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TCA Alternatives: Neuropathic pain

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Endorsed by Pharmacy Administration, Neurology

Goals of therapy

- The primary goal is a clinically meaningful improvement in function. This can be assessed using the PEG Tool (Pain intensity, interference with Enjoyment of life and interference with General activity).[1]
- A reasonable goal for pain relief is a 30-50% reduction in pain. A goal of achieving complete or near complete pain relief is unrealistic.[2]
- Treatment responders are also likely to experience improvement in sleep, depression, fatigue and quality of life.[2]

Summary of medication treatment options

- There are no well-designed studies establishing the superiority of one medication (or class of medications) over another in the treatment of neuropathic pain in terms of efficacy and safety.[2,3]
- Most studies assessing medications for the treatment of neuropathic pain are of low quality.[2]
- Pain relief with medications tends to have a U-shaped distribution, rather than a bell-shaped distribution, with participants either achieving good levels of pain relief or little to none.[2]
- Recent Cochrane reviews suggest that gabapentin, duloxetine and pregabalin have the best evidence for the treatment of neuropathic pain when considering efficacy, safety and tolerability. Although, for all drugs, only a small subset of patients will respond to treatment.[4-6]
- The Cochrane reviews are consistent with recommendations in evidence-based guidelines for the treatment of pain from the United Kingdom.[3,7]
- Of note, both the Cochrane review & NICE guidelines took into account the evidence revealed as part of the gabapentin litigation in the United States.[3-4]

Table 1: Evidence summary for medications with best evidence of efficacy[4-6]

Medication	Initial Dose	Indication	Study Outcomes (Relative risk vs placebo)			
			≥50% reduction in pain	NNT	Patient-reported improvement*	NNT
Gabapentin	300 mg daily	PHN	1.6	8	1.3	10
		DPN	1.9	6	1.7	5
Duloxetine	30 mg daily	DPN	1.7	5	NR	NR

*Patient global impression of change much or very much improved; PHN = postherpetic neuralgia; DPN = diabetic peripheral neuropathy; NR = not reported; NNT = number needed to treat; NP = non-preferred

- Other medication treatments with positive, low quality evidence for efficacy include:
  - TCAs (largest body of evidence = amitriptyline)[8-11]
  - Venlafaxine[12]
  - Lidocaine[13]
- Medication treatments with uncertain evidence for efficacy include:
  - Capsaicin cream[14]

Patient Counseling Points

- Reinforce the focus on function as the primary goal of treatment.
- The full effect of the medication may take up to 2-4 weeks.
- Reinforce lifestyle management (stress reduction, regular eating & sleeping, regular exercise).

Evidence Summary Detail

Gabapentin[4]

- A Cochrane review found some evidence for benefit of gabapentin in the treatment of postherpetic neuralgia and painful diabetic neuropathy; although the author's concluded that over half of those treated with gabapentin will not have worthwhile pain relief.
- This review takes into account evidence that was made available through litigation in the United States.
    - Postherpetic neuralgia (gabapentin ≥1,800 mg daily vs placebo)
        - ≥ 50% reduction in pain: RR 1.6, NNT = 8
        - Patient global impression of change much or very much improved: RR 1.3, NNT = 10
    - Painful diabetic neuropathy (gabapentin 600 mg – 3,600 mg daily vs placebo)
        - ≥ 50% reduction in pain: RR 1.9, NNT = 6
        - Patient global impression of change much or very much improved: RR 1.7, NNT = 5
- NNH for select adverse events: 11 for somnolence/drowsiness/sedation, 8 for dizziness, 21 for peripheral edema, 13 for ataxia/gait disturbance

Duloxetine[5]

- A Cochrane review found moderate quality evidence that duloxetine in doses of 60 mg and 120 mg is effective for treating pain in diabetic peripheral neuropathy.
    - Painful diabetic neuropathy (duloxetine 60 mg/day vs placebo)
        - ≥ 50% reduction in pain: RR 1.7, NNT = 5
        - Only mean improvements on patient global impression of change were reported. The mean difference between duloxetine and placebo on this scale was 0.54 to 0.6. A change of one point on this scale has been suggested as a clinically meaningful difference.

Pregabalin[6]

- A Cochrane review found high quality evidence that pregabalin in doses >150 mg daily is effective in a minority of patients for treating pain in postherpetic neuralgia and painful diabetic neuropathy.
    - Post herpetic neuralgia
        - ≥ 50% reduction in pain: RR 2.5-2.7, NNT 4-5
        - Patient global impression of change much or very much improved: RR 1.8-2.3; NNT 5-6
    - Painful diabetic neuropathy
        - ≥ 50% reduction in pain: RR 1.5-1.7, NNT 5-11
        - Patient global impression of change much or very much improved: 1.3-1.8, NNT 4-5
- NNH for select adverse events: 2-5 for somnolence and dizziness, respectively

<u>Other therapies</u>

TCAs[8-11]

- Several Cochrane reviews found little evidence for a beneficial effect to support the use of TCAs in the treatment of neuropathic pain.
- The author's note that amitriptyline, which has the largest body of evidence, is widely used as a first-line treatment for neuropathic pain and suggested that it should continue to be used, but noted that only a minority of people will experience adequate benefit.
- For other TCAs, the authors note that there may be a role in patients who have not obtained pain relief from other treatments.

Venlafaxine[12]

- Five small studies showed moderate benefit; however, the evidence was low quality.
- The authors conclude that venlafaxine is a reasonably well-tolerated drug and may provide some benefit in patients who have not obtained pain relief from other treatments.

Topical lidocaine[13]

- Individual studies indicate that topical lidocaine is effective for pain relief, though the evidence is low quality. The authors note that clinical experience supports efficacy in some patients.

Topical capsaicin[14]

- A Cochrane review concluded that there is insufficient evidence to draw conclusions about the efficacy of topical capsaicin in the treatment of neuropathic pain.

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