PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #363
OPIOIDS FOR NEUROPATHIC PAIN
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Background Neuropathic pain is caused by damage of the somatosensory nervous system leading to abnormal neural excitability (1). Patients often describe it as 'burning', 'tingling' or 'shooting' down a nerve distribution, and some may experience allodynia where they feel pain from non-painful stimuli like air or light touch on skin. Approximately 10% of the general population has neuropathic pain (2). The role of opioids for neuropathic pain is controversial and examined in this *Fast Fact*.

Why Try Opioids for Neuropathic Pain? Opioids are broad-spectrum analgesics. While there are numerous non-opioid adjuvant medications and analgesic-based interventions available to patients with neuropathic pain, these interventions have their own associated risks and side-effects. Besides, many who are nearing end-of-life from a progressive illness may already be on opioids. These patients may have trouble swallowing oral medications and they often have renal dysfunction, limiting their ability to tolerate many non-opioid adjuvants. Only a minority of patients with neuropathic pain experience a clinical benefit from one analgesic intervention and require multi-modal therapies (3). Therefore, the clinical question of dose-escalating or initiating an opioid vs adding a non-opioid adjuvant arises frequently.

Opioids vs Non-Opioids for Neuropathic Pain Large systematic reviews and meta-analyses have examined opioids as a class for neuropathic pain of any etiology. Although these studies have led to disparate conclusions (3-8), a Cochrane review and a 2015 meta-analysis suggest that "strong opioids" (i.e. oxycodone, methadone, and morphine) at doses ranging from 15-240 mg oral morphine equivalents (OMEs) reduce neuropathic pain by at least 33% from baseline (3,4). These "strong opioids" were found to have a number-needed-to-treat (NNT) of 4.3 after 4-12 weeks of treatment and a number-needed-to-harm (NNH) of 11.7. For comparison, meta-analyses noted an NNT of 3.6 for tri-cyclic antidepressants or TCAs (such as amitriptyline or nortriptyline), 6.4 for serotonin-norepinephrine reuptake inhibitors or SNRIs (such as duloxetine or venlafaxine), 7.2 for gabapentin, 7.7 pregabalin, and 8.7 for capsaicin for neuropathic pain. The NNH is 13.4 for TCAs, 11.8 for SNRIs, 25.6 for gabapentin, 13.9 for pregabalin, and 8.7 for capsaicin (see *Fast Facts #49, #187, #197, #271, #288, & #289) (4)*. Constipation, somnolence, delirium, dizziness, and dry mouth are the most commonly reported adverse effects of opioids. Maximum effectiveness was associated with 180 mg OMEs/day, with no additional benefit for higher doses (3,4). While TCAs, SNRIs, gabapentin, or pregabalin are considered by many experts to be first-line analgesics for neuropathic pain, opioids are often considered as second or third-line agents for many patients or as a co-analgesic when prompt pain relief during titration of a first-line medication is required (4). There is little published evidence on NSAIDs and acetaminophen for neuropathic pain, though commonly prescribed (9,10).

Clinical Evidence for Individual Opioids Although oxycodone, morphine, and methadone are the most studied opioids for neuropathic pain, there are no well-designed studies to compare the safety or efficacy of any one specific opioid over another.

- Hydromorphone: One randomized study explored its efficacy but with a high risk of bias and incomplete outcomes data (11). Hence, there is insufficient evidence to support or refute its role for neuropathic pain.
- Fentanyl: There is insufficient evidence to support fentanyl for neuropathic pain, based on one randomized study of 258 participants at patch doses of 12-50 mcg/hr for 12 weeks (12).
- Methadone: Randomized control trials have shown some efficacy but it is unclear if methadone offers any additional neuropathic pain control over other opioids (8,13) (see *Fast Fact #171*).
- Tramadol and Tapentadol: Tramadol at doses of 100-400 mg/day has achieved 30% neuropathic pain relief compared with placebo in study periods of 4-6 weeks, with NNT of 3.8 and NNH of 8.3 (14) (see *Fast Fact #290*). Tapentadol, a similar analgesic, has also improved neuropathic pain at doses of 100-500 mg/day in 8-12-week study periods (15-18).

- Buprenorphine: experts cite its kappa receptor antagonism as a theoretical advantage for alleviating neuropathic pain over other opioids, but no well-controlled trials have yet confirmed this. It is considered a partial opioid agonist, as such it may be less associated with delirium and constipation. It can be a reasonable agent for opioid-naïve patients being initiated on an opioid. However, rotating patients to buprenorphine from other opioids be complicated and is best done by only experienced clinicians (see *Fast Fact* # 268) (19).
- Other: There is no supporting evidence nor clinical rationale for the targeted selection of codeine, hydrocodone, or oxymorphone for neuropathic pain (20,21). Although not a true opioid agonist, dextromethorphan has been associated with significant neuropathic pain relief, especially for diabetic neuropathy, at doses of 120-920 mg/day for up to 3 months in duration (8). A high prevalence of intolerable side effects (drowsiness and dizziness especially) limits its use, however.

Conclusion While opioids are not first-line agents for most patients with neuropathic pain, meta-analyses suggest they have efficacy when prescribed as monotherapy or part of a multi-modal regimen for patients with refractory, function-impairing neuropathies, especially when prognosis is short. A ceiling effect has been observed when opioids are prescribed for neuropathic pain and the benefit of increasing the opioid dose for beyond 180-240 mg/day should be pursued only on an individual patient basis.

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