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FAST FACTS AND CONCEPTS #187

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Background Tricyclic antidepressants (TCAs) have long been recognized as effective agents for neuropathic pain. Due to their sedating and anticholinergic side effects there has been much interest in newer antidepressant agents with different side effect profiles. This Fast Fact reviews the use of non-tricyclic antidepressants for neuropathic pain.

Pharmacology Serotonin (5HT) and norepinephrine (NE) mediate descending inhibition of ascending pain pathways in the brain and spinal cord. Experience has suggested that antidepressants which enhance NE action are more effective analgesics than those which predominantly enhance 5HT action, such as with many of the newer antidepressants. TCAs are thought to cause analgesia by NE and 5HT reuptake inhibition; they also have other pharmacologic properties that may contribute to analgesia such as reducing sympathetic activity, NMDA-receptor antagonism, anticholinergic activity, and sodium-channel blockade. Non-tricyclic antidepressants seem to be less efficacious for neuropathic pain (see below): this may in part be because of their 'cleaner' pharmacodynamic profiles.

Clinical Evidence Most randomized controlled trials of non-tricyclic antidepressants for pain have been for diabetic peripheral neuropathy or post-herpetic neuralgia. There have been few studies in other neuropathic conditions and none in cancer-related pain. There have been very few head-to-head comparisons of antidepressants, which limits understanding of their relative efficacy.

- **Selective Serotonin Reuptake Inhibitors (SSRIs):** *Fluoxetine* is not effective for neuropathic pain. *Paroxetine* and *citalopram* have shown only mild benefit for HIV-related and diabetic neuropathy in small studies. Other SSRIs have not been evaluated.
- **Serotonin Norepinephrine Reuptake Inhibitors (SNRIs):**
 - Low doses of *venlafaxine* are predominantly serotonergic, but higher doses add substantial noradrenergic effects. Doses of 150-225 mg/day appear to have mild to moderate analgesic effect (30-50% reduction in pain) with a number needed-to-treat (NNT) of 4.6 in painful diabetic neuropathy (only one out of every 4-5 patients treated will benefit). In contrast, many trials of TCAs for neuropathic pain have shown NNT of 2-3. One head-to-head trial showed venlafaxine 225 mg/day had the same tolerability as 150 mg/day of imipramine (a TCA), but venlafaxine was less effective for pain. Side-effects of venlafaxine include nausea, sedation, headache and dizziness. The usual starting dose is 37.5 mg daily, increasing weekly in 37.5 mg increments. Use of venlafaxine for analgesia is not FDA approved; a 75 mg tab costs approximately \$3.70 (average US wholesale price).
 - *Duloxetine* has been shown to have a mild to moderate analgesic effect in industry-sponsored trials in diabetic peripheral neuropathy (NNT 5.2) at a dose of 60 mg daily. Onset of analgesia is at about 1 week, with maximum effect at about 4 weeks. A dose of 60 mg BID may lead to increased analgesia but at the expense of an increased risk of side-effects, particularly nausea, sedation, constipation, sweating, and insomnia. *Duloxetine* is licensed for use in diabetic peripheral neuropathic pain in the USA. A 60 mg tab costs approximately \$3.50.
- **Other Antidepressants** *Bupropion* is a dopamine and norepinephrine reuptake inhibitor and was found to have a mild analgesic effect in one study involving 41 patients with a mix of neuropathic pain syndromes. *Mirtazapine* has a complicated pharmacology and has not yet been evaluated as an analgesic.

Summary There are relatively well defined and preferred therapies for neuropathic pain including newer generation anticonvulsants (such as gabapentin), TCAs, and opioids in select patients. In patients with ongoing pain despite treatment with these agents, or who are intolerant to them, venlafaxine or duloxetine may be helpful. There are no comparative studies between non-tricyclics for neuropathic pain, thus an agent should be selected based on its side-effect profile, cost, and familiarity with use.

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