FAST FACTS AND CONCEPTS #187
NON-TRICYCLIC ANTIDEPRESSANTS FOR NEUROPATHIC PAIN
Pippa Hawley B.Med, FRCPC

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 newer antidepressants which enhance NE action are more effective analgesics than many older antidepressants which predominantly enhance 5HT action. 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 a few well controlled studies in the treatment and prevention of chemotherapy induced peripheral neuropathy (CIPN) but limited good data in other neuropathic conditions.

• 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):
  ○ Venlafaxine: Low doses of 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, TCAs have shown a NNT of 2-3. Pilot data, in additional to one randomized controlled trial, support the use of extended release venlafaxine in preventing the onset of CIPN if given at doses of 25 mg to 75 mg a day one hour prior to chemotherapy infusion as well as 11 days after. 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). In addition, a randomized controlled trial showed relatively small but significant neuropathic pain relief compared with placebo. Onset of analgesia is at about 1 week, with maximum effect at about 4 weeks. A dose of 60 mg a day has been best studied for both diabetic peripheral neuropathy and CIPN; 60 mg BID may lead to increased analgesia but at the expense of an increased risk of nausea, sedation, constipation, sweating, and insomnia. Duloxetine has an FDA indication for use in diabetic peripheral neuropathic pain in the USA. A 60 mg tab costs approximately $3.50.

• Other Antidepressants Buproprion is a dopamine and norepinephrine reuptake inhibitor with mild analgesic effect according to one study involving 41 patients with a mix of neuropathic pain syndromes. Mirtazapine has a complicated pharmacology with unknown analgesic effects.

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.

References


*Fast Facts and Concepts* are edited by Sean Marks MD (Medical College of Wisconsin) and associate editor Drew A Rosielle MD (University of Minnesota Medical School), with the generous support of a volunteer peer-review editorial board, and are made available online by the [Palliative Care Network of Wisconsin](http://palliativecarenetworkofwisconsin.org) (PCNOW); the authors of each individual *Fast Fact* are solely responsible for that *Fast Fact*’s content. The full set of *Fast Facts* are available at [Palliative Care Network of Wisconsin](http://palliativecarenetworkofwisconsin.org) with contact information, and how to reference *Fast Facts.*

**Copyright:** All *Fast Facts and Concepts* are published under a Creative Commons Attribution-NonCommercial 4.0 International Copyright ([http://creativecommons.org/licenses/by-nc/4.0/](http://creativecommons.org/licenses/by-nc/4.0/)). *Fast Facts* can only be copied and distributed for non-commercial, educational purposes. If you adapt or distribute a *Fast Fact*, let us know!

**Disclaimer:** *Fast Facts and Concepts* provide educational information for health care professionals. This information is not medical advice. *Fast Facts* are not continually updated, and new safety information may emerge after a *Fast Fact* is published. Health care providers should always exercise their own independent clinical judgment and consult other relevant and up-to-date experts and resources. Some *Fast Facts* cite the use of a product in a dosage, for an indication, or in a manner other than that recommended in the product labeling. Accordingly, the official prescribing information should be consulted before any such product is used.