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Review Article

Topical Drug Delivery in the Treatment of Chronic Pain: A Review

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Abstract

Chronic inflammatory or neuropathic pain are chronic syndromes poorly treated by commonly recommended systemic pharmacological therapies, partly due to dose-limiting side effects or adverse events. The use of topical therapeutics for chronic pain is growing and benefits from the reduced potential for adverse effects and the ability to target directly peripheral pathological processes. The current review identifies and describes the limitations of various commonly prescribed systemic pharmacological therapies for chronic inflammatory and neuropathic pain. It also justifies increased research to develop topical therapeutics for chronic pain, mainly localized inflammatory and neuropathic pain. The review discusses the various classes of topical treatments used for chronic pain, including agents that block sensory inputs; provide mechanism-based therapeutics; activate inhibitory systems; include combinations that produce multimodal therapeutic effects; and are targeted to mucosal tissues. It can be argued that current topical therapeutics for chronic pain rely too heavily on local anesthetics and capsaicinoids. More research is needed on multimodal topical therapies and/or targeted at the peripheral sources of pathology. Novel topical therapeutic development would also benefit from further research on topical co-drugs, drug-drug salts, co-crystal and hydrates, and ionic liquids.

Keywords: α2-adrenergic agents; Anticonvulsants; Capsaicinoids; Local anesthetics; NSAIDs; Opioids

Introduction

Topical analgesics are localized treatments applied to the skin or mucous membranes that reduce pain by acting on the underlying tissue and peripheral nerve endings [1]. After penetrating the external surface, these agents act on varying targets in the local tissue and sensory nerve terminals to reduce the induction and transmission of pain signals to the central nervous system (CNS). Targets of action include peripheral afferent nerves, sympathetic efferents, or various adjacent cells (e.g., mast, immune, and endothelial cells) whose actions are impinging on afferent nerves. Topically applied analgesics treat acute pain from wounds, ulcers, muscle aches, sprains, and strains [2]. They are also recommended to treat chronic osteoarthritis, neuropathic, and complex regional pain syndrome [3-5].

Topical analgesic formulations are available in various forms, including solutions, ointments, creams, gels, foams, sprays, patches, or plasters. The composition of topical preparations determines their ability to breach the relatively impermeable epidermal skin, specifically, the *stratum corneum*, which is the outermost layer of the epidermis. Topical formulations with active ingredients of lower molecular weight and greater lipophilicity can more efficiently permeate the skin to reach their local targets. Novel approaches to enhancing skin penetration include those with liposomes, lecithin organogels, flexible vesicles, and nanocarriers that enhance skin permeability [1]. Micro-emulsions and nano-emulsions are also used to improve skin penetration through the solubilization of lipophilic and low molecular weight active ingredients [1]. Another critical determinant of topical delivery is the physical status of the skin as determined by age, sex hormones, skin type, and integrity [6]. Furthermore, the concentration of active ingredients in topical formulations, frequency of administration, and duration of exposure to the agents all factor into the successful delivery and effectiveness of topical treatments [6].

Analgesics applied on the skin are used for either topical or transdermal drug delivery. While topical analgesics cross the skin

barrier to act on the local tissue with little systemic uptake, transdermal analgesics are designed to act on remote targets, usually the CNS, after being absorbed directly into the systemic circulation. This approach is used to bypass gastrointestinal absorption and hepatic first-pass metabolism. The serum therapeutic level achieved with the transdermal route is comparable to other systemic routes, as is the frequency of side effects and potential drug-drug interactions associated with it. In contrast, topical analgesics are designed to achieve optimal delivery of local drug levels for pain-relieving peripheral effects, while reducing systemic absorption to minimize the risk of adverse effects (Table 1).

Benefits	Shortcomings
Steady and therapeutic tissue concentrations achieved with minimal systemic absorption	Difficulties in formulating optimal molecular size and physicochemical properties required for efficient dermal penetration
Bioavailability unaffected by gastrointestinal absorption and hepatic first-pass effect	Bioavailability is affected by individual variations in skin permeability and local drug metabolism
Greater patient compliance	Limited use in disease conditions altering dermal absorptive properties

Table 1: The benefits and shortcomings of topically delivered analgesics.

Topical analgesics currently used clinically or under experimental study generally fall into five categories, including those that: (1) block sensory inputs; (2) target a peripheral source of underlying pathology; (3) activate peripheral inhibitory mechanisms; (4) are multi-targeted topical combinations; or (5) are primarily intended for mucosal pain conditions (see Table 2 for list of most used topical analgesics, their mechanisms of action and clinical usage).

Topical Agent	Mechanism of Action	Experimental/Clinical Use	NNT (95% CI)
Local Anesthetics 5% Lidocaine patch	Suppress activity of voltage-gated Na^+ channels on sensory afferents	PHN, PDN	4.4 (2.5 - 17.5) [7]
Capsaicinoids 8% Capsaicin patch	Overstimulate & desensitize TRPV1 channels on sensory afferents	PHN, PDN, HIV-neuropathy	10 (6.3 - 28) [18]
NSAIDs e.g. Diclofenac gel	Suppress inflammation through COX inhibition	Soft tissue injury (muscle strains, sprains)	1.8 (1.5 - 2.1) [15]
		osteoarthritis, rheumatism, back pain	9.8 (7.1 - 16) [33]
Nitrates	Release nitric oxide for vasodilation	PDN	4 (2-7) [41]
Clonidine (0.1% gel)	Block of NE-mediated vasoconstriction & nociceptor hyperexcitability	PDN	8.88 (4.3 - 50) [43]

NNT: Number Needed to Treat; CI: Confidence Interval; PHN: Post-Herpetic Neuralgia; PDN: Painful Diabetic Neuropathy; TRPV1: Transient Receptor Potential Vanilloid-1; HIV: Human Immunodeficiency Virus; NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; COX: Cyclooxygenase; NE: Norepinephrine.

Table 2: Common topical analgesics with their mechanism of action and indications.

Topical Therapeutics that Block Sensory Input

Local anesthetics

Topical local anesthetic formulations typically contain lidocaine with the occasional inclusion of tetracaine or prilocaine. These local anesthetics act as neuronal membrane stabilizers that inhibit the opening of voltage-gated sodium channels to impair the propagation of sensory input. They have been explicitly demonstrated to block spontaneous discharges from regenerating nerve fibers in which sodium channels are upregulated. They additionally act on keratinocytes, endothelial, immune, and mast cells to inhibit the release of inflammatory mediators.

Lidocaine is available in a 5% preparation (gel, cream, or patch) and 8% spray. The 5% lidocaine patch is approved for first-line use in Post-Herpetic Neuralgia (PHN). The patch, worn for 12 hours out of every 24 hours, relieves dynamic allodynia to mechanical stimulation in PHN patients. 5% topical lidocaine also alleviates post-surgical neuropathy, carpal tunnel syndrome, and diabetic- and cancer-related neuropathies. In a randomized control trial (RCT), seven days of administration of a 5% lidocaine patch produced 50% relief from ongoing pain in patients with focal peripheral neuropathy of varying etiologies. With a number needed to treat (NNT) of 4.4 (95% CI 2.5-17.5), the efficacy was comparable to other systemic agents like gabapentin and TCAs [7]. 5% topical lidocaine formulations also relieve pain associated with complex regional pain syndrome (CRPS – type II), neuropathy after surgeries such as amputation, thoracotomy and mastectomy, carpal tunnel syndrome, idiopathic sensory polyneuropathy, intercostal, ilioinguinal and myofascial neuralgia, neuromas, meralgia paresthetica, diabetic neuropathy, and cancer-related neuropathy [8-10]. The analgesic effects of topical lidocaine depend on peripheral actions, as typically, only 3% of the drug penetrates the systemic circulation. Its long-term use in localized neuropathic pain provides sustained pain relief, only causing brief, reversible erythema and no systemic side effects [11].

Other topical local anesthetics include combinations of lidocaine with tetracaine (7% each in a cream), lidocaine with tetracaine (70 mg each in a self-heating patch), and lidocaine with prilocaine (2.5% each in an EMLA cream). These preparations are commonly used to treat patients with acute pain. Topical EMLA cream alleviates the pain of facial and perineal lacerations [12,13]. The cream is also effective as an analgesic for wound-related pain associated with chronic leg ulcers [14].

Capsaicinoids

Capsaicinoids, which include drugs like capsaicin, zucapsaicin, olvanil and resiniferatoxin, act by binding to the transient receptor potential vanilloid 1 (TRPV1), activating a non-selective cation channel expressed on nociceptors. While this activation causes the initial release of various neuropeptides, repeated application, or single exposure to high concentrations, of capsaicin causes over-stimulation followed by desensitization of TRPV1, depletion of neuropeptides, and a reversible degeneration of sensory terminals. The outcome is a reduced or lost function of nociceptors that produces hypoalgesia.

Capsaicin and its synthetic cis isomer, zucapsaicin, have been used clinically as topical analgesics. Low-concentration (0.025-0.075 %) capsaicin creams, gels, and patches are available over the counter to treat localized neuropathic pain but are not much more effective than placebo treatments [15]. Yet, low-dose topical capsaicin is clinically approved to treat knee osteoarthritis [16]. A 0.025% capsaicin cream used four times daily produces clinically significant pain alleviation in these patients (effect size: 0.41, 95% CI 0.17-0.64) [17].

A high-concentration (8%) capsaicin patch produces analgesic effects in cancer Chemotherapy-Indued Peripheral Neuropathy (CIPN), HIV-neuropathy, neuropathic back pain, Painful Diabetic Neuropathy (PDN), PHN, and post-traumatic neuropathy. A single treatment with an 8% capsaicin patch produced significant pain relief in post-herpetic neuralgia at 2 to 12 weeks with an NNT of 10 (95% CI 6.3-28) to obtain 30% pain reduction [18]. Similarly, the patch produced analgesia in painful HIV-neuropathy lasting 2 to 12 weeks with an NNT of 11 (95% CI 6.2-47) for 30% analgesia. Patients with mixed localized neuropathic pain received more significant relief from allodynia with an 8% capsaicin patch than oral pregabalin [19].

While low-concentration formulations of capsaicin need repeated administration for effective pain reduction, a single 30-60 min application of the 8% capsaicin patch produces analgesic effects lasting up to 3 months [18]. Local reactions like burning pain, erythema, swelling, and pruritus after the topical treatment are more frequent and severe with these high-concentration patches. Thus, an 8% capsaicin patch treatment should be conducted in the presence of a healthcare professional. The adverse effects can be managed by pretreatment with local anesthetics or cooling after patch application. Even at low concentrations, capsaicin causes a reversible degeneration of sensory and autonomic intraepidermal nerve fibers (IENFs) [20].

Zucapsaicin is a synthetic cis isomer of capsaicin with a similar mechanism of action but produces fewer adverse local reactions. The 0.075% zucapsaicin (civamide) cream alleviated pain and physical dysfunction in patients with knee osteoarthritis in a 12-week-long multicenter RCT [21]. No measurable systemic absorption of the drug was detected, and local reactions like burning and rash occurred in only 5% of the patients. In an open-label trial, a 12-month long-term continuation of treatment with 0.075% zucapsaicin produced a 34% reduction of osteoarthritic pain score from baseline. The synthetic vanilloid olvanil is non-pungent and appears to desensitize TRPV1 channels without initially activating and sensitizing nociceptors [22]. Olvanil and resiniferatoxin, which have pungent effects like capsaicin, have not been tested in humans but produce analgesic effects in laboratory animals [22,23].

Anticonvulsants

Like local anesthetics, most anticonvulsant drugs reduce sodium channel activity, but unlike local anesthetics, they produce a use-dependent reduction of sodium channels. In this manner, they target abnormal or excessive neuronal activity without significantly impacting normal activity [24]. Anticonvulsant

drugs have not been used topically in sufficient studies and are not approved for neuropathic pain patients. Recently, however, a few studies suggest promising topical use of anticonvulsant drugs for neuropathic pain. Phenytoin reduces the amplitude of action potentials at sodium-dependent channels by enhancing their steady-state inactivation [24]. Topical 5-10% phenytoin effectively reduced neuropathic pain in a case series of 70 patients [25]. Another use-dependent sodium channel blocker, ambroxol, is more selective for TTX-resistant sodium channels, including NaV1.8 and NaV1.9, expressed on nociceptors [26]. A recent study showed that 20% topical ambroxol effectively relieved pain in 7 patients with traumatic neuropathic pain, including patients resistant to the analgesic effects of 5% lidocaine or 8% capsaicin [26]. Gabapentin is another anticonvulsant; in this case, one that binds to the α2δ subunits of calcium channels, reducing calcium currents and nerve injury-induced trafficking of calcium channels [27]. Topical 6% gabapentin reduced pain in 18 of 23 patients with PHN, CRPS, PDN, trigeminal neuralgia, and other neuropathic pain syndromes [28]. Due to the use-dependent nature of these agents and the considerable reduction of systemic side effects or adverse events associated with their topical application, topically administered anticonvulsant drugs may prove helpful in treating neuropathic pain.

Topical Analgesics that Target Peripheral Sources of Pathology

NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) produce anti-inflammatory and analgesic effects by reversibly inhibiting the cyclooxygenase-dependent metabolism of arachidonic acid into various inflammatory mediators, including prostaglandins and prostacyclin. Topical NSAIDs reduce the sensitization of peripheral nociceptors by inflammatory mediators that underlies acute and chronic inflammatory and musculoskeletal pain. As these inflammatory mediators are mechanistically involved in numerous acute and chronic inflammatory conditions, NSAID use is directly aimed at key peripheral sources of pathology. NSAIDs reduce the sensitization of nociceptors induced by these mediators [29]. Several topical NSAIDs are effective in acute pain conditions, including sprains, muscle and joint strains, and overuse injuries. However, since these same inflammatory mediators play a role in developing and maintaining neuropathic pain [29], it is not surprising that recent studies have shown that topical NSAIDs also produce analgesic effects in patients with neuropathies. Thus, 1.5-5% diclofenac relieved pain in patients with PHN, CRPS, and orofacial neuropathic pain [30,31]. Aspirin, ibuprofen, and ketoprofen are combined with other topical drugs to treat neuropathic pain of varying etiologies, including PHN and radiculopathy [29].

In a recent systematic review, topical diclofenac gel (1.2-2.3% Emulgel) produced a 50% reduction in acute musculoskeletal pain with an NNT of 1.8 (95% CI 1.5-2.1) [32]. For topical ketoprofen gel, the NNT was 2.5 (95% CI 2.0-3.4), and that of topical ibuprofen gel was 3.9 (95% CI 2.7-6.7). The treatments were given at least once daily for up to seven days. NNT calculations for each topical preparation included 2-5 RCTs with 240-350 participants in moderate to high-quality studies. A slightly lower efficacy was found for plaster preparations of diclofenac and ketoprofen in patients with acute musculoskeletal pain with NNTs between 3.2 and 8.2. The topical use of NSAIDs was associated with mild and transient local irritation with erythema and pruritus, but not at a higher frequency than their placebo counterparts. Systemic adverse effects are rare, as plasma concentrations of NSAIDs after topical administration is less than 5% of the level attained through systemic routes [32].

Topical administration of diclofenac and ketoprofen produces analgesia in chronic musculoskeletal pain, including knee osteoarthritis. In studies with this condition, treatment with topical diclofenac gel or solution achieved at least a 50% reduction in pain after 6 to 12 weeks, yielding an NNT of 9.8 (95% CI 7.1-16). The NNT for topical ketoprofen gel was 6.9 (95% CI 5.4-9.3). These values come from a recent Cochrane systematic review meta-analysis that included 4-6 moderate quality trials with more than 5,000 patients [33]. The efficacy of topical NSAIDs was also studied in non-musculoskeletal chronic pain conditions. An RCT in a small cohort of patients with PHN and complex regional pain syndrome (CRPS) showed that a 1.5% topical solution of diclofenac significantly improved self-reported pain [31].

Nitrates

Nitrates like glyceryl trinitrate (GTN) and isosorbide dinitrate are agents that release nitric oxide (NO) and produce vasodilation by increasing guanylate cyclase levels in vascular smooth muscle [34]. Although these types of agents are typically associated with ischemic pain, such as angina [35], there is evidence that their topical application produces analgesia in various pain conditions [36], including neuropathic, where there is evidence of endoneurial ischemia [37]. NO donors achieve analgesia by acting on ATP-sensitive K+ channels and may potentiate the actions of opioids [36]. There is growing evidence for the analgesic effects of topical nitrates in pain conditions like CRPS, PDN, and musculoskeletal pain due to tendinopathies [38-40]. GTN spray given for four weeks significantly reduced pain scores compared to placebo in a group of 50 patients with PDN enrolled in a double-blind crossover RCT. The NNT was calculated to be 4 (95% CI 2–7) [40]. Similarly, topical GTN patches used in patients with acute shoulder tendinopathies reduced pain intensity, though its long-term benefit could not be determined [39]. Headaches are a common side-effect of systemic absorption of nitrates and can occur after topical treatment with GTN.

Clonidine

Clonidine is a presynaptic α2-adrenergic agonist used systemically or transdermally as an antihypertensive agent. Clonidine also has analgesic effects when administered topically [41]. Its analgesic mechanisms may depend on alleviating microvascular dysfunction by inhibiting vasoconstrictive norepinephrine (NE) released from peripheral sympathetic terminals innervating the microvasculature [42]. It may also reduce nociceptor hyperexcitability by directly activating α2-adrenergic and I2-imidazoline receptors on nerve fibers [43] or reducing abnormal excitability of nociceptors after downregulating adenylate cyclase [44]. Topical clonidine (cream, gel, or patch) reduces pain associated with PHN, PDN, trigeminal neuralgia, and CRPS [43,45].

Topical clonidine relieves PDN, as demonstrated by a meta-analysis of two studies that resulted in an NNT of 8.88 (95% CI 4.3-50) to obtain a 30% reduction in pain [42]. The studies of nearly 350 patients examined the analgesic effect of 0.1-0.2% clonidine gel applied to both feet 2-3 times daily for 8-12 weeks. The limited efficacy of topical clonidine in PDN has led to its recommended use only when alternative treatment options have been exhausted due to inefficacy, contraindications, and side effects. Topical clonidine lacks undesirable adverse effects like dry mouth, sedation, and hypotension that occur with its systemic administration [42].

N-methyl-D-aspartate (NMDA) antagonists

NMDA antagonists, including ketamine, dextromethorphan, and memantine, are given systemically for chronic pain but are not widely used because of significant side effects and adverse events, including psychomimetic effects, dizziness, sedation, loss of appetite, and nausea [46]. Glutamate is released from the peripheral terminals of nociceptive afferents and acts on various glutamatergic receptors, including NMDA receptors found on peripheral nociceptor terminals [47], which are upregulated in response to injury [48]. This provides the basis for the topical use of NMDA antagonists for neuropathic pain. Various open trials and randomized controlled trials (RCTs) demonstrate topical ketamine, as a cream, ointment, or gel (either alone or with other agents), is effective for neuropathic pain (including PDN, PHN) and CRPS at various concentrations (0.5-20%). However, not all RCTs have supported the enthusiastic evidence of open trials [49]. Generally, these concentrations do not result in significant adverse effects or detectable plasma levels of drugs or metabolites [50]. As ketamine is a non-selective agent with additional actions on calcium channels, and cholinergic, monoaminergic, and opioidergic receptors, it will be essential to determine whether more selective agents produce similar effects on neuropathic pain when given topically. Although a topical patch containing dextromethorphan and other agents is available, it has not been studied in neuropathic pain patients [51].

Topical Therapeutics that Activate Inhibitory Systems

Opioids

The three major classes of opioid receptors (μ,δ, and κ) are all present on sensory nerve endings and various immune and skin cells. They may be upregulated in painful pathological conditions [52]. Opioid receptors are coupled to Gi and Go proteins that inhibit adenylyl cyclase and modulate ion channels, resulting in inhibitory effects on pain transmission in nociceptors [52]. However, few studies have assessed the impact of topical opioid drugs on chronic pain, except for painful skin ulcers and mouth sores associated with chemotherapeutics [53]. In the studies, gel formulations of morphine and diamorphine alleviated pain in palliative care patients with pressure ulcers. While a systematic review concluded that evidence for the analgesic effects of peripherally injected opioids was weak [54], the potential use of topical opioids for chronic inflammatory and neuropathic pain remains untested.

Cannabinoids

Cannabinoid receptors are present on peripheral nerve terminals, keratinocytes, and immune cells in the skin [55]. Their activation inhibits cutaneous nociceptors by reducing adenylate cyclase, mitogen-activated protein kinase, and flux through various ion channels [55]. There is preliminary evidence for the topical analgesic use of cannabinoids in neuropathic pain. In patients with symptomatic peripheral neuropathy of varying etiologies, an RCT assessing topical treatment with cannabidiol oil administered for four weeks revealed a significant reduction in pain [56]. Similarly, a four-week-long open-label topical treatment with a cream containing the cannabinoid receptor agonist N-palmitoylethanolamine alleviated pain in patients with post-herpetic neuralgia [57].

Topical cannabidiol has reduced pain and promoted healing in a case series of pediatric patients with the blistering skin disorder epidermolysis bullosa [58]. Similarly, topical application of medical cannabis reduced pain by over 30% in a prospective case series of patients with pyoderma gangrenosum. This ulcerative inflammatory skin condition produces intense, opioid-resistant pain [59].

GABA agonists

Agents acting as agonists at the GABA-B receptor produce inhibitory effects on synaptic transmission by increasing the intracellular influx of K+ and decreasing the influx of Ca2+ ions [60]. Until recently, the GABA-B agonist baclofen is often combined with other topical agents [8]. However, recent studies demonstrate the analgesic effects of topical 2-5% baclofen for

chronic pain associated with either acromegaly or herniated lumbar discs [61,62]. As these reports were both case studies, the burden of evidence awaits controlled clinical trials and systematic reviews, as yet not completed.

Antidepressants

Various studies have suggested that antidepressant drugs often prescribed orally for neuropathic pain may produce analgesia when applied topically. Antidepressants, such as amitriptyline and doxepin, have multiple peripheral effects, including actions on opioid, cholinergic, histaminergic, and adenosine receptors, as well as various ion channels [64]. Limited studies have indicated analgesic effects of topical 1-10% amitriptyline and 3-5% doxepin in neuropathic pain and CRPS [63,64]. However, a recent systematic review concluded there was weak evidence for the analgesic effects of topical amitriptyline. Low doses of amitriptyline produced little or no effect. In contrast, high doses indicated analgesic effects, but in poorly controlled case studies, analgesia was accompanied by side effects or adverse events likely caused by systemic absorption [65].

Topical combinations

Topical combinations of analgesics may produce greater efficacy due to their potential to impact multiple pathological processes. The most studied topical analgesic combination for chronic pain comprises the antidepressant amitriptyline and the NMDA receptor antagonist ketamine. While amitriptyline has multiple peripheral effects, including actions on opioid, cholinergic, histaminergic, and adenosine receptors, and various ion channels, ketamine blocks the glutaminergic N-methyl-D-aspartate (NMDA) receptors with additional actions on calcium channels, and cholinergic, monoaminergic and opioid receptors. Ketamine also induces NO synthesis, increasing vasodilation and reducing pro-inflammatory cytokines [65].

RCTs that investigated the singular use of either agent to treat chronic pain conditions have produced mixed results giving inconsistent indications for their analgesic efficacy [50,64]. Nonetheless, a two-week-long treatment with the topical combination of amitriptyline 2% and ketamine 1% produced a 33% reduction in average daily pain in an RCT of patients with PHN [65]. Furthermore, a double-blind RCT that compared this topical combination to oral gabapentin in PHN has revealed that four weeks of the topical combination treatment produced comparable pain-relieving effects to gabapentin with no significant difference in analgesic efficacy [65]. Similarly, a double-blind RCT indicated a combination of ketamine (1.5%) and amitriptyline (3%) with the addition of baclofen (0.75%) in pluronic lecithin organogel reduced symptoms of tingling, cramping and burning pain in the hands of patients with chemotherapy-induced painful neuropathy [66].

Compounding amitriptyline or ketamine with various drugs such as lidocaine, gabapentin, pregabalin, baclofen, or clonidine adds to the suppression of excitation, or the enhancement of inhibition, already produced by these two agents. Importantly, as the penetration of these agents into the systemic circulation is typically so low it is undetectable after topical administration, concerns about adverse systemic drug-drug interactions are not warranted. Thus, multimodal drug combinations, which would be inconceivable for systemic therapy, are generally perfectly safe in topical drug compounding [67-69].

Topical Therapeutics for the Mucosal Tissue

Given the relative ease of drug absorption at these sites, painful pathologies of mucosal tissues are sensitive to topical analgesics. Oral mucositis after chemotherapy is commonly treated with topical morphine mouth rinse (0.1-0.2%) and gel (0.1 %) [53]. Orofacial neuropathic pain, pulpitis, and chemotherapy-induced mucositis are effectively treated with oral (lozenge, gum, mouthwash, gel, etc.) therapies, including 0.01-0.25% capsaicin, 2% amitriptyline, 0.2% topical clonidine, and 5% ketamine [70]. Topical steroids in pastes, ointments, and mouthwashes relieve pain due to aphthous ulcers [73]. Local anesthetics gels and creams have also demonstrated efficacy in relieving mild-to-moderate pain of oral mucosal lesions caused by trauma and ulceration [71].

For pain pathologies in the rectal, genital, and perineal areas, including vulvodynia, proctodynia, and pudendal neuralgia, topical agents 1–2.5% amitriptyline (alone or combined with other agents), 2–6% gabapentin and 2% ketamine are effective [70].

Current Advancements in Topical Analgesics

Research efforts to develop effective topical therapeutics for acute and chronic pain are ongoing. New topical formulations of local anesthetics, NSAIDs, and capsaicin with an improved constitution and dosing are being investigated in clinical trials for different pain conditions. More interestingly, novel therapeutics like funapide (XEN402), a selective NaV1.7/1.8 channel antagonist, are being investigated to treat PHN.

Recent studies demonstrate synergistic analgesic effects are produced in animal models of CRPS and neuropathic pain using combinations of agents that target more specific pathophysiological mechanisms associated with these conditions. Deep tissue and/or endoneurial microvascular dysfunction contributes to the pathophysiology of CRPS and neuropathic pain [72]. Reducing microvascular dysfunction using topical combinations of nitric oxide donors or α2-adrenergic agonists (which increase thermoregulatory blood flow) with type IV phosphodiesterase (PDE) inhibitors (which increase nutritive blood flow) produces synergistic analgesic effects in animal models of CRPS and neuropathic pain [73,74]. Thus, topical combinations of α2-

adrenergic agonists (clonidine and apraclonidine) or NO donors (linsidomine, S-nitroso-N-acetylpenicillamine) with PDE inhibitors (pentoxifylline and lisofylline) produce analgesic effects that are much greater than the analgesic effects of the individual agents given on their own. Given that the anti-allodynic effects of these treatments are paralleled by their anti-ischemic effects, it suggests their synergistic analgesic effects may depend partly on disease-modifying actions. One such combination, clonidine + pentoxifylline, produces significantly greater analgesic effects than either of the single agents in a surrogate of neuropathic pain (post-capsaicin ischemia-induced pain) in healthy human volunteers [75].

Another potential for advancement in topical analgesics can come through using analgesic combinations in the form of co-drugs, drug-drug salts, co-crystals, and ionic liquids. These preparations are made by pairing multi-targeted analgesic agents based on therapeutic complementarity and physicochemical properties to achieve better solubility and bioavailability. While co-drugs are conjugates typically bound together by covalent chemical bonds, drug-drug salts, co-crystals, and hydrates are crystalline compounds of two or more active drugs linked by ionic or hydrogen bonds. Ionic liquids are salts in liquid form. The synthesis of such analgesic combinations has been reported and constitutes agents with local anesthetic, anti-inflammatory, antidepressant, and opioid activities. Some examples are lidocaine-ibuprofen, lidocaine-etodolac, lidocaine-aspirin, aspirin-tramadol, and celecoxib-tramadol all pending investigations as topical analgesic formulations [76,77]. Recent studies also show that salts or co-crystals of vasodilatory pharmaceuticals with antioxidant nutraceuticals are analgesic in animal models of models of neuropathic pain and CRPS [78,79].

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