Review Article

Topical Treatment of Peripheral Neuropathic Pain: Applying the Evidence

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Abstract

Context. Patients with peripheral neuropathic pain (NP) may only achieve partial pain relief with currently recommended first-line oral treatments, which are also associated with systemic adverse events. Topical treatments are currently considered second- or third-line options, but a recent pharmacologic treatment algorithm has called for broader first-line use of these agents. This has highlighted a need to communicate the benefits associated with topical agents, in particular around the efficacy, targeted local action, and limited systemic availability resulting in minimal systemic adverse events and drug-drug interactions.

Objectives. This review aims to evaluate the evidence base for topical therapies currently used to treat peripheral NP, discuss the evidence comparing these treatments head-to-head with oral standard of care, and evaluate how they fit into treatment regimens in the "real world."

Methods. This is a narrative review.

Results. Two topical treatments are currently licensed: lidocaine 5% medicated plaster (post-herpetic neuralgia) and the capsaicin 8% patch (peripheral NP). When compared head to head with the oral standard of care (pregabalin), the lidocaine 5% medicated plaster provided similar relief of pain associated with post-herpetic neuralgia but did not meet the primary predefined criteria for noninferiority. The capsaicin 8% patch, however, demonstrated noninferior efficacy when compared head-to-head with pregabalin across a wide range of peripheral NP etiologies. Importantly, both treatments demonstrated effective pain relief without the systemic adverse events associated with oral therapies.

Conclusion. First-line use of topical agents may be of particular benefit in patients where the safety and tolerability of oral therapy is a concern. J Pain Symptom Manage 2017;53:614–629.

Key Words

Peripheral neuropathic pain, topical, capsaicin 8% patch, lidocaine 5% medicated plaster

Introduction

Neuropathic pain (NP) occurs when the nervous system itself is diseased or damaged[1] and has been defined as "occurring as a direct consequence of a lesion or disease of the somatosensory nervous system."[2] Peripheral NP, which includes conditions such as post-traumatic neuralgia, post-herpetic neuralgia (PHN), painful diabetic neuropathy (pDPN), and HIV-related neuropathy[3] is extremely challenging to treat.

International guidelines and recommendations from the European Federation of Neurological Societies[4] and the Special Interest Group on Neuropathic Pain (NeuPSIG) of the International Association for the Study of Pain[5] recommend oral medicines such as tricyclic antidepressants, anticonvulsants (including gabapentin and pregabalin), and selective serotonin and noradrenalin reuptake inhibitors as first-line options (Table 1). Despite becoming the mainstay of

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Table 1
Current Oral and Topical Therapies According to Guideline Recommendations for Use

Treatment	Daily dose/regimen	Guideline Recommendations	
		NeuPSIG[5]	EFNS[4]
Anticonvulsants			
Pregabalin	150–600 mg/day		First-line NP, except trigeminal neuralgia
	300–600 mg/day	First-line NP	
Gabapentin	1200–3600 mg/day	First-line NP	First-line NP, except trigeminal neuralgia
Gabapentin extended release or enacarbil	1200–3600 mg/day	First-line NP	
Antidepressants			
Tricyclic antidepressants	25–150 mg/day	First-line NP	First-line NP, except trigeminal neuralgia; safety concerns in the elderly
SNRI: Duloxetine	60–120 mg/day	First-line NP	First-line painful DPN
SNRI: Venlafaxine	150–225 mg/day	First-line NP	First-line painful DPN
Opioids			
Tramadol	200–400 mg/day	Second-line NP	Second-line NP, except select conditions[a]
Strong opioids	Individual titration	Third line	Second- or third-line NP
Cannabinoids			
Cannabinoids			Second-line MS and peripheral NP for refractory cases
Topical			
Lidocaine 5% medicated plasters	3 or fewer per day	Second-line peripheral NP; first line when there are concerns with side-effects or safety of first-line treatments, particularly in frail and elderly patients	First-line PHN, especially the elderly if there are concerns regarding CNS side effects
Capsaicin cream			Second-line PHN
Capsaicin 8% patches	One to four patches to the painful area for 30 minutes (feet) or 60 minutes (other areas of the body excluding above the neck) every three months	Second-line peripheral NP	Second-line painful HIV neuropathies or PHN
Other			
Botulinum toxin A	50–200 units, sc, to the painful area every three months	Third line, specialist use for peripheral NP	

NeuPSIG = Special Interest Group on Neuropathic Pain; EFNS = European Federation of Neurological Societies; NP = neuropathic pain; SNRI = serotonin-norepinephrine reuptake inhibitor; DPN = diabetic painful neuropathy; MS = multiple sclerosis; PHN = post-herpetic neuralgia; CNS = central nervous system; HIV = human immunodeficiency virus; sc = subcutaneous.
[a]Tramadol is recommended by the EFNS for second-line use, except for patients with exacerbations of pain (for the tramadol/acetaminophen combination) or for those with predominant co-existing non-neuropathic pain.

therapy for peripheral NP,[6] these oral therapies may provide only satisfactory pain relief in 30%–40% of patients[7] and are also associated with undesirable systemic side effects.[6,8] Consequently, many individuals with NP experience persistent pain, poor quality of life (QoL), and high health care use.[9]

Topical agents may be preferable to current first-line systemic therapies; localized activity and low systemic absorption avoids issues associated with oral or intravenous routes, such as gastric disturbances and variable serum concentrations, and results in a low risk of drug-drug interactions.[10,13] Two topical treatments are currently licensed by the European Medicines Agency (EMA) for peripheral NP: lidocaine 5% medicated plaster for PHN only[11] and the capsaicin 179 mg (8% w/w) cutaneous patch (capsaicin 8% patch) for all types of peripheral NP.[12] Both the capsaicin 8% patch and lidocaine 5% patch are approved for the management of NP associated with PHN by the Food and Drug Administration.[13,14]

The NeuPSIG of the International Association for the Study of Pain has recently updated its recommendations for the pharmacologic management of peripheral NP.[5] These recommendations take into account the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system of evaluation, which look at quality of evidence, effect size, tolerability and safety, and values and preferences (Table 2). Although the tricyclic antidepressants, gabapentinoids, and serotonin-norepinephrine reuptake inhibitors remain first-line treatment options, the topical lidocaine 5% medicated plaster and capsaicin 8% patch are now recommended as second-line therapy for peripheral NP. It is worth noting, however,

Table 2
Summary of GRADE Recommendations for Capsaicin 8% Patch and Lidocaine 5% Medicated Plaster[5]

GRADE Category	Capsaicin 8% Patch	Lidocaine 5% Medicated Plaster
Quality of evidence	High	Low
Balance between desirable and undesirable effects		
Effect size	Low	Unknown
Tolerability and safety[a]	Moderate-high	High
Values and preferences	High	High
Cost and resource allocation	Moderate-high	Moderate-high

GRADE = Grading of Recommendations Assessment, Development, and Evaluation.
[a]Common side effects: lidocaine 5% medicated plaster: local irritation; capsaicin patches: local pain, edema, and erythema.

that since the publication of these guidelines, further evidence has been made available demonstrating noninferiority of the capsaicin 8% patch to pregabalin in a head-to-head trial (A Study to Compare QUTENZA With Pregabalin for the Treatment of Peripheral Neuropathic Pain (PNP) After 8 Weeks of Treatment [ELEVATE]).[15] The evidence for topical clonidine was found to be inconclusive.[5]

Following a review of current guidelines and the evidence to date, a new pharmacologic treatment algorithm for localized NP has suggested that primary care physicians and non-pain specialists should consider first-line use of topical analgesic agents more broadly.[16] Under the proposed model, patients with a "good response" should continue treatment, those with a "partial response" should have systemic therapy added, and those with "no response" should switch to systemic therapy and/or be referred to a pain specialist. The authors noted that education around the efficacy, limited systemic adverse events, and drug-drug interactions is needed to encourage widespread adoption of topical treatments in the first-line setting.

This review aims to address this educational need by evaluating and discussing the evidence base for topical therapies in patients with peripheral NP and assessing how these topical agents fit into clinical practice. Importantly, this review also highlights and contextualizes findings from direct, head-to-head studies of topical treatments vs. oral standard of care, including the ELEVATE trial of the capsaicin 8% patch vs. pregabalin for the treatment of peripheral NP, which was recently published.[15]

Evidence for Lidocaine

The lidocaine 5% medicated plaster was first registered in 1999 in the United States and has been approved by both the EMA and the U.S. Food and Drug Administration for the symptomatic relief of NP associated with previous herpes zoster infection (i.e., PHN) in adults.[11] Its exact mechanism of action is uncertain, but the primary clinical target is understood to be concerned with interrupting the action potential on neurons through voltage-gated sodium channels, to which it binds in a 1:1 ratio.[17] Long-term pain relief with the lidocaine 5% medicated plaster may be because of both reduced peripheral nerve input (counteracting central sensitization) and reduced nerve fiber density in the epidermis.[18,19]

Each 10 × 14 cm lidocaine medicated plaster contains 700 mg (5% w/w) of lidocaine in a white hydrogel plaster, and a maximum of three patches can be applied once for up to 12 hours within a 24-hour period.[11] Patients can apply the patch themselves, although it is recommended that they are re-evaluated after two to four weeks to ensure analgesic benefit is achieved. Only around 3% of the lidocaine is systemically absorbed, but potential risks from secondary metabolites mean that long-term treatment with lidocaine 5% medicated plasters is only recommended if there is a therapeutic benefit for the patient, and caution is advised in those with severe hepatic or renal impairment.[11]

Evidence for the Approval of Lidocaine

Positive results for the lidocaine 5% medicated plaster were first seen in a few small placebo-controlled (vehicle patch) clinical trials, mainly in PHN, showing this topical medication to be generally effective and well tolerated (Table 3).[20–26] In particular, one randomized, placebo-controlled, two-way, crossover study in 40 patients with peripheral NP (of various causes) found the lidocaine 5% medicated plaster to be effective in relieving ongoing pain ($P = 0.017$) and allodynia ($P = 0.023$) within the first eight hours after application, with effects lasting up to one week.[25] However, the recent GRADE analysis of the evidence for the lidocaine 5% medicated plaster by NeuPSIG found the quality of evidence to be low and only recommends the treatment as a second-line option in patients with PHN.[5]

Head-to-Head Evidence for Lidocaine vs. Oral Standard of Care

To date, only one study has compared the lidocaine 5% medicated plaster directly with an oral standard of care.[27] In this open-label, multicenter noninferiority

Table 3

Randomized, Double-Blind Studies Providing Evidence for Lidocaine 5% Medicated Plaster Therapy in Patients With Peripheral NP

Study design	Patient population	Primary Outcomes: Efficacy	Primary Outcomes: Safety	Associated publication
Lidocaine 5% medicated plaster[28]				
Lidocaine 5% medicated plaster vs. placebo plaster SC, R, DB, PC, CO study One plaster applied for 12 hours, followed by plaster-free interval of 12 hours. 14-day treatment period, separated by a 14-day washout	Severe unilateral inguinal post-herniorrhapy pain (more than six months) $n = 21$	• Primary end point: percentage change in summed pain intensity (six median values, 2× daily assessments for three days) • Results: Lidocaine 5% medicated plaster: 6.6% Placebo: 0.4% $P = 0.33$	Only one AE: mild erythema with lidocaine and placebo treatment (resolved after completion)	Bischoff et al. (2013)
Lidocaine 5% medicated plaster vs. placebo plaster MC, EE, R, W study Eight-week, OL phase followed by two-week, DB, PC phase; up to three plasters applied for ≥12 hours daily	PHN $n = 263$ (OL phase) $n = 71$ (DB phase)	• Primary end point: Time-to-exit (two-point reduction or more in pain relief on two consecutive days using six-point VAS in DB phase) • Results: Lidocaine 5% medicated plaster: 13.5 days (FAS), 14 days (PP) Placebo plaster: 9.0 days (FAS), 6 days (PP) • $P = 0.151$ (FAS), $P = 0.0398$ (PP)	• Most common drug-related AEs were skin and subcutaneous tissue disorders; no SAEs considered drug related • Total drug-related AEs: 12.8% OL phase: 16.0% • DB phase: 4.2%	Binder et al. (2009)[b]
Lidocaine 5% medicated plaster vs. placebo plaster MC, R, DB, PC, two-period, CO study Four-week treatment period, up to three plasters, applied for ≤18 hours	Cancer patients with postsurgical incisional pain for one month or more $n = 28$	• Primary end point: Average weekly pain intensity rating • Results: Lidocaine 5% medicated plaster: 4.1 Placebo: 3.8 $P = 0.36$	• Reported toxicities were not significantly different for either group or time period	Cheville et al. (2009)
Lidocaine 5% medicated plaster vs. vehicle plaster MC, R, DB, PC, two-way, CO study 2× seven-day treatment periods, up to four plasters applied for ≥12 hours daily for seven days	Peripheral NP $n = 58$ (PHN $n = 32$)	• Primary end point: Ongoing pain intensity from two hours to seven days compared with pretreatment levels • Results: Lidocaine: pain intensity decreased at all time points ($P < 0.001$) Placebo: pain intensity decreased at all time points ($P < 0.05$)	• Frequency of events did not differ between the lidocaine and placebo groups Lidocaine phase AEs: $n = 20$ Placebo phase AEs: $n = 17$	Meier et al. (2003)
Lidocaine 5% medicated plaster vs. placebo plaster Two-center, R, DB, PC, parallel-group study	PHN $n = 96$	• Primary outcome: Efficacy variables of NPS subitems[a] • Results: Lidocaine 5% medicated plaster was statistically superior to	• Not reported	Galer et al. (2002)[b]

(*Continued*)

Table 3
Continued

Study design	Patient population	Primary Outcomes: Efficacy	Primary Outcomes: Safety	Associated publication
Treatment duration three weeks		vehicle patch in all four composite analyses: • NPS 10 ($P = 0.043$); NPS 8 ($P = 0.042$), NPS NA ($P = 0.022$), and NPS 4 ($P = 0.013$)		
Lidocaine 5% medicated plaster vs. placebo (vehicle) plaster Two-center, EE, R, W study. More than one-month (OL) lidocaine 5% medicated plaster followed by 2× two-week DB, PC, CO with no washout. Up to three plasters applied for ≥12 hours daily for ≤28 days.	PHN $n = 32$	• Primary end point: Time to exit (two-point reduction or more in pain relief on two consecutive days using six-point VAS) • Results: Lidocaine plaster: >14 days Placebo (vehicle): 3.8 days $P < 0.001$	• No statistical difference between lidocaine 5% and placebo plasters with regard to AEs	Galer et al. (1999)[b]
Lidocaine 5% medicated plaster vs. placebo (vehicle) plaster SC, R, DB, PC, CO study Four sessions: 2× lidocaine 5% medicated plaster, 1× placebo patch (and 1× session with observation only), up to three plasters applied for ≥12 hours daily	PHN $n = 40$	• Primary assessment: Pain intensity (assessed using VAS) • Results: Mean pain intensity (VAS) reduced with lidocaine compared with vehicle (4–12 hours; $P \leq 0.038$) or no treatment (0.5–12 hours; $P \leq 0.21$)	• Patches were well tolerated and without systemic adverse events	Rowbotham et al. (1996)[b]

NP = neuropathic pain; SC = single center; R = randomized; DB = double blind; PC = placebo controlled; CO = cross over; AE = adverse event; MC = multicenter; EE = enriched enrollment; W = withdrawal; OL = open label; PHN = post-herpetic neuralgia; VAS = visual analogue scale; FAS = full analysis set; PP = per protocol; SAE = serious adverse event; NPS = Neuropathic Pain Scale.
[a]NPS 10: The sum of all 10 NPS descriptors (on a scale of 0–100); NPS 8: a standardized average score defined as the sum of the scores of all 8 descriptor subitems (other than "intensity" and "unpleasant"), normalized to range 0–100; NPS NA: a standardized average score defined as the sum of the scores of all 8 subitems, not intended to include measurement of allodynia/hyperalgesia (i.e. other than "skin sensitivity" and "surface pain"), normalized to range 0–100; NPS 4): a standardized average score defined as the sum of the scores of 4 descriptors— "sharp," "hot," "dull," and "deep" pain—normalized to range 0–100.
[b]Lidocaine study supporting license approval.

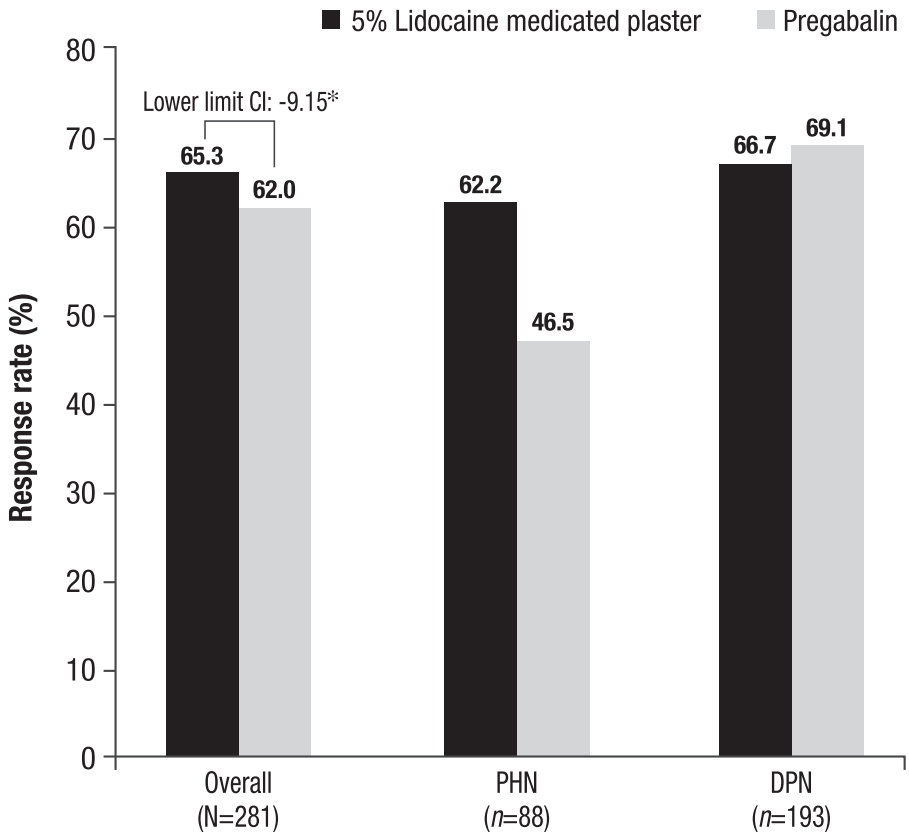

Fig. 1. Response rate after treatment with lidocaine 5% medicated plaster or pregabalin in patients with PHN and DPN (PPS).[27] CI = confidence interval; DPN = painful diabetic polyneuropathy; PHN = post-herpetic neuralgia; PPS = per protocol set. "*" Indicates below the predefined margin for noninferiority of −8 percentage points.

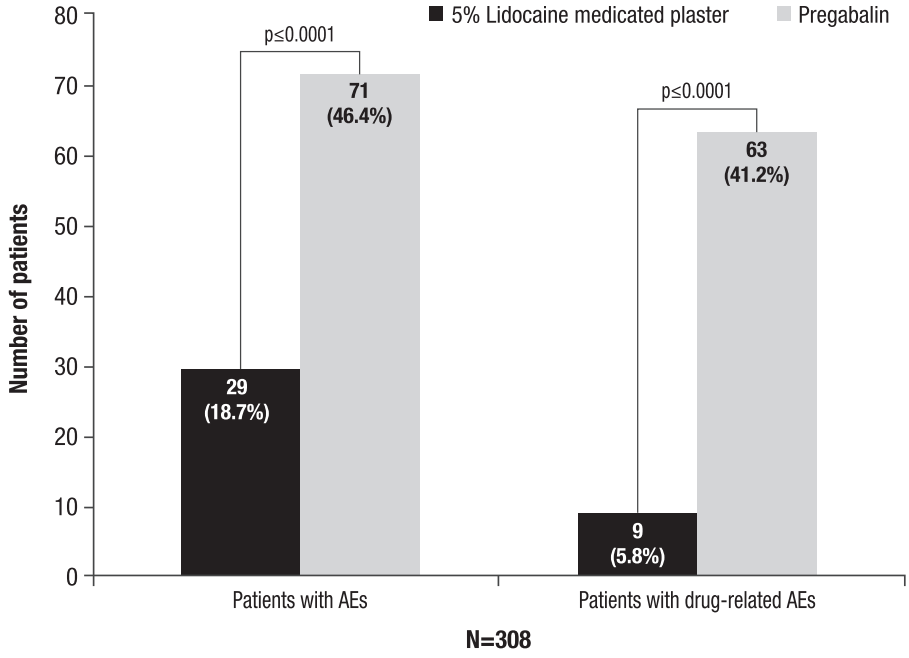

Fig. 2. Treatment-emergent and drug-related adverse events with lidocaine 5% medicated plaster and pregabalin (SAS).[27] AE = adverse event; SAS = safety analysis set.

Table 4
Randomized, Double-Blind Studies Providing Evidence for Capsaicin 8% Patch in Patients with Peripheral NP

Study design	Patient population	Primary Outcomes: Efficacy	Primary Outcomes: Safety	Associated publication
Capsaicin 8% patch studies[35,36,38]				
Capsaicin 8% patch vs. placebo patch DB, R, PC, MC study 1× 30-minute treatment to feet	PDPN (feet) $n = 369$	• Primary end point: percentage change in average daily pain from baseline to between weeks 2 and 8 Capsaicin 8% patch: −27.4% Placebo patch: −20.9 • $P = 0.025$	• TEAEs: Capsaicin 8% patch: 46.8% Placebo patch: 33.9% • Majority of TEAEs mild to moderate in severity • Three patients with severe drug-related TEAEs (application site reactions, all in capsaicin 8% patch group)	Simpson et al. (2017)
Capsaicin 8% patch (30 or 60 minutes) vs. SOC alone MC, OL, R, controlled safety study Repeat treatment (up to 7, ≥8-week intervals over 52 weeks) with 30- or 60-minute capsaicin 8% patch application to feet, or SOC alone	PDPN (feet) $n = 468$	• Efficacy end point: mean percentage change in average pain Capsaicin 8% patch: −37.5% (30 minutes); −40.8% (60 minutes) • SOC alone: −13.9%	• Primary end point: reduction in Norfolk QoL-DN total score from baseline to EoS Capsaicin 8% patch: −27.6 (30 minutes); −32.8% (60 minutes) SOC alone: −6.7% • PRAEs: Capsaicin 8% patch: 67.3% (30 minutes), 69.4% (60 minutes) • SOC alone: 48.4	Vinik et al. (2015)
Capsaicin 8% patch vs. capsaicin 0.04% patch DB, R, controlled study 1 × 30- or 60-minute application	Painful HIV-AN; $n = 494$	• Primary end point: mean percentage change in NPRS score from baseline to weeks 2−12 Capsaicin 8% patch: 29.5% reduction (30 + 60 minutes); 30.0% reduction (60 minutes); 19.1% reduction (30 minutes) Capsaicin 0.04% patch: 24.5% reduction $P = 0.097$	• Mild-to-moderate transient application site pain and erythema were the most common AEs: Capsaicin 8% patch group: 90% control group: 62% • More patients treated with capsaicin 8% patch vs. control had severe application site events: 19% vs. 2%, respectively	Clifford et al. (2012)
Capsaicin 8% patch vs. capsaicin 0.04% patch MC, DB, R, conformational study 1 × 60-minute treatment	PHN; $n = 418$	• Primary end point: percentage change in NPRS score from baseline to weeks 2−8 • Results: Capsaicin 8% patch: 32.0% Capsaicin 0.04% patch: 24.4% $P = 0.011$	• TEAEs were mainly application site specific: Capsaicin 8% patch: 96% Capsaicin 0.04% patch 78% • These AEs were transient and mild-to-moderate in severity	Irving et al. (2011)
Capsaicin 8% patch vs. capsaicin 0.04% patch MC, DB, R, PG, PC study 1× 60-minute treatment, 12-week study duration	PHN; $n = 402$	• Primary end point: percentage change in NPRS score from baseline to weeks 2−8 • Results: Capsaicin 8% patch: 29.6% Capsaicin 0.04% patch: 19.9% $P = 0.001$	• Higher incidence of AEs with capsaicin 8% patch due mainly to local application-site reactions Capsaicin 8% patch: 99% • Capsaicin 0.04% patch: 88%	Backonja et al. (2008)

Capsaicin 8% patch (treatment) vs. capsaicin 0.04% patch (control) MC, DB, R, controlled study 1× 30-, 60-, or 90-minute application	Painful HIV-AN $n = 307$	• Primary end point: percentage change in NPRS score (average pain in last 24 hours) from baseline to weeks 2–12 • Results: Capsaicin 8% patch group: 22.8% Capsaicin 0.04% patch: 10.7% reduction for controls $P = 0.0026$	• Self-limited, mild-to-moderate local skin reactions commonly observed	Simpson et al. (2008)

NP = neuropathic pain; DB = double blind; R = randomized; PC = placebo controlled; MC = multicenter; TEAE = treatment emergent adverse event; OL = open label; Norfolk QoL-DN = Norfolk Quality of Life–Diabetic Neuropathy; PRAE = post-randomization adverse event; HIV-AN = human immunodeficiency virus-associated neuropathy; NPRS = Numeric Pain Rating Scale; AE = adverse event; PHN = post-herpetic neuralgia; PG = parallel group.

trial, 311 patients with PHN or pDPN were randomized 1:1 to either pregabalin (two times daily, titrated to effect) or 5% medicated plaster. The primary end point was response rate at four weeks in the per protocol set (PPS; $n = 281$), defined as pain reduction averaged over the last three days from baseline of two points or more or an absolute value of four points or less on the Numeric Pain Rating Scale. Noninferiority was not shown for the lidocaine 5% medicated plaster compared with pregabalin for the primary end point (65.3% vs. 62.0%, respectively; $P < 0.007$; confidence interval [CI] lower limit of −9.15, which was below the predefined margin of −8 percentage points). However, for a group of 88 patients with PHN (which is the licensed indication), a higher response was seen in those patients treated with the lidocaine 5% medicated plaster than with pregabalin (62.2% vs. 46.5%, respectively) (Fig. 1).

Importantly, patients in the lidocaine 5% medicated plaster group experienced significantly fewer adverse events (either treatment emergent or drug related) compared with the pregabalin group ($P < 0.0001$) (Fig. 2). Overall, 16/48 adverse events reported by patients who received the lidocaine 5% medicated plaster were drug related, the most common being headache and application site irritation. In contrast, 161 of 194 adverse events reported by pregabalin recipients were drug related; these were commonly related to the nervous system, gastrointestinal tract, or general disorders, such as fatigue.[27]

Fig. 3. Achievement of a ≥30% decrease in NPRS score from baseline to Week 8 (FAS) with capsaicin 8% patch vs. pregabalin.[15] CI = confidence interval; FAS = full analysis set; NPRS = Numeric Pain Rating Scale.

Table 5
Treatment-Emergent Adverse Events with Capsaicin 8% Patch Compared with Pregabalin in ELEVATE Study[15]

TEAE	Capsaicin 8% patch, $n = 282$	Pregabalin, $n = 277$
Overall n (%)	173 (61.3)	151 (54.5)
Application site pain	67 (23.8)	0 (0.0)
Erythema	59 (20.9)	1 (0.4)
Burning sensation	44 (15.6)	0 (0.0)
Application site erythema	25 (8.9)	0 (0.0)
Pain	15 (5.3)	2 (0.7)
Headache	3 (1.1)	26 (9.4)
Abdominal pain upper	2 (0.7)	8 (2.9)
Nausea	1 (0.4)	30 (10.8)
Asthenia	1 (0.4)	9 (3.2)
Dizziness	0 (0.0)	51 (18.4)
Somnolence	0 (0.0)	43 (15.5)
Weight increased	0 (0.0)	17 (6.1)
Vertigo	0 (0.0)	14 (5.1)
Dry mouth	0 (0.0)	13 (4.7)
Fatigue	0 (0.0)	12 (4.3)
Peripheral edema	0 (0.0)	11 (4.0)
Disturbances in attention	0 (0.0)	8 (2.9)
Diarrhea	0 (0.0)	7 (2.5)
Days free from drug-related TEAE, %	90.5	70.4

TEAE = treatment-emergent adverse event.

Patient perception and satisfaction play an important role in the treatment of peripheral NP. Overall, irrespective of treatment group, two-thirds of patients with PHN reported their treatment satisfaction to be "good," "very good," or "excellent." Notably, mean change for the EuroQol five dimensions questionnaire (EQ-5D) estimated health state score from baseline and Patient Global Impression of Change Scale favored the lidocaine 5% medicated plaster indicating improved health-related QoL with topical medication. The differences between the patient subpopulations for efficacy and patient-reported outcomes suggest that patients with PHN may particularly benefit from topical treatment. This is reflected by the indication of the lidocaine 5% medicated plaster for the symptomatic relief of NP associated with PHN in adults.[11,12]

Other Evidence for Lidocaine

The paucity of double-blind randomized clinical trials evaluating lidocaine for the treatment of peripheral NP has been highlighted in a recent Cochrane review, which identified 12 studies ($n = 508$) all comparing topical lidocaine with placebo.[28] The review identified that various formulations had been used (i.e., 5% medicated plaster, gel and cream and an 8% spray) in studies of differing designs, each involving relatively few participants with various neuropathic conditions outside the current license. The studies were mainly of short duration (i.e., up to 12 weeks) and it was not possible to determine whether the early response to topical lidocaine is maintained long term. The authors, therefore, concluded that the available studies support the use

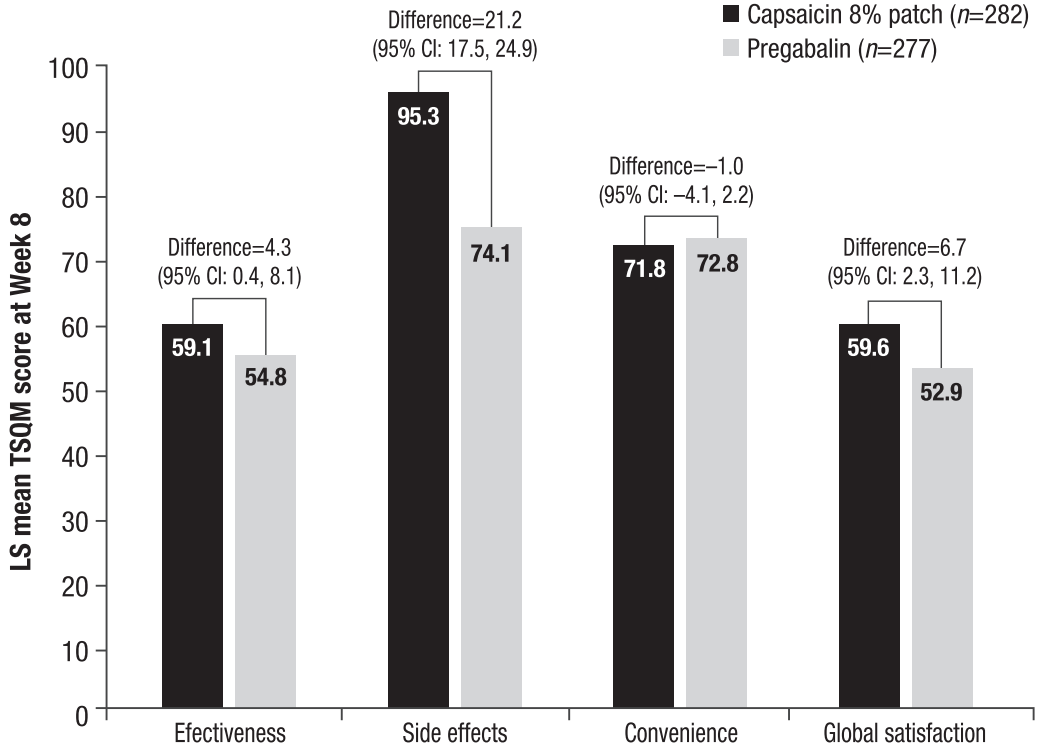

Fig. 4. Treatment satisfaction scores for medication use at Week 8 with capsaicin 8% patch vs. pregabalin.[15] CI = confidence interval; LS = least square; TSQM = Treatment Satisfaction Questionnaire for Medication.

of topical lidocaine 5% medicated plasters in patients with PHN and noted that that this topical treatment is well tolerated in the short term.[28]

Evidence for Capsaicin

The capsaicin 8% patch was first approved for nondiabetic patients with peripheral NP but has subsequently received EU approval for a label extension to include all patients with peripheral NP, either alone or in combination with other medicinal products for pain.[12] Capsaicin is the active component in fruits of the genus *Capsicum* and an agonist of the transient receptor potential vanilloid-I receptor (TRPVI).[29] It causes an initial enhanced sensitivity of TRPV1-expressing cutaneous nociceptors, followed by persistent desensitization leading to a durable analgesic effect.[30] Morphologically, capsaicin causes a significant reduction in epidermal nerve fiber density, recovering after 24 weeks in healthy volunteers.[30]

Each 14 × 20 cm patch is designed to deliver a single therapeutic dose of capsaicin over 30 minutes (feet) or 60 minutes (other locations), after which time the patch is removed. The treatment area should be determined and marked by a physician, and only a physician (or healthcare professional under the supervision of a physician) should apply the capsaicin 8% patch. A maximum of four patches can be applied in a single treatment, which may be repeated every 90 days if required.[12]

Evidence for the Approval of Capsaicin 8% Patch

The approval of the capsaicin 8% patch was based on randomized, double-blind, placebo-controlled studies in patients with PHN,[31,32] painful HIV neuropathy,[33,34] and pDPN,[35–37] which have demonstrated rapid and sustained pain relief after a single treatment,[31–35] and long-term safety and efficacy of repeat treatments over 52 weeks.[36,37] The most recent of these studies A Study to Evaluate Efficacy and Safety of a Single Application of Capsaicin 8%Transdermal Delivery System Compared to Placebo in Reducing Pain Intensity in Subjects With Painful Diabetic Peripheral Neuropathy (PDPN) (STEP)[35] was the first assessment of the efficacy and safety of the capsaicin 8% patch vs. placebo in patients with pDPN. Patients treated with the capsaicin 8% patch showed statistically significant improvements in pain relief ($P = 0.025$) and sleep quality ($P = 0.030$) compared with placebo, and treatment was well tolerated with no associated sensory deterioration or new safety concerns (Table 4).

The recent NeuPSIG GRADE analysis found the quality of evidence for the capsaicin 8% patch to be high (Table 2), and currently recommends the capsaicin 8% patch as second-line treatment of peripheral NP.[5]

Head-to-Head Evidence for Capsaicin 8% Patch Vs. Oral Standard of Care

The recent head-to-head, open-label, randomized (1:1), multicenter, noninferiority study (ELEVATE) is the only randomized controlled trial to directly compare the capsaicin 8% patch with a first-line oral treatment.[15] This study assessed the efficacy and tolerability of the capsaicin 8% patch with pregabalin in 559 nondiabetic adult patients with various etiologies of peripheral NP.[15] Importantly, patients had to be either naive to treatment with the capsaicin 8% patch and either naive to treatment with pregabalin and gabapentin, or, in the opinion of the investigator, had not received adequate treatment with pregabalin or gabapentin. The primary outcome of efficacy was ≥30% pain relief from baseline to Week 8, and the primary analysis was performed in the full analysis set (FAS) and PPS. The capsaicin 8% patch was shown to provide noninferior pain relief to an optimized dose of pregabalin; the primary outcome was achieved by 55.7% of patients in the capsaicin 8% patch group and by 54.5% in the pregabalin group (FAS). The difference (capsaicin 8% patch−pregabalin) in the proportion of responders was 1.2% for the FAS analysis, with an odds ratio 1.03 (95% CI 0.71, 1.50), which was above the predefined margin for noninferiority of 0.693 (Fig. 3); analysis of the PPS population also found the capsaicin 8% patch to be noninferior to pregabalin (odds ratio 1.03, 95% CI 0.70, 1.52). In addition, time to onset of pain relief was found to be significantly shorter with capsaicin 8% patch vs. pregabalin (7.5 vs. 36.0 days, respectively; $P < 0.0001$).

To reflect current clinical practice and to try to minimize the occurrence of treatment-emergent adverse events (TEAEs) as much as possible, the study included an up- and down-titration scheme for pregabalin, performed over a period of four weeks, with the optimal dose maintained from weeks 4 to 8. Although the number of TEAEs was higher with the topical capsaicin 8% patch, compared with pregabalin, it was associated with fewer systemic side effects (Table 5). TEAEs with the topical patch were largely application-related site reactions, which were generally mild-to-moderate and did not lead to study drug discontinuation in any patient. In contrast, 24 patients (8.5%) withdrew from the pregabalin group due to TEAEs. Three serious adverse events were reported in the study: one with the capsaicin patch (burn at application site) and two with pregabalin (cardiac failure and swollen tongue). Overall, a greater proportion of patients withdrew from the study because of either a lack of efficacy or insufficient tolerability with pregabalin (9.7%), compared with the capsaicin 8% patch (0.7%), and more capsaicin-treated patients

were willing to continue treatment by study end compared with those treated with pregabalin (78.4 vs. 66.4%, respectively). Furthermore, the ELEVATE study highlighted significant differences in patient perception of effectiveness, side effects, and global satisfaction (Fig. 4), all favoring the capsaicin 8% patch.[15]

Other Evidence for Capsaicin 8% Patch

The study findings that led to the approval of the capsaicin 8% patch are supported by a Cochrane review of six randomized, double-blind, placebo-controlled studies involving 2073 patients: four studies of PHN and two of painful HIV neuropathy.[38] More patients achieved high levels of controlled pain relief with the capsaicin 8% patch vs. control (0.04% capsaicin for blinding), and patients with high levels of pain relief also reported additional improvements in sleep, fatigue, depression, and an improved QoL. Serious adverse effects were no different between the two groups[38]; however, a lack of long-term safety data after repeated applications was noted at the time.

Safety and Effectiveness of Repeated Administration of QUTENZA Patches for Treatment of Pain Caused by Nerve Damage (STRIDE) was the first prospective study to assess the long-term safety, tolerability, and analgesic effectiveness of capsaicin 8% patch repeat treatment (up to six retreatments) over 52 weeks, in 306 patients with a broad range of peripheral NP etiologies.[39,40] Repeated treatment with the capsaicin 8% patch was well tolerated and did not result in a detrimental change in sensation or raise any new safety concerns.[40] Although a large proportion of patients discontinued the study (130 patients, 42.5%), only 1% of cases were due to drug-related TEAEs.[40] Furthermore, the capsaicin 8% patch was associated with a substantial and sustained reduction of pain; the overall change in average daily pain intensity was −2.1 (SD 1.7; 95% CI −2.46 to −1.78) from baseline to Month 12 for 100 patients who received four consecutive capsaicin 8% patch applications. Patient Global Impression of Change also improved with capsaicin 8% patch treatment: just more than 31% of patients reported themselves to be "very much improved" or "much improved" at the end of this long-term study.[39]

Evidence for Other Topical Therapies

Topical administration of locally acting agents, including cannabinoids, has been reported on a case-study basis, but no evidence from randomized controlled trials is available to discuss. Botox injections have some evidence base for pain relief supported by a few small clinical trials but fall outside the scope for this review because of the subdermal, injection-based application process.

Investigational data for topical clonidine, amitriptyline, and ketamine are available for discussion.

Topical Clonidine

Topical clonidine, an α-adrenergic receptor agonist, is currently under investigation for the treatment of peripheral NP because of its locally mediated effect that may reduce hypersensitivity after nerve injury.[41,42] Its potential to provide pain relief in some patients was first shown in two early small trials in sympathetically maintained pain (six patients)[43] and pDPN (41 patients).[44] The pDPN study was a two-stage, double-blind, randomized, enrichment study; although no significant difference between topical clonidine and placebo was observed in the first one-week treatment period, a significant difference was achieved in the second phase. This involved only 12 responders from the first phase who reported 20% reduction in pain with clonidine than placebo ($P = 0.015$).[44] A post hoc analysis of these data suggested that patients who describe their pain as being sharp and shooting have a greater likelihood of responding to clonidine. In a small pilot open-label study of 17 patients with orofacial pain, only partial pain reduction with topical clonidine was reported in five of 10 patients with "neuropathic pain" other than trigeminal neuralgia; however, more promising pain relief was reported in four of seven patients with "neuralgia-like" pain,[45] which would confirm the previous study finding that clonidine may be more effective in paroxysmal pain.

Although findings from these initial observations were varied, they provided the rationale for exploring topical clonidine in a randomized (1:1) double-blind, placebo-controlled clinical trial of 179 patients with pDPN.[46] Topical clonidine was found to be well tolerated, with no serious adverse events reported and was more effective compared with placebo ($P < 0.05$) for those patients who felt pain when exposed to capsaicin (used as a test of nociceptor function). Therefore, patients with pDPN who have functional nociceptors may potentially benefit from this type of topical treatment, but its use in this population is currently unlicensed and further clinical trials are warranted.

Amitriptyline and Ketamine

Amitriptyline is an antidepressant with notable action across a wide range of ion channels and receptors.[47–49] Although the extensive number of target sites has led to limited use of amitriptyline as an oral therapy due to adverse events, local administration of amitriptyline has been investigated as a potential candidate for the treatment of peripheral NP. These studies include several topical formulations of varying doses and investigate its use both as

monotherapy and in combination with topical ketamine, an anesthetic agent usually administered orally or via subcutaneous infusion.

One double-blind, placebo-controlled crossover study randomized 35 patients with postsurgical NP ($n = 13$), PHN ($n = 8$), or diabetic painful neuropathy ($n = 14$) to apply 5% amitriptyline, 5% lidocaine, or placebo twice daily for one week. No statistical significance for either amitriptyline or lidocaine was reached compared with placebo, although the authors noted that lack of efficacy might have been because of low baseline pain scores.[50]

A pilot double-blind study evaluating the topical combination of 1% amitriptyline and 0.5% ketamine failed to show a treatment effect after a treatment period of two days. However, an open-label extension of up to one week in 11 patients did demonstrate significant pain relief from days 3 to 7 with the combination cream vs. placebo.[51] A larger double-blind study in 92 patients with diabetic neuropathy ($n = 20$), PHN ($n = 14$), and postsurgical/post-traumatic pain ($n = 58$) randomized patients to one of four creams (placebo, 2% amitriptyline, 1% ketamine, or 2% amitriptyline−1% ketamine combined) three times daily for three weeks. No significant effect was found for any treatment compared with placebo at the primary end point (Week 3)[52]; however, a six-month, open-label extension of the study completed by 21 patients (diabetic neuropathy [$n = 3$]; PHN [$n = 2$]; postsurgical/post-traumatic pain [$n = 16$]) found that by Month 6, patients reported an average of 34% reduction in pain, with five patients reporting 50% reduction or more in pain and one achieving 100% reduction in pain.[53]

Importantly, in all these studies, blood assessments revealed minimal systemic absorption and few adverse events were reported. Taken together, these studies show the potential benefit of topical amitriptyline and ketamine in providing pain relief, but further randomized trials are needed to establish the appropriate dose and length of treatment to fully understand the role of this combination in treating peripheral NP.

Observational, Noninterventional, and Retrospective Evidence for Topical Treatments

When considering the different therapeutic approaches, it is important to take account of data from observational, noninterventional, and retrospective studies. These data often have the advantage of high patient numbers and can be used post-approval to help to identify patient types that most benefit from treatment. These data can also provide an opportunity to investigate how treatments are being integrated within clinical practice. Few data of topical patch use in patients with peripheral NP outside randomized, controlled trials have been published, but those that are available provide further support to the evidence base.[54–56]

Observational Evidence for Lidocaine 5% Medicated Plaster

Only one large, retrospective, observational study has investigated the efficacy and safety of the lidocaine 5% medicated plaster in a cohort of French patients ($n = 467$) who had been treated in pain centers between 2001 and 2006 with various types of peripheral NP. Overall, 20.6% of the patients had PHN (the current indication) and more than three-quarters (76.3%) had other types of peripheral NP including post-surgery pain, post-traumatic pain, and cancer-related pain.[54] In the overall population, the mean duration of treatment was less than three months in 42% of patients, three to 12 months in 37%, and more than a year in 21% of patients. Treatment resulted in a >50% reduction in pain intensity in 46% of patients and a reduction of at least 30% in 82% of patients.[54]

Noninterventional Evidence for Capsaicin 8% Patch

One of the largest noninterventional studies of topical medical patches was the three-month QUEPP (Qutenza—safety and effectiveness in peripheral NP) study.[56,57] This was conducted in Germany between March 2011 and 2012 and evaluated the safety and effectiveness of a single application of the capsaicin 8% patch in 1044 nondiabetic patients with peripheral NP. Approximately 41% of patients had at least 30% pain relief, whereas a further 24% experienced at least 50% pain relief, during the follow-up period (between weeks 1 or 2 and Week 12 after treatment) in this real-world setting. Over the three-month period, the levels of pain intensity also declined by around 25% in these patients. Significant improvements in pain attacks, sleep parameters, daytime tiredness, and the additional intake of analgesic drugs were also reported (all $P \leq 0.001$).[55] Of interest, patients with a history of pre-existing peripheral NP of less than six months had the highest treatment response to the capsaicin 8% patch; 30% and 50% responder rates in these patients were around 62% and 39%, respectively, compared with 42% and 23% in patients experiencing pain for six months to two years; 41% and 22% in those with pain for more than two to 10 years; and 32% and 14% in those with pain for >10 years.[57] These findings suggest that early initiation of topical capsaicin 8% patch treatment is of particular benefit to patients.

The prospective, noninterventional ASCEND study was performed to characterize the retreatment interval, patch use, and clinical effectiveness of the

capsaicin 8% patch in routine clinical practice in seven European countries. Interim results for 340 patients are available[58]; eight weeks after first capsaicin 8% patch treatment, 42.7% of patients achieved a 30% reduction in mean Numeric Pain Rating Scale score, and 24.8% achieved a 50% reduction. The median time from first to second treatment was 22 weeks and from second to third was a further 20 weeks, and the mean number of patches used at the first, second, and third applications was 1.4 (0.74), 1.5 (0.65), and 1.6 (0.94), respectively. Taken together, these results suggest that capsaicin 8% patch use and retreatment intervals are stable across successive treatments and indicate consistent efficacy.[57]

Patient Selection and Place of Topical Treatments in Clinical Practice

From a clinical perspective, it is always helpful to be able to predict which patients will most benefit from particular types of pain management strategies. Attempts to predict which patients are most likely to respond to topical lidocaine have generally been unsuccessful,[59,60] only showing trends in small patient populations,[61] or in patient populations outside the current license (PHN). Based on a retrospective review of data from 41 patients, pain specialists from 17 countries identified localized pain, hyperalgesia, and/or allodynia and other positive sensory symptoms (such as dysesthesia) as having a positive predictive value for the efficacy of lidocaine 5% medicated plaster in patients with chronic back pain with neuropathic components.[62] In contrast, widespread pain and negative sensory symptoms were identified as being negative predictors for efficacy.[62] Patients who are lidocaine naive may benefit from topical lidocaine 5% medicated plaster treatment,[27] and both European Federation of Neurological Societies and NeuPSIG recommend that this topical patch be used first line when there are concerns about side effects or the tolerability of systemic oral treatments, particularly in frail or elderly patients.[5,63] However, caution is advised in certain patient populations, in particular patients with severe hepatic or renal impairment.[11]

Effective lidocaine pretreatment and high pretreatment pain score variability have been identified as positive predictors of treatment response to the capsaicin 8% patch.[64] Based on data from 1248 patients across four double-blind, randomized controlled studies of the capsaicin 8% patch compared with an active control, patients are more likely to respond if they do not have a rigid and fully manifested chronic pain process with severe central plastic changes.[64] A further meta-analysis of six randomized controlled studies found that a baseline pain intensity score of 4 or less was a predictor of sustained and complete response in patients with PHN and HIV neuropathy.[65] Other characteristics associated with response to capsaicin 8% patch were absence of allodynia, presence of hypoesthesia, and McGill Pain Questionnaire sensory score <22 (patients with PHN) and the female sex (patients with HIV neuropathy).[65]

As capsaicin acts on the vanilloid receptors, patients with preserved warmth sensitivity and continuous burning pain are likely to be the best responders to the capsaicin 8% patch. In addition, patients experiencing pain for less than six months may benefit most from topical capsaicin 8% patch treatment, as shown in the QUEPP study.[58] Given these findings, the capsaicin 8% patch may be a good option where renal and hepatic impairment is of concern as there is no restriction for its use in these patient groups.[12]

Practical Considerations

Although efficacy, safety, and tolerability are the primary considerations when selecting the optimal pain therapy, it is also of value to understand the practical elements of different topical treatments. The capsaicin 8% patch must be applied by a physician (or a health care professional under the supervision of a physician), for 30 minutes (to the feet) or 60 minutes (to other areas of the body), with retreatment every 90 days as required. In contrast, the lidocaine 5% medicated plaster can be applied by patients themselves for up to 12 hours within a 24-hour period, but patients require evaluation at two to four weeks after treatment initiation. Considering these differences, clinicians will need to factor patient preference, monitoring requirements, duration of treatment administration, duration of analgesic benefits, and any potential for nonadherence between patient- and physician-administered topical treatments, alongside the efficacy and safety data when choosing between these topical agents.

Conclusions and Recommendations for Future Research

Topical agents that have an effect on the peripheral nervous system are effective at delivering rapid, targeted pain relief of peripheral NP without the side effects associated with systemic, oral therapies.[15,27] Two topical agents are currently licensed by the EMA, the lidocaine 5% medicated plaster specifically for patients with PHN[11] and the capsaicin 8% patch for adults with peripheral NP.[12] The Food and Drug Administration has approved both agents for the management of NP associated with PHN[13,14] Given their proved efficacy, local action, and favorable safety

profile, first-line use of these topical agents may be useful in various patient groups, such as those where there are concerns about systemic side effects, compliance, and in patients who are frail or elderly.[5,63]

Predicting the patient profile that would gain the most benefit from early treatment would be advantageous, thereby avoiding "trial and error" management scenarios that often arise.[66] Evidence from the clinical, observational, and noninterventional studies for capsaicin 8% patch supports early treatment use with short duration of pain having a positive predictive value on the efficacy of this topical treatment.[55,64] Initial screening with a local anesthetic (e.g., lidocaine) could also help to identify those patients who would respond best to the capsaicin 8% patch.[64] Evidence of predictors of efficacy with the lidocaine 5% medicated plaster is not as strong as for the capsaicin 8% patch, but it has been proposed by several pain specialists that they are effective for localized pain, hyperalgesia, and/or allodynia and where there is a positive sensory input.[62] This treatment may also benefit patients who are treatment naive and those who are refractory to oral treatment.[5,54] Further studies designed to evaluate factors that might predispose to a successful outcome with these topical approaches are awaited to help guide treatment.[3]

At present, one study has compared the lidocaine 5% medicated plaster directly with a first-line oral agent and one study has compared the capsaicin 8% patch directly with a first-line oral agent.[15,27] Noninferiority was not shown for the lidocaine 5% medicated plaster when investigated head-to-head with pregabalin,[27] but the ELEVATE trial successfully showed that capsaicin 8% patch was noninferior to pregabalin in relieving pain when compared head-to-head across a wide variety of peripheral NP etiologies.[15] Despite this recent evidence, there is an urgent need for more high-quality head-to-head, randomized, controlled studies for topical treatments to enable direct comparisons of treatment outcomes with current first-line oral therapies.[67,68] These studies should be of sufficient duration and include specific patient subtypes at risk of refractory peripheral NP.[68]

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