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Lidocaine Topical Systems in the Treatment of Postherpetic Neuralgia

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Abstract

Shingles (herpes zoster) occurs when the latent varicella zoster virus is reactivated after an initial infection, typically resulting in a painful unilateral rash. Postherpetic neuralgia (PHN) describes a syndrome of persistent neuropathic pain following the resolution of the herpes zoster rash. The 5% and 1.8% lidocaine topical system (LTS) is indicated for the treatment of pain associated with PHN. The PubMed database was searched for "postherpetic neuralgia lidocaine" with limiters on clinical studies, clinical trials, randomized controlled trials, and meta-analyses, completed in the past 10 years. Lidocaine is a well-established voltage-gated, sodium-channel inhibitor that blocks certain sodium channels reducing ectopic discharges, reducing pain. There is no disease-modifying pharmacological therapy for PHN, and treatment aims at providing symptomatic relief. The 5% LTS is available as a 10 x 14 cm patch to be adhered to dry, intact, non-irritated skin. These plasters may be cut to the proper size and shape, if needed. Pain associated with PHN can be severe, distressing, and debilitating, and the 5% LTS has been shown to be an effective and well-tolerated treatment option. Combination therapy may be helpful. The current body of evidence recommend anticonvulsants (gabapentin or pregabalin), tricyclic antidepressants, or topical lidocaine plasters as the first line of approach; opioids and topical capsaicin are second-line options. Since it is a topical lidocaine product, it avoids the side effects associated with systemic therapies for PHN, such as gabapentinoids or opioids. Adverse events tend to be mild, self-terminating, and relate mainly to application site reactions.

Keywords: *Colorectal Cancer; Review; Screening; Treatment*

Abbreviations

EQ-52: European 5-Dimension Quality of Life Index; FDA: Food and Drug Administration; LMP: Lidocaine Medicate Plaster; LTS: Lidocaine Topical System; PHN: Postherpetic Neuralgia; SF-MPQ: Short Form McGill Pain Questionnaire

Introduction

Shingles (herpes zoster) occurs when the latent varicella zoster virus is reactivated after an initial infection. The varicella zoster virus is a highly contagious DNA virus which can remain latent for decades in the sensory ganglia after chickenpox; if it is reactivated, it travels away from the sensory ganglia toward the epidermis, typically resulting in a painful unilateral rash (not crossing the midline) [1]. Symptoms may precede the rash, including pain, pruritus, headache, photophobia, and a sense of malaise and may worsen when the rash appears. The rash usually resolves in two to four weeks but may leave scars [2]. Acute herpes zoster is associated with decreased health-related quality of life, increased anxiety and depression, and sleep disturbances [3].

Postherpetic neuralgia (PHN) describes a syndrome of persistent neuropathic pain (three months or more) following the resolution of the herpes zoster rash. Reactivation of the latent varicella zoster virus may also produce chronic neuropathic pain without rash (zoster

sine herpete), a condition similar to PHN that is far more challenging to diagnose [4]. Pain associated with PHN may be perceived as constant or intermittent burning, aching, or throbbing that occurs in the absence of a stimulus. A stimulus may provoke pain out of proportion to the stimulus as many PHN patients have hyperalgesia and develop allodynia [1]. In fact, allodynia occurs in the majority of PHN patients (about 70%) and can be particularly devastating and debilitating to patients as well as challenging to treat effectively [5].

About one million people develop herpes zoster annually in the U.S. [6] and 5% to 20% of this population will develop PHN [7]. PHN is diagnosed as pain that persists three or more months after shingles and may last for years. There is no clear first-choice approach to the management of PHN pain. The literature and guidelines recommend anticonvulsants (gabapentin or pregabalin), tricyclic antidepressants, or topical lidocaine plasters as the first line of approach; opioids and topical capsaicin are second-line options [8-14]. A new capsaicin patch has come to market. PHN patients may become discouraged as their pain is challenging to treat. There is evidence that combination therapy may be helpful [10,15-18]. There is no disease-modifying pharmacological therapy for PHN, and current treatment aims solely at providing symptomatic relief.

The annual rate of acute herpes zoster is 3.4 cases per 1000 people but it increases with age, such that prevalence is greater in the population ≥ 50 years and rises each decade thereafter [19,20]. The ZOCAD study (n = 4,518 at 54 centers in France) found that PHN occurred more often in men than women, but PHN patients with chronic neuropathic pain were more frequently women than men [21]. Reports of which sex has the greater risk for PHN conflict [22]. An observational study by Bouhassira., *et al.* reported that male sex was a predictive factor for PHN [23]. However, a cohort study on risk factors for PHN reports that the risk of PHN is greater for women than men [24].

The 5% lidocaine topical system (5% LTS) consists of a medicated patch and has been available since about 1999 in over 50 countries around the world (Versatis®, Grunenthal GmbH, Aachen, Germany and Lidoderm®, Endo Pharmaceuticals, Malvern, Pennsylvania, USA). It is indicated for the treatment of pain associated with PHN. In a few countries it is also approved for treating localized neuropathic pain. It has been estimated to have been used globally in over 23 million patients [25]. However, problems with plaster adhesion reduced patient compliance and led to the development of adhesion scales by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to better quantify the extent of the problem. This, in turn, led to the development of a new 1.8% lidocaine topical system (ZTLIDO® topical system, SCILEX Pharmaceuticals, San Diego, California, USA) based on a polymer matrix, which is bioequivalent to the original 5% lidocaine medicated plaster/patches.

Objective of the Study

It is the objective of this paper to describe recent studies on the safety and effectiveness of the 5% LTS in the treatment of pain and other symptoms associated with PHN and to describe the transition to the new 1.8% LTS. This is a short narrative review of recent literature.

Methods

In October 2018, PubMed database was searched for "postherpetic neuralgia lidocaine" with limiters to select only clinical studies, clinical trials, randomized controlled trials, and meta-analyses completed in the past 10 years. One hundred twenty-five results were obtained. These results were then search manually based on these inclusion criteria: full-text availability, English language, and clinical relevance to our topic of the use of the 5% lidocaine patch in the treatment of PHN pain. Exclusion criteria were: individual case studies, reviews, and studies of treatments not involving the use of the lidocaine patch, that is, lidocaine infusion therapy and lidocaine injections. Studies that evaluated costs, cost-effectiveness, or healthcare resource allocation as endpoints were excluded. Retrospective, open-label, and case-series studies were included if they met other criteria. Studies that included but were not limited to treatment of PHN pain (such as studies that enrolled patients with various forms of localized neuropathy) were included providing at least a subset of patients had PHN. Studies of neuropathic pain that excluded PHN were excluded. A total of 9 articles were obtained.

The bibliographies of these articles were also examined for supporting or supplemental material. Additional research was conducted to provide details on the mechanisms of action of lidocaine in PHN.

Results

All of the articles retrieved dealt with the 5% lidocaine medicated patch. As the Lidoderm and Versatis topical systems are considered bioequivalent to the 1.8% lidocaine medicated patch [26], a summary of these results is important to evaluate the effectiveness and safety of these patches.

Pathogenesis of PHN

Once varicella zoster virus infection resolves, the virus establishes latency in the dorsal root ganglia neurons where it typically remains dormant for decades because of the cell-mediated immunity to the virus acquired during the primary infection [27]. A failed immune-system control can cause the dormant virus to reactivate. The risk for immune failure increases with advancing age, stress, certain medications, and certain medical conditions. The reactivated virus can then spread through the peripheral sensory nerve fibers toward the skin level resulting in a unilateral vesicular rash in the dermatome innervated by the ganglion. The most commonly affected sites for shingles are the thoracic dermatomes. This reactivation is followed by an inflammatory response that may destroy the peripheral and central neurons and their fibers, resulting in pain [27]. After the shingles outbreak has cleared, damaged peripheral nerves may still no longer effectively inhibit nociceptive signals, leading to a lowering of the pain threshold and spontaneous ectopic discharges. As a result, pain persists after the shingles which is characterized by hyperalgesia (extreme sensitivity to even mild stimuli) and allodynia. Inflamed nerves may also impede descending inhibitory pain pathways and lead to central sensitization and chronic neuropathic pain [28]. Pain is reported by about 90% of individuals with PHN and this pain can adversely affect mobility, self-care, quality of life, and the patient's ability to take care of the activities of everyday living [29].

The mechanisms of action of the lidocaine plaster/patch

Lidocaine is a well-established voltage-gated, sodium-channel inhibitor that blocks certain sodium channels (Nav1.7 and Nav1.8) within the dermal nociceptors of A-δ and C-fibers [30-32]. By reducing ectopic discharges, this blockade reduces pain. Lidocaine also appears to inhibit inflammatory processes, suppress nitric oxide production, and regulate T-cell activity [33,34]. Lidocaine may also activate the transient receptor potential (TRP) channels in such a way that it depolarizes the membranes and produces an analgesic effect by reducing electrical activity in nerves that contain TRP channels [35].

The 5% LMP is available as a 10 x 14 cm patch to be adhered to dry, intact, non-irritated skin. Up to three patches may be applied at one time and patches may be worn up to 12 hours; patients should have at least 12 consecutive hours without a patch every 24 hours [36]. These plasters may be cut to the proper size and shape, if needed. Application of the 5% LMP typically produces an initial soothing, cooling "patch effect" [25]. Maximum serum concentrations of lidocaine were observed between 9 and 12 hours after patch application [37]. In a healthy individual, the elimination half-life of the 5% LMP is about 7.6 hours, but half-life times may be affected by dysfunctions in the cardiac, renal, or hepatic system [37]. The 5% LMP should only be used with caution (if at all) in patients with severe cardiac, renal, or hepatic dysfunction [36].

Unfortunately, the 5% LMP appeared to be particularly prone to adhesion issues. Based on total cases reported to the FDA Adverse Events Reporting System (FAERS) that relate to product adhesion, the 5% LMP (Lidoderm® product, marketed in the USA) was far more likely to have adhesion issues than other patches (See table 1).

	Transdermal Fentanyl	Transdermal Buprenorphine	Transdermal Nicotine	Topical Lidocaine
Total cases	46,966	37,295	26,495	1,936
Product adhesion issues	3,288	1,755	948	1,347
Percentage of cases reporting problems with adhesion	7.00%	4.71%	3.58%	69.58%

Table 1: *Adhesion problems have occurred disproportionately more frequently with transdermal lidocaine plasters/patches than with other patch systems. From the FDA Adverse Events Reporting System Public Dashboard, data as of March 31, 2018. These data apply to the Lidoderm® patch, marketed in the USA.*

Poor adhesion may have numerous consequences. In the reports, patches fell off or did not adhere entirely decreasing the amount of drug delivered; patients sometimes had to replace patches, which increased cost of treatment; patches that fell off might pose a danger if they came in contact with children or pets [38,39]. A Harris poll telephone survey conducted in May 2016 in the USA among 153 adults using the 5% LMP (Lidoderm) or PHN pain found 49% of respondents said the patches "sometimes" or "never" stayed in place and 89% reported some detachment issues with plasters. About half of respondents (46%) said they sometimes used tape to help keep the plasters in place [40].

This has led to the development of the 1.8% LTS (ZTLIDO®). This topical system was designed such that one 1.8% LTS is bioequivalent to one 5% LMP and has the same efficacy. The nonaqueous polymer matrix technology used in the 1.8% LTS allows for 12-hour adhesion even during moderate exercise. The polymer matrix patches are thinner, more flexible, and have a perforated release liner that is easier to peel off. The 1.8% LTS is thin (0.08 cm compared to 0.16 cm for the 5% LTS) and lighter (2g vs. 14g, respectively). In an adhesion study conducted by the manufacturer (n = 47), more than 90% of patients had greater than 90% adhesion after a 12-hour administration period with the 1.8% LTS [26,41] When the patch was evaluated during moderate exercise, there was some minor lifting at the corners reported but over 50% of subjects had greater than 75% adhesion [41].

In order to quantify adhesive properties, the FDA developed a 5-point adhesion scale (See table 2). Using this scale and tests conducted by the manufacturer, the new 1.8% LTS offered better adherence at 3, 6, 9, and 12 hours after application ($p < 0.0001$). The European Medicines Agency developed its own assessment scale based on percentage of adhesion. In an unpublished open-label study by the manufacturer it was found that the 1.8% LTS had 91% adhesion at 12 hours compared to the 5% LMP which had 64% adhesion at 12 hours.

Rating	Criteria	Description
0	≥ 90% adherence	Essentially no lifting from the skin
1	≥ 75% < 90% adherence	Some edges lifting from the skin
2	≥ 50% < 75% adherence	Lifting but involving less than half of the patch
3	> 0% < 50% adhered but not detached	More than half of the patch lifting off the skin but without the patch falling off
4	0% adhered, detached	Patch completely off the skin

Table 2: *The FDA scale for evaluating patch adherence. The European Medicines Agency developed its own scale using a percentage system (percent detached).*

Effectiveness

The literature contains no published clinical trials of the 1.8% LTS for treatment of PHN pain. There are studies of the 5% LMP, a short overview of which appears in table 3. Some of these studies compared the 5% LMP to other treatments while others just evaluated the 5% LMP without comparator or placebo. None of the nine studies in our review mentioned the issue of plaster adherence.

	Decrease in mean pain intensity	Painful area decreased in size	Allodynia improved	Sleep quality improved	No. of concomitant analgesics used at baseline and during study	Patients who did not need further concomitant pain treatments
Amato 2017 (results for only PHN patients, n = 204)	43% vs. baseline at 60 d	Yes, significantly	Yes	Yes	1.4 at baseline vs. 1.0 at 60 d	15% at baseline vs. 40% at 60 d
Baron 2009	66.4% of 5% LMP vs. 61.5% of oral pregabalin responders at 4 wk with LMP associated with larger decreases in pain intensity. 5% LMP pt had -2.4 reduction in pain intensity compared to -2.0 for pregabalin	NR	57.8% of LMP pt decreased compared to 25.0% of oral pregabalin	NR	NR	NR
Binder 2009	51.7% achieved at least moderate pain relief in run-in phase and were considered responders. Pain reductions of ≥ 30% and ≥ 50% occurred in 39.5% and 25.9% of all pt	NR	At baseline, 19% had extremely painful allodynia which reduced to 13.6% and 14.3% in non-randomized and randomized responders, respectively	25.8% had sleep difficulties at baseline, dropping to 10.8% in non-randomized responder or from 33.8% at baseline to 7.0% in randomized responder. Non-responders did not have improved sleep.	NR	NR

Clere 2011	NR	NR	NR	NR	Mean concomitant treatments decreased to 1.6 ± 0.8 ($p < 0.001$)	89.4% had concomitant treatment at start of study, decreased to 85.0% at end of study ($p = 0.046$)
Delorme 2011	73.2% of patients had an improvement in maximum pain intensity and 45.5% had 50% or more reduction in pain intensity (7.5% had no change)	NR	NR	NR	81.9% of pt had received 2-5 different treatments and all decreased significantly with the greatest reduction in patients ≥ 70 yr	NR
Hans 2009	For new treatment: 5.9 ± 1.4 at baseline to 3.9 ± 1.6 at 12 weeks then stable at 3.9 ± 2.3 for 12 mo	NR	For new treatment, 9.3% had extremely painful allodynia at baseline, decreasing to 3.3% at 12 months. 43.3% of study population had painful allodynia at baseline, decreasing to 15.2% at 12 mo	NR	52.2% were taking at least 1 concomitant medication at baseline; number and dosing of these medications were kept stable during the study	NR
Malec-Milewska 2015	Decrease of 5.01 ± 1.67 at 8 weeks	NR	NR	NR	NR	NR
Rehm 2010	Mean pain reduction at 4 wk was 7.6 ± 6.66	NR	50.0% reported allodynia at baseline, decreased to 16.7% at 4 wk	NR	Rescue medication decreased at 4 and 8 wk	NR
Sabatoski 2012	Mean pain relief of 4.3 ± 0.9 achieved at about 6 wk (n = 27)	NR	NR	NR	NR	NR

Table 3. *An overview of pain control as measured in studies of the 5% LMP.*

d: Day; LMP: Lidocaine Medicated Plaster; NR: Not Reported; PHN: Postherpetic Neuralgia; pt: Patient; wk: Week; yr: Year.

Studies without comparators

Studies of PHN and other neuropathies

Three studies enrolled patients with PHN as well as other neuropathies. Amato and colleagues enrolled in a study 503 patients with localized neuropathic pain, of whom 204 had PHN. Patients were treated with the 5% LMP. Responders in this study were defined as those achieving at least 30% relief in pain intensity as graded on a numeric rating scale. The greatest response rate in this study occurred in PHN patients at 60 days with 91.2% of responders; there were 68.1% responders at 30 days.

A retrospective observational study of the use of 5% LTS for treating pain in 467 patients with refractory chronic neuropathic pain (including but not limited to PHN) found the 5% LTS reduced pain by more than 50% in 45.5% of all patients and reduced consumption of co-analgesics [42]. The mean duration of treatment with 5% LTS was < 3 months, 3 - 12 months, and over one year in 42.1%, 45.5%, and 21.1% of the population, respectively.

In a long-term, open-label study, 20 patients with some form of localized neuropathic pain (20% with PHN) were deemed responders to 5% LTS. Response was defined the achievement of a pain reduction of two or more points on the numerical rating scale where 10 is the most severe pain imaginable. Patients were interviewed at three and five years after treatment started. At three years and five years, 50% and 40% of responder-patients, respectively, were still using the 5% LTS with no decline in effectiveness. Of those who discontinued the 5% LTS (n = 12), five had died of an unrelated cause, four reported they no longer required pain control, two could no longer get insurance coverage for the plaster, and one was lost to follow-up [43].

Geriatric PHN patients

A prospective, non-interventional observational study was conducted in France in which 625 elderly PHN patients were allowed to be treated with 5% LMP under the national compassionate use program. Because it was a compassionate use program, documentation was voluntary (except for the required reporting of adverse events). Patients were allowed to use other concomitant treatments, such as tricyclic antidepressants, gabapentinoids, NSAIDs, and others. In the overall efficacy population in the study, the use of the 5% LMP decreased concomitant PHN treatments by at least one treatment per patient at the end of the observation period ($p < 0.001$) with an incidence of AEs of 2.6% [44].

LMP-naive vs. LMP-experienced patients

A 12-month, multicenter, open-label study in 249 PHN patients ≥ 50 years treated with the 5% LMP found in newly recruited patients, the mean average pain intensity upon entering the study on an 11-point scale was 5.9 ± 1.4 and decreased to 3.9 ± 1.6 at 12 weeks and stabilized at 3.9 ± 2.3 till the end of the year-long study [45]. In patients who entered the study having previously been treated with 5% LMP, pain was 3.9 ± 1.9 at baseline, decreasing to 3.4 ± 2.0 at the conclusion of the study. In patients who opted to continue treatment in the extension phase (total of 24 months), pain relief levels were sustained.

Long-term PHN pain

A prospective study of patients with persistent pain following acute herpes zoster with a pain intensity score of ≥ 4 were treated with the 5% LMP and were regularly monitored over a study period of four years (102 patients entered the one-year study and 27 patients remained in the study for four years). Pain scores were much or very much improved in about 80% of patients at all visits on the Clinical Global Impression of Change and the Patient's Global Impress of Change questionnaire [46].

Studies of the 5% LMP versus comparators or placebo

Four studies compared the 5% LMP to other treatment options or to placebo.

5% LMP versus oral pregabalin

The first head-to-head comparison of the 5% LMP versus an oral anticonvulsant was published in 2009. A four-week, two-stage, randomized, adaptive, open-label, non-inferiority study was designed to compared 5% LMP to oral pregabalin twice daily over four weeks for treating patients with PHN (n = 96) or painful diabetic peripheral neuropathy (n = 204) [47]. Pregabalin was titrated to effect with all patient initiated on 150 mg/day pregabalin and increased to 300 mg/day by the second week; those patients who had inadequate analgesia at the 300 mg/day dose (defined as pain score of 4 or higher on the numeric rating scale) could be increased stepwise in dose up to a maximum dose of 600 mg/day. Responders were defined as those who averaged a pain reduction of ≥ 2 points or an absolute value of ≤ 4 points on an 11-point numerical rating scale as measured against baseline values and over the last three days of the study. Overall, 66.4% of LMP patients and 61.5% of pregabalin patients were responders but in the subset of PHN patients, there were more responders to 5% LMP than oral pregabalin (62.2% vs. 46.5%). It should be noted that among patients with painful peripheral diabetic neuropathy, the responders for 5% LMP and oral pregabalin were similar (66.7% vs. 69.1%, respectively). Quality of life improved more in 5% LMP patients than the oral pregabalin patients, although both groups showed improvement over baseline. Quality of life was measured on the EuroQol-5 dimension quality of life index (EQ-52) [47].

A two-stage, adaptive, randomized, open-label, non-inferiority study of PHN patients compared the 5% LMP to twice-daily oral pregabalin tablets titrated to effect and also combination therapy (5% LMP plus pregabalin) [48]. The 5% LMP was associated with greater pain reduction than pregabalin and was more effective in reducing "worst pain" than pregabalin, suggesting that the 5% LMP was non-inferior to pregabalin and had a favorable safety profile. Various pain endpoints were measured (daily assessments of worst pain in past 24 hours on an 11-point rating scale, mean number of rescue paracetamol tablets taken in the past three days prior to the clinic visit, time to onset of response, comparison of pain at baseline versus the first day of a three-day period with a decreased average pain intensity during the last 24 hours by at least 2 points of scores of 4 or less in the last three days, the Neuropathic Pain Symptom Inventory, allodynia severity, the Short Form McGill Pain Questionnaire (SF-MPQ), and Patient Global Impression of change. Response was defined as a reduction average over the last three days from baseline of 2 or fewer or an absolute value of 4 or fewer points on an 11-point numerical rating scale. Responder rates were 82.1% for the 5% LMP compared to 65% for pregabalin. Pain intensity during the preceding 7 days improved by -25.9 ± 23.14 for the 5% lidocaine plaster compared to -17.2 ± 25.57 for pregabalin patients. Patients who received inadequate analgesia using the 5% LMP only or oral pregabalin only were treated with combination therapy and received pain relief: in the plaster group, the mean pain intensity reduction over combination-phase baseline was -27.8 ± 21.60 and in the pregabalin-only group was -33.7 ± 22.75. At baseline, 50% of the 5% LMP-only patients and 69% of the pregabalin-only patients reported having "painful" or "extremely painful" allodynia. When these patients entered the combination treatment group, these numbers dropped to 16.7% and 25.0%, respectively. The consumption of rescue analgesics decreased with 5% LMP patients and combination patients (5% LMP plus pregabalin) but not with the pregabalin-only group [48].

5% LMP versus sympathetic nerve blocks

The 5% LMP was compared to sympathetic nerve blocks in multimodal treatment for PHN-related pain in a retrospective, consecutive, case-series study (n = 60) [49]. Inclusion criteria specified PHN with allodynia. Data from 60 consecutive patients treated with sympathetic nerve blocks were compared to data from 60 subsequent patients treated with 5% LMP. Failure rates were statistically similar with 18.9% of sympathetic nerve block patients and 27.1% of 5% LMP patients achieving "poor results." The average change in pain scores over 8 weeks was 5.88 ± 2.41 for sympathetic nerve blocks compared to 5.01 ± 1.67 for lidocaine patients (p = 0.02). There were significantly more patients reporting complete freedom from pain among the sympathetic nerve block patients (34.4%) than the 5% LMP patients (13.5%) [49].

Placebo-controlled study

There was one study of the 5% LMP versus placebo. A double-blind, placebo-controlled, parallel-group, multicenter study enrolled PHN patients aged 50 years or more first in a two-week double-blind, placebo-controlled phase at 33 centers across Europe. To be in-

cluded in the study, patients had to have neuropathic pain associated with PHN for three months or more with a mean pain intensity of at least 4 on an 11-point scale. The endpoint was the time-to-exit the study defined as the number of days after randomization when there was a ≥ 2-point decrease in pain relief on two consecutive days compared to mean pain relief in the last week of active treatment. For per-protocol patients (n = 34), the median time to exit the study was 14.0 days for lidocaine patches (range 3 - 14 days) compared to 6.0 days (range 1 to 14 days) for placebo, p = 0.0398 [50].

Safety

Prescribing information states that about 16% of those using the 5% LMP may experience an adverse reaction, the most common of which are application site reactions such as irritation, redness, or burning. Pruritus has also been reported [36]. Localized cutaneous reactions tend to be mild and resolve spontaneously. It has been observed that they occur with both the 5% LMP as well as a placebo plaster, suggesting the reaction may not be related to the lidocaine [51,52].

A Cochrane meta-analysis of topical lidocaine studies (including but not limited to the 5% LMP) reported that adverse events were similar between topical lidocaine and placebo groups and most were mild to moderate and typically localized cutaneous reactions, including erythema, rash, pruritus, and site reactions [53]. This meta-analysis included studies of various topical lidocaine products and different types of neuropathic pain populations, including but not limited to PHN. A small four-year study of the 5% LMP (n = 27) found that drug-related adverse events did not increase over time; the frequency of these events was the same in the initial 12-month study phase as it was in the 36-month extension period [46]. A short summary of safety data from these studies appears in table 4.

Combination therapy

People with PHN may take multiple analgesic agents. While this may be effective in some cases, polypharmacy can put a patient at risk for drug-drug interactions. In a descriptive analysis of the Amato study, patients at baseline (n = 503), 59.3% took opioids, 40.4% took gabapentinoids, 20.7% acetaminophen (paracetamol), 11.1% nonsteroidal anti-inflammatory drugs (NSAIDs), 10.2% antidepressants and 1.8% corticosteroids [54]. After being prescribed the 5% LMP and using it for 30 days, the use of all agents decreased except for antidepressants (which rose to 14.6%); the use of concomitant agents decreased again at 60 days. This study included but was not solely composed of PHN patients (others had other forms of neuralgia or musculoskeletal pain) [54]. Most patients in this study took one or two concomitant pain remedies in addition to using the 5% LMP; the median number of concomitant medications dropped from 1.4 per patient at baseline to 1.0 per patient at 60 days. At baseline in the study, 15% of patients did not need concomitant analgesics; at 60 days after using the 5% LMP, 40% did not need concomitant analgesics [54].

Combination therapy of 5% LMP plus pregabalin was associated with a higher incidence of adverse events than the use of 5% LMP monotherapy. Pregabalin was associated with dizziness (18.8%), fatigue (16.7%), somnolence (6.3%), and headache (6.3%), whereas the main adverse events associated with the 5% LMP were application site reactions [48].

Study discontinuations

Patients are free to drop out of studies for any reason, but discontinuations can often shed important insights into treatments. A summary of discontinuations and reasons for them appears in table 5.

Study	Population	Discontinuations	Comments
Amato 2017	Pain pt, including but not limited to PHN	38/503 or 7.55%	37% discontinued for lack of efficacy
Baron 2009	Pain patients, including but not limited to PHN, treated with 5% LMP	9/155 or 5.8% (LMP group)	Note that oral pregabalin patients in this study had 39/153 discontinuations (25.5%)
Binder 2009	PHN	12/265 or 4.5%	One discontinuation for AE was in the placebo group
Clere 2011	Elderly PHN, compassionate use	6/625 (1.0%) all application site events	
Delorme 2011	Neuropathic pain pt, retrospective study (20% had PHN)	14/467 (3%)	Five-year study
Hans 2009	PHN patients	11/249 (4.4%)	12-month study
Malec-Milewska 2015	PHN pt	No dropouts	Retrospective case series
Rehm 2010	PHN pt	2/50 (4.0%)	
Sabatowski 2012	102 pat with persistent pain following acute herpes zoster infection entering study	3/102 (2.9%)	All discontinuations occurred because of application-site hypersensitivities

Table 5*: Discontinuations in studies of the 5% LMP. None of these studies specifically mentioned problems with patch adhesion. PHN: Postherpetic Neuralgia; pt: Patient.*

Treatment of PHN in elderly populations

Geriatric patients are at elevated risk for PHN, and analgesic prescribing choices for this population must take into account slowed metabolic rate, comorbid conditions, and the possibility of polypharmacy. In a subgroup analysis using data from three clinical trials and grouping patients by age (< 70 and ≥ 70 years), it was found that the 5% LMP provided effective pain control and reduced the severity of allodynia in elderly PHN patients with good tolerability and safety. Drug-related adverse events occurred in 20% of the older and 15% of younger patients, and primarily involved skin and application-site reactions [55]. This review found no evidence that the 5% LMP could not be considered safe and effective in the geriatric population of PHN patients.

Discussion

The subset of shingles patients who develop PHN often face moderate to severe neuropathic pain that can persist for months and even years. Although there are limited long-term studies on the use of the 5% LMP in PHN patients, the work from Hans and colleagues suggests that tolerance does not build up in patients for topical lidocaine and that pain relief is both stable and durable for at least two years [45]. Other studies have demonstrated that 5% LMP offers effective but short-term pain control for PHN. Tolerability appears to be good with most AEs related to cutaneous and/or application site reactions. Although it was not our purpose to compare the 5% LMP to other treatments for neuropathic pain, such as gabapentinoid therapy or opioids, it is reasonable to state that systemic pain therapies are associated with systemic side effects, which at times may be severe.

The LMP is an important addition to the pain control armamentarium, in particular because PHN tends to be a disease of the elderly for whom pain control options can become complex owing to polypharmacy, comorbidities, slower drug metabolism, and other factors. In the study by Delorme and colleagues, the 5% LMP reduced consumption of pain relievers in all neuropathic pain patients but with the greatest reduction in the elderly (≥ 70 years) [42]. Since many of these co-analgesics, such as antidepressants, anticonvulsants, and psychotropics are associated with multiple and potentially severe adverse events, this could be an important consideration when evaluating the 5% LMP patch for geriatric pain patients. Combination therapy, for example the 5% LMP plus pregabalin, has been shown to provide effective and durable pain control and the medicated plaster does not interact with the systemic drug [46]. However, systemic drug therapies for PHN may have adverse effects in elderly patients on cognition such as vigilance, decision-making, and semantic memory. For that reason, topical treatments such as 5% LMP may be of special importance [56].

Sympathetic nerve blockade is a treatment for pain related to PHN that has fallen somewhat out of favor, although a retrospective case-series study from Poland reported good results in a study that compared this treatment to 5% LMP [49].

A drawback to the overall success of the 5% LMP was the issue of patch adherence. The 5% patch was relatively thick and inflexible and many patients reported that it lifted or detached completely. This reduced patient compliance, possibly increased cost of treatment (as patients had to use new plasters), and likely decreased patient satisfaction. The thinner, more flexible, easier-peel 1.8% topical system offers similar therapeutic benefits [26] in a more patient-friendly package with better adherence. Of great interest in this evolution is the fact that once adhesion was recognized on both sides of the Atlantic by regulatory bodies as being an issue, new metrics were developed and applied to assess the problem.

It should be noted that the U.S. Food and Drug Administration has placed a black-box warning on topical lidocaine for local anesthesia for methemoglobinemia.

Conclusion

Pain associated with PHN can be severe, distressing, and debilitating, and the 5% LMP has been shown to be an effective and well-tolerated treatment option which is recognized in established guidelines. Since it is a topical lidocaine product, it avoids the side effects associated with systemic therapies for PHN, such as gabapentinoids or opioids. Adverse events tend to be mild, self-terminating, and relate mainly to application site reactions. Long-term studies strongly suggest that tolerance for pain relief does not build up in PHN patients, even with years of patch use. Issues related to adhesion with the 5% lidocaine medicated patch may be overcome with the new polymer-matrix 1.8% topical system, which is thinner, more flexible, and offers greater adhesive properties with similar safety and effectiveness.

Bibliography

1. Gharibo C and Kim C. "Neuropathic pain of postherpetic neuralgia". *Pain Medicine News* 9 (2011): 84-92.

2. CDC. Shingles (Herpes Zoster) (2014).

3. Drolet M., *et al*. "The impact of herpes zoster and postherpetic neuralgia on health-related quality of life: a prospective study". *Canadian Medical Association Journal* 182.16 (2010): 1731-1736.

4. Gilden D., *et al*. "Neurological disease produced by varicella zoster virus reactivation without rash". *Current Topics in Microbiology and Immunology* 342 (2010): 243-253.

5. Johnson RW., *et al*. "Herpes zoster and postherpetic neuralgia: optimizing management in the elderly patient". *Drugs and Aging* 25.12 (2008): 991-1006.

6. Harpaz R., *et al*. "Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP)". *MMWR Recommendations and Reports* 57.5 (2008): 1-30.

7. Klompas M., *et al*. "Herpes zoster and postherpetic neuralgia surveillance using structured electronic data". *Mayo Clinic Proceedings* 86.12 (2011): 1146-1153.

8. Garnock-Jones KP and Keating GM. "Lidocaine 5% medicated plaster: a review of its use in postherpetic neuralgia". *Drugs* 69.15 (2009): 2149-2165.

9. Finnerup N., *et al*. "Algorithm for neuropathic pain treatment: an evidence based proposal". *Pain Management Nursing* 118.3 (2005): 289-305.

10. Dworkin RH., *et al*. "Pharmacologic management of neuropathic pain: evidence-based recommendations". *Pain* 132.3 (2007): 237-251.

11. Finnerup NB., *et al*. "An evidence-based algorithm for the treatment of neuropathic pain". *Medscape General Medicine* 9.2 (2007): 36.

12. Finnerup NB., *et al*. "The evidence for pharmacological treatment of neuropathic pain". *Pain* 150.3 (2010): 573-581.

13. Attal N., *et al*. "EFNS guidelines on pharmacological treatment of neuropathic pain". *European Journal of Neurology* 13.11 (2006): 1153-1169.

14. Dubinsky RM., *et al*. "Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology". *Neurology* 63.6 (2004): 959-965.

15. Fashner J and Bell AL. "Herpes zoster and postherpetic neuralgia: prevention and management". *American Family Physician* 83.12 (2011): 1432-1437.

16. Nalamachu S and Morley-Forster P. "Diagnosing and managing postherpetic neuralgia". *Drugs and Aging* 29.11 (2012): 863-869.

17. Argoff CE. "Review of current guidelines on the care of postherpetic neuralgia". *Postgraduate Medicine* 123.5 (2011): 134-142.

18. Mallick-Searle T., *et al*. "Postherpetic neuralgia: epidemiology, pathophysiology, and pain management pharmacology". *Journal of Multidisciplinary Healthcare* 9 (2016): 447-454.

19. Johnson RW and Rice AS. "Clinical practice. Postherpetic neuralgia". *The New England Journal of Medicine* 371.16 (2014): 1526-1533.

20. Insinga R., *et al*. "The incidence of herpes zoster in a United States administrative database". *Journal of General Internal Medicine* 20.8 (2005): 748-753.

21. Laurent B., *et al*. "Prevalence and impact on quality of life of post-herpetic neuralgia in French medical centers specialized in chronic pain management: the ZOCAD study". *Medecine Et Maladies Infectieuses* 44.11-12 (2014): 515-524.

22. Forbes HJ., *et al*. "A systematic review and meta-analysis of risk factors for postherpetic neuralgia". *Pain* 157.1 (2016): 30-54.

23. Bouhassira D., *et al*. "Patient perspective on herpes zoster and its complications: an observational prospective study in patients aged over 50 years in general practice". *Pain* 153.2 (2012): 342-349.

24. Forbes HJ., *et al*. "Quantification of risk factors for postherpetic neuralgia in herpes zoster patients: A cohort study". *Neurology* 87.1 (2016): 94-102.

25. Baron R., *et al*. "The 5% Lidocaine-Medicated Plaster: Its Inclusion in International Treatment Guidelines for Treating Localized Neuropathic Pain, and Clinical Evidence Supporting its Use". *Pain and Therapy* 5.2 (2016): 149-169.

26. Sciliex. Scilex Presdents ZTlido Data on Superior Adhesion over Lidocaine Patch Formulation (2018).

27. Gershon AA., *et al*. "Varicella zoster virus infection". *Nature Reviews Disease Primers* 1 (2015): 15016.

28. Hadley GR., *et al*. "Post-herpetic Neuralgia: a Review". *Current Pain and Headache Reports* 20.3 (2016): 17.

29. Serpell M., *et al*. "Burden of post-herpetic neuralgia in a sample of UK residents aged 50 years or older: findings from the Zoster Quality of Life (ZQOL) study". *Health and Quality of Life Outcomes* 12 (2014): 92.

30. Persaud N and Strichartz GR. "Micromolar lidocaine selectively blocks propagating ectopic impulses at a distance from their site of origin". *Pain* 99.1-2 (2002): 333-340.

31. Chevrier P., *et al*. "Differential modulation of Nav1.7 and Nav1.8 peripheral nerve sodium channels by the local anesthetic lidocaine". *British Journal of Pharmacology* 142.3 (2004): 576-584.

32. Krumova EK., *et al*. "Lidocaine patch (5%) produces a selective, but incomplete block of Adelta and C fibers". *Pain* 153.2 (2012): 273-280.

33. Shiga M., *et al*. "The effects of lidocaine on nitric oxide production from an activated murine macrophage cell line". *Anesthesia and Analgesia* 92.1 (2001): 128-133.

34. Tanaka A., *et al*. "Inhibitory effect of lidocaine on T cells from patients with allergic asthma". *The Journal of Allergy and Clinical Immunology* 109.3 (2002): 485-490.

35. Jara-Oseguera A., *et al*. "TRPV1: on the road to pain relief". *Current Molecular Pharmacology* 1.3 (2008): 255-269.

36. Medicines Management Programme. Lidocaine 5% Medicated Plaster (Versatis). Prescribing and Cost Guidance (2017).

37. Versatis Product Information. VERSATIS (Lignocaine) 5% w/w, Dermal Patch (2012).

38. Ghosh A., *et al*. "Current pharmaceutical design on adhesive based transdermal drug delivery systems". *Current Pharmaceutical Design* 21.20 (2015): 2771-2783.

39. Banerjee S., *et al*. "Aspect of adhesives in transdermal drug delivery systems". *International Journal of Adhesion and Adhesives* 50 (2014): 70-84.

40. Harris Poll. "Harris Poll Conducted Online". Harris Poll (2016).

41. Gudin J., *et al*. "Adhesion Characteristics of a Topical Lidocaine Patch 1.8% (36 mg)". PAIN Week Poster (2018).

42. Delorme C., *et al*. "Treatment of neuropathic pain with 5% lidocaine-medicated plaster: Five years of clinical experience". *Pain research and management* 16.4 (2011): 259-263.

43. Wilhelm IR., *et al*. "Long-term treatment of neuropathic pain with a 5% lidocaine medicated plaster". *European Journal of Anaesthesiology* 27.2 (2010): 169-173.

44. Clere F., *et al*. "5% lidocaine medicated plaster in elderly patients with postherpetic neuralgia: results of a compassionate use programme in France". *Drugs and Aging* 28.9 (2011): 693-702.

45. Hans G., *et al*. "Efficacy and tolerability of a 5% lidocaine medicated plaster for the topical treatment of post-herpetic neuralgia: results of a long-term study". *Current Medical Research and Opinion* 25.5 (2009): 1295-1305.

46. Sabatowski R., *et al*. "Safety and efficacy outcomes of long-term treatment up to 4 years with 5% lidocaine medicated plaster in patients with post-herpetic neuralgia". *Current Medical Research and Opinion* 28.8 (2012): 1337-1346.

47. Baron R., *et al*. "5% lidocaine medicated plaster versus pregabalin in post-herpetic neuralgia and diabetic polyneuropathy: an open-label, non-inferiority two-stage RCT study". *Current Medical Research and Opinion* 25.7 (2009): 1663-1676.

48. Rehm S., *et al*. "Post-herpetic neuralgia: 5% lidocaine medicated plaster, pregabalin, or a combination of both? A randomized, open, clinical effectiveness study". *Current Medical Research and Opinion* 26.7 (2010): 1607-1619.

49. Malec-Milewska M., *et al*. "5% lidocaine medicated plasters vs. sympathetic nerve blocks as a part of multimodal treatment strategy for the management of postherpetic neuralgia: a retrospective, consecutive, case-series study". *Neurologia I Neurochirurgia Polska* 49.1 (2015): 24-28.

50. Binder A., *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". *Clinical Drug Investigation* 29.6 (2009): 393-408.

51. Galer BS., *et al*. "Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study". *Pain* 80.3 (1990): 533-538.

52. Rowbotham MC., *et al*. "Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia". *Pain* 65.1 (1996): 39-44.

53. Derry S., *et al*. "Topical lidocaine for neuropathic pain in adults". *Cochrane Database of Systematic Reviews* 7 (2014): CD010958.

54. Amato F., *et al*. "Efficacy and safety of 5% lidocaine-medicated plasters in localized pain with neuropathic and/or inflammatory characteristics: an observational, real-world study". *European Review for Medical and Pharmacological Sciences* 21.18 (2017): 4228-4235.

55. Sabatowski R., *et al*. "Treatment of postherpetic neuralgia with 5% lidocaine medicated plaster in elderly patients - subgroup analyses from three European clinical trials". *Current Medical Research and Opinion* 33.3 (2017): 595-603.

56. Pickering G., *et al*. "Cognitive function in older patients with postherpetic neuralgia". *Pain practice* 14.1 (2014): E1-E7.

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