Compounded Topical Analgesics for Chronic Pain

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Analgesic medications compounded for topical use are gaining popularity for the management of chronic pain. The advantages of topical pain medications include reduction of systemic adverse effects, improved patient acceptance, few drug interactions, ease of dose determination, avoidance of first-pass metabolism, and direct access to the target site. Compounded topical medications typically use a mixture of 3 or more single medications to achieve multiple complementary effects at lower doses of each individual medication. Herein, we review the mechanisms, adverse effects, and evidence for some of the most commonly used medications in topical compounds for pain management. Because more topical medications are used for chronic pain, dermatologists can expect an increase in irritant and allergic contact dermatitis related to these medications.

An estimated 116 million Americans experience chronic pain, treatment of which has resulted in an epidemic of opioid abuse and misuse in the United States.[1] Alternative methods for pain treatment are being explored, and current investigations have shown 1 option that may help reduce narcotic prescriptions: topical compounded pain medications. Topical analgesics and anesthetics (eg, creams, gels, patches) are formulated for local delivery to the skin, targeting sensory nerve endings and adjacent tissues after dermal penetration of the drug.[2] Topical agents are gaining popularity for use in certain pain conditions, including musculoskeletal pain and neuropathic pain such as diabetic neuropathy and postherpetic neuralgia.[3,4]

Topical administration allows for efficient, painless delivery of medications while reducing systemic adverse effects associated with parenteral or oral administration. Other benefits of topical drug delivery include improved patient adherence and acceptance, few drug interactions, ease of dose determination, avoidance of first-pass metabolism, and direct access to the target site.[5] In contrast to single medications, compounded topical agents are based on the strategy of using low-dose, multiple, concomitant, and complementary therapies. Compounds are usually 3 or more medications incorporated into a base that enhances epidermal penetration. Typically, a patient can apply the compound at 8-hour intervals on a regular basis and as often as every 2 hours as needed for breakthrough pain.[6] In a recent survey, practicing prescribers described compounded pain creams as not only effective but also safe for their patients.[7] In addition, more than 83% of individuals with chronic pain reported a significant reduction in their pain after using compounded prescription pain creams. More than a third of patients reduced their oral pain medications while using topical compounds, reporting that their pain levels were reduced by more than half on average.[8] However, multiple clinical trials of individual and concomitant formulations of topical analgesics have demonstrated mixed outcomes in reducing pain compared with placebo (Table 1).

It is important to note that although topical analgesics are relatively safe, 6% of the patients reported adverse effects, especially "rashes."[8] With more physicians prescribing topical compounded pain creams and patients chronically using them for pain treatment, dermatologists are likely to encounter an increase in cases of irritant contact dermatitis and allergic contact dermatitis (ACD) to pain medications. This review discusses the most common medications used in compounded pain creams, their mechanism of action, and the reported adverse effects of topical administration. Of note, ACD has only been described to a few of the ingredients used in topical compounded pain medications, and these cases are discussed where applicable.

KETAMINE

Ketamine acts on the *N*-methyl-D-aspartic acid receptor (NMDAR), located on nerve fibers and in the central nervous system.[31] The NMDAR and related ionotropic glutamate receptors are present on peripheral primary afferent neurons in the hairy skin of humans.[32] Inflammation in the periphery increases the number of NMDARs on peripheral nerve fibers.[33] Ketamine and its major metabolite norketamine work as anesthetic agents by noncompetitively blocking action on NMDARs.[34,35]

TABLE 1. Summary of Studies Using Topical Analgesics

Agent	Concentration	Authors	No. Participants	Type of Pain	Duration of Treatment	Results
Ketamine	1%	Lynch et al,[9] 2005	92	Diabetic neuropathy, postherpetic neuralgia, postsurgical, posttraumatic pain with allodynia	3 wk	29% reduction in pain
	5%	Mahoney et al,[10] 2012	17	Diabetic neuropathy	4 wk	No statistical difference
	1%	Barros et al,[11] 2012	12	Postherpetic neuralgia	15 d	No statistical difference
Gabapentin	2%–6%	Boardman et al,[12] 2008	51	Vulvodynia	8 wk	65% reduction in pain
	6%		Enrolling	Vulvodynia	13 wk	Currently in phase 2 trial
Clonidine	0.1%	Campbell et al,[13] 2012	182	Diabetic neuropathy	12 wk	41% reduction in pain
	0.2%	Epstein et al,[14] 1997	17	Orofacial pain: neuropathic and/or neuralgia	4 wk	36% reduction in neuropathic pain; 54% reduction in neuralgia pain
Amitriptyline	0.1%	Wrzosek et al,[15] 2015	344	Neuropathic pain	8–12 wk	30% reduction in pain
	2%	Lynch et al,[9] 2005	92	Diabetic neuropathy, postherpetic neuralgia, postsurgical/posttraumatic pain with allodynia	3 wk	No statistical difference
	5%	Ho et al,[16] 2008	35	Postsurgical neuropathic pain, postherpetic neuralgia, diabetic neuropathy	1 wk	No statistical difference
Lidocaine	5%	Binder et al,[17] 2009	265	Postherpetic neuralgia	2 wk	50% reduction in pain
	5%	Ho et al,[16] 2008	35	Postsurgical neuropathic pain, postherpetic neuralgia, diabetic neuropathy	1 wk	Statistically reduced pain
	5%	Devers et al,[18] 2000	16	Peripheral neuropathic pain	2–12 wk	81% of patients reported pain relief
Capsaicin	5%	Meier et al,[19] 2003	40	Peripheral neuropathic pain	1 wk	Statistically reduced pain
	0.075%	Mason et al,[20] 2004	656	Chronic musculoskeletal pain	4 wk	50% reduction in pain
				Chronic neuropathic pain	8 wk	
	8%	Maihofner and Heskamp,[21] 2014	1044	Peripheral neuropathic pain	12 wk	25% reduction in pain
	0.075%	Casanueva et al,[22] 2013	130	Fibromyalgia	6 wk	29% reduction in pain
	0.025%	Kulkantrakorn et al,[23] 2013	33	Diabetic neuropathy	8 wk	No statistical difference
NSAIDs	0.5%–10%	Derry et al,[24] 2015	8386	Strains, sprains, or sports injuries	2 wk	50% reduction in pain

Compounded					
2.5%	Kim et al,[25] 2014	99	Myofascial pain syndrome	2 wk	No statistical difference
1.5%	Ahmed et al,[26] 2015	28	Neuropathic pain	2 wk	No statistical difference
2% ketamine, 4% amitriptyline	Gewandter et al,[27] 2014	462	Chemotherapy-induced peripheral neuropathy	6 wk	No statistical difference
4% amitriptyline, 1% baclofen, 2% ketamine	Barton et al,[28] 2011	208	Chemotherapy-induced peripheral neuropathy	4 wk	Statistically reduced pain
4% amitriptyline, 2% ketamine	Lockhart,[29] 2004	250	Postherpetic neuralgia	3 wk	30% reduction in pain
2% baclofen, 2% amitriptyline	Nyirjesy et al,[30] 2009	38	Vestibulodynia	33 wk	71% reduction in pain

For neuropathic pain, treatment with ketamine has traditionally been via intravenous routes, although intramuscular and subcutaneous infusions have also been tried.[36–40] However, administration by these routes is limited by central adverse effects such as hallucinations and nightmares. Frequent abuse of ketamine can even cause long-term memory impairment.[41]

Topical application consists mainly of case studies and is considered an off-label use.[9,42–46] One double-blind, placebo-controlled trial showed that ketamine 1% was not effective in patients with neuropathic pain[9]; however, this finding may have been due to suboptimal drug concentrations. In open studies of topical ketamine, therapeutic effects seemed to strengthen with repeated application.[43,44,46] Furthermore, the plasma levels of ketamine and its active metabolite, norketamine, are below the limits of detection after the creams are applied. Topical ketamine at 50 mg/mL was shown to not elicit any local or systemic adverse effects,[47] whereas intravenous ketamine was shown to have adverse effects such as tachycardia, intracranial hypertension, vivid dreams and hallucinations, and the potential for urinary tract toxicity.[48]

Although topical ketamine is simple and inexpensive to use and systemic absorption seems to be minimal, further exploration of the therapeutic potential of topical NMDA blockers is warranted.

GABAPENTIN

Gabapentin may have the structure of the GABA neurotransmitter but does not interact significantly with this neurotransmitter or with any other neurotransmitter.[49] Although its exact mode of actions is not known, gabapentin seems to act on calcium channels by inhibiting ion entry and as a glutamate antagonist.[50,51] Its lipophilic characteristic allows for gabapentin to pass through the blood-brain barrier.[52] Its antihyperalgesic action reduces hyperexcitability of neurons in the dorsal horn of the spinal cord, which is responsible for central sensitization, and has proven to be clinically useful in the control of ectopic discharges from injured peripheral nerve sites.[53,54]

Gabapentin taken orally has been used for treatment of partial seizures,[55] postherpetic neuralgia,[56] migraine headaches,[57] and other pain syndromes.[58,59] Fortunately, gabapentin has a low profile of adverse effects and few interactions with other medications because it requires high doses to achieve neuropathic pain relief. Adverse effects include somnolence, ataxia, nystagmus, and asthenia, all of which can decrease patient compliance.[60,61]

Topical gabapentin has been empirically used off-label as a single agent or in combination with amitriptyline and other drugs for neuropathic pain, with a retrospective study suggesting benefit of topical gabapentin for vulvodynia.[12] Furthermore, topical gabapentin possesses minimal adverse effects compared with those usually associated with systemic use of gabapentin.

CLONIDINE

Originally approved as an oral product to treat hypertension, clonidine is a presynaptic α_2-adrenergic receptor agonist used to

treat acute and chronic pain. Alpha-2 receptors are present on nociceptors in the epidermis and are concentrated at the site of peripheral nerve injury.[62] Activation of these G protein–coupled receptors leads to release of an inhibitory G protein, which in turn downregulates adenylate cyclase and other second messengers thought to play a role in initiating and maintaining the abnormal excitability of nociceptors.[63] Clonidine produces analgesia for both acute and chronic pain when used via intravenous, intrathecal, or epidural injection.[64–66] However, systemic and central use of clonidine is limited by undesirable adverse events including sedation, dry mouth, hypotension, and rebound hypertension.[67,68]

Clonidine is lipophilic, allowing for easy penetration of the skin to reach the local antinociceptive pathways. Treatment with topical clonidine is considered off-label. It reduces pain from diabetic neuropathy, although studies indicate that efficacy depends on the relative functionality of nociceptors in the skin. In addition, clonidine applied to the site of injury reduces hypersensitivity in inflammatory nerve injury.[69] This finding reflects clonidine's action on sensory neurons to reduce excitability, on immune cells to reduce cytokine production, and on microvasculature to improve blood flow. These observations provide a rationale for continued exploration of topical clonidine in human clinical trials of neuropathic pain.[13]

Topical clonidine can also relieve hyperalgesia in patients with sympathetically maintained pain. Thus, a transdermal patch of clonidine (α_2-adrenergic receptor agonist) was reported to provide some pain relief in some cases of sympathetically maintained pain[70] and diabetic neuropathy.[71] In other studies, 0.2% topical clonidine provided pain relief in a pilot study of oral neuropathic pain.[14] Treatment with clonidine was safe and without the problematic adverse effects typically associated with systemic therapies.[13]

A recent Cochrane review found limited evidence that topical clonidine provided benefit in peripheral diabetic neuropathy.[15] The review concluded that topical clonidine may be useful in treating peripheral diabetic neuropathy when no better treatment options are available because of lack of efficacy, contraindications, or adverse events. Additional trials are needed to assess topical clonidine in other neuropathic conditions.

The clonidine transdermal patch has demonstrated potential for producing ACD.[72] The occurrence of allergic contact sensitivity to transdermal clonidine varies but increases with dose and duration of use. In 1 study, 90% of 72 sensitized patients presented with contact sensitivity by 20 weeks.[72] The eczematous rash was most often localized to the site of application, although generalized eruptions have been reported.[73,74]

AMITRIPTYLINE

Amitriptyline, a first-generation tricyclic antidepressant, inhibits serotonin and noradrenaline reuptake and blocks sodium channels. Sodium channel blockade by amitriptyline prevents excessive nociceptor discharge by blocking the action potential, a mechanism similar to a local anesthetic such as lidocaine. Furthermore,

amitriptyline could possibly act indirectly on NMDARs because there is evidence that sodium channels are involved in modulating NMDARs.[75]

Amitriptyline cream (off-label use) acts as a slow-release formulation and has, in 1 case trial, shown success in decreasing neuropathic pain by one third without any adverse effects.[76] When combined with ketamine cream, topical amitriptyline showed promising results in neuropathic pain state and also in the management of refractory proctodynia.[9,77] One study showed significant relief from postherpetic neuralgia using amitriptyline 4% and ketamine 2%.[29] In some case reports, pain relief was rapid, with patients experiencing pain reduction within 20 minutes of application.[76]

Amitriptyline used topically has some limited evidence of effectiveness in the treatment of localized pain.[78] Several randomized controlled trials did not show benefit with amitriptyline 1% or amitriptyline 2% cream versus placebo.[9] Case reports of higher strength amitriptyline (5% and 10%) have shown dose-related efficacy but also systemic adverse effects, including slower cognition and difficulty concentrating. Local redness was the most common adverse effect, but this may have been due to the vehicle.[76] Subjects from both the amitriptyline cohort and the vehicle control reported redness, although the redness was not severe and disappeared by the next day, making it likely to have been an irritant dermatitis.[79] The mildness and reversibility of these effects support the safety of the topical application of amitriptyline.

BACLOFEN

Although the precise mechanism of action is not fully known, baclofen acts as an agonist on the GABA$_B$ receptor, causing a decrease in calcium membrane conductance and increase in potassium. Hyperpolarization of primary afferent fibers results in inhibition of both monosynaptic and polysynaptic transmission at the spinal cord level. The GABA$_B$ receptors are well known to be widely distributed throughout the central nervous system.[80] In the periphery, the GABA$_B$ receptors are found in cutaneous layers on fine nerve endings and keratinocytes. Although a GABAergic agent when administered orally, baclofen's hypothesized topical mechanism of action may be related to its potassium channel opening property.[81]

Topical baclofen has been used empirically (off-label use) in combination with amitriptyline for vulvodynia[30] and has been studied as a single agent for chemotherapy-induced painful neuropathy.[28] One double-blind randomized placebo-controlled trial evaluated a compounded topical gel containing baclofen, amitriptyline, and ketamine to alleviate neuropathic pain, numbness, and tingling of chemotherapy-induced peripheral neuropathy.[28] The compound gel significantly improved both sensory ($P = 0.053$) and motor subscales ($P = 0.021$) over the placebo. The greatest improvements involved relief of tingling, cramping, and shooting/burning pain in the hands. Furthermore, the topical gel seemed to improve symptoms of neuropathy without evidence of systemic toxicity.[28]

CYCLOBENZAPRINE

Cyclobenzaprine is a skeletal muscle relaxant pharmacologically related to tricyclic antidepressants. It acts centrally to reduce somatic motor activity by influencing both alpha and gamma motor neurons. Cyclobenzaprine has been used to treat chronic pain due to musculoskeletal disorders and fibromyalgia.[82] Cyclobenzaprine is often compounded into topical analgesics (off-label use) for musculoskeletal conditions because it is highly effective in muscle tissue at the site of pain, allowing for effective dosing without the systemic adverse effect of somnolence.[83]

Recently, a case of ACD was reported in a patient using a topical compounded medication that contained cyclobenzaprine.[84] The patient's pain medication contained ketamine 10%, diclofenac 5%, baclofen 2%, bupivacaine 1%, cyclobenzaprine 2%, gabapentin 6%, ibuprofen 3%, and pentoxifylline 3%. Although the patient reported pain relief with use of the medication, he also began to report an itchy rash at the site of application. After patch testing separate ingredients of the original medication (using the concentrations in the original pain medication), cyclobenzaprine was isolated as the causative allergen. Allergic (over irritant) contact dermatitis was subsequently confirmed by testing serial dilutions of cyclobenzaprine (2%, 1%, 0.2%, 0.02%, and 0.002%) read at 48 and 96 hours, demonstrating a crescendo response to concentrations as low as 0.02%.[84]

LIDOCAINE

Lidocaine's proposed mechanism of action is nonselective blockade of voltage-gated sodium channels on sensory afferents at the site of application, resulting in reduced ectopic discharge and reduced signal propagation.[85] Topical lidocaine is thought to produce pain relief through decreased ectopic discharges within peripheral sensory afferents.

A recent Cochrane review identified 12 studies comparing topical lidocaine versus placebo or an active control.[86] The 5% medicated patch, gel, and cream were used along with an 8% spray. These contain high concentrations of lidocaine because it crosses the skin poorly. There was some indication that topical lidocaine was beneficial in these studies and no evidence of an effect of lidocaine on the incidence of adverse events or withdrawals. Therefore, lidocaine 5% may be effective in patients with localized peripheral neuralgia, including postherpetic neuralgia, for several weeks with a low risk of adverse reactions.[86]

Topical lidocaine, medicated as a plaster or patch, is approved for use for postherpetic neuralgia in the United States. The patch is generally well tolerated, and application site reactions are transient and resolve after patch removal. A systematic review of 5% lidocaine medicated plaster compared with other treatments for postherpetic neuralgia indicates that the medicated plaster relieves pain and reduces allodynia compared with placebo.[87]

Adverse effects of topical local anesthetics are minimal and include localized skin irritation and swelling that generally disappears within 2 to 3 hours after the local anesthetic is removed from the skin. There are usually no significant systemic adverse effects or dermal reactions, and plasma lidocaine levels remain low.[88] Safety and tolerability are similar for either 12- or 24-hour application of lidocaine patches.[89] In fact, they produce levels well below therapeutic levels used in lidocaine infusions.

Despite this relative safety, there are reports of patients dying from overdoses of compounded lidocaine gel.[90] Two deaths have been linked to application of a compounded lidocaine and tetracaine gel before laser hair removal treatment. Both victims applied the gel to over half their bodies and put an occlusive wrapping over it. This resulted in fatal systemic absorption because postmortem blood analysis revealed elevated lidocaine levels.[90] Therefore, for patients using topical lidocaine, it is important to avoid use on widespread body areas under occlusion.

Allergic contact dermatitis to topical lidocaine is on the rise because of the growing number of over-the-counter products containing lidocaine frequently used by the aging population. One study showed an overall prevalence of ACD to local and topical anesthetics at 2.4%.[91] Although this figure is lower compared with those in some previous reports, it does present a significant problem.[92,93]

CAPSAICIN

Capsaicin is the active ingredient in chili peppers. Topical capsaicin targets the vanilloid receptor 1, eventually leading to depletion of substance P, a neurotransmitter known to cause pain and inflammation, from sensory neurons.[94,95] It causes activation and subsequent dying back of nociceptive nerve endings, resulting in local desensitization after a period of initial irritation. However, it often induces a painful burning sensation at the application site, which many patients have trouble tolerating.[96,97]

Topical formulations of capsaicin at low concentrations have been widely available as an over-the-counter remedy for treatment of musculoskeletal and neuropathic pain for decades. Capsaicin is offered as a topical analgesic cream in low concentrations (0.025%–0.075%) and as a patch formulation at a higher concentration (8%). Degeneration of nerve terminals within the epidermis occurs after repeated application of 0.075% capsaicin for 3 weeks[98] and acute application of the high-concentration patch.[95]

Although an earlier systematic review of capsaicin in neuropathic pain found topical capsaicin better than placebo for the treatment of chronic pain from neuropathic and musculoskeletal disorders,[20] a more recent Cochrane review found insufficient data to draw conclusions regarding its efficacy for neuropathic pain.[99] All studies reported rare systemic adverse effects but common local adverse skin reactions to capsaicin early in treatment. This local skin irritation was usually mild and disappeared after 1 to 2 weeks of treatment.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed drugs worldwide and are responsible

for approximately one quarter of all adverse drug reactions.[100] Topical administration of NSAIDs allows for local, enhanced drug delivery to affected tissues without the systemic adverse effects of peptic ulcer disease, gastrointestinal hemorrhage, and renal impairment. After topical administration, systemic NSAID concentration is typically less than 5% and 15% compared with equivalent oral administration. Compared with oral formulations, topical NSAIDs have a superior safety profile with adverse effects such as rash and pruritus at the site of application occurring in approximately 10% to 15% of patients.[100]

One meta-analysis suggested that topical NSAIDs were more effective than placebo.[101] However, the authors concluded that available evidence indicated that during the first week of treatment, topical NSAIDs were inferior to oral NSAIDs. A separate meta-analysis examined the use of topical NSAIDs for chronic musculoskeletal pain and concluded that they are effective and safe.[102] The Cochrane Database review suggested that topical NSAIDs can provide good levels of pain relief without significant systemic adverse effects associated with oral NSAIDs, for the treatment of acute musculoskeletal pain.[103] Local adverse events were irritation of the area to which the topical NSAID was applied, including redness/erythema and itch/pruritus. These were usually described as mild and transient.

COMPOUNDING BASE

When a topical analgesic is applied directly to the skin, it must pass through the stratum corneum, which is often the rate-limiting barrier for the absorption of must drugs. For compounds used exclusively for the treatment of skin conditions, passive diffusion into the superficial epidermis may be sufficient. In those cases, a vehicle such as petrolatum can be used. On the other hand, for a drug to be delivered into the general circulation, a vehicle must maintain affinity for both lipid and aqueous environments to be absorbed effectively. Highly hydrophilic drugs will not absorb easily through the stratum corneum, whereas highly lipophilic drugs will absorb well through this layer. However, in the aqueous layer of the epidermis, hydrophilic drugs will absorb better than lipophilic drugs. Thus, the delivery agent of the medication must have both hydrophilic and hydrophobic elements to allow for maximum penetration. Several adjuvants such as viscosity and permeation enhancers, emollients, and preservatives are added to the active components. One such permeation enhancer, lecithin, has shown particular success in transdermal delivery systems. Lecithin is a naturally occurring mixture of diglycerides of stearic, palmitic, and oleic acids linked to phosphatidylcholine. As an amphoteric surfactant, lecithin enables many drugs to penetrate into the dermal layer.[104] These additives act to increase absorption, reduce the drug concentration, and maintain the drug at the target site.[105]

A compounded base that contains penetration enhancers is preferred and clinically proven to be more efficacious than simple creams, gels, and ointments. The following enhanced bases are readily compounded: Pluronic lecithin organogel, Speed Gel, vanishing penetrating cream (VanPen), Lipoderm, and DemiGel. Pluronic lecithin organogel is widely used because its nonionic nature allows it to be compatible with diverse systems and its surfactant properties enhance penetration. Pluronic lecithin organogel consists of poloxamers, lecithin, and isopropyl palmitate. Poloxamers act as surfactants to increase water solubility of hydrophobic substances, whereas isopropyl palmitate acts as an emollient and solubilizing agent for lecithin. Pluronic lecithin organogel disrupts the lipid layers of the stratum corneum so that the medication can enter the systemic circulation via the dermal-epidermal blood flow. VanPen and Lipoderm are similar to Pluronic lecithin organogel and equally effective but have added emollients to provide better rub-in and longer-lasting moisture. Speed gel is a fluid transdermal gel that allows for enhanced penetration but can only hold a limited amount of medication. Although these bases use lecithin to cross the stratum corneum to various degrees, each depends on formulation and preparation.[6] It is not clear whether these permeation enhancers can increase the risk of irritant contact dermatitis or ACD to the medications that they are designed to deliver. Furthermore, marked variability of individual patients' skin properties may influence percutaneous absorption and distribution of the drug when applied topically.

ADVERSE EFFECTS

Although trials and case studies have demonstrated that topical analgesics are relatively safe, topical application of high-concentration creams do carry some risk. Topical application can function as a systemic delivery system. The degree of body surface covered and the intactness of the skin where it is applied should be taken into account because disease conditions may enhance systemic absorption. For example, 10% amitriptyline produces systemic adverse effects,[76] whereas extensive skin application of doxepin 5%[106] or multiple local anesthetic applications[107] can lead to systemic toxicity such as death as previously described with lidocaine gel.

Data from 1 compounding pharmacy reported that more than 160,000 prescriptions for topical compounded medications were filled in 2013. Among the most popular compounded topical pain medications is a compound containing ketamine 10%, meloxicam 1%, baclofen 2%, bupivacaine 1%, clonidine 0.2%, cyclobenzaprine 2%, gabapentin 6%, and pentoxifylline 3%. It is primarily designed for neuropathic/inflammatory combination pain found in peripheral neuropathy, diabetic neuropathy, severe tendonitis/tendonosis, or failed back syndrome. Of the 2013 prescriptions filled, 496 patients reported to the pharmacy having experienced an adverse drug reaction. According to personal communication from Jeff Elbl, a pharmacy representative from Bellevue Pharmacy, the most common adverse drug reactions associated with this compounded medication are redness, rash, itching, and burning, although blistering has been reported.

Because most reports of cutaneous adverse events from topical pain medications describe the reactions as mild and transient,

the most common cause of cutaneous reactions from topical medications is likely irritant contact dermatitis. However, ACD to topical pain medications is on the rise, as described in several aforementioned cases. When patients present with dermatitis from topical medications, it is important to distinguish between irritant contact dermatitis and ACD on the basis of history and patch testing. Compared with ACD that usually lasts for weeks and is characterized by prominent itching, irritant reactions are usually described as transient and burning or tingling. On patch testing, irritant reactions tend to be dose dependent and have a decrescendo response (improve over time after removal of the patch), whereas allergic reactions tend to worsen (crescendo) after patch removal. In addition, it is important to remember that compounding bases commonly contain irritants and allergens, so one must also test the base and, if necessary, the ingredients in the base to determine the causative agent.

CONCLUSIONS

A wide variety of formulations, including creams, gels, and patches, have been studied. Topical analgesics provide a therapeutic option with simplicity of application, decreased adverse effects, and decreased drug-drug interactions for patients with neuropathic and other disabling chronic pain syndromes. The pharmaceutical industry is taking interest in developing some of these options into topical products. Topical preparations containing opioids, local anesthetics, antidepressants, glutamate receptor antagonists, α-adrenergic receptor agonists, adenosine, cannabinoids, cholinergic receptor agonists, gabapentinoids, prostanoids, bradykinin, adenosine triphosphate biogenic amines, and nerve growth factor are each at various developmental stages.[96]

However, there is overall a lack of quality evidence for topical treatments in neuropathic pain, and data are often conflicting. This may be due to the location and surface area of application, as well as differences in formulations used.[108] Extemporaneous compounding allows clinicians to individualize patient therapy, but there may be variability of extemporaneous preparations.[3,109] Studies tend to be small and of short duration, and most studies have focused on specific conditions such as postherpetic neuralgia or diabetic neuropathy; the extent to which results can be applied to other forms of neuropathic pain is unknown.[110] Therefore, uncertainty exists in extrapolating study results to other preparations and conditions.

Topical analgesics are an important addition in the treatment of neuropathic and other chronic pain syndromes. As compounded topical agents become more prevalent in treating chronic pain, it is worthwhile for clinicians and patients to have a better understanding of how these medications work. Furthermore, dermatologists should be alert to the potential for irritant contact dermatitis and ACD from these agents. Customized patch testing is a valuable tool in determining the offending allergen, especially when multiple active ingredients are found in a compounded medication.

REFERENCES

1. Compton WM, Volkow ND. Major increases in opioid analgesic abuse in the United States: concerns and strategies. *Drug Alcohol Depend* 2006;81(2):103–107.
2. Cairns BE. *Peripheral Receptor Targets for Analgesia: Novel Approaches to Pain Management.* New Jersey, NJ: Wiley; 2009.
3. Argoff CE. Topical analgesics in the management of acute and chronic pain. *Mayo Clin Proc* 2013;88(2):195–205.
4. Zur E. Topical treatment of neuropathic pain using compounded medications. *Clin J Pain* 2014;30(1):73–91.
5. Zempsky W. Topical analgesics in treating neuropathic and musculoskeletal pain. *Pain Medicine News* 2013;11(10):7–10.
6. Jones M. Chronic neuropathic pain: pharmacological interventions in the new millennium. *Int J Pharm Compd* 2000;4(1):6–15.
7. Warner M, Tuder D. A brief survey on prescriber beliefs regarding compounded topical pain medications. *Int J Pharm Compd* 2014;18(3):182–188.
8. Bennett A. Topical prescription creams reduce pain in five of every six chronic pain patients, without need for opioids or other narcotics. Patient Outcomes Analytics; 2013. Available at: http://globenewswire.com/. Accessed January 19, 2016.
9. Lynch ME, Clark AJ, Sawynok J, et al. Topical 2% amitriptyline and 1% ketamine in neuropathic pain syndromes: a randomized, double-blind, placebo-controlled trial. *Anesthesiology* 2005;103(1):140–146.
10. Mahoney JM, Vardaxis V, Moore JL, et al. Topical ketamine cream in the treatment of painful diabetic neuropathy: a randomized, placebo-controlled, double-blind initial study. *J Am Podiatr Med Assoc* 2012;102(3):178–183.
11. Barros GA, Miot HA, Braz AM, et al. Topical (S)-ketamine for pain management of postherpetic neuralgia. *An Bras Dermatol* 2012;87(3):504–505.
12. Boardman LA, Cooper AS, Blais LR, et al. Topical gabapentin in the treatment of localized and generalized vulvodynia. *Obstet Gynecol* 2008;112(3):579–585.
13. Campbell CM, Kipnes MS, Stouch BC, et al. Randomized control trial of topical clonidine for treatment of painful diabetic neuropathy. *Pain* 2012;153(9):1815–1823.
14. Epstein JB, Grushka M, Le N. Topical clonidine for orofacial pain: a pilot study. *J Orofac Pain* 1997;11(4):346–352.
15. Wrzosek A, Woron J, Dobrogowski J, et al. Topical clonidine for neuropathic pain. *Cochrane Database Syst Rev* 2015;8:Cd010967.
16. Ho KY, Huh BK, White WD, et al. Topical amitriptyline versus lidocaine in the treatment of neuropathic pain. *Clin J Pain* 2008;24:(1)51–55.
17. Binder A, Bruxelle J, Rogers P, et al. Topical 5% lidocaine (lignocaine) medicated plaster treatment for post-herpetic neuralgia: results of a double-blind, placebo-controlled, multinational efficacy and safety trial. *Clin Drug Investig* 2009;29:(6)393–408.
18. Devers A, Galer BS. Topical lidocaine patch relieves a variety of neuropathic pain conditions: an open-label study. *Clin J Pain* 2000;16:(3)205–208.
19. Meier T, Wasner G, Faust M, et al. Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo-controlled study. *Pain* 2003;106:(1-2)151–158.
20. Mason L, Moore RA, Derry S, et al. Systematic review of topical capsaicin for the treatment of chronic pain. *BMJ* 2004;328(7446):991.
21. Maihofner CG, Heskamp ML. Treatment of peripheral neuropathic pain by topical capsaicin: Impact of pre-existing pain in the QUEPP-study. *Eur J Pain* 2014;18(5):671–679.

22. Casanueva B, Rodero B, Quintial C, et al. Short-term efficacy of topical capsaicin therapy in severely affected fibromyalgia patients. *Rheumatol Int* 2013;33(10):2665–70. doi: 10.1007/s00296-012-2490-5.

23. Kulkantrakorn K and Lorsuwansiri C. Sensory profile and its impact on quality of life in patients with painful diabetic polyneuropathy. *J Neurosci Rural Pract* 2013;4(3):267–270.

24. Derry S, Moore RA, Gaskell H, et al. Topical NSAIDs for acute musculoskeletal pain in adults. *Cochrane Database Syst Rev* 2015;6:CD007402.

25. Kim DH, Yoon KB, Park S, et al. Comparison of NSAID patch given as monotherapy and NSAID patch in combination with transcutaneous electric nerve stimulation, a heating pad, or topical capsaicin in the treatment of patients with myofascial pain syndrome of the upper trapezius: a pilot study. *Pain Med* 2014;15(12):2128–2138.

26. Ahmed SU, Zhang Y, Chen L, et al. Effect of 1.5% topical diclofenac on clinical neuropathic pain. *Anesthesiology* 2015;123(1):191–198.

27. Gewandter JS, Mohile SG, Heckler CE, et al. A phase III randomized, placebo-controlled study of topical amitriptyline and ketamine for chemotherapy-induced peripheral neuropathy (CIPN): a University of Rochester CCOP study of 462 cancer survivors. *Support Care Cancer* 2014;22(7):1807–1814.

28. Barton DL, Wos EJ, Qin R, et al. A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. *Support Care Cancer* 2011;19(6):833–841.

29. Lockhart E. Topical analgesics. *J Pain* 2014;5(3):S82.

30. Nyirjesy P, Lev-Sagie A, Mathew L, et al. Topical amitriptyline-baclofen cream for the treatment of provoked vestibulodynia. *J Low Genit Tract Dis* 2009;13(4).

31. Coggeshall RE, Carlton SM. Receptor localization in the mammalian dorsal horn and primary afferent neurons. *Brain Res Brain Res Rev* 1997;24(1):28–66.

32. Kinkelin I, Brocker EB, Koltzenburg M, et al. Localization of ionotropic glutamate receptors in peripheral axons of human skin. *Neurosci Lett* 2000;283(2):149–152.

33. Carlton SM, Coggeshall RE. Inflammation-induced changes in peripheral glutamate receptor populations. *Brain Res* 1999;820(1–2):63–70.

34. Anis NA, Berry SC, Burton NR, et al. The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. *Br J Pharmacol* 1983;79(2):565–575.

35. Ebert B, Mikkelsen S, Thorkildsen C, et al. Norketamine, the main metabolite of ketamine, is a non-competitive NMDA receptor antagonist in the rat cortex and spinal cord. *Eur J Pharmacol* 1997;333(1):99–104.

36. Backonja M, Arndt G, Gombar KA, et al. Response of chronic neuropathic pain syndromes to ketamine: a preliminary study. *Pain* 1994;56(1):51–57.

37. Arendt-Nielsen L, Petersen-Felix S, Fischer M, et al. The effect of N-methyl-D-aspartate antagonist (ketamine) on single and repeated nociceptive stimuli: a placebo-controlled experimental human study. *Anesth Analg* 1995;81(1):63–68.

38. Grant IS, Nimmo WS, Clements JA. Pharmacokinetics and analgesic effects of i.m. and oral ketamine. *Br J Anaesth* 1981;53(8):805–810.

39. Eide PK, Jørum E, Stubhaug A, et al. Relief of post-herpetic neuralgia with the N-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. *Pain* 1994;58(3):347–354.

40. Mercadante S, Lodi F, Sapio M, et al. Long-term ketamine subcutaneous continuous infusion in neuropathic cancer pain. *J Pain Symptom Manage* 1995;10(7):564–568.

41. Curran HV, Monaghan L. In and out of the K-hole: a comparison of the acute and residual effects of ketamine in frequent and infrequent ketamine users. *Addiction* 2001;96(5):749–760.

42. Kronenberg RH. Ketamine as an analgesic: parenteral, oral, rectal, subcutaneous, transdermal and intranasal administration. *J Pain Palliat Care Pharmacother* 2002;16(3):27–35.

43. Gammaitoni A, Gallagher RM, Welz-Bosna M. Topical ketamine gel: possible role in treating neuropathic pain. *Pain Med* 2000;1(1):97–100.

44. Crowley KL, Flores JA, Hughes CN, et al. Clinical application of ketamine ointment in the treatment of sympathetically maintained pain. *Int J Pharm Compd* 1998;2(2):122–127.

45. Finch PM, Knudsen L, Drummond PD. Reduction of allodynia in patients with complex regional pain syndrome: a double-blind placebo-controlled trial of topical ketamine. *Pain* 2009;146(1–2):18–25.

46. Quan D, Wellish M, Gilden DH. Topical ketamine treatment of postherpetic neuralgia. *Neurology* 2003;60(8):1391–1392.

47. Poyhia R, Vainio A. Topically administered ketamine reduces capsaicin-evoked mechanical hyperalgesia. *Clin J Pain* 2006;22(1):32–36.

48. Quibell R, Prommer EE, Mihalyo M, et al. Ketamine*. *J Pain Symptom Manage* 2011;41(3):640–649.

49. Gidal BE. New and emerging treatment options for neuropathic pain. *Am J Manag Care* 2006;12(9 suppl):S269–S278.

50. Gee NS, Brown JP, Dissanayake VU, et al. The novel anticonvulsant drug, gabapentin (Neurontin), binds to the alpha2delta subunit of a calcium channel. *J Biol Chem* 1996;271(10):5768–5776.

51. Shimoyama M, Shimoyama N, Hori Y. Gabapentin affects glutamatergic excitatory neurotransmission in the rat dorsal horn. *Pain* 2000;85(3):405–414.

52. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain* 1999;83(3):389–400.

53. Pan HL, Eisenach JC, Chen SR. Gabapentin suppresses ectopic nerve discharges and reverses allodynia in neuropathic rats. *J Pharmacol Exp Ther* 1999;288(3):1026–1030.

54. Maneuf YP, Gonzalez MI, Sutton KS, et al. Cellular and molecular action of the putative GABA-mimetic, gabapentin. *Cell Mol Life Sci* 2003;60(4):742–750.

55. Honarmand A, Safavi M, Zare M. Gabapentin: an update of its pharmacological properties and therapeutic use in epilepsy. *J Res Med Sci* 2011;16(8):1062–1069.

56. Edelsberg JS, Lord C, Oster G. Systematic review and meta-analysis of efficacy, safety, and tolerability data from randomized controlled trials of drugs used to treat postherpetic neuralgia. *Ann Pharmacother* 2011;45(12):1483–1490.

57. Mathew NT, Rapoport A, Saper J, et al. Efficacy of gabapentin in migraine prophylaxis. *Headache* 2001;41(2):119–128.

58. Rapchuk IL, O'Connell L, Liessmann CD, et al. Effect of gabapentin on pain after cardiac surgery: a randomised, double-blind, placebo-controlled trial. *Anaesth Intensive Care* 2010;38(3):445–451.

59. Dallocchio C, Buffa C, Mazzarello P, et al. Gabapentin vs. amitriptyline in painful diabetic neuropathy: an open-label pilot study. *J Pain Symptom Manage* 2000;20(4):280–285.

60. Dahl JB, Mathiesen O, Moiniche S. 'Protective premedication': an option with gabapentin and related drugs? A review of gabapentin and pregabalin in the treatment of post-operative pain. *Acta Anaesthesiol Scand* 2004;48(9):1130–1136.

61. Magalhaes E, Mascarenhas AM, Kraychete DC, et al. Gabapentin to treat sacral perineural cyst-induced pain. Case report. *Rev Bras Anestesiol* 2004;54(1):73–77.

62. Riedl MS, Schnell SA, Overland AC, et al. Coexpression of alpha 2A-adrenergic and delta-opioid receptors in substance P-containing terminals in rat dorsal horn. *J Comp Neurol* 2009;513(4):385–398.

63. Lavand'homme PM, Ma W, De Kock M, et al. Perineural alpha(2A)-adrenoceptor activation inhibits spinal cord neuroplasticity and tactile allodynia after nerve injury. *Anesthesiology* 2002;97(4):972–980.

64. Hassenbusch SJ, Gunes S, Wachsman S, et al. Intrathecal clonidine in the treatment of intractable pain: a phase I/II study. *Pain Med* 2002;3(2):85–91.

65. Sierralta F, Naquira D, Pinardi G, et al. alpha-Adrenoceptor and opioid receptor modulation of clonidine-induced antinociception. *Br J Pharmacol* 1996;119(3):551–554.

66. Eisenach JC, DuPen S, Dubois M, et al. Epidural clonidine analgesia for intractable cancer pain. The Epidural Clonidine Study Group. *Pain* 1995;61(3):391–399.

67. Dias VC, Tendler B, Oparil S, et al. Clinical experience with transdermal clonidine in African-American and Hispanic-American patients with hypertension: evaluation from a 12-week prospective, open-label clinical trial in community-based clinics. *Am J Ther* 1999;6(1):19–24.

68. Puskas F, Carnporesi EM, O'Leary CE, et al. Intrathecal clonidine and severe hypotension after cardiopulmonary bypass. *Anesth Analg* 2003;97(5):1251–1253.

69. Romero-Sandoval A, Eisenach JC. Perineural clonidine reduces mechanical hypersensitivity and cytokine production in established nerve injury. *Anesthesiology* 2006;104(2):351–355.

70. Davis KD, Treede RD, Raja SN, et al. Topical application of clonidine relieves hyperalgesia in patients with sympathetically maintained pain. *Pain* 1991;47(3):309–317.

71. Byas-Smith MG, Max MB, Muir J, et al. Transdermal clonidine compared to placebo in painful diabetic neuropathy using a two-stage 'enriched enrollment' design. *Pain* 1995;60(3):267–274.

72. Maibach HI. Oral substitution in patients sensitized by transdermal clonidine treatment. *Contact Dermatitis* 1987;16(1):1–8.

73. Polster AM, Warner MR, Camisa C. Allergic contact dermatitis from transdermal clonidine in a patient with mycosis fungoides. *Cutis* 1999;63(3):154–155.

74. Prisant LM. Transdermal clonidine skin reactions. *J Clin Hypertens (Greenwich)* 2002;4(2):136–138.

75. Sandroni P, Davis MD. Combination gel of 1% amitriptyline and 0.5% ketamine to treat refractory erythromelalgia pain: a new treatment option? *Arch Dermatol* 2006;142(3):283–286.

76. Kopsky DJ, Hesselink JM. High doses of topical amitriptyline in neuropathic pain: 2 cases and literature review. *Pain Pract* 2012;12(2):148–153.

77. Lehman JS, Sciallis GF. Effective use of topical amitriptyline hydrochloride 2.5% and ketamine hydrochloride 0.5% for analgesia in refractory proctodynia. *J Drugs Dermatol* 2008;7(9):887–889.

78. Liebregts R, Kopsky DJ, Hesselink JM. Topical amitriptyline in post-traumatic neuropathic pain. *J Pain Symptom Manage* 2011;41:e6–e7.

79. Gerner P, Kao G, Srinivasa V, et al. Topical amitriptyline in healthy volunteers. *Reg Anesth Pain Med* 2003;28(4):289–293.

80. Smith GD, Harrison SM, Birch PJ, et al. Increased sensitivity to the antinociceptive activity of (+/−)-baclofen in an animal model of chronic neuropathic, but not chronic inflammatory hyperalgesia. *Neuropharmacology* 1994;33(9):1103–1108.

81. Reis GM, Duarte ID. Baclofen, an agonist at peripheral GABAB receptors, induces antinociception via activation of TEA-sensitive potassium channels. *Br J Pharmacol* 2006;149(6):733–739.

82. Arnold LM, Keck PE Jr, Welge JA. Antidepressant treatment of fibromyalgia. A meta-analysis and review. *Psychosomatics* 2000;41(2):104–113.

83. Bryson E, Hartman R, Arnold J, et al. Skin permeation and antinociception of compounded topical cyclobenzaprine hydrochloride formulations. *Int J Pharm Compd* 2015;19(2):161–166.

84. Turrentine JE, Marrazzo G, Cruz PD Jr. Novel use of patch testing in the first report of allergic contact dermatitis to cyclobenzaprine. *Dermatitis* 2015;26(1):60–61.

85. Gammaitoni AR, Davis MW. Pharmacokinetics and tolerability of lidocaine patch 5% with extended dosing. *Ann Pharmacother* 2002;36(2):236–240.

86. Derry S, Wiffen PJ, Moore RA, et al. Topical lidocaine for neuropathic pain in adults. *Cochrane Database Syst Rev* 2014;7:Cd010958.

87. Wolff RF, Bala MM, Westwood M, et al. 5% lidocaine-medicated plaster vs other relevant interventions and placebo for post-herpetic neuralgia (PHN): a systematic review. *Acta Neurol Scand* 2011;123(5):295–309.

88. Argoff CE, Galer BS, Jensen MP, et al. Effectiveness of the lidocaine patch 5% on pain qualities in three chronic pain states: assessment with the Neuropathic Pain Scale. *Curr Med Res Opin* 2004;20(suppl 2):S21–S28.

89. Gammaitoni AR, Alvarez NA. 24-Hour application of the lidocaine patch 5% for 3 consecutive days is safe and well tolerated in healthy adult men and women. *Pain Med* 2002;3(2):172–172.

90. Ukens C. Coed death tied to compounded drug. 2005: Drug Topics.

91. To D, Kossintseva I, de Gannes G. Lidocaine contact allergy is becoming more prevalent. *Dermatol Surg* 2014;40(12):1367–1372.

92. Warshaw EM, Belsito DV, Taylor JS, et al. North American Contact Dermatitis Group patch test results: 2009 to 2010. *Dermatitis* 2013;24(2):50–59.

93. Warshaw EM, Schram SE, Belsito DV, et al. Patch-test reactions to topical anesthetics: retrospective analysis of cross-sectional data, 2001 to 2004. *Dermatitis* 2008;19(2):81–85.

94. Cunningham AL, Dworkin RH. The management of post-herpetic neuralgia. *BMJ* 2000;321(7264):778–779.

95. Knotkova H, Pappagallo M, Szallasi A. Capsaicin (TRPV1 Agonist) therapy for pain relief: farewell or revival? *Clin J Pain* 2008;24(2):142–154.

96. Sawynok J. Topical analgesics for neuropathic pain: preclinical exploration, clinical validation, future development. *Eur J Pain* 2014;18(4):465–481.

97. Peikert A, Hentrich M, Ochs G. Topical 0.025% capsaicin in chronic post-herpetic neuralgia: efficacy, predictors of response and long-term course. *J Neurol* 1991;238(8):452–456.

98. Nolano M, Simone DA, Wendelschafer-Crabb G, et al. Topical capsaicin in humans: parallel loss of epidermal nerve fibers and pain sensation. *Pain* 1999;81(1–2):135–145.

99. Derry S, Moore RA. Topical capsaicin (low concentration) for chronic neuropathic pain in adults. *Cochrane Database Syst Rev* 2012;9:Cd010111.

100. Heyneman CA, Lawless-Liday C, Wall GC. Oral versus topical NSAIDs in rheumatic diseases: a comparison. *Drugs* 2000;60(3):555–574.

101. Lin J, Zhang W, Jones A, et al. Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials. *BMJ* 2004;329(7461):324.

102. Mason L, Moore RA, Edwards JE, et al. Topical NSAIDs for chronic musculoskeletal pain: systematic review and meta-analysis. *BMC Musculoskelet Disord* 2004;5:28.

103. Massey T, Derry S, Moore RA, et al. Topical NSAIDs for acute pain in adults. *Cochrane Database Syst Rev* 2010;(6):Cd007402.

104. Franckum J, Ramsay D, Das NG, et al. Pluronic lecithin organogel for local delivery of anti-inflammatory drugs. *Int J Pharm Compd* 2004;8(2):101–105.

105. de Paula E, Cereda CM, Tofoli GR, et al. Drug delivery systems for local anesthetics. *Recent Pat Drug Deliv Formul* 2010;4(1):23–34.

106. Zell-Kanter M, Toerne TS, Spiegel K, et al. Doxepin toxicity in a child following topical administration. *Ann Pharmacother* 2000;34(3):328–329.

107. Lutwak N, Howland MA, Gambetta R, et al. Even 'safe' medications need to be administered with care. *BMJ Case Rep* 2013;2013: bcr2012006204.

108. Jorge LL, Feres CC, Teles VE. Topical preparations for pain relief: efficacy and patient adherence. *J Pain Res* 2010;4:11–24.

109. de Leon-Casasola OA. Multimodal approaches to the management of neuropathic pain: the role of topical analgesia. *J Pain Symptom Manage* 2007;33(3):356–364.

110. Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc* 2010;85(suppl 3):S3–S14.