Clinical Pearls of Pain Treatment: Neuropathic Pain

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Objective

Identify appropriate pharmacologic options for the treatment of neuropathic pain

Pain Signaling Overview

NMDA (ascending, pro-pain)

5-HT, NE, GABA (descending, anti-pain)

Na+ and Ca++ Channels

Afferent nerves:

A-Beta: myelinated, fast transmission

A-Delta: myelinated, nociceptive stimuli (instantaneous pain)

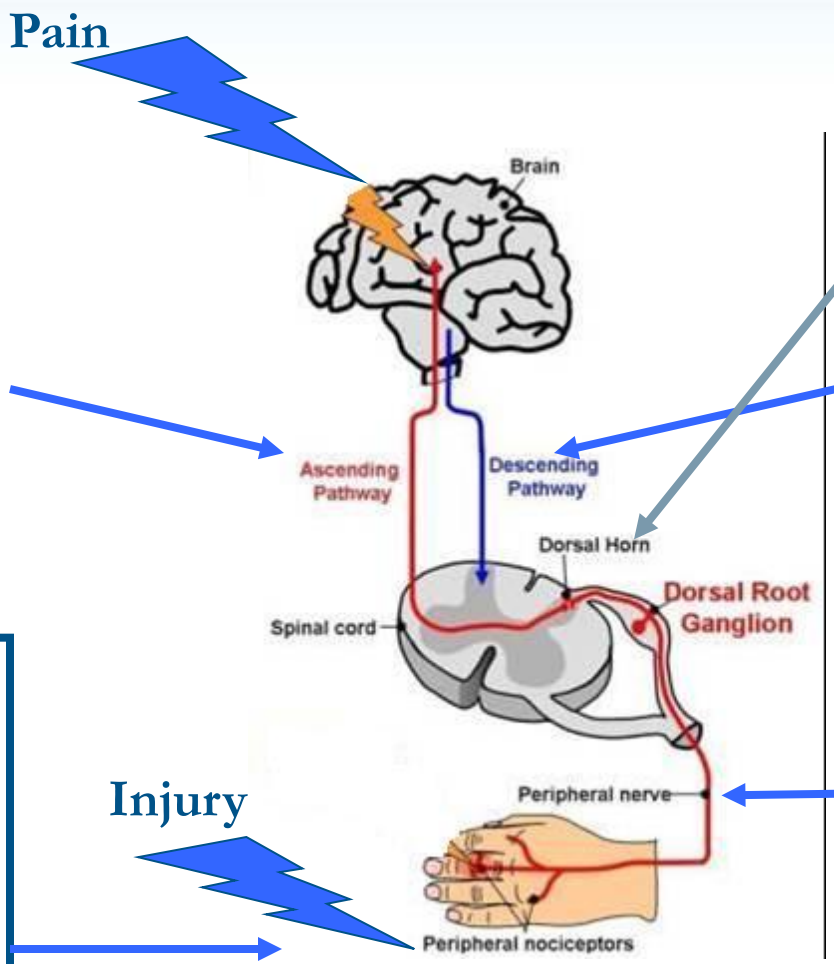
C-fibers: intense nociceptive stimuli (dull, achy pain)

Inflammatory mediators sensitize nociceptors:

Bradykinins

Prostaglandins

Substance P



Neuropathic Etiologies

- Alcohol dependence
  - Concentration gradient damage similar to DM
  - Vitamin deficiency (thiamine, B12)
- Chemotherapy
- Painful diabetic neuropathy (PDN)
- Fibromyalgia (FM)
- HIV/AIDS
- Nerve compression
- Nutritional deficiency
  - E.g. thiamine, niacin, folic acid
- Toxins
  - E.g. arsenic, lead, mercury, organophosphates

Pain Ther. 207;6(1):S35-42.

Antidepressants

Evidence for Use: Tricyclic Antidepressants

Most studied class in neuropathic pain

- PDN primary model in studies
  - Cochrane Review: 46 trials of TCAs in NP
  - Showed significant pain score improvement with TCAs vs. placebo
  - Comparative evidence between the TCAs
    - No significant differences found in trials
  - TCAs have been studied against: tramadol, capsaicin, fluphenazine, and venlafaxine
    - Amitriptyline > tramadol, capsaicin, fluphenazine

Cochrane Lib. 2007;Issue 4

Tolerability: TCAs

- Anticholinergic effects
  - Dry mouth
  - Increased fall risk
  - Delirium risk
- Orthostasis
- QTc prolongation
- Sedation
- Weight gain
- Mortality risk in overdose

Evidence for Use: Venlafaxine

Trial	Intervention	Design	Results
Rowbotham et al. 2004 244 patients	Venlafaxine XR (75 mg OR 150 to 225 mg) Placebo	Double-blind 6 weeks	VAS Scores: - 75 mg: reduced 32% - 150 to 225 mg: reduced 50% - Placebo: reduced 27% - p<0.001

Sindrup et al.
 	
2003
 	
40 patients
	Venlfaxine XR 225 mg
	
	Imipramine 150 mg
		Double-blind
		
		Crossover
		
		12 weeks
			11-point Likert Scale:
			- Baseline: 7 points
			- 12 week:
			  - Venlafaxine 5 points
			  - Imipramine 5.3 points

VAS: visual analog scale

Pain. 2004;110:697-706
Neurology. 2003;60:1284-1289

Evidence for Use: Duloxetine

Duloxetine vs Placebo in Patients with Painful Diabetic Neuropathy

Intervention	Baseline Score (SD)	12-Week Score (SE)	p-value
Placebo N=115	5.8 (1.5)	3.89 (0.22)	NS
20 mg/day N=115	5.9 (1.6)	3.54 (0.21)	NS
60 mg/day N=113	6.0 (1.7)	**3.11 (0.22)**	**≤ 0.01**
120 mg/day N=114	5.9 (1.4)	**2.66 (0.23)**	**≤ 0.001**

Pain. 2005;116:109-118

Evidence for Use: Duloxetine

Patients achieving > 50% reduction in pain:

- Placebo= 29 (26%)
- Duloxetine 20 mg/day= 46 (41%) ($p<0.05$)
- Duloxetine 60 mg/day= 55 (49%) ($p<0.05$)
- Duloxetine 120 mg/day= 57 (52%) ($p<0.05$)

Safety measures:

- No significant difference in lab values or BP
- Somnolence, nausea, constipation, and dizziness were more frequent in 120 mg/day group
- Constipation and somnolence more frequent in 60 mg/day group vs. placebo

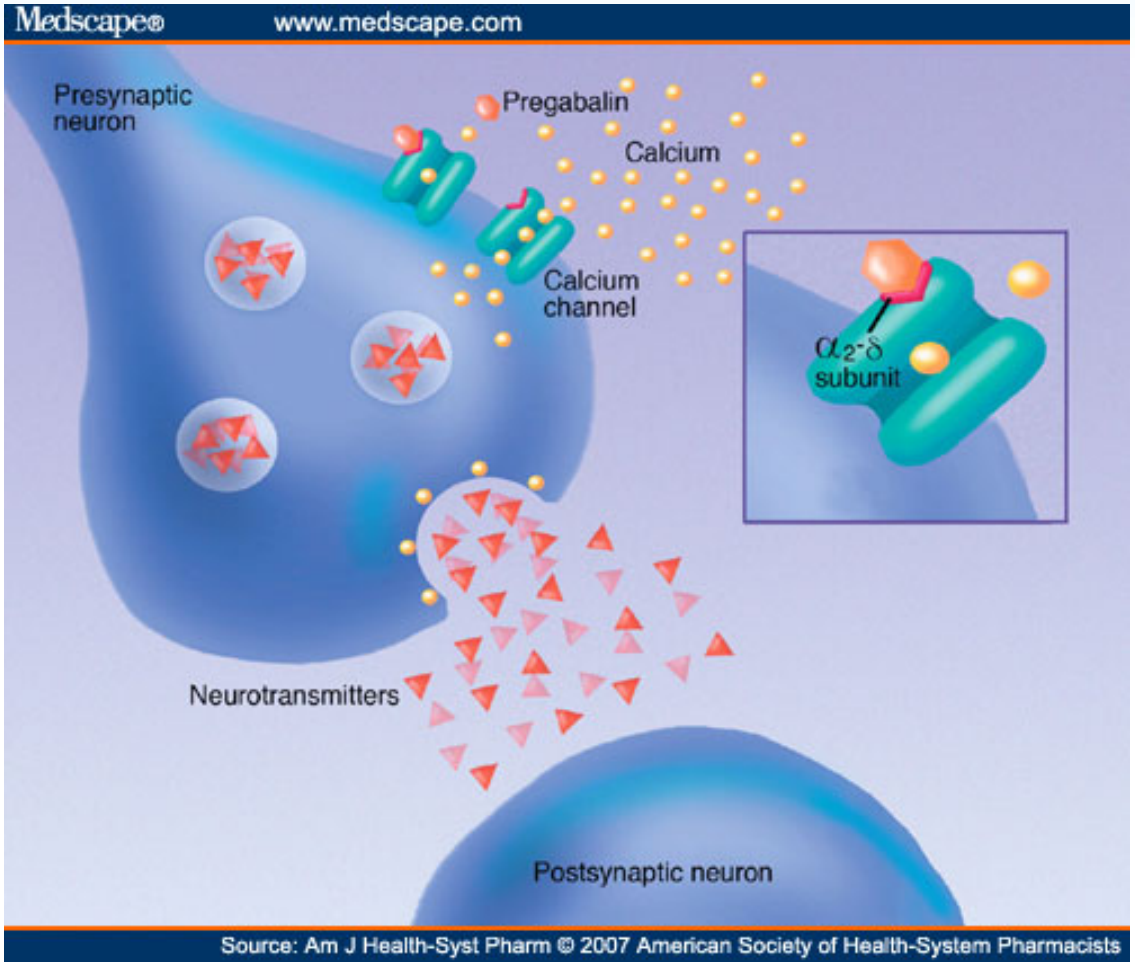
Pain. 2005;116:109-118

Antidepressant Summary

- TCAs:
  - Most studied
  - Limited by tolerability
  - Potential prescriber discomfort
- Venlafaxine:
  - Target doses with norepinephrine activity (≥150 mg)
  - Comparable to imipramine
- Duloxetine:
  - Target doses ≥60 mg
  - Dose related adverse events

Anticonvulsants

Mechanism: Gabapentin & Pregabalin



Ca++ channel *modulator*

↓ Calcium influx
↓ Glutamate release
↓ Excitatory signal transmission
↓ Pain (hopefully)

Evidence for Use: Pregabalin

Intervention	Baseline Score (SD)	Endpoint Score (SE)	p-value
Placebo N=97	6/6 (1.5)	5.06 (0.21)	NS
Pregabalin 75 mg/day N=77	6.7 (1.3)	4.91 (0.24)	0.626
Pregabalin 300 mg/day N=81	6.2 (1.4)	**3.8 (0.23)**	**0.0001**
Pregabalin 600 mg/day N=82	6.2 (1.5)	**3.6 (0.23)**	**0.0001**

Neurology. 2004;63:2104-2110

Summarized Results: Pregabalin

Patients receiving >30% reduction in pain:

- Placebo: 33%
- Pregabalin 300 mg/day: 62%
- Pregabalin 600 mg/day: 65%

Patients receiving >50% reduction in pain:

- Placebo: 18%
- Pregabalin 300 mg/day: 46%
- Pregabalin 600 mg/day: 48%

Safety:

- Dizziness, somnolence and peripheral edema more frequent in 600 mg/day group vs. placebo
- Dizziness and somnolence more frequent in patients treated with 300 mg/day vs. placebo

Lamotrigine for Neuropathy

Na+ channel blocker→ inhibits glutamate release

Cochrane Review (2013)

- 12 RCTs included (n = 1511 patients)
- Lamotrigine 200 – 400 mg/day vs. placebo
- No difference in benefit vs. placebo [HIGH quality of evidence]
- ~10% patients developed rash (NNH 27)

Cochrane Lib. 2013;12.

Carbamazepine for Neuropathy

Na+ channel blocker

Cochrane Review (2014)

- 10 RCTs (n = 480 patients)
  - Trigeminal neuralgia, PDN, post-stroke neuropathy (FM NOT included)
- CBZ 100 – 2400 mg/day vs. placebo or active
- CBZ provided superior pain relief (>50% reduction) vs. placebo (NNT 2) [LOW quality of evidence]
- ~27% patients had side effects (NNH 3)

Cochrane Lib. 2014;4.

Tramadol

Tramadol → M1 via CYP2D6 & CYP3A4

- μ-opioid receptor agonism: M1 >> tramadol
- 5-HT & NE reuptake inhibition: tramadol >> M1

Drug interactions

- CYP2D6 & 3A4 INHIBITORS ↓ analgesia
- Potential for serotonin toxicity

Seizure risk

- Most common in first ~10 days of therapy and in overdose scenarios

Cochrane Lib. 2006;3.

Opioids for Neuropathy

Falling out of favor for **chronic** neuropathy

- Recent pain guidelines emphasize psychological interventions and non-opioid Rx therapies
- Risk vs. benefit on case-by-case basis

Cochrane Review (2013)

- 14 RCTs (n = 845 patients) of duration < 12 weeks
- Short-term benefit observed (NNT = 6 to achieve >50 % pain relief)
- No significant benefit in functioning observed

Cochrane Lib. 2013;8.

Conclusions

Efficacy and Tolerability

Class/Agent	NNT (>50% pain reduction)	NNH (drop out due to side effect)
TCAs	3.6	13.4
SNRIs	6.4	11.8
Gabapentin	7.2	25.6
Pregabalin	7.7	13.9
Tramadol	4.7	12.6
Strong Opioids	4.3	11.7

N = 229 RCTs

Lancet Neurol. 2015;14(2):162-73.

International Association for Study of Pain (NeuPSIG)

Place in Therapy	Medication	Evidence
1st Line	TCAs	STRONG
	SNRI	STRONG
	Pregabalin/gabapentin	STRONG
2nd Line	Tramadol	WEAK
	Lidocaine topical	WEAK
	Capsaicin topical	WEAK
3rd Line	Botox SC injection	WEAK
	Strong opioids	WEAK
Don't Use	Lamotrigine	STRONG
	Cannabinoids	WEAK
	Valproate	WEAK

Lancet Neurol. 2015;14(2):162-73.

NICE 2017 Guidelines

Place in Therapy	Medication
1st Line	Amitriptyline
	Duloxetine
	Pregabalin/Gabapentin
2nd line	Tramadol– short term
	Capsaicin cream*
Do Not Use	Cannabis
	Lacosamide
	Lamotrigine
	Levetiracteam
	Opioids
	Tramadol- long term
	Venlafaxine

NICE Clinical Guideline 173

Assessment Question

Which of the following pharmacologic options is NOT a potential first line recommendations for neuropathic pain?

A) Gabapentin
B) Tramadol
C) Venlafaxine
D) Amitriptyline

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References

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