoids and their derivatives are highly lipid soluble, and that following topical application, there is still the potential for systemic actions. Topical delivery of less lipid soluble derivatives merits attention.

### 3.5 α-Adrenergic receptors

Effects of peripheral delivery of α-adrenergic receptor (α-AR) agonists have been explored in the context of the influence of the sympathetic nervous system on pain (Baron et al., 1999; Gibbs et al., 2008; Coderre and Bennett, 2010) and potential analgesic effects (Pertovaara, 2006, 2009). Several observations are relevant: (1) sympathetic-sensory coupling occurs at multiple sites, including sensory nerve endings and within DRGs; (2) peripheral administration of nora-
drenaline (NA) to humans facilitates pain following inflammation and nerve injury; (3) upregulation or down-regulation of ARs occurs following inflammation and nerve injury; (4) both behavioural and electrophysiological studies support a pronoceptive role for peripheral α2-ARs and an antinociceptive role for peripheral α2-ARs; (5) some peripheral actions of ARs result from effects on immune or inflammatory cells; (6) influences of ARs on pain signalling can vary with pathological condition, time and strain of experimental animal (Pertovaara, 2006, 2009).

Several earlier clinical studies explored the potential for peripheral AR agonists to produce analgesia, an attractive approach for these agents because central actions lead to sedation and decreased blood pressure. Thus, a transdermal patch of clonidine (α2-AR agonist) was reported to provide some pain relief in some cases of sympathetically maintained pain (4 out of 6, Davis et al., 1991) and diabetic neuropathy (12 out of 41, Byas-Smith et al., 1995; 7 out of 24, Zeigler et al., 1992). Whether clonidine acted systemically or locally was not always clear, but some observations did suggest a locally mediated effect. More recently, preclinical studies have demonstrated that topical clonidine produces anti-hypersensitivity responses following nerve injury when applied to the hindpaw (Li et al., 2007; Ragavendran et al., 2013); furthermore, clonidine applied to the site of injury reduces hypersensitivity in inflammatory nerve injury (Romero-Sandoval and Eisenach, 2007). α2-AR actions on sensory neurons (reducing excitability), immune cells (reducing cytokine production) and microvasculature (improving blood flow) are variously implicated in such actions. These observations provide a rationale for continued exploration of topical clonidine in human clinical trials of neuropathic pain (Campbell et al., 2012).

### 3.6 Glutamate receptors

Multiple ionotropic and metabotropic glutamate receptors are present in DRG cells and on sensory afferent nerve endings (Miller et al., 2011). Glutamate is synthesized and packaged within sensory afferents, transported to the periphery, and then released in response to tissue injury and noxious stimulation; it may then function autologously on adjacent nerve endings (Miller et al., 2011). Peripheral N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and kainite receptors and Group I metabotropic glutamate receptors (mGluR1, mGluR5) enhance pain, providing a rationale for exploring peripheral administration of antagonists for these receptors as analgesics (Goudet et al., 2009; Miller et al., 2011). Peripheral actions of ketamine (NMDA receptor antagonist) have been explored in healthy human volunteers; when given by localized subcutaneous injection near the test site, ketamine attenuated some sensory indices of pain in an experimental burn injury model (Warncke et al., 1997; Pedersen et al., 1998), but had no effect on responses to intradermal capsaicin (Gottrup et al., 2004). When administered as a gel, ketamine 5% reduced pain responses to capsicain, but this occurred following applications to both sides of the body, and actions were considered to be systemic (Pöyhä and Vainio, 2006). However, in subjects with CRPS-1, topical ketamine 10% cream altered sensory function on the symptomatic side, but largely not on the asymptomatic side; minimal plasma levels were detected, suggesting a local action (Finch et al., 2009). Ketamine has been applied topically in several instances of neuropathic pain in randomized controlled studies and case reports (section 4.3, 4.4). Given the peripheral tissue plasticity that occurs in neuropathic pain (section 2.3, 2.4), the issue of whether responses in healthy volunteers adequately predict topical responses to ketamine remains to be decided.

### 3.7 Adenosine receptors

Adenosine A1 receptors (A1Rs) in the spinal cord and periphery are implicated in antinociception in acute, inflammatory and neuropathic pain (Zylka, 2011; Sawynok, 2013). A1Rs are expressed on small and medium diameter primary sensory neurons (Lima et al., 2010), as are nucleotidases [ecto-5'-nucleotidase (CD73), prostatic acid phosphatase (PAP)] that hydrolyse AMP to adenosine (Taylor-Blake and Zylka, 2010; Sowa et al., 2010b). Antinociception results from interactions with several recognized second messenger systems within neurons (Lima et al., 2010; Sowa et al., 2010a; Hurt and Zylka, 2012). With respect to neuropathic pain, peripheral administration of adenosine A1R agonists and PAP reduce hypersensitivity responses following nerve injury (Goldman et al., 2010; Hurt and Zylka, 2012).

The role of peripheral adenosine systems, and specifically activation of A1Rs on peripheral sensory nerves in inhibiting pain, is now receiving renewed attention. This reflects several developments including: (1) identification of nucleotidases (CD73, PAP) that generate endogenous adenosine from nucleotides in nociceptive circuits (Zylka et al., 2008; Sowa et al., 2010b); (2) implication of peripheral adenosine (and nucleotides) in acupuncture analgesia in mice...
3.8 Antidepressants

Oral administration of tricyclic antidepressants (e.g., amitriptyline, nortriptyline), as well as newer generation dual NA and serotonin (5-HT) reuptake inhibitors (e.g., duloxetine, venlafaxine), are well-recognized treatments for neuropathic pain (Attal et al., 2010; Dworkin et al., 2010; Finnerup et al., 2010). Antidepressants exhibit several pharmacological actions, including: (1) block of NA and 5-HT reuptake by inhibiting membrane transporters; (2) block of Na⁺ channels, as well as interactions with K⁺ and Ca²⁺ channels; (4) interactions with receptor systems known to participate in pain regulation (acetylcholine, histamine, opioid, α-adrenoceptors, β-adrenoceptors, γ-aminobutyric acid, adenosine, NMDA); (4) inhibition of release of inflammatory mediators; many of these mechanisms potentially may lead to antinociception following systemic administration of antidepressants (Micó et al., 2006; Verdu et al., 2008). In preclinical studies, peripheral administration of antidepressants produces antinociception in models of neuropathic pain (Esser and Sawynok, 1999; Ulugol et al., 2002), and many of the actions contributing to systemic analgesia also may contribute to peripheral activity. Antidepressants also exhibit local anaesthetic properties when injected close to the nerve (Gerner, 2004), but at high concentrations, neurotoxic effects are observed and caution is advised with this mode of administration (Strumper and Durieux, 2004). In humans, there are several controlled trials and case reports of pain relief following topical application of antidepressants both when given to somatic sites for neuropathic pain and when applied to specialized compartments (section 4.3, 4.4).

3.9 Vasodilators

Disturbances in deep tissue microvascular function are implicated in CRPS-1 (Coderre and Bennett, 2010), as well as in several other experimental forms of neuropathic pain (Ragavendran et al., 2013), and this provides a rationale for examining effects of topical delivery of vasodilators. Topical application of α₂-AR agonists (clonidine and apraclonidine), nitrates or NO donors (linsidomine, S-nitroso-N-acetylpenicillamine), and inhibitors of phosphodiesterase (pentoxifylline) and phosphatidic acid (lisofylline), all individually alleviate mechanical allodynia to some degree in a model of CRPS-1 when applied to the plantar hindpaw (Ragavendran et al., 2013). Topical combinations of several of these agents, at doses lower than when applied individually, also alleviate mechanical allodynia in this model, indicating a synergistic interaction (Ragavendran et al., 2013). These topical combinations of agents are also active in several other preclinical models of neuropathic pain (Ragavendran et al., 2013). There are now several clinical reports that topical delivery of vasodilators (glyceryl trinitrate, isosorbide dinitrate) can provide pain relief in diabetic neuropathy (Supporting Information Tables S1 and S2), providing support for the usefulness of this approach.

4. Clinical studies of topical analgesics for neuropathic pain

4.1 Lidocaine

A patch containing lidocaine (5% w/v, 10 × 14 cm, 3 patches/day for 12 h applied to intact skin, removal for 12 h; LMP) is approved for use for PHN in the United States and several European countries. A recent review has summarized efficacy and safety studies (randomized, controlled, open-label) and case reports using LMP up to early 2012 (Mick and Correa-Illanes, 2012). The patch is generally well tolerated and application site reactions are transient and resolve following patch removal. Lidocaine is proposed to act on voltage-gated Nax channels on abnormally excitable Aδ- and C-fibres leading to reduction in ectopic discharges and reduced spontaneous pain, allodynia and hyperalgesia; lidocaine actions in nociceptor deprived skin are less well understood, but may involve additional actions (section 3.1).

The efficacy of LMP for PHN in short- and long-term controlled trials and open-label studies is described in two comprehensive reviews of older (Davis and Galer, 2004) and subsequent studies (Garnock-Jones and
Keating, 2009). A systematic review of 5% LMP compared to other treatments for PHN indicates 5% LMP provides pain relief and reduces allodynia compared to placebo, with low adverse event rates (Wolff et al., 2011). An open-label trial compared topical 5% LMP with oral pregabalin for PHN, and this indicated a 66% response rate for LMP and 62% for pregabalin (Baron et al., 2009a). A combination extension trial of those with an inadequate response to monotherapy (either LMP or pregabalin) had a further reduction in pain with addition of the other treatment (Baron et al., 2009b; Rehm et al., 2010). Brain imaging in PHN patients with functional magnetic resonance imaging (fMRI) indicates that 5% LMP reduced spontaneous pain and neuropathic pain scores compared to baselines, and resulted in a reduction in activity in brain regions involved in sensory and affective, as well as reward-related, regions in response to pain (Geha et al., 2007).

The results of trials in which LMP has been used for other pain conditions were summarized recently (Mick and Correa-Illanes, 2012). For PDN, there are four open-label trials (Mick and Correa-Illanes, 2012), and all demonstrate reductions in pain compared to baseline. One PDN trial was larger (n = 204) and compared LMP to oral pregabalin; it reported a similar response rate of 60%–70% for the two treatments (Baron et al., 2009a). The 2012 review also summarizes studies for post-operative, post-traumatic and scar pain (n = 13), neuropathic pain (n = 7), CRPS (n = 2), cancer with neuropathic pain (n = 3), carpal tunnel syndrome (n = 2), myofascial pain (2), osteoarthritis (n = 3), low-back pain (n = 6), acute herpes zoster (n = 1) and acute surgical pain (n = 1) (Mick and Correa-Illanes, 2012). These trials represent a mix of designs (case reports, open-label trials, add-on trials, pilot studies, retrospective case series, placebo-controlled trials, comparative trials), and generally report reductions in pain (post- vs. pre-treatment) and improvements in quality of life. However, the number of study participants is limited (only 10 out of 40 trials have n > 50), and only some (9 out of 40) were placebo controlled trials.

A recent study has examined 5% LMP compared to a placebo patch and conducted parallel fMRI in chronic back pain patients (Hashmi et al., 2012). It showed that 50% of subjects in both placebo and LMP groups exhibited a > 50% reduction in pain, but there was no difference between LMP and placebo group outcomes. There was also no difference in the change in pain in responder subgroups for LMP and placebo. fMRI indicated decreases in brain activity related to pain in both groups following treatment. This study suggested that the patch itself produces a potent placebo effect in a significant number of chronic back pain patients. Given that all trials reporting benefits in low back pain have been open-label trials and case reports (Mick and Correa-Illanes, 2012), placebo effects may be important contributors to results reported in those trials.

### 4.2 Capsaicin

Topical formulations of low concentrations of capsaicin (0.025%–0.075%, creams, lotions, patches) have been widely available as an over-the-counter remedy for treatment of musculoskeletal and neuropathic pain since the early 1980s, although there are earlier reports of its use in folk medicine (Anand and Bley, 2011). Most clinical studies using these formulations (3–5 applications/day, for 2–6 weeks) were published before 2000. A recent review of low concentration capsaicin cream (0.075%) for neuropathic pain found n = 6 studies which were small and heterogeneous in terms of pain conditions; it concluded there was too little data for pooled analysis, that local skin reactions (erythema, burning) were common (number-needed-to-harm of 2.5) and that capsaicin was without meaningful effect beyond placebo (Derry and Moore, 2012). An earlier analysis of these studies had indicated a number-needed-to-treat (NNT) of 6.6 for neuropathic pain (Derry et al., 2009). A recent double-blind placebo controlled trial of 0.025% capsaicin gel for PDN reported no significant pain relief (Kulkantakorn et al., 2012). Treatment guidelines relegate topical capsaicin cream in low concentrations to a second- or third-line medication for those who cannot tolerate, or do not respond adequately to, first- and other second-line medications (Attal et al., 2010; Dworkin et al., 2010; Finnerup et al., 2010).

A high concentration capsaicin patch (8% w/w, trans-capsaicin, which is identical to the naturally occurring molecule, in an adhesive layer, NGX-4010) has been approved for use for PHN in the United States and for peripheral neuropathic pain in several European countries (McCormack, 2010; Haanpää and Treede, 2012). The patch is applied for 30 min or 60 min, and application site reactions (erythema, pain, pruritus, oedema) are controlled by ice, topical local anaesthetics, and oral analgesics for up to 5 days following treatment (Webster et al., 2011a, 2011b, 2012). Patch application results in reduced pain compared to a low concentration patch (0.04%, to control for local sensations) for up to 12 weeks in PHN (Backonja et al., 2008, 2010) and in HIV-distal polyneuropathy (Simpson et al., 2008). The long-term
safety of the capsaicin patch was examined for up to 1 year with three to four patch applications at intervals of > 12 weeks; there was no evidence of impaired neurological function (Simpson et al., 2010). Post hoc analysis of controlled PHN studies of NGX-4010 indicated that patients not using oral neuropathic pain medications reported a greater reduction in pain compared to those using oral medications, suggesting lack of additivity of the topical NGX-4010 with oral medications (Irving et al., 2012). Meta-analysis estimates NNT values for 30%–50% reductions in pain over time were 7.0–8.8 for PHN and 5.8–11.0 for HIV neuropathy (Derry et al., 2013). This analysis cautions against uncertain risks for epidermal innervation with repeated applications over long periods.

4.3 Investigational agents

There have been an increasing number of controlled trials examining the potential analgesic properties of topical applications of several investigational agents since circa 2000 (Supporting Information Table S1). Agents examined include vasodilators (isosorbide dinitrate, glyceryl trinitrate), α-adrenergic agents (clonidine), local anaesthetics (lidocaine), antidepressants (doxepin, amitriptyline), glutamate receptor antagonists (ketamine) and various combinations of these agents. Most trials are small (< 50 per group), although some involve n = 90–100/group (Barton et al., 2011; Campbell et al., 2012). Each trial is supported by a mechanistic rationale and preclinical observations, and this information shows promise for topical analgesics to assist in treating neuropathic pain. However, it is not always clear if optimal concentrations of individual agents, or combinations of agents, have been used. For some agents, there are also studies reporting on effects of topical applications of drugs in healthy volunteers, such as for amitriptyline (Gerner et al., 2003) or ketamine (Pöyhönen and Vainio, 2006), but in view of the tissue plasticity that occurs in neuropathic pain (sections 2.3, 2.4), it is not clear if these studies can adequately predict potential analgesic properties of these agents in clinical conditions.

There is also a growing number of case reports showing that topical applications of many of the agents examined in small trials exhibit analgesia, and these cover a diverse range of neuropathic pain conditions (Supporting Information Table S2). In many instances, several oral medications have already been tried, but the condition is considered refractory. Intriguingly, some of these reports indicate relief of central neuropathic pain (spinal intramedullary cavernoama, Kopsky et al., 2012a; multiple sclerosis, Kopsky et al., 2012b). A challenge inherent in these reports is the wide range of concentrations that seem effective (ketamine used from 0.5% to 10%, amitriptyline from 1% to 5%) (Supporting Information Table S2). Controlled trials also indicate use of a wide range of concentrations (Supporting Information Table S1). Further studies will need to standardize concentrations and explore the relative effectiveness in different neuropathic pain conditions. A pragmatic approach for case exploration could involve starting with low and moving to higher concentrations if there is no effect, sequential application of individual components, and exploration of different combinations of topical agents. Furthermore, when a favourable treatment response is obtained, N-of-1 trials (subject alternates between active topical treatment and placebo) are encouraged to distinguish the effect from placebo (e.g. Kopsky et al., 2012b). It is important to note that while topical analgesics are relatively safe, as demonstrated by incidence of adverse effects in trials and tolerability in individual case studies, there are limits to attend to in terms of composition (topical application of high concentration creams can function as a systemic delivery system; Scott et al., 1999), the degree of body surface covered (< 10% of body surface), the intactness of the skin where it is applied (disease conditions may enhance systemic absorption), and the total dose administered in relation to an oral equivalent. Thus, 10% amitriptyline produces systemic adverse effects (Kopsky and Keppel Hesselink, 2012), while extensive skin application of doxepin 5% (Zell-Kanter et al., 2000) or multiple local anaesthetic applications (Lutwak et al., 2013) lead to systemic toxicity. Considerations for compounding topical medications for neuropathic pain have recently been reviewed (Zur, 2013).

4.4 Local drug delivery to specialized compartments

There are now several clinical reports of topical analgesics providing pain relief for treatment of pelvic pain (rectal, genital and perineal pain). While these conditions are not necessarily neuropathic pain (section 2.3), they exhibit clinical features characteristic of neuropathic pain (burning pain, allodynia, spontaneous and provoked pain). There are case series reports that vulvodynia (localized, generalized) responds to topical gabapentin 2%–6% (n = 35, 80% response rate; Boardman et al., 2008), topical amitriptyline 2% (n = 150, 50% response rate; Pagano and Wong, 2012), and topical 2% amitriptyline + 2% baclofen...
(n = 38, 71% response rate; Nyirjesy et al., 2009). There is also: (1) a case report of a topical combination of 2.5% amitriptyline + 0.5% ketamine producing long-term pain relief for proctodynia (Lehman and Scallis, 2008), (2) a retrospective analysis of topical 1%–2% amitriptyline + 0.5% ketamine for genital, rectal or perineal pain (n = 13; 54% with pain relief ≥50% and 85% with some pain relief; Poterucha et al., 2012), (3) a case report of 2% ketamine, 1% amitriptyline and 1% gabapentin applied rectally for treating pudendal neuralgia (Zur, 2013).

Topical analgesics are also being explored for orofacial neuropathic pain, and this includes localized delivery to the oral compartment. Several delivery systems are potentially available for local drug applications to the orofacial area, including creams or patches for extraoral sites (as for somatic sites); for intraoral sites, mucoadhesive creams, medicated gum/candy/lozenges, tissue covering stents and mouthwashes or rinses are possible (Padilla et al., 2000). A retrospective study of use of topical medications for extraoral neuropathic pain (4% carbamazepine, 1% lidocaine, 4% ketoprofen, 4% ketamine, 4% gabapentin) indicates a 41% response rate to topical analgesics, and 52% response rate to oral + topical analgesics (Heir et al., 2008). In other studies, 0.2% topical clonidine provided pain relief in a pilot study of oral neuropathic pain (Epstein et al., 1997), while 5% doxepin mouth rinse relieved mucositis pain in patients with cancer (Epstein et al., 2006, 2008). There are also case reports of ketamine rinse treating mucositis pain (Slatkin and Rhiner, 2003), amitriptyline gel treating pulpitis pain (Moghadamnia et al., 2009), and a drug combination delivered as a stent (carbamazepine 4%, lidocaine 1%, ketoprofen 4%, gabapentin 4%) treating intraoral neuropathic pain (Haribabu et al., 2013). Topical clonazepam, whereby a tablet is sucked without swallowing and then spit (Gremeau-Richard et al., 2004) or the tablet dissolved orally before swallowing (Amos et al., 2011), has been reported to be beneficial for treating stomatodynia or burning mouth syndrome. Finally, lidocaine eye drops attenuate pain associated with ophthalmic PHN (Kanai et al., 2010), and 0.5% gallium maltolate effectively reducing trigeminal PHN (Bernstein, 2012). There is also a recent analysis of open-label applications of 5% LMP in 24 cases of trigeminal neuropathic pain: 54% report benefit, 17% minimal change and 25% no change (Kern et al., 2013).

Collectively, these studies and case reports indicate that a proportion of those with pelvic and oral pain can respond to topical applications of analgesics, as with applications to somatic sites. Localized delivery approaches should be considered for further development as potentially helpful adjunctive therapy for such conditions. Considerations for formulating topical analgesics for such specialized compartments have been published recently (Zur, 2013).

4.5 Predicting responses to topical analgesics

Not all patients respond to topical analgesics, and there is interest in determining which factors might predict who might benefit from this approach. While only a limited number of studies have addressed such factors, either prospectively or retrospectively, some factors do show promise for predicting responses. The continued exploration of such factors will provide valuable adjunctive information to assist in clinical decision making.

4.5.1 Pain characteristics

There is growing clinical experience using 5% LMP for neuropathic pain. A two-day conference (44 pain specialists, 17 countries) held in 2009 considered factors that might predict benefit in low back pain with neuropathic components, and in neuropathic pain following trauma (Nicolaou et al., 2011). Localized pain, hyperalgesia and/or allodynia, and positive symptoms were considered positive predictors, while widespread pain and negative symptoms were regarded as negative predictors. Localized neuropathic pain is a general concept, and a working definition has now been proposed (pain characterized by consistent and circumscribed area(s) of maximum pain associated with negative or positive sensory signs and/or spontaneous symptoms characteristic of neuropathic pain) (Mick et al., 2012). With orofacial pain, extraoral pain and continuous pain do not consistently predict good outcomes, but were considered as possible contenders based on clinical experience (Kern et al., 2013).

4.5.2 Patient characteristics

Enriched enrolment trials, in which subjects undergo an open-label phase to determine a clinical response to treatment before entering a controlled phase of a trial, have been developed (Katz, 2009). Some topical analgesic trials have used an enriched enrolment approach. For example, in the open-label run-in phase of a PHN trial, 96 out of 156 (62%) responded when treated for 8 weeks with 5% LMP (Binder et al., 2009). By comparison, 165 out of 256 (63%) of those with peripheral neuropathy responded to oral pregabalin over a
4-week run-in phase (Gilron et al., 2011). Open-label trials also yield responder rates, e.g. 63%–68% of those with PHN and PDN respond to 5% LMP (Baron et al., 2009a), while 44%–47% respond to topical NGX-4010 (Webster et al., 2011b). By comparison, 47%–68% of those with PHN and PDN respond to oral pregabalin over 4 weeks (Baron et al., 2009a).

4.5.3 Psychological factors
Catastrophizing (involves elements of rumination, magnification and helplessness) has been associated with heightened pain experience (Sullivan et al., 2001). This factor has been shown to predict lesser pain reduction responses in a trial of investigational topical analgesics in neuropathic pain (Mankovsky et al., 2012). It will be of interest to assess the role of this factor in further trials of topical analgesics.

4.5.4 Quantitative sensory testing and epidermal nerve fibres
The potential capacity of these factors to predict responses to topical 5% LMP has been examined. In a group of 18 PHN patients, two subgroups were identified – group I with preserved and/or sensitized nociceptors (no sensory loss), and group II with impaired nociceptors (reduced heat responses) (Wasner et al., 2005). LMP was effective in the entire group, and subgroup analysis indicated that LMP reduced pain both in those with intact and those with impaired nociceptor function (Wasner et al., 2005). In another study in those with painful distal sensory neuropathies (diabetic, non-diabetic), sensory nerve conduction, vibration sensation, QST measures of small fibre function, and epidermal nerve fibre density did not predict responses to 5% LMP (Herrmann et al., 2006). Neither of these approaches appears to predict treatment responses.

4.5.5 Responses to capsaicin
In a recent trial on topical clonidine gel 0.1% for PDN, subjects were initially tested with 0.1% capsaicin applied to a 1 cm diameter area of skin midway between the calf and ankle (Campbell et al., 2012). The intent-to-treat population (n = 179) showed little response to clonidine when compared to placebo. However, there was a significant difference compared to placebo in those who responded to capsaicin (≥1 on 5-point scale, 45% of subjects). As the response score to capsaicin increased, there was a progressive decrease in the numbers of subjects, but a significant difference from placebo was manifest in each of these subgroups. In addition, 97 out of 179 trial subjects had skin biopsy samples and epidermal nerve fibre density determined; those who responded to capsaicin (≥1) showed a higher nerve fibre density than those that showed no response. It was noted that the capsaicin test is simple, takes little time, does not need specialized equipment or personnel, and could easily be included in future clinical trials or clinical practice.

4.5.6 Post-hoc analysis
Some studies have conducted post hoc analysis of responses to topical analgesics and note distinct subgroups of responders. Thus, in a PDN trial of NGX-4010 (91 subjects), four subgroups were identified – those with increased pain (3%), those with no change in pain (31%), those with pain relief that diminished over 12 weeks (32%), and those with maintained pain relief over 12 weeks (34%) (Martini et al., 2012). The authors speculated that QST or patient factors (e.g. disease severity, genetics) might be worthy of analysis. Disease duration of PHN has been shown to contribute to outcomes with topical NGX-4010 (Webster et al., 2010).

5. Prospects for the future
There is currently a greatly increased understanding of the involvement of the peripheral compartment in neuropathic pain; this includes the role of sensory nerves and their terminations in the dermis and epidermis in pain signalling, plasticity that occurs within nerve endings following injury to nerves and adaptive changes in response to that injury, the role of the immune system following nerve injury, and the contribution of skin cells to epidermal-neuronal communication following nerve injury. With this understanding comes an appreciation of much potential for pharmacologically modifying signalling by delivering drugs selectively to the peripheral compartment. Local delivery allows for higher local tissue levels and potential recruitment of more mechanisms of action than can be attained by systemic drug levels, lower plasma concentrations and fewer systemic adverse effects (including drug interactions), and with better tolerability, the potential for exploring more drug combinations. There is now a significant body of evidence that topical lidocaine (5% LMP) and capsaicin (8% patch) produce pain relief in neuropathic pain conditions (section 4.1, 4.2). Comparative studies and network analysis indicate response rates and magnitude of analgesia are similar for topical and oral anal-
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References


The above text is a continuation of the previous content and discusses the importance of topical analgesics in the management of neuropathic pain. It highlights the challenges associated with using a compounding approach and the need for more prospective controlled studies to address this issue. The text also emphasizes the growing interest in compounding formulations for neuropathic pain and notes the importance of determining the best concentration to use and selecting appropriate drug combinations. Challenges for using a compounding approach include the inclusion of several agents and considering factors such as selecting an appropriate vehicle for a particular drug, determining the concentration applied, and combinations used. Challenges for using a compounding approach include the inclusion of several agents and considering factors such as selecting an appropriate vehicle for a particular drug, determining the concentration applied, and combinations used. Challenges for using a compounding approach include the inclusion of several agents and considering factors such as selecting an appropriate vehicle for a particular drug, determining the concentration applied, and combinations used. The text concludes with a discussion on the importance of understanding factors that predispose to successful outcomes with topical approaches and the need for more prospective controlled studies to address this issue.


**Supporting Information**

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

**Table S1.** Controlled trials of topical application of investigational agents for neuropathic pain.

**Table S2.** Case and case series reports of topical drug applications for neuropathic pain.