Treatment of Neuropathic Pain: What Does the Evidence Say? or Just the Facts Ma'am

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Objectives

1. Review current medications utilized to manage neuropathic pain, including MOA, side effects, drug interactions and efficacy.
2. Discuss current evidence based medicine concerning the management of neuropathic pain.

Which of the following is least likely to be a symptom of neuropathic pain (NP)?

A. Prickling or tingling

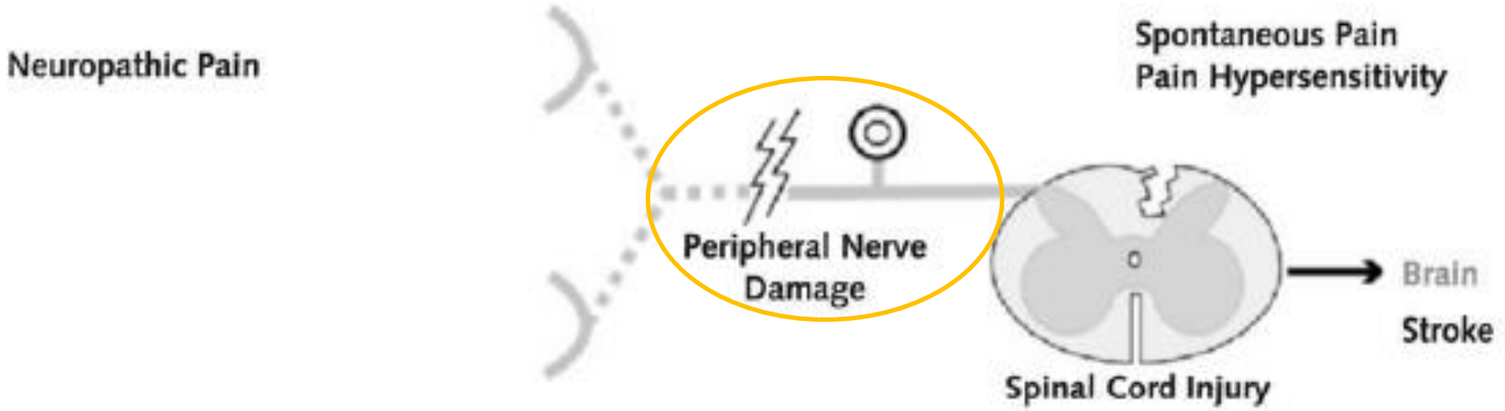
B. Burning pain

C. Pain evoked by light touch

D. Severe cramping pain

Neuropathic Pain

- Pain in association with damage to, or a lesion of the nervous system.



CDC 2016 Guidelines Quote

"Several guidelines agree that **first- and second-line drugs** for neuropathic pain include **anticonvulsants** (gabapentin or pregabalin), **tricyclic antidepressants**, and **SNRIs. … Interventional approaches** such as epidural injection for certain conditions (e.g., lumbar radiculopathy) can provide short-term improvement in pain."

Wallen M, Gillies D. Intra-articular steroids and splints/rest for children with juvenile idiopathic arthritis and adults with rheumatoid arthritis. Cochrane Database Syst Rev 2006:(1):CD002824.
Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. Cochrane Database Syst Rev 2006;2:CD005328.
Buchbinder R, Green S, Youd JM. Corticosteroid injections for shoulder pain. Cochrane Database Syst Rev 2003;1:CD004016.
Food and Drug Administration. Epidural corticosteroid injection: drug safety communication. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2014

Pharmacologic Management

- First Line Agents
  - Antidepressants
    - TCAs (NNT 3.6)
      - nortriptyline, desipramine
    - SNRIs (NNT 6.4)
      - venlafaxine, duloxetine
  - Anticonvulsants
    - Gabapentin (NNT 6.3/8.3)
    - Pregabalin (NNT 7.7)
- Second/Third Line agents
  - Local anesthetics (limited use)
    - Lidocaine
    - Capsaican (NNT 10.6)
  - Opioids
    - Tramadol (NNT 4.7)
    - Oxycodone and Morphine (NNT 4.3)

Antidepressants

Tri-cyclic Antidepressants (TCADs)

- MOA:
  - 5HT and NE reuptake blockade
  - Modulate monoamine neurotransmitters
  - Sodium and Potassium channel modulation
  - NMDA-receptor activity
  - Antihistaminic
- Usually requires lower doses
  - 30-50% of dose for depression
- ADRs
  - Anticholinergic effects:
    - Usually mild with the lower doses
    - Greater incidence in the elderly or use of high doses
    - Lower incidence with desipramine
  - Sedation, tachycardia

TCAD Generations

- Tertiary Amines
  - Amitriptyline 10-300mg
  - Doxepin 10-300mg
  - Imipramine 10-300mg
- Secondary Amines
  - Nortriptyline 10-250mg
  - Desipramine 10-300mg

TCADs

- Finnerup NB et al. Pharmacotherapy for neuropathic pain in adults: systematic, meta-analysis, and updated NeuSPIG recommendations. Lancet Neurol. 2015;14:2:162-73.
  - 18 placebo controlled trials
    - 12 of these were with amitriptyline 25-150mg/d
    - No evidence of dose-response effect
    - Quality of evidence was moderate
    - Combined NNT for 15 studies was 3.6

TCA major side effects

Anti-cholinergic	Sedation	Orthostasis	+Slight +++High ++Moderate ++++Very high
			Tertiary Amines
++++	++++	++	Amitriptyline (Elavil)
+++	+++	++	Clomipramine (Anafranil)
++	+++	++	Doxepin (Silenor)
++	++	+++	Imipramine (Tofranil)
			Secondary Amines
+++	++	+	Amoxapine (Asendin)
+	**+**	**+**	**Desipramine (Norpramin)**
+++	+	+	Nortriptyline (Pamelor)

SNRI Antidepressants

- MOA
  - Block the presynaptic re-uptake of 5HT3 and NE leading to enhanced action of descending inhibitory pathways
  - Alternative for those unable to tolerate TCADs
  - Similar efficacy with better tolerability

- Duloxetine (Cymbalta)
  - Demonstrated efficacy and indicated by FDA
  - Nausea most common ADR so start with 30mg/d
  - 60 mg once daily with max of 120mg/d

- Venlafaxine (Effexor)
  - Not indicated secondary questionable efficacy
  - 150-225 mg daily in divided doses
  - May causes cardiac conduction abnormalities, ↑ BP

- SSRI's not effective for neuropathic pain

SNRIs

- Finnerup NB et al. Pharmacotherapy for neuropathic pain in adults: systematic, meta-analysis, and updated NeuSPIG recommendations. Lancet Neurol. 2015;14:2:162-73.
  - 14 trials total
    - 9 with Duloxetine 20-120mg/d
    - 4 with Venlafaxine 150-225mg/d (2 were positive while 2 were negative)
    - 1 with Desvenlafaxine (Negative result)
    - Quality of evidence was high
    - Combined NNT was 6.4

AAN 2017 Update Review

- Waldfogel JM et al. Pharmacotherapy of diabetic peripheral neuropathy pain and quality of life. Neurology. 2017;88:1958-1967
- Looked specifically at Diabetic Peripheral Neuropathy
- Reviewed existing trials and they concluded:
  - Venlafaxine was effective – limited data and trials
  - Duloxetine was effective

Anticonvulsants

Which of the following anticonvulsants is a first line option for NP?

A. Levetiracetam

B. Gabapentin

C. Cabamazepine

D. Lamotrigine

Anticonvulsants

- Alternative 1st line agents

- MOA
  - Suppresses neuronal discharges
  - Reduces release of excitatory neurotransmitters

- Gabapentin (Neurontin)
  - Initial dose = 100-300mg/d with target dose of 1800-3600mg/d (Usually given TID)
  - Weight gain, peripheral edema, somnolence, dizziness (dose dependent)

- Pregabalin (Lyrica)
  - Initiate 75mg/d with target dose of 300-600mg/d (Usually given BID)
  - Peripheral edema, dizziness, somnolence, tremor

Anticonvulsants

- Finnerup NB et al. Pharmacotherapy for neuropathic pain in adults: systematic, meta-analysis, and updated NeuSPIG recommendations. Lancet Neurol. 2015;14:2:162-73.
  - 18 of 25 trials with Pregabalin (150-600mg/d) were positive
    - Dose response effect was noted
    - Quality of evidence was high
    - Combined NNT was 7.7
  - 14 trials with Gabapentin 900-3600mg
    - 6 trials with Gabapentin ER 1200-3600mg/d
    - Combined NNT 6.3 for Gabapentin and 8.3 for ER formulation
    - No dose response effect was noted

Most trials with other antiepileptic medications were negative and many have poor safety profiles

AAN 2017 Update Review

- Waldfogel JM et al. Pharmacotherapy of diabetic peripheral neuropathy pain and quality of life. Neurology. 2017;88:1958-1967
- Looked specifically at DPN
- Reviewed existing trials and they concluded:
  - Pregablin was effective
  - Gabapentin was ineffective*****
  - Oxcarbazepine was effective

Opioids

Based on EBM which opioid agonists is considered second line for management of NP?

A. Tramadol
B. Morphine
C. Oxycodone
D. Fentanyl

Opioids

- Considered when other agents are ineffective
  - Usually given in combination with 1st line agents
  - May require higher doses – watch those MEQs

- ADRs
  - Sedation
  - Constipation
  - Itching

- Tramadol (NNT 4.7)
  - 5HT and NE reuptake inhibitor
  - C-IV - Considered weak opioid
  - Caution in seizure patients

- Methadone most effective of the opioids
  - NMDA receptor antagonism with SNRI effects
  - Blackbox warning with QT prolongation
  - Use discouraged so consider oxycodone or morphine

Opioids

- Finnerup NB et al. Pharmacotherapy for neuropathic pain in adults: systematic, meta-analysis, and updated NeuSPIG recommendations. Lancet Neurol. 2015;14:2:162-73.
  - 7 trials with Tramadol
    - All positive
    - Quality of evidence was moderate
    - Combined NNT 4.7
  - 13 trials with strong opioids (Oxycodone and Morphine)
    - 10 trials were positive with best results around 180mg MEQ
    - Dependency and abuse potential increases around 80 MEQ
    - Quality of evidence was moderate
    - Combined NNT 4.3

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Miscellaneous

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- Finnerup NB et al. Pharmacotherapy for neuropathic pain in adults: systematic, meta-analysis, and updated NeuSPIG recommendations. Lancet Neurol. 2015; 14:2:162-73.
  - Lidocaine patches were used in post-surgical neuropathic pain and post herpetic neuralgia
    - Results were mixed, but worked better for short term relief
  - Capsaicin patch 8% > 0.04% in HIV related neuropathy and post-herpetic
    - Quality of evidence high
    - Combined NNT 10.6
  - Botulinum toxin A 50-200u x 1 dose
    - Several small trials were positive but one large trial was negative
    - ***Found effective for DPN per AAN article

Recommendations

Recommendations from Meta-analysis

	FIRST LINE DRUGS			SECOND LINE DRUGS			THIRD LINE DRUGS	
	SNRIs duloxetine venlafaxine	TCAs	Pregabalin Gabapentin Gabapentin ER/enacarbil	Tramadol	Capsaicin 8% patches	Lidocaine patches	Strong opioids	BTX-A
Quality of evidence								
	High	Moderate	High	Moderate	High	Low	Moderate	Low
Balance between desirable and undesirable effects								
Effect size	Moderate	Moderate	Moderate	Moderate	Low	Unknown	Moderate	Moderate
Tolerability and safety	Moderate	Low -Moderate	Moderate-high	Low-moderate	Moderate-high	High	Low-moderate	High
Values and preferences								
	Low-moderate	Low-moderate	Low-moderate	Low-moderate	High	High	Low-moderate	High
Cost and resource allocation								
	Low-moderate	Low	Low-moderate	Low	Moderate-high	Moderate-high	Low-moderate	Moderate-high
Strength of recommendation								
	Strong	Strong	Strong	Weak	Weak	Weak	Weak	Weak
Neuropathic pain conditions	All	All	All	All	Peripheral	Peripheral	All	Peripheral

Treating Neuropathies can be Painful

- NP is difficult to manage
- Incidence is increasing secondary to uncontrolled DM
  - AAN 2017 Article may be resource for DPN
- Current meta-analysis (2015) did not differentiate the type of NP for each trial so data we are operating on is limited
  - Need to determine exact type of neuropathy since EBM guidelines change
- Requires more than one mode of treatment
- Most medications have side effects that can be dangerous
- Good news opioids work, Bad news opioids work
- Most trials have moderate evidence

Best Practice Recommendations

- Know the current EBM literature with regard to quality of evidence and NNT
- First line medications may be used for various types of NP
- Many choices are affordable and efficacy is not compromised
- Start dosing low and titrate to response
- Only about 50% find relief from medications and that is usually partial relief
- Leading to use of >1 modality for management, include nonpharmacologic strategies