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REVIEW

Multimodal Therapies for the Treatment of Neuropathic Pain: The Role of Lidocaine Patches in Combination Therapy: A Narrative Review

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ABSTRACT

Neuropathic pain (NP) has a population presence of up to 10%. Both systemic agents and topical agents are recommended as first-line therapy for the treatment of NP but monotherapy provides adequate pain relief only in < 50% of the cases. This has created the need for multimodal combination therapy, a practice that is becoming more common. Combination therapy with multiple systemic agents has a risk for drug–drug interactions and adverse events (AEs), while add-on therapy with a topical agent such as lidocaine patches minimizes such risks. The focus of this review was to find if there is evidence from trials that combination therapy of the topical lidocaine patches with systemic agents will have better efficacy and/or less risk of AEs than the combination of two systemic agents. Since gabapentinoids are one of the most common systemic agents used in first-line NP therapy, the objective of this review was to summarize the safety and efficacy data and evaluate the benefit–risk ratio from three gabapentinoid combinations; gabapentinoid plus opioids, gabapentinoid plus antidepressants, and gabapentinoid plus topical lidocaine patches. Reviews of clinical trials of combinations of gabapentinoids plus other systemic agents (opioids or antidepressants) were associated with increased AEs and dropouts while improvement in analgesic efficacy was inconsistent. Clinical trials where the patients were provided topical lidocaine patches when their first treatment with a gabapentinoid was inadequate demonstrated improved analgesic efficacy with minimal additional AEs. This led to the conclusion that topical lidocaine patches—associated with minimal systemic adverse effects and proven benefits in various neuropathic pain (NP) conditions—can enhance the likelihood of achieving meaningful pain relief when used as adjuvant therapy for NP.

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Key Summary Points

Monotherapy for neuropathic pain (NP) provides adequate pain relief only in < 50% of cases, creating the need for multimodal combination therapy.

Combination therapy with multiple systemic agents has a risk for drug–drug interactions and adverse events (AEs), while add-on therapy with lidocaine patches minimizes such risks.

Combinations of systemic agents (gabapentinoid plus opioid or antidepressant) were associated with increased AEs and dropouts while improvement in analgesic efficacy was inconsistent.

The clinical trials reviewed here have demonstrated that the combination of systemic gabapentinoids plus topical lidocaine patches improve analgesic efficacy with minimal additional AEs.

Lidocaine patches can improve the likelihood of achieving meaningful pain relief when used as adjuvant therapy.

INTRODUCTION

Neuropathic pain is pain arising as a direct consequence of a lesion or disease affecting the somatosensory system [1]. Clinical manifestations of NP include burning, tingling, numbness, electric shocks, itching, and intolerance to temperature [2]. It arises secondarily to many different underlying conditions and can be classified as peripheral or central [2]. Peripheral NP conditions include: diabetic peripheral neuropathy (DPN), chemotherapy-induced peripheral neuropathy, radicular pain, postsurgical chronic neuropathic pain, trigeminal neuralgia and postherpetic neuralgia (PHN). Central NP conditions (nociplastic pain) include multiple sclerosis, poststroke pain, spinal cord injury-related pain, and complex regional pain syndrome [2, 3]. NP has a population prevalence of 6.9–10% [4].

Several guidelines for the treatment of NP have been issued (Table 1) [2, 5–7]. First- and second-line treatment recommendations include: gabapentinoids (i.e., gabapentin or pregabalin), tricyclic antidepressants (TCAs), serotonin–norepinephrine reuptake inhibitors (SNRIs), topical lidocaine, topical capsaicin, and opioids. Less than 50% of patients find adequate pain relief, which is due in part to suboptimal efficacy and/or dose-limiting adverse effects (AEs) [8–10]. A large retrospective analysis of a claims database found that 57% of patients with PHN treated with gabapentinoids switched to another therapy and another 34% of patients added a second therapy [10]. Suboptimal dosing may limit efficacy as only 69% of pregabalin patients and 14% of gabapentin patients were successful in being titrated up to a minimal effective dose [10]. In patients who do not achieve adequate pain relief with single first-line therapies, treatment guidelines recommend combining first-line therapies or adding tramadol, a synthetic opioid to the first-line therapy (Fig. 1) (Table 1) [2]. Because first-line therapy leaves so many patients with inadequate pain relief, combination therapy has become more common in clinical practice [8]. Combination therapy can be beneficial when medications are chosen based on differing mechanisms of action, often leading to additive or synergistic therapeutic benefits with enhanced tolerability and safety [8].

Side effects can be a limiting factor when combining drugs. The side effects of agents used to treat NP are listed in Table 2 [11–16]. Systemic agents (tricyclic antidepressants (TCAs), serotonin–norepinephrine reuptake inhibitors (SNRIs), gabapentinoids, and opioids) used in the treatment of NP have central nervous system-related side effects including somnolence, dizziness, sedation, dry mouth, and also have precautions and warnings about their use (Table 2). Lidocaine patches have primarily local dermal side

Table 1 Summary of NP guidelines

Guideline source	CDC [7]	Comprehensive Algorithm on Management of NP 2019 [2]	EFNS (European Federation of Neurological Societies) 2010 [5]	NeuPSIG (International Association for the Study of Pain) 2015 [6]
Indication	All neuropathic pain	All neuropathic pain	PHN	All neuropathic pain
First line	Gabapentin	Gabapentin	Gabapentin	Gabapentin
	Pregabalin	Pregabalin	Pregabalin	Gabapentin ER
	TCAs	TCAs	TCAs	Pregabalin
	SNRIs	SNRIs	Lidocaine plasters	Duloxetine
	Topical lidocaine	Topical lidocaine		Venlafaxine
		Topical capsaicin		TCAs
Second line		Combination of first-line agents	Strong opioids	Lidocaine patch
			Capsaicin	Capsaicin patch
		Tramadol		Tramadol

effects that are usually mild to moderate and transient (Table 2). Combination therapy using two systemic drugs has the risk of drug–drug interactions or drug–disease interactions and systemic side effects. On the other hand, topical agents have the advantage of minimal systemic exposure, and therefore topical agents can be combined with systemic drugs to achieve an additive effect with minimal risk of systemic interactions [17].

Recent reviews that used systematic searches have been made to evaluate the effectiveness and safety of combination therapy for NP in adults [8, 18, 19]. The search criteria used for these reviews only allowed for the inclusion of evidence from double-blinded, randomized clinical trials. As there had been no clinical trials

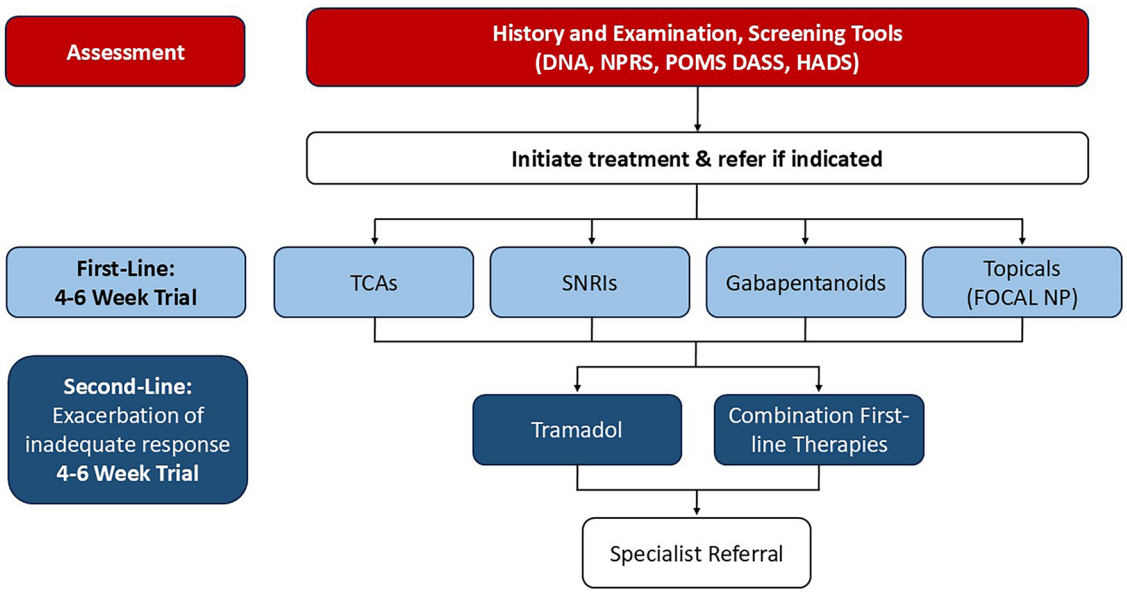

Fig. 1 Algorithm for the management of chronic NP [2]

Table 2 Side effects associated with first-line therapies for neuropathic pain

Medication class	Major/common side effects	Precautions	References
TCAs	Sedation, dry mouth, blurred vision, weight gain, urinary retention	Cardiac disease, glaucoma, suicide risk, seizure disorder, concomitant use of tramadol	[11]
SNRIs	Nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis	Hepatotoxicity, orthostatic hypotension, serotonin syndrome, severe skin reactions, mania, glaucoma, blood pressure increases, sexual dysfunction, glucose control in diabetes	[12]
Gabapentin	Sedation, dizziness, peripheral edema	Renal insufficiency	[13]
Pregabalin	Sedation, dizziness, peripheral edema	Renal insufficiency	[14]
Opioids	Nausea/vomiting, constipation, drowsiness, dizziness, seizures, respiratory depression	History of substance abuse, suicide risk, driving impairment during treatment initiation, seizure disorder, concomitant SSRI/SNRI/TCA use, respiratory depression	[15]
Topical lidocaine patch	Local erythema, rash	None	[16]

SSRI selective serotonin reuptake inhibitors

of combination therapy for NP that included lidocaine patches that were double-blinded and randomized, any evidence from clinical trials for the effectiveness of combination therapy for NP including lidocaine patches was not found or evaluated in these systematic reviews. Lidocaine patches are considered first- or second-line therapy in most guidelines for the treatment of NP (Table 1), thus any evidence for the utility of lidocaine patches for combination therapy of NP would be of interest.

The rationale for this review was: 1—Since monotherapy for NP is effective in less than 50% of cases, there is a need for multimodal combination therapy to adequately treat pain in many patients with NP [8–10] 2—Since using a lidocaine patch in combination therapy for NP has a minimal risk for drug–drug interactions and systemic side effects, the focus of this review was to find if there is evidence from trials that combination therapy of the topical lidocaine patches with systemic agents will have better efficacy and/or less risk of AEs than the combination of two systemic agents; 3—Since gabapentinoids are one of the most common systemic agents used in first-line NP therapy and topical lidocaine patches are one of the most prevalent topical agent used, we compared the efficacy and side effects of gabapentinoids plus other systemic agents to the use of gabapentinoids plus topical lidocaine patches. The objective of this review was to summarize the safety and efficacy data of three gabapentinoid combinations: gabapentinoid plus opioid, gabapentinoid plus antidepressants (TCAs and SNRIs), and gabapentinoid plus topical lidocaine patches. Additionally, the review aimed to evaluate the benefit–risk ratio of each combination.

METHODS

Using recently published systematic reviews [8, 18, 19], we identified combination studies of NP involving gabapentinoids plus opioids, or gabapentinoids plus antidepressants. In addition, we searched for and then reviewed publications of

trials involving gabapentinoid plus topical lidocaine patches [17, 20–22].

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Two recent systematic reviews [8, 18] covered combination therapy for neuropathic pain. Neither review includes studies where lidocaine patch was a part of the combination therapy but they provide a wealth of information on studies of combination therapy starting with gabapentinoids followed by opioids or antidepressants.

Two studies were found where combination therapy for NP started with gabapentinoid treatment and lidocaine patches were added as therapy in those patients who did not achieve adequate pain relief with the gabapentinoid therapy alone [17, 20–22].

Gabapentinoid plus opioid combination studies: Six combination therapy trials were found where the patients were treated with a gabapentinoid and an opioid [23–28]. These six trials included 931 patients (Table 3). Overall, these six trials gave mixed results on the efficacy of pain relief. Efficacy with combination therapy was superior to monotherapy in four studies [24–27], however there was no difference in efficacy between monotherapy and combination therapy in the other two studies [23, 28]. AEs, particularly dizziness and somnolence, were higher in the combination group in most of these studies and dropouts due to AEs were often higher in the combination groups.

Gabapentinoid plus antidepressant combination studies: Three combination therapy trials with 472 patients were examined, where the patients were treated with a gabapentinoid and an antidepressant (Table 4) [29–31]. Two of the studies used antidepressants of the TCA class [29, 31] and one study used an antidepressant of the SNRI class [30]. Combination therapy was superior in efficacy to monotherapy in two studies [29, 31]. There was no difference between treatments in efficacy in one study [30]. Dropouts due to AEs were higher and dry mouth was more frequent with combinations in one study [29]. Dry mouth AEs were in 60% of patients with combination therapy while only at 17% with gabapentin monotherapy in a second study [31]. There was no difference in treatment-emergent adverse events (TEAEs) between treatment groups in another study [30].

Gabapentinoid plus lidocaine patch combination studies: Two studies of gabapentinoid plus lidocaine patch combination therapy were identified [17, 20–22].

In the first study [17], 107 patients with NP and DPN, PHN, or lower back pain (LBP) who had incomplete response to gabapentin monotherapy were treated for 2 weeks with lidocaine patches in addition to continuing the gabapentin therapy. For treatment with the lidocaine patches, up to four lidocaine patches (560 cm^2) were applied to the area of maximal peripheral pain in for up to 24 h in each 24-h period [17]. Statistically significant ($p < 0.001$) improvements in measures of pain intensity and pain relief (Brief Pain Inventory (BPI) scores for worst pain, least pain, average pain, pain right now, and pain relief) were reported after 2 weeks with the combination therapy compared to baseline measures. Statistically significant ($p < 0.05$) improvements in measures of pain interference with general activity, mood, walking ability, normal work, relationships with others, sleep and enjoyment of life were also noted. The patches were well tolerated and all treatment-related AEs were mild to moderate. There were no indications of any AEs that may have resulted from drug–drug interactions [17].

The second study was presented in three publications [20–22]. It was a two-stage study; the first part was a non-inferiority study comparing pregabalin to the 5% lidocaine patch, and the second stage was a combination therapy study of pregabalin plus the 5% lidocaine patch (Fig. 2 depicts the complete trial design for these studies). For treatment with the lidocaine patches, up to three or four lidocaine patches (depending on the size of the painful area} were applied to the painful area for up to 12 h within each 24-h period [20–22]. In

Table 3 Summary of gabapentinoid plus opioid combination studies

Study	Design	Indication	*N*	Treatment	Analgesic efficacy	Safety
Baron (2015) [23]	Randomized, controlled, multicenter trial	Low back pain (neuropathic)	313	1. Tapentadol PR + pregabalin 2. Tapentadol PR	No difference	TEAEs: Dizziness and somnolence higher in combination arm (43/159, 27%) than tapentadol arm (26/154, 17%)
Dou (2017) [24]	Randomized, controlled, single-center, cross-over trial	Neuropathic cancer pain	40	1. Morphine + pregabalin 2. Morphine	Minimal effective dose of morphine was statistically significantly lowered in combination with pregabalin vs. monotherapy	Combination treatment (pregabalin + morphine) associated with higher frequency of dry mouth and somnolence compared with placebo
Caraceni (2004) [25]	Randomized, controlled, multicenter trial	Neuropathic cancer pain	121	1. Gabapentin + opioid 2. Opioid	Average pain score was statistically significantly reduced in combination arm vs. monotherapy	Dropouts due to AEs: 6/80 in the combination group vs. 3/41 in the monotherapy group
Gilron (2005) [26]	Randomized, controlled, single-center, cross-over trial	DPN, PHN	57	1. Gabapentin + morphine 2. Gabapentin 3. Morphine 4. Placebo	Mean daily pain score was statistically significantly lower in the combination group vs. monotherapy groups	Combination groups had higher rates of constipation and dry mouth compared with monotherapy groups

Table 3 continued

Study	Design	Indication	*N*	Treatment	Analgesic efficacy	Safety
Hanna (2008) [27]	Randomized, controlled, multicenter trial	DPN	338	1. Gabapentin + oxycodone 2. Gabapentin	Pain scores were statistically significantly reduced in the combination group vs. monotherapy	The combination group had higher rates of constipation, nausea, vomiting, dizziness, fatigue and somnolence. The combination group had higher rate of dropouts due to AEs (27/169) vs. monotherapy (9/169)
Zin (2010) [28]	Randomized, controlled, single center	DPN, PHN	62	1. Pregabalin + oxycodone 2. Pregabalin	No difference	Dropouts because of AEs: 4/29 in the combination group vs. 0/33 in the pregabalin monotherapy group

Table 4 Summary of gabapentinoid plus antidepressant studies

Study	Design	Indication	*N*	Treatment	Analgesic efficacy	Safety
Holbech (2015) [29]	Randomized, controlled, multicenter, crossover trial	Polyneuropathy	73	1. Pregabalin + imipramine 2. Imipramine 3. Pregabalin 4. Placebo	The combination arm had lower pain score than monotherapy arms	Dropouts due to AEs higher on combination arm (7/73) vs. imipramine (3/73), pregabalin (2/73), or placebo (1/73). Frequent AEs include: tiredness, dizziness, and dry mouth
Tesfaye (2013) [30]	Randomized, controlled, multicenter trial	DPN	343	1. Pregabalin + duloxetine 2. Duloxetine 3. Pregabalin	No difference	No statistically significant differences between treatment groups for TEAE
Gilron (2009) [31]	Randomized, controlled, single-center trial	PHN, DPN	56	1. Gabapentin + nortriptyline 2. Nortriptyline 3. Gabapentin	Mean daily pain intensity was statistically significantly lowered during combination treatment vs. either monotherapy	At the maximum tolerated dose, dry mouth was significantly more frequent with nortriptyline or the combination therapy compared to gabapentin alone

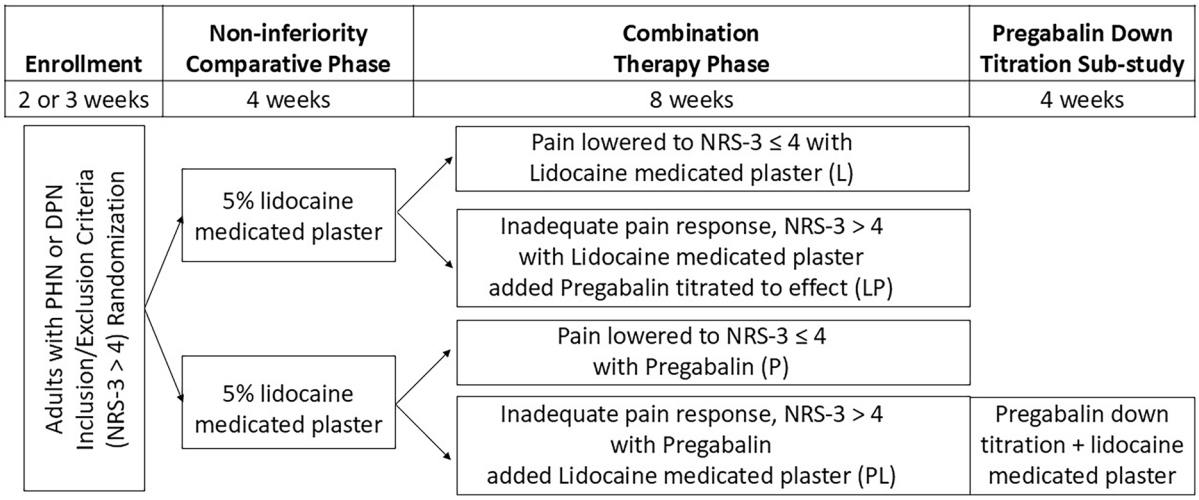

Fig. 2 Study design for the two-stage non-inferiority and combination therapy trial with pregabalin and the 5% lidocaine-medicated plaster of adults with PHN and DPN [20–22]*. *NRS-3 = average pain intensity over the last 3 days measured on the 11-point numerical rating scale (0 = no pain to 10 = worst pain imaginable)

the first stage of the study, 311 patients with DPN or PHN were treated in a randomized, open-label, multicenter, non-inferiority trial with randomization to either pregabalin or to the 5% lidocaine patch for 4 weeks and the results were presented by Baron et al. [21]. In the second stage, patients with inadequate pain relief from either arm of the first part were treated with combination therapy for 8 weeks with lidocaine patches added to those who took pregabalin in the first stage and with pregabalin added to those who used the lidocaine patch in the first stage [22]. Those patients who achieved adequate pain relief in the first stage continued on with monotherapy. The results of the second stage of the study are presented in Baron et al. [22]. A third publication on this trial reported specifically on the results for the patients with DPN in all the stages of the study [20]. In these studies, pain intensity was measured using NRS-3 scale, (11-point scale, 0=no pain, 10=pain as bad as you can imagine). Inadequate pain relief after the first part was defined as patients with NRS-3 scores that were>4 after the first 4 weeks of monotherapy.

In the first stage of the study, which lasted 4 weeks, the randomized non-inferiority trial segment, 66.4% and 61.5% of patients receiving lidocaine patches or pregabalin, respectively, achieved pre-defined responder criteria for pain relief. Further, only 5.8% of patients in the lidocaine group discontinued due to AEs while 25.5% of patients discontinued due to AEs in the pregabalin group. Although the first stage of this trial was a non-inferiority part, Baron et al. [21] concluded that first-line treatment with the lidocaine patch was more effective than pregabalin for patients with PHN and that the lidocaine patch and pregabalin were comparable and with patients with DPN.

The second, combination therapy, stage of the study continued over the next 8 weeks [22]. The adequate responders continued on their monotherapy regimen (either pregabalin or lidocaine patch) while the inadequate responders of each dosing group were treated with combination therapy. The inadequate responders from the lidocaine group (n=57) added pregabalin (LP group) to the existing lidocaine patch therapy and the inadequate responders from the pregabalin group (n=44) added lidocaine patches (PL group) to the existing pregabalin therapy [22]. Patients in both combination therapy groups (LP or PL) achieved clinically relevant reductions in pain values with improvements similar between the two groups (~48% reduction in pain intensity). The average NRS-3 scores of the LP group and PL group after the 4 weeks of monotherapy were at 6.1 and 5.7, respectively, before the addition of pregabalin and declined to 3.6 and 4.0, respectively, after the 4 weeks of combination therapy. There were

also improvements in patient treatment satisfaction and patient's global impression of change. AEs were in line with previous reports for the two treatments and combination therapy was generally well tolerated [22].

The second stage continued in the PL group with a 4-week study of the possible down titration of the pregabalin dose [22]. Patients in the PL group who had adequate response to combination therapy (combination therapy patients pregabalin first then with added lidocaine patches) ($n=31$) entered into a 4-week pregabalin down titration phase while continuing on the lidocaine patch (patients were taking 300 or 600 mg/day before the start of the down titration). For the patients with DPN, 20 out of 21 were able to reduce their pregabalin dose by at least 150 mg/day [22]. All ten of the patients with PHN were able to stop the pregabalin part of the combination therapy while maintaining sufficient analgesic efficacy using the lidocaine patch alone [22]. Thus, dose reductions or elimination of pregabalin therapy was achieved with lidocaine patch therapy.

The third publication about this study, Rehm et al. [20], reports the results for only the patients with PHN who were part of the Baron studies above. The patients with PHN who received pregabalin and then had lidocaine patches added for the combination therapy achieved a further 48% reduction in pain intensity comparing the combination therapy with the pregabalin monotherapy baseline [20]. Drug-related AEs occurred in 5.9% of patients with combination treatment (PL), most of them related to pregabalin [20]. The authors concluded that lidocaine 5% patch is at least as effective as pregabalin for pain relief in PHN with a favorable safety profile and a resulting positive benefit–risk ratio [20]. In patients unresponsive to either monotherapy, combination therapy provided additional efficacy and is well tolerated [20].

DISCUSSION

Topical lidocaine patches as an add-on therapy to gabapentinoids demonstrated clinically relevant reductions of pain in these trials while AEs were mild or moderate [17, 20–22]. Patients with NP and PHN, DPN or LBP were included in the trials. More tolerable safety profile may be attributed to lack of drug–drug interactions between the topical lidocaine patches and the systemic gabapentinoids and limited systemic drug exposure from lidocaine patches.

The randomized, open-label, non-inferiority phase reported by Baron et al. [21] demonstrating the non-inferiority of lidocaine patches to pregabalin adds evidence of the effectiveness of lidocaine patches as first-line therapy for NP. Down titration studies by Baron et al. [22] and Rehm et al. [20] suggest there can be other benefits from combination therapy with lidocaine patches, including the ability to lower the dose of the gabapentinoid after a period of combination therapy while maintaining efficacy, thus lowering the risk of AEs.

The data from these trials [17, 20–22] provides evidence that lidocaine patches used as add-on therapy to gabapentinoids can be effective in treating NP pain associated with DPN, PHN, and LBP with a minimal additive risk of AEs.

By contrast, data from studies using combination systemic therapies (opioids or antidepressants added to gabapentinoids) demonstrated mixed efficacy results. In each study, there is the concern of increased AEs, and the concern that AEs are increasing because of drug–drug interactions and additive systemic AEs. The reviews of Balanaser et al. [18] and Afonso et al. [8] took an intensive look at combination therapies for the treatment of NP. Neither systematic review found evidence that supported recommendations for regular use of any specific combination, with drug–drug interactions between the systemic agents as a limiting factor [8, 18].

The lidocaine patch studies cited here have limitations. These include that the combination stage of each study is not randomized, and there is no placebo control [17, 20–22]. Instead of randomized clinical trials, the patients in these studies were treated similarly to real-world practice. First, one drug is trialed, and in patients who get inadequate pain relief, multi-modal combination therapy is tried. With this scenario, in the lidocaine patch add-on trials, add-on therapy with lidocaine patches demonstrated an additional ~ 48% reduction in pain relief.

Table 5 Summary of gabapentinoid plus lidocaine patch studies

Study	Design	Indication	*N*	Treatment	Analgesic efficacy	Safety
White (2003) [16]	Open-label, non-randomized, multicenter trial	PHN, DPN, LBP	107	1. Gabapentin + lidocaine patch	BPI scores for worst, least, average, pain right now, and pain relief scores were statistically significantly lower compared with baseline	The most frequently reported treatment-related AEs were somnolence (1.9%), paresthesia (1.9%), and dermatitis (1.9%). All treatment-related AEs were mild to moderate
Baron (2009A) [20], Baron (2009B) [21]	Two-stage adaptive, randomized, open-label, multicenter, non-inferiority study followed by a combination therapy stage	PHN, DPN	311	1. Pregabalin + lidocaine patch 2. Pregabalin	Combination therapy resulted in clinically relevant reductions in pain values in addition to improvements achieved during the 4 weeks of pregabalin monotherapy. Considerable improvements in patients' treatment satisfaction were reported	Combination therapy was generally well tolerated
Rehm (2010) [20]	Randomized, open-label, multicenter, non-inferiority study	PHN	98	1. Pregabalin + lidocaine patch 2. Pregabalin	49% reduction in pain intensity with combination treatment (vs. monotherapy baseline)	Drug-related AEs occurred in 5.9% of patients with combination treatment (PL), most of them related to pregabalin

These two trials provide evidence that combination therapy with lidocaine patches can be effective against NP that occurs with conditions such as DPN, PHN, and LBP. This review and the cited studies using lidocaine patches as add-on therapy in NP [17, 20–22] are all sponsored and funded by companies producing and marketing lidocaine patches.

Looking beyond multimodal therapy with lidocaine patches involving gabapentinoids, two other studies support the use of lidocaine patches as add-on therapy in NP [32, 33]. Tsai et al. found in an open-label, single-arm trial that lidocaine topical patches reduced pain intensity in neuropathic cancer patients already receiving opioid treatment [32]. Martini et al., in a retrospective study of 130 patients in their database, found that the 5% lidocaine-medicated plaster was efficacious in patients with localized NP poorly responsive to pharmacological therapy [33].

More evidence for the benefits of multimodal therapy with lidocaine patches and plasters comes from a study by Li et al. that analyzed the lidocaine plaster in combination with gabapentin in the treatment of herpes zoster neuralgia [34]. Pain was reduced in the combination group compared to either monotherapy. They concluded that the combination had better analgesic effects in the treatment of herpes zoster neuralgia with fewer incidences of AEs and helped in some cases to reduce the dosage of gabapentin [34].

Despite the limitations, the studies strongly suggest that lidocaine patches are an efficacious, safe, and well-tolerated add-on treatment to gabapentinoids. More studies on the use of lidocaine patches as an add-on therapy for the treatment of NP may be valuable to pursue (see Table 5).

Lidocaine patches come in multiple forms that are bioequivalent, meaning they deliver the same amount of lidocaine to the skin (Table 6) [35–37]. They can differ in the amount of lidocaine in the patch, the percent of the lidocaine delivered, the thickness of the patch, the adhesive used, and the amount of adhesive [35–37]. They can also differ in their adhesive properties [38]. The generic lidocaine patches are similar to the Lidoderm patch in the amount and percent of lidocaine in the patch, the thickness of the patch, and the adhesive used. The lidocaine topical system 1.8% differs in many ways from these other patches. It is flexible and has been shown to adhere substantially better than the 5% lidocaine patches while delivering a bioequivalent amount of lidocaine [38]. Due to their superior adhesive properties, the lidocaine topical systems 1.8% provide more consistent drug delivery and greater utility in real-world settings [39–41].

Table 6 Characteristics and composition of prescription lidocaine topical formulations

Patch	Bioequivalent to Lidoderm patch	Design	Lidocaine	Lidocaine (mg)	Adhesive mix (g)	Relative thickness of DIA layer[a]	Adhesive
Lidoderm [36]		DIA	5%	700	14	1.0	Acrylic-based hydrogel
ZTlido [16]	Bioequivalent	DIA	1.8%	36	2.0	0.14	Polyisobutylene adhesive matrix
Generic 5% lidocaine patches [37]	Bioequivalent	DIA	5%	700	14	1.0	Acrylic-based hydrogel

DIA drug-in-adhesive

[a]Assumes density of DIA layers are approximately the same, as these patches are all the same size, 10 × 14 cm, the thickness of the DIA layer will be proportional to the amount of adhesive mix used

CONCLUSIONS

In the studies reviewed, combinations of systemic agents (gabapentinoid plus opioid or antidepressant) were associated with increased AEs and dropouts while improvement in efficacy was inconsistent. Combinations of systemic gabapentinoids plus topical lidocaine patches can improve efficacy with minimal additional AEs. Topical lidocaine patches, which are associated with minimal systemic adverse effects and have demonstrated benefits in various neuropathic pain (NP) conditions, can enhance the likelihood of achieving meaningful pain relief when used as adjuvant therapy.

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Declarations

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Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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