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CLINICAL FOCUS: PAIN MANAGEMENT
REVIEW

Utility of lidocaine as a topical analgesic and improvements in patch delivery systems

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ABSTRACT

Interest in and use of topical analgesics has been increasing, presumably due to their potential utility for relief of acute and chronic pain. Topically applied agents with analgesic properties can target peripheral nociceptive pathways while minimizing absorption into the plasma that leads to potential systemic adverse effects.

Clinical trials have found 5% lidocaine patches to be effective and well tolerated for the treatment of post-herpetic neuralgia (PHN) with a minimal risk of toxicity or drug–drug interactions. With this patch formulation, the penetration of lidocaine into the skin produces an analgesic effect without producing a complete sensory block. Use of topical lidocaine is supported by clinical practice guidelines, including first-line treatment by the American Academy of Neurology (guidelines retired 2018), the European Federation of Neurological Societies and second-line by the Canadian Pain Society.

FDA approved 5% lidocaine patches in 1999, and a 1.8% topical lidocaine system in 2018 – both indicated for the treatment of pain secondary to PHN. The 1.8% system offers a more efficient delivery of lidocaine that is bioequivalent to 5% lidocaine patches, but with a 19-fold decrease in drug load (i.e., 36 mg versus 700 mg) as well as superior adhesion that allows the patch to maintain contact with the skin during the 12-h administration period.

Although topical lidocaine formulations have advanced over time and play an important role in the treatment of PHN, a variety of other conditions that respond to topical lidocaine have been reported in the literature including PHN, lower back pain, carpal tunnel syndrome, diabetic peripheral neuropathy, and osteoarthritis joint pain. Other neuropathic or nociceptive pain syndromes may respond to topical lidocaine in select cases and warrant further study. Clinicians should consider local anesthetics and other topical agents as part of their multimodal treatments of acute and chronic pain.

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1. Introduction

The treatment of pain remains a clinical challenge, and healthcare professionals are faced with choosing from a limited selection of analgesics and nonpharmacologic therapies. The toxicities of over-the-counter and prescription systemic agents such as acetaminophen, NSAIDs, and opioids are well documented and often lead to treatment limiting adverse effects [1–5]. In a training module on 'Treating Chronic Pain without Opioids', CDC recommends that clinicians consider topical agents including lidocaine as alternative first-line therapies, as they are thought to be safer than systemic medications [6].

Interest in and use of topical analgesics has been increasing, presumably due to their potential utility for relief of acute and chronic pain and relative lack of systemic adverse effects. These agents are available in a variety of formulations, both prescription and OTC, including gels, salves, liquids, sprays, and patches. One topical agent that has been frequently used by clinicians is the local anesthetic, lidocaine. This review offers an overview of lidocaine and its utility as a topical analgesic for musculoskeletal and neuropathic pain.

The well-accepted concept of multimodal analgesia involves interrupting the inflammatory cascade and pain signals at various points along neural pathways. Pain is mediated by specialized sensory neurons known as nociceptors located in the skin, soft tissues, muscles, and virtually all organs except for the brain [7]. Peripheral nociceptors are made up of small A delta and C fibers – so called 'first-order neurons' that convey pain signals through the dorsal horn into second-order cells located in the spinal cord [7]. From here, ascending signals relay the message to higher cortical centers, primarily the thalamus and cortex, for further modulation and pain processing [7,8]. Our understanding of the physiological processes that transmit pain has progressed over the years, with increasing appreciation for contribution by modulation of the pain signal in the periphery. Four major processes thought to be involved in pain pathway include, perception, transduction, transmission, and modulation [7,8].

Local anesthetics have the potential to interrupt transduction and transmission of nerve impulses. Specifically, lidocaine produces analgesia by blocking voltage-gated sodium channels,

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which are responsible for the propagation of action potentials [9]. When lidocaine binds, it induces a conformational change in the channel that blocks the influx of sodium, therefore preventing depolarization [10]. Sodium channels are expressed on A delta and C fibers and blockage results in a reduction of the ectopic discharges thought to underlie certain aspects of persistent pain [11].

2. Neuropathic pain

Neuropathic pain (NP) is a pathological process in the peripheral or central nervous system (CNS) defined by International Association for the Study of Pain (IASP) as pain caused by a lesion or disease of the somatosensory nervous system [12]. While many NP conditions are initiated by damage to the peripheral nervous system, their chronicity appears to rely on maladaptive processes within the CNS. Neuronal hyperexcitability and central sensitization lead to altered pain processing so that pain occurs spontaneously, and responses to noxious and innocuous stimuli are pathologically amplified [13]. The resulting symptoms include allodynia (pain which results from a stimulus that normally would not induce pain) and hyperalgesia. Patients experience paroxysms of burning, shooting, electrical sensations, as well as painful and non-painful numbness [14]. Examples of NP include postherpetic neuralgia (PHN), diabetic peripheral neuropathy (DPN), carpal tunnel syndrome, complex regional pain syndrome, and post-traumatic/post-surgical pain [15]. Pharmacologic treatments options for NP include antidepressants, anticonvulsants, topical local anesthetics and opioids [16,17].

Clinical practice guidelines for NP have been published by a number of organizations, including the European Federation of Neurological Societies (EFNS) [18], the National Institute for Health and Care Excellence (NICE) of the UK [19], the International Association for the Study of Pain [20], and the Canadian Pain Society (CPS) [21].

PHN is a painful neuropathic condition characterized by persistent allodynia or hyperalgesia in the area of a previous herpes zoster eruption [22]. It typically occurs in a unilateral dermatomal fashion, with the most common sites being the thoracic nerves and the ophthalmic division of the trigeminal nerve [23]. It is more common in the elderly and immune-compromised patients and has been reported to increase healthcare resource utilization and negatively impact quality of life (QoL) [22,24]. Various treatment guidelines are available, most of which recommend medications such as tricyclic antidepressants, gabapentin, lidocaine patch, and opioids for treating the pain of postherpetic neuralgia (Table1) [18,20,25].

Clinical trials have found 5% lidocaine patch to be effective and well tolerated for the treatment of PHN with a minimal risk of systemic adverse effects or drug–drug interactions [26–28]. In the US, prescription strength lidocaine patches are FDA-approved only for the relief of pain associated with PHN. They have been recommended as a first-line treatment of PHN by the American Academy of Neurology guidelines (retired in 2018) [25], the European Federation of Neurological Societies [18] and second-line by the Canadian Pain Society (Table 1) [21].

3. Lidocaine

Lidocaine is an amide anesthetic and class 1-b antiarrhythmic. It was first synthesized and approved in the US in the 1940s. [29] It has utility both systemically and topically as an anesthetic and analgesic agent and is available in both prescription and over the counter (OTC) formulations including gels, creams and ointments, sprays, and patches (plasters).

Table 1. Clinical practice guideline recommendations – postherpetic neuralgia.

	First line	Second line	Third line	Fourth line
AAN (Dubinsky et al [25]. (Guidelines retired Feb. 2018)	Gabapentin Lidocaine Patch Tricyclic antidepressants Pregabalin Opioids	Topical aspirin Topical capsaicin Methylprednisolone	Acupuncture Benzydamine cream Dextromethorphan Indomethacin Lorazepam Vincristine iontophoresis Vitamin E Zimelidine	Biperidin Carbamazepine Chlorprothixene Cryocautery Dorsal root entry zone lesion Extract of *Ganoderma lucidum* He:Ne laser irradiation Ketamine Methylprednisolone, iontophoresis Morphine sulfate, epidural Nicardipine Piroxicam, topical Stellate ganglion block Triamcinolone, intralesional
CPS [21]	Gabapentinoids Tricyclic antidepressants	Tramadol Opioids Lidocaine Patch	Cannabinoids	SSRIs Lamotrigine Lacosamide Topiramate Valproic acid Methadone
EFNS [18]	Gabapentinoids Tricyclic antidepressants Lidocaine Patch	Topical Capsaicin Opioids		

AAN, American Academy of Neurology; CPS, Canadian Pain Society; EFNS, European Federation of Neurological Societies; SNRIs, Serotonin and norepinephrine reuptake inhibitors.

Lidocaine is a stable, crystalline, colorless solid whose hydrochloride salt is water-soluble [10]. Structurally, lidocaine contains an amide group as well as a tertiary amine. As an amine, lidocaine is in equilibrium between a positively charged cation and an uncharged, lipid soluble, free base. The uncharged, free base of lidocaine can readily penetrate the lipid matrix of the outer layer of skin. Lidocaine has a pKa of 7.9 and slightly basic conditions will favor formation of the free base and increase penetration. Lidocaine has an n-octanol/water coefficient of 43/1 at pH 7.4, making it lipophilic favoring distribution in tissues [30].

Lidocaine's absorption is dependent upon the total dose administered, the route by which it is delivered, and blood supply to the site [10]. Similar to other local anesthetics, the mechanism of action of lidocaine for local or regional anesthesia is by reversible blockade of nerve fiber impulse firing. When applied topically, lidocaine needs to permeate through the skin to act as an anesthetic or analgesic. The outer layer of skin is made up of keratinized stratified squamous epithelium that it forms a permeability barrier that keeps water both in and out of the body. This barrier is largely produced by a lipid matrix that exists between the cells of the stratified squamous endothelium. Compounds that are polar and water-soluble cannot penetrate this barrier, but lipid-soluble compounds like lidocaine can and therefore reaches areas where peripheral nerve fibers are found.

Topical lidocaine absorption will also be affected by the thickness and surface area of the stratum corneum at the site of application, local vascularity and the duration of application. Typically, the maximal penetration depth of lidocaine when applied topically is from 8 to 10 mm [31]. Absorption is higher at mucosal sites [10] such as the mouth where lidocaine sprays are used for dental, anesthetic and surgical procedures. With currently available patches, the penetration of lidocaine into the skin produces an analgesic effect without producing a complete sensory block [32].

Lidocaine pharmacokinetics have been studied in healthy volunteers, patients with chronic pain, and those with cardiac arrhythmias [10]. An intravenous bolus of lidocaine followed by continuous infusion typically yields therapeutic plasma levels in the range of 1.5–5 mcg/ml, with toxicity expected above those levels [10]. In the systemic circulation, lidocaine is rapidly metabolized by the liver and has a half-life of 1.5 to 2 h [32]. Metabolites produced from lidocaine include monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which have activity similar to, but less potent than that of lidocaine [30].

3.1. Lidocaine formulations

Topically, lidocaine is available in gels, ointments (creams), sprays and patches – also referred to as plasters in some parts of the world, and more recently recognized by FDA as a 'topical delivery system' (TDS) dosage form [33]. Prescription formulations have a multitude of indications, including the production of local or regional anesthesia by topical application to mucous membranes, infiltration and nerve blocks. As of now, lidocaine patch formulations are approved only for the treatment of PHN [30,32].

Also available OTC, lidocaine has many uses including for the treatment of insect bites, minor burns, sunburn, other skin irritations, hemorrhoids, and back pain. These OTC products are not indicated for more advanced pain syndromes like neuropathic pain. The lidocaine concentration in these formulations is limited to a maximum of 4%, lower than the concentration in prescription formulations. It is noted that in 2003 FDA has expressed safety concerns over external (topical) analgesics in the patch, poultice, and plaster form and consequentially ruled that these dosage forms have not been determined to be generally recognized as safe and effective [34]. Marketing and promotion of OTC products fall under different regulatory requirements than prescription drugs; this leads to labeling of many of these products with indications (actual or implied) that are not supported by well-controlled clinical safety and efficacy studies. These preparations often lack openly available data on pharmacokinetics, with unknown maximum plasma concentration potentials – even with use as directed. As systemic absorption varies based on formulation, safety may be an issue with some OTC preparations – especially with multiple repetitive applications. There have been reports of great individual variability in absorption and metabolism for these products [35]. A 2012 study compared five commonly available lidocaine preparations (three of which were OTC) and their levels of systemic absorption when applied to the face. The OTC preparations had the highest serum lidocaine and MEGX levels. There were significant inter-individual differences between the serum levels of MEGX and lidocaine in four out of five groups [35]. This study demonstrated that although topical anesthetics are considered safe, some individuals had unpredictably high absorption levels that could possibly result in adverse events [35]. This study also demonstrated that the concentration of lidocaine, the formulation of the drug, and the individual patient all have significant effects on serum levels of lidocaine, especially with OTC preparations that may not have undergone the rigorous clinical trials or safety studies in humans as required by FDA for approved prescription products [35].

Lidocaine may be combined with other anesthetics, such as prilocaine in a mixture of local anesthetics. An example of this is EMLA™, a topical cream, disc or patch (not available in all countries) containing 2.5% lidocaine and 2.5% prilocaine. With this product, local analgesia or anesthesia is achieved after 60 min with a duration of at least 2 h [36]. A gram of EMLA™ cream contains 25 mg of lidocaine and 25 mg of prilocaine. EMLA™ cream is indicated for topical analgesia of intact skin in connection with needle or catheter insertion, superficial surgical procedures or topical analgesia of leg ulcers. When using the cream, dosage and application time recommendations need to be carefully followed, especially in infants and children, as application to large surface areas for an extended amount of time can lead to adverse events including methemoglobinemia, seizures and life-threatening cardiovascular collapse [36].

3.2. Safety of topical lidocaine

Topical lidocaine is generally regarded as safe. Adverse reactions are typically dose-related and similar in nature to those

observed with other local anesthetics. The most common adverse events are application site reactions, including skin irritation that is usually mild and transient [15,28,30,32]. Applying lidocaine topically allows the targeted delivery of lidocaine with low systemic exposure, hence a lower risk of systemic toxicity than with mucosal or intravenous administration. While the risk of systemic absorption of topical products is relatively low, overuse of OTC agents, compounding lidocaine in higher doses, using on broken or inflamed skin and occluding the site of application can lead to excessive exposure; patients should be counseled against use by these means [30,32,36]. Adverse systemic side effects may include dizziness, drowsiness, muscle twitches, seizures, respiratory distress, loss of consciousness, and cardiac arrest. [30,32,36] Caution should also be used while using lidocaine in patients receiving Class I antiarrhythmic drugs as the toxic effects are additive and potentially synergistic [30,32,36]

4. Five percent lidocaine hydrogel patches

Lidoderm®, the first lidocaine patch introduced in the US received FDA approved in 1999. It is a prescription 5% lidocaine hydrogel patch indicated for the treatment of neuropathic pain secondary to PHN [30]. The patches consist of an aqueous adhesive material (hydrogel) containing 5% lidocaine by weight – with 700 mg of lidocaine in 14 g of the adhesive material applied to a non-woven backing material and non-perforated polyethylene terephthalate (PET) release liner [30]. Per the label, up to three patches can be applied to the painful area for up to 12 h on, followed by 12 h off. The patches can be cut into smaller pieces to conform to localized painful areas. Analgesic data from PHN studies suggest that some subjects using lidocaine patches achieved pain relief within 30 min [30].

Clinical trials that led to the approval of the 5% lidocaine hydrogel patch included a double-blind, crossover study and an enriched enrollment trial for relief of pain secondary to PHN [26,28]. Patients (n = 35) with PHN had the 5% lidocaine hydrogel patch, a placebo patch, or no treatment in separate sessions lasting 12 h. The 5% lidocaine patch reduced pain intensity at all time points from 30 min to 12 h compared to the placebo patch or to no-treatment. The patch was well tolerated without systemic side effects [26]. In the enriched enrollment trial, 32 patients who had been using the patch for at least 1 month were randomized to continue on the patch or to a placebo patch. The primary endpoint of the 14-day study was 'time to exit', whereby subjects were allowed to exit based on their pain relief score. The median time to exit for the 5% lidocaine hydrogel patch was greater than 14 days, while with the vehicle patch it was 3.8 days – suggesting an analgesic benefit to the active treatment. At study completion, 25/32 (78.1%) of subjects preferred the lidocaine patch treatment phase as compared with 3/32 (9.4%) placebo ($P < 0.001$). No statistical difference was noted between the active and placebo treatments with regards to side effects [28].

A small survey on a 5% lidocaine-medicated plaster examined long-term treatment in patients with localized neuropathic pain conditions [37]. Patients were queried about ease and duration of use, pain relief, tolerability and the development of tolerance over time. After 36 months, half of the initial responders to the plaster continued its use with no obvious decline in effectiveness. After 5 years, 40% continued treatment and maintained effective analgesia. There were no intolerable adverse effects leading to discontinuation, but application site reactions were noted when using the patch beyond the indicated duration [37].

A review of studies that focused on data related to safety and tolerability of the 5% lidocaine hydrogel patch found that the patch demonstrated good tolerability in both the short- and long term with a minimal risk for systemic adverse drug reactions [38]. Mean peak blood lidocaine concentrations for the 5% lidocaine hydrogel patch were reported to be 0.13 μg/mL [30], approximately 1/10 the blood concentration required to treat cardiac arrhythmia [30] and about 1/38 the concentration that produces toxicity [15]. Mild to moderate application site reactions were the most common adverse event associated with use of lidocaine patches [15,28,30,32].

Clinical use and practice guidelines for lidocaine patches vary. FDA has approved lidocaine patches for the treatment of pain secondary to PHN [30,32]. Clinical guideline recommendations from the American Academy of Neurology (AAN), European Federation of Neurological Societies (EFNS) and Canadian Pain Society (CPS) for the treatment of PHN are summarized in Table 1. Lidocaine patches are recommended as first-line treatment by the AAN and EFNS and second-line by the CPS, though the AAN guidelines were retired in 2018 [18,21,25].

Although lidocaine patches are approved for the treatment of pain secondary to PHN in the US, wide-spread off-label use for other pain syndromes is reported. A study published in 2012 showed that over 80% of usage of these patches was off-label, and 74% of the patients were prescribed this therapy for the treatment of non-neuropathic pain [39].

5. Utility of topical lidocaine

Although there is a lack of consensus among experts regarding the role of topical lidocaine in the treatment of pain, its use has been reported as beneficial in a variety of conditions which will be reviewed below.

5.1. Postherpetic neuralgia

A retrospective cohort analysis was done that assessed health-care utilization secondary to PHN and examined the medical records of a matched cohort of nearly 40,000 PHN patients treated between 2010 and 2014 [40]. This report found that recommended first-line medications including lidocaine patch, pregabalin, and tricyclic antidepressants – were underutilized in PHN patients. Instead, second- or third-line treatments (i.e. opiates and capsaicin) or NSAIDs (which are not recommended and have been shown in a meta-analysis to be ineffective for NP [41]) were frequently used as the initial treatment [40]. After no treatment (32% of patients), opioids were the most common initial treatment used (22% of PHN patients), followed by gabapentin (15% of PHN patients) and NSAIDs (9% of PHN patients). Lidocaine patches were only used initially in 8% of PHN patients. The

use of opioid therapy initially led to higher excess health-care costs relative to the costs of matched patients who were started on recommended first-line therapies. The data suggest an opportunity for improved adherence to painful PHN practice guidelines for first-line therapy [40]. Greater adherence to the guidelines also has the potential to lead to less use of opioids and therefore decreased risks associated with their usage [40].

There is evidence that using lidocaine patches as an adjunct or in combination with other therapies can be effective with relief of pain secondary to PHN [15]. A post hoc analysis of two open-label, nonrandomized, prospective, multicenter clinical trials in PHN patients who experienced insufficient pain relief with NSAIDS, opioids, TCAs, and gabapentenoids found that adding the lidocaine patches to their existing therapy resulted in significant effects in reducing pain and improving the QoL [15]. This further supports the use of topical lidocaine in the multimodal treatment of NP.

Thus, there is enduring evidence for the effectiveness of lidocaine patches for treating pain secondary to PHN with a low risk of systemic adverse events. Better education is needed so that clinicians can appropriately follow NP guidelines including the use of first-line therapies such as topical lidocaine for refractory painful PHN.

5.2. Diabetic peripheral neuropathy

Although not indicated for the treatment of DPN, some studies suggest that topical lidocaine may be a useful therapy for the treatment of DPN. Reviews on the use of lidocaine patches to treat DPN have been published [42,43]. Two studies on treatment of pain associated with DPN of 4 weeks duration directly compared lidocaine patches to oral pregabalin [44,45] and there are three open-label studies of the patches in DPN [46–48]. The results of a systematic review of treatments for DPN of that compared the lidocaine patch to other interventions including placebo suggested that the lidocaine patches were comparable for pain reduction to amitriptyline, capsaicin, gabapentin, and pregabalin and may be associated with fewer and less significant adverse side effects as compared to these mostly systemic agents[42]. The authors of the review concluded that the results are limited by the number and size of the studies and that further studies are warranted[42].

5.3. Carpal tunnel syndrome

Three pilot studies suggest that topical lidocaine may be effective and safe in treating carpal tunnel syndrome [49–51]. In the first of these studies, daily use of the 5% lidocaine hydrogel patch was compared to a single injection of lidocaine plus methylprednisolone for 4 weeks in 40 randomized patients[49]. In the second study, the 5% lidocaine hydrogel patch was compared to naproxen 500 mg twice daily for 6 weeks of treatment in 100 randomized patients[50], and the third study compared EMLA cream (lidocaine 2.5% plus prilocaine 2.5%) to a single injection of methylprednisolone acetate 40 mg in 65 randomized patients for 4 weeks of treatment [51]. In each of these studies, effective pain relief was reported for the topical lidocaine groups [49–51]. Suggesting topical lidocaine may be useful for treatment of pain secondary to carpal tunnel syndrome. As this painful condition represents a significant source of disability, further studies are warranted.

5.4. Lower back pain (LBP)

Chronic LBP may consist of both nociceptive and neuropathic components for which lidocaine patches may be of benefit [52]. Treatment of patients with moderate to severe LBP with the lidocaine patch was studied in two uncontrolled, open-label, 6-week, pilot studies [53,54]. There were 71 and 131 subjects in these two studies. In each study, the patch significantly reduced pain intensity and improved the patients' QoL [53,54]. Several studies suggest that the lidocaine patch can be combined with oral therapies or used as an add-on therapy. A prospective, open-label, add-on, 2-week, pilot study of 28 patients with moderate to severe LBP who had only a partial response to gabapentin-containing analgesic regimens found the lidocaine patch provided significant improvements of all composite measures of the neuropathic pain scale [47]. In an open-label, multicenter, 2-week, pilot study of 71 patients with LBP and a partial response to gabapentin-containing analgesic regimens, add-on treatment with the lidocaine patch led to significant improvements in pain intensity and pain relief scores and to significant improvements for all domains of QoL measurements [48]. Although lidocaine is not indicated for LBP, these limited studies suggest that lidocaine patches combined with oral therapies may be a treatment option for patients with LBP [52]. As low back pain is a significant cause of disability and opioid utilization in the US, further research on topical analgesics in this condition is clearly warranted.

5.5. Osteoarthritis pain

The efficacy of the lidocaine patch has been studied in trials in a total of 257 patients with osteoarthritis (OA) of the knee. A prospective, open-label, 2-week, multicenter, monotherapy study of the lidocaine patch in 20 patients who had inadequate relief of pain with current analgesics found that use of the lidocaine patch led to significant improvement in the WOMAC (Western Ontario and McMaster Universities Arthritis Index) score, in pain intensity and in QoL measurements [55]. A prospective, open-label, 2-week, multicenter, add-on therapy trial of the lidocaine patch in 137 patients with OA of the knee and who had an incomplete response to stable analgesic therapy found significant improvement in pain intensity, WOMAC sum score and QoL [56]. The third study, a prospective, open-label, 2-week, multicenter, monotherapy, and add-on therapy trial of 100 subjects with OA of the knee found significant improvement in all four Neuropathic Pain Scale composite measures for both monotherapy and for add-on therapy [57]. Although it is not indicated for treatment of OA, these open-label trials suggest that the lidocaine patch could prove useful as an adjunct therapy

for OA, although confirmation is needed from randomized, controlled trials.

6. New developments in topical lidocaine formulations

6.1. Anhydrous lidocaine topical system 1.8%

A new prescription topical lidocaine patch uses a novel drug delivery technology for topical lidocaine (ZTlido™, Scilex Pharmaceuticals, Inc.) [32]. It received FDA approval for treating PHN and entered the US market late in 2018. This new patch system (note: FDA has redefined this dosage form from 'patch' to 'system', but the terms are interchangeable for this discussion) offers significant advantages over the hydrogel lidocaine patch and its generic equivalents. With the 1.8% system, there is more efficient delivery of lidocaine that requires a lower drug load to achieve the same therapeutic effect and superior adhesion that allows the patch to remain in better contact with the skin during the 12-h dosing period [32].

With the original 5% lidocaine patch and most of its generics, the lidocaine is included as part of a hydrogel adhesive mixture [30]. These patches have high water content within the gel polymer system that results in a thicker and heavier adhesive patch. The original 5% lidocaine hydrogel patch contains 700 mg of lidocaine, yet only delivers a small amount of lidocaine to and through the skin [30]. Approximately 3 ± 2% of the lidocaine in the patch reaches systemic circulation and at least 665 mg remains in the patch after use [30].

Accidental exposure to the large amount of residual drug remaining in the patch may present safety issues not only to the patient but also to others including family members, caregivers, children, and pets [30]. A Guidance for Industry was issued by FDA concerning this issue with transdermal drug delivery systems (TTDS), transmucosal drug delivery systems (TMDS), and topical patches [58]. Safety issues may arise with these drug delivery systems because of the large amount of drug remaining in the used product. The Guidance gives examples of adverse events arising from overdosing because of a patient's failure to remove TTDS after the end of the intended use period, and children dying from inadvertent exposure to discarded TTDS [58]. Prescribing information for 5% lidocaine patches and associated generics contain warnings about the 'large' amount of lidocaine remaining in the used patch, accidental exposure in children and pets, and excessive dosing from applying the patches for longer than recommended [30].

In contrast, the recently approved 1.8% lidocaine topical system contains only 36 mg of lidocaine per patch (compared to 700 mg in the hydrogel patch) [30,32]. It consists of a thin, single-layer anhydrous adhesion system that serves two functions: (1) less drug is needed within the patch to achieve therapeutic effect, and (2) improved adhesion. These improvements are made without compromise to the dermal safety of the product, which is reflected in the same local tolerance between the 1.8% lidocaine topical system and 5% lidocaine patches. The delivery of lidocaine from the anhydrous 1.8% lidocaine topical system is more efficient than it is from the 5% lidocaine hydrogel patch resulting in a significant difference in bioavailability (~48% versus ~3%). Despite the significant difference in the amount of lidocaine in the patches, a single-dose, crossover, pharmacokinetic (PK) bioequivalence study showed that the anhydrous 1.8% lidocaine topical system demonstrated equivalent exposure (AUC) and peak concentration (C_{max}) as the 5% lidocaine hydrogel patch [32,59]. These bioequivalence data demonstrate that 1.8% lidocaine topical systems deliver an equivalent amount of lidocaine as the 5% lidocaine hydrogel patch despite having a significantly lower drug load (36 mg versus 700 mg) and consequentially a lower product strength (1.8% versus 5%) [30,32]. Likewise, only a small amount of lidocaine will remain in the transdermal lidocaine 1.8% system patch after use, which is reflected in the label and contrasts with the 5% lidocaine patch labels that warn against the large amount of residual drug [30,32].

The 5% lidocaine patch and the 1.8% lidocaine topical system are similar in size (10 cm x 14 cm), but the adhesive composition and biopharmaceutical dynamics also allows for a significantly thinner patch (system) (0.8 mm vs. 1.71 mm). The thinness of 1.8% topical lidocaine system along with the malleability of the nonaqueous polymer adhesive allows for a pliable patch that maintains contact with the skin during activity and at contour-challenged areas of the body. Like the 5% patch, the 1.8% lidocaine topical system can be cut into smaller pieces to conform to localized painful areas of the skin [30,32].

7. Adhesion of lidocaine patches

A commonly reported issue with topical patch products including the 5% lidocaine hydrogel patch is adhesion. FDA Adverse Events Reporting System found that for the lidocaine patch, about 70% of concerns reported regarded poor product adhesion [60]. This is a much higher rate compared with other patch products such as buprenorphine, fentanyl or nicotine patches [60]. Sustained and uniform adhesion of the patch is important for drug delivery and hence effectiveness.

An October 2018 draft FDA guidance provided recommendations for the design and conduct of studies evaluating the adhesive performance of a transdermal or topical delivery system (TDS) [33]. For the comparative assessment of adhesion, a 5-point adhesion scale was recommended in which each score corresponds to a specified range of adhered surface area for the TDS [33]. In a 54 subject clinical adhesion performance study with the 1.8% lidocaine topical system, 47 subjects (87%) had adhesion scores of 0 (≥90% adhered) for all evaluations performed every 3 h during the 12 h of administration, seven subjects (13%) had adhesion scores of 1 (≥75% to <90% adhered) for at least one evaluation, and no subjects had scores of 2 or greater (<75% adhered) [32]. At the 12-h time point, 49 subjects (91%) had a score of 0 (≥90% adhered), supporting the advanced adhesion technology utilized in the formulation [32].

The superior adhesion profile of the 1.8% lidocaine topical system relative to 5% lidocaine patches was also demonstrated in a separate comparative clinical adhesion study [61,62]. With the 1.8% lidocaine topical system, 75% of the patches maintained ≥90% adhesion for 12 h compared while only 13.6% of the 5% lidocaine hydrogel patches maintained this level of

adhesion over the same treatment period [61,62]. In a third study, the adhesion of the 1.8% lidocaine topical system was compared with a generic (Mylan Pharmaceuticals Inc. Morgantown, WV) 5% lidocaine patch [62]. The 1.8% system maintained a mean adhesion >90% across all time points (0, 3, 6, 9, and 12 h) whereas the generic 5% patch had a mean adhesion of 80% at Time 0 (i.e., immediately after patch application) that progressively fell below a mean of 50% before 6 h [62]. This specific 5% lidocaine (Mylan) generic was selected for this third study because is not a hydrogel adhesive system and like 1.8% lidocaine topical system, it too involves a thin single-layer nonaqueous adhesive and has a lower drug load versus the original patch (140 mg versus 700 mg) [63]. Yet this 5% generic non-hydrogel system was observed to have distinctly worse adhesion profile compared to both the original 5% lidocaine patch and 1.8% lidocaine topical system [62]. While this disparity is expected relative to 1.8% lidocaine topical system, this finding is surprising relative to the original 5% lidocaine patch as the generics are expected to have comparable adhesion performance (along with bioequivalent PK and comparable dermal irritation profile). Further studies may be warranted to confirm the disparity.

The superior adhesion profile of the 1.8% lidocaine topical system should contribute to consistent drug delivery, minimize inappropriate patch replacements, and may have potential patient compliance and pharmacoeconomic benefits. Equally important is that the improvement in adhesion does not come at a sacrifice to dermal sensitization and irritation. In a provocative dermal sensitization and irritation clinical study (1.8% lidocaine topical system versus 5% lidocaine patch), both products presented with no sensitization [59], with a mean irritation score of 0.37 versus 0.04, respectively, on a 0–7 scale where a score of 0 is no irritation and a score of 7 is a strong reaction spreading beyond the application site. Although the 1.8% lidocaine topical system presented with statistically worse irritation, the mean irritation scores for both products were well below a score of 1 (barely perceptible erythema) are not considered clinically significant [59]. These data, along with formal irritation assessments performed in other sponsor-conducted studies, lead to 1.8% lidocaine topical systems having the same local tolerance/application site reactions language in the labels [30,32,59].

8. Conclusions

Topical analgesic benefits include targeted drug delivery, avoidance of the oral route and relative lack of systemic adverse effects. Local anesthetics block nociceptive signals and are of benefit when treating acute and chronic nociceptive and neuropathic pain. Lidocaine has proven effective as a topical analgesic, with a variety of prescription and OTC formulations available. There is a general lack of data regarding the safety, effectiveness, and pharmacokinetics of OTC lidocaine preparations. A newer and thinner topical lidocaine patch system has shown superior adhesion and a more efficient and consistent delivery of lidocaine, which may prove to be of benefit when treating neuropathic pain secondary to PHN. Prescription lidocaine patches are FDA approved for the treatment of pain related to PHN and are included in neuropathic pain management guidelines, which should be a focus of education for clinicians who treat these patients.

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Declaration of interest

Dr. Gudin reports other from AcelRx Pharmaceuticals, other from BioDelivery Sciences International, other from Averitas Pharma, other from KemPharm, other from Mallinckrodt Pharmaceuticals, other from Nektar Therapeutics, other from Quest Diagnostics, other from Scilex Pharmaceuticals, other from Salix Pharmaceuticals, and other from Virpax Pharmaceuticals outside the submitted work.

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