Journal of Pain Research

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REVIEW

The topical 5% lidocaine medicated plaster in localized neuropathic pain: a reappraisal of the clinical evidence

This article was published in the following Dove Press journal:
Journal of Pain Research
12 February 2016
Number of times this article has been viewed

Oscar A de León-Casasola[1,2]
Victor Mayoral[3]

[1]Department of Anesthesiology, Division of Pain Medicine, Roswell Park Cancer Institute, [2]University at Buffalo, School of Medicine and Biomedical Sciences. NY, USA; [3]Anesthesiology Department, Pain Management Unit, University Hospital of Bellvitge, L'Hospitalet de Llobregat, Spain

Abstract: Topical 5% lidocaine medicated plasters represent a well-established first-line option for the treatment of peripheral localized neuropathic pain (LNP). This review provides an updated overview of the clinical evidence (randomized, controlled, and open-label clinical studies, real-life daily clinical practice, and case series). The 5% lidocaine medicated plaster effectively provides pain relief in postherpetic neuralgia, and data from a large open-label controlled study indicate that the 5% lidocaine medicated plaster is as effective as systemic pregabalin in postherpetic neuralgia and painful diabetic polyneuropathy but with an improved tolerability profile. Additionally, improved analgesia and fewer side effects were experienced by patients treated synchronously with the 5% lidocaine medicated plaster, further demonstrating the value of multimodal analgesia in LNP. The 5% lidocaine medicated plaster provides continued benefit after long-term (≤7 years) use and is also effective in various other LNP conditions. Minor application-site reactions are the most common adverse events associated with the 5% lidocaine medicated plaster; there is minimal risk of systemic adverse events and drug–drug interactions. Although further well-controlled studies are warranted, the 5% lidocaine medicated plaster is efficacious and safe in LNP and may have particular clinical benefit in elderly and/or medically compromised patients because of the low incidence of adverse events.

Keywords: 5% lidocaine medicated plaster, clinical evidence, localized neuropathic pain, postherpetic neuralgia, review

Introduction

Neuropathic pain, one of the underlying causes of chronic pain, may result from a lesion or a disease of the somatosensory system.[1] Depending on the site of the lesion within the nervous system, the origin of neuropathic pain can be either central or peripheral.[2,3] Although prevalence estimates vary, neuropathic pain is reported to affect up to ~18% of the population in developed countries,[4] with up to ~60% of patients presenting with localized symptoms (localized neuropathic pain [LNP]).[5,6] Based on the International Association for the Study of Pain definition of neuropathic pain, LNP is defined as a type of neuropathic pain that is "characterized by consistent and circumscribed area(s) of maximum pain associated with negative or positive sensory signs and/or spontaneous symptoms characteristic of neuropathic pain".[7] Common LNP conditions, predominantly occurring in elderly individuals, include postherpetic neuralgia (PHN), diabetic polyneuropathy (DPN), and neuropathic postoperative pain.[2,8–10] Neuropathic pain conditions can be debilitating, with a serious negative impact on patient functioning, daily activities, and overall quality of life (QoL).[11,12]

The management of neuropathic pain is complex and multidisciplinary, requiring thorough physician knowledge of the various underlying pain mechanisms involved,

Correspondence: Oscar A de León-Casasola
Department of Anesthesiology, Division of Pain Medicine, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263, USA
Email oscar.deleon@roswellpark.org

the pharmacological options available for optimal pain management, and the individual needs of the patient (eg, elderly, receiving multiple medications).[13] Nevertheless, despite the availability of numerous management guidelines, many patients do not receive adequate pain management, and many are not satisfied with their treatment.[13] Pharmacological treatment options include the topical 5% lidocaine medicated plaster, tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors, gabapentin and pregabalin, and opioids.[8,13–15]

As discussed previously,[14] the 5% lidocaine medicated plaster (a 10 cm×14 cm adhesive plaster, containing 700 mg [5% w/w] lidocaine; Versatis®, Grünenthal) has a dual mode of action by providing a mechanical barrier effect and a pharmacological action via voltage-gated sodium channel blockade as a direct result of lidocaine action.

Numerous reviews and clinical guidelines recommend the topical 5% lidocaine medicated plaster as a first-line option for LNP,[16–28] with the majority of clinical evidence available for patients with PHN. However, due to differences in data analysis and without significant changes in the available data in the last 5 years (see "Discussion" section), recommendations are not always aligned.[29] The topical 5% lidocaine medicated plaster is approved in ~50 countries worldwide for the symptomatic relief of neuropathic pain associated with previous herpes zoster infection; in nine of these countries, it is also approved for the treatment of LNP. It is estimated that, since the first marketing approval in 1999 and up to June 2014, the topical 5% lidocaine medicated plaster has been prescribed to ~20 million patients worldwide.[30]

This article presents an updated narrative appraisal of the clinical evidence (efficacy and safety in clinical trials, in addition to extensive experience gained in daily clinical practice) with the topical 5% lidocaine medicated plaster in LNP, focusing primarily on its use in patients with PHN and DPN and presenting a brief overview of recent evidence in other LNP conditions. In order to provide a reappraisal of the clinical evidence for the use of the 5% lidocaine medicated plaster in the treatment of LNP conditions, all efficacy and safety studies (randomized, controlled, or open label with a well-described methodology), case reports, and observational studies on the 5% lidocaine medicated plaster were retrieved from a PubMed literature search (1960 to September 30, 2015). Additional references were identified from the reference lists of published articles. Search terms were "lidocaine" and ("patch" or "topical") or "lidocaine medicated plaster". Inclusion of studies was based mainly on the methods section of the trials. If available, large, well-controlled trials with appropriate statistical methodology were preferred.

Clinical evidence with the topical 5% lidocaine medicated plaster in LNP

PHN or painful DPN

PHN is the most common chronic complication of the reactivation of the herpes zoster virus that results in shingles, manifesting as LNP, with ~20% of patients with herpes zoster reporting some pain at 3 months after the onset of symptoms. The frequencies of herpes zoster infection and PHN increase with age.[9] Painful DPN, a common chronic complication that occurs in up to ~20% of patients with diabetes, is associated with a significant negative impact on the patient's QoL[31–33]

Several articles have previously reviewed clinical trials in which the topical 5% lidocaine medicated plaster was administered to patients with localized PHN[14,27,34] or DPN.[14,35] An overview of topical 5% lidocaine medicated plaster clinical trials is provided here for completeness, in addition to a review of more recent experience gained in daily clinical practice and in long-term studies.

One of the earliest clinical trials to demonstrate the efficacy of the 5% lidocaine medicated plaster was a four-session (12 hours each session), randomized, double-blind, vehicle-controlled study in 35 patients with established PHN affecting the torso or extremities.[36] Lidocaine plasters were applied in two of the four sessions, a vehicle plaster in one session, and the remaining session was a no-treatment observation session. Compared with no-treatment observation, 5% lidocaine medicated plasters significantly ($P<0.05$) reduced pain intensity at each time point (from 30 minutes to 12 hours and from 4 to 12 hours) compared with vehicle plasters. Lidocaine plasters were superior to both no-treatment observation ($P<0.0001$) and vehicle ($P=0.033$) in mean category pain relief scores. Minimal systemic absorption of lidocaine was observed (maximum blood lidocaine level 0.1 μg/mL). No systemic side effects were reported.[36]

Two clinical studies used a randomized, withdrawal (enriched enrollment) design.[37,38] In the study by Galer et al,[37] patients had been treated successfully with topical 5% lidocaine medicated plasters on a regular basis for at least 1 month before study enrollment. Subjects were subsequently enrolled in a randomized, two-treatment period, vehicle-controlled, crossover study. The primary efficacy variable was "time to exit" due to a lack of efficacy (defined as a decrease in pain relief score by two or more categories on a six-item pain relief scale for any 2 consecutive days). The median time to exit with the lidocaine plaster was

significantly greater than with the vehicle plaster (>14 days vs 3.8 days, $P<0.001$). At study completion, significantly more patients expressed a preference for the lidocaine plaster than the vehicle plaster (78.1% vs 9.4%, $P<0.001$). There were no statistically significant between-group differences with regard to side effects.[37]

The study by Binder et al,[38] a double-blind, placebo plaster-controlled, parallel group study, was conducted at 33 outpatient centers in 12 European countries between April 2003 and June 2004. Patients aged ≥50 years with PHN and neuropathic pain persisting ≥3 months postrash healing and mean pain intensity of ≥4 on the 11-point numerical rating scale (NRS-11) were enrolled in an 8-week open-label, active treatment (5% lidocaine medicated plaster) run-in phase. Responders entered a 2-week, double-blind phase and were randomized to the 5% lidocaine medicated plaster or a placebo plaster. Patients applied up to three plasters for up to 12 hours/day. The primary endpoint was time to exit due to a ≥2-point reduction in pain relief on 2 consecutive days of plaster application using a six-item verbal rating scale. Among the 263 patients entering the initial 8-week run-in phase, 51.7% (n=137) achieved at least moderate pain relief on active treatment (responders). Seventy-one responders completed the entire 8-week initial phase and subsequently entered the double-blind phase and were randomized to the 5% lidocaine medicated plaster (n=36) or a placebo plaster (n=35). Median time to exit was numerically longer for the 5% lidocaine medicated plaster than the placebo plaster group (13.5 [range: 2–14] vs 9.0 [range: 1–14] days, $P=0.151$). For per-protocol patients (n=34), median time to exit was significantly longer in the 5% lidocaine medicated plaster than the placebo plaster group (14.0 [range: 3–14] vs 6.0 [range: 1–14] days, $P=0.0398$). During the 8-week run-in phase, treatment with the 5% lidocaine medicated plaster was associated with clinically relevant improvements in extremely painful and painful allodynia, QoL, and sleep measures, particularly in patients identified as responders.[38]

The 5% lidocaine medicated plaster reduced pain intensity in patients with PHN with impaired nociceptor function (determined by heat pain thresholds and histamine-induced flare)[39] but not in those with preserved function in a randomized, double-blind, placebo-controlled substudy in 40 patients from a larger study in patients with any focal neuropathic pain.[40]

Recently, Casale et al[41] reported data from a retrospective case review of eight patients with PHN who received the 5% lidocaine medicated plaster. The study cohort comprised mainly elderly patients taking multiple drugs (a mean of four ± two nonanalgesic drugs) to treat comorbidities, representing a population that is at a high risk of drug–drug interactions. Good pain relief (of at least 30%) was observed during a 3-month follow-up period, and pain relief was associated with a 46% reduction in the size of the painful area after 1 month (from 236.38±140.34 to 128.80±95.7 cm^2) and a 66% reduction after 3 months (to 81.38±59.19 cm^2). Although these observations confirm the effectiveness of the 5% lidocaine medicated plasters in the treatment of PHN, the authors of this study also noted that reduction in the size of the painful area represents a possible additional clinical benefit of the 5% lidocaine medicated plaster that warrants confirmation in large randomized controlled clinical trials.[41] This outcome was also reported in a prospective, observational study of 19 patients with traumatic injuries to peripheral nerves that were accompanied by LNP of >3 months duration.[42] The 5% lidocaine medicated plaster effectively reduced both pain intensity and the size of the painful area, and no local or systemic adverse effects were reported.[42] This observation has significant neurobiological implications as it suggests that long-term treatment may be associated with a reversal of central sensitization, as judged by the reduction in the receptive field zone.[43]

Painful DPN

As overviewed in Table 1, the effectiveness and safety of the 5% lidocaine medicated plaster have been evaluated in several open-label studies in patients with DPN,[44–48] some of which also included patients with PHN[44,46–48] or low back pain.[44,46]

The comparative efficacy and tolerability of the 5% lidocaine medicated plaster and pregabalin were evaluated in one study (discussed in more detail later).[47] In the study that enrolled only patients with clinically defined painful DPN of >3 months' duration, significant improvements in pain and QoL outcomes were observed after 3 weeks of treatment with up to four 5% lidocaine medicated plasters daily for 18 hours.[45] Patients received the 5% lidocaine medicated plaster as add-on therapy to a stable analgesic regimen. The mean daily pain rating (using the Brief Pain Inventory [primary outcome]) reduced from 6.3±1.5 (baseline) to 3.6±2.1 (week 3; $P\leq0.001$). Significant improvements were also observed from baseline to week 3 in sleep quality (26.9 vs 59.6; $P\leq0.001$), all individual aspects and the overall summary score of pain interference assessed by the Brief Pain Inventory (summary score: 32.1±15.6 vs 20.3±16.2; $P\leq0.001$), Beck Depression Inventory scores (10.5±6.7 vs 7.2±5.7; $P\leq0.001$), and the Profile of Mood States tension–anxiety (5.2±6.8 vs 2.4±5.6; $P\leq0.001$),

Table 1 Overview of studies using the 5% lidocaine medicated plaster for the treatment of painful diabetic polyneuropathy

Study design	n	Age (years) % female	Baseline average daily pain intensity[a]	Daily applied plasters	Treatment duration	Main efficacy outcomes (end of observation)
White et al[44]						
Open-label, multicenter, pilot study, add-on to gabapentin-containing treatment regimens	49	37.7 (12.6) 53%	6.3 (1.6)[b]	2.5 (1.0), 24 hours on	2 weeks	Pain intensity and pain relief scores improved $P<0.0001$[b] QoL[c] improved for all domains $P<0.05$
Barbano et al[45]						
Open-label, flexible dosing, add-on	56	NA	6.3 (1.5)	Up to 4, 18 hours on	3 weeks	Average daily pain intensity 3.6 (2.21) $P\leq0.001$ QoL[c] improved for all domains $P\leq0.01$ Improvements were maintained during a 5-week extension with reduction/discontinuation of concomitant analgesics
Argoff et al[46]						
Prospective, open-label, pilot study, add-on	41	56.7 (12.6) 58.5%	NA	2.7 (1.1), 24 hours on	2 weeks	Improvement of all composite measures of the NPS $P<0.001$
Baron et al[47]						
Phase III, randomized, open-label, multicenter, two-stage adaptive, noninferiority study, monotherapy, comparator: pregabalin up to 600 mg/day	105	60.9 (10.0) 57.1%	6.9 (1.3)[d]	2.83, up to 12 hours on	4 weeks	Treatment response rate comparable: 67% for lidocaine plaster, 69% for pregabalin; proportions of 30% and 50% reductions in NRS-3 scores comparable Greater improvements in QoL based on EQ-5D for lidocaine plaster; comparable reduction in allodynia severity Study completers with adequate response to monotherapy continued for another 8 weeks and demonstrated additional decreases in NRS-3 scores (available data include DPN and PHN patients)[48]

Notes: Unless stated otherwise, all data are mean (standard deviation). For comparative studies, only lidocaine data are shown. Reprinted with permission from Taylor & Francis Ltd. Mick G, Correa-Illanes G. Topical pain management with the 5% lidocaine medicated plaster – a review. *Curr Med Res Opin.* 2012;28(6):937–951.[14] [a]11-point scale (0= no pain, 10= worst imaginable pain). [b]Includes data from patients with postherpetic neuralgia (11) and low back pain (47). [c]Assessment with Brief Pain Inventory. [d]Over preceding 3 days (NRS-3).

Abbreviations: DPN, diabetic polyneuropathy; EQ-5D, EuroQol-5 Dimension quality of life index; NA, not available; NPS, neuropathic pain scale; NRS, numerical rating scale; PHN, postherpetic neuralgia; QoL, quality of life.

depression–dejection (7.3±8.5 vs 4.7±6.3; $P \leq 0.01$), anger–hostility (5.6±7.0 vs 4.0±6.0; $P \leq 0.05$), fatigue–inertia (11.0±6.7 vs 8.4±6.7; $P \leq 0.001$), and total mood disturbance (44.6±24.6 vs 35.2±19.1; $P \leq 0.001$) scales. Improvements were maintained for up to a total of 8 weeks in a subgroup of patients (tapering of concomitant analgesic therapy was permitted during the 5-week extension phase). There was no systemic accumulation of lidocaine, and adverse events were minimal (mostly minor application-site events).[45]

A systematic review and meta-analysis of the 5% lidocaine medicated plaster in patients with DPN indicated that the effects of the 5% lidocaine medicated plaster on pain reduction are comparable to those of amitriptyline, capsaicin, gabapentin, and pregabalin.[35] In the meta-analysis, all interventions remained effective compared with placebo (mean difference in change of pain from baseline compared with placebo, amitriptyline: −12.58 [95% confidence interval {CI}, −16.66 to −8.50]; capsaicin: −9.40 [95% CI, −13.92 to −4.88]; gabapentin: −10.22 [95% CI, −17.25 to −3.19]; pregabalin: −10.53 [95% CI, −14.74 to −6.32]; 5% lidocaine medicated plaster: −9.10 [95% CI, −13.93 to −4.26]), and the 5% lidocaine medicated plaster was comparable to all other interventions (amitriptyline: 3.48 [95% CI, −0.78 to 7.75]; capsaicin: 0.31 [95% CI, −4.39 to 5.00]; gabapentin: 1.12 [95% CI, −6.02 to 8.27]; and pregabalin: 1.43 [95% CI, −2.96 to 5.83]). The authors concluded that topical agents such as the 5% lidocaine medicated plaster may be associated with fewer and less clinically significant adverse events than is the case for systemic agents. However, the results of the systematic review were limited by the number and size of studies included, warranting further well-designed studies in this patient population.[35]

Compared with pregabalin

The 5% lidocaine medicated plaster has been compared with pregabalin in an open-label trial in patients with PHN (n=96) or painful DPN (n=204).[47,49] At baseline, patients had a mean pain intensity score of 6.75 on the 11-point NRS during the previous 3 days (NRS-3). Patients received the topical 5% lidocaine medicated plaster (applied to the most painful skin area) or twice-daily pregabalin capsules (150–600 mg/d titrated to effect) in a 1:1 ratio at 51 European centers in this two-stage, randomized, open-label, multicenter, noninferiority study. During the initial 4-week comparative stage, the response rate (average reduction from baseline of ≥2 points or an absolute value of ≤4 points on the NRS-3) in the full analysis set (all randomized patients who received at least one dose of the investigational products and for whom at least one postbaseline assessment of pain intensity [NRS-3] was available) was 66.4% (101/152) with the 5% lidocaine medicated plaster and 61.5% (91/148) with pregabalin, indicating noninferiority of the 5% lidocaine medicated plaster to pregabalin (P=0.00229). When the results were analyzed by indication, more patients in the PHN group responded to the 5% lidocaine medicated plaster than to pregabalin treatment (63.3% vs 46.8%; statistical data not reported), while in the painful DPN group, the between-treatment response was comparable (68.0% vs 68.3%).

Among the secondary end points, ≥30% (57.8% vs 48.8%) and ≥50% (35.6% vs 20.9%) reductions in NRS-3 scores were greater with the 5% lidocaine medicated plaster than with pregabalin in patients with PHN but not in patients with DPN ([59.6% vs 56.4%] and [40.4% vs 37.2%]). Despite greater baseline values in patients with PHN than in those with painful DPN, reductions in the rates of "painful" and "extremely painful" allodynia were greater with the 5% lidocaine medicated plaster (57.8% at baseline to 25.0%) than with pregabalin (62.8%–41.2%) in patients with PHN; the between-treatment reduction in allodynia severity was comparable in patients with painful DPN. Significantly fewer patients using the lidocaine patch 5% experienced drug-related adverse events compared with those taking pregabalin ($P<0.0001$). Adverse events associated with the use of the 5% lidocaine medicated plaster were mainly mild-to-moderate application-site reactions, whereas, in pregabalin recipients, adverse events mainly affected the central nervous system and were of moderate-to-severe intensity.[47]

In combination with pregabalin

The benefits of the 5% lidocaine medicated plaster in combination with pregabalin for 8 weeks were evaluated in patients with PHN or painful DPN[48,50] who had an inadequate response to monotherapy for 4 weeks in the first phase of the comparative study.[47,49] Patients continuing on monotherapy demonstrated additional decreases in NRS-3 scores. However, patients receiving combination therapy achieved further mean reductions in NRS-3 scores, above those experienced during the initial 4 weeks of monotherapy.[48] These improvements were similar between patients who started with pregabalin and added 5% lidocaine medicated plaster (5.8±0.8 to 4.0±1.7; n=43) and those who initially received the 5% lidocaine medicated plaster and then added pregabalin (6.1±1.0 to 3.6±1.5; n=57). In a secondary analysis of only patients with PHN from the first phase of the comparative study who were unresponsive to either the 5% lidocaine medicated plaster (n=18) or pregabalin (n=17)

monotherapy, combination therapy provided additional efficacy and was well tolerated.[50] The results of these two studies give further support to the concept of multimodal analgesia[51] and suggest that patients treated this way can experience not only better analgesia but also less bothersome side effects that are frequently observed with high doses of pregabalin or gabapentin.

LNP of different etiologies

In addition to its efficacy and safety in PHN and DPN, the 5% lidocaine medicated plaster has been evaluated in a diverse range of other LNP conditions, including myofascial pain syndrome,[52–54] burn sequelae in children,[55] cervical radiculopathy,[56] inguinal postherniorrhaphy pain,[57] postsurgical neuropathic pain in patients with cancer,[58] cancer pain with neuropathic components or trigeminal neuropathic pain,[59] orofacial pain,[60] persistent postmastectomy pain,[61] and various other conditions[62] (Table 2). Most reports indicate clinical benefits with the 5% lidocaine medicated plaster in various LNP conditions. However, two double-blind, placebo-controlled, crossover studies in patients with severe, persistent, inguinal postherniorrhaphy pain,[57] or postsurgical neuropathic pain in patients with cancer,[58] reported no significant benefit with the 5% lidocaine medicated plaster (Table 2). In studies where the safety of the 5% lidocaine medicated plasters was evaluated, a very low incidence of local or systemic adverse events was reported.

In daily clinical practice

In addition to the evidence gained in the clinical trial setting, the use of the topical 5% lidocaine medicated plaster has been evaluated in the daily clinical practice setting in patients with LNP.[63–68]

In an effectiveness study performed at 42 US centers (large institutional primary care programs and academic centers, including pain centers, neurologists, and pain specialists affiliated with a university), the 5% lidocaine medicated plaster was associated with significant reductions from baseline in all mean pain intensity and composite scores at each time point in 332 patients with PHN (P=0.0001). Overall, 66% of patients reported improvements in pain intensity after 7 days of treatment; ~43% of patients who did not respond after 7 days experienced improvement in pain intensity after 14 days of treatment.[63] These findings suggest that when initiating therapy with the 5% lidocaine medicated plaster, a trial of at least 14 days should be implemented before censoring patients as nonresponders. Moreover, if there is some degree of improvement, the plaster should not be removed, and other antineuropathic medications should be started to conform with the multimodal therapeutic approach in order to obtain adequate pain relief.[20]

The day-to-day clinical use of the topical 5% lidocaine medicated plaster was evaluated in a prospective, observational study as part of a compassionate use program in 625 elderly patients (mean age 73.6 years) with PHN in France.[64] Treatment with the 5% lidocaine medicated plaster resulted in a significant quantitative reduction in concomitant neuropathic pain treatments and associated side effects, while maintaining the quality of analgesia. The safety analysis showed that the 5% lidocaine medicated plaster was well tolerated, with the incidence of adverse events being 2.6% (n=16). Adverse events were mainly related to application-site reactions, for which six patients discontinued treatment, and no events were considered serious.[64]

Another prospective, observational study evaluated patients' perceptions of the topical 5% lidocaine medicated plaster in almost 1,000 patients with chronic neuropathic pain in daily clinical practice in Germany.[65] In this patient population, where 44.8% had PHN, patients perceived the 5% lidocaine medicated plaster as an efficacious treatment of chronic neuropathic pain (mean pain intensity >24 hours improved by 5.1 points [74%] from 6.9±1.6 points at baseline, assessed using the NRS-11). The most notable treatment effects were in patients with PHN or DPN. A 30% reduction in overall pain intensity was observed within the first 2–3 weeks, with continuous further reductions until the end of the study. Marked improvements in anxiety and depression scores (40% and 52%, respectively) and in pain-related restrictions in activities of daily living (66%) and QoL (157%) were also noted. The mean burden of pain (calculated on a 0–100 scale as the sum of three pain intensity scores [lowest, average, highest intensity] plus modified pain disability index sum score plus [40 minus QoL impairment by pain inventory sum score]) was reduced by 56.2 points (73%) from 77.5 points at baseline. Greatest pain relief and associated improvements in pain-related restrictions were observed within the first 5 weeks of treatment; however, beneficial effects continued until the end of the 12-week observation period.[65] Consequently, this study showed that the treatment of these individuals with 5% lidocaine medicated plasters was associated with an improvement not only in the level of analgesia but also in anxiety, depression, and QoL measurements. This is a very important finding because the success of an analgesic therapy should not be assessed solely by the effects it has on pain but also on QoL variables. This was also the case in a study conducted within a large teaching hospital in the UK. Pain, functioning, and patient satisfaction were improved significantly in 408 evaluable hospital patients of whom 197 were

Table 2 Summary of selected studies evaluating the use of the 5% lidocaine medicated plaster in patients with localized neuropathic pain (LNP) conditions

LNP condition (reference)	Study type (number of patients)	Main outcomes
Myofascial pain syndrome (MPS)		
Dalpiaz and Dodds[52]	Single case report	Pain threshold ($P<0.001$) and general activity ($P<0.05$) increased with LMP.
Affaitati et al[53]	r, c (LMP, PL, or TPI) (n=60 [20 patients/group])	Subjective symptoms: no change from baseline (PL); decreased (LMP or TPI; $P<0.001$). Pain thresholds: no change from baseline (PL); increased (LMP or TPI; $P<0.001$). Additional treatment requested: only PL ($P<0.001$). No adverse events occurred in any group.
Lin et al[54]	r, db, pr, pc (n=60): LMP (n=31), PL (n=29)	At day 14, pain intensity (using the VRS) decreased from baseline in the LMP group (1.06±0.79 vs 1.64±0.65); pain intensity was significantly greater in the PL group than in the LMP group at day 14 (1.50±0.76 vs 1.06±0.79; $P=0.03$).
Burn sequelae in children		
Orellana Silva et al[55]	pr, uc (n=14)	Pain intensity (FACES): 6.8±1.6 (initial), 0 (final) in 11 of 12 patients; (DN4): −6 (initial), −2.3 (final). All patients reported improved functionality. Plasma lidocaine levels: ≤27.45 ng/mL (>180 times below critical levels). No adverse reactions occurred.
Cervical radiculopathy		
Mattozzi[56]	Retrospective chart review (n=60): LMP (n=30) or mesotherapy (n=30)	Both treatments (mesotherapy or LMP) were effective (quantitative data not reported).
Severe, persistent, inguinal postherniorrhaphy pain		
Bischoff et al[57]	r, db, pc, co (n=21)	No difference in summed pain intensity differences between LMP and PL in all 21 patients (mean difference 6.2% [95% CI =−6.6% to 18.9%]; $P=0.33$). Quantitative sensory testing demonstrated increased pressure pain thresholds after LMP compared with PL ($P=0.007$).
Postsurgical NP in cancer patients		
Cheville et al[58]	r, db, mc, pc, co (n=28)	No significant intergroup differences were detected in pain intensity ratings. Individual BPI-SF scores for general activity ($P=0.02$), work ($P=0.04$), and relations with others ($P=0.02$) were lower with LMP than with PL.
Cancer pain with NP components or trigeminal NP		
Kern et al[59]	Retrospective case series (n=65 evaluable cases): cancer pain with NP components (n=41); trigeminal NP (n=24)	Cancer pain with NP components CGIC: very much improved (24.4%), much improved (48.8%), minimally improved (14.6%), no change (12.2%). Trigeminal NP CGIC: very much improved (16.7%), much improved (37.5%), minimally improved (16.7%), no change (25%), minimally worse (4.2%).
Orofacial pain		
Casale et al[60]	Single case report	Pain intensity (0–10 cm VAS): >10 (baseline), 6.7 (LMP for 14 days). Reduced size of the painful area (quantitative data not reported). Quality of life (EuroQol): 0.64 (baseline), 0.87 (LMP for 14 days).
Persistent postmastectomy pain		
Cruto et al[61]	Retrospective review of medical records (n=11)	LMP, either alone or in combination with systemic drugs, achieved significant pain control after the first week of therapy (quantitative data not reported).
Various LNP etiologies		
Likar et al[62]	Retrospective case series (n=27 evaluable cases): dorsalgia (n=16); postoperative/posttraumatic pain (n=7); both (n=1); phantom limb pain (n=1); PHN (n=1); unspecified (n=1)	During the 6-month observation period, overall mean pain intensity (NRS 0-10) decreased by 4.98 points to 3.5±2.6. Reductions were also observed for neuralgiform pain (5 points to 2.9±2.6 at baseline) and burning pain (3 points to 2.2±2.7). Mean sleep quality improved from 4.6±2.6 (baseline) to 5.5±1.8 (Likert scale 0 [worst possible sleep] to 10 [best possible sleep]). LMP was well tolerated.

Abbreviations: BPI-SF, Brief Pain Inventory-Short Form; c, controlled; CGIC, clinical global impression of change; co, crossover; db, double-blind; DN4, Douleur Neuropathique 4 pain-rating scale; FACES, Wong–Baker FACES® pain-rating scale; LMP, 5% lidocaine medicated plaster; mc, multicenter; NP, neuropathic pain; NRS, numerical rating scale (0= not present, 10= worst possible state); pc, placebo-controlled; PHN, postherpetic neuralgia; PL, placebo; pr, prospective; r, randomized; TPI, trigger point infiltration; uc, uncontrolled; VAS, visual analog scale; VRS, verbal rating scale (0= no pain, 1= mild pain, 2= moderate pain, 3= severe pain, 4= very severe pain).

already receiving this form of therapy.[67] Before using the plaster, the median pain score (assessed using the NRS-11) was 8 (interquartile range: 7–9). One month after therapy was started, pain decreased to a level of 6 of 10 in all patients and to 5 of 10 in those who were already receiving this form of therapy. Reductions were statistically significant ($P<0.001$ for both groups). The majority of current users (93.3%) reported the plasters to be effective. All measures

of functioning were significantly improved in current users: sleep (63.3% vs 20.1%, $P<0.001$), mood (59.2% vs 18.6%, $P<0.001$), and activity level (50.0% vs 19.5%, $P<0.001$). Median patient satisfaction scores (ranked from 0 [extremely dissatisfied] to 10 [extremely satisfied]) were 5 (interquartile range: 1–8) and 7 (5–9) in the overall population and current users, respectively.

Long-term use

Long-term use of the topical 5% lidocaine medicated plaster (for up to 5 years) has been evaluated in several clinical trials[69–71] and a >7-year follow-up survey.[72] Furthermore, extensive long-term experience (>20 million patients) has been gained since the introduction of the 5% lidocaine medicated plaster into numerous markets worldwide in 1999.[30]

The long-term treatment of neuropathic pain symptoms in patients with PHN was evaluated in a 12-month, open-label, noncomparative, phase III study conducted at 34 outpatient clinics in 12 European countries (247 evaluable patients).[69] Up to three 5% lidocaine medicated plasters were applied to the painful area for up to 12 hours each day, with a treatment-free period of at least 12 hours required per day. Patients were permitted to continue receiving concomitant medication. In newly recruited patients (n=97), the mean average pain intensity (NRS-11) scores at baseline, week 12, and at the end of the 12-month study were 5.9±1.4, 3.9±1.6, and 3.9±2.3, respectively. Pain intensity also decreased from baseline (3.9±1.9) to study end (3.4±2.0) in pretreated patients (n=150; no statistical data reported). Pain relief values were consistent with reductions in pain intensity and were sustained in the long term. Overall, a total of 77.3% (191 of 247) of patients were classified as "improved" from baseline. Infections (eg, bronchitis and nasopharyngitis) were the most common adverse events. In total, 48 treatment-related adverse events (mainly mild-to-moderate administration-site disorders) occurred in 31 (12.4%) patients.[69]

A total of 102 patients (mean age 71 years, 64% female) continued from the main 12-month long-term study[69] into an extension phase of up to 3 years (total of up to 4 years treatment with the 5% lidocaine medicated plasters).[70] Mean pain relief of at least 4.3 on the six-point verbal rating scale, which had been achieved after 6 weeks in the initial 12-month phase of the study, was maintained throughout this 3-year extension period. At all visits, global impression of change, assessed by the investigator and patient using the clinical global impression of change and patient's global impression of change questionnaires, respectively, were "much" or "very much" improved in ~80% of patients. For global evaluation of the 5% lidocaine medicated plaster, clinicians and patients were asked how they rated the study medication at each visit – poor, fair, good, very good, and excellent. At the final visit, the 5% lidocaine medicated plaster was rated as "excellent", "very good", or "good" by 91% (67/74) of physicians and 88% (67/76) of patients. Compared with the initial 12-month study, there was no increased frequency of treatment-related adverse events during the 3-year extension phase.[70] These results indicate that the 5% lidocaine medicated plaster appears to provide effective long-term treatment of neuropathic pain symptoms in patients with PHN without evidence of tolerance or tachyphylaxis.[69,70]

A retrospective, observational study investigated the efficacy and safety of the 5% lidocaine medicated plaster in 431 evaluable patients (25.0% aged >70 years) with refractory chronic neuropathic pain who attended eleven pain centers in France over a 5-year time period.[71] Treatment of refractory neuropathic pain with the 5% lidocaine medicated plaster clearly demonstrated efficacy and an excellent safety profile. The 5% lidocaine medicated plaster reduced pain intensity by >50% or ≥30% in 45.5% and 82.2% of patients, respectively. Statistically significant reductions in the use of analgesics (World Health Organization step I [13.2%], step II [23.7%], step III [9.1%,]; all $P<0.0001$) and coanalgesics for neuropathic pain (tricyclic antidepressants [14.9%, $P<0.0001$], antiepileptics [20.8%, $P<0.0001$], and serotonin reuptake inhibitors [4.9%, $P=0.005$]) were observed in the overall population, with even greater reductions in patients aged >70 years.[71]

Under a compassionate use agreement, 20 geriatric patients (mean age 75 years) who had used the topical 5% lidocaine medicated plaster in clinical trials and were offered to continue therapy (mean duration 7.6 years [range: 4–15 years]) completed a survey to assess effectiveness, tolerability, and patient satisfaction.[72] Patients reported a high degree of satisfaction with long-term 5% lidocaine medicated plaster use as judged by overall satisfaction, comparison of efficacy with previous treatment, pain relief, dosing convenience, ability to perform normal daily activities, and tolerability.[72]

The long-term safety of the topical 5% lidocaine medicated plaster has been reported in a pooled analysis of clinical trial data for 502 patients with PHN and from spontaneous safety reports from consumers and health-care professionals in ~20 million patients (as of July 2014).[15,30] In the majority of patients with adverse drug reactions, application-site erythema and application-site pruritus were the most frequently reported side effects. No serious adverse drug reactions

occurred.[15] Moreover, based on postmarketing surveillance experience in ~20 million patients worldwide, application-site reactions or reports of a lack of drug efficacy were the majority of adverse events reported spontaneously, findings that concur with the safety profile identified during the clinical development program.[30]

Effects on QoL

Improvements in QoL have been reported in several studies of the topical 5% lidocaine medicated plaster in patients with LNP.[45,47,63]

In an open-label effectiveness study, 249 of 332 patients with PHN reported improved QoL after treatment with the 5% lidocaine medicated plaster for 7 days, with further improvements until the end of the study (28 days; P=0.0001). For all measures of pain intensity, pain relief, and interference with QoL, improvements from baseline were equally significant regardless of the time interval since the onset of shingles.[63]

In 300 evaluable patients with PHN (n=96) or painful DPN (n=204), the 5% lidocaine medicated plaster improved QoL (based on the EuroQol-5 dimension QoL index) to a greater extent than pregabalin.[47] The mean change in EuroQol-5 dimension estimated health state score from baseline (all patients) was 0.12 and 0.04 in 5% lidocaine medicated plaster and pregabalin recipients, respectively.[47] Other measures of health-related QoL, Patient's Global, and Clinical Global Impression of Change scores indicated greater improvements with the 5% lidocaine medicated plaster than pregabalin in the PHN group but not in the painful DPN group.[47]

The 5% lidocaine medicated plaster (maximum of four plasters daily for 18 hours) also significantly improved QoL ratings (sleep quality, pain interference, depression, and mood) in 56 patients with painful DPN (19 of whom had DPN with allodynia) in an open-label 3-week study (Table 1).[45] A subgroup of patients received the 5% lidocaine medicated plaster for an additional 5 weeks, during which taper of concomitant analgesic therapy was permitted; QoL benefits were maintained during the extended treatment period.[45]

Discussion

This review provides an updated summary of the published clinical experience with the 5% lidocaine medicated plaster in a wide range of LNP conditions. The data presented suggest that the topical 5% lidocaine medicated plaster is an effective and well-tolerated treatment option in patients with LNP, particularly those with PHN. Indeed, numerous systematic reviews and international guidelines include the topical 5% lidocaine medicated plaster as a first-line option in PHN.[16–26,28]

In contrast, a recent systematic review/meta-analysis, using Grading of Recommendations Assessment, Development, and Evaluation criteria and an assessment of number needed to treat (NNT) for 50% pain relief as a primary measure, recommends the 5% lidocaine medicated plaster as a second-line treatment of peripheral neuropathic pain.[29] The analysis included randomized, double-blind, placebo-controlled studies with parallel group or crossover study designs that had at least ten patients per group – from these data, NNTs were generated. Randomized, enriched enrollment withdrawal trials were summarized separately. As discussed earlier, a number of pivotal studies of the topical 5% lidocaine medicated plaster were enriched enrollment/withdrawal studies, a study design that is not conducive to inclusion/consideration in meta-analyses. This is despite the fact that this study design is in agreement with regulatory authority (eg, US FDA) guidance for the approval of analgesic medications.[73] Enrichment designs can be useful to determine the success of a medication when compared to placebo because it allows for the decrease in early study dropouts caused by adverse events. This is particularly important in studies evaluating the therapeutic effect of a pain medication because the placebo effect is very strong in patients with pain. Furthermore, an enriched enrollment randomized withdrawal trial design allows the ability to detect desirable efficacy in a subgroup (and may, therefore, provide a strategy for establishing pharmacokinetic and pharmacogenetic patient profiles), and it can cope with initial dose titration to mimic clinical practice,[74] with the promise of greater translational impact.[75] Based on a comparison of results from enriched and nonenriched enrollment randomized withdrawal clinical trials of opioids in chronic noncancer pain, there also appears to be no difference in efficacy between enriched and nonenriched studies.[76] However, in the systematic review by Finnerup et al,[29] one of the consequences of summarizing enriched enrollment studies separately and excluding studies in everyday clinical practice, which represent a large proportion of actual usage, is that NNTs were not determined for the 5% lidocaine medicated plaster, resulting in a weak recommendation for use.

The use of NNT can be criticized for several reasons and can only be calculated reliably for parallel designed, placebo-controlled studies with comparable inclusion and exclusion criteria.[17] As study designs for the 5% lidocaine medicated plaster trials were mainly withdrawal designs, NNT calculation was often not possible. Thus, by using this assessment method, very few

studies with NNT data are available for the 5% lidocaine-medicated plaster. However, the available NNT data are in line with those recommended as first-line medications.[17] In fact, in patients with various localized peripheral neuropathic pain syndromes, including the presence of mechanical allodynia, the 5% lidocaine medicated plaster as an add-on therapy reduced ongoing pain and allodynia with an NNT of 4.4 (2.5–17.5).[17] This is an important observation because, in clinical practice, multimodal therapy is considered the "gold standard" for the treatment of localized peripheral neuropathic pain.[77,78] Moreover, there is a knowledge gap in the majority of systematic reviews and clinical guidelines, as they have not been able to provide recommendations for the treatment of individuals who fail monotherapy.[16–26,28,29] In fact, for patients who are treated based on these guideline recommendations and do not experience at least 50% pain control, the core of the NNT concept, clinicians are currently using multimodal therapy with the addition of a second, third, or even fourth medication based on the age of the patient, potential for drug–drug interactions, potential for side effects, and opportunity to also treat comorbid conditions (eg, insomnia, depression, or anxiety). Consequently, the available guidelines have very little clinical application to daily practice as data on the use of multimodal therapy in the treatment of neuropathic pain are lacking.[79] Moreover, there are serious flaws in performing the analysis of the studies as it was done for the guidelines:

1) Recommendations are mainly based on NNTs that are derived from the evaluation of pain based on visual analog scales. Clinical pain researchers have recognized that this evaluation may not be accurate, and patient global impression of pain improvement, psychosocial functioning, and activity are now utilized to fully evaluate the success of analgesic medication.
2) The role of anxiety and depression in amplifying pain symptoms is also not accounted for in these studies.
3) The placebo effect introduced by the research nurses may also be a potential bias in these evaluations.[80–82]
4) The statistical design varies from study to study. Some studies use the baseline evaluation carried forward, whereas others use the last evaluation carried forward when analyzing data for patients who dropped out of the studies. This has not been accounted for in the analysis done for the guidelines.
5) The maximum dose used for the majority of the medications studied varies from study to study. Thus, efficacy can be expected to vary as well. Clinicians are universally using higher doses/numbers of plasters for the treatment of their patients as postmarketing studies have demonstrated increased analgesic efficacy when this approach is utilized.

Consequently, it is not surprising that the general findings of the recent evaluation by Finnerup et al[29] are largely reflected in a recent Cochrane review of all topical lidocaine preparations that found no evidence from good-quality randomized controlled studies to support the use of topical lidocaine to treat neuropathic pain, although individual studies indicated that it was effective for pain relief.[83] The Cochrane review also noted that clinical experience supports the efficacy of topical lidocaine in some patients.[83] Despite the general paucity of direct comparative data from randomized, controlled studies, there is a substantial body of clinical evidence and experience that the 5% lidocaine medicated plaster is a valuable and safe option in the management of LNP. Given the recognition that LNP is a subset of neuropathic pain, a treatment algorithm was developed recently in order to identify patients with LNP and to guide targeted topical treatment with the 5% lidocaine medicated plaster.[84] Generally, the more localized the pain (ie, the area of an A4 sheet of paper) the better the results of topical treatment.[84]

The 5% lidocaine medicated plaster is easy to use, improves patient QoL, has a good tolerability profile, and is associated with a lack of systemic adverse events and a low potential for drug–drug interactions (particularly when compared with systemic medications); moreover, in contrast to systemic therapies, there is no requirement to titrate the dose.[15,85] These characteristics are particularly beneficial in elderly and medically complicated patients, including those with underlying comorbidities that require a polypharmacy management approach.[85] Indeed, the most recent NeuPSIG recommendations also acknowledge the first-line use of the 5% lidocaine medicated plaster as a safe and well-accepted option, particularly in frail or elderly individuals, where adverse effects or safety issues associated with systemic therapy are of concern.[29] Extensive postmarketing surveillance has confirmed the favorable safety profile of the 5% lidocaine medicated plaster, supporting its first-line use in the treatment of LNP after herpes zoster infection.[15]

Based on the results of randomized, controlled, and open-label trials and numerous studies designed to gauge response and experience in real-life clinical practice settings, the use of the 5% lidocaine medicated plaster would appear to be indicated as the first step in the treatment of LNP as part of a multimodal approach or as a single agent. Recent developments with regard to the potential clinical benefit of reducing the size of the painful area using the 5%

lidocaine medicated plaster warrant further investigation in well-controlled clinical studies.

Acknowledgments

The authors thank David P Figgitt, PhD, Content Ed Net, for providing medical writing support in the preparation of this article. Funding for medical writing support was provided by Grünenthal.

Disclosure

Dr de León-Casasola and Dr Mayoral are members of advisory boards for Grünenthal. The content of this publication is based upon an in-depth discussion on this topic by all the authors. The views expressed are therefore based on authors' opinions and do not represent the views of Grünenthal or the Journal. The authors report no other conflicts of interest in this work.

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