Title

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Journal

Pain Medicine, 27(3)

ISSN

1526-2375

Authors

Lawson, Erin

Singla, Priyanka

Adler, Jeremy

et al.

Publication Date

2026-03-01

DOI

10.1093/pm/pnaf130

Peer reviewed

Pain Medicine, 2026, **27**, 279–316
https://doi.org/10.1093/pm/pnaf130
Advance access publication 29 September 2025
Special Article

OXFORD

NEUROPATHIC PAIN SECTION

Topical analgesics for neuropathic pain: an evidence-informed guide for the practicing clinician

Erin Lawson, MD*[,1], Priyanka Singla, MD[2], Jeremy Adler, DMSc[3], Charles E. Argoff, MD[4], Jeffrey J. Bettinger, PharmD[5], Arun Bhaskar, MD[6], Hance Clarke, MD[7], Anthony Eidelman, MD[8], Salman Hirani, MD[9], W. Michael Hooten, MD[10], Jordan Tishler, MD[11], Mark S. Wallace, MD[3], Antje M. Barreveld, MD[12]

[1]Coastal Pain and Spinal Diagnostics, Carlsbad, CA 92009, United States
[2]Anesthesiology and Pain Medicine, University of Virginia, Charlottesville, VA 22903, United States
[3]Division of Pain Medicine, Department of Anesthesiology, University of California San Diego, CA 92037, United States
[4]Comprehensive Pain Center, Albany Medical College, Albany, NY 12208, United States
[5]Pain Management, Saratoga Hospital Medical Group, Saratoga Springs, NY 12866, United States
[6]Pain Management Centre, Charing Cross Hospital, Imperial College Healthcare NHS Trust, London W6 8RF, United Kingdom
[7]Department of Anesthesia and Pain Management, Toronto General Hospital, Toronto, ON M5G 2C4, Canada
[8]Neuromedicine Pain Division, University of Rochester Medical Center, Rochester, NY 14618, United States
[9]Comprehensive Pain Center, Department of Anesthesiology and Perioperative Medicine, Oregon Health & Science University, Portland, OR 97239, United States
[10]Anesthesiology and Perioperative Medicine, Mayo Clinic College of Medicine, Rochester, MN 55905, United States
[11]Mass General Brigham, Harvard Medical School, Boston, MA 02115, United States
[12]Department of Anesthesiology, Tufts School of Medicine, Pain Medicine, Newton-Wellesley Hospital, Newton, MA 02459, United States

*Corresponding author: Coastal Pain and Spinal Diagnostics, 6221 Metropolitan St, Carlsbad, CA 92009, United States. Email: eflawson@gmail.com

Abstract

Objective: To evaluate available evidence for the efficacy and safety of topical analgesics for neuropathic pain and to offer treatment guidance.

Methods: An expert panel searched PubMed (Medline) and reference lists of published articles for available literature assessing 8 categories of topical analgesics used to treat various neuropathic pain conditions. The panel rated the level of analgesic efficacy evidence for each treatment and considered safety, ease of use, and cost. The degree of consensus on the recommendations among the panelists was measured.

Results: There was strong evidence and high consensus that capsaicin 8% is effective for diabetic peripheral neuropathy and postherpetic neuralgia and that lidocaine is effective for postherpetic neuralgia. There was strong evidence and moderate consensus that capsaicin 8% could be effective for HIV-induced neuropathy. There was moderate evidence and high consensus that lidocaine is likely effective for diabetic peripheral neuropathy, idiopathic neuropathy, and postsurgical neuropathy and that capsaicin 8% might be effective for chemotherapy-induced peripheral neuropathy and complex regional pain syndrome. Evidence was weak for other topical medications, though the panel strongly agreed that antidepressants might help with postherpetic neuralgia, complex regional pain syndrome, postsurgical neuropathy, and post-traumatic neuropathy; that nonsteroidal anti-inflammatory drugs could help with postsurgical neuropathy; and that gabapentin might benefit vulvodynia. There was less agreement about whether antidepressants might benefit diabetic peripheral neuropathy, chemotherapy-induced peripheral neuropathy, and vulvodynia and whether capsaicin 8% could be effective for postsurgical neuropathy.

Conclusions: Recommendations were based on a survey and grading of existing literature and, when strong evidence was lacking, the collective clinical expertise of panelists.

Keywords: neuropathic pain; topical analgesics; capsaicin; lidocaine; postherpetic neuralgia; diabetic peripheral neuropathy.

Introduction

Neuropathic pain is a significant chronic pain burden and clinical challenge because of its complex pathophysiology and the limited efficacy of available treatments.[1,2] The estimated prevalence of neuropathic pain in the general population is 7% to 8%, and only 40% to 60% of patients reportedly achieve sufficient pain relief with pharmacotherapy.[3] Oral medications such as gabapentinoids and antidepressants form the mainstay of therapy; however, their potential benefit is limited by dose-related systemic side effects, risk of drug interactions and toxicity, and insufficient pain relief.[4]

Topical analgesics are also prescribed for neuropathic pain and might offer a more favorable side effect profile because of the minimized drug exposure of FDA-approved topical analgesics compared with oral medications. However, the potential benefits are counterbalanced by several factors. First, only 3 topical analgesic preparations are FDA-approved for a

Received: 17 February 2025. **Revised:** 8 August 2025. **Accepted:** 11 September 2025

neuropathic pain condition. Second, many topical preparations are used off-label, often compounded without standardized manufacturing processes or rigorous clinical trials to evaluate their efficacy and safety. Third, compounded topical agents in particular can be costly and inconvenient, lacking consistent insurance coverage and requiring frequent applications. Fourth, variations in compounding vehicle formulations (some of which might not be truly topical) can affect drug release, absorption, and ultimately, both efficacy and safety. Finally, cannabinoids, herbal agents, and other agents that lack strong regulatory oversight further complicate the landscape with inconsistent active ingredient concentrations. Despite these limitations, topical analgesics might retain a safety advantage over oral medications, and their use continues to grow.[5]

Evidence-based medicine is understood to unite individual clinical expertise with the best available clinical research evidence.[6] Health care providers often use clinical judgment to select and prescribe non–FDA-approved topical analgesics but lack adequate evidence-based recommendations for options to consider or avoid. Published meta-analyses and clinical reviews of topical analgesics note the paucity of literature and are limited in providing a treatment framework for use.[3,7–9] Although only lidocaine 5% patch (Lidoderm®), lidocaine topical system 1.8% (ZTlido®), capsaicin 8% patch, and capsaicin 8% topical system (Qutenza®) have FDA approval for use in specific chronic pain conditions,[10,11] many lesser-studied topical medications are also widely used clinically to mitigate neuropathic pain.

Recognizing the lack of adequately powered and designed studies for many topical analgesics (other than capsaicin and local anesthetics) for neuropathic pain, the American Academy of Pain Medicine Foundation (AAPMF) commissioned the present project to fill a gap in published consensus. Despite widespread use of topical analgesics for neuropathic pain, patients and prescribers need an informed guide, which this article is intended to provide.

This interdisciplinary consensus panel aimed to review and assess the quality of literature, as well as to develop clinical recommendations for practical use. The goal was to equip health care professionals with the knowledge needed to effectively incorporate topical analgesics into the management plan for their patients experiencing neuropathic pain.

Methods

The AAPMF convened an interdisciplinary panel with broad clinical experience (Appendix 1), which met in Scottsdale, Arizona, on March 6, 2024, to review the scientific literature and devise clinical recommendations for the use of topical analgesics in the treatment of neuropathic pain. The consensus panel was selected to represent a broad range of health care providers, with some members having experience with topical analgesic clinical trials and publications (see Supplement 1 for panelist backgrounds).

The panel had previously voted by email survey to establish the most important questions to address, with the following questions receiving an affirmative response by 73% or more of panel members:

- What is the basic science/mechanism? (82%)
- What are the quality and level of clinical evidence? (100%)
- Is there benefit/reduction in pain and at what level? (100%)
- Are there potential adverse effects and/or reasons to avoid use? (100%)
- Are there barriers to use (eg, cost, application)? (73%)
- Are there recommendations with regard to modes of delivery (eg, patch, ointment, gels, creams, solutions)? (73%)

Via essay, the panel further identified the following questions as pertinent:

- What gaps in evidence point to recommendations for further study?
- How does one identify patients who would benefit from topical analgesics?
- How does one approach patient discussion of topical analgesics options?

Peer-reviewed journals were searched in PubMed (Medline) for relevant studies pertaining to 8 topical medication categories and 13 neuropathic pain conditions (see Appendix 2 for the search strategy). The selection of 8 topical medication categories and 13 neuropathic pain conditions was determined by expert panel consensus. A modified Delphi process was used, in which commonly encountered clinical scenarios were emphasized. First, a list of medications and neuropathic pain conditions was shared with the entire panel for review. Second, medications and pain conditions were added or removed according to group decision. Third, search terms were created from the final list of medications and diseases.

The targeted literature review search in PubMed (Medline), conducted on February 2, February 7, and June 10, 2024, was not limited by study type or treatment date, in recognition of the paucity of adequately powered and designed studies for many of the topical analgesics (with the exception of capsaicin and local anesthetics) examined for use in neuropathic pain. Only studies published in English were included because of feasibility constraints. Authors did not conduct a systematic review or a formal critical appraisal of each individual study but relied on consensus panel input to weigh the quality and applicability of available evidence, with emphasis on clinical relevance in practice.

Inclusion criteria were relevant topical medication categories and neuropathic pain diagnoses, as follows:

Medication categories:

- Capsaicin (including low and high dose)
- Local anesthetics (lidocaine, bupivacaine, tetracaine)
- Nonsteroidal anti-inflammatory drugs (NSAIDs) (diclofenac, piroxicam, ketoprofen)
- Antidepressants (amitriptyline)
- Anticonvulsants (gabapentin)
- N-methyl-D-aspartate (NMDA) receptor antagonists (ketamine)
- Cannabinoids (cannabidiol [CBD], tetrahydrocannabinol [THC], hemp)
- Herbal medications

Neuropathic pain diagnoses:

- Diabetic peripheral neuropathy (DPN)
- Idiopathic peripheral neuropathy

- Postherpetic neuralgia (PHN) or zoster or herpes zoster or shingles
- Complex regional pain syndrome (CRPS) or reflex sympathetic dystrophy or causalgia
- Chemotherapy-induced neuropathy
- HIV-induced neuropathy
- Facial neuralgia or trigeminal neuralgia
- Postsurgical pain syndrome or postmastectomy pain or post-thoracotomy pain or post-hernia pain
- Postamputation pain or stump pain
- Ischemia pain or neuropathic pain due to ischemia
- Traumatic nerve injury
- Vulvodynia
- Coccydynia or coccyx pain or coccygodynia

Exclusion criteria were irrelevant or clinically inapplicable studies (eg, capsaicin-induced pain studies), animal studies, and irrelevant diagnoses (eg, musculoskeletal pain). Working in teams by medication category (Appendix 1), panel members screened abstracts for relevancy and included systematic reviews, randomized controlled trials (RCTs), other trial designs (ie, nonrandomized, noncontrolled), observational/retrospective studies, and case studies with clinical applicability. Included studies were not limited to large RCTs, given the relative paucity of RCTs for most medication categories. In the case that panel members identified a clinical interest, they were assigned categories accordingly. Panel members read full texts, scanned reference lists, and found additional clinically relevant references to include in the panel discussion for each medication class. Selected studies were presented and discussed at the group meeting in person.

Each panelist rated the level of certainty of evidence using a modified version of the most recent US Preventive Services Task Force (USPSTF) definitions,[12] as previously used in consensus guidelines[13] (Table 1). Strength of consensus among panelists was assessed as defined in Table 2.[13] The panel used the consensus definition approach previously described in published guidelines of the Polyanalgesic Consensus Conference.[13] Given the limited number of currently prescribed topical analgesics evaluated by even a single large RCT and the prescription or suggestion by prescribers of other topical analgesics lacking completed RCTs, clarification of consensus rates across the expert panel was deemed essential. Panelists completed a questionnaire designed to elicit their individual clinical expertise with regard to the efficacy and appropriate use of topical medications for each neuropathic pain condition (see the "Definitions" section for the definition of *efficacy*). Responses were synthesized to form the final clinical recommendations. These recommendations were based on evidence of efficacy and, when strong evidence was lacking, were based on the collective clinical expertise of the panel with regard to effective use.

Table 1. Levels of certainty with regard to net benefit.

Level of certainty	Description
High	The evidence includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies. **Evidence Level** **I-A**—*At least 1 controlled and randomized clinical trial, properly designed*
Moderate	The available evidence is sufficient to determine the effects of the service on health outcomes, but confidence in the estimate is constrained by such factors as: • The number, size, or quality of individual studies. • Inconsistency of findings across individual studies. • Limited generalizability of findings to routine primary care practice. • Lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, which provides enough evidence to alter the conclusion. **Evidence Level** **I-B**—*Well-designed, controlled, nonrandomized clinical trials (prospective observational studies conforming to STROBE criteria)* or **I-C**—*Retrospective cohort or large case studies (>14 subjects)*
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: • The limited number or size of studies. • Important flaws in study design or methods. • Inconsistency of findings across individual studies. • Gaps in the chain of evidence. • Findings not generalizable to routine primary care practice. • Lack of information on important health outcome. **Evidence Level** **II**—*Expert opinion based on risk: benefit or based on case reports*

Table 2. Strength of consensus.

Strength of consensus	Definition*
Strong	>80% consensus
Moderate	50%–79% consensus
Weak	<49% consensus

* Percentage response was calculated for any category that received responses from at least half (7/13) of panelists.

Definitions

A *topical medication* is one with an intended local effect at the application site. Although transdermal formulations, including fentanyl and buprenorphine, produce systemic effects when absorbed into the bloodstream, some transdermal medications, such as lidocaine and capsaicin, are considered topical analgesics when their effect is intended locally.

Medications included in this article have an intended topical local effect on skin and adjacent tissues rather than a transdermal systemic effect. These agents are neither designed nor formulated for systemic absorption, and their therapeutic approach does not rely on central nervous system penetration. In contrast, delivery systems of transdermal medications intended for systemic absorption contain permeation promotors. Permeation promoters disrupt the lipid components of the stratum corneum by altering hydrocarbon chains or the lamellar packing to enhance medication permeation.[15] Topical medications intended for local effect lack these permeation enhancers. It is noted that at higher doses or concentrations, topical medications might exhibit characteristics of transdermal medications, with unintended systemic uptake. Systemic absorption is considered a complication of high-dose topical use. For topical medications for which such systemic side effects have been noted in patients (as in ketamine

and amitriptyline), the potential for this adverse effect limits the recommended concentration.

For the purposes of this article, *efficacy* was defined as the ability of a treatment to reduce pain. No required threshold or extent of pain reduction was specified because the available literature does not consistently apply standardized or universal definitions or numeric thresholds for what constitutes clinically meaningful pain relief. As such, the panel reported pain reduction outcomes as presented in each study, in recognition of the variability in measurement tools and definitions across the literature.

Results

Studies are shown in Tables 3.1 through 3.8, with study quality examined for design, number of participants, neuropathic pain disease state, topical analgesic formulation, doses, comparators, study duration, and efficacy outcomes.[14,16–119] Tables 3.1 through 3.8 prioritize RCTs, followed by nonrandomized, noncontrolled trials; observational/retrospective studies; and case studies with clinical applicability. Adverse drug reactions with topical medications were usually dose dependent, mild, and transient, though allergic contact dermatitis could last weeks and might worsen (rather than improve) after patch removal.[120] Table 4 reports the levels of certainty of evidence and consensus among panelists. Table 5 delineates the regional sources, traditional uses, and mechanisms of action (MOAs) for topical herbal medications.[5,74,95,103,121–159]

Discussion

Analgesics that have been FDA approved for topical treatment of a neuropathic pain condition (commercially manufactured)

Of the topical analgesics reviewed here, capsaicin and lidocaine are FDA approved for specific neuropathic pain states: capsaicin 8% patch and capsaicin 8% topical system for PHN and DPN, and lidocaine 5% patch and lidocaine topical system 1.8% for PHN. These medications are unique among those considered in this review because of the comparatively strong body of literature supporting their use. Our expert panel was, therefore, able to base clinical recommendations on more rigorous research in these cases.

Capsaicin (including low and high dose)

MOAs

Capsaicin is a transient receptor potential vanilloid 1 (TRPV1) agonist leading to calcium and sodium ion influx resulting in depolarization, action potential initiation, and pain signal transmission.[127–130] Both high-dose (8%) and low-dose (0.025%–0.075%) topical formulations are available and were considered. Analgesia results from probable nerve desensitization and reduced epidermal nerve fiber density, particularly at the higher-concentration formulation (8%).

Clinical studies

The panel reviewed the evidence shown in Table 3.1.[14,16–40] Additional evidence included 1 overview of Cochrane database reviews assessing topical analgesics in various disease states, which found moderate-quality evidence of limited efficacy with high-concentration capsaicin for PHN.[7]

PHN is the disease state with the most RCT literature support for capsaicin treatment. Risk ratios calculated for >50% reduction in pain over 2–8 weeks from 4 double-blind, placebo-controlled randomized trials[16–19] favored high-dose capsaicin. For DPN, a single RCT demonstrated superiority of a capsaicin patch over a placebo patch,[20] and open-label, randomized trials[14,21] demonstrated pain reduction. One RCT[28] evaluating the 8% capsaicin patch for postsurgical neuropathic pain (PSNP) showed a 5-point greater improvement on the numerical rating scale than was reported for placebo; however, this difference did not reach statistical significance.

For HIV-induced peripheral neuropathy, RCTs found heterogeneous results but tended to favor use of capsaicin 8% patch.[23,25,40] Moreover, an open-label, randomized trial[26] demonstrated clinically meaningful pain reduction.

Safety

The most common adverse effects were transient pain and erythema after application.[160]

Considerations with capsaicin

Repeated application of capsaicin 8% appears to reduce peripheral neuropathic pain in some who did not respond to a first application,[161] but optimal dose and long-term effects are unknown. Skin biopsies in patients with diabetic and chemotherapy-induced neuropathy before and after treatment with a capsaicin 8% patch have shown signs suggestive of neural fiber regeneration and restoration and nerve growth factor normalization.[14,36] However more research is necessary to understand the clinical implications of these findings.

Capsaicin 8% patch requires application in a clinic with a minimum interval of 3 months between applications. The cost and clinic time required could pose barriers to treatment in outpatient settings. This is important because high-dose capsaicin's average wholesale price near the time of publication was approximately $955 per patch for cash-paying patients, plus application fees.[162] For DPN, treatment typically involves application of 2 patches per foot (4 total), amounting to $3782.64 per session. For PHN, between 1 and 4 patches could be required, depending on the area of pain. Additional challenges might include prior authorization hurdles and insurance coverage prerequisites. Several studies compared the cost-effectiveness of high-dose capsaicin to that of oral agents for neuropathic pain and favored capsaicin.[163–166] The advantage is seen with the potential of a single patch application for 3 or more months to reduce oral pain medication usage and thus costs.[163,164] In contrast, low-dose capsaicin creams (0.025%, 0.075%, and 0.1%) that are available over the counter (OTC) cost approximately $8 per ounce[157] and require frequent (up to 4 times per day) reapplications, reducing feasibility and increasing costs. More cost-saving data could support moving capsaicin 8% to a first-line treatment.

The panel identified evidence gaps with capsaicin, which include the effects of long-term administration, the patients who are likely to respond, the efficacy and timing of repeated applications, potential effects on neural regeneration, and cost-effectiveness. Blinding in controlled trials of capsaicin might be difficult because of discomfort with its application.

Local anesthetics (lidocaine, bupivacaine, tetracaine)

MOAs

Lidocaine patches work topically to primarily produce analgesia rather than anesthesia by favorably blocking

Table 3.1. Evidence of neuropathic pain efficacy by topical medication class: capsaicin.

Disease state	Study	Design (*n*)	Medication, dose/ delivery (*n*)	Comparator (s) (*n*)	Duration	Outcome(s)	Significance
PHN ≥6 mo	Backonja et al, 2008	RCT, double-blind, multicenter (402)	Capsaicin 8% patch	Capsaicin 0.04%	2–8 wk efficacy endpoint	Mean NPRS scores: Capsaicin 8%: −29.6% Capsaicin 0.04%: −19.9%	*P*=.001
PHN ≥6 mo	Irving et al, 2011	RCT, double-blind, multicenter (418)	Capsaicin 8% patch	Capsaicin 0.04%	2–8 wk efficacy endpoint	Mean NPRS scores: Capsaicin 8%: −32.0% Capsaicin 0.04%: −24.4%	*P*=.011
PHN	Webster et al, *J Pain* 2010	RCT, double-blind, multicenter (299)	Capsaicin 8% patch	Capsaicin 0.04%	2–8 wk efficacy endpoint	Mean NPRS scores: Capsaicin 8%: −26.5% Capsaicin 0.04%: −17.3%	*P*=.0286
PHN ≥3 mo	Webster et al, *BMC Neurol* 2010	RCT, double-blind, multicenter (155)	Capsaicin 8% patch	Capsaicin 0.04%	2–8 wk efficacy endpoint	Mean NPRS scores: Capsaicin 8%: −36.5% Capsaicin 0.04%: −29.9% Post hoc: PHN ≥6 months NPRS scores: Capsaicin 8%: −37.6% Capsaicin 0.04%: −23.4%	*P*=.296 *P*=.0291
DPN	Simpson et al, *J Pain* 2017	RCT, double-blind (369)	Capsaicin 8% patch	Placebo patch	2–8 wk efficacy endpoint	Average daily pain score change: Capsaicin: −27.4% Placebo: −20.9%	*P*=.025
PDPN	Anand et al, 2022	OLRT (50)	Capsaicin 8% patch + SOC	SOC alone	3 mo	Reduction in NPRS score only in capsaicin 8% patch+ SOC	*P*=.0001
PDPN	Vinik et al, 2016	OLRT (468)	Capsaicin 8% patch+ SOC (60 min, 30 min)	SOC alone	52 wk	Norfolk Quality of Life–Diabetic Neuropathy total scores: 30 min + SOC: −27.6% 60 min+ SOC: −32.8% SOC alone: −6/7%	*P* value not calculated
Neuropathic pain, various etiologies	Webster et al, 2011	Ob (PHN=25; HIV-associated=1; PDPN=91)	Capsaicin 8% patch+ lidocaine 4% pretreatment		2–12 wk efficacy endpoint	Mean NPRS scores: PHN: −28% PDPN: −31%	*P* value not calculated
HIV-associated distal sensory polyneuropathy	Clifford et al, 2012	RCT, double-blind (494)	Capsaicin 8% patch	Capsaicin 0.04% patch	2–12 wk efficacy endpoint	Capsaicin 8%: −29.5% Capsaicin 0.04%: −24.5%	*P*=.097
HIV-associated distal sensory polyneuropathy	Simpson et al, *Neurology* 2008	RCT, double-blind, multicenter (307)	Capsaicin 8% patch	Capsaicin 0.04% patch	2–12 wk efficacy endpoint	Mean NPRS scores: Capsaicin 8%: −22.8% Capsaicin 0.04%: −10.7%,	*P*=.0026
HIV-associated distal sensory polyneuropathy	Brown et al, 2013	Integrated analysis 2 RCTs (339)	Capsaicin 8% patch (60 min, 30 min)	Capsaicin 0.04% patch	2–12 wk efficacy endpoint	Mean NPRS scores (30 min): Capsaicin 8%: −27.0% Capsaicin 0.04%: −15.7%	*P*=.0026
HIV-associated distal sensory polyneuropathy	Simpson et al, 2014	OLRT (272)	Capsaicin 8% patch		40 wk (post 12-wk RCT)	Mean NPRS scores: 1 treatment: −25.8% 2 treatments: −27.1% 3 treatments: −24.6% 4 treatments: −22.7%	*P* value not calculated
HIV-associated neuropathy	Simpson et al, *J Pain Symptom Manage* 2008	Ob (12)	Capsaicin 8% patch (60 min)		2–12 wk efficacy endpoint	Mean NPRS reduction: 40%	*P*=.002

(continued)

Table 3.1. (continued)

Disease state	Study	Design (*n*)	Medication, dose/ delivery (*n*)	Comparator (s) (*n*)	Duration	Outcome(s)	Significance
Peripheral neuropathic pain (various etiologies)	Gálvez et al, 2017	Ob (306, including HIV-induced=80)	≤6 Capsaicin 8% patches		52 wk	BPI All pain types: −1.9% ±1.89	*P* value not calculated
PSNP: inguinal postherniorrhaphy	Bischoff et al, 2014	RCT, double-blind (46)	Capsaicin 8% patch	Placebo patch	1 mo	NRS summed pain intensity difference [95% CI]: 5.0 [0.09 to 9.9]; not significant	*P*=.046
Peripheral neuropathic pain	Haanpää et al, 2016	OLRT (559)	Capsaicin 8% patch	Pregabalin (optimized)	8 wk	NPRS ≥30% mean decrease from baseline: Capsaicin: 55.7% Pregabalin: 54.5% Time to onset of pain relief significantly less w/capsaicin vs pregabalin: 7.5 vs 36.0 d	*P* < .0001
Peripheral neuropathic pain	Cruccu et al, 2018	OLRT (488)	Capsaicin 8% patch	Pregabalin (optimized)	8 wk	Complete dynamic mechanical allodynia resolution: Capsaicin: 24.1% Pregabalin: 12.3%	*P*=.001
Peripheral neuropathic pain	Maihofner & Heskamp, 2013	Ob (1044)	≤4 Capsaicin 8% patches		12 wk	≥30% responder: 42.7% ≥50% responder rate: 23.7% Mean pain intensity: −24.7%	Treatment with patch significantly reduced pain at 1, 4, 8, and 12 weeks *P* ≤ .001
Peripheral neuropathic pain	Höper et al, 2014	Ob	Capsaicin 8% patch		12 wk	Mean NPRS past 24-hr scores; painDETECT questionnaire: Significantly reduced pain intensity, sensory abnormalities Better treatment response associated with short disease duration, high painDETECT scores	Pooled data analysis of seven phase II and III trials revealed that about 44% of the patients had a pain reduction of at least 30% 2–12 weeks after capsaicin 8% treatment. The highest reduction of symptoms was found for pain attacks in PHN (37.8%) and allodynia in PNP (36.4%). Extent of pain reduction was greater in patients with a short duration of pain. *P* value not calculated
Peripheral neuropathic pain	Mankowski et al, 2017	Ob (412)	Capsaicin 8% patch		≤52 wk	Mean NPRS scores: 2–8 wk: −26.6% ≥30% responder: 44%	*P* value not calculated
Peripheral neuropathic pain	Hansson et al, 2018	Ob (382 treated, 181 retreated)	Capsaicin 8% patch		8 wk	Mean NPRS scores: −1.05 ≥30% responder: 28% treated, 31% retreated	*P* < .001

(continued)

Table 3.1. (continued)

Disease state	Study	Design (*n*)	Medication, dose/ delivery (*n*)	Comparator (s) (*n*)	Duration	Outcome(s)	Significance
CIPN	Filipczak-Bryniarska et al, 2017	Ob, single-center (18)	Capsaicin 8% patch		12 wk	Mean NRS scores reduced: 7.45 to 0.20 At 8 d: Higher reduction with lower vs higher sensitivity to neurotoxic agent: 69.55% (±12.09%) vs 49.40% (±20.34%)	*P*=.02
CIPN	Anand et al, 2019	Ob (16)	Capsaicin 8% patch		3 mo	Mean NPRS scores: −1.27 Touch-evoked pain: −1.823 Cold-evoked pain: −1.456	*P*=.02 *P*=.03 *P*=.03
CIPN	Ramnarine et al, [Abstract] 2016	Ob (19)	Capsaicin 8% patch		4 wk	>30% pain reduction via BPI: 37% (7/19)	*P*=.04
CIPN	Marec et al, [Abstract] 2016	Ob (28)	Capsaicin 8% patch		6 mo	Pain reduction by No. of patients: <30%: 5 30%–50%: 2 50%–70%: 10 70%–90% 10	*P* value not calculated
CRPS	Robbins et al, 1998	Ob (13)	Capsaicin 5%–10%		4 wk	Pain VAS mean score: Week 1 reduction: 8.0 to 3.0 Week 4: 4.5	*P* value not calculated

Significance cell left blank when not reported or unavailable.
Abbreviations: BPI = Brief Pain Inventory; CIPN = chemotherapy-induced peripheral neuropathy; DPN = diabetic peripheral neuropathy; NPRS = numeric pain rating scale; NRS = numerical rating scale; Ob = observational/retrospective; OLRT = open-label randomized trial; PDPN = painful diabetic peripheral neuropathy; PHN = postherpetic neuralgia; PSNP = postsurgical neuropathic pain; RCT = randomized controlled trial; SOC = standard of care; VAS = visual analog scale.

Table 3.2. Evidence of neuropathic pain efficacy by topical medication class: local anesthetics.

Disease state	Study	Design (*n*)	Medication, dose/ delivery (*n*)	Comparator(s) (*n*)	Duration	Outcome(s)	Significance
PSNP PHN DPN	Ho et al, 2008	RCT, double-blind, crossover (35)	Lidocaine 5% cream	Amitriptyline 5% cream Placebo cream	6 wk	VAS change from baseline (0–100): reduction with lidocaine; no significant change with amitriptyline or placebo. In pairwise comparison, lidocaine and placebo each reduced pain more than amitriptyline.	$P < .05$ $P < .05$
PHN DPN	Baron et al, 2009	RCT, open-label, 2-stage, multicenter (300: PHN=96; DPN=204)	Lidocaine 5% patch	Pregabalin capsules titrated to effect	4 wk	Average 3-day NRS reduction: 30% and 50% reductions were greater w/ lidocaine than pregabalin. More lidocaine than pregabalin responders with PHN (62.2% vs. 46.5%); Both Tx were comparable for DPN (66.7% vs 69.1%). Noninferiority of 5% lidocaine medicated plaster to pregabalin in reduction of at least 2 points or an absolute value of 4 or less on the NRS-3 scale after 4 weeks of treatment.	P=.00229
PHN	Rowbotham et al, 1996	RCT, double-blind (35)	Lidocaine 5% patch (up to 3)	Vehicle patch	Four 12-h sessions	Lidocaine significantly reduced pain intensity at all time points (4–12 h) compared with vehicle patches.	P<.001
PHN	Galer et al, 1999	RCT, enriched, crossover (32)	Lidocaine patch	Vehicle patch		Median time to exit: Lidocaine: >14 d vs vehicle: 3.8 d	$P < .001$
PHN	Galer et al, 2002	RCT, double-blind (96)	Lidocaine 5% patch	Vehicle patch	3 wk	Neuropathic pain scale: Lidocaine improved all assessed pain qualities to a greater extent than vehicle (placebo) patch.	78.1% of subjects preferred lidocaine patch, compared with 9.4% who preferred placebo. Statistical significance was achieved for those who preferred the lidocaine patch over the vehicle patch ($P < .001$).
PHN	Wang et al, 2023	RCT, multicenter (240)	Lidocaine patch	Placebo patch	4 wk	VAS mean (SD) decrease: lidocaine: 14.01 (14.35) vs placebo: 9.36 (12.03)	P=.0088
PHN	Binder et al, 2009	RCT, double-blind, multicenter, enriched (71)	Lidocaine 5% patch (up to 3)	Placebo patch	2 wk	Median time to exit: lidocaine: 13.5 d (range 2–14) vs placebo: 9.0 d (range 1–14)	P=.151
PHN	Katz et al, 2002	Open-label, non-randomized (332)	Lidocaine 5% patch (up to 3)		28 d	BPI-SF mean pain intensity: Day 7: 66% of patients reported pain intensity improvement. Day 14: 43% of previous nonresponders reported pain intensity improvement. Day 28: 60% of patients reported moderate-to-complete pain relief.	$P < .0001$ study conclusion vs baseline P=.0001 vs baseline

(continued)

Table 3.2. (continued)

Disease state	Study	Design (*n*)	Medication, dose/ delivery (*n*)	Comparator(s) (*n*)	Duration	Outcome(s)	Significance
PHN	Galer & Gammaitoni, 2003	Ob, open-label, geriatric patients (20)	Lidocaine 5% patch		7.6 y	Mean satisfaction scores (−5 to +5): Overall: 4.0 Compared with previous Tx: 4.3 Pain relief: 3.8 Convenience: 3.9 Normal activities: 3.9 Tolerability: 4.3	*P* value not calculated
PHN	Clère et al, 2011	Ob, multicenter, elderly patients, previous antidepressants/anticonvulsants, efficacy group (273)	Lidocaine 5% patch (up to 3)		Median: 1 mo	Overall lidocaine efficacy population: significant mean reduction of 1 concomitant PHN Tx per patient	$P < .001$
AHN PHN prevention	Bianchi et al, 2021	Ob (38)	Lidocaine 5% patch		8 wk	Pain intensity: Wk 1 significant reduction with further improvement Wk 4 and Wk 8 Complete response Wk 8: AHN 63.2%; PHN 31.6% Rescue therapy decrease Wk 2 to Wk 8: AHN 57.9% to 10.5%; PHN steady at 68.4%	*P* value not calculated for efficacy in pain reduction Not at statistically different efficacy between groups *P*=.236 Total responder more frequent in AHN group *P*=.054
PHN: by anatomic site	Nalamachu et al, 2013	Open-label, post-hoc, multicenter (332)	Lidocaine 5% patch		4 wk	BPI average pain intensity: significant improvement from baseline; no differences by site: 1.50–2.04 Significantly more adverse effects w/ head vs extremities or trunk	$P \leq .002$ *P*=.006 *P*=.02
PHN: sleep/quality of life	Binder et al, 2016	OLRT	Lidocaine 5% patches		8 wk	SF-MPQ (15 pain descriptors) baseline to Wk 8: Decrease in "severe" pain Increase in "none/mild" pain Lidocaine Tx: less trouble falling asleep, less sleep medication, fewer awakenings, improved quality of life	*P* value not calculated
DPN	Barbano et al, 2004	Open-label, flexible dosing (56)	Lidocaine 5% patch (up to 4)		3 wk w/5-wk extension	Mean change in BPI pain score: significant improvement at 3 wk: 6.4 to 3.6 Maintained in subgroup at 5 wk	$P \leq .001$
PSNP: knee surgery	Pickering et al, 2019	RCT, double-blind, single-center (36)	Lidocaine 5% patch	Placebo patch	3 mo	Day 7 to 3 mo: Dynamic mechanical allodynia diminished ≥30% in 96% (23/24) of patients and ≥50% in 83% (20/24) of patients Over 3 mo: Cold pain threshold improved Maximal mechanical pain threshold improved	*P*=.003 *P*=.001 *P*=.007

(continued)

Table 3.2. (continued)

Disease state	Study	Design (*n*)	Medication, dose/ delivery (*n*)	Comparator(s) (*n*)	Duration	Outcome(s)	Significance
PSNP: inguinal postherniorrhaphy	Bischoff et al, 2013	RCT, double-blind, crossover (21)	Lidocaine 5% patch	Placebo patch	14 d Tx; 14 d washout	Summed NRS: No pain intensity difference between groups Increased pressure pain thresholds w/ lidocaine demonstrated in quantitative sensory testing	*P*=.33
PSNP	Palladini et al, 2019	RCT, double-blind (363)	Lidocaine 700 mg patch as sole or add-on Tx	Placebo	12 wk	NRS change in 24-h average pain intensity: reduction greater w/lidocaine vs placebo (−1.70 vs −1.47) but not statistically significant	*P*=.1533
PSNP: w/cancer	Cheville et al, 2009	RCT, double-blind, crossover, multicenter (28)	Lidocaine patch	Placebo patch	4 wk each study period	NRS administered weekly: No significant intergroup differences	Week 1 *P*=.91 Week 4 *P*=.92
PSNP: orthopedic scar site	Macedo et al, 2021	RCT (37)	Lidocaine 5% patch	Therapeutic massage	90 d	Pain VAS: greater improvement with lidocaine, though pain improved in both groups	Decrease in pain for lidocaine *P* < .05 No significant difference in response in treatment groups *P*=.158 Interaction effect 0.060
PSNP: post-thoracotomy	Sansone et al, 2017	RCT (33)	Lidocaine 5% patch	Placebo patch	8 wk	NRS scores: significant improvement w/lidocaine compared w/placebo	*P* < .01
PSNP: breast cancer surgery	Fassoulaki et al, 2000	RCT (46)	Lidocaine-prilocaine 20 g cream	Placebo	3 mo	Tx group significantly less vs placebo for: Pain in the chest wall Pain in axilla Total incidence of chronic pain Intensity of chronic pain	*P*=.004 *P*=.025 *P*=.002 *P*=.003
PTNP/PSNP	Hans et al, 2009	Open-label, non-randomized, single-center (40)	Lidocaine 5% patch		12 wk	Mean VAS score: Pretreatment: 7.225±1.209 Follow-up: 4.625±1.675 VAS scores were significantly reduced after 4 weeks and after 12 weeks	*P*<.001 *P*<.001
PTNP	Correa-Illanes et al, 2012	Ob (19)	Lidocaine 5% patch		Mean: 19.5 ± 10.0 wk	Pain NRS mean: Baseline: 6.7 ± 1.6 Post-Tx: 2.8 ± 1.5 (≥3-point reduction in 79% of patients, ≥50% reduction in 57.9% of patients)	*P*<.0005
PTNP/PSNP: burn/ degloving/surgical scars	Correa-Illanes et al, 2010	Ob, case series (29)	Lidocaine 5% patch		Mean: 13.9± 10.2 wk	NRS mean: Baseline: 6.66±1.84 Post-Tx: 2.72±1.65, a 58.2%±27.8% reduction Painful area decreased by 16.5±13.7 cm^2	*P*<.0005 reduction in painful area

(continued)

Table 3.2. (continued)

Disease state	Study	Design (*n*)	Medication, dose/ delivery (*n*)	Comparator(s) (*n*)	Duration	Outcome(s)	Significance
Vulvodynia	Carey et al, 2022	Rationale & design: RCT, multicenter, 4 Tx arms	Lidocaine 5%+ estradiol 0.5 mg/mL 0.02% compound cream+ oral placebo	Oral nortriptyline+ placebo cream Combined peripheral cream+ central pill treatments Placebo cream+ placebo pill	Up to 24 wk	Decrease in daily pain score seen with 7-wk lidocaine Tx	P=.004
Trigeminal neuralgia: acute	Zhou et al, 2023	Ob (152)	Lidocaine 2.4% aerosol		30 min	Pain VAS score decrease in 109 responders: Baseline: 8.3±1.1 15 min: 0.8±1.0 30 min: 1.7±1.0	77.6% and 70.4% subjects with effective pain reduction at 15 and 30 min, respectively. Treatment might provide better clinical outcomes in V2 TN (P<.001), V3 TN (p=.001), and V2 + V3 TN (P<.001). Patients who were taking carbamazepine or oxcarbazepine were less likely to experience immediate pain relief. (P=.001).
Trigeminal neuralgia	Yu et al, 2023	Ob (103)	Lidocaine 5% patch		Up to 3 mo	Efficacy as Barrow Neurological Institute score (I-III) improvement ≥ I grade from baseline: 2 wk: 21.4% 1 mo: 21.4% 2 mo: 18.4% 3 mo: 16.5%	V2 TN P<.001 V3 TN P=.001 V2 + V3 TN P<.001
Trigeminal neuralgia	Khawaja et al, 2013	Case (14)	Lidocaine 5% patch		4 wk minimum	Pain levels improved in 12 of 14 9 reduced adjuvant medication 2 stopped adjuvant Tx	Twelve of 14 patients responded to topical lidocaine plasters. There was a reduction in the level of ongoing pain from 9.8 (range 7–10) to 4.7 (3.5–10) after using the topical 5% lidocaine plasters (P<.05; 95% CI).
Trigeminal neuralgia: lingual nerve injuries, inferior alveolar nerve injuries	Renton et al, 2012	Case series (216)	Lidocaine 5% patches in multimodal Tx settings			Reduced pain and allodynia in 7% of patients with inferior alveolar nerve injuries, most often as sole therapy	Requested
HIV-associated distal sensory polyneuropathy	Estanislao et al, 2004	RCT, double-blind, crossover, multicenter (64)	Lidocaine 5% gel	Placebo	Tx: 2 wk Washout: 2 wk Crossover: 2 wk	Average pain scores did not differ between groups at Week 2 of each phase	Requested

(continued)

Table 3.2. (continued)

Disease state	Study	Design (*n*)	Medication, dose/ delivery (*n*)	Comparator(s) (*n*)	Duration	Outcome(s)	Significance
HIV-associated distal sensory polyneuropathy	Dorfman et al, 1999	Open-label (27)	Lidocaine 5% gel			46% reduction in mean pain scores: Baseline: 7.11 Post-treatment: 3.81 75% of patients reported moderate relief or better	$P < .001$
Idiopathic distal sensory polyneuropathy	Herrmann et al, 2005	Open-label, flexible dosing (20)	Lidocaine 5% patch (up to 4)		3 wk+ 5-wk extension	Mean daily diary pain ratings: Wk 3: Significantly improved Wk 5: Improvements maintained in subgroup; 25% of subjects tapered concomitant analgesics	From baseline to week 3, 40% of patients demonstrated a ≥30% reduction in weekly mean daily diary pain ratings and 30% of patients demonstrated a ≥50% reduction; from baseline to week 8, 65% of patients demonstrated a ≥ 30% reduction and 55% of patients demonstrated a ≥50% reduction. P=.004
CRPS	Calderón et al, 2016	Ob, single-center (10 in CRPS group)	Lidocaine 5% patch as add-on Tx		6 mo	CRPS group: 6/10 achieved ≥50% NRS score reduction Mean NRS score reduced by 51% from baseline: 7.9 to 3.9	$P < .001$
Peripheral neuropathic pain: various etiologies	Meier et al, 2003	RCT, double-blind, crossover (40)	Lidocaine 5% patch	Placebo	7 d	Lidocaine: 31% ≥50% response Placebo: 8.1% ≥50% response	As an add-on therapy, the lidocaine patch 5% was clearly effective in reducing ongoing pain (P=.017) and allodynia (P=.023) during the first 8 h after application and that the patches also worked well over a period of 7 days (P=.018) in diverse focal PNPS.

Abbreviations: AHN = acute herpetic neuralgia; BPI = Brief Pain Inventory; BPI-SF = Brief Pain Inventory–Short Form; case = case study; CRPS = complex regional pain syndrome; DPN = diabetic peripheral neuropathy; NRS = numerical rating scale; Ob = observational/retrospective; OLRT = open-label randomized trial; PHN = postherpetic neuralgia; PNPS = peripheral neuropathic pain syndrome; PSNP = postsurgical neuropathic pain; PTNP = post-traumatic neuropathic pain; RCT = randomized controlled trial; SD = standard deviation; SF-MPQ = Short-Form McGill Pain Questionnaire; Tx = treatment; VAS = visual analog scale.

Table 3.3. Evidence of neuropathic pain efficacy by topical medication class: nonsteroidal anti-inflammatory drugs.

Disease state	Study	Design (*n*)	Medication, dose/ delivery (*n*)	Comparator(s) (*n*)	Duration	Outcome(s)	Significance
PHN	Kim et al, 2011	RCT (18)	Piroxicam 48-mg patch (up to 3)	Lidocaine 700 mg patch (up to 3) Placebo patch (up to 3)	3 d per Tx 1 wk washout	VAS scores: Overall pain intensity: significant decrease w/piroxicam, lidocaine but not placebo; lidocaine superior after 12 to 48 h Lidocaine patch superior for allodynia after 12 h, hypoesthesia after 24 h, paresthesia after 48 h Piroxicam superior for dull pain after 12 h Both Tx effective for burning, prickling: no differences	$P < .05$ $P \geq .05$
Neuropathic pain (mainly PHN CRPS)	Ahmed et al, 2015	RCT, double-blind, crossover (28)	Diclofenac 1.5% lotion	Placebo	2 wk	Overall pain VAS scores: Diclofenac: 4.9 (1.9 SD) Placebo: 5.6 (2.1 SD) Burning pain: Diclofenac: 2.9 (2.6 SD) Placebo: 4.3 (2.8 SD) No statistical differences in constant pain, shooting pain, hypersensitivity	P=.04 P=.01
PHN	Tajti et al, 1999	RCT, double-blind (40)	Acetylsalicylic acid	Lidocaine		Percentage pain improvement (no statistical difference): Acetylsalicylic acid: 72.2 (19.9 SD) Lidocaine: 72.8 (25.3 SD)	P=.778
AHN PHN	Bareggi et al, 1998	Ob, randomized order (19: AHN=11; PHN=8)	Aspirin/diethyl ether mixture 750 mg	Oral aspirin 500 mg	1 wk washout	VAS scores decrease from baseline: Aspirin/diethyl ether mixture: 82.6% Oral aspirin: 15.4% Poor response to oral: 79% Good response to topical: 95% Skin concentrations: 80- to 100-fold more with topical vs oral	Pain significantly decreased by 82.6% after topical and 15.4% after oral aspirin.
AHN PHN	Kochar et al, 1998	Ob (52)	Aspirin in chloroform			SF-MPQ: 1–5 min: most patients had relief 30–40 min: maximum relief 5–6 h: relief persisted	Most of the patients experienced relief of pain within 1–5 minutes after the aspirin-chloroform application.
AHN PHN	De Benedittis & Lorenzetti, 1996	RCT, double-blind, crossover (37: AHN=15; PHN=22)	Aspirin / diethyl ether mixture	Indomethacin ether mixture Diclofenac / diethyl ether mixture		Pain relief from baseline significant with aspirin but not other 2 Tx Duration of pain relief significant with aspirin but not other 2 Tx Good-to-excellent results with aspirin: AHN: 87% PHN: 82%	$P < .05$ $P < .01$

(continued)

Table 3.3. (continued)

Disease state	Study	Design (*n*)	Medication, dose/ delivery (*n*)	Comparator(s) (*n*)	Duration	Outcome(s)	Significance
AHN PHN	King 1993	Ob (42 consecutive)	Aspirin (325 mg) in chloroform		Followed until pain subsided / management failed	SF-MPQ: All decreased pain, max relief at 20–30 min, lasting 2–4 h	All patients reported substantially decreased pain promptly after treatment, with maximum relief at 20 to 30 minutes and lasting 2 to 4 hours.
PHN	Nicholls, 1993 (abstract not available)	Case	Piroxicam gel				
AHN PHN	De Benedittis et al, 1992	Ob, open-label (45 consecutive: AHN=28; PHN=17) +RCT, double-blind, crossover (11)	Aspirin / diethyl ether mixture	Indomethacin mixture Diclofenac ether mixture Placebo		Open-label: Good-to-excellent results: AHN: 93%; PHN: 65%; fewer AHN progressed to PHN RCT: Pain relief significant compared w/placebo w/aspirin but not other 2 Tx	$P < .05$
PSNP	Chien et al, 2013	Case (1)	Diclofenac 1.5%+ dimethyl sulfoxide gel+ imipramine (titrated to 50 mg)		3 wk follow-up	Pain decrease on first Tx: 9/10 to 2/10 Rash developed over 3 wk; 1% diclofenac substituted; imipramine discontinued	*P* value not applicable
Vulvodynia	Kim et al, 2018	Ob (10)	Meloxicam 0.3%/ lidocaine 5% gel applied twice daily		1 Tx	Moderate improvement in most subjects; 2 discontinued due to local burning/stinging	No *P* value calculated. Of the 8 participants, 6 had a subjective improvement in their symptoms with the use of the combination gel.

Abbreviations: AHN = acute herpetic neuralgia; case = case study; CRPS = complex regional pain syndrome; Ob = observational/retrospective; PHN = postherpetic neuralgia; PSNP = postsurgical neuropathic pain; RCT = randomized controlled trial; SD = standard deviation; SF-MPQ = Short-Form McGill Pain Questionnaire; Tx = treatment; VAS = visual analog scale.

Table 3.4. Evidence of neuropathic pain efficacy by topical medication class: antidepressant medications.

Disease state	Study	Design (*n*)	Medication, dose/ delivery (*n*)	Comparator(s) (*n*)	Duration	Outcome(s)	Significance
CIPN	Barton et al, 2011	RCT, double-blind (208)	Amitriptyline 40 mg–baclofen 10 mg–ketamine 20 mg in pluronic lecithin organogel	Placebo gel	4 wk	Baseline-adjusted sensory subscale: "trend for improvement" compared w/placebo	Sensory subscale: P=.053 Motor subscale: P=.021
CIPN	Gewandter et al, 2014	RCT, double-blind (462)	Ketamine 2%–amitriptyline 4% cream	Placebo	6 wk	No effect on adjusted mean difference in CIPN scores: 0.17	P=.363
PSNP PHN DPN	Ho et al, 2008	RCT, crossover (35)	Amitriptyline 5% cream	Lidocaine 5% cream Placebo	6 wk	No reduction in pain intensity VAS with amitriptyline or placebo	$P < .05$
DPN	Kiani et al, 2015	RCT, double-blind (102)	Amitriptyline 2% cream	Capsaicin 0.75% cream	12 wk	Pain VAS from baseline significant for both groups	$P < .001$
DPN PHN PSNP/PTNP	Lynch et al, *Anesthesiology* 2005	RCT, double-blind (92)	Amitriptyline 2% cream	Ketamine 1% cream Amitriptyline 2%–ketamine 1% cream Placebo cream	3 wk	Average daily pain NRS reduction: 1.1–1.5 in all groups (no differences)	P=.27
PHN DPN PSNP/PTNP	Lynch et al, 2003	RCT, double-blind, crossover+ OLRT (20)	Amitriptyline 1% cream	Ketamine 0.5% cream Amitriptyline 1%–ketamine 0.5% cream Placebo	2-d RCT+ 7-d open label	Pain VAS: no statistically significant difference from placebo in double-blind phase	There was no statistically significant difference from placebo after 2 days for any treatment during the double-blind component of the trial. In the 11 subjects who used the combination cream, there was a statistically significant effect, with subjects reporting significantly greater analgesia by days 3 to 7 according to measures of pain and pain relief.
Chronic neuropathic pain	McCleane 2000	RCT, double-blind (151)	Doxepin 3.3% cream	Capsaicin 0.025% cream Doxepin 3.3%–capsaicin 0.025% cream Placebo	4 wk	Average pain VAS change: Doxepin: −0.9 (95% CL: 0.34–1.46) Capsaicin: −1.12 (95% CL: 0.44–1.8) Doxepin/capsaicin: 1.07 (95% CL: 0.39–1.75) Placebo: no change	$P < .001$ $P < .001$ P <.001
Neuropathic pain from radiation dermatitis	Uzaraga et al, 2012	Ob, pilot (16)	Amitriptyline–ketamine–lidocaine		2 wk	Significant pain reduction: Pretreatment to 30 min posttreatment Significant burning reduction: pretreatment to 2 wk posttreatment	$P < .05$ $P < .05$

(continued)

Table 3.4. (continued)

Disease state	Study	Design (*n*)	Medication, dose/ delivery (*n*)	Comparator(s) (*n*)	Duration	Outcome(s)	Significance
Peripheral neuropathic pain	Lynch et al, *J Pain* 2005	Open label (28)	Amitriptyline 2%–ketamine 1% cream		6–12 mo	Pain NRS reduction: At 6 mo: 34% (SD=37%) At 12 mo: 37% (SD=40%)	*P* value not calculated
Vulvodynia Pudendal neuralgia	Ruoss et al, 2021	Obs (376 analyzed; 345 excluding partial responders)	Amitriptyline 0.5% + estriol 0.03% in organogel		Survey respondents w/ prescription: May 2017–Feb 2020	Effective by age: <30 y: 21 of 41 (51.2%) 30–50 y: 78 of 117 (66.7%) ≥50 y: 109 of 187 (58.3%)	*P* value not calculated for efficacy
DPN Chronic idiopathic axonal polyneuropathy	Kopsky & Hesselink *Pain Pract* 2012	Case (2)	Amitriptyline 5%, 10%			DPN: 5% complete relief in hands; 10% complete relief in hands and feet w/ in 20 min Idiopathic: 5% near complete relief in toes but not heels; 10% reduced pain but caused drowsiness	*P* value not applicable
Central neuropathic pain in multiple sclerosis	Kopsky et al, *Case Rep Med* 2012	Case + placebo controlled (1)	Amitriptyline 5%, 10%	Placebo (alternated wk with active)		Dose-related pain relief initially Placebo-controlled: pain relief with active 5% cream (no allodynia)	*P* value not calculated
PTNP	Liebregts et al, 2011	Case (1)	Amitriptyline 5% cream		8 mo	Pain NRS: 10/10 to 2/10 with each application after 20 min	*P* value not applicable
CRPS	Kopsky et al, 2011	Case (1)	Amitriptyline 5% cream		1 mo	Pain NRS: 30% reduction (9/10 to 6–7/10)	*P* value not applicable

Abbreviations: Case = case study; CIPN = chemotherapy-induced peripheral neuropathy; CRPS = complex regional pain syndrome; DPN = diabetic peripheral neuropathy; NRS = numerical rating scale; Ob = observational/retrospective; OLRT = open-label randomized trial; PHN = postherpetic neuralgia; PSNP = postsurgical neuropathic pain; PTNP = post-traumatic neuropathic pain; RCT = randomized controlled trial; VAS = visual analog scale.

Table 3.5. Evidence of neuropathic pain efficacy by topical medication class: anticonvulsant medications.

Disease state	Study	Design (*n*)	Medication, dose/delivery (*n*)	Comparator(s) (*n*)	Duration	Outcome(s)	Significance
Vulvodynia	Boardman et al, 2008	Ob (35 evaluable)	Gabapentin 2%–6%		≥8 wk	Mean pain score: −4.77, 95% CI: −5.47 to −4.07 28 of 35 (80%) subjects: ≥50% pain score improvement	*P* value not calculated for pain reduction
Vulvodynia-associated itching	Verstraelen et al, 2015	Case (1)	Gabapentin 6% cream		1-yr follow-up	Pain free w/oral duloxetine 60 mg daily; 6% gabapentin cream twice daily	*P* value not applicable

Abbreviations: Case = case study; Ob = observational/retrospective.

Table 3.6. Evidence of neuropathic pain efficacy by topical medication class: N-methyl-D-aspartate receptor antagonists (ketamine).*

Disease state	Study	Design (*n*)	Medication, dose/delivery (*n*)	Comparator(s) (*n*)	Duration	Outcome(s)	Significance
PHN	De Barros et al, 2012	RCT, double-blind, crossover (12)	S-Ketamine 1% ointment	Placebo	15 d both Tx periods; 7-d washout	Pain scores (0–10): No significant differences	$P > .1$
DPN	Mahoney et al, 2012	RCT, double-blind (17)	Ketamine 5% cream	Placebo cream	1 mo	Pain scores: no significant treatment effect; pain improved significantly over time in both groups	No significant treatment main effect

Abbreviations: DPN = diabetic peripheral neuropathy; PHN = postherpetic neuralgia; RCT = randomized controlled trial; Tx = treatment.
* Ketamine combination studies shown in Table 3.4, Antidepressant Medications.

Table 3.7. Evidence of neuropathic pain efficacy by topical medication class: cannabinoids.

Disease state	Study	Design (*n*)	Medication, dose/delivery (*n*)	Comparator(s) (*n*)	Duration	Outcome(s)	Significance
Peripheral neuropathy (symptomatic, multiple etiologies)	Xu et al, 2020	RCT, double-blind, crossover (29)	250 mg CBD oil up to 4/d	Placebo oil up to 4/d	4 wk	Mean Neuropathic Pain Scale administered biweekly: Statistically significant decrease trend in CBD group vs placebo: Intense pain Sharp pain Cold sensations Itchy sensations	$P < .05$

Abbreviations: CBD = cannabidiol; RCT = randomized controlled trial.

abnormally functioning (sensitized) sodium channels, particularly Nav1.7 and Nav1.8, in the dermal nociceptors of A delta and C fibers, thereby reducing ectopic discharges and raising the peripheral ectopic discharge threshold.[148–155] This occurs because the concentration of lidocaine at the application site is high enough to bind to sodium channels in damaged fibers but not in undamaged ones. Additionally, lidocaine inhibits inflammatory processes by regulating T-cell activity and suppressing the production of nitric oxide. Finally, lidocaine activates the TRP (transient receptor potential) channels TRPV1 and TRPA1 expressed in nociceptive sensory neurons.

Clinical studies

The panel reviewed studies shown in Table 3.2.[41–73] Most literature for this category investigated treatment with lidocaine patches, with some studies conducted with gel and spray delivery vehicles. There was 1 Cochrane database systematic review of topical lidocaine for neuropathic pain.[167] There were 1 systematic review of PHN,[2] 2 systematic reviews investigating 5% lidocaine patch compared with other pharmacological interventions in PHN[168] and DPN,[169] 1 systematic review and meta-analysis of topical lidocaine and PSNP,[148] and 1 meta-analysis of RCTs of lidocaine patch for postoperative pain.[170] Evidence supported the use of a

Table 3.8. Evidence of neuropathic pain efficacy by topical medication class: herbal medications.

Disease state	Study	Design (*n*)	Medication, dose/ delivery	Comparator(s)	Duration	Outcome(s)	Significance
Menthol:							
Carpal tunnel syndrome	Sundstrup et al, 2014	RCT, triple-blind, crossover (10)	Topical menthol 4%	Placebo gel	3 h	Pain intensity (Modified VAS): −1.2 (95% CI: −1.7 to −0.6), a significant reduction compared with placebo; effect size moderate (Cohen's *d*=0.63)	*P* =.026
Phantom limb pain	Vase et al, 2013	Prospective, open-label (24)	l-Menthol 40%		Post-application	Effects on sensitivity (cold allodynia, wind-up pain): Level of phantom limb pain was related to wind-up pain after brush stimulation, but not related to pinprick stimulation.	*P*=.011 *P* =.233
CIPN, scar pain	Fallon et al, 2015	Prospective, open-label (51)	Menthol 1% cream		4–6 wk	BPI total scores change: 82% of 38 evaluable patients significantly improved median score: from 47 (interquartile range, 30 to 64) to 34 (6 to 59)	*P*<.001
CIPN	Cortellini et al, 2017	Case (1)	Menthol 1% aqueous cream		4 mo	Pain NRS: Cycle 1: 6 Cycle 2: 5 Cycle 3: 4 Cycle 4: 4 Cycle 5: 3	
Postradiotherapy neuropathic pain	Brid et al, 2015	Case (1)	l-Menthol 5%, aqueous cream		150 d	BPI-SF pain intensity subscale: from 18 at baseline to 12	*P* value not applicable
Peppermint:							
PHN	Davies et al, 2002	Case (1)	Peppermint 10% oil			Immediate improvement up to 4–6 h	*P* value not applicable
Citrullus colocynthis:							
DPN	Heydari et al, 2016	RCT, double-blind (60)	2 mL *Citrullus colocynthis* in sesame oil	Placebo	3 mo	Significant pain relief compared w/ placebo	*P*<.001
CIPN	Rostami et al, 2019	RCT, double-blind (34)	*Citrullus colocynthis*	Placebo	2 mo	No significant differences	*P*=.879
Costus speciosus:							
CIPN	Heydarirad et al, *J Altern Complement Med* 2020	RCT (50)	*Costus speciosus*	Topical paraffin placebo	4 wk	Significant pain intensity reductions compared w/placebo	*P* =.001

(continued)

Table 3.8. (continued)

Disease state	Study	Design (*n*)	Medication, dose/ delivery	Comparator(s)	Duration	Outcome(s)	Significance
Eremostachys laciniate:							
Carpal tunnel syndrome (mild–moderate pain)	Eftekharsadat et al, 2011	RCT (40)	*Eremostachys laciniate* ointment+ oral diclofenac 25 mg daily+ nocturnal wrist splints	Placebo ointment + oral diclofenac 25 mg daily+ nocturnal wrist splints	4 wk	VAS: significant reductions in pain intensity compared w/placebo	$P < .001$
Lavender:							
Carpal tunnel syndrome	Eftekharsadat et al, 2018	RCT (48)	Lavender essential ointment+ nocturnal wrist splints	Placebo ointment+ nocturnal wrist splints	40 d	Significant pain improvements compared w/placebo Significant pinch grip strength improvements compared w/placebo Significant improvements compared w/placebo in composite measure of hand function validated for carpal tunnel syndrome	$P=.001$ $P=.01$ $P=.03$
***Trachyspermum ammi* (ajwain):**							
Peripheral neuropathy, neuropathic foot pain	Petramfar et al, 2016	RCT, double-blind (92)	Ajwain 10% cream	Placebo cream	4 wk	Significant reductions compared w/placebo: Foot burning Painful foot tingling Allodynia	$P < .001$ $P < .001$ $P=.023$
CIPN	Heydarirad et al, *J Altern Complement Med* 2020	RCT, double-blind (30)	Ajwain cream	Placebo cream	4 wk	No significant pain differences	$P=.372$
***Linum usitatissimum* (flaxseed/linseed):**							
Carpal tunnel syndrome	Hashempur et al, 2014	RCT, double-blind (100)	Topical linseed oil+ nocturnal wrist splints	Placebo+ nocturnal wrist splints	4 wk	Significantly greater improvements compared w/placebo in symptom severity, functionality	$P < .001$
Carpal tunnel syndrome	Setayesh et al, 2017	RCT (49)	Topical flaxseed oil	Nocturnal hand splints		Significantly greater symptomatic, functional improvements in flaxseed group	$P < .001$
Chamomile:							
Carpal tunnel syndrome	Hashempur et al, 2015 & 2017	2 RCTs (112)	Topical chamomile+ nocturnal wrist splints	Topical placebo + nocturnal wrist splints	4 wk	Significantly greater symptomatic, functional improvements in chamomile groups	$P < .02$

(continued)

Table 3.8. (continued)

Disease state	Study	Design (*n*)	Medication, dose/ delivery	Comparator(s)	Duration	Outcome(s)	Significance
Nutmeg:							
DPN	Motilal & Maharaj, 2013	RCT, double-blind, single-center (74)	Nutmeg extract	Placebo	4 wk	No significant pain differences (both significantly reduced)	Reductions in worst and average pain: $P \leq .001$ Reductions in interference with walking, sleep, mood, burning, pins and needles, and tingling: $P<.05$
Commercially available blend of 6 homeopathic agents and 5 plant-based essential oils:							
Peripheral neuropathy, plantar foot pain	Li, 2010	RCT, double-blind, crossover (60)	Blend of 6 homeopathic agents (St. John's wort, wolfsbane, club moss, phosphorus, poison ivy, rye ergot) and 5 plant-based essential oils (geranium, lavender, bergamot, tea tree, eucalyptus)	Placebo	1 wk	Significantly greater pain reduction in active group	$P < .050$

Abbreviations: BPI = Brief Pain Inventory; BPI-SF = Brief Pain Inventory–Short Form; case = case study; CIPN = chemotherapy-induced peripheral neuropathy; DPN = diabetic peripheral neuropathy; NRS = numerical rating scale; PHN = postherpetic neuralgia; RCT = randomized controlled trial; VAS = visual analog scale.

topical lidocaine 5% patch for treatment of PHN[2, 168] but was less robust for its use in DPN[169] and PSNP.[148] At the time of the 2014 Cochrane review, data were limited, and the authors concluded that there was possible benefit in neuropathic pain, with good tolerability.[167]

Table 4. Levels of certainty of evidence with regard to net benefit.*

Medication category to treat disease state	Evidence level	Consensus level
Capsaicin for DPN	High	Strong
Capsaicin for PHN	High	Strong
Local anesthetics for PHN	High	Strong
Capsaicin for HIV-induced neuropathy	High	Moderate
NSAIDs for PHN	Moderate	Strong
Local anesthetics for IPN	Moderate	Strong
Local anesthetics for DPN	Moderate	Moderate
Local anesthetics for PSNP	Moderate	Moderate
Capsaicin for CIPN	Moderate	Moderate
Capsaicin for CRPS	Moderate	Moderate
Local anesthetics for PTNP	Moderate	Low
Antidepressants for PHN	Low	Strong
Antidepressants for CRPS	Low	Strong
Antidepressants for PSNP	Low	Strong
Antidepressants for PTNP	Low	Strong
NSAIDs for PSNP	Low	Strong
Anticonvulsants for vulvodynia	Low	Strong
Antidepressants for DPN	Low	Moderate
Antidepressants for CIPN	Low	Moderate
Capsaicin for PSNP	Low	Moderate
Antidepressants for vulvodynia	Low	Moderate

* Table includes medications with levels of evidence achieving strong or moderate consensus by at least half of panelists.
Abbreviations: CIPN= chemotherapy-induced peripheral neuropathy; CRPS= complex regional pain syndrome; DPN= diabetic peripheral neuropathy; IPN= idiopathic peripheral neuropathy; NSAIDs= nonsteroidal anti-inflammatory drugs; PHN= postherpetic neuralgia; PSNP= postsurgical neuropathic pain; PTNP= post-traumatic neuropathic pain.

For PHN, RCTs reported superiority of a lidocaine patch compared with placebo, vehicle patches,[43–46] and pregabalin.[42] Lidocaine patch application also demonstrated decreased spontaneous pain brain activity in PHN, as seen on functional magnetic resonance imaging.[155]

Although RCT evidence for its use in DPN was less robust, lidocaine 5% was found to be likely noninferior to the usual first-line treatment with oral anticonvulsants, with benefits for quality of life and fewer adverse events.[42] For PSNP, RCT results were mixed and varied by surgery type, with positive results in breast cancer surgery[61] and thoracotomy.[60] For PSNP and neuropathic pain after trauma, efficacy evidence leaned toward benefit in a nonrandomized study of 40 consecutive patients treated with lidocaine 5%.[62]

Mixed efficacy results with 5% gel were found for HIV-induced neuropathy.[69,73] For trigeminal neuralgia, the patients most likely to achieve benefit from a lidocaine 5% patch had facial trigger points and mild-to-moderate pain.[66]

Safety

Topical lidocaine did not increase the risk of adverse events.[148] Side effects reported in trials were mild-to-moderate application site reactions that included erythema, pruritus, rash, burning sensation, and edema.[66,151] Only 3% of the dose has been reported to reach systemic circulation.[171] Pharmacokinetic, safety, and tolerability testing of lidocaine 5% patches applied over 72 hours revealed no adverse events and plasma concentrations well below typical antiarrhythmic or toxicity levels.[172] Bioequivalence and safety are similar with lidocaine topical system 1.8% and lidocaine patch 5%.[173]

Considerations with local anesthetics

Lidocaine 5% patch is highly recommended in treatment guidelines for its excellent tolerability and safety (which can

Table 5. Herbal medications: mechanisms of action, sources, and uses.

Herbal medication	Mechanisms of action	Regional sources/uses
Menthol	Interacts with multiple transient receptor potential cation channels; TRPM8 agonist	Oil extract derived from the genus *Menta* (mint) with analgesic properties that have been recognized for thousands of years.
Citrullus colocynthis (bitter apple)	Preclinical studies: Reduces proinflammatory cytokines, eg, IL-6, IL-1ß, TNF	Herb indigenous to Africa and Asia
Costus speciosus (crepe ginger)	Preclinical studies: Anti-inflammatory effects are associated with serum reductions in IL-1ß, IL-6, TNF, and prostaglandin E2 levels	
Eremostachys laciniate	Preclinical studies: anti-inflammatory, analgesic effects reported but precise mechanisms remain unelucidated	Herb traditionally used throughout Iran, Turkey, and Azerbaijan
Lavender oil (major active components: linalool and linalyl acetate)	Preclinical studies: Inhibits synthesis of 4 proinflammatory cytokines: IL-6, IL-8, IL-β, TNF Inhibits lipopolysaccharide-induced inflammation in human monocytes	More than 30 species and dozens of subspecies cultivated around the world
Trachyspermum ammi (ajwain)	Precise mechanisms of purported analgesic effects not consistently reported	Spice from India, used widely for broad range of neurological conditions
Linum usitatissimum (flaxseed/linseed)	Inhibits leukotriene, prostaglandin, cyclooxygenase, lipoxygenase	
Chamomile	Preclinical studies: Suppresses production of proinflammatory cytokines	
Nutmeg	Preclinical studies: Inhibits COX-2 expression and substance P release	Seeds of evergreen tree, *Myristica fragrans*, ground to produce nutmeg

Abbreviations: COX-2= cyclooxygenase-2; IL= interleukin; TNF= tissue necrosis factor; TRPM8= transient receptor potential cation channel subfamily M member 8.

increase patients' treatment adherence), its long-term efficacy, and its documented reductions of painful areas.[64,151,174] Treatment guidelines list lidocaine patch as a second-line PHN treatment option, which becomes first-line in frail or elderly patients or when there are concerns about side effects or the safety of first-line treatments.[8,175] The second-line recommendation in those guidelines is in recognition that the number needed to treat (NNT) for 50% pain relief was uncertain, the therapeutic gain demonstrated in RCTs was modest against placebo, and the level of evidence was low compared with systemic agents.[8,175] Some PHN studies suggest increased benefit with longer treatment duration,[48] continued satisfaction with long-term treatment,[49] and rapid healing and PHN prevention with early patch use in herpes zoster acute neuralgia.[51]

Questions around efficacy with different patient populations remain. Previously described predictors of success with lidocaine 5% patch treatment for back pain with neuropathic components and for postsurgical and nonsurgical pain include localized pain, hyperalgesia and/or allodynia, and other positive sensory symptoms, such as dysesthesia.[176] Negative predictors were widespread pain and negative sensory symptoms.

Much confusion surrounds the labeled percentages of active lidocaine across various preparations. The percentage relates to the weight of lidocaine relative to the weight of the entire product. Therefore, the percentage listed does not translate to bioavailability or how much active lidocaine is transferred to the tissue. For example, as stated previously, lidocaine topical system 1.8% and lidocaine patch 5% are considered bioequivalent, but most preparations do not report their bioavailability.

The panel recognized that the efficacy of an OTC 4% formulation versus the widely studied 5% formulation is uncertain, and evidence-informed recommendations are based on 5% formulations. An 8% solution is also available, but literature for that formulation is not robust. Lidocaine in cream or gel form is considered less convenient than the patch, which is worn for 12 of every 24 hours.[7] An additional benefit is that the patch protects against the mechanical stimulation that can cause pain. However, the difficulty of securing the patch with adhesion is a common barrier to its use.[70,177,178]

As with other topical medications, cost could hinder the use of lidocaine for some patients. A topical lidocaine 1.8% patch is priced at approximately $411 per box of 30 films. Patients might use up to 3 patches daily, resulting in a potential monthly cost of $1233. Medicare typically covers most of this cost for patients with PHN after the deductible has been met. For those with private insurance, pharmaceutical manufacturers might offer copay assistance, reducing the monthly cost to $24 for 90 films; however, this is generally limited to FDA-approved indications, such as PHN. Similarly, a 5% lidocaine patch that is FDA approved for PHN is priced around $470 to $550 per box of 30 patches without insurance, or approximately $15 to $18 per patch. Although coverage for PHN is common under Medicare and some private plans, use of lidocaine for off-label indications might not be reimbursed, limiting broader patient access. Cost for the OTC 4% formulation is not covered by insurance. Lidocaine gel might be considered when the patch is unavailable or too costly or when application problems interfere with its use.

The panel acknowledged gaps in knowledge with regard to how long to advise patients to wear the patch. Prior research indicated that patients with DPN[54] and idiopathic neuropathic pain[70] tolerated up to 4 lidocaine 5% patches daily for up to 18 hours. The panel suggested areas for further study, including efficacy and ease of use with different formulations, optimal preparation of topical lidocaine, effective treatment duration and follow-up, surgery types that might see optimal outcomes,[148] and cost analysis.

Medications that have not been FDA approved for topical treatment of any neuropathic pain condition (compounded from pharmaceutically produced ingredients)

The following medication categories are not FDA approved for topical treatment of neuropathic pain and are not available as commercially manufactured topical products. Instead, they are prepared through compounding by pharmacies, which use pharmaceutically produced active pharmaceutical ingredients. These medication categories are used off-label for topical use in neuropathic pain. These categories of topical medications have not undergone the rigorous process of FDA approval for topical use in neuropathic pain and lack strong clinical trial evidence. For these agents, the expert panel considered the limited available research alongside clinical experience in forming recommendations.

Nonsteroidal anti-inflammatory drugs (diclofenac, piroxicam, ketoprofen, salicylates)

MOAs

NSAIDs exert their effects primarily by inhibiting cyclooxygenase (COX) enzymes, which are responsible for the synthesis of proinflammatory prostaglandins.[5] Inflammatory mechanisms are implicated in chronic pain conditions. Both COX-1 and COX-2 isoforms are expressed in human skin, particularly in keratinocytes, Langerhans cells, and dermal fibroblasts.[179] Under physiological conditions, COX-1 is constitutively expressed and involved in maintaining normal skin homeostasis, while COX-2 is inducible and significantly upregulated in response to ultraviolet radiation, mechanical injury, or inflammatory stimuli.[180] This local expression of COX enzymes in the skin provides the mechanistic basis for the anti-inflammatory effects of topical NSAID formulations in treating localized pain and inflammation.

Clinical studies

The panel reviewed 11 studies involving NSAIDs (Table 3.3).[74–83] Evidence of benefit was low quality or conflicting. Of the evidence reviewed, 9 studies included at least some subjects with PHN.[74–81] A double-blind RCT investigated topical diclofenac 1.5% versus placebo in various neuropathic pain states, mainly PHN or CRPS, and found benefits in pain reduction, but the sample size was small and treatment duration was only 2 weeks.[75] Another RCT in PHN compared piroxicam to lidocaine and placebo and found that both treatment groups had reduced pain intensity, though lidocaine's analgesia was superior for some types of pain, including allodynia.[74] A double-blind RCT found topical acetylsalicylic acid to be as effective as lidocaine for PHN.[76] The most studied medication in PHN was aspirin / diethyl ether, which demonstrated strong benefit over indomethacin / ethyl ether and diclofenac / ethyl ether.[79] Additional results, including from case and observational studies, were mixed, and studies often lacked robust methodologies.

Safety

Very few adverse reactions were reported, with some scattered reports of rash, skin sensitivity, erythema, and pruritus.[74,75,82]

Considerations with NSAIDs

NSAIDs are a known class for pain treatment, but evidence is sparse in neuropathic pain, particularly after the early 2000s. Mechanisms of analgesia do not directly target the processes involved in neuropathic pain conditions. However, patients do use NSAIDs topically for the benefits of safety, localized action, and ease of use. Topical salicylate is a common OTC choice of patients, although evidence for its efficacy in neuropathic pain is lacking or not robust,[76,79,81,181–184] and it is not often recommended in practice guides. Cost analysis for compounded NSAIDs is uncertain. Gaps include a need for RCTs.

Antidepressants (amitriptyline, doxepin)

MOAs

The antidepressants reviewed, including amitriptyline and doxepin, block the reuptake of norepinephrine and serotonin, increasing pain-modulating chemicals.[95,121–123] The primary analgesic effects of these types of antidepressants revolve around their noradrenergic activity, which helps stabilize neuronal membranes throughout peripheral neurons. Antidepressants might also induce peripheral analgesia by blocking sodium channels and inhibiting inflammatory mediators. Serotonin (5-HT) receptors have been identified in epidermal keratinocytes, melanocytes, and dermal fibroblasts. These receptors play roles in modulating skin functions, including inflammation, immune responses, and pruritus. The presence of these receptors in skin cells suggests that antidepressants could exert local effects when applied topically, potentially influencing skin homeostasis and inflammatory processes.[185]

Clinical studies

Clinical trials and case studies are shown in Table 3.4.[41,84–96] A primary systematic review,[186] 1 nonsystematic review,[121] and 1 summary of published and unpublished trials investigating an amitriptyline/ketamine combination were identified.[187] Evidence of benefit was low quality or conflicting. Of 6 RCTs investigating amitriptyline alone or in combination for neuropathic pain,[41,84–88] 1 found benefit, and 5 did not find benefit, [41,84,85,87,88] including 1 trial that suggested pain relief that was not statistically significant compared with placebo.[84] One double-blind RCT of efficacy and safety found amitriptyline 2% to be as effective as low-dose capsaicin 0.75% in reducing DPN pain, with fewer side effects (skin dryness and itching in the amitriptyline group compared with itching, blister formation, and erythema in the capsaicin group), though lack of placebo limits strength of evidence.[86] A single controlled clinical trial found that doxepin 3.3% and 3.3% doxepin / 0.025% capsaicin modestly improved neuropathic pain.[95]

Uncontrolled trials suggest that topical amitriptyline is effective for peripheral neuropathic pain in combination with ketamine[90] and ketamine/lidocaine.[89] Case reports show benefit with topical amitriptyline 5% for DPN, post-traumatic neuropathic pain, CRPS, and neuropathic pain associated with multiple sclerosis.[92–94,96]

Safety

Side effects were absent or minimal in all studies that used up to 5% amitriptyline and 3.3% doxepin, with approximately 1% to 5% of treated patients experiencing transient application site burning. Systemic absorption with drowsiness was reported with a 10% amitriptyline formulation.[92] Amitriptyline at 10% might exhibit unintended systemic uptake, which is considered a complication of high-dose topical use.

Considerations with antidepressants

The panel recommends keeping topical amitriptyline concentration below 10% and monitoring for symptoms of systemic uptake.

Anticonvulsants (gabapentin)

MOAs

The anticonvulsant gabapentin modulates the alpha-2-delta subunits of voltage-gated calcium channels, which reduce calcium influx and neurotransmitter release when activated.[5] Gabapentin might also block NMDA receptors, activate voltage-gated K+ channels, and inhibit inflammatory mediators. In the skin, these voltage-gated calcium channels are expressed on peripheral nociceptive nerve endings, particularly in conditions of neuropathic pain, where upregulation could occur. Modulation of calcium channel activity in peripheral nerves might contribute to reduced excitability and transmission of pain signals. Voltage-gated calcium channels have been identified in epidermal keratinocytes, where they play a role in calcium signaling and skin barrier regulation.[188] Expression of voltage-gated calcium channels on peripheral nociceptive nerve endings innervating the skin supports the rationale for topical gabapentin formulations targeting localized neuropathic pain.

Clinical studies

The panel reviewed 2 clinical studies (Table 3.5)[97,98] and 1 review of topical analgesics for this category.[189] Limited evidence from single observational studies or case reports suggests that gabapentin 6% might be effective for vulvodynia, burning pain, and itching.[97,98,189]

Safety

Side effects were considered negligible compared with those reported with systemic gabapentin.[189]

N-methyl-D-aspartate receptor antagonists (ketamine)

MOAs

The NMDA receptor antagonist ketamine inhibits glutamate production, reducing excitability and pain transmission in neurons both centrally and peripherally.[156] Preclinical studies have suggested that ketamine modulates neuropathic pain by downregulating peripheral mechanisms involving NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, and kainite receptors.

NMDA receptors are expressed in human skin under physiological conditions, particularly within the stratum granulosum of the epidermis. Specifically, NMDAR1 expression has been demonstrated to correlate with the formation of the granular layer, indicating a role in epidermal differentiation and barrier function.[190] In addition to keratinocytes, NMDA

receptors have also been identified in cutaneous nerve endings and are believed to contribute to peripheral pain signaling. Although direct expression of NMDA receptors in Langerhans cells remains to be definitively established, recent research highlights their ability to interact with sensory neurons via various neurotransmitter receptors. These findings support a potential role for NMDA receptor–mediated signaling in neuroimmune communication at the skin level.[191]

Clinical studies

Studies reviewed are shown in Table 3.6,[99,100] in addition to combination studies previously shown in Table 3.4.[84,85,87–90] The panel also found 1 nonsystematic review examining analgesic effects of topical ketamine in various neuropathic pain states.[156] Results are mixed, as are the concentrations studied and preparation with co-analgesics. Small studies of topical ketamine alone did not find statistically significant benefit for neuropathic pain.[99,100] Smaller non–placebo-controlled trials of topical ketamine in combination with amitriptyline[90] and lidocaine[89] found benefit for peripheral neuropathic pain.

Safety

Mild side effects have been reported, including localized skin sensitivity, localized photosensitivity, dizziness, and minor cognitive impairment.[156] One panel member noted systemic side effects with topical ketamine 10% applied vaginally. Systemic absorption is considered a complication of high-dose topical use or application at mucous membranes.

Considerations with ketamine

It has been suggested that lack of ketamine efficacy could stem from low concentrations and the ineffectiveness of a cream base as the delivery vehicle. Dosages vary in compounded formulations, with 10% cream being the most commonly prescribed.[156] The panel recommends considering the risk of systemic uptake of topical medications, including ketamine, when applied at higher doses and on mucous membranes. The panel recommends keeping topical ketamine concentration below 10% and monitoring for symptoms of systemic uptake.

Considerations with topical compounded medications

Topical compounded medications—often combining agents such as anticonvulsants, antidepressants, NSAIDs, local anesthetics, and NMDA receptor antagonists—can be effective options for localized neuropathic pain. An example formulation containing diclofenac 2%, gabapentin 5%, amitriptyline 5%, and ketamine 5% in a 30-gram supply (typically lasting 30 days) ranges in cost from $55 to $150, depending on the compounding pharmacy. These medications are generally not covered by insurance. Pricing varies by the number and concentration of active ingredients, with higher costs associated with unique or high-concentration formulations. In contrast, bulk or frequently compounded formulations might offer more affordable pricing because of economies of scale.

Products that are not pharmaceutically produced or regulated (cannabinoids and herbal)

The following categories include cannabinoids (eg, THC and CBD) and herbal preparations, which are not pharmaceutically manufactured or regulated in a standardized manner. These products are often available as OTC supplements or through dispensaries, but they lack the consistency, quality control, and regulatory oversight of FDA-approved medications. As such, there is considerable variability in formulation, potency, and purity. This category has the least robust body of evidence among those reviewed. Because of the limited availability of high-quality clinical trial data, the expert panel's recommendations for the use of these agents rely heavily on clinical experience and preliminary findings.

Cannabinoids (CBD, THC, hemp)

MOAs

Cannabinoids, including CBD and THC, affect the endocannabinoid system present in all tissues through interaction with G protein–linked receptors CB1 and CB2, as well as G-protein receptors, non–G-protein receptors, and transient receptor potential (TRP) cation channels.[124–126] CB1 receptors are found primarily in the central nervous system. CB2 receptors are active in immune response, which could play a role in modulating neuropathic pain. TRP receptors respond to painful stimuli.[125] Cannabinoids modulate both "classic" endocannabinoid receptors (CB1 and CB2) found in the skin, as well as accessory receptors, such as TRPV1 and G protein–coupled receptor 55, which are implicated in pain.[124–126] Theoretically, CBD could ameliorate the development of neuropathic pain by inhibiting the accumulation and activation of microglial cells in the dorsal spinal cord.[126]

Clinical studies

The panel reviewed 1 study (Table 3.7).[192] The small, low-quality RCT contained 29 volunteers with peripheral neuropathy. Results showed statistically significant reductions ($P < .05$) over placebo in intense and sharp pain, as well as cold and itchy sensations, with 250 mg CBD delivered to the skin in an oil base. The study authors acknowledged as limitations the small sample size, which might have magnified treatment effects, and the inclusion of multiple neuropathic pain etiologies. There were no high-quality RCTs examining the effects of topical CBD or THC for neuropathic pain.

Safety

Topical cannabinoids are well tolerated, with nonserious, transient skin dryness or rash being the most frequent unwanted effects. However, more troublesome rashes were reported in 4 of 100 volunteers (4%) who received CBD in an oil base.[193] Compounded cannabinoids have low water solubility, high lipophilicity, and large molecule size, which hinder absorption.[194]

Considerations with cannabinoids

There is biological rationale for the use of cannabinoids in neuropathic pain; however, bioavailability is an issue. Compared with the bioavailability of cannabinoids in the lung (~30%) and gut (10%–15%), bioavailability through the skin is essentially zero unless unreasonable or infeasible doses are applied. Pharmaceutical technologies like nanoemulsions, penetrative bases, or microneedle patches could overcome this limitation in the future.[125] Techniques involving ethanolized liposomes and permeation enhancers could improve cannabinoid products' skin and muscle solubility.[195–198] No commercially available products currently use this level of sophistication.

The panel found little evidence of efficacy for topical cannabinoids in neuropathic pain.[124] This might be attributable to the poor topical bioavailability. However, safety with

topical cannabinoids is high, and many patients use and express satisfaction with topical CBD and THC products, including suppositories for vulvodynia. Because of the endocannabinoid role in mitigating neuropathic pain, the panel calls for research on concentrations and bases that maximize penetration of the dermis, as well as larger RCTs in humans.

Challenges with compounded cannabinoids extend to the ingredients themselves, which are loosely regulated at the state level and can be derived from hemp, which is fully unregulated at the federal level, raising concern about purity, dosing, and type of cannabinoids used.[193] This issue is particular to cannabinoids, in contrast to other topical products that are compounded extemporaneously; for example, although amitriptyline compounded cream is not regulated, the amitriptyline powder used to compound the formulation is.

Claims of CBD's usefulness for pain and the demonstrated anti-inflammatory effects of some other cannabinoids are largely derived from animal studies, with effects in humans unconfirmed.[199] Limited clinical trials of topical CBD and THC in adult humans for pain, though showing promise, are small and have yet to be reproduced.[192,200] Placebo effect with CBD might be high and influenced by expectations.[201]

Topical CBD and THC products are available in a range of formulations and concentrations, with prices varying accordingly. For example, a CBD topical containing 300 mg in 1.5 oz is priced around $33, while a larger 3.4-oz CBD topical could cost $40. Combination products containing both CBD and THC—such as one with 145 mg CBD and 45 mg THC in a 15-mL container—are priced around $35. These products are not covered by insurance, and pricing depends on the type of cannabinoid (CBD vs THC), concentration, brand, and dispensary. Importantly, these products generally lack standardized quality control, and ingredient content is not independently verified.

Herbal medications

MOAs

Herbal medications are an eclectic group of products with myriad mechanisms of action.[103,131–147] Many results are preclinical. A large number of plant-derived herbal medicinal products are available worldwide[202] to promote health and to treat a broad range of health problems, including neuropathic pain. Although no universally recognized classification system exists,[203] herbal medicinal products can be generally categorized by product constituents and indicated use. In the United States, the FDA classifies all herbal medicinal products as food supplements and, as a result, the manufacturing, labeling, marketing, and distribution of these products are not subject to any regulatory oversight.[204] Herbal medicinal products are available in multiple forms including (1) chopped, dried, powdered, or whole plant material; (2) tablet or capsule; and (3) water-based liquids, oils, ointments, creams, lotions, or gels. The majority of herbal medicinal products are taken orally, brewed as tea, or inhaled as aromatherapy, but a smaller number are used topically to specifically treat neuropathic pain.

Menthol is an oil extract derived from the genus *Mentha* (mint),[131] and its analgesic properties have been recognized for thousands of years.[159] The topical analgesic effects are mediated primarily by menthol's complex interactions with multiple transient receptor potential cation channel subfamily and member proteins.[131]

Citrullus colocynthis, or bitter apple, is an herb that is indigenous to Africa and Asia.[158] In preclinical studies, the analgesic effects of topical *C. colocynthis* are attributed to inhibition of proinflammatory cytokines, including interleukin (IL)-6, IL-1ß, and tissue necrosis factor (TNF).[132,133]

Costus speciosus, commonly known as crepe ginger, has anti-inflammatory effects associated with serum reductions in IL-1ß, IL-6, TNF, and prostaglandin E2 levels in preclinical studies.[134]

Eremostachys laciniata is an herb traditionally used throughout Iran, Turkey, and Azerbaijan. Although the exact mechanisms have not been fully elucidated, *E. laciniate* has anti-inflammatory and analgesic effects in preclinical studies.[136,205]

The genus *Lavandula*, commonly known as lavender, includes more than 30 species and dozens of subspecies that are cultivated around the world. The major active components of whole lavender oil are linalool and linalyl acetate.[137] In preclinical studies, lavender oil inhibited proinflammatory cytokine production (IL-6, IL-8, IL-ß, TNF)[138] and lipopolysaccharide-induced inflammation in human monocytes.[139]

Trachyspermum ammi, also known as ajwain, is used widely for a broad range of neurological conditions. Although ajwain has purported analgesic effects, precise mechanisms of action have not been consistently reported.[140–143]

Linum usitatissimum, commonly known as linseed or flaxseed, inhibits leukotriene, prostaglandin, cyclooxygenase, and lipoxygenase.[144,145]

Matricaria chamomilla, otherwise known as chamomile, suppresses production of proinflammatory cytokines in animal models.[146]

Myristica fragrans is an evergreen tree, and seeds from this genus are ground to produce nutmeg. In preclinical studies, anti-inflammatory effects of nutmeg are related to suppression of cyclooxygenase expression and substance P release.[147]

A topical herbal medicinal product containing homeopathic substances and plant-based essential oils is commercially available for treatment of neuropathic pain. Neuragen PN® is a blend of 6 homeopathic agents and 5 plant-based essential oils. The 6 homeopathic agents are St. John's wort (*Hypericum perforatum*), wolfsbane (*Aconitum napellus*), club moss, (*Lycopodium clavatum*), phosphorus, poison ivy (*Rhus toxicodendron*), and rye ergot (*Secale cornutum*). The 5 essential oils are geranium oil (*Pelargonium graveolens*), lavender oil (*Lavandula angustifolia*), bergamot oil (*Citrus aurantium*), tea tree oil (*Melaleuca alternifolia*), and eucalyptus oil (*Eucalyptus globulus*).

Clinical studies

In addition to the clinical trials and case studies shown in Table 3.8,[101–119] the panel found 1 review of RCTs for neuropathic pain[158] and 1 nonsystematic review examining herbal drugs and plants for treatment of neuropathic pain.[206] The clinical trials vary in product concentrations, dosages, composition of carrier solutions, and presence of contaminants or other herbal constitutes.

There were several positive RCTs of herbal medications for carpal tunnel syndrome, reaching a high level of evidence by the panel's grading criteria.[101,110,111,113–116] Though not included in the initial search strategy, carpal tunnel syndrome

was noted as an important disease state during the review of the literature. In addition, limited evidence suggests that some essential oil active components relieve neuropathic pain, and there might be contributory and bidirectional emotional relief involved.[207]

Safety

The herbal market is not regulated by the FDA, and safety and toxicity data are mostly lacking and variable among substances, but serious adverse effects are rare.

Considerations with herbals

Numerous topical herbal medicines are in clinical use[202] to treat a broad range of health problems, including neuropathic pain (Table 5). Although no universally recognized classification system exists,[203] herbal products can generally be categorized by product constituentes and indicated uses.

Herbal medicines are classified by the FDA as food supplements and are not subject to regulatory oversight in manufacturing, labeling, marketing, or distribution.[204] Clinical studies that focus on active ingredients could bring needed clarity around optimal dosages and treatment routes.

Topical herbal medications such as menthol, linseed, flaxseed, and chamomile are available in various formulations, with prices ranging widely—for example, menthol creams can cost $45 for 4.2 oz or $50.90 for 120 g, while chamomile ointments range from $24 for 1.7 oz to $35.67 for 2 oz. Combination herbal ointments are also available, typically priced between $23 for 3 oz and $42 for 1.7 oz. These products are not covered by insurance, and pricing varies significantly by store and brand. Importantly, there is no standardized verification of active ingredients or concentrations in these products, and they generally lack quality control, raising concerns about consistency, efficacy, and safety.

Considerations with compounded or unregulated formulations

Compared with commercial, FDA-approved drugs that have been tested for safety and efficacy, compounded medications made extemporaneously are not reviewed by the FDA, are not manufactured under federal Good Manufacturing Practices regulations, and do not have specific labeling requirements for safe prescribing and use.[208] State boards of pharmacy oversee drug compounding involving commercially produced medications. However, there is no formal regulation or oversight for herbal medications, including CBD and THC products.

Lack of regulatory oversight and growing demand have spawned many CBD formulations, particularly from hemp, that lack uniform accepted standards in production, labeling, quality control, and pharmaceutical grade.[193] The many hemp-derived cannabinoids have almost no safety or efficacy research, and evaluation of these products has revealed significant contamination and improper isomerization.

Quality control issues can result in dosing inconsistencies and contamination risks for all compounded medications, including topicals. Although systemic risks of such problems are low for the class, providers should be aware that the risks exist.

The effectiveness of topical treatments depends on the specific neuropathic pain condition and the drug concentration. An RCT of 399 patients, 133 with neuropathic pain, assessing different multidrug topical analgesic creams, found no significant difference in efficacy compared with placebo.[209] However, because the study did not specify the etiology of the neuropathic pain (and the effectiveness of topical compounds is often disease specific), the results are not generalizable. Furthermore, the 2% lidocaine concentration used was well below that of commercially available patches.

The vehicle (eg, cream, foam, gel, lotion, ointment) plays a role in targeting delivery to the affected area. Specific vehicle characteristics are beyond the scope of this article; however, overall lipophilicity and molecular weights are usually key characteristics. Active ingredients with lower lipophilicity generate more permeation from the base across the skin for active ingredients. The fluctuating water solubilities of skin layers and soft tissues also complicate optimal permeation and diffusion. Furthermore, different bases affect drug release and skin permeation,[210–213] and adhesion quality of topical patches also affects medication delivery.[177,178] Additional study of permeability, stability, and drug efficacy of different topical bases would be helpful.

Recommendations

Panel recommendations are shown in Table 6 and further summarized in Table 7. Clinical vignettes are shown in the Supplementary Material (Supplement 3). Additional clinical considerations, including special populations, are in Table 8.[214,215] Recommendations are presented in the following order:

- FDA-approved indications for medications that are commercially manufactured and have the most robust evidence for neuropathic pain:
  - Capsaicin 8% patch and capsaicin 8% topical system approved for PHN and DPN
  - Local anesthetics: lidocaine 5% patch and lidocaine topical system 1.8% approved for PHN
- Medications with less robust evidence and no FDA-approved indications for neuropathic pain and more reliance on clinical experience and expertise:
  - NSAIDs
  - Antidepressants
  - Anticonvulsants
  - NMDA/ketamine
- Medications without FDA-approved indications for neuropathic pain, with the least evidence and oversight, and with the most reliance on clinical experience and expertise:
  - CBD, THC
  - Herbal medications

The medication categories have little robust evidence, with the exception of the capsaicin 8% patch and the lidocaine 5% patch and 1.8% topical system. However, the panel considered that the evidence grading system slants toward medications with large RCTs completed for FDA approval, versus topicals for which that process has not been completed. Panel members agreed that they often look to treatments with less robust evidence that have demonstrated effectiveness in clinical practice, and they made recommendations accordingly.

The high-concentration capsaicin patch (8%) has the most efficacy evidence of the topical analgesics included in this review and is usually considered a second-line treatment behind oral agents.[8] Low-dose creams (typically containing capsaicin 0.025% or 0.075%)[7] neither are very effective nor

Table 6. Clinical recommendations for the use of topical medications in neuropathic pain.

Disease state	FDA-approved for topical treatment of a neuropathic pain condition, commercially manufactured		Not FDA-approved for topical treatment of any neuropathic pain condition [a,b]						
	Capsaicin	Local anesthetics	NSAIDs	Antidepressants	Anticonvulsants	NMDA receptor antagonists	CBD	THC	Herbals
DPN	**** #	****		*	*				
PHN	**** #	**** #	***	***		*			
IPN	*	***							
CIPN	*	**		*	*	*	*		
CRPS	**	**	*	*	*	*			
HIV-induced neuropathy	****	***		*	*				
Facial neuralgia	*	*		*		*			
PSNP	*	***		*		*			
PAP	*	*	*	*	*	*			
Ischemic pain	*	*							
PTNP	*	**		*					
Vulvodynia		*		*	*	*			
Coccydynia	*	*	*	*		*			
CTS	*	*	*				*		*

Asterisk and color-coding guide:

#	FDA-approved for this indication
****	**Recommend** use of topical analgesic based on evidence and/or clinical expertise. **With strong consensus**
***	**Recommend** use of topical analgesic based on evidence and/or clinical expertise. **With moderate or low consensus**
**	**Consider** use of topical analgesics despite lack of evidence given clinical experience and limited risk. **With strong consensus**
*	**Consider** use of topical analgesics despite lack of evidence given clinical experience and limited risk. **With strong consensus**
	Insufficient evidence to use topical analgesic. Determine on case-by-case basis

All other agents available through compounding pharmacy.
[a] NSAIDs commercially available for the topical treatment of musculoskeletal pain.
[b] CBD/THC availability varies with state laws.
Abbreviations: CBD= cannabidiol; CIPN= chemotherapy-induced peripheral neuropathy; CRPS= complex regional pain syndrome; CTS= carpal tunnel syndrome; DPN= diabetic peripheral neuropathy; IPN= idiopathic peripheral neuropathy; NMDA= N-methyl-D-aspartate; NSAIDs= nonsteroidal anti-inflammatory drugs; PAP= postamputation pain; PHN= postherpetic neuralgia; PSNP= postsurgical neuropathic pain; PTNP= post-traumatic neuropathic pain; THC= tetrahydrocannabinol.

are considered practical because of the need to reapply frequently. The panel would not discourage patients who are already using cannabinoid products but would not actively recommend them to patients. For all disease states, safety with herbal topicals is high, and in general, adjuvant use for symptom relief by patients should not be discouraged. Mild or moderate pain might have the best response.

For topical analgesics overall, PHN and DPN are the disease states with the most robust data. For disease states other than PHN and DPN, evidence that topical medications are effective is drawn mostly from uncontrolled studies and case studies with inherent limitations. These include anticonvulsants in vulvodynia[97,98,189] and capsaicin patch 8% in PSNP (for which the FDA is evaluating a possible indication), with support from fairly large observational studies[31–34] that show prolonged pain reductions. Smaller observational studies[35,36, 216] show promising pain reduction in chemotherapy-induced peripheral neuropathy and CRPS[39] with capsaicin. Lidocaine in CRPS, idiopathic neuropathic pain, and vulvodynia (in combination with estrogen) has positive but sparse literature support.[70,71] Uncontrolled trials suggest that topical amitriptyline is effective for peripheral neuropathic pain in combination with ketamine[90] and ketamine/lidocaine.[89] Case reports show benefit of topical amitriptyline 5% for diabetic neuropathy, PSNP, CRPS, and neuropathic pain associated with multiple sclerosis.[92–94,96]

Limitations

Acknowledged limitations are inherent to the nonsystematic review. Because this article is not a systematic review, it is not a comprehensive listing of all possible studies or topical medication options. The panel's intent was to collect and summarize clinical evidence specifically in human subjects using medications that are currently available and in clinical use. As such, animal studies were not included, as this work was focused on a clinically oriented evidence base. It is acknowledged that some relevant studies or agents might not have been included. The panel recognizes that the exclusion of non–English-language international studies could influence the strength and scope of the data considered, as well as the resulting clinical recommendations. This is a noted limitation of the present article. The panel relied on its members' consensus input to weigh the quality and applicability of available evidence, with emphasis on clinical relevance in practice. The panel acknowledges the resultant limited transparency around how evidence was upgraded or downgraded. The panel acknowledges the variability in the strength of recommendations and applied a modified version of the most recent

Table 7. Summary of clinical recommendations.

Diabetic peripheral neuropathy
- **Level of evidence:**
  - High level of evidence with strong consensus for capsaicin
  - Low level of evidence with moderate consensus for antidepressants
- **Panel recommendations:**
  - Recommend with strong consensus capsaicin and local anesthetics
  - Consider with low–moderate consensus antidepressants and anticonvulsants

Postherpetic neuralgia or zoster or herpes zoster or shingles
- **Level of evidence:**
  - High level of evidence with strong consensus for capsaicin
  - Moderate level of evidence with moderate consensus for local anesthetics
  - Low level of evidence with moderate consensus for antidepressants
- **Panel recommendations:**
  - Recommend with strong consensus capsaicin and local anesthetics
  - Recommend with low–moderate consensus NSAIDs and antidepressants
  - Consider with low–moderate consensus NMDA-receptor antagonists

Idiopathic peripheral neuropathy
- **Level of evidence:**
  - Moderate level of evidence with strong consensus for local anesthetics
- **Panel recommendations:**
  - Recommend with low–moderate consensus for local anesthetics
  - Consider with low–moderate consensus capsaicin

Complex regional pain syndrome
- **Level of evidence:**
  - Moderate level of evidence with moderate consensus level for capsaicin
  - Low level of evidence with strong consensus for antidepressants
- **Panel recommendations:**
  - Consider with strong consensus capsaicin and local anesthetics
  - Consider with low–moderate consensus NSAIDs, antidepressants, anticonvulsants, NMDA-receptor antagonists

Chemotherapy-induced neuropathy
- **Level of evidence:**
  - Moderate level of evidence with moderate consensus level for capsaicin
  - Low level of evidence with moderate consensus for antidepressants
- **Panel recommendations:**
  - Consider with strong consensus local anesthetics
  - Consider with low–moderate consensus capsaicin, antidepressants, anticonvulsants, NMDA-receptor antagonists, cannabinoids

HIV-induced neuropathy
- **Level of evidence:**
  - High level of evidence with moderate consensus for capsaicin
- **Panel recommendations:**
  - Recommend with strong consensus capsaicin
  - Recommend with low–moderate consensus local anesthetics
  - Consider with low–moderate consensus antidepressants and anticonvulsants

Facial neuralgia or trigeminal neuralgia
- **Level of evidence:**
  - Low level of evidence with low consensus for all drug categories
- **Panel recommendations:**
  - Consider with low–moderate consensus capsaicin, local anesthetics, antidepressants, NMDA-receptor antagonists

Postsurgical pain syndrome or postmastectomy pain or post-thoracotomy pain or post-hernia pain, postsurgical-induced neuropathic pain
- **Level of evidence:**
  - Moderate level of evidence with moderate consensus for local anesthetics
  - Low level of evidence with strong consensus for antidepressants and NSAIDs
  - Low level of evidence with moderate consensus for capsaicin
- **Panel recommendations:**
  - Recommend with low–moderate consensus local anesthetics
  - Consider with low–moderate consensus capsaicin, antidepressants, NMDA-receptor antagonists

Postamputation pain or stump pain
- **Level of evidence:**
  - Low level of evidence with low consensus for all drug categories
- **Panel recommendations:**
  - Consider with low–moderate consensus capsaicin, local anesthetics, NSAIDs, antidepressants, anticonvulsants, NMDA-receptor antagonists

Ischemia pain or neuropathic pain due to ischemia
- **Level of evidence:**
  - Moderate level of evidence with strong consensus for local anesthetics
- **Panel recommendations:**
  - Consider with low–moderate consensus local anesthetics and capsaicin

(continued)

Table 7. (continued)

Traumatic nerve injury, post-trauma neuropathic pain
- **Level of evidence:**
  - Low level of evidence with strong consensus for antidepressants
- **Panel recommendations:**
  - Consider with strong consensus local anesthetics
  - Consider with low–moderate consensus capsaicin, antidepressants

Vulvodynia
- **Level of evidence:**
  - Low level of evidence with strong consensus for anticonvulsants
  - Low level of evidence with moderate consensus for antidepressants
- **Panel recommendations:**
  - Consider with low–moderate consensus local anesthetics, antidepressants, anticonvulsants, NMDA-receptor antagonists

Coccydynia or coccyx pain or coccygodynia
- **Level of evidence:**
  - Low level of evidence with low consensus for all medication categories
- **Panel recommendations:**
  - Consider with low–moderate consensus capsaicin, local anesthetics, NSAIDs, antidepressants, NMDA-receptor antagonists

Carpal tunnel syndrome
- **Level of evidence was not considered**
- **Panel recommendations:**
  - Consider with low–moderate consensus capsaicin, local anesthetics, NSAIDs, cannabinoids, and various herbals

Abbreviations: NMDA= N-methyl-D-aspartate; NSAIDs= nonsteroidal anti-inflammatory drugs.

Table 8. Clinical considerations for topical analgesics.

Topical medications compounded in combination:	Because topical analgesics are rarely used as monotherapy and the class overall has high safety data, it is reasonable to combine medications on the theory that different mechanisms of action could have synergistic effects, but evidence is lacking. Combination medications often have a lidocaine base.
Special populations:	Topical analgesics should be considered as alternative or adjuvant treatments in elderly patients, those with cognitive decline, and patients on multiple medications that require caution in pharmacological dosing. This is because polypharmacy associated with comorbid conditions increases risk for toxicity, drug–drug interactions, and falls or injuries, and drugs used to treat neuropathic pain, including opioids, tricyclic antidepressants, and anticonvulsants, raise the risk for sedation, dizziness, and falls.
Considerations in clinical decision-making:	Advantages of topical analgesics: • Minimal systemic absorption and effects • Targeted, local analgesic action • Relative safety • Ease of combining with other medications in a multimodal treatment regimen • Potential reduced reliance on opioid and other psychoactive oral medications • Preference of most patients to try a topical rather than an oral medication Drawbacks of topical analgesics: • Cost of compounded and patch formulations • Insufficient or absent insurance coverage • Difficulty of performing head-to-head comparisons for safety and efficacy and large placebo effect • Unregulated status, particularly in herbal and cannabinoid markets

USPSTF definitions grading system to reflect the quality of evidence. However, given the heterogeneity of the available data and the lack of sufficient studies for a quantitative synthesis, the panel did not perform a meta-analysis.

This is not a meta-analysis of placebo-controlled trials, which is due in part to the limited availability of adequately powered and designed studies for many of the topical analgesics (with the exception of capsaicin and local anesthetics) examined for use in neuropathic pain. Thus, relevant nonrandomized and non–placebo-controlled studies, broader types of clinical trials, and expert opinion were considered. The use of a single research database could mean that relevant studies were missed.

The two most extensively studied neuropathic pain conditions were PHN and DPN, which limits generalizability to other neuropathic pain conditions. Although many neuropathic pain conditions might respond to drugs with similar mechanisms, this hypothesis remains unproven. A high degree of heterogeneity among studies is likely given the breadth of the search and inclusion criteria, but this was not formally assessed.

The effectiveness of topical combination therapies is a critically important topic and one that warrants its own focused, systematic review. The lack of such review is a limitation of the present article, and a focused systematic review is recommended by the panel as a future research topic.

A significant limitation of topical analgesics is the plausibility of their mechanistic effect. Because these medications do not achieve systemic blood levels, their ability to impact pain biologically is questionable. For instance, ketamine's

pain-relieving effects are mediated by receptors in the central nervous system, which cannot be reached via topical application. Therefore, further mechanistic and pharmacokinetic studies are needed to clarify the role and limitations of topical formulations in treating neuropathic pain, including how the underlying disease state affects their MOA.

Panel members voted on the included pain conditions, with an emphasis on disease states commonly encountered and considered clinically relevant by practicing pain specialists. The panel acknowledges the complexity of classifying certain pain states, including ischemic pain,[217] stump pain, CRPS Type 1,[218] coccydynia,[219] and vulvodynia.[220,221] These conditions often involve multifactorial pain mechanisms, including neuropathic, nociceptive, and nociplastic components. Because CRPS Type 1 and vulvodynia are often associated with small-fiber neuropathy, the panel judged that both include a significant neuropathic component that warrants consideration in clinical practice.

A direct comparison between topical agents included would be valuable for clinical decision-making but is beyond the scope of this article. The panel acknowledges this limitation. The existing literature in this area is limited, with many studies being small, short in duration, or focused on comparisons with oral analgesics or various topical combinations rather than direct head-to-head trials between individual topical agents. Head-to-head comparisons of many topical analgesics do not exist. In the absence of such robust data, expert panel recommendations guided evaluations—an approach deemed necessary given the current evidence gaps.

Although literature is sparse, one randomized, placebo-controlled study of the effectiveness of a lidocaine 5% patch and a capsaicin 8% patch conducted in South Asian male patients with diabetic peripheral neuropathic pain found the capsaicin 8% patch to have greater efficacy in terms of pain reduction.[222] The difference in pain reduction was significant ($P < .01$); however, the authors acknowledged that the study was likely underpowered.

The present article primarily addresses short-term safety concerns, as these were included in studies reviewed. Whereas FDA-approved medications such as topical lidocaine and capsaicin 8% have long-term safety data, comprehensive long-term data for other topical mediations are scarce. Capsaicin 8% patch safety data suggest transient short-term risks of application, with rare cases of full-thickness (third-degree) and deep partial-thickness (second-degree) burns after administration for an unapproved indication and/or unapproved frequency of dosing at an application site where there had been prior skin trauma.[223] Low risk of long-term safety concerns has also been reported for the lidocaine 5% topical patch.[224] Possible local anesthetic toxicity with excessive dosing or methemoglobinemia in susceptible patients are risks with short- or long- term application.[225] The assumption that long-term risks are minimal because of low systemic absorption and the localized effect of topical medications is not conclusively supported by current research. Therefore, the panel acknowledges the lack of long-term safety data as a limitation of the present article. Further research is needed to fully understand the long-term safety profile of these treatments.

There is a lack of standardized guidance on optimal dosing, duration, and reapplication frequency for many topical agents. Likewise, the lack of dosing and administration guidelines is a recognized limitation of this article. Although lidocaine and capsaicin patches have been studied more extensively and include manufacturer-provided instructions, most other compounded or less commonly used topical agents lack such standardized protocols. This gap in clinical guidance was one of the key motivations for undertaking the present review, as the panel sought to synthesize the available clinical data to help inform evidence-based use where formal guidelines are lacking.

Cost comparisons are confounded by several factors. For instance, insurance coverage varies widely across states and among insurers, and compounded topical medications can differ significantly in both formulation and pricing. Additionally, the capsaicin 8% patch, as well as the 5% and 1.8% lidocaine patches, are not covered by many insurance plans, which limits both accessibility and the ability to obtain consistent pricing data. Provider fees for application and consultation also vary significantly, adding further complexity. As a result of this variability and the paucity of standardized cost data, direct comparisons of medication costs remain challenging. This represents a limitation of the present article.

Topical analgesics can be prohibitively expensive, limiting real-world accessibility (see Supplementary Material: Supplement 2). For instance, capsaicin 8% costs medical offices $908.44 per patch, while Centers for Medicare and Medicaid Services reimbursement to patients is based on $3.377 per unit—amounting to $945.66 per patch, as each contains 280 units. Treating both feet for DPN requires 4 patches, totaling $3782.64. For PHN, application ranges from 1 to 4 patches, depending on the size of the affected skin surface. Additionally, procedural application fees increase costs to patients. Lidocaine 1.8% costs $411 per box of 30 films, and with a typical use of up to 3 films daily, the monthly cost reaches $1233. Although Medicare covers most costs for PHN once the deductible has been met, private insurance coverage is typically restricted to FDA-approved uses, with copay cards reducing the monthly cost to $24 for 90 films. In contrast, compounded formulations (eg, diclofenac 2%, gabapentin 5%, amitriptyline 5%, ketamine 5%) vary in price, with a 30-gram supply ranging from $55 to $150, depending on the pharmacy. Given the favorable safety profiles and evidence of efficacy in hard-to-treat neuropathic pain, we call on insurance providers to improve access to these medications and expand coverage beyond limited indications to better support individualized pain management.

Intended for practical use in general outpatient populations with neuropathic pain, the present guide is aimed at assuring a high level of practice. Its recommendations are not mandatory, not applicable to every clinical situation, and not intended to replace clinical judgment.

Summary

The primary objective of this review is to create an evidence-informed and clinically useful guide for health care professionals, including physicians, physician associates and assistants, nurse practitioners, and pharmacists, to assist them in the appropriate selection and use of topical analgesics for managing neuropathic pain. This guide draws on graded evidence but also clinical practice experience, particularly when evidence is sparse. Gaps identified for future research include how to identify patients whose pain might respond to topical agents, optimal combination regimens, and more robust study of individual medications other than capsaicin and

lidocaine, including topical agents that are not regulated by the FDA.

Acknowledgments

Beth Dove, of Dove Medical Communications, LLC, Salt Lake City, Utah, provided writing assistance and editing for the submitted manuscript in accordance with the guideline of the International Committee of Medical Journal Editors defining the roles of authors and contributors, and received payment for services from the foundation. All authors contributed to the consensus-building discussions, analysis and interpretation of data, drafting or critical revision of the manuscript for scientific soundness and intellectual content, and approval of the final article.

Supplementary Material

Supplementary material is available at *Pain Medicine* online.

Funding

Support for this project was received as unrestricted grants from Scilex Holding Company andAveritas Pharma. The AAPMF is a 501c3 charitable organization founded in 2011 to support the core purpose of the AAPM to advance and promote the full spectrum of multidisciplinary pain care, education, advocacy, and research to improve the function and quality of life for people in pain. The AAPMF provided travel reimbursement for participants to attend the March 2024 meeting in Scottsdale, Arizona. Authors received honoraria. The findings and scientific conclusions in this report are those of the authors and do not reflect the position of any funding source or its representatives, who were not present during panel discussions related to these findings and who had no input into the design, analysis, interpretation of results, or preparation of this article and all products of this venture.

Conflicts of Interest

J.A. serves on the Averitas Pharma, Inc., Saluda Medical, and Collegium Pharmaceutical, Inc. speakers' bureaus and serves as an advisory consultant for Vertex Pharmaceuticals Incorporated. C.E.A. is a consultant for Xgene Pharmaceutical and Vertex Pharmaceuticals Incorporated; serves as a consultant and on the speakers' bureau for AbbVie Inc, Averitas Pharma, Inc., Lundbeck, and Scilex Holding Company; and reports institutional research support from AbbVie Inc, Eli Lilly and Company, and Lundbeck. J.J. B. is a consultant for Scilex Holding Company. A.B. reports no conflicts of interest. A.M.B. is an advisor for Lin Health and Noema Pharma and a consultant and speakers' bureau member for Vertex Pharmaceuticals Incorporated. H.C. is president of the Canadian Consortium for the Investigation of Cannabinoids; is funded by a Merit Award by the Department of Anesthesiology and Pain Medicine, University of Toronto; and holds a Canada Research Chair in Chronic Pain, Mental Health, and Substance Use. A.E. reports compensation for serving on the Averitas Post-Surgical Neuropathic Pain Adjudication Committee between July 2021 and November 2024. W.M.H. reports grant support from the FDA and National Institutes of Health. S.H. reports no conflicts of interest. E.L. reports no conflicts of interest. P. S. received compensation as a lecturer for an ECHO session at the University of Alaska and as a reviewer for an Elsevier clinical short review. J.T. is president of the Association of Cannabinoid Specialists and reports Trokie stock ownership. M.S.W. reports institutional support for a clinical trial from 2024 to 2025 and compensation for advisory board participation on September 26, 2023, from Averitas Pharma, Inc.

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