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Everybody's Greasing UP, But Should You Rub It In? A Review of Topical Analgesics and Available Evidence in Clinical Trials

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Disclosure

Consulting Fee (eg, Advisory Board): Purdue Pharma LP

Learning Objectives

- Discuss the rationale for compounded topical analgesics
- Review commercially available topical analgesic options
- Describe the mechanism of action and clinical applications of topical analgesics
- Analyze where evidence exists for efficacy with topical analgesics
- Evaluate the efficacy of various topical analgesics and their role in chronic pain

Pretest Question #1

Capsaicin 8% patch is approved for which indication in Europe but not in the United States?

A. Postherpetic neuralgia (PHN)

B. Dynamic mechanical allodynia (DMA)

C. Peripheral neuropathy (PN)

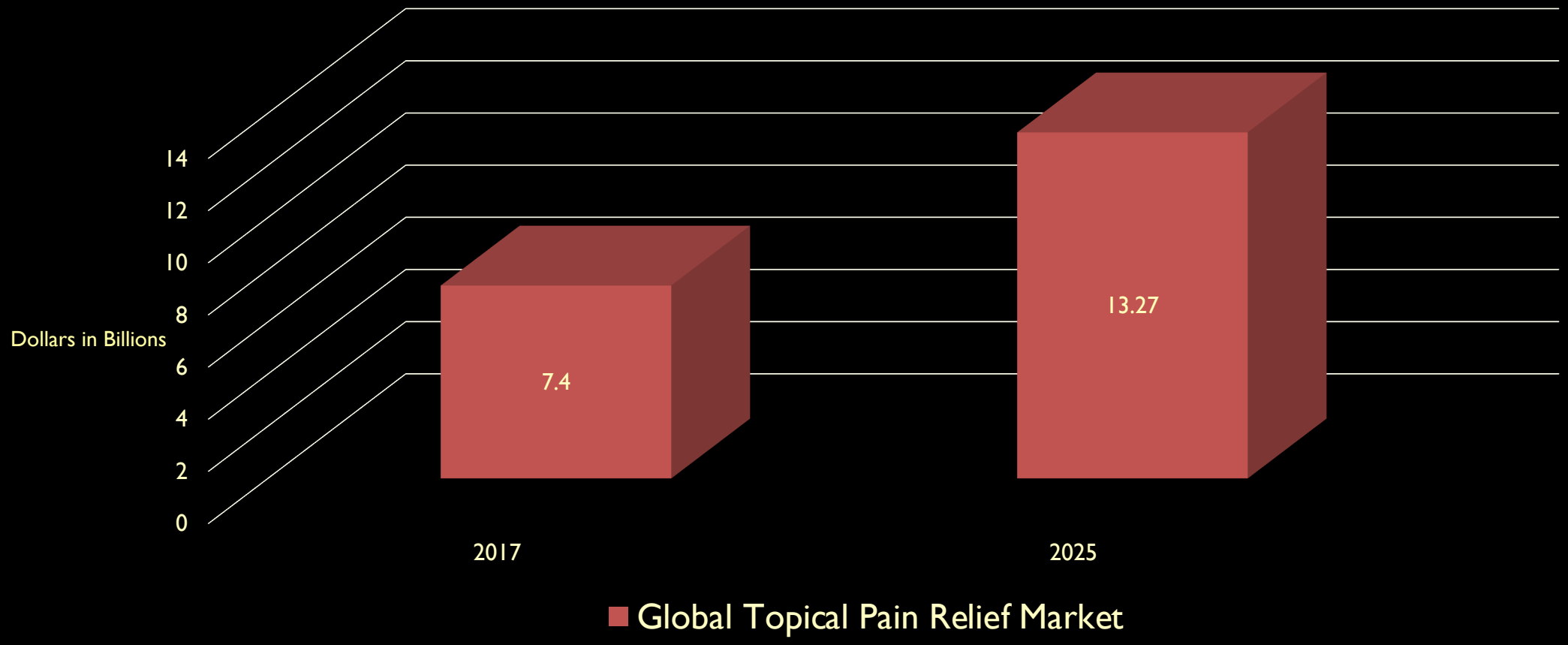
D. Diabetic peripheral neuropathy (DPN)

Pretest Question #2

Which prescription oral NSAIDs are also available as prescription topical formulations in the US?

A. Ketoprofen
B. Meloxicam
C. Celecoxib
D. Diclofenac
E. All of the above

Projected Growth of Topical Analgesic Market



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Dosage Forms and Delivery Methods

Topical

- Local effect
- Under application site
- Not intended for systemic absorption
- Low risk for adverse effects

Transdermal

- Designed to penetrate into systemic circulation
- Achieve therapeutic plasma concentrations
- Alternative dosage form
- Avoid GI or infusion related adverse effects

Various Topical Analgesics

Agent	Availability	Use(s)
Capsaicin	OTC/RX	-Postherpetic neuralgia -HIV neuropathy (off label) -Minor pain
Camphor	OTC	-Minor pain -Pruritus
Diclofenac	RX	-Osteoarthritis -Acute pain -Actinic keratosis
Histamine dihydrochloride	OTC	-Nociceptive pain relief
Lidocaine	OTC/RX	-Postherpetic neuralgia -Localized pain -Pain and itching of anorectal disorders
Menthol	OTC	-Nociceptive pain relief
Menthol/methyl salicylate	OTC	-Nociceptive pain relief
Trolamine salicylate	OTC	-Nociceptive pain relief
Turpentine	OTC	-Nociceptive pain relief

Considerations for Topical Analgesics

Advantages

- Limited systemic absorption
- Effective for localized pain
- Tissue concentration > oral
- Limited adverse effect profile

Disadvantages

- Erratic local absorption
- Variable depth of penetration
- Inaccuracy of dosing
- Require frequent applications
- Oleaginous “greasy” feeling
- Expensive

Salicylate-Containing Rubefacients

Nociceptive Pain

Focus Area:

Menthol/Methyl Salicylate

Salicylate-Containing Rubefacients

- **MOA:** rubefacients cause irritation of the skin, and are believed to relieve pain in muscles, joints, and tendons, and other musculoskeletal pains in the extremities by counterirritation

- Irritation of the sensory nerve endings alters or offsets pain in the underlying muscle or joints that are served by the same nerves

Moore RA, Derry S, Mcquay HJ. Cochrane Database Syst Rev. 2010;(7)

Menthol/Methyl Salicylate

- **Menthol** is an alcohol (peppermint oil)
  - Topically acts to dilate blood vessels, causing a cooling sensation and analgesic effect

- **Methyl salicylate** is an ester oil (wintergreen oil)
  - Topically induces skin redness and irritation leading to analgesic effect
  - Converted to salicylate in the skin

Derry S, et al. Cochrane Database Syst Rev. 2014;(11):CD007403
Center for Drug Evaluation and Research. Application 02-029 . Medical Review(s).

Methyl Salicylate – Key Considerations

- Methyl salicylate is used as a flavoring agent (inactive ingredient) in oral drug products up to a maximum potency of 16 mg

- Allowed as an inactive ingredient in topical gels up to a maximum concentration of 1%

- The maximum systemic salicylate level, in a trial evaluating co-administration of 10 patches (containing 105 mg methyl salicylate/patch), was 0.6782 mg/dL
  - 18-fold lower than the minimum value associated with mild toxicity symptoms
  - ~20% of topically-applied methyl salicylate may be absorbed

47 FR 54646 at 54660; December 3, 1982
Center for Drug Evaluation and Research. Application 02-029 . Medical Review(s).

Salicylate-Containing Rubefacients – Evidence

Cochrane meta-analysis (2014)

- Acute conditions, NNT=3.2, RR=1.9
- Chronic conditions, NNT=6.2, RR=1.6
- Limitation: quality, validity, and size of available studies

Evidence does not support the use of topical salicylate-containing rubefacients for either acute or chronic musculoskeletal pain

Derry S, et al. Cochrane Database Syst Rev. 2014;(11):CD007403

Capsaicin

Nociceptive Pain and Neuropathic Pain

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Capsaicin

- **MOA:** capsaicin, the pungent component of hot chili pepper, is a vanilloid receptor (VR1) agonist
  - Specifically classified as an agonist of the transient receptor potential vanilloid 1 (TRPV1) receptor
- TRPV1 is an ion channel-receptor complex expressed on nociceptive nerve fibers in the skin that detect noxious painful stimuli
- Capsaicin causes an initial enhanced stimulation of the TRPV1
  - Depletion of substance P and desensitization
- Analgesia is mediated by death of distal nerve twigs (C fibers)
  - Reversible loss of autonomic and sensory nerve fibers
  - Autonomic nerves recover in 40-50 days, sensory nerves in 140-150 days

Gibbons CH et al. *Ann Neurol*. 2010; 68(6):888–898.

Moore RA, Derry S, Mcquay HJ. Cochrane Database Syst Rev. 2010;(7)

Crimi N et al. *Clin Exp Allergy*. 1992; 22(10):933–939.

Capsaicin OTC products

Dosage forms

- Creams (0.025%, 0.075%, 0.1%)
- Patches (0.025%)
- Liquid (0.1%, 0.15%)

Application tips:

- Use gloves; wash hands with soap and water after use
- Do not use immediately BEFORE or AFTER a bath or shower
- Do not use on wounds or damaged skin, with a heating pad, with other external analgesic products

Capsaicin 8% Patch

- FDA approved for the management of neuropathic pain associated with postherpetic neuralgia (PHN)
- European Medicines Agency (EMA) approved for peripheral neuropathic pain
- Patch (14 cm x 20 cm) 179 mg of capsaicin
- Only physicians or healthcare professionals under close physician supervision may administer
  - 1-4 patch(es) applied for 60-minute duration, frequency not to exceed every 3 months
  - Pre-treatment with topical anesthetic (± oral analgesic) prior to application; removal with cleansing gel post-application

Center for Drug Evaluation and Research. Application 022395. FDA Medical Review.
European Medicines Agency. Qutenza Capsaicin 8% patch

Capsaicin – Key Considerations

Low dose capsaicin:

- Neuropathic conditions NNT=6.4 (4 weeks), 5.7 (8 weeks)
- Musculoskeletal conditions NNT=8.1
- Neuropathic and musculoskeletal pain, NNH=9.8

High dose capsaicin:

- Neuropathic conditions NNT=6-9
- Adverse events from capsaicin are mainly at the application site (burning, stinging, erythema)

Mason L, et. al. BMJ. 2004;328(7446):991.
Derry S, et al. Cochrane Syst Rev 2013 (2).

Capsaicin – Guidelines

American Academy of Neurology (AAN 2004/2011)

- 2nd line postherpetic neuralgia
- Level B evidence for painful diabetic neuropathy

European Federation of Neurological Societies (EFNS 2010)

- 2nd/3rd line for postherpetic neuralgia
  - Level A (8% patch), Level B (cream) efficacy rating for PHN

International Association for the Study of Pain (IASP 2015)

- Capsaicin 8% patch, 2nd line for peripheral neuropathic pain syndromes

National Institute for Clinical Excellence (NICE 2017)

- Capsaicin reasonable alternative to oral medications for peripheral neuropathy
  - Oral medications 1st line
- Capsaicin cream > capsaicin 8% patch

Dubinsky RM, et al. Neurology 2004: 63: 959-65.
Bril V, et al. Neurology 2011; 76: 1758-65.
Attal N, et al. Eur J Neuro 2010; 17: 1113-23.
Finnerup NB, et al. Lancet Neurol 2015; 162-73.

Lidocaine

Neuropathic Pain

Focus Area: Lidocaine 5% Patch

Topical Lidocaine

MOA: lidocaine is an amide-type local anesthetic agent and is suggested to stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses

- Reduces the frequency rather than the duration of sodium channel opening

Derry S, et al. Cochrane Database Syst Rev. 2014;(7):CD010958.

Lidocaine 5% Patch

- **FDA approved indication:** relief of pain associated with postherpetic neuralgia
- Apply up to 3 patches to most painful areas for up to 12 hours within a 24 hour period
  - 12 hours on/12 hours off
  - Patch is **10 cm x 14 cm containing 700 mg of lidocaine**
- Patches may be cut into smaller sizes prior to removal of the release liner
- Approximately 3 ± 2% of the dose applied is expected to be absorbed
  - At least 95% (665 mg) of lidocaine will remain in a used patch
  - May be utilized for alternative pain sites

Lidocaine – Key Considerations

Topically administered lidocaine is approximately 70% bound to plasma proteins

- Systemic concentration does not increase with daily use

Mean peak blood concentration of lidocaine ~0.13 µg/mL

- ~1/10 of the therapeutic concentration required to treat cardiac arrhythmias
- ~1/50 of concentrations associated with toxicity (5 µg/mL)
  - Concentrations higher than 0.25 µg/mL have been observed in some individuals

Center for Drug Evaluation and Research. Application 20-612 . FDA Medical Review.

Topical Lidocaine – Guidelines

American Academy of Neurology (AAN 2004/2011)

- 1st line postherpetic neuralgia
- 2nd line painful diabetic neuropathy (Level C Evidence)

European Federation of Neurological Societies (EFNS 2010)

- 1st line for postherpetic neuralgia

International Association for the Study of Pain (IASP 2015)

- 2nd line for mixed neuropathies

National Institute for Clinical Excellence (NICE) (2017)

- Reasonable due to safety
- Insufficient evidence for efficacy

Dubinsky RM, et al. Neurology 2004: 63: 959-65.
Bril V, et al. Neurology 2011; 76: 1758-65.
Attal N, et al. Eur J Neuro 2010; 17: 1113-23.
Finnerup NB, et al. Lancet Neurol 2015; 162-73.

Topical NSAIDS

Nociceptive Pain

Focus Area:
Topical Diclofenac

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Topical NSAIDS

MOA: reversibly inhibit the enzyme cyclooxygenase (prostaglandin endoperoxide synthase or COX), mediating production of prostaglandins and thromboxane A2

Topical application is based on the ability of NSAIDs to inhibit cox enzymes locally and peripherally, with minimum systemic uptake

- More effective for smaller joints and superficial tissue due to lack of penetration
- Tissue concentration (subcutis, muscles, tendons) several times higher than oral

Moore RA, et al. Cochrane Database Syst Rev. 2010;(7)

Topical Diclofenac Pharmacokinetics

Diclofenac Prescription Dosage Forms						
Brand Name	Form	Strength	Dose	Cmax (ng/mL)	Tmax (hr)	AUC (ng/hr/mL)
Diclofenac (Voltaren, Cataflam, Generic)	Tablets	50 mg	TID	2270 ± 778	6.5	3890 ± 1710
Voltaren	Gel	1%	48 g/day*	53.8 ± 32	10	807 ± 478
Solaraze	Gel	3%	2 g TID x 6 days	5 ± 5	4.5 ± 8	9 ± 19
Flector	Patch	1.3%	BID x 5 days	1.3 – 8.8	120	96
Pennsaid	Topical Solution	1.5% w/w	QID x 7 days	19.4 ± 9.3	4 ± 6.5	745.2 ± 374.7
***This is above the maximum daily dose recommended**						

FDA Labeling

Class Effect Warnings?

Topical NSAIDs

- GI risk
- Cardiac risk

Is there enough evidence to support labeling?

Center for Drug Evaluation and Research. Drugs@FDA Diclofenac Package Inserts.

Addressing NSAID Related Concerns

Evans (1995) Case Control Study

- Concluded topical nonsteroidal anti-inflammatory drugs were not significantly associated with upper gastrointestinal bleeding and perforation

Petersen B, Rovati S (2009) Review

- Systemic concentrations unlikely to have COX-1 mediated effects like interfere with platelet aggregation or compromise gastric protection

Simon (2009) Double-Blind, Double-Dummy, Randomized Controlled Trial

- Addition of topical NSAID to oral did not significantly increase adverse effects
- Authors conclude combination preferable to increase in oral NSAIDs

Evans JM, et al. BMJ. 1995;311(6996):22-6.
Petersen B, Rovati S. Clin Drug Invest 2009; 29(1):1-9
Simon L et al. *Pain.* 2009; 143(3):238-245.

Addressing NSAID Related Concerns

Therapeutic Goods Administration (Australia) Safety Review of Diclofenac (2014)

- Query of EMA's Adverse Drug Reporting System (ADRS)
  - 84 reports of adverse events with topical diclofenac
  - 3 events when oral diclofenac excluded
    - 2 reports of liver function test abnormalities
    - 1 report of GI bleed

- Safety Review Conclusion:
  - Risk/benefit for topical diclofenac remains favorable
  - Paucity of evidence of serious systemic side effects with topical diclofenac

Therapeutic Goods Administration: Safety Review of Diclofenac.

Topical Diclofenac- Key Considerations

- Topical formulations produce negligible systemic concentrations[1]
- In comparison with opioids, injectables, and corticosteroids, topical NSAIDS have the lowest NNT (3) to see a benefit for hip and knee OA
- Opioids and corticosteroids do not improve the function and stiffness nearly as well as topical NSAIDS

[1]Petersen B, Rovati S. Clin Drug Invest 2009; 29(1):1-9
[2] Zhang W, Nuki G, Moskowitz R et al. Osteoarthritis and Cartilage 2010;18:476-499.

Topical NSAIDs-Clinical Practice Guidelines

American College of Rheumatology (2020)

- First line for knee OA (preferred over oral)
  - Alternative for hand OA

VA/DoD (2014)

- Alternative to first line oral NSAIDS for knee osteoarthritis (OA)

NICE (2014)

- First line for knee and hand OA

Osteoarthritis Research Society International (OARSI 2019)

- 1st Line for knee OA (preferred over oral)

Non-Surgical Management of Hip and Knee Osteoarthritis Working Group. Dept of Vet Affairs, DoD; 2014.
National Collaborating Centre for Chronic Conditions. National Institute for Health and Clinical Excellence (NICE) (2014).
Hochberg MC, et al. Arthritis Care Res 2012 Apr;64(4):465-74
Physician Summary. Non-Surgical Treatment of Osteoarthritis of the Knee. OARSI.

Focus area: Ketamine, Clonidine, Prazosin, Gabapentin

Compounded Topical Analgesics

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Topical Ketamine

Peripheral MOA:

- NMDA receptor antagonism
- Toll-like Receptor 4 (TRL4) inhibition

Compounded Formulations:

- Concentrations: 0.5%-20%
- Numerous co-analgesic combinations

Plasma Concentration Considerations:

- Generally topical systemic plasma levels below detection (<20ng/mL)
  - IV/IM analgesic plasma concentrations: 100-300 ng/mL

Kopsky D. J.,et al. Minerva Anestesiologica 2015 April;81(4):440-9.
Sawynok J. Anesth Analg. 2014;119(1):170-8

Topical Clonidine

Peripheral MOA:

2015 Cochrane Review:

- Number needed to treat for an additional beneficial outcome (NNTB) 8.33, [95% CI: 4.3 - 50]
- RR: 1.35, [95% CI: 1.03 -1.77]
- Concluded may give partial pain relief for only some people with peripheral diabetic neuropathy

Wrzosek A,et al.*Cochrane Database of Systematic Reviews* 2015.

Topical Prazosin

Peripheral MOA:

- a1-adrenoceptor antagonist

Drummond, et al 2016

- Prazosin hydrochloride 1% cream
  - Inhibited dynamic allodynia in patients with an adrenergic component to pain
  - Inhibited hyperalgesia to stimulation on limb affected by complex regional pain syndrome (CRPS) but not in non-affected limbs

Drummond ES, et al. Eur J Pain. 2016;20(6):926-35.

Topical Gabapentin

Peripheral MOA

- Peripheral inhibitory action on the generation of ectopic discharges caused by nerve injury
- Suppress the release of substance P and calcitonin gene-related peptide (CGRP)
- Blockade of the peripheral glutamate receptors

Hiom et al 2015

- Retrospective review of 23 patients
- 6% w/w gabapentin applied 3 times per day to the affected site (maximal area 20cm2) x 1 month
- 11 achieved a clinically meaningful 30% reduction in pain

Concentration considerations

- Topical gabapentin 6% gel across porcine skin, estimated peak plasma gabapentin concentration (0.3µg/ml) vs oral gabapentin (2-20 µg /ml)

Park HJ, et al. Can J Anaesth. 2010;57(7):664-71.
Hiom S, et al. Br J Dermatol. 2015;173(1):300-2.

Compounded Topical Agent Considerations

- Toxicity reports
  - Unknown safety and efficacy
- Inconsistent with FDA approved route and/or indication
  - Centrally-acting medications delivered peripherally
- Unknown optimal dosing
- Drug combinations not proven safe or effective
- Variation in drug vehicles
  - Lack of standardization
- Cost ($$$)

Evidence for Compounded Topical Analgesics

- Cost
  - 2013 – Tricare spent $259 million in 2013
  - 2014 – DoD spent $746 million on compounded medications in 2014
  - 2015 – Medicare Part D spent ~$500 million
- Congress required evidence of compounded topical analgesic efficacy
  - DoD funded study at Walter Reed
  - August 2015 to February 2018
  - 399 participants (> 50% female, 43% active military)
- Double-blind, double-dummy, randomized placebo-controlled trial
  - Instructed to apply cream 3 times a day
  - Keep pain diary

Brutcher et al. *Ann Intern Med.* 2019; 170:309-318.

Evidence for Compounded Topical Analgesics (cont'd)

- All participants divided into 3 groups based on type of localized pain
  - Nociceptive pain – ketoprofen, baclofen, cyclobenzaprine, lidocaine
  - Neuropathic pain – ketamine, gabapentin, clonidine, lidocaine
  - Mixed pain – ketamine, gabapentin, diclofenac, cyclobenzaprine, lidocaine

- Randomized into 2 groups
  - Topical analgesics
  - Placebo cream

- Results published February 2019
  - No statistically significant results for any of the 3 groups compared to placebo

Brutcher et al. *Ann Intern Med.* 2019; 170:309-318.

Summary

- Topical analgesics play an important role in management of localized pain
- Evidence for 1st line use is growing for some types of pain
- Provides solutions to common treatment challenges for pain patients
- Minimal risk of systemic adverse effects

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D. Diclofenac
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QUESTIONS?

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