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REVIEW

Topical Lidocaine for Chronic Pain Treatment

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Abstract: Topical lidocaine is widely used in current practice for a variety of pain conditions. This literature review shows that its limited absorption and relative lack of systemic adverse events are an attractive analgesic option for a number of vulnerable patients. Topical lidocaine has been approved by health authorities for the treatment of post-herpetic neuralgia in a number of countries, and studies present some degree of evidence of its efficacy and safety in postsurgical pain, diabetic peripheral neuropathy, carpal tunnel syndrome, chronic lower back pain and osteoarthritis. Topical lidocaine may be a great alternative alone or in addition to systemic drugs and non-pharmacological approaches for an optimized pain management and in multimodal analgesia.

Keywords: lidocaine plaster, topical, local, neuropathic pain, musculoskeletal pain

Introduction

Pain treatment is a major health concern and often limited by safety hazards of systemic drugs.[1] In Europe, the prevalence of chronic pain is estimated to affect 25–30% of the population.[2] Despite recommended treatments, more than 60% of patients suffering from chronic pain show no improvement or a poor response and often experience adverse effects (AE).[3] Recommendations for chronic pain treatment underline that topical agents could be used as first- or second-line treatment by International Pain Guidelines.[4–9] Interest in and use of topical analgesics have been increasing because of their potential efficacy in acute and chronic pain and relative lack of systemic AEs.

Lidocaine, an amino amide anesthetic. has been approved in the United States in the 1940s[10] and is largely used in clinical practice. In the 1990s, a patch formulation of lidocaine 5% was developed and approved by the Food and Drug Administration (FDA) for the treatment of postherpetic neuralgia (PHN).[3,11]

Considering the pharmacokinetics of 5% lidocaine plaster (5LP), each plaster contains 700 mg of lidocaine for which a maximum of three plasters applied simultaneously for 12 hours is allowed.[12] Only 3% ± 2% of this maximum recommended dose is systemically absorbed and more than 95% (665mg) remain in the applied medicated plaster. Once absorbed, lidocaine binds predominantly to alpha-1- acid glycoprotein and presumably diffuses passively across the placental and blood–brain barriers. Lidocaine is metabolized in the liver to non-active metabolites that are excreted by the kidneys with an elimination half-life of 7.6 hours. A dosage adjustment is however not required.[12]

Concerning its pharmacodynamics, lidocaine is a non-selective, voltage-gated sodium channel blocker (especially Nav 1.7 and 1.8) on sensory afferents of small damaged or dysfunctional pain fibers at the site of application.[13] It acts by

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stabilizing neuronal membranes and affects both the generation and conduction of nerve impulses (reduction of ectopic discharge and signal propagation in A delta and C fibers). Lidocaine may also activate some irritant receptors (TRPV1, TRPA1) on keratinocytes and immune cells contributing to its analgesic effect.[14]

Considering the large use of topical lidocaine worldwide, this review focuses on the literature, reviews and randomised clinical trials (RCTs) to evaluate how topical lidocaine may be a valuable alternative for an optimized pain management and in multimodal analgesia.

Methods

Search Strategy

A literature review was conducted through an exhaustive electronic search of Medline, PubMed, Google Scholar, and Cochrane databases. Key words such as "topical lidocaine", "lidocaine patch", "lidocaine plaster", "chronic pain", "postsurgical persistent pain", "postherpetic neuralgia", "diabetic peripheral neuropathy", "carpal tunnel syndrome", "chronic lower back pain" and "osteoarthritis pain" were used without limitation in language or date of publication. The last search was conducted in May 2021. This manuscript adheres to the applicable PRISMA guidelines.

Study Selection

Our search was restricted to meta-analyses, parallel and cross-over randomized controlled trials (RCTs) and prospective studies, comparing topical lidocaine to controls. This search included studies concerning lidocaine as a pharmacological drug to treat pain. Inclusion criteria were established prior to article review:

- Design: meta-analyses, double- or single-blind, cross-over or parallel, versus placebo or active control RCTs; prospective studies.
- Etiology: Neuropathic pain (postsurgical persistent pain (PSPP); PHN; diabetic peripheral neuropathy (DPN); carpal tunnel syndrome), musculoskeletal pain (chronic lower back pain (CLBP); osteoarthritis pain (OA)).
- Outcomes (primary or secondary): topical lidocaine efficacy defined by a significant change in pain using diverse measures (Numerical rating scale score (NRS), Dynamic mechanical allodynia (DMA), Visual Analog Scale score (VAS), median-to-exit, response rate, Neuropathic Pain Scale (NPS), Average Pain Intensity (API), Western Ontario and McMaster Universities Arthritis Index (WOMAC)).

During the selection process, all studies not related to lidocaine (animal studies, protocols, letters to editors, expert opinions, or comments) have been excluded after selection based on the title, abstract, and full text, if necessary. Due to language limitations, this review only included articles in English with no limitation on study year or country. Two researchers independently reviewed the papers, and discrepancies were resolved through discussion and consensus.

Data Extraction and Analysis

Data for the selected studies were extracted as follows: study design, characteristics of subjects, pain types and control groups, outcome measurements and effectiveness. Pain types were classified as NP and musculoskeletal pain. NP was divided in PSPP, PHN, DPN and carpal tunnel syndrome and musculoskeletal pain was divided in CLBP and OA.

Risk of Bias Assessment

This review is a scoping review, and risk assessment was focused on blinding and randomization, but did not evaluate selection attrition or other biases.

Results

A total of 3366 articles were identified after database research and 112 were eligible for this review. After having discarded duplicates, screened abstracts, and removed excluded publications (Figure 1), 43 articles were included in this review: 5 meta-analyses/systematic reviews, 3 Cochrane reviews and 23 RCTs. Furthermore, 12 prospective studies have been identified.

Non-Specific Chronic Pain

A number of publications included studies with several chronic pain etiologies, PSPP, PHN, DPN or CLBP and did not analyse their population according to each etiology. According to studies, lidocaine plaster reduces neuropathic symptoms and allodynia in patients with peripheral painful neuropathy, compared to placebo.[15,16] Furthermore, in healthy volunteers and patients, the lidocaine-medicated plaster causes variable effects on different sensory thresholds (cold, warmth, touch, hot pain and mechanical pain).[17] Reduction of the allodynia area is an important factor in the

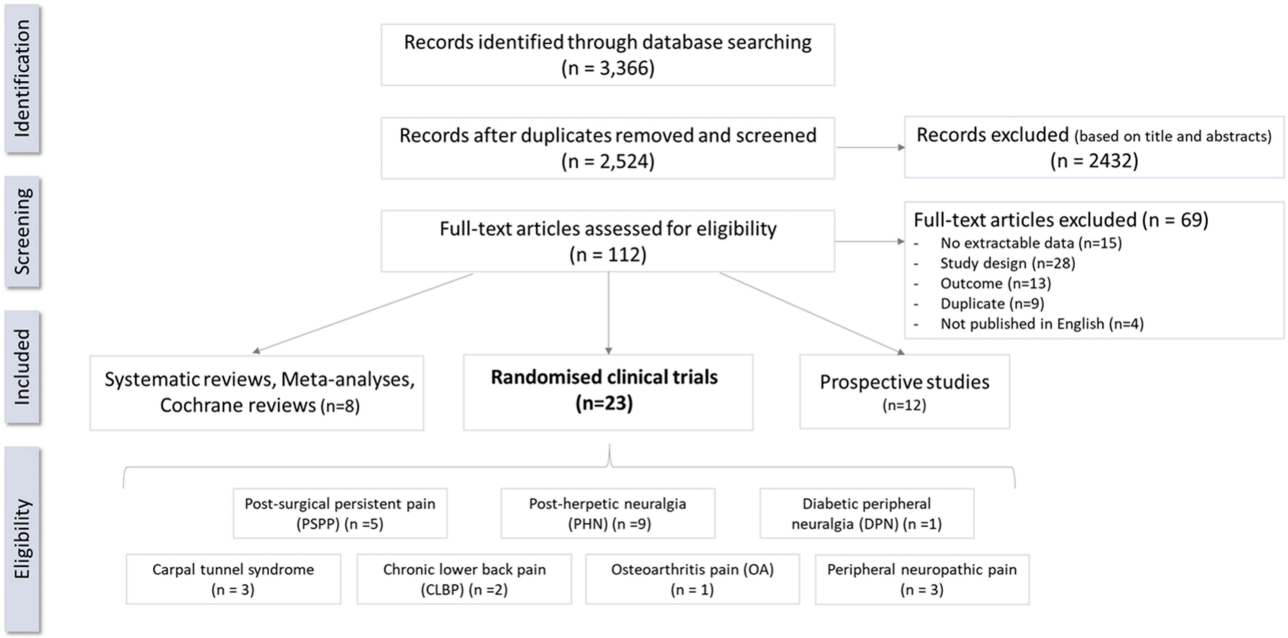

Figure 1 Flowchart of the literature on topical lidocaine.

improvement of quality of life.[17,18] Thus, a systematic review and meta-analysis realized on 229 articles showed weak GRADE recommendations but proposed 5LP in second line. It has been recommended for PNP and especially in elderly patients where 5LP becomes first-line option.[4] Another systematic review and network meta-analysis including 43 RTCs evaluated efficacy and safety of lidocaine 700mg medicated plaster versus (vs) pregabalin. This review describes no clear difference in efficacy between treatments but 5LP shows better AE profile.[19] Regarding Cochrane reviews, Derry et al found no evidence from good-quality RCTs to recommend use of lidocaine in NP although clinical experience and individuals' studies present improvement in pain relief.[20,21] However, a randomized controlled study realized in 46 patients with PNP with 4-week treatment shows a reduction in pain of 0.3 NRS points (95% confidence interval [CI]: 0.1–0.5) and pain-related sleep disturbance of 0.6 points (95% CI: 0.4–0.8) over placebo ($p=0.007$ and $p < 0.001$) and significant pain relief ($p=0.036$) (Table 1).[22] Another study with 5% lidocaine cream realized on 35 patients with PSPP, PHN or DPN demonstrates a significant reduction in pain intensity with topical lidocaine.[23] Meier et al, 2003 describes that, as an add-on therapy, 5LP was effective in reducing ongoing pain ($p=0.017$) and allodynia ($p=0.023$) during the first hours after application and over a period of 7 days ($p=0.018$) in diverse PNP.[15] Finally, a prospective study with patients suffering from PHN, DPN or CLBP shows a significant effectiveness (using the Brief Pain Inventory measures) in all groups with a good tolerability (Table 1).[24]

Neuropathic Pain

Neuropathic pain, a type of chronic pain, is a pathological process in the peripheral or central nervous system (CNS) and presents as one of the most challenging pain syndromes to identify and treat. Its worldwide prevalence is estimated to be 6.9–10% in the global population.[25] It is defined as "pain that arises as a direct consequence of lesion or disease affecting the somatosensory system".[26] Examples of NP include PHN,[17,27] DPN,[28] carpal tunnel syndrome[29] and PSPP.[17,30,31] PSPP is frequently reported in the literature as a disabling complication of many surgical procedures. Nerve injury–induced NP has repeatedly been proposed as a major cause of PSPP.[32] Studies on neuropathic characteristics of PSPP have been carried out mostly on patients undergoing procedures associated with a high incidence of nerve injury, including breast cancer surgery,[30,33] thoracotomy,[34] inguinal hernia repair[35] and limb amputation.[36]

Concerning PSPP, a total of five RCTs and one prospective study focused on PSPP have been retrieved: four studies did show a positive result and two studies did not show reduction of pain with 5LP.[17,30,37–39] A randomized controlled trial demonstrates the effectiveness of 5LP on several neuropathic characteristics, in psychophysical responses and

Table 1 Randomized Clinical Trials with Topical Lidocaine in Non-Specific Chronic Pain

Authors	Population	Design*	Treatment	Sample Size	Maximum Dose/Nb of Plasters	Follow-Up Weeks	Concomitant Medication	Primary Outcome
Demant et al, 2015[22]	Peripheral neuropathic pain (NP, PSPP, PHN)		5% Lidocaine plaster (n=NR) vs Placebo (n=NR) Irritable nociceptor vs non irritable nociceptor	NR 15 25	3	4	No	NRS and pain-related sleep disturbance reduced (p = 0.007 and p < 0.001)
Ho et al, 2008[23]	PSPP, PHN, DPN		5% Lidocaine cream vs 5% amitriptyline cream vs Placebo	35 35 35	6–10 mL	6	Yes	VAS score reduction (p<0.05)
Meier et al, 2003[15]	Peripheral neuropathic pain		Group 1: 5% Lidocaine plaster-placebo Group 2: Placebo – 5% lidocaine paster (n=20)	20 20	4	3	Yes	Ongoing pain (p=0.017) and allodynia (p=0.023) reduction during the first 8 h after application and over a period of 7 days (p=0.018)

Note: *All studies are randomized, double blind, crossover and versus (vs) placebo, unless specified.
Abbreviations: PSPP, posttraumatic/post-surgical persistent pain; PHN, postherpetic neuralgia; DPN, diabetic peripheral neuropathy; NR, not reported; No, no concomitant medication.

clinical allodynic symptoms (Table 2).[17] Another study describes a clinically relevant reduction of pain in the 5LP arm where the pain reduction was numerically higher than in the placebo but without effect statistically significant (least squares mean [LS mean] [standard error] for placebo plaster −1.47 [0.16] versus −1.70 [0.16] for lidocaine; [LS] difference [SE] between treatments −0.23 [0.23], one-sided p=0 0.1533).[37] Furthermore, Sansone et al show a significant greater reduction in pain score in the 5LP group compared with the placebo group (baseline to week 4, −2.9 vs −0.7, p<0.01; baseline to week 8, −4.3 vs 0.0, p<0.01).[38] A prospective observational study describes that 78.9% of patients with traumatic injury to peripheral nerves, reduced their NRS score by 3 points or more and 94.7% presented a > reduction of the pain area.[40] Other studies do not show a reduction of pain intensity with 5LP in cancer patients with persistent incisional pain[30] or in patients with persistent inguinal postherniorrhaphy.[39] Further studies are needed in other types of surgery for bring more information.

Regarding PHN, one meta-analysis, one systematic review, one Cochrane review, nine RCTs and three prospective studies have been found and presented positive results except in the Cochrane review.[27,28,37,41–50] A recent meta-analysis[48] conducted on 12 studies concludes that topical lidocaine is preferable to other topical drugs for PHN. It is the most effective and tolerable drug. It may restrain inflammatory factors of damaged tissue, that play an important role in pain. A systematic review[49] concludes in the same direction in considering 5LP as a first-line treatment option for PHN in view of its efficacy and tolerability, a noticeable change since from the previous Cochrane study.[50]

Several RCTs present good results of lidocaine in PHN (Table 1). Indeed, a study realized on 24 patients

Table 2 Randomized Clinical Trials with Topical Lidocaine in Neuropathic Pain Conditions

Authors	Population	Design*	Treatment	Sample Size	Maximum Dose/Nb of Plasters	Follow-Up Weeks	Concomitant Medication	Primary Outcome
Pickering et al, 2019[17]	PSPP	Parallel	5% Lidocaine plaster vs placebo	24 12	2	12	Yes	Dynamic mechanical allodynia (DMA) diminished of ≥30% over 3 months (p=0.003)
Palladini et al, 2019[37]	PSPP		5% Lidocaine plaster vs placebo	180 183	3	12	"plaster only" or "add-on"	Numerical Rating Scale (NRS): p=NS
Sansone et al, 2017[38]	PSPP	Single-blind	5% Lidocaine plaster vs Placebo	33 30	NR	8	NR	NRS pain scores improved (p<0.01)
Bischoff et al, 2013[39]	PSPP		5% Lidocaine plaster vs placebo	21 21	1	4	Yes	Summed Pain Intensity (SPID): p=NS
Cheville et al, 2009[30]	PSPP		5% Lidocaine plaster vs placebo	14 14	3	8	Yes	Weekly pain intensity ratings: p=NS
Kanai et al, 2010[42]	PHN (ophthalmic)		4% Lidocaine eye drops vs placebo	12 12	0.4mL (single app.)	2	Yes	Visual Analog Scale (VAS) score decreased (p<0.01).
Kanai et al, 2009[41]	PHN		8% Lidocaine spray vs placebo	12 12	0.1mL/single spray, 30 times	1	Yes	VAS score decreased (p<0.01).
Binder et al, 2009[27]	PHN		5% Lidocaine plaster vs placebo	36 35	3	2	Yes	Higher median time-to-exit (p=0.0398) (per protocol).
Baron et al, 2009[28]	PHN	Open label, active-controlled, non-inferiority study	5% Lidocaine plaster vs pregabalin	50 48	3	4	No	Greater responder rate (62.2% vs 46.5%) (per protocol).
Lin et al, 2008[45]	PHN	Parallel	5% Lidocaine plaster vs placebo	23 23	1	2 days	Yes	Pain intensity reduction at rest (p=0.005) and during movement (p=0.007).
Galer et al, 2002[47]	PHN	Parallel	5% Lidocaine plaster vs placebo	67 29	NR	3	NR	Neuropathic Pain Scale (NPS) scores reductions (p=0.043).
Galer et al, 1999[46]	PHN		5% Lidocaine plaster vs placebo	16 16	3	4	NR	Median-time to-exit significantly higher (*p*<0.001).
Rowbotham et al, 1996[44]	PHN		5% Lidocaine plaster vs placebo	35 35	3	4	Yes	VAS scores reductions from 4h to 12h (p<0.05).
Rowbotham et al, 1995[43]	PHN		5% Lidocaine gel vs placebo	20 19	200–800 cm^2 of skin covered	3	Yes	VAS scores reductions in torso-limb group at 8h and 24h (p<0.05)
Baron et al, 2009[28]	DPN	Open label, active-controlled, non-inferiority study	5% Lidocaine plaster vs pregabalin	107 106	4	4	No	Comparable response rate (66.7% vs 69.1%).

(*Continued*)

Table 2 (Continued).

Authors	Population	Design*	Treatment	Sample Size	Maximum Dose/Nb of Plasters	Follow-Up Weeks	Concomitant Medication	Primary Outcome
Moghtaderi et al, 2009[59]	Carpal tunnel syndrome	Parallel, open-label, active-controlled	2.5% lidocaine plus 2.5% prilocaine vs methylprednisolone acetate 40 mg	35 35	Daily app. vs one injection	4	NR	Pain intensity diminution in both groups ($p < 0.001$).
Nalamachu et al, 2006[57]	Carpal tunnel syndrome	Parallel, open label, active-controlled	5% Lidocaine plaster vs 1% lidocaine injection, methylprednisolone acetate	20 20	1 vs 0.5cc, 40mg	4	NR	Worst pain, average pain, and pain "right now" diminution in both groups ($p<0.05$)
Nalamachu et al, 2006[58]	Carpal tunnel syndrome	Parallel, open-label, active-controlled	5% Lidocaine plaster vs naproxen 1000mg	52 48	3	6	NR	Average Pain Intensity (API) scores reduced 5LP (p <0.0001) and naproxen (p=0.0004) Difference between treatments (p=NS)

Note: *All studies are randomized, double blind, crossover and versus (vs) placebo, unless specified.
Abbreviations: PSPP, posttraumatic/post-surgical persistent pain; PHN, postherpetic neuralgia; DPN, diabetic peripheral neuropathy; NR, not reported; No, no concomitant medication.

with ophthalmic PHN who received 4% lidocaine eye drops or placebo demonstrates a significant decrease in the visual analog scale (VAS) score in the eye (baseline: 5.9±2.2 cm; 15 minutes after eye drops: 0.9±1.8 cm, mean±SD; $p<0.01$) with a significant mean change between lidocaine and placebo group.[42] In another study, 8% lidocaine pump spray is used and compared to placebo in PHN patients: a greater decrease in VAS score was observed in the lidocaine group (6.1±1.7 cm before spray to 2.3±2.5 cm at 15-minute post-spray; $p<0.01$) and placebo group (6.1±1.7 cm to 5.7±1.6; $p<0.05$). The mean change between lidocaine and placebo is significant ($p<0.01$).[41] Binder et al consider that 5LP is a valuable treatment option for patients with PHN with a median time-to-exit of 14.0 [3–14] in the lidocaine group and 6.0 [1–14] in the placebo group (p=0.0398).[27] An open label randomized non-inferiority study between 5LP and pregabalin follow-up for 4 weeks shows, after stratification by type of NP, more patients' responders to 5LP than to pregabalin in PHN patients (62.2% vs 46.5%, per protocol set).[28] In another randomized study, the effectiveness of 5LP compared to placebo has been demonstrated with differences of mean reduction of pain intensity between groups of 14.7 (4.7–24.8, p=0.005) in favor of 5LP.[45] Four older RCTs concluded with similar positive results in favor of 5LP and are described in Table 1.[43,44,46,47]

Regarding prospective studies, a total of 249 patients are followed in 2 long-term studies (treatment ≥12 months with 5LP) and demonstrate effectiveness of 5LP by maintained reductions in pain intensity associated with a good tolerability in PHN patients.[51,52] Finally, an open-label non-randomized prospective study that aimed to determine the impact of 5LP on pain quality associated with chronic pain using the Neuropathic Pain Scale (NPS) describes, in a subgroup analysis, a numerical advantage for all 4 NPS composite measures for the PHN patients.[53]

Considering DPN, two systematic reviews and meta-analysis, one RCT and one prospective study have been selected, all of them showing positive results.[28,54–56] Very few studies comparing topical lidocaine to other agents exist for DNP. A systematic review and meta-analysis on pharmacological therapy for DPN, shows that 5LP had the highest probability of 30% reduction compared with placebo (1.84, [1.39, 2.21]).[54] Another review[55] concluded that limited evidence suggested 5LP provided comparable pain reduction to amitriptyline, capsaicin, pregabalin and gabapentin in DNP and may be associated with fewer AEs. The authors correctly acknowledge that the few small included trials provide limited evidence, and this should be taken into account when interpreting the results. Only one open-label non-inferiority study realized in 161 DPN patients showed comparable pain relief in the lidocaine and pregabalin groups (67% vs 69%, respectively);

however, a better quality of life was observed in the lidocaine group (Table 1).[28] Regarding prospective open-label study, Barbano et al describe significant improvement in pain and quality-of-life during 3 weeks of treatment.[56]

For carpal tunnel syndrome, only three randomized and open-label studies focused on carpal tunnel syndrome with no statistical difference between treatments. However, these studies reported pain relief in both groups suggesting that topical lidocaine may be effective and safe in treatment of carpal tunnel syndrome (Table 1).[57–59] In two pilot studies, 5LP was compared to an injection of lidocaine/methylprednisolone for 4 weeks in 40 randomized patients[57] and was compared to naproxen (500 mg x 2/d) for 6 weeks in 100 randomized patients.[58] The last trial used prilocaine+lidocaine cream compared to an injection of methylprednisolone (40mg) for 4 weeks in 65 randomized patients.[59] Studies do not report statistically significant difference between treatments, but this difference was often not evaluated and further studies are warranted.

Musculoskeletal Pain

Musculoskeletal diseases are defined as a group of diseases that affect different structures of the musculoskeletal system (nerves, tendons, muscles, joints, ligaments, bones, blood vessels) and supporting structures such as intervertebral discs.[60,61] Some studies have reported that musculoskeletal diseases and pain considerably contribute to reduced productivity and poorer quality of work, increase dependence levels and demands on health systems, especially considering musculoskeletal aging.[62,63] CLBP is one of the most prevalent musculoskeletal disorders and affects 70% to 85% of the adult population.[64] One year after the onset of low back pain, 45% to 75% of patients still experience pain,[65] representing important expenses in health care.[64]

A total of two RCTs and three prospective studies focused on CLBP have been found with positive results.[53,66–69] Considering OA, only one open-label RCT and three prospective studies have been selected, one study did not show any difference in effectiveness/tolerability, while the other prospective studies did show positive results (Table 3).[57–59,70]

In CLBP, the majority of studies are open-label and uncontrolled[53,68,69]; only two studies are RCTs[66,67] and used different tools to measure pain (Brief Pain Inventory, the Visual Analog Scale, the Short-Form McGill Pain Questionnaire, and the Neuropathic Pain Scale) (Table 1). Hashmi et al demonstrated a statistically significant reduction in pain in both groups (5LP vs placebo) without difference between the treatment groups.[66] In an open-label study, the lidocaine plaster induced a statistically significant reduction in pain with QOL and depression improvement.[69] One of these open-label CLBP studies showed in 29 patients an improvement of composite measures of NP[53] and suggested that lidocaine plaster may be used as an add-on therapy. Functional magnetic resonance imaging studies after 5LP treatment reported a decrease in pain-related brain activity in the medial prefrontal cortex compared to baseline.[66,68] Although these studies are limited, CLBP is a real cause of disability and of opioid use in the US, suggesting the need to find other alternatives such as lidocaine plasters combined with appropriate oral therapies.[18] In the context of the opioid crisis, general recommendations favor opioid-sparing analgesia. Topical treatments have an increasing role to play in analgesia, given their good benefit–risk balance and the possibility to diminish the use of step 2 and 3 opioids.

Concerning OA, topical analgesics, including NSAIDs and capsaicin, are recommended in guidelines for OA pain,[5,60] but topical lidocaine is poorly documented. Only one open-label RCT compares the effectiveness of 5LP with celecoxib in the treatment of OA-related knee pain.[70] In this study, no difference in effectiveness and tolerability was found between both treatments (WOMAC OA subscale scores: 5LP, 12.087; celecoxib 200 mg/d, 12.514) and mean rates of change over time (baseline to week 2, −1.5916 vs −1.6513 per week; weeks 2–6, −0.0168 vs −0.119 per week; weeks 6–12, –0.1818 vs −0.1579 per week). Furthermore, three open-label prospective studies tried to evaluate the efficacy of lidocaine plasters in a total of 257 patients with knee OA. Burch et al obtained significant improvement in pain intensity, WOMAC (Western Ontario and McMaster Universities Arthritis Index) score and QOL in 137 patients with OA of the knee with an incomplete response to analgesic therapy.[71] Similar results are reported in another study realized in 20 patients with inadequate relief of pain.[72] Finally, a significant improvement in all composite measures of the Neuropathic Pain Scale is demonstrated both in monotherapy and add-on therapy.[73] Although lidocaine is not indicated for OA, the results of these open-label studies suggest that lidocaine plaster may offer an option to patients not relieved by usual treatments. Further randomized and controlled trials are needed to confirm this hypothesis.

Table 3 Randomized Clinical Trials with Topical Lidocaine in Musculoskeletal Pain

Authors	Population	Design*	Treatment	Sample Size	Maximum Dose/Nb of Plasters	Follow-Up Weeks	Concomitant Medication	Primary Outcome
Castro and Dent, 2017[67]	CLBP	Parallel	5% Lidocaine plaster (Rx) vs 3.6% lidocaine plaster+1,25% menthol (OTC) vs placebo	NR	NR	NR	NR	Non-inferiority of OTC compared with Rx for efficacy, side effects and quality of life. Versus placebo, OTC proved superiority for efficacy, general activity and normal work
Hashmi et al, 2012[66]	CLBP	Parallel	5% Lidocaine plaster vs placebo	15 15	NR	2	NR	Pain intensity, sensory and affective qualities of pain or pain related brain activation at any time point (p=NS)
Kivitz et al, 2008[70]	OA	Parallel, open label, active-controlled	5% Lidocaine plaster vs celecoxib 200mg	69 74	1–1/3	12	Yes	WOMAC OA subscale scores and mean rates of change over time (p=NS)

Note: *All studies are randomized, double blind, crossover and versus (vs) placebo, unless specified.
Abbreviations: CLBP, chronic low back pain; OA, osteoarthritis pain; NR, not reported; No, no concomitant medication.

Tolerability and Safety

Topical lidocaine is generally reported as safe and with a good tolerability. The risk of AEs is limited because little systemic diffusion reduces the risk of potential interactions with concomitant medications. The most frequently reported AEs are found at the application site, including skin reactions (itch, erythema, burning, rash, edema and dermatitis). These are often mild and spontaneously resolve within a few minutes to hours after plaster removal.[11,24,74] Studies showed 5LP is well tolerated in long-term use with sustained pain relief for different types of NP.[17,37] However, hepatic or renal disease may occasionally need dose adjustment in order to avoid toxic blood lidocaine concentrations, especially in patients with mild to moderate or hepatic impairment. Potential risks of systemic effects (respiratory distress, seizures, dizziness, loss of consciousness, drowsiness and cardiac arrest)[11,74] could occur in patients treated also with other local anesthetics or Class I antiarrhythmic drugs (eg, mexiletine and tocainide). For DPN and PHN, lidocaine was reported to be better tolerated than systemic pregabalin (AEs rate, 5.8% with lidocaine-medicated plaster, versus 41.2% with oral pregabalin).[28]

Discussion

Lidocaine is usually recommended as a first-line drug but is underutilized in PHN patients.[75] Instead, second- or third-line treatments (ie, opiates and capsaicin) or NSAIDs (which are not recommended and have been shown in a meta-analysis to be ineffective for NP[76]) are frequently used as the initial treatment.[75] Gudin et al report that lidocaine patches were only used initially in 8% of PHN patients, while 32% of them received no treatment; opioids were the most common initial treatment (22%) followed by gabapentin (15%) and NSAIDs (9%). Those treatments that do not follow official recommendations cause excessive health-care costs, and increase the risk of opioid overuse.[75] In DPN, pregabalin and duloxetine are the only medications approved by the FDA. Based on current practice guidelines, these medications, with gabapentin and amitriptyline, should be considered for initial treatment. Second-line and third-line therapies include opioid-like medications (tramadol and tapentadol), venlafaxine, desvenlafaxine, and topical agents (lidocaine patches and capsaicin cream).[77] Lidocaine patch may be an useful therapy for the treatment of pain relief in DPN.[78]

One of the advantages of topical lidocaine is that it avoids the systemic route of drug metabolism compared to

other routes, especially in persons with comorbidities. The traditional route of administration in pain medication for patients with chronic or acute pain is oral therapy, although this may be limited in a number of conditions (comorbidities, end-organ damage, AEs, and drug interactions).[79,80] The oral route exhibits a variety of potential AEs, especially in vulnerable patients and older patients with comorbidities and polypharmacy.[81,82] Indeed, pharmacokinetic and pharmacodynamic age-related changes (decreased absorption, impaired distribution, hepatic metabolism and renal clearance) increase the risk of multiple disorders, including gastrointestinal disorders, confusion, sedation and memory loss often causing poor compliance in geriatric populations.[81] Guidelines in NP treatment have been published and recommended 5LP as a possible first-line treatment for frail and elderly patients.[4] A review of various studies showed effectiveness in elderly patients with polypharmacy.[83] The cognitive deficits widely observed in NP patients taking antidepressants are not found with 5LP. In this vulnerable population, topical pain management is an interesting alternative to alleviate pain and maintain cognitive integrity.[81]

Topical agents offer other advantages compared to oral analgesics, including avoidance of hepatic first-pass metabolism, less fluctuation in drug levels, a lower total systemic daily dose and the possibility to be more specific with a treatment directly on the affected area.[84] Another advantage is the possibility of combining it with other systemic drugs in order to achieve an additive effect without systemic drug interaction or additional side effects.[85] In addition to its efficacy and safety, local treatment with lidocaine is easy to administer and displays a good patient compliance. The possibility of coupling up to three plasters or trimming the plaster to fit different body sites allows a good adaptation to the particular pain site. A clinical trial[17] clearly shows excellent patient compliance and efficacy in pain following knee arthroplasty.

To our knowledge, the efficacy of pain relief by lidocaine has not been established in large studies in children.[86–89] A recent prospective study supports the efficacy of 5LP in children and adolescents with localized neuropathic pain as part of a multidisciplinary pain approach with good tolerability and safety.[90] However, caution is needed because of the immaturity of some neural systems and of pain pathways undergoing a series of transitional functional states before reaching maturity.[91] Caution is also needed because of the theoretic risk of systemic absorption of lidocaine and its severe toxic effects in case of accidental mucosal absorption (by rubbing the patch on the eye or sucking on the mixture).

Topical agents have however a few drawbacks, including poor product adhesion (1.8% lidocaine topical system presents superior adhesion profile than 5LP) and an application on an area with good skin integrity to avoid risk of toxicity. A variety of formulations have been studied but not commercialized worldwide and not standardized, with prescription in some countries or OTC in others.[9,92] Studies are usually of short duration with a small number of participants, not double-blind, and with a poor description of the placebo when there is one. The type of pain is often limited to PHN or DPN, while the main cause of NP in real life is post-surgery NP.[31]

Practice Guidelines on topical lidocaine are regularly published by manufacturers and researchers.[9,12,75,93] These may be summarized in the 10 following points:

1. Topical lidocaine should be used as directed by health care professionals and according to directions of the manufacturer.
2. Over the counter 4% lidocaine patch is a medication and should be used accordingly.
3. Allergic adverse events may occur, and drug interactions should be prevented.
4. Five percent lidocaine patch may be applied to the painful area for 12 hours per day with a 12-hour break.
5. The patch should cover the whole painful area, especially the target zone, if any.
6. It must fit the size of the painful area; it is possible to cut before peeling off the release liner.
7. The maximum dose is three patches a day, 12 in a 24-hour period.
8. Topical lidocaine is applied only to intact skin, not to open wounds, burns, or broken or inflamed skin, avoiding contact with the eyes.
9. Any burning sensation or local irritation requires removal of the patch until irritation subsides.
10. It should be used with caution in severe hepatic or cardiac disease.

In conclusion, topical lidocaine is widely used in current practice for a variety of pain conditions. Its limited absorption and relative lack of systemic adverse events is an attractive analgesic option for a number of vulnerable patients. Topical lidocaine has been approved by health authorities for the treatment of post-herpetic neuralgia in a number of countries, and studies present some degree of evidence of its efficacy and safety in PSPP, DPN, carpal tunnel syndrome,

CLBP and OA. Health authorities worldwide endorse opioid-sparing analgesia and topical treatments have an increasing role to play in this context, with their very favorable benefit–risk balance. Topical lidocaine may be a great alternative alone or in addition to systemic drugs and non-pharmacological approaches for an optimized pain management and in multimodal analgesia.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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