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OVERVIEW OF TOPICAL LIDOCAINE USES WITH FOCUS ON PRESCRIPTION PATCH FORMULATIONS

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Valerie Gonzales, Pharm.D., Clinical Pharmacist
Lauren Heath, Pharm.D., MS, BCACP, Clinical Pharmacist
Joanne LaFleur, Pharm.D., MSPH, Associate Professor University of Utah College of Pharmacy

University of Utah College of Pharmacy, Drug Regimen Review Center
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Abbreviations

AAN, American Academy of Neurology

CADTH, Canadian Agency for Drugs and Technologies in Health

CNS, central nervous system

DHHS, Department of Health and Human Services

EFNS, European Federation of Neurological Societies

FDA, Food and Drug Administration

HIV, human immunodeficiency virus

LBP, low back pain

LNP, localized neuropathic pain

NeP, neuropathic pain

NeuPSIG IASP, Neuropathic Pain Special Interest Group of the International Association for the Study of Pain

NCCN, National Comprehensive Cancer Network

NICE, National Institute for Health and Care Excellence

PA, prior authorization

RCT, randomized controlled trial

SNRIs, serotonin-noradrenaline reuptake inhibitors

TCA, tricyclic antidepressant

Introduction

The first objective of this report is to provide an overview of the on-label and off-label uses described in pharmacy compendia (ie, Micromedex) for topical lidocaine. Topical lidocaine is available by prescription and as over-the-counter products (OTCs) in a variety of formulations. Topical prescription products are approved for anesthetizing irritated or inflamed oral and oral-pharynx mucous membranes or are approved for the treatment of pain related to postherpetic neuralgia (PHN), urethritis, or clinical procedures (eg, intubation, dermatologic surgeries, or procedures involving urethra). OTCs are labeled for temporary relief of localized pain; or pain/itch due to minor, burns, sunburns, cuts/abrasions, insect bites, skin irritation, or anorectal disorders (eg, hemorrhoids, anal fissure), with the indication specific to each product. The mechanism of action for lidocaine for mitigating painful sensations stems from its ability to hamper neuronal action potentials though inhibition of voltage-gated sodium channels within neuronal cell membranes.[1]

Due to the opioid epidemic, The Centers for Medicaid and Medicare Services advocates providing access to non-opioid options that are safe and effective for managing pain in order to rely less heavily on strong opioids.[2] In the CDC's 2016 guideline addressing opioid prescribing, authors support the use of non-opioid alternatives for chronic pain and propose topical lidocaine as an option for neuropathic pain. Supporting access to non-opioid treatment modalities and consideration for lidocaine specifically for neuropathic pain was reiterated in the 2019 best-practice guidance from the US Pain Management Best Practices Inter-Agency Task Force of the US Department of Health and Human Services (DHHS). Yet, authors were not specific to the types of neuropathic pain for which lidocaine has demonstrated efficacy.[3] Thus, the second objective of this report is to determine whether disease-specific guideline recommendations or systematic-review information exist that may further inform prescribing of topical lidocaine and its potential to be used as an alternative to opioid-therapy in the ambulatory setting for off-label neuropathic pain conditions. Since prescribing of lidocaine prescription patches for Utah Medicaid patients is currently restricted via prior authorization, we also payed special attention as to whether systematic review or guideline information supported the use of lidocaine patches for the management of pain not otherwise specified as neuropathic pain.

Prior authorization (PA) criteria (last updated 6/1/21) for lidocaine prescription patches requires either the patient have a diagnosis for the approved indication (postherpetic neuralgia pain) or requires that the provider document the clinical rationale for requesting the patch form instead of preferred topical lidocaine formulations. Additionally, the PA form notes that approval may be granted for "…common, accepted, standard-of-care uses if the request is accompanied by sound clinical rationale and supporting literature (included with this request)."[4] Currently, the topical lidocaine products with preferred status on Medicaid Preferred Drug List (PDL) are the generic cream, ointment, gel, and solution along with the generic combination products, lidocaine/hydrocortisone rectal cream and lidocaine/prilocaine— which do not require a prior authorization.

Methods

To accomplish the first objective of summarizing indications for topical lidocaine products, prescription product information was obtained from the DAILYMED database of the US National Library of Medicine (dailymed.nlm.nih.gov). OTC product packages viewable at retail pharmacy websites were also reference for indications and dosing instructions. The FDA's approved drug database (www.accessdata.fda.gov/scripts/cder/daf/) and NDC database were used to determine the market category of products (https://www.accessdata.fda.gov/scripts/cder/ndc/index.cfm).

As search for review literature regarding topical lidocaine for the management of pain in the ambulatory setting was performed in the Cochrane Library, Ovid-Medline, and in Epistemonikos (a database compiling systematic reviews pertinent to healthcare decision-making compiled from multiple databases such as Cochrane, PubMed, Embase, CINAHL, and LILACS, among others[5]). Example search strings are provided in Appendix A. Information regarding topical lidocaine, particularly the patch formulation, in the ambulatory setting was the focus for this review. Additional clinical-practices guidelines or grey literature evidence reviews were searched at the following websites.

- Centers for Disease Control and Prevention (CDC) or the US Department of Health & Human Services (DHHS)
    - CDC website: https://www.cdc.gov/opioids/providers/prescribing/guideline.html
    - Website for Pain Management Best Practices Inter-Agency Task Force of the DHHS: https://www.hhs.gov/ash/advisory-committees/pain/index.html?language=es
- Canadian Agency for Drugs and Technologies in Health: https://www.cadth.ca/
- Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain: https://www.iasp-pain.org/group/neuropathic-pain-neupsig/
- American Academy of Pain Medicine: https://painmed.org/clinical-guidelines/
- American Society of Regional Anesthesia and Pain Medicine
- European Academy of Neurology: https://www.ean.org/research/ean-guidelines/guideline-reference-center
- American Academy of Rheumatology: https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines
- National Institute for Health and Care Excellence
    - https://www.nice.org.uk/guidance
- National Comprehensive Cancer Network (NCCN): https://www.nccn.org/guidelines/category_3

Appendix B lists guidelines screened in full-text for information regarding topical lidocaine as an option for pain management.

Background

About 20% (50 million) of US adults experience chronic pain, based on data from the 2016 National Health Interview Survey (NHIS); nearly 40% (19.6 million) of these are considered to suffer from high-impact chronic pain that limits quality of life or work activities.[6] A 2019 report from the DHHS acknowledges that "Patients with complex and persistent pain often experience barriers to care related to nonexistent or insufficient insurance coverage and reimbursement for evidence-based medical, behavioral, and complementary pain management services."[7] For those who go on to receive opioids for the management of chronic pain, about 21-29% misuse the medication and 8-12% develop opioid use disorder (per the US National Institute on Drug Abuse).[8,9] Limited therapeutic modalities compounded by social-economic constrains likely contributes to patient challenges to living with chronic pain and influences reliance on opioids.

Following the trend of rising opioid-overdose deaths over the last decade, there has been push from the CDC and health agencies, including Utah's, to motivate prescribers to move away from resorting to opioids as first-line or routine therapy for chronic pain that is unrelated to cancer, palliative, or end-of-life care.[3,7,9,10] The development of, and access to, safe and effective non-opioid alternatives is needed given that the long-term benefit of opioids for chronic pain is unclear and since many patients do not experience sufficient pain relief or functional improvement with opioids. Although opioids are commonly used for the treatment of low back pain, headache, and fibromyalgia, the CDC's 2016 guideline for prescribing opioid therapy pointed out limited or insufficient evidence supporting long-term opioid use for those indicaitons.[3] Moreover, it was found that initiation of opioid therapy for chronic osteoarthritic pain of the back, hip, or knee was not superior to a non-opioid, mixed pharmaceutical approach for improving pain-related function over 12 months.[11]

The 2016 CDC opioid-prescribing guideline emphasized that "…although evidence on long-term benefits of **nonopioid** therapies is **also** limited, these therapies are also associated with short-term benefits, and risks are much lower," so they should be considered for chronic pain.[3] The guideline proposes use of non-opioid pharmacologic therapy **when benefits outweigh risks** in light of the patient-specific context.[*] For example, NSAIDs may be inappropriate for those with peptic ulcer disease, hypertension, renal insufficiency, or heart failure. Fall risk/propensity should be considered for sedating options (eg, antidepressants and anticonvulsants).[3]

Both the 2016 CDC guideline and the 2019 best-practice guidance by the US DHHS Pain Management Best Practices Inter-Agency Task Force[†] recommended lidocaine **particularly for neuropathic pain**,

[*] Although the CDC guideline comments that patients should not generally receive opioids first-line for chronic pain, authors state that patients should not be required to first "fail" non-opioid therapy before being allowed opioid therapy. Instead, "…expected benefits specific to the clinical context should be weighed against risks before initiating therapy."[3] Example situations highlighted where an opioid may be chosen first-line may include serious illness with poor prognosis for return to previous level of function; contraindications to other therapies; and clinician/patient agreement that the overriding goal is patient comfort.[3]

[†] The Task Force was assembled as part of the 2016 Comprehensive Addiction and Recovery Act to address research gaps and recommendations for pain management using a variety of modalities: restorative therapies,

among other non-opioid options (eg, tricyclic and SNRI antidepressants, select anticonvulsants, and topical capsaicin).[3,7] If opioids are needed, the CDC guideline additionally proposes combining opioids with non-opioid therapies in order to improve response and function.[3]

As an overview of the extensive uses of topical lidocaine for painful conditions or procedural-related pain, we first list the available dosage forms and their approved and off-label indications per pharmacy compendia. This is followed by a review of clinical guideline recommendations and systematic review information for various pain syndromes to better understand the place in therapy of lidocaine patches.

Topical Lidocaine Dosage Forms

Topical lidocaine dosage forms on the market constitute FDA-approved prescription products, OTCs, and products that are labeled 'Rx only' but that have not undergone a formal FDA approval process. **Table 1** lists examples of OTC lidocaine products along with the FDA-approved prescription products. At the bottom of the table, under "Other" is a list of (a) products with medical device status, or (b) products that have an NDC (national drug directory code) and are marketed as "by prescription only" but that have not been evaluated or established by FDA to be safe and effective; nor has their labeling been approved by FDA.

Table 1. Topical Lidocaine Dosage Forms

OTCs	FDA-Approved Prescription Drug Products
Cream	
Generic 3% & 4%; Blue Tube/ Aloe 4%; AneCream 4% & 5%; LC-5%; Lidocaine Plus 4%; Lipocaine 5%; LMX 4%; LMX 5%; RectaSmoothe 5%; RectiCare 5%; Xolido 2%; Xolido XP 4%	
Gel	
Alocane Emergency Burn 4%; Good Sense Aloe with Lidocaine 0.5%; Leader Burn Relief 1% ; Lidogel 2.8% ; Regenecare 2%; Sun Burnt Plus 4%; Topicaine: 4%; Topicaine 5%	Glydo 2% prefilled syringe and generic Generic 2% Akten 3.5% ophthalmic gel
Intradermal	
	Zingo Jet Autoinjector 0.5 mg and Generic
Lotion	
Eha 4%; RadiaGuard Advanced 1%	
Ointment	
	Generic: 5%
Pad	
Alocane Emergency Burn Max Str: 4%	

Continuation of footnote from previous page: interventional procedures, behavioral health approaches, and complementary and integrative health approaches, in addition to pharmacotherapy.

Table 1. Topical Lidocaine Dosage Forms

Patch	
First Care Pain Relief 4%; Lidaflex 4%; Lidocaine Max St 24 Hours 4%; Lidocaine Pain Relief: 4%; Lidocanna: 4%; Re-Lieved Maximum 4%; Salonpas 4%; TheraCare Pain Relief: 4%; Generic Lidocaine 4% Patches	Lidoderm 5% ER Patch and generic ZTlido 1.8% ER Patch
Solution	
Aspercreme with Lidocaine 4 %	Generic viscous oral solution 2% Topical solution 4% Laryng-O-Jet 4%
Spray	
Alocane Emergency Burn 4% LevigoSP 2.5%/0.13% with lidocaine/benzalkonium	
Swab	
LidoDose: 3%	
Combinations	
Lidopatch (lidocaine hydrochloride/menthol 3.6%/1.25%) patch	Lidocaine/prilocaine 2.5%/2.5% cream Oraqix Subgingival Jelly (lidocaine/prilocaine) Pliaglis (lidocaine/tetracaine 7%/7%) Synera (lidocaine/tetracaine 70mg/70mg) patch

Other

I. Products marketed as prescription only products (RX only) but that have not been evaluated or established by FDA to be safe and effective; nor has their labeling been approved by FDA. These products are not located among the FDA's approved drug database (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm) and have the market category of "unapproved drug, other" in the FDA's NDC database (https://www.accessdata.fda.gov/scripts/cder/ndc/index.cfm)

- Gen7T 3.5% lotion, Gent 7T Plus menthol patches
- Lidocaine 3% Lotion (eg, NDC 71850182001)
- Lidocaine 5% ointment (certain NDCs, eg, 00395613059, 69512015005)
- Lidocaine 50 mg suppository (NDC 69101015024)
- Lidocanna 4% patches
- Lidogel 2.8% Gel
- Lidotral 3.88% cream
- Lidopin 3% and 3.25% cream
- LidoRx 3% Gel
- Lido-Sorb 3% lotion
- Lidovex 3.75% cream
- ointment
- Lidozion 3% lotion
- Lidtopic Max 10 % cream
- Lidotrans 5%
- Lydexa 4.12% cream
- Lidocaine/hydrocortisone
- Microvix LP (NDC 72275-0714-77)
- Zionodil 3% lotion

Table 1. Topical Lidocaine Dosage Forms

II. Products with Medical Device Status

Astero 4% (lidocaine), hydrogel wound dressing (RX only);

- "Indicated for associated pain, painful wounds and wound healing in either open and closed injuries or conditions. Conditions of pain include topical pain, postsurgical pain and pain associated w/various types of closed or open wounds. Conditions of closed wounds include soft tissue and bony injuries caused by contusions, hematomas, crush injuries and sprains/strains due to torsion, traction, compression and/or blunt trauma."[12]

7T Lido 2% lidocaine, hydrogel wound dressing (RX only)

- "…intended to be used under the supervision of a healthcare professional to be used as local management of skin wounds, including pressure ulcers, venous stasis ulcers, first and second degree burns, and superficial wounds and scrapes"[13]

Lidotrex (2% lidocaine, 1.2% collagen, 1% aloe vera) hydrogel wound dressing (RX only)

- Intended for the management of localized painful skin wounds including pressure ulcers, venous stasis ulcers, superficial wounds and scrapes, 1st and 2nd degree burns[14]

Indications for Topical Lidocaine Products

I. FDA-approved indications are compiled in **Table 2** from the pharmacy compendia, Micromedex.

Table 2. FDA-Approved Uses[a] for Topical Lidocaine Compiled from Micromedex[15]

Indication	Form	Approved Age for Use	Micromedex Efficacy Summary/ Recommendation Strength/ Evidence Strength[b]
Mouth and oropharynx mucous membrane, topical anesthetic	▪ oint 5% ▪ viscous 2% solution ▪ Oraqix (lidocaine/ prilocaine) for periodontal procedures	Adult, yes Pediatric, yes for oint and viscous but no for Oraqix	Adults/Pediatrics: Effective, Class IIa (IIb for Oraqix), B
Postherpetic neuralgia	▪ 1.8% topical system (ZTLido) ▪ 5% patch (Lidoderm)	Adult, yes Pediatric, no	Adults: Evidence favors efficacy, Class IIa, B
Skin local anesthetic; temporary relief of pain associated with minor burns, including sunburn, abrasions of the skin, and insect bites for ointment	▪ oint 5% ▪ lidocaine/prilocaine cream	Adult, yes Pediatric, yes	Adults/Pediatrics, Effective, Class IIa, B
Topical anesthetic to skin prior to venipuncture or IV cannulation	intradermal injection (Zingo) lidocaine/prilocaine cream lidocaine/tetracaine patch (for superficial venous access)	Adult, yes Pediatric, yes for 3 years or older	Adults/Pediatrics: Effective, Class IIa(B) for cream, and IIb(B) for Zingo Evidence favors efficacy, IIa(B) for lidocaine/tetracaine patch (ie, Synera)
Anesthetic for urinary procedure or urethritis for 2% jelly; Genital mucous membrane anesthetic for lidocaine/priolcaine cream	2% jelly lidocaine/prilocaine cream	Adult, yes Pediatric, no	Adults: Effective, Class IIa, B Pediatrics: Effective, Class IIa, B; for combination cream only
Endotracheal intubation or laryngoscopy, anesthetic lubrication (applied to larynx or trachea)	2% jelly 5% oint	Adult, yes Pediatric, yes for 5% oint	2% jelly: Adults/Pediatrics: Evidence favors efficacy, Class IIb, B 5% oint: Adults/Pediatrics: Effective, Class IIa, B
Dermatological procedures, anesthetic	Lidocaine iontophoretic system Lidocaine/tetracaine cream or patch	Adult, yes Pediatric, yes: ≥3 years for	Adults/Pediatrics: Effective, Class IIa, B

Table 2. FDA-Approved Uses[a] for Topical Lidocaine Compiled from Micromedex[15]

Indication	Form	Approved Age for Use	Micromedex Efficacy Summary/ Recommendation Strength/ Evidence Strength[b]
		Synera patch; ≥5 years for system	
Procedure on eye, topical anesthetic	ophthalmic gel 3.5%	Adult, yes Pediatric, no	Adults: Evidence favors efficacy, Class IIa, B

Abbreviations: cr, cream; oint, ointment

[a] Note that these approved indications are respective to the FDA-approved products or OTC products and do not necessarily translate to the products that are marketed for prescription only but that are not FDA approved or established as safe/effective. Nor are approved uses for IV or SQ injection included in the table(eg, as innerve blocks, ventricular arrhythmia management)

[b] *Definitions*

- Effective = based on evidence and/or expert opinion that the treatment is effective for the specific indication
- Evidence favors efficacy= Conflicting evidence and/or expert opinion, but the weight of evidence and/or expert opinion favors efficacy
- Class IIa = Recommended in most cases since treatment is considered to be useful, and is indicated in most cases.
- Class IIb = Recommended in some cases since the treatment may be useful
- B = evidence is based on either data from meta-analyses of randomized controlled trials with conflicting conclusions; small or methodologically flawed (ie, with biases) randomized controlled trials; or nonrandomized studies (eg, cohort, case-control studies, or observational studies).

Note that lidocaine products with a medical-device designation (eg, Astero, 7T Lido, Lidotrex) are generally intended for the management of pain and healing of open or closed wounds (eg, pressure ulcers, venous stasis ulcers, first and second degree burns, postsurgical pain, soft tissue and bony injuries as a result of trauma, contusions, hematomas, crush injuries and sprains/strains); see table 1 on page 10.

II. Off-label uses **per pharmacy compendia** (ie, Micromedex; none listed by Lexicomp) with evidence ratings are provided in **Table 3**. According to Micromedex, topical lidocaine is potentially useful for the following off-label purposes: diabetic neuropathy and cancer-related pain (with the patch formulation); and partial thickness burn, anal fissure, or pressure ulcer debridement (with various lidocaine-containing creams).

Table 3. Off-Label Topical Uses Listed in Micromedex for Lidocaine Products[15]

	Efficacy/Recommendation/Strength of Evidence[a]
Neuropathy due to diabetes mellitus	Adults: Evidence favors efficacy, Class IIb, B (studies used **5% patch or plaster**)
Cancer-Related Pain	Adults: Optional (lidocaine **patch**)[16]
Burn, partial thickness	Adults: Effective, Class IIb, B (for 1 mg/cm^2 of a 5% cream)
Anal fissure	Pediatrics: Evidence favors efficacy, Class IIb, B (for lidocaine/prilocaine cream)
Debridement- pressure ulcer	Adults: Effective, Class IIa, B (for lidocaine/prilocaine cream)[17]
Cough associated with laryngeal procedure	Adults: Evidence favors efficacy, Class IIb, B (lidocaine topical spray for laryngeal mask airway insertion, in combination with thiopentone)
Hiccoughs, Intractable	Adults: Evidence favors efficacy, Class IIb, C (for 2% viscous lidocaine solution)
Indigestion	Adults: Evidence favors efficacy, Class IIb, B (for 2% viscous lidocaine solution plus antacid)
Postoperative complications: stridor and laryngospasm following tonsillectomy and adenoidectomy	Adults: Evidence favors efficacy, Class IIb, A (topical 2% lidocaine at 4 mg/kg sprayed to the subglottic, glottic, and supraglottic areas before endotracheal intubation)
Cataract surgery	Adults: Evidence favors efficacy, Class IIb, B (lidocaine 4% drops or lidocaine 2% gel)

[a] *Definitions*

Efficacy
- Effective = based on evidence and/or expert opinion that the treatment is effective for the specific indication
- Evidence favors efficacy= Conflicting evidence and/or expert opinion, but the weight of evidence and/or expert opinion favors efficacy

Recommendation
- Class IIa = Recommended in most cases since treatment is considered to be useful, and is indicated in most cases.
- Class IIb = Recommended in some cases since the treatment may be useful
- Optional = there is limited evidence based on prospective cohort studies, which is considered insufficient to make a recommendation for or against the use of the treatment

Strength of Evidence
- A = evidence based on meta-analyses of randomized controlled trials with homogeneity in results between individual studies; or based on multiple, well-designed large randomized clinical trials.
- B = evidence is based on either data from meta-analyses of randomized controlled trials with conflicting conclusions; small or methodologically flawed (ie, with biases) randomized controlled trials; or nonrandomized studies (eg, cohort, case-control studies, or observational studies).
- C = based on expert opinion or consensus, case reports or case series

III. OTC indications and dosing for lidocaine single-ingredient products are provided in **Table 4**. Directions for use of these products typically describe to stop use or to consult a doctor if pain persists longer than 7 days (or if symptoms worsen or do not improve within 7 days).

Table 4. OTC Indications and Dosage, by Formulation[a]

Formulation brand examples	Labeled Use	Dosage
1% or 4% Lotion RadiaGuard Advanced; Eha 4%	For temporary relief of pain (and itching) due to minor burns, sunburn, cuts/scrapes, insect bites, or minor skin irritations. RadiaGard is marketed for radiation relief	≥**2 years of age:** apply to affected area up to 3-4 times daily
3% Swab LidoDose	Marketed for pain associated with penetration of the skin such as during dialysis, vaccinations, venipuncture and other procedures	≥**2 years of age**: apply to area 3-5 minutes prior to procedure no more than 4 times daily
4% Gel Alocane Emergency Burn Max; Sun Burnt Plus; Topicaine	For first degree burns including due to flame, sun, electricity, heat, light, or friction	≥**2 years of age**: apply to affected area no more than 3-4 times daily
4% Liquid with roll on applicator or spray Aspercreme Lidocaine	For temporary relief of minor pain	≥**12 years** of age: apply a thin layer to affected area every 6 to 8 hours; up to 3 applications per 24 hours
4% Spray Aspercreme Lidocaine Dry Spray	For temporary relief of minor pain	≥**12 years** of age: spray affected area every 6 to 8 hours; up to 3 applications per 24 hours
4% Cream AneCream,Blue Tube with Aloe; LMX 4; Xolido XP	For temporarily relief of pain and itching due to minor cuts, burns, irritation, or insect bites	≥**2 years of age:** apply externally to the affected area up to 3-4 times daily
4% Patch Asperflex Max; Salonpas; Lido King; Aspercreme Max Strength; Re-Lieved Max Strength	Topical anesthetic for temporary relief of pain	Asperflex Max: ≥**12 years of age**: apply to affected area, using up to 1 patch per **24 hours** Salonpas, Lido King: ≥ **12 years of age**: use 1 patch up to 3-4 times daily, using individual patch for up to **8 hours** Aspercreme Lidocaine Max, or Re-Lieved Max: ≥**12 years of age**, apply to affected area using 1 patch up to **12 hours**

Table 4. OTC Indications and Dosage, by Formulation[a]

5% Rectal Cream or Gel AneCream; LC-5; Lidocaine 5%; Lipocaine5, LMX 5; RectaSmoothe; RectiCare; Topicaine 5	For relief from hemorrhoids, anal fissure, and other anorectal disorders; helps alleviate burning and itching	≥**12 years and older**, apply to affected area up to 6 times daily

[a] OTC use and dosing information was referenced at (dailymed.nlm.nih.gov) and at CVS.com where images of the product packaging can be viewed along with the product monograph

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Neuropathic Pain

Neuropathic pain (NeP) is estimated to affect between 7% to 10% of the general population and is thought to be under-recognized.[18,19] NeP may manifest as a constant burning pain, intermittent stabbing pain, lancinating pain, and allodynia, leading to poor sleep and function.[20,21] The definition of NeP often cited in the literature is by the International Association for the Study of Pain (IASP), as pain caused by a lesion or disease of the somatosensory nervous system.[22] This includes postherpetic neuralgia (or may stem from other viral infection such as HIV[23]), diabetic polyneuropathy, radiculopathy, post-amputation neuralgia, post-traumatic/postsurgical neuropathic pain**,** complex regional pain syndrome type II, central post-stroke pain, trigeminal neuralgia, and spinal cord injury or lesion pain. Other conditions where neuropathic pain can manifest include multiple sclerosis, post-partum pain,[24] cancer, and medication-induced.[22] Overlooked causes may include cryptogenic or chronic idiopathic axonal polyneuropathy (CIAP),[25] alcohol-induced neuropathy,[26] gluten sensitivity related,[27] Parkinson's disease, paraneoplastic,[28] hereditary neuropathies,[29] and immune-mediated neuropathies (eg, Guillain–Barre´ syndrome, chronic inflammatory demyelinating polyradiculoneuropathy [CIDP]).[30,31,32] Yet, this may not be an exhaustive list of conditions that can arise neuropathic pain. Conditions such as complex regional pain syndrome type I, low back pain without radicular pain, fibromyalgia, and atypical facial pain do not meet the IASP neuropathic pain definition.[22] Nonetheless, some authors have referred to fibromyalgia as neuropathic (ie, CDC guideline).[3]

When topical lidocaine is recommended by experts for neuropathic pain, it is typically recommended for localized neuropathic pain (LNP).[22] LNP comprises about 55% to 60% of neuropathic pain conditions.[21,33] As suggested by the term, localized neuropathic pain (LNP) affects a specific, consistent demarcated area.[19,34,35] In a 2020 European cross-sectional descriptive study, LNP comprised 43% of the chronic pain population in the primary care setting.[36] Neuropathic low back pain (nLBP), postsurgical neuropathic pain, and diabetic neuropathy were the main causes, with other less frequent causes being postherpetic neuropathy, neuropathic pain following surgical intervention for cancer, or other. Patients with LNP often had comorbid conditions: cardiovascular disease (32%), depression (28%), diabetes (21%), arthritis (32%; osteo, rheumatoid, or psoriatic), other inflammatory disorder (15%), cancer (6%), fibromyalgia (10%), or other condition (25%). About a third of patients relied on a sleep aid. Utilization of topical monotherapy was more common in patients with mild-intensity or short duration LNP; whereas,

patients with higher pain intensity burden were more likely to be treated with systemic therapies +/- topical treatment. Lidocaine 5% plaster (which is similar to the 5% patch[37,38])[‡] was used in 15% of patients and was often used in combination with neuromodulators, opioids, NSAIDs, or corticosteroids.[36]

Table 5 compiles medications that have an FDA-approval for neuropathic pain, with indications specific to the etiologies of postherpetic neuralgia, diabetic peripheral neuropathy (DPN), or spinal cord injury. Tapentadol is the only opioid among these but is intended for severe pain when other options have failed. Though other opioids have been studied for neuropathic pain, opioids can cause CNS depression and long-term use is associated with addiction, endocrine changes (eg, androgen deficiency, bone demineralization), and sleep apnea.[10,39-43] Patients and prescribers may view topical therapy as advantages, as this route is generally considered to pose less risk of systemic adverse effects or drug–drug interactions, and has a positive tolerability profile compared to systemic options.[21,22,31,33] Pickering et al, 2017 expert consensus review on the management neuropathic pain notes that 60% of patients experience insufficient pain relief with systemic medications.[21]

Table 5. Agents with FDA-approval for Neuropathic Pain Conditions[44-50]

Indications related to conditions with painful symptoms
Duloxetine ▪ Diabetic peripheral neuropathic pain in adults Additional indications for other conditions with pain symptoms ▪ Chronic musculoskeletal pain including osteoarthritis of the knee and low back pain in adults ▪ Management of fibromyalgia
Capsaicin 8% Patch (Qutenza) ▪ Postherpetic neuralgia in adults ▪ Diabetic peripheral neuropathy of the feet in adults
Carbamazepine ▪ Trigeminal neuralgia (IR and ER)

[‡] The 5% plaster is a European product (ie, brand name Versatis) that is a lidocaine transdermal system similar to the US lidocaine 5% patch, as it is also a hydrogel (10 cm X 14 cm) that contains 700 mg of lidocaine from which only about 3% of the drug is systemically absorbed.37. Gudin J, Webster LR, Greuber E, Vought K, Patel K, Kuritzky L. Open-Label Adhesion Performance Studies of a New Lidocaine Topical System 1.8% versus Lidocaine Patches 5% and Lidocaine Medicated Plaster 5% in Healthy Subjects. *J Pain Res.* 2021;14:513-526, 38. Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. 5% lidocaine medicated plaster versus pregabalin in post-herpetic neuralgia and diabetic polyneuropathy: an open-label, non-inferiority two-stage RCT study. *Curr Med Res Opin.* 2009;25(7):1663-1676.

Table 5. Agents with FDA-approval for Neuropathic Pain Conditions[44-50]

Gabapentin ▪ Postherpetic neuralgia in adults
Gabapentin enacarbil (Horizant) ▪ Postherpetic neuralgia in adults Additional indications for other conditions with pain symptoms ▪ Moderate to severe restless leg syndrome
Lidocaine 5% (Lidoderm) and 1.8% (ZTLido) Prescription Patches ▪ Pain relief for postherpetic neuralgia in adults
Pregabalin ▪ Diabetic peripheral neuropathic pain in adults (IR and ER) ▪ Neuropathic pain associated with spinal cord injury (IR) ▪ Postherpetic neuralgia (IR and ER) Additional indications for other conditions with pain symptoms ▪ Fibromyalgia (IR)
Tapentadol ER (Nucynta) ▪ Diabetic peripheral neuropathy**:** for severe pain that requires daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate Additional indications for other conditions with pain symptoms ▪ Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate

Abbreviations: ER, extended-release formulation IR, immediate-release formulation

Note: This table does not include agents that can be used for unique/localized specific forms of other nerve disease states (eg, neuromyelitis optica spectrum disorder) or agents for headache/migraine

The following sections review information from guidelines and/or systematic reviews about use of lidocaine patches or plaster for specific types of neuropathic pain.

Localized Neuropathic Pain (LNP)

In older **guidelines**, topical lidocaine was recommended as a first-line or second-line agent for the management of LNP.[51,52] More recent guidelines (2014 onward)[53] have placed topical lidocaine as a second to fourth-line option[53] due to the limited high-quality evidence. Moreover, guidelines differ with respect to placement before or after trial of opioid analgesics.[22,53] The 2014 Canadian guideline lists 5% lidocaine patches or gel as fourth-line options for neuropathic pain but second-line for PHN.[53] The 2015 guideline by NeuPSIG-IASP described shifting lidocaine patches from first-line to second-line preference due to weak quality of evidence supporting benefits in the broad NeP population.[22] Despite weak evidence, authors maintained lidocaine patches as an option for peripheral neuropathic pain because of its "… excellent safety profile," and provider/patient values and preference in the context of limited alternative medications that often pose tolerability issues.[22] In this guideline, pregabalin, gabapentin,

duloxetine, venlafaxine, and TCAs were the recommended first-line options. Nonetheless, authors highlighted that lidocaine 5% patches may be considered first-line for treating LNP in frail and/or elderly patients and as a means to mitigate safety issues (eg, side effects, drug-drug interactions). Other second-line options described were the capsaicin 8% patch for peripheral neuropathic pain and tramadol; third-line agents were sustained release oxycodone and morphine, and botulinum toxin-A, each with a weak recommendation.[22]

Expert consensus statements that focus on the management of LNP, as opposed to the broader topic of NeP addressed in the aforementioned guidelines, have advised that lidocaine 5% and capsaicin 8% topical patches be considered as first-line therapy for LNP, regardless of the etiology.[21] With respect to patch formulations, patients with localized allodynia may benefit from a patch at the problematic area since the patch provides a mechanical barrier against the stimuli (eg, rubbing of clothing or inadvertent touching).[21] Factors that would preclude use of such topical treatments are broken, atrophic, or infected skin at the site of application.[33] Review authors have described that lidocaine patches are well-tolerated, providing sustained pain relief over long-term treatment. [21,34,54]

Reviews of 5% lidocaine patch or plaster mention various etiologies where evidence suggests positive benefits for reducing pain in different LNP conditions:[55-58]

- Myofascial pain syndrome (2 randomized controlled trials [RCTs][59,60])
- Complex regional pain syndrome type II (case reports, [57,61,62] and prospective observational study)[57,63]
- Burn sequelae in children (prospective uncontrolled study[64])
- Cervical radiculopathy (retrospective chart review)[55]
- Cancer pain with neuropathic components or trigeminal neuropathic pain (case series[55])
- Orofacial pain (case report[55])
- Chronic postsurgical pain/scars following postmastectomy or thoracotomy (RCT[65] and observational evidence[34,55])
- Post-traumatic or post-surgical neuropathy (small 3 month RCT in patients following knee surgery;[66] small RCT, 48 hours post shoulder surgery;[67] small RCT, postoperative gynecology surgery;[68] small RCT for post-sternotomy pain and total opioid cumulative dose at 48 hours;[69] case series in post-thoracotomy pain or postmastectomy pain[70])
- Carpal tunnel (2 randomized controlled studies, up to 6 weeks of treatment)[58,71]
- Various (case series of patients with amputation, posttraumatic pain, or complex regional pain syndrome;[54] mixed peripheral neuropathy pain syndromes population, RCT[72]; idiopathic sensory polyneuropathy, observational, uncontrolled study[73])

Based on a 2021 systematic review, there were no *placebo-controlled* RCTs available assessing whether patients achieve a clinically meaningful response (CMR) with topical lidocaine for the management neuropathic pain related to postherpetic neuralgia, diabetic neuropathy, or trigeminal neuralgia (with CMR generally defined as at least a 30% improvement in pain or in pain and function).[20] Anticonvulsants and SNRIs were supported by moderate-certainty evidence, and opioids by low-certainty evidence for providing a CMR in the treatment of neuropathic pain: risk ratio for achieving a CMR was 1.54 (95% CI

1.45 to 1.63) for anticonvulsants; 1.45 (95% CI 1.33 to 1.59) for SNRIs; and 1.37 (95% CI 1.19 to 1.57) for opioids.[20]

Painful Diabetic Peripheral Neuropathy (DPN)

Painful DPN is a common condition that affects as many as 15.3–72.3 per 100,000 patient years.[18] The condition can be disabling, interfering with daily activities and contributing to psychosocial impairment and reduced quality of life.[74] Early symptoms often involve small fibers, presenting as pain and dysesthesia (ie, sensations of burning, lancinating, and tingling) that can be contact induced and accompanied by hyperalgesia and nighttime worsening.[74,75] Painful small-fiber neuropathy may also occur in 10% to 30% of patients with prediabetes. Large fiber neuropathy produces numbness and loss of protective sensation and is a risk factor for diabetic foot ulceration. The development of DPN may be delayed or slowed with optimized glucose control.[74]

Upon the development of painful DPN, pain-reducing pharmacotherapy should be offered to patients per the 2021 American Diabetes Association (ADA) guideline.[75] Agents with an FDA-approved indication for painful DPN (other than diabetic ulcers or gastroparesis) include duloxetine and pregabalin immediate and extended release (ER). Capsaicin 8% topical system (Qutenza) is approved for pain due to DPN of the feet.[46] Tapentadol ER (Nucynta ER) is approved for painful DPN when alternative options have been inadequate and when pain is severe enough to require daily, ongoing opioid use.[47] Opioids including tapentadol or tramadol are not advised as a first or second-line treatment for painful DPN according to the 2017 position statement by the ADA, due to the high risk of addiction and other adverse events.[74] **In the most recent guideline by the ADA (2021 Standards of Care) topical lidocaine is not mentioned as a treatment option.** Rather, initial recommended agents include gabapentin, pregabalin, and duloxetine (with high-quality evidence).[75] Other medications mentioned as potentially effective are tricyclic antidepressants, venlafaxine, carbamazepine, and topical capsaicin, without an evidence rating provided.

The 2011 American Academy of Neurology (AAN) guideline for DPN noted low-level evidence in support of the lidocaine patch for pain associated with DPN based on two class III studies (eg, nonrandomized, nonblinded trial with less favorable controls).[76,77] Other guideline and review authors have proposed topical lidocaine as an option for *localized, peripheral neuropathic pain* especially if there is concern or problems with CNS side effects with the oral options.[22,78] Regarding opioids, the 2011 AAN guideline and several international guidelines have listed the class as a second- or third-line option but often a lower-potency agent and/or dosing is to be initiated (tramadol is mentioned as most studied in 2011 Canadian guideline[79]).[22,76,80] Generally, a personalized approach is supported in guidelines with therapy tailored to maximize response with the least side effects possible.[81] Despite low-quality, limited evidence with lidocaine patches, it is considered to have a favorable tolerability and safety profile relative to oral therapies;[21,33,34,56] so, this could be a good option for a patient, with respect to their unique patient history/co-morbidities, over systemic therapies with potentially more side effects.[22,82]

Recent systematic reviews cite only 1 RCT with topical lidocaine for DPN, in which 5% lidocaine plaster, up to 4 plasters per 12 hour application (a European product that is similar to the lidocaine 5% patch[37]) was compared to placebo and pregabalin up to 600 mg/day (open-label arms, over 4 weeks).[34,81,83] Lidocaine plaster was found to provide similar pain relief compared to pregabalin (in the DPN subgroup,

n=204) but further improvement in quality of life was observed in the lidocaine arm.[38] Additionally, there were less drug-related adverse events and discontinuations with lidocaine versus pregabalin. Compared with placebo, patients treated with the lidocaine plaster were significantly more likely to achieve a clinically meaningful reductions in pain, by 30% or 50% decrease from baseline (based the single available RCT).[83] Other small, short-term, non-controlled studies also suggest improved pain intensity/relief scores with lidocaine plaster added-on to the patient's existing stable analgesic regimen.[34,55] Indirectly comparing meta-analysis effect estimates, the lidocaine plaster appears to be similarly effective to opioids and other agents (eg, pregabalin, and SNRIs) for improving pain (per numeric rating scale) and providing a 30% or 50% reduction in DPN pain.[83] Review authors have highlighted that lidocaine plaster can be a suitable option, *although supported by limited evidence*, with the advantage of having a lower systemic side effect burden than oral options.[56,83]

Low Back Pain (LBP)

Pain may be a generated from both nociceptive and neuropathic mechanisms in patients with LBP.[84] Several open-label, uncontrolled studies and case series have suggested 5% lidocaine patches are efficacious for the reduction of low back pain with a neuropathic component.[85-89] The longest of these studies assessed 6 weeks of treatment.[85] Based on expert opinion, positive predictors of the patient having good response with lidocaine patch include localized pain, hyperalgesia and/or allodynia.[84] These positive findings, together with the medication posing less systemic side effect risk, have led to the patch being highlighted by specialists as a suitable option for use in LBP.[1,87] Nonetheless, the scant RCT evidence available (1 small study in 30 patients) has failed to show separation of lidocaine 5% from placebo with respect to efficacy. After 2 weeks of treatment, lidocaine 5% and the placebo patch arms both had at least 50% of patients achieving a 50% decrease in pain from baseline.[90] Authors highlighted that a potent placebo-effect cannot be ruled out when it comes to the efficacy of lidocaine patches in chronic back pain patients.[85,90] With limited evidence available, further research is necessary to confirm the positive effect of lidocaine rather than a placebo effect from the patch apart from lidocaine.[57]

Lidocaine patches were not mentioned as a treatment option in several recent US and international guidelines addressing the management of LBP, likely do to the lack of high-level controlled study evidence in LBP.[91-95] In the 2020 guideline by the North American Spine Society (NASS), authors state that evidence was insufficient to make a recommendation *for or against* the use of lidocaine patch for LBP.[94,96]

Postherpetic Neuralgia (PHN)

The treatment of PHN has been addressed under the umbrella of neuropathic pain in which the following agents were strongly recommended in the 2015 guideline by NeuPSIG-IASP: pregabalin, gabapentin, tricyclic antidepressants (eg, amitriptyline), serotonin-norepinephrine reuptake inhibitors (eg, duloxetine).[22] Lidocaine patches and capsaicin 8% patches were weakly recommended as second-line options; yet, in 2010, the European Federation of Neurological Societies considered lidocaine plaster a first-line therapy for PHN.[22,97] Based on survey information, it appears that lidocaine patches are often used as monotherapy or as part of a multimodal pain regimen in PHN.[98] Authors have noted some observational evidence suggesting improvements in pain intensity when lidocaine 5% patches were used adjunctively to systemic therapies (eg, NSAIDs, opioids, TCAs, gabapentin) in patients who had

experienced insufficient relief with systemic monotherapy.[71] Additionally, treatment with lidocaine plaster was better tolerated, with less drug-related adverse events and discontinuations, in a 4 week RCT compared to pregabalin, while also leading to a greater proportion of responders (in the PHN group, n=96) and further improvement in quality of life compared to pregabalin.[38]

Products that are FDA approved for the treatment of PHN are the oral therapies, gabapentin, gabapentin enacarbil, and pregabalin; and the topical patches, lidocaine 5% (eg, Lidoderm and generic), lidocaine 1.8% (ZTLido), and capsaicin 8% (Qtenza). Approval of the 1.8% lidocaine patch for PHN, in 2018, relied on efficacy and safety data from the 5% patch (Lidoderm) in addition to pharmacokinetic and dermal safety studies of the 1.8% formulation. The newer 1.8% formulation provides comparable, low-level systemic drug exposure to the lidocaine 5% patch but uses a lower concentration of drug per patch (36 mg/patch versus 700 mg/patch). Dosing is the same for both products: up to three patches can be applied at a time for up to 12 hours, followed by 12 hours off. Patches can be cut to size. The FDA approval review described that ZTLido was developed to provide better adhesive ability. Phase I adhesion studies suggest improved adhesion with ZTLido versus Lidoderm or the generic Mylan 5% products.[37]

Table 6. Lidocaine Patches, Product Information[44,45,99]

Product	Labeling in common	Other notes in labeling
Lidocaine 5% (Lidoderm and generics)	**Indication**: for relief of pain associated with postherpetic neuralgia in adults **Dosage**: apply up to a maximum of 3 patches or topical systems at a time for up to 12 hours in a 24-hour period (with 12 hours off).	▪ The 5% patch may not stick if it gets wet; should avoid contact with water (ie, bathing, swimming, or showering)
ZTLido 1.8% Topical System	▪ Smaller application areas (ie, lower dosage) is recommended for patients who are debilitated or with impaired elimination **Administration** ▪ Should apply to intact skin, covering the most painful area ▪ May cut into smaller pieces prior to removing the release liner ▪ Avoid applying external heat sources to patch/topical system since this could increase exposure	▪ One ZTLido topical system provides equivalent drug exposure as to one Lidoderm 5% patch ▪ Can be used during moderate exercise (eg, biking for 30 minutes) ▪ Can be exposed to water (eg, showering for 10 minutes or immersion for 15 minutes)

Neuropathic Pain Related to Cancer

Neuropathic caner pain is described to result from peripheral or central nerve damage "…as a consequence of compression by or infiltration of the tumor or from treatment toxicity," producing burning, numbing, or shooting painful sensations with or without additional neurological manifestations (eg, sensory changes, muscle weakness, or autonomic dysfunction).[16] In a 2017 European guideline,

authors recommended lidocaine patches as a treatment option for neuropathic pain due to cancer based on level III evidence (ie, non-experimental descriptive studies).[16,100] A 2019 National Comprehensive Cancer Network (NCCN) guideline notes that lidocaine gel and patch forms have data suggesting they are helpful for reducing cancer-related neuropathic pain; however, authors do not give a specific graded recommendation regarding their use.[101]

Other NeP conditions where topical lidocaine was not mentioned in disease-specific clinical guidelines or systematic reviews:

- **Trigeminal neuralgia**: Experts have described that trigeminal neuralgia does not respond to typical agents used for other neuropathies.[22] Carbamazepine and oxcarbazepine are first-line agents for classical trigeminal neuralgia. Lamotrigine, gabapentin, botulinum toxin type A, pregabalin, baclofen, and phenytoin are alternative options as monotherapy or add-on therapy.[97,102] The recent European Academy of Neurology guideline on trigeminal neuralgia (2019) does not mention topical lidocaine as a treatment option for this condition.[102]

- **Alcohol-induced peripheral neuropathy**: There is a high prevalence of peripheral neuropathy in chronic alcohol abusers (about 47%) but very little high-level evidence on the management of neuropathy for this population.[26] A recent systematic review concludes that limited data is generally supportive of abstinence and/or vitamin supplementation (B-vitamins including thiamine), and no information is cited regarding topical lidocaine in this population.[26]

- **Chronic inflammatory demyelinating polyradiculoneuropathy** (CIDP): The 2010 European guideline for the management of CIDP described, "There is a dearth of evidence concerning general aspects of treatment for symptoms of CIDP such as pain and fatigue."[103] A recent systematic review for the management of pain in CIDP reiterates this point. Add-on neuromodulators (eg, gabapentin, TCAs, SNRIs) and opioids have been used for the management of pain in this population when pain persists despite standard-of-care treatment for moderate to severe CIDP-related disability with intravenous immunoglobulin or steroid therapy, but based on only weak level evidence (ie, case reports) and response appears variable.[30,103] The use of topical lidocaine for this population was not described.[30,103]

- **HIV-related neuropathy**: In patients suffering from HIV-related neuropathy, capsaicin 8% cutaneous patch was considered effective, based on level A evidence, in the 2010 guideline by the European Federation of Neurological Societies.[21] Among reviews that comment on the management of HIV-related neuropathy, capsaicin is the topical therapy option described;[104] lidocaine patches in this specific population has not been sufficiently studied.[23,34,55,58]

Pediatrics

Neuropathic pain can also occur as a symptom (acute or chronic) in pediatric conditions. For example, 5% of shingles cases occur in children and about 1 in 4 of these pediatric cases develop postherpetic neuralgia, according to the Dallas Children's Medical Center.[105] Risk factors include a history of chickenpox and weakened immune systems (ie, AIDS or certain cancers).[105] Moreover, children are not invincible to traumatic injury/accidents that may cause neuropathic damage/pain or other NeP causes (CRPS, congenital diseases, metabolic related, or cancer-treatment related).[106,107] Unfortunately, there is a paucity of evidence (and particularly high quality evidence) regarding pharmacologic interventions for chronic pediatric pain.[108] The lack of FDA-approved neuropathic pain treatments specifically for pediatric patients leaves off-label use of therapies to accommodate the treatment need.

Reviews focused on the management of non-cancer chronic pain in pediatric patients mainly describe 5% lidocaine plaster or patches, as opposed to other lidocaine formulations, for neuropathic pain in pediatric patients.[106,109,110] Uncontrolled observational or descriptive reports we are aware of include the setting of burn injury in children,[64] vaso-occlusive crises pain in sickle cell disease,[111] or for post-surgical pain/painful scar (case reports following colostomy, thoracotomy or laminectomy[112]).

- In a study with a pharmacokinetic evaluation for the 5% plaster in 14 pediatric patients (age range 8 to 16 years; mean age of 11 years, 7 months) with NeP related to burn injury, up to half a plaster was applied for 12 hours in a 24 hour period over 3 months.[64] Based on plasma measurements taken up to 60 hours after patch application, authors commented that all measured plasma concentrations of lidocaine were well below the level associated with toxicity. Moreover, the concentrations "…were also much lower than those achieved with other topical lidocaine formulations (such as eutectic mixture of lidocaine and prilocaine [EMLA])."[64] The plaster was well-tolerated as no patients developed local reactions. With the positive findings authors commented that that larger studies should be undertaken to continue establishing the safety and efficacy of this therapeutic option for pediatric NeP.[64]

In 2020, the Canadian Agency for Drugs and Technologies in Health commissioned a review of clinical guidelines addressing chronic pain treatment in pediatric patients. They found only one evidence-based guideline meeting their inclusion criteria.[113] In this 2018 guideline by the Scottish Government, authors recommended considering lidocaine 5% patches for localized neuropathic pain in pediatric patients, "…particularly when aiming to improve compliance with physiotherapy regimes," based on level 3 evidence (ie, non-analytical studies).[113,114] Authors describe a lack of high-quality evidence for lidocaine patches but positive findings for safety and efficacy among case series reports.[112,114,115] Other options mentioned as possibly helpful for pediatric neuropathic pain were gabapentinoids and TCAs. Experts among the Pain in Children Special Interest Group (PICSIG) of the British Pain Society have recommended that the lidocaine plaster be considered early on in a multidisciplinary treatment approach for neuropathic pediatric-pain management, as there is much reluctance toward using long-term antidepressant or antiepileptic medication in children and adolescents.[109] The advised dose recommend per application (12 hours on, 12 hours off) was up to one plaster for children <30 kg, up to two plasters for 30 kg to 60 kg and up to three plasters if >60 kg.[109] Oncology specialists also have

recommended lidocaine 5% patches for cancer-related neuropathic pain, second-in-line to gabapentinoids and TCAs in the ambulatory setting; authors advised one lidocaine patch per 12 hours.[110]

Acute Pain

One meta-analysis (MA) was identified that addressed lidocaine patches for acute post-surgical pain.[116] Authors located 5 controlled trials, accounting for 251 adult patients. No significant difference was found for the primary meta-analytic outcomes: pain scores at 24 hours after patch application, cumulative opioid consumption over 24 hours, or hospital stay. Although the differences were not significant, point-estimates tended to favor lidocaine.[116] An RCT of 80 patients published after this MA, did not identify differences in pain reduction with lidocaine 5% versus placebo for post-thoracotomy pain or total opioid consumption 3 days post-procedure, but authors note that this may have been due to lower than expected pain scores and low opioid use overall in each group.[117]

Other Chronic Musculoskeletal Pain

In a 2014 expert opinion paper by orthopedic surgery specialists from the Division of Orthopaedic Surgery, Albany Medical Center, authors describe that lidocaine patches may have a modest efficacy for chronic low back pain and chronic osteoarthritis pain.[118] Cited references track back to either mentions of lidocaine for neuropathic pain or very limited, weak evidence (uncontrolled observational studies) for conditions undefined as neuropathic (non-radicular LBP, osteoarthritis of the knee).[119,120] Due to the design of these open-label observational studies, the original investigators explained that the positive effect from lidocaine patches "…may have been due to treatment effect, placebo effect, changes in underlying disease state, or a combination of these factors;" and so must be clarified with well-designed RCTs.[121]

Although evidence supporting the use of topical lidocaine is limited for pain not otherwise described as neuropathic, instances where practitioners may be inclined to select lidocaine patches on a case-by-case basis for musculoskeletal pain may relate to the following:

- Inadequate pain relief with single-therapy regimens in the management of chronic pain[121]
- Need for an alternative an option if other indicated topicals (NSAID or capsaicin) or systemic therapies are not tolerated or pose drug-disease or drug-drug interactions; or as effort to avoid side effects and negative outcomes related to chronic opioid use.[104]
    - For example, NSAIDs may be inappropriate for those with peptic ulcer disease, hypertension, renal insufficiency, or heart failure. Fall risk/propensity, especially in the elderly, or the impact of sedation that limits function at work or school may make sedating medications unfavorable for some patients (eg, antidepressants and anticonvulsants).[3]

Osteoarthritis (OA)

The 2019 guideline from the American College of Rheumatology and Arthritis Foundation described that there was insufficient data to make a recommendation regarding topical lidocaine preparations for OA.[122] The lack of recommendation for topical lidocaine, including patches, is consistent with the 2020 OA guideline from NICE.[123] Systematic reviews cite observational, non-controlled evidence suggesting osteoarthritic pain reduction (of the knee) after 2 weeks of treatment with lidocaine patch either as monotherapy or add-on therapy; however, authors highlight that the suggested benefits should be confirmed by further research in well-designed controlled studies.[57,58,120]

Pharmacotherapies that are strongly recommended by the American College of Rheumatology include oral and topical NSAIDs along with intra-articular steroids but preference of each depends on the affected location (ie, knee, hand, hip). Other options with lower grade of recommendation included acetaminophen, tramadol, and duloxetine for the knee, hip, and hand; topical NSAIDs, intra-articular steroids, and chondroitin for the hand; and topical capsaicin for the knee.[122]

A 2018, opioid-sparing RCT reported no significant benefits (pain-related function or pain intensity) of an opioid-based treatment approach over a non-opioid focused treatment approach for osteoarthritic pain.[11] Nonetheless, the study was not designed to determine whether efficacy was due to lidocaine patches rather than other topicals or non-opioid systemic agents included in the multimodal non-opioid treatment arm (Step 1 was acetaminophen and/or NSAIDs; Step 2 included add-on gabapentin, TCA, or topical treatment with capsaicin or lidocaine; Step 3 drugs were pregabalin, duloxetine, or tramadol).[11]

Guidelines for other chronic pain conditions without mention of topical lidocaine

Upon scanning a variety of clinical practice guidelines for musculoskeletal disorders, we found no mention of topical lidocaine for the following conditions (respective guideline in parentheses):

- Spondyloarthritis, ankylosing spondylitis and nonradiographic axial spondyloarthritis (2019 ACR[124] , 2017 NICE[125]); Psoriatic arthritis (2018 ACR[126])
- Juvenile idiopathic arthritis (eg, non-systemic polyarthritis, sacroiliitis, or enthesitis) (2019 ACR[127])
- Rheumatoid arthritis (2021 ACR[128], 2018 NICE[129])
- Osteoarthritis (2020 NICE [123])
- Gout (2020 ACR[130])
- Chronic widespread pain and/or fibromyalgia (2017 EULAR[131]; British Pain Society 2014[132]; 2013 Canadian Pain Society and Canadian Rheumatology Association[133])
- Canadian guideline for opioid therapy and chronic noncancer pain,[42] 2017

Reports addressing opioid consumption during the use of lidocaine patches

- A 2020 systematic review for RCTs addressing post-operative acute pain management in patients undergoing surgery concluded that transdermal lidocaine may be of benefit for post-surgical pain reduction (eg, 6 to 72 hours post-surgery) versus placebo in certain types of surgery (eg, laparoscopic, but not all) with low risk of toxicity.[134] Yet, outcomes regarding short-term consumption of opioids varied among studies: 2 of 6 studies measuring opioid use resulted in a significant reduction in opioid consumption versus placebo during the post-operative hospital stay, while the other 4 studies did not result in significant differences.[134]

- We are also aware of 2 additional RCTs following the publication of the aforementioned 2020 systematic review.
    - A small RCT of 57 patients reported a reduction in pain and the cumulative opioid dose 48 hours post-sternotomy with the 5% lidocaine patch versus placebo.[69]
    - A small RCT of 65 patients reported a reduction in pain following cesarean section with the 5% lidocaine patch versus placebo at 36 hours post-procedure, yet the cumulative tramadol dose, measured at 24 hours post-surgery, was similar between the 2 treatment arms.[135]

- Based on a case report, a patient suffering from a chronic leg ulceration due to necrobiotic xanthogranuloma (a rare, chronic form of non-Langerhans histiocytosis) was reported to benefit from use of lidocaine 5% patches and was able to reduce opioid use as a result of pain relief from lidocaine.[136]

Safety

Relative to systemic options for pain management, expert reviewers largely consider topical lidocaine such as the 5% patch to have a favorable safety profile,[21,55,137] as the risk of drug-drug interactions and systemic side effects/toxicity is "much reduced."[34] Baron et al, 2016, further describe that themes among the literature regarding lidocaine plaster/patch for treating localized neuropathy were (1) the excellent tolerability and safety of the plaster, which can increase patients' adherence to treatment, (2) continued efficacy over long-term treatment, and (3) significant reduction in the size of the painful area."[34,54]

The 2014 Canadian guideline comments that "Systemic side effects [with topical lidocaine] are extremely rare as a result of negligible blood levels"[53]

- **Absorption with lidocaine patch formulations:** Prescribing information for Lidoderm describes that when used within the labeled dosing recommendations, about 3% of the dose applied is absorbed into the systemic circulation and the mean peak blood concentration of lidocaine is about a tenth of the therapeutic concentration employed for treating cardiac

arrhythmias.[44,99,138] Low systemic delivery is also expected with the ZTlido 1.8% (lidocaine topical system) considering that one ZTlido system provides an equivalent lidocaine exposure to one Lidoderm patch.[45]

Following a review of the literature, an expert consensus panel summarized that about 5% of patients may experience adverse reactions with lidocaine plaster/patch, based on controlled studies.[21] These are usually transient local skin reactions (eg, pruritus, erythema, burning, rash, edema and dermatitis). One comparative study found lidocaine plaster was better tolerated for treating DPN and PHN compared to pregabalin: total adverse events rate with lidocaine plaster was 5.8% versus 41.2% with oral pregabalin.[21,38]

Special populations

- **Severe hepatic or renal insufficiency:** Lidocaine is highly hepatically metabolized to nonactive metabolites that are renally excreted (<10% excreted as unchanged drug).[45,138] In healthy volunteers, the elimination half-life of lidocaine was 7.6 hours but may be delayed in cardiac, renal or hepatic insufficiency. Though recommendations for specific dose adjustments are not provided in product labeling, there are labeled warnings that impaired elimination (ie, via severe hepatic disease) places patients at greater risk of toxicity.[45] Severe renal disease may also pose risk.[21] Labeled dosing for the patch system yields an average peak blood concentration of 0.13µg/mL, "…but concentrations higher than 0.25 µg/mL have been observed in some individuals."[138] A toxic blood level of lidocaine is expected at 5µg/mL onward.[45]

- **Pregnancy:** There is insufficient human data in pregnant women for topical lidocaine, short-term or long-term, to inform about the drug-associated risk for major birth defects and miscarriage. Animal data with lidocaine subcutaneous infusion at 45 times the maximum recommended daily dosage (respective to the patch system) during the period of organogenesis resulted in lower fetal body weights.[45] Lidocaine readily crosses the placenta and is excreted into human milk.[21,139] Cord:maternal serum concentration ratios documented with IV and epidural administration were between 50 to 70%. Briggs et al describes, "In one report, offspring of mothers receiving continuous lumbar epidural blocks had significantly lower scores on tests of muscle strength and tone than did controls…"; case reports suggest lidocaine may cause central nervous system depression at high serum concentrations in the newborn; but some reports describe no adverse outcomes during continuous infusion epidural analgesia.[139] Overall, Briggs et al Drugs in Pregnancy and Lactation rates lidocaine as compatible during pregnancy and as probably compatible during breastfeeding.[139] Nonetheless, caution is warranted for use during nursing.[45]

Common adverse effects

for topical lidocaine include local irritation, pruritus, erythema, and rash.[1,45] Labeling for the intradermal lidocaine powder (Zingo) formulation, for numbing the skin before venipuncture or IV cannulation, lists common adverse effects as local erythema (53%-67%), petechiae (44%-46%), edema (4%-8%), and pruritus (1%-9%).[140]

Warnings

- A **boxed warning** for life-threatening and fatal events in infants and young children is labeled for the oral topical 2% viscous solution. Postmarketing cases of seizures, cardiopulmonary arrest,

and death have been reported in children under 3 years of age following use of viscous lidocaine without adherence to dosing and administration recommendations.[141]

- **Excessive Dosing/Overexposure**: Applying more than the recommended quantity of patches per area, or use for longer or more frequent than recommended could result in supra-therapeutic concentrations and toxicity. Implications of hepatic and renal impairment should be considered since lidocaine is metabolized by the liver, and the parent molecule and metabolites are excreted by the kidneys (<10% as unchanged drug).[138] Avoid placing on non-intact skin or application of external heat sources to the application area.[45]

- **Methemoglobinemia (MET)**: Cases of methemoglobinemia have been reported while using lidocaine. Patients at higher risk of MET are those under 6 months of age, those with glucose-6-phosphate dehydrogenase deficiency, history of congenital or idiopathic methemoglobinemia, cardiac or pulmonary insufficiency, or those with exposure to oxidizing agents (eg, chlorine, ammonium perchlorate). Signs of MET include cyanotic skin discoloration and/or abnormal coloration of the blood; serve MET can lead to seizures, coma, arrhythmias, and death.

- **Application site reactions and/or hypersensitivity is possible**: Although cross sensitivity with other para-aminobenzoic acid (PABA) derivatives is uncertain, patients with history or reactions to PABAs should be warned and monitored. [45]

- **Accidental Exposure**: store and dispose lidocaine products properly, keeping out of the reach of children especially and pets.
    - Due to the large amount of lidocaine remaining in the 5% patch after it has been worn as directed, there is risk of accidental exposure to children and pets if not disposed properly. Although there is a smaller amount of residual drug remaining after the wear of the ZTLido patch, the bioavailability of the formulation is high, so care must still be taken to dispose of the patch properly after use.

Potential drug-drug interactions[44,45]

- There is potential for additive toxicity if lidocaine is used in combination with Class I antiarrhythmics (eg, tocainide and mexiletine) or other products containing local anesthetic agents; weigh risk vs. benefit prior to such concomitant use.
    - Patients may be at increased risk of **methemoglobinemia** if used in combination with nitrates/nitrites (eg, nitrous oxide, nitroprusside), local anesthetics (eg, benzocaine, bupivacaine, prilocaine), certain antineoplastic agents (eg, cyclophosphamide, hydroxyurea), certain antibiotics (nitrofurantoin, sulfonamides), anticonvulsants (phenytoin, sodium valproate), or other drugs (acetaminophen, metoclopramide); see package insert for full list of example agents.

Considerations for Discussion Regarding Lidocaine Patches

i. Utah Medicaid fee-for-service utilization of lidocaine prescription patches

- Over the last year (September 2020 through August 2021), there were **60 pharmacy claims for 5% lidocaine patches, attributed to 25 patients**. All utilizers were adults (ie, no pediatric claims), and no claims were found for the 1.8% patch.

- Utilization of lidocaine patches is influenced by the prior authorization criteria (PA) and quantity limits currently in place for these products. The lidocaine 5% and 1.8% patches are listed as non-preferred on the Utah Medicaid PDL[§] with dispensing restricted to a supply of 90 patches per 30 days. This limit is consistent with the labeled maximum recommended dosage (ie, up to 3 patches in a 24 hour period). Drug-specific prior authorization criteria (last updated 6/1/21) requires prescribing to be for the treatment of postherpetic neuralgia, or requires the provider's documentation of the clinical rationale for requesting the patch instead of other topical lidocaine forms. The PA form also notes that "Approval may also be considered for common, accepted, standard-of-care uses if the request is accompanied by sound clinical rationale and supporting literature (included with this request)."[4]

ii. The Utah Medicaid DUR Board may consider discussing the allowable scope of use for lidocaine patches for off-label chronic pain management purposes:

- In addition to the on-label indication of postherpetic neuralgia pain, pharmacy compendia (Micromedex) listed 2 off-label indications where patients may benefit from a lidocaine prescription patch: neuropathy due to diabetes mellitus, and cancer-related pain. In addition, burn-injury was listed as an off-label use for lidocaine 5% cream.
- Despite lower grade evidence, **clinical guidelines have recommended lidocaine patches as an option particularly for localized neuropathic pain** because of its positive safety profile and provider/patient values and preference in the context of limited alternative medications that often pose tolerability issues.[21,22,53] However, guidelines and expert consensus statements have varied regarding whether lidocaine patches (versus systemic options) are a primary, secondary, or tertiary-line of treatment in pain conditions with a neuropathic component. Two disease-specific guidelines concluded that there was insufficient evidence to make a recommendation *for or against the use* of topical lidocaine either for osteoarthritis[122] or for low back pain[93] (despite some observational studies suggesting benefits); yet, the guidelines broadly addressing

[§] Topical lidocaine products with preferred status on the Utah Medicaid PDL are generic lidocaine cream, gel, ointment, and solution as single ingredient; and the generic combination products, lidocaine/hydrocortisone rectal cream and lidocaine/prilocaine. Non-preferred products include the Lidotrel 3.88% cream, lidocaine generic lotion, lidocaine generic patch, Lidoderm patch, Lydexa 4.12% cream, and Ztlido 1.8% patch; and the **c**ombination products, Epifoam, generic lidocaine/hydrocortisone rectal gel, Pliaglis (lidocaine/tetracaine), and Synera (lidocaine/tetracaine).

neuropathic pain seem to imply lidocaine patches as an option for neuropathic low back pain. Positive predictors for treatment success with the lidocaine patch in LBP include localized pain, hyperalgesia, and/or allodynia, based on expert opinion.[84] Moreover, pain specialists have highlighted that a benefit of the patch is that it provides a barrier on the skin, which can be particularly useful for localized allodynia.[21]

- Since there is an unmet need with the lack of approved medications for pediatric neuropathic pain, pediatricians are limited to off-label options. Positive findings for the safety and efficacy of the lidocaine plaster have been demonstrated in uncontrolled, observational studies or case series reports.[64,112,114,115] Despite the limited low-quality evidence, two international guidelines recommended the lidocaine plaster for pediatric neuropathic pain; one of these describes that there is reluctance by practitioners to use long-term antidepressant or antiepileptic medication in children and adolescents, so a non-systemic option is often preferred.[106] The dose recommend per application (12 hours on, 12 hours off) was up to one lidocaine plaster for children <30 kg, up to 2 plasters for 30 kg to 60 kg and up to three plasters if >60 kg.[106] Pediatricians in the oncology setting also propose lidocaine 5% patches as an option for neuropathic pain (authors advised 1 patch per 12 hours).[107]

iii. If neuropathic pain is required as a pre-requisite for coverage of lidocaine patches, via prior authorization, note the ***limitations of ICD-10 coding for determining whether the patient suffers from neuropathic pain***

- Scholz et al described the "…complexity of ICD-10 codes, and the incomplete or inaccurate coverage of relevant clinical conditions, risk underreporting of chronic pain," including neuropathic pain.[142] Possible consequences of this are underrepresentation of the patient's pain condition, inefficiently applied resources (eg, therapies) by insurers, or unsound public health strategies by policy makers.[142] Although some patients may be positively identified as having neuropathic pain by reviewing their ICD-10 coding, some cases may be incorrectly assumed as negative since current ICD-10 coding does not always facilitate conveying whether the patient suffers from neuropathic pain ***as a symptom*** of the diagnosed condition or disease. Thus, if authorization is dependent on the patient having a neuropathic pain component and neuropathic pain is unidentifiable from the patient's ICD-10 coding, we recommend consultation with the provider to gain a more thorough understanding of patient's condition.

iv. In the context of the opioid epidemic and recommendations from US healthcare agencies urging for access to non-opioid alternatives, and in light of potential insufficient relief with systemic therapies (non-opioid and opioid options) for chronic pain (including neuropathic pain), the following approaches *and their feasibility* may be considered:

- Potential point-of-sale strategies to allow faster access to non-preferred lidocaine patches, upon a prescription by their provider, particularly for patients at risk of opioid-related adverse events who could potentially be recognized in a simple manner by the computer system at the point-of-sale.
    - Recognition may be based on one or more of the following: the patient having a recent opioid prescription; ICD-10 history related to opioid dependence, long-term opioid

therapy, opioid use disorder, or other addiction/abuse ICD-10 related codes for other drugs of abuse.
    - Prompt approval could be considered so that the patient does not have to walk away without the non-opioid alternative and possibly resort to opioid use while awaiting later-day processing of a prior authorization. Claims for non-preferred products may be reviewed retrospectively against the patient's diagnosis coding and provider consultation to verify the patient has a neuropathic pain inducing condition. Provider outreach could be employed to address whether the patient has tried less costly alternatives where there is not strong support of one formulation over the other.
- A case-by-case approach, with provider consultation, may be considered for lidocaine patches as a last-in-line option for localized non-specific pain (not otherwise diagnosed as neuropathic) where the provider views other options as inappropriate (eg, side effect risk or drug-disease interaction outweighs benefits) or where trials of other options have failed or have been insufficient.

Summary

Considering the negative societal impacts of the opioid epidemic, the CDC and DHHS have advocated for patient access to non-opioid alternatives for the management of chronic pain. Access to non-opioid pharmacotherapy is even more pertinent when there may be insufficient insurance coverage/resources for behavioral and complementary pain management services. For those who go on to receive opioids for chronic pain, about 8-12% develop opioid use disorder.[8,9] The CDC and the US Pain Management Best Practices Inter-Agency Task Force have highlighted topical lidocaine as an option particularly for neuropathic pain (NeP) among other non-opioid treatment modalities.[3]

Approved indications for topical lidocaine products are specific to the formulation, but include postherpetic neuralgia for the patches; or, for other topicals, include anesthetization for irritated oral/oral-pharynx mucous membranes, urethritis, or painful clinical procedures (eg, intubation, dermatologic surgeries, or procedures involving urethra). Despite the narrow approved indication for lidocaine patches, they have been widely recommended for the treatment of peripheral or localized neuropathic pain (LNP).

The strength of recommendation provided in evidence-based guidelines for the use of the lidocaine patch or plaster to treat neuropathic pain is generally graded as weak due to limited high quality or inconsistent studies, and positive findings in narrow subpopulations of LNP etiologies.[21,22,53] Despite lower grade evidence, authors maintain lidocaine patches as an option because of its favorable safety profile, and provider/patient values or preference in the context of limited alternative medications that often pose tolerability issues. A 2017 expert consensus statement, focused on the management of *localized* NeP, advised that lidocaine 5% and capsaicin 8% topical patches be considered as first-line therapy for localized NeP, *regardless of the etiology*.[21]

As a supplement to guidelines addressing general NeP, we reviewed disease-specific guidelines for conditions that can illicit NeP. Lidocaine patches were recommended as an option, especially in the face

of side effects or drug-disease interactions with systemic therapies, for the following conditions (but based on low-level evidence): diabetic peripheral neuropathy (DPN)[77] and neuropathic pain due to cancer.[16] Two other disease-specific guidelines concluded that there was insufficient evidence to make a recommendation *for or against the use* of topical lidocaine for osteoarthritis[122] or low back pain (LBP)[93] (despite presence of some observational studies suggesting benefits). Yet, other guidelines broadly addressing neuropathic pain seem to implicate lidocaine patches as an option for localized neuropathic LBP. Based on expert opinion, positive predictors for treatment success with the lidocaine patch for LBP are localized pain, hyperalgesia, and/or allodynia.[84] With respect to other musculoskeletal or widespread pain conditions (unspecified as neuropathic pain), there were many disease-specific guidelines we screened that lacked mention of lidocaine patches as a treatment option (see list on page 25).

Lidocaine patches are largely reported as well-tolerated. Skin reactions are the most common side effect but are usually transient once the patch is removed.[34,71] The lidocaine plaster appeared better tolerated, with less drug-related adverse events and discontinuations, than with oral pregabalin treatment in a 4-week RCT of patients with neuropathic pain due to DPN or PHN.[38] Patients and prescribers may find advantages with topical therapy, as this route is considered to pose less risk of systemic adverse effects or drug–drug interactions, and has a positive tolerability profile, compared to systemic options for pain (eg, SNRIs, TCAs, gabapentinoids, opioids).[21,22,31,33] Moreover, patient's pain may persist despite treatment with systemic therapy. A 2017 expert consensus review on the management neuropathic pain noted that 60% of patients experience insufficient pain relief with systemic medications.[21]

The 2019 report by the US Pain Management Best Practices Inter-agency Task Force emphasized an individualized, patient-centered approach during the treatment of pain.[7] Providers may find lidocaine patches as a favorable option for trial even in the face of limited evidence, since patients may have inadequate response, intolerability, or drug-disease interaction concerns with the systemic options available.

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Appendix A: Literature Database Searches

Epistemonikos

(lidocaine and (patch* or transdermal or plaster* or 5% or 1.8%) and pain)) AND publication type (Systematic Review) [106 Systematic Review results, September 6, 2021]

Cochrane Library

lidocaine [Title/Abstract keyword] =>58 Systematic Review results (August 17th)

OvidMedline

1. (lidocaine and (patch* or transdermal or plaster* or "5%" or "1.8%") and pain).ti,ab.
2. (Medline or Embase or Pubmed or search*).tw. or (systematic-review or meta-analysis).tw,mp,pt. or meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "Systematic Review"/ or ((systematic* adj3 review*) or (systematic* adj2 search*)).ti,ab,kw,kf. or review.pt.
3. 1 AND 2
4. limit 4 to yr="2012 -Current" [138 results September 21, 2021]

Appendix B: Clinical Guidelines

Guideline Resources Used for the Preparation of this Review

Chronic Pain or Pain Management

- 2019 Guidance from the Pain Management Best Practices Inter-Agency Task Force of the US DHHS[7]
- 2018 Scottish government guideline for management of chronic pain in children[114]
- 2017 Canadian Guideline for Opioid therapy and noncancer pain[42]
- 2016 CDC Guideline for Prescribing Opioids for Chronic Pain[3]

Neuropathic Pain

- 2015 Updated NeuPSIG recommendations for adults with neuropathic pain[22]
- 2014 Canadian Pain Society guideline for chronic neuropathic pain[53]
- 2013 NICE guideline (173): The pharmacological management of neuropathic pain in adults in non-specialist settings [143]
- 2010 EFNS guidelines on the pharmacological treatment of neuropathic pain[144]

Diabetic Neuropathy

- 2021 American Diabetes Association (ADA) Standards of Medical Care in Diabetes[75]
- 2017 ADA Position Statement Regarding Diabetic Neuropathy[74]
- 2011 American Academy of Neurology (AAN) Evidence-based guideline for clinicians; Treatment of painful diabetic neuropathy[77]

Low Back Pain

- 2020 NICE guideline update[95]
- 2019 VA/DoD guideline[93]
- 2017 American College of Physicians[91]

Cancer Pain

- Adult Cancer Pain, NCCN Clinical Practice Guidelines in Oncology[101]

Rheumatologic Painful Conditions

- 2020 NICE guideline for the treatment of osteoarthritis[123]
- 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee[122]

- 2019 American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network guideline for Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis[124]
- 2017 NICE guideline for spondyloarthritis[125]

- 2021 American College of Rheumatology, Management of rheumatoid arthritis in adults[128]
- 2018 NICE guideline for the management of rheumatoid arthritis in adults [129]
- 2019 American College of Rheumatology, Juvenile idiopathic arthritis guideline (eg, non-systemic polyarthritis, sacroiliitis, or enthesitis)[127]
- Gout (2020 ACR[130])

Fibromyalgia

- 2017 European League Against Rheumatism guideline for the management of fibromyalgia[131]
- 2014 British Pain Society guideline for the management of chronic widespread pain including fibromyalgia[132]
- 2013 Canadian Pain Society and Canadian Rheumatology Association guideline for the care of patients with fibromyalgia[133]

Other Conditions

- 2019 European Academy of Neurology guideline on trigeminal neuralgia[102]
- 2010 European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy[103]

Expert Consensus Statements and Treatment Algorithms

- 2020 International work group consensus on intervention for lumbar facet joint pain[94]
- 2019 Neuropathic pain in pediatric oncology[110]
- 2018 British Pain Society, Lidocaine plasters for localized pain[137]
- 2017 Localized Neuropathic pain, Pickering et al[21]
- 2016 Treatment algorithm for localized neuropathic pain, Allegri et al[33]

Table 1. Select Guidelines for the Management of Pain

Professional Organization and Guideline	Pertinent Points Related to Non-opioid Therapy for Treatment of Pain
Pain Management Best Practices	
Guidance from the Pain Management Best Practices Inter-Agency Task Force of the US DHHS, 2019[7]	Select comments regarding gaps in care: ▪ "Multimodal, non-opioid therapies are underutilized in the perioperative, inflammatory, musculoskeletal, and neuropathic injury settings." ▪ "Chronic pain is often ineffectively managed for a variety of reasons, including clinician training, patient access, and other barriers to care…" Excerpts mentioning lidocaine ➢ "Use procedure-specific, multimodal regimens and therapies when indicated in the perioperative period, including various non-opioid medications, ultrasound-guided nerve blocks, analgesia techniques (e.g.,

	lidocaine, ketamine infusions), and psychological and integrative therapies to mitigate opioid exposure." ➢ "For neuropathic pain, as a first-line therapy, consider anticonvulsants (e.g., gabapentin, pregabalin, carbamazepine, oxcarbazepine), SNRIs (e.g., duloxetine, venlafaxine), TCAs (e.g., nortriptyline, amitriptyline), and topical analgesics (e.g., lidocaine, capsaicin)."
Scottish government guideline for management of chronic pain in children, 2018[114]	• Regarding off-label use, such use should better serve the patient's needs than an authorized alternative and be supported with evidence/experience; the clinical rationale should be documented. • Topical analgesics (lidocaine patches or capsaicin): high quality evidence is lacking in children, however, case series studies report positive outcomes on patient functionality with lidocaine patches (ie, low quality evidence) • Authors recommend acetaminophen and NSAIDs to be considered, limiting use to the shortest possible duration • For localized, non-CRPS (chronic regional pain syndrome) or localized non-neuropathic pain, a topical NSAIDs should be considered • Antiepileptic drugs (eg, gabapentin first choice, pregabalin second choice) may be considered for neuropathic pain, particularly by a specialist, as part of a multimodal treatment approach • Los dose amitriptyline can be considered for functional gastrointestinal disorders (moderate quality evidence), chronic headache, chronic widespread pain and mixed nociceptive/neuropathic back pain (very low quality evidence); nortriptyline is a less sedating alternative to amitriptyline. • Opioids are rarely indicated for chronic pediatric pain and if used should be for as short of a duration as possible
Canadian Guideline for Opioid therapy and noncancer pain, 2017[42]	• Optimize nonopioid pharmacotherapy and nonpharmacologic therapy prior to trial of opioids (strong recommendation). • Opioids are suggested for persistent/problematic pain despite having made effort to optimize non-opioid options under the following conditions. Patients should have a stabilized psychiatric condition, if applicable, prior to stating an opioid (weak recommendation) and (b) and opioids are strongly recommended against in a patient with an active substance use disorder.
CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016[3]	• Expected benefits/risks of pain-therapy options should be considered in light of the patient-specific clinical context before initiation. • Although non-opioid therapies are preferred, this does not mean that all patients should be required to sequentially "fail" nonpharmacologic and nonopioid pharmacologic therapy for access to opioid therapy for chronic pain. Situations in which opioid therapy may be chosen first-line may include serious illness with poor prognosis for return to previous level of function, contraindications to other therapies, and clinician and patient agreement that the overriding goal is patient comfort. • For fibromyalgia and headache, the expected benefits of initiating opioids are unlikely to outweigh risks regardless of previous nonpharmacologic and nonopioid pharmacologic therapies used. • "If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate, to provide greater benefits to patients in improving pain and function." • "Although NSAIDs can be used for exacerbations of nociceptive pain, other medications (e.g., tricyclics, selected anticonvulsants, or **transdermal lidocaine**) generally are recommended for neuropathic pain."

Neuropathic Pain	
Updated NeuPSIG recommendations for adults with neuropathic pain, 2015[22]	***First-line agents*** that are strongly recommended • SNRI antidepressants duloxetine and venlafaxine (high-quality evidence; moderate tolerability/safety) • pregabalin, gabapentin and gabapentin ER/enacarbil (high-quality evidence; moderate to high tolerability/safety) • tricyclic antidepressants (TCAs) (moderate-quality evidence; low to moderate tolerability/safety) • "In select circumstances, e.g when there are concerns due to side effects or safety of first-line treatments, particularly in frail and elderly patients, lidocaine patches may be considered as first-line." ***Second-line agents, due to weak evidence supporting use***: • tramadol (moderate-quality evidence; low to moderate tolerability/safety) • lidocaine patches for peripheral neuropathy (eg, 1–3 patches to the painful area for up to 12 hours) (low-quality evidence; highly tolerated/safe) • high-concentration capsaicin patches for peripheral neuropathy; however the long-term safety is unclear in which the concern is for the degeneration of epidermal nerve fibers (high-quality evidence; moderate to high tolerability/safety) ***Third-line*** • subcutaneous botulinum toxin-A; to be used by specialist (low-quality evidence; highly tolerated/safe) • strong opioids (moderate-quality evidence; low to moderate tolerability/safety) **Inconclusive**: combination therapy, capsaicin cream, carbamazepine, topical clonidine, lacosamide, lamotrigine, oxcarbazepine, tapentadol, SSRI antidepressants, topiramate, zonisamide Combination of pregabalin/gabapentin and duloxetine/TCAs may be considered as an alternative to increasing dosages in monotherapy for patients unresponsive to monotherapy with moderate dosages
Canadian Pain Society guideline for chronic neuropathic pain, 2014[53]	**First-line Pharmacotherapy**: anticonvulsants (gabapentin, pregabalin) and certain antidepressants (duloxetine, venlafaxine, TCAs); carbamazepine is first-line only for tic douloureux (idiopathic trigeminal neuralgia) **Second-line**: tramadol and opioid analgesics; lidocaine patches if treating PHN **Third-line**: cannabinoids **Fourth-line**: Topical lidocaine, SSRIs, other anticonvulsants (lamotrigine, lacosamide), methadone, tapentadol, botulinum toxin
2013 NICE guideline (173): The pharmacological management of neuropathic pain in adults in non-specialist settings [143]	For treatment of all neuropathic pain *except trigeminal neuralgia* • Initial therapies to offer: amitriptyline, duloxetine, gabapentin or pregabalin • If the initial choice is inadequate or intolerable, offer one of the remaining 3 drugs, and consider exhausting these options before proceeding to other second tier agents • Second tier agents include short-term tramadol if acute rescue therapy is needed; and capsaicin cream for localized neuropathic pain in those wishing avoid oral treatments • Treatments to be initiated while under specialist care: venlafaxine, capsaicin patch, lacosamide, lamotrigine, levetiracetam, morphine, oxcarbazepine, topiramate, ongoing tramadol, cannabis sativa extract

	For trigeminal neuralgia offer carbamazepine for initial treatment; seek specialist's advice if ineffective
	Diabetic Peripheral Neuropathy (DPN)
American Diabetes Association (ADA) Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes—2021[75]	• Optimization of glucose control is recommended to prevent or delay the development of neuropathy in patients with T1DM and to slow the progression of neuropathy in patients with T2DM • Initial Recommended medications for diabetic neuropathic pain (Level A Recommendation): Pregabalin, duloxetine, or gabapentin • Additional options that may be considered: tricyclic antidepressants, venlafaxine, carbamazepine, and topical capsaicin. • Lidocaine is not mentioned in the guideline for neuropathic pain
ADA 2017 Position Statement Regarding Diabetic Neuropathy[74]	Treatment of neuropathic pain in diabetes ***Initial options recommended***: • pregabalin or duloxetine (Level A) • Gabapentin (Level B) *Other options*: • Tricyclic antidepressants (effective but use with caution due to higher risk of serious side effects). (Level B) • Opioids are not recommended as first- or second-line due to addiction risk and other side effects (Level E)
American Academy of Neurology (AAN) Evidence-based guideline for clinicians Treatment of painful diabetic neuropathy—2011[77]	Non-opioid pharmacotherapy options **Strong evidence** (level A) in support of offering pregabalin **Moderate evidence** (level B): gabapentin, duloxetine, amitriptyline, venlafaxine, capsaicin and isosorbide dinitrate spray, sodium valproate • sodium valproate should be avoided in women of childbearing age, and may cause weight gain and worsening of glycemic control so is usually not the first choice **Weak evidence** (level C): Lidoderm patch Opioids Moderate evidence (level B): Dextromethorphan, morphine sulfate, tramadol, and oxycodone may be considered • Substantial adverse events include sedation, nausea, and constipation with these agents. Use of opioids is also associated with the development of novel pain syndromes (eg, rebound headache) and chronic uses leads to tolerance **Combinations**: venlafaxine may be added to gabapentin to improve response (weak evidence) The **placebo effect** observed in studies reviewed can be considerable, attributing up to a 50% pain reduction. Despite DPN being a chronic disease, there "…are *no data on the efficacy of the chronic use of any treatment*, as most trials have durations of 2 to 20 weeks. It is important to note that the evidence is limited, the degree of effectiveness can be minor, the side effects can be intolerable, the impact on improving physical function is limited…"

Osteoarthritis	
2019 American College of Rheumatology/ Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee[122]	**Strongly recommended**: Oral NSAIDs (for knee, hip, and hand), topical NSAIDs (for knee), intra-articular steroids (for knee and hip) **Conditionally recommended**: • acetaminophen, tramadol, duloxetine (for knee, hip, and hand) • topical NSAIDs intra-articular steroids, and chondroitin (for hand) • topical capsaicin (for knee; formulation/strength no specified) There is insufficient data to make a recommendation regarding topical lidocaine preparations for OA

AAN Level of Evidence (see guideline for full description of definition for each level)[77]

- **Level I =** A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population
- **Level II =** An RCT with methodological with intervention and population of interest, or a prospective matched cohort study with masked or objective outcome assessment in a representative population
- **Level III =** All other controlled trials in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement

Other Notes:

Complex regional pain syndrome is characterized as continuous regional pain that is disproportionate in duration or severity with respect to the usual course of pain after the trauma or lesion. The pain is usually distal with variable progression over time.[145] CRPS type II occurs following nerve damage (eg, stroke). The pain may be felt as burning, allodynia, and/or hyperalgesia. Pain can become exacerbated by movement, pressure, or temperature changes, or stress. Blood flow abnormalities to the region occur and may present edema, skin color and temperature changes. Other symptoms include sweating abnormalities, dystrophy in skin/nails, hair/bone, impairment in motor function and joint mobility. Complications include phlebitis, cellulitis, atrophy, weakness, and trophic changes in bone, joints, and muscles. Social and physical impairments may lead to inability to perform activities of daily living, occupational and recreation activities and ultimately contribute to inappropriate drug use and psychological comorbidities.[145]