ON PINS & NEEDLES: PHARMACOTHERAPY FOR NEUROPATHIC PAIN

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VA PORTLAND HEALTH CARE SYSTEM
APRIL 23, 2022

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DISCLOSURE

- I have no actual or potential conflicts of interest in relation to the content or delivery of this presentation

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OBJECTIVES

By the end of this presentation, the learner should be able to:

- Compare efficacy and safety of first line therapies for neuropathic pain
- Discuss the evidence for off-label use of medications for neuropathic pain
- Given a patient with neuropathic pain, recommend appropriate pharmacotherapy

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PRE-TEST QUESTIONS

1. Of first line therapies for neuropathic pain, which medication class has the greatest evidence of efficacy?
   a) Gabapentinoids
   b) Tricyclic antidepressants
   c) N-methyl-D-aspartate antagonists
   d) Serotonin-norepinephrine reuptake inhibitors

2. Which of the following would be most appropriate for off-label use in neuropathic pain?
   a) Lamotrigine
   b) Sertraline
   c) Doxepin cream
   d) Topiramate

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PRE-TEST QUESTIONS

3. Which of the following is most appropriate for a 75-year-old patient complaining of pain, tingling, and some numbness in bilateral lower extremities after experiencing impaired cognition with gabapentin 300mg three times daily?
   a) Duloxetine 20mg daily
   b) Amitriptyline 25mg nightly
   c) Tramadol 50mg four times daily
   d) Memantine 5mg daily

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BACKGROUND & PATHOPHYSIOLOGY

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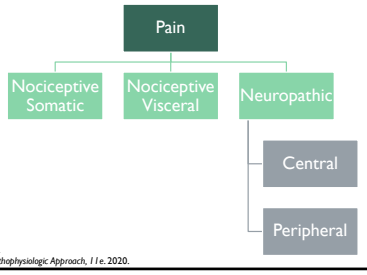
CLASSIFICATION OF PAIN



Bates et al. *Pain Med.* 2019;20(1):S2-12.
Costantino et al. *Pharmacotherapy: A Pathophysiologic Approach, 11e.* 2020.

7

NOCICEPTIVE SOMATIC PAIN

Description	Etiologies
• Sharp, dull, aching, localized, worse with movement • Often able to point to direct location	• Trauma, arthritis, musculoskeletal

Costantino et al. *Pharmacotherapy: A Pathophysiologic Approach, 11e.* 2020.

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NOCICEPTIVE VISCERAL PAIN

Description	Etiologies
• Diffuse, gnawing, cramping, pressure • Difficult to localize	• Gastrointestinal, cardiac, renal, malignant

Costantino et al. *Pharmacotherapy: A Pathophysiologic Approach, 11e.* 2020.

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NEUROPATHIC PAIN

Description

- Burning, numbness, pins & needles, tingling, stabbing, shooting, electrical, itching, temperature intolerance, hyperpathia, allodynia
- Radicular

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Costantino et al. *Pharmacotherapy: A Pathophysiologic Approach, 11e*. 2020.
Rathmell et al. *Harrison's Principles of Internal Medicine, 20e*. 2018.

10

NEUROPATHIC PAIN COMMON ETIOLOGIES

Central

- Multiple sclerosis, poststroke, spinal cord injury, trigeminal neuralgia

Peripheral

- Diabetic or chemotherapy-induced peripheral neuropathy, radicular, trigeminal neuralgia, postsurgical, postherpetic neuralgia*

*can progress to central

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Bates et al. *Pain Med*. 2019;20(1):S2-12.
Colloca et al. *Nat Rev Dis Primers*. 2017;3:17002.

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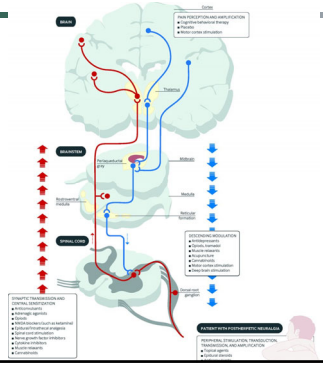

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Cohen et al. *BMJ*. 2014;348:f7656.

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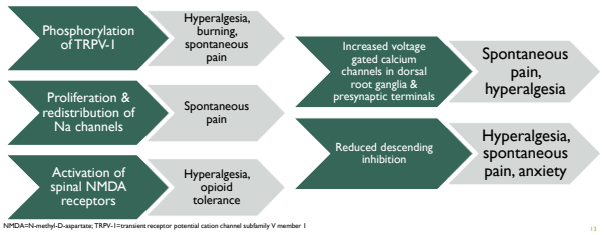
PATHOPHYSIOLOGY



NMDA=N-methyl-D-aspartate; TRPV-1=transient receptor potential cation channel subfamily V member 1

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Cohen et al. *BMJ*. 2014;348:f7656.

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IMPACT OF NEUROPATHIC PAIN

Up to 7-8% of general population

- 20-25% of chronic pain patients

Significant impact on quality of life

- Rated worse than non-neuropathic pain
- Can lead to catastrophizing and kinesiophobia

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Bates et al. *Pain Med*. 2019;20(1):S2-12.
Smith et al. *Pain*. 2020;161(9):S127-37.

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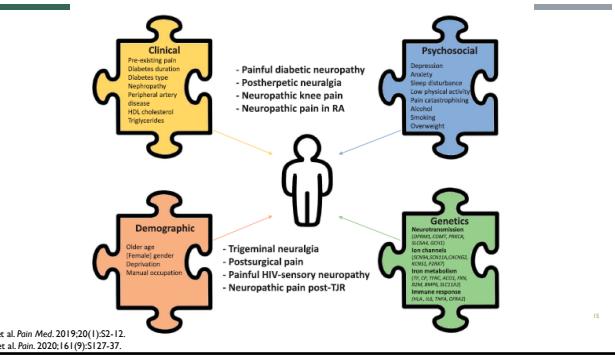

Bates et al. *Pain Med*. 2019;20(1):S2-12.
Smith et al. *Pain*. 2020;161(9):S127-37.

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PHARMACOTHERAPY

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TREATMENT GUIDELINE CONSENSUS?

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FIRST LINE THERAPIES

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FIRST LINE THERAPIES

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Bates et al. *Pain Med*. 2019;20(1):S2-12.
Cruccu et al. *Pain Ther*. 2017;6(1):S35-42.

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TRICYCLIC ANTIDEPRESSANTS

Mechanism

- Serotonin & norepinephrine reuptake inhibition
- Histamine & acetylcholine inhibition

Efficacy & Tolerability

- NNT 3.6
- NNH (major ADR, withdrawal) 28
- NNH (minor ADR) 9

NNT=number needed to treat; NNH=number needed to harm

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Bates et al. *Pain Med*. 2019;20(1):S2-12.
Cohen et al. *BMJ*. 2014;348:f7656.
Cruccu et al. *Pain Ther*. 2017;6(1):S35-42.
Saarto et al. *Cochrane Database Sys Rev*. 2007;4:CD005454.

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TRICYCLIC ANTIDEPRESSANTS

Medication	Dosing	Precautions & Pearls
Amitriptyline	10-25 mg nightly or in divided doses → 150 mg	Cardiac arrhythmias, orthostasis, urinary retention, dry mouth, falls, weight gain
Imipramine	50 mg daily or in divided doses → 150 mg	Avoid in elderly
Nortriptyline	10-25 mg daily → 100 mg	Secondary amines (nortriptyline, desipramine) more selective for NE → less sedation, better tolerated
Desipramine	12.5 mg nightly → 250 mg	Adequate trial: 4-8 weeks at max tolerated dose

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Bates et al. *Pain Med*. 2019;20(1):S2-12.
Cruccu et al. *Pain Ther*. 2017;6(1):S35-42.
Lexicomp. Wolters Kluwer. 2021. Accessed 10 Sept 2021.

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SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

Mechanism

- Serotonin & norepinephrine reuptake inhibition

Efficacy & Tolerability

- NNT 6.4
- NNH 11.8

NNH=number needed to harm; NNT=number needed to treat

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Bates et al. *Pain Med.* 2019;20(1):S2-12.
Cohen et al. *BMJ.* 2014;348:f7656.
Finnerup et al. *Lancet Neurol.* 2015;14(2):162-73.

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SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

Medication	Dosing	Precautions & Pearls
Duloxetine	20-30 mg daily → 60-120 mg Target dose: 60 mg	Nausea, insomnia, drowsiness, hepatotoxicity Risk of withdrawal with abrupt cessation (venlafaxine > duloxetine)
Venlafaxine	37.5-75 mg daily → 150-225 mg Target dose: 150 mg	Adequate trial: 4-6 weeks at max tolerated dose

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Bates et al. *Pain Med.* 2019;20(1):S2-12.
Lexicomp. Wolters Kluwer. 2021. Accessed 10 Sept 2021.

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GABAPENTINOIDS

Mechanism

- Structurally related to GABA
- Inhibit alpha-2-delta subunit of voltage gated calcium channels → decreased release of excitatory neurotransmitters

Efficacy & Tolerability

- Gabapentin: NNT 6.3, NNH 25.6
- Pregabalin: NNT 7.7, NNH 13.9, decreased cost of care compared to gabapentin

GABA=gamma-aminobutyric acid; NNH=number needed to harm; NNT=number needed to treat

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Bates et al. *Pain Med.* 2019;20(1):S2-12.
Cohen et al. *BMJ.* 2014;348:f7656.
Finnerup et al. *Lancet Neurol.* 2015;14(2):162-73.
Sicras-Mainar et al. *J Comp Eff Res.* 2018;7:615-25.

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GABAPENTINOIDS

Medication	Dosing	Precautions & Pearls
Gabapentin	100-300 mg 1-3 times daily → 3,600 mg/day in divided doses	Somnolence, fatigue, dizziness, edema, weight gain
	Target dose: 1,800 mg/day	Direct switch if not able to tolerate one
Pregabalin	150 mg in 2-3 divided doses → 600mg/day in divided doses	Adequate trial: 4-6 weeks, at least 2 weeks at maximally tolerated dose

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Bates et al. *Pain Med.* 2019;20(1):S2-12.
Lexicomp. Wolters Kluwer. 2021. Accessed 10 Sept 2021.

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TOPICAL THERAPIES

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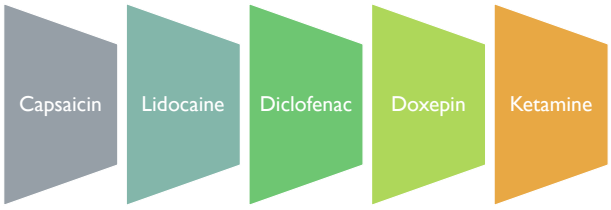
TOPICAL THERAPIES



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Bates et al. *Pain Med.* 2019;20(1):S2-12.
Casale et al. *Curr Pain Headache Rep.* 2017;21(15):1-9.

27

TOPICAL CAPSAICIN

Mechanism

- Activation of TRPV1, release of substance P
- Chronic exposure → overstimulation & desensitization, reversible nerve degeneration

Phosphorylation of TRPV-1 → Hyperalgesia, burning, spontaneous pain

Considerations

- FDA approved indications: diabetic neuropathy & neuropathic pain
- Efficacy: 8% formulations (Qutenza®) > 0.025%, 0.075%, 0.1% formulations
- Painful on initial application, requires consistent use for effect
- Burning may reactivate with hot bathing

TRPV-1=transient receptor potential cation channel subfamily V member 1

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Bates et al. *Pain Med.* 2019;20(1):S2-12.
Casale et al. *Curr Pain Headache Rep.* 2017;21(15):1-9.
Lexicomp. Wolters Kluwer. 2021. Accessed 10 Sept 2021.

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TOPICAL LIDOCAINE

Mechanism

- Na channel blockade → local anesthetic

Proliferation & redistribution of Na channels → Spontaneous pain

Considerations

- Efficacy demonstrated in post-herpetic neuralgia & diabetic neuropathy (5% formulations)
- Safe & well-tolerated in elderly
- Available in variety of formulations
- Patch: 12 hours on 12 hours off, max of 3 at once, may cut to fit area

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Bates et al. *Pain Med.* 2019;20(1):S2-12.
Casale et al. *Curr Pain Headache Rep.* 2017;21(15):1-9.
Lexicomp. Wolters Kluwer. 2021. Accessed 10 Sept 2021.

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TOPICAL DICLOFENAC

Mechanism

- Reversibly inhibits COX-1&2 → decreased prostaglandin synthesis
- Anti-inflammation & analgesia

Considerations

- Moderate efficacy in post-herpetic neuralgia & complex regional pain syndrome (1.5% formulation)
- Systemic absorption <5%, low incidence of adverse events

COX=cyclooxygenase

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Bates et al. *Pain Med.* 2019;20(1):S2-12.
Casale et al. *Curr Pain Headache Rep.* 2017;21(15):1-9.
Lexicomp. Wolters Kluwer. 2021. Accessed 10 Sept 2021.

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TOPICAL DOXEPIN

Mechanism

- Tricyclic antidepressant
- Antihistamine

Considerations

- Approved for pruritus
- Similar overall pain relief to capsaicin, no effect on shooting pain or sensitivity
- Patient preference doxepin > capsaicin in randomized trials
- Increased risk of drowsiness when applied >10% body surface area

Casale et al. *Curr Pain Headache Rep.* 2017;21(15):1-9.
Lexicomp. Wolters Kluwer. 2021. Accessed 10 Sept 2021.
McCleane et al. *J Clin Pharmacol.* 2000;49:574-9.

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TOPICAL KETAMINE

Mechanism

- NMDA receptor antagonist → decreased glutamate

Considerations

- Not more beneficial than placebo for post-herpetic & diabetic peripheral neuropathy (0.5%, 1%, 5% formulations)
- Potential place in therapy: decrease in allodynia & complex regional pain syndrome (10% formulation)
- Negligible systemic absorption, low side effect profile

NMDA=N-methyl-D-aspartate

Aiyer et al. *Clin J Pain.* 2018;34:450-67.
Bates et al. *Pain Med.* 2019;20(1):S2-12.
Casale et al. *Curr Pain Headache Rep.* 2017;21(15):1-9.
Lexicomp. Wolters Kluwer. 2021. Accessed 10 Sept 2021.

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SECOND LINE THERAPIES

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SECOND LINE THERAPIES

Combination therapy

Tramadol

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Bates et al. *Pain Med*. 2019;20(1):S2-12.

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COMBINATION THERAPY

- 45% of patients utilize two or more medications
- Significant part of management by most guidelines, however, limited evidence on effective strategies
- Increased efficacy from multiple mechanisms of action
- Dose reductions of individual agents → decreased incidence of side effects

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Bates et al. *Pain Med*. 2019;20(1):S2-12.
Vorobeychik et al. *CNS Drugs*. 2011;25(12):1023-34.

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COMBINATION THERAPY

Study	Trial Design	Treatments	Primary Outcome	Adverse Effects
Gilron et al, 2009	6-week RCT, CO, DB	Gabapentin vs. nortriptyline vs. combination	Better pain control with combination	Decreased with combination
Holbech et al, 2015	5-week RCT, CO, DB	Pregabalin vs. imipramine vs. combination vs. placebo	Decreased pain scores with combination	Increased with combination
Simpson et al, 2001	8-week RCT, DB	Gabapentin + venlafaxine vs. gabapentin + placebo	Better pain relief with gabapentin + venlafaxine	Similar in both groups
Tesfaye et al, 2013	16-week RCT, DB	High dose pregabalin vs. high dose duloxetine vs. moderate dose combination	No difference in mean pain scores	Similar in all groups

RCT=randomized controlled trial; CO=cross-over; DB=double-blind

Gilron et al. *Lancet*. 2009;374:1252-61.
Holbech et al. *Pain*. 2015;156(5):958-66.
Simpson et al. *J Clin Neuromusc Dis*. 2001;3(2):53-62.
Tesfaye et al. *Pain*. 2013;154(12):2616-25.
Vorobeychik et al. *CNS Drugs*. 2011;25(12):1023-34.

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TRAMADOL

Mechanism

- Weak mu-opioid agonist
- Serotonin & norepinephrine reuptake inhibitor

Reduced descending inhibition → Hyperalgesia, spontaneous pain, anxiety

Efficacy & Tolerability

- NNT 4.7
- NNH 12.6

Considerations

- Recommended for acute exacerbations of neuropathic pain
- 50-100 mg every 4-6 hours
- CNS depression, respiratory depression, constipation, seizures, serotonin syndrome

NNH=number needed to harm; NNT=number needed to treat

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Bates et al. *Pain Med.* 2019;20(1):S2-12.
Lexicomp. Wolters Kluwer. 2021. Accessed 10 Sept 2021.

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THIRD LINE THERAPIES

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THIRD LINE THERAPIES

- N-methyl-D-aspartate (NMDA) antagonists
- Anticonvulsants
- Selective serotonin reuptake inhibitors (SSRIs)

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Bates et al. *Pain Med.* 2019;20(1):S2-12.
Finnerup et al. *Lancet Neurol.* 2015;14(2):162-73.

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N-METHYL-D-ASPARTATE INHIBITORS

Mechanism

- NMDA receptor antagonist → decreased glutamate

Medication	Efficacy	Precautions
Ketamine	Oral: 1/3 studies with clinical benefit IV: 13/13 studies with some clinical benefit	Sedation, hallucinations, CNS depression
Memantine	2/7 studies showed clinical benefit over placebo	Agitation, confusion, constipation
Amantadine	IV infusions: 2 studies with benefit, 1 study less effective than lidocaine	Confusion, hallucinations, hypotension
Dextromethorphan	4 studies showing clinical benefit, 2 showing no effect	Confusion, agitation, dizziness

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Aiyer et al. *Clin J Pain*. 2018;34:450-67.
Bates et al. *Pain Med*. 2019;20(1):S2-12.
Lexicomp. Wolters Kluwer. 2021. Accessed 10 Sept 2021.

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ANTICONVULSANTS

Medication	Mechanism	Efficacy	Precautions
Carbamazepine	Inhibit Na channels & NMDA antagonism	8/9 studies demonstrating clinical benefit, especially trigeminal neuralgia	SIADH, CNS depression
Valproic Acid	Inhibit Na channels & enhance GABA & NMDA antagonism	4/5 studies demonstrating some clinical benefit	CNS depression, GI, thrombocytopenia, alopecia, metabolic imbalance
Lamotrigine	Inhibit Na channels & release of glutamate	No evidence of benefit	CNS depression, GI
Topiramate	Inhibit Na channels & enhance GABA	No evidence of benefit	CNS depression, GI

SIADH=syndrome of inappropriate secretion of antidiuretic hormone

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Aiyer et al. *Clin J Pain*. 2018;34:450-67.
Lexicomp. Wolters Kluwer. 2021. Accessed 10 Sept 2021.
Wiffen et al. *Cochrane Database Syst Rev*. 2013;11:CD010567.

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SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Mechanism

- Serotonin reuptake inhibition

Medication	Efficacy	Precautions
Fluoxetine	More effective than placebo for idiopathic facial pain & diabetic neuropathy Less effective than amitriptyline head-to-head	GI, decreased libido, drowsiness, insomnia
Paroxetine	More effective than placebo for diabetic neuropathy Less effective than imipramine head-to-head	QTc prolongation (cital)
Citalopram	More effective than placebo for diabetic neuropathy	

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Bates et al. *Pain Med*. 2019;20(1):S2-12.
Lexicomp. Wolters Kluwer. 2021. Accessed 10 Sept 2021.
Saarto et al. *Cochrane Database Syst Rev*. 2007;4:CD005454.

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KNOWLEDGE CHECK

1. Of first line therapies for neuropathic pain, which medication class has the greatest evidence of efficacy?
   a. Gabapentinoids
   b. Tricyclic antidepressants
   c. N-methyl-D-aspartate antagonists
   d. Serotonin-norepinephrine reuptake inhibitors

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KNOWLEDGE CHECK

1. Of first line therapies for neuropathic pain, which medication class has the greatest evidence of efficacy?
   a. Gabapentinoids
   b. Tricyclic antidepressants
   c. N-methyl-D-aspartate antagonists
   d. Serotonin-norepinephrine reuptake inhibitors

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KNOWLEDGE CHECK

2. Which of the following would be most appropriate for off-label use in neuropathic pain?
   a. Lamotrigine
   b. Sertraline
   c. Doxepin cream
   d. Topiramate

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KNOWLEDGE CHECK

2. Which of the following would be most appropriate for off-label use in neuropathic pain?
   a. Lamotrigine
   b. Sertraline
   c. **Doxepin cream**
   d. Topiramate

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FOURTH LINE THERAPIES

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OPIOIDS

Mechanism

Reduced descending inhibition → Hyperalgesia, spontaneous pain, anxiety

- Mu-opioid agonism → inhibition of ascending & descending pain pathways

Considerations

- Place in therapy inconsistent across guidelines
- Lack of long-term efficacy vs. significant side effects

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Bates et al. *Pain Med*. 2019;20(1):S2-12.
Finnerup et al. *Lancet Neurol*. 2015;14(2):162-73.

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FIFTH LINE THERAPIES

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TARGETED DRUG DELIVERY

- Intrathecal administration of medication to dorsal hood of spinal cord

Medication	Mechanism	Efficacy	Precautions
Morphine	Mu-opioid agonist	2 RCTs: similar pain relief compared to comprehensive medical management Non-controlled, prospective trials: improvement in VAS pain score	Respiratory depression, formulation of granulomas, myoclonus, constipation
Ziconotide	Non-opioid calcium channel blocker	3 RCTs: effective analgesia with long term effect in cancer and non-cancer pain	Contraindication: history of psychosis CNS depression, increased creatinine kinase

RCT=randomized controlled trial; VAS=visual analog scale 50

Bates et al. *Pain Med*. 2019;20(1):S2-12.
Deer et al. *Pain Med*. 2019;20(4):784-98.

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ALTERNATIVE THERAPIES

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ALTERNATIVE THERAPIES

Supplement	Rationale
B vitamins	Deficiencies may cause peripheral neuropathy B12 associated with symptom relief in diabetic neuropathy Caution use of B6
Vitamin D	Independent risk factor in diabetic neuropathy 2,000 units daily and 50,000 units weekly x 8 weeks resulted in significant VAS pain decrease
Magnesium	Inhibition of NMDA receptors
Alpha-lipoic acid	600 mg/day associated with decreased total symptom score in diabetic peripheral neuropathy
Acetyl-L-carnitine	1.5-2 g/day in three divided doses associated with reduced pain compared to placebo

NMDA=N-methyl-D-aspartate; VAS=visual analog scale 52

Baute et al. *Curr Treat Options Neurol.* 2019;21(44):1-15.
Di Stefano et al. *J Pain Res.* 2019;12:1341-51.
Natural Medicines Database. Therapeutic Research Center. 2021. Accessed 13 Sep 2021.

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EMERGING THERAPIES

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EMERGING THERAPIES


Safety and efficacy of repeated injections of botulinum toxin A in peripheral neuropathic pain (BOTNEP): a randomised, double-blind, placebo-controlled trial

ORIGINAL ARTICLE

OPEN

Summary

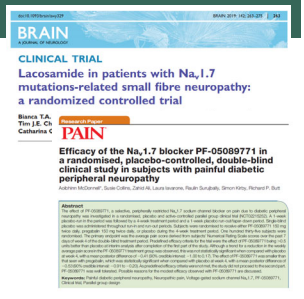
Background Data from pre neuropathic pain, but the administration of botulinu

Methods We did a randomi

Fulranumab in Patients With Pain Associated With Postherpetic Neuralgia and Postraumatic Neuropathy

Efficacy, Safety, and Tolerability Results From a Randomized, Double-blind, Placebo-controlled, Phase-2 Study

Hao Wang, PhD Gary Romano, MD, PhD,† Margaret Fedgchin, PharmD,‡ Lucille Russell, MD,† Panna Sanga, MD,† Kathleen M. Kelly, MD,† Mary Ellen Prosnicl, MAS,† and John Thipphawong, MD†*


BRAIN

A JOURNAL OF NEUROLOGY

CLINICAL TRIAL

Lacosamide in patients with $Na_v1.7$ mutations-related small fibre neuropathy: a randomized controlled trial

Research Paper

PAIN

Efficacy of the $Na_v1.7$ blocker PF-05089771 in a randomised, placebo-controlled, double-blind clinical study in subjects with painful diabetic peripheral neuropathy

Abstract

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KNOWLEDGE CHECK

3. Which of the following is most appropriate for a 75-year-old patient complaining of pain, tingling, and some numbness in bilateral lower extremities after experiencing impaired cognition with gabapentin 300mg three times daily?
   a. Duloxetine 20mg daily
   b. Amitriptyline 25mg nightly
   c. Tramadol 50mg four times daily
   d. Memantine 5mg daily

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55

KNOWLEDGE CHECK

3. Which of the following is most appropriate for a 75-year-old patient complaining of pain, tingling, and some numbness in bilateral lower extremities after experiencing impaired cognition with gabapentin 300mg three times daily?
   a. Duloxetine 20mg daily
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   c. Tramadol 50mg four times daily
   d. Memantine 5mg daily

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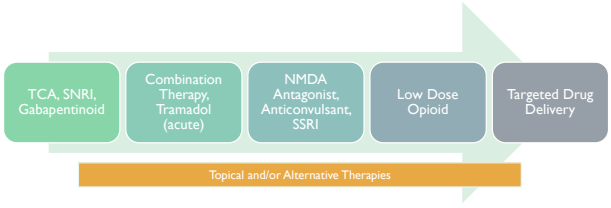
SUMMARY



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Bates et al. *Pain Med.* 2019;20(1):S2-12.

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QUESTIONS?

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VA PORTLAND HEALTH CARE SYSTEM

APRIL 23, 2022

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WHAT ABOUT CANNABIS?

- 16 studies covering 1750 participants
- Products: THC/CBD oromucosal spray, nabilone, inhaled herbal, dronabinol
- Quality of evidence: very low to moderate
- Primary outcome: cannabis-based medicines may increase number of patients achieving 50% or greater pain relief compared with placebo (21% versus 17%; risk difference (RD) 0.05 (95% confidence interval (CI) 0.00 to 0.09))
- Safety: more participants withdrew from studies d/t ADRs compared to placebo
- 2017 National Academy of Sciences report states that cannabis may be effective treatment for chronic pain, particularly neuropathic pain. IASP 2021 and NICE 2019 report that evidence doesn't meet the threshold for recommendation of use

59

Mucke et al. *Cochrane Database Syst Rev.* 2018;3(3):CD012182.

59