

## Neuropathic Pain Treatment

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Newer generic approvals: Gabapentin, Oxcarbazepine, Lamotrigine, Divalproex

Tentative approval: Topiramate

Neuropathic pain (NP) is defined as "pain initiated or caused by a primary lesion or dysfunction in the nervous system." (1) It is a heterogeneous group of conditions which include diabetic peripheral neuropathy (DPN), post herpetic neuropathy (PHN), spinal cord injury, trigeminal neuralgia, post stroke pain, HIV-associated neuropathy and phantom limb pain, among others. It is characterized by changes within the neural pathways that result in chronic pain even in the absence of a continuing stimulus. It has multiple etiologies and may be associated with inflammation, trauma, ischemia, metabolic disorders and other insults to the peripheral or central somatosensory nervous system. Symptoms include spontaneous burning, aching or shooting pain sensations, abnormal sensitivity to normal, innocuous stimuli, or increased sensitivity to noxious stimuli. (2) Despite different etiologies and multiple lesions giving rise to NP, many of these conditions share common clinical phenomena like: no visible injury, paradox combination of sensory loss and hyperalgesia in the painful area, paroxysms and a gradual increase of pain following repetitive stimulation. (3) Allodynia (pain from a normally innocuous stimulus), which occurs more commonly in PHN than DPN, is extremely treatment-resistant. (4) A variety of pharmacologic agents from different therapeutic classes have been used for NP treatment. Even so, only 40-60% of patients obtain even partial pain relief for NP with existing pharmacologic agents.(5) Methodology, small sample sizes, short duration studies, lack of head to head trials, and variability in drug classes for treatment of different types of NP limit comparative analysis of many medications.

### Tricyclic Antidepressants (TCAs)

TCAs are used as first line agents for many neuropathic pain states. They have been found more useful in DPN, PHN, post-stroke pain, non-diabetic polyneuropathy, and post-mastectomy pain than in spinal cord injury pain, phantom limb pain, or pain in HIV-neuropathy. In painful polyneuropathy, there is a trend towards better effect of balanced serotonin and norepinephrine reuptake inhibitors than of mainly norepinephrine drugs. (5) The TCAs are believed to modulate pain by non-selectively blocking norepinephrine and serotonin reuptake neurons, blocking calcium channels, presynaptic reuptake inhibition of N-methyl-D-aspartate (NMDA) receptors and having a local anesthetic-like effect from sodium channel blockade. (4) The secondary amine TCAs (nortriptyline and desipramine) are sometimes preferred since they are better tolerated than tertiary amine TCAs (amitriptyline and imipramine) but all have comparable analgesic efficacy. Patients with ischemic heart disease or with an increased risk of sudden cardiac death should avoid TCAs. An electrocardiogram is recommended before beginning TCA treatment if over 40 years old. (6) They can all cause or exacerbate cognitive impairment, gait disturbances, and falls in elderly patients. Dosing should be the lowest possible and titrated upward slowly until pain is controlled or side effects limit continuation. Toxic levels of TCAs may result if TCAs are given together with drugs that inhibit cytochrome P450 2D6 such as SSRI's. (6)

### SNRI Antidepressants

Duloxetine inhibits the reuptake of both serotonin and norepinephrine. Three trials found Duloxetine at doses of 60-120 mg/daily superior to placebo for patient-reported pain in patients with painful DPN. (1) Responses are seen at 60 mg/day, dose response curves begin to flatten after 60 mg/day for diabetic neuropathy (4) and daily dosing is associated with fewer side effects. Nausea is the most frequent side effect and it occurs less frequently when treatment is started at 30 mg daily and titrated after one week to 60 mg daily.(6) Food increases bioavailability.(4) It is metabolized by cytochrome 2D6 and 1A2 so is subject to drug interactions. Duloxetine should be avoided in renal impairment (creatinine clearance <30 ml/min) and reduced doses should be used in severe cirrhosis. It must be gradually tapered off for risk of discontinuation syndrome.(6)

Venlafaxine inhibits serotonin reuptake at lower dosages and both serotonin and norepinephrine reuptake at higher dosages (>150mg/day). Randomized controlled trials (RCT) in patients with painful DPN and painful polyneuropathies of various types demonstrated efficacy at dosages of 150-225 mg/day. Other studies have demonstrated inconsistent or negative results.(5) One small trial comparing venlafaxine versus imipramine showed similar efficacy on a number of pain scales with no statistically significant difference in the likelihood of achieving pain relief. (1) Severe renal disease prolongs elimination by 50%.(4) Monitoring of cardiac function is recommended in those with cardiac risk. Venlafaxine must also be gradually tapered off.(6)

### Gabapentin

Gabapentin has been shown effective for painful DPN, phantom limb pain, PHN, Guillain-Barre syndrome, acute and chronic spinal cord injury pain, and neuropathic cancer pain.(6) Gabapentin is thought to reduce pain by binding to subunits of the calcium channel, decreasing the release of glutamate, norepinephrine, and substance P. However, analgesic activity is dependent upon the integrity of the descending brainstem serotonergic pathway. It also facilitates NMDA receptor depolarization on GABAergic inhibitory neurons in the dorsal horn. Loss of GABAergic inhibitory neurons will reduce gabapentin responses.(4) It appears more effective for DPN than for PHN.(4) Gabapentin was consistently more effective than placebo for pain relief or improvement in function in 12 placebo-controlled trials.(1) The 3 largest trials (n=229,305 and 334) consistently found gabapentin at doses of 1800mg to 3600 mg/day superior to placebo on at least some measure of pain relief and at least some domain of quality of life.(1) There are no head to head studies comparing gabapentin to pregabalin at this time. In adjusted indirect analyses comparing separate placebo controlled trials of the two drugs, there were no significant differences between gabapentin and pregabalin in the likelihood of achieving pain relief. The only statistically significant difference between the two was observed on the SF-36 Vitality score where gabapentin was superior to pregabalin by less than 10 points.(1) One systematic review found no difference between gabapentin versus amitriptyline for the proportion of patients experiencing pain relief.(7)

Gabapentin requires slow dose titration (2-6 weeks) up to 1800-3600 mg/day before peak effect is seen.(5) Divided doses have greater bioavailability. Dose reductions are needed in renal impairment. Drowsiness, peripheral edema, ataxia, dizziness, and cognitive impairment in the elderly are common side effects. Confusion is a less common side effect. Gabapentin and pregabalin are associated with more somnolence/sedation compared to venlafaxine.(1) A withdrawal syndrome can occur if stopped abruptly.(4) Gabapentin is now available in generic form. Indirect analysis from a systematic review indicates a lower likelihood of withdrawal due to adverse events with gabapentin vs. pregabalin at comparable doses, but no difference in overall rates of withdrawal, somnolence/sedation or dizziness between the two drugs were seen.(1)

**Pregabalin**

Pregabalin is a structural congener of gabapentin.(4) It has been approved for both DPN and PHN. In a systematic review of 8 trials, pregabalin was consistently more effective than placebo for NP. Pregabalin was moderately superior to duloxetine for the proportion of patients experiencing significant pain relief, but there were no differences between pregabalin, gabapentin and venlafaxine on indirect analysis.(1) In trials that evaluated higher and lower doses of pregabalin, the higher doses of pregabalin (300 mg+/day) were more effective than lower doses (75-150 mg/day) when compared to placebo, but were also associated with more adverse events.(1) Unlike gabapentin, pregabalin has linear pharmacokinetics, and dose titration can be reached within 1-2 weeks, but it still requires divided doses similar to gabapentin. It has demonstrated anxiolytic effects in RCTs.(5) It causes drowsiness, dizziness, peripheral edema and weight gain. Pregabalin is associated with more dry mouth than venlafaxine.(1) Like gabapentin, it has no clinically important drug interactions, but needs dose reductions in renal impairment and the elderly.(5) Both gabapentin and pregabalin need to be slowly tapered off when discontinuing, over a minimum of 1 week.

**Other Antiepileptics**

Carbamazepine, valproic acid, lamotrigine, oxcarbazepine, and topiramate have all shown inconsistent results in various forms of NP.(9) **Carbamazepine** has been used for trigeminal neuralgia based on small, short duration studies completed in the 1960's. Carbamazepine has yielded inconsistent results in trials for other types of NP.(6) Doses need to be adjusted in renal impairment. **Oxcarbazepine** seems to have similar efficacy to carbamazepine in the treatment of trigeminal neuralgia; however, overall, there are only limited data regarding efficacy and safety in other neuropathic pain syndromes.(2) **Topiramate** is a weak carbonic anhydrase inhibitor with multiple mechanisms of action possibly relevant to NP, but demonstrates mixed results in the treatment of neuropathic pain syndromes.(2) In many of the trials, withdrawal rates are high due to adverse effects. **Lamotrigine** showed evidence of pain relief in small RCTs, but intention-to-treat analyses were negative in three larger RCTs, two of which were in painful DPN.(6) Another open label trial suggested lamotrigine may reduce pain intensity in patients with painful diabetic neuropathy.(11) It also demonstrated mixed results in trials assessing pain reduction in HIV-associated polyneuropathy. In a small study, patients with incomplete spinal cord injury or evoked allodynia and wind-up-like pain experienced a positive effect from lamotrigine.(10) Two small studies indicate its usefulness in trigeminal neuralgia and one study demonstrated effectiveness in sciatic pain.(2) Lamotrigine needs careful dose titration to reduce the risk of potentially serious skin reactions. Many drugs in this class have narrow therapeutic indexes and high side effect profiles so patients need to be monitored closely. Indirect analysis from a recent systematic review of placebo-controlled trials found gabapentin and pregabalin each moderately superior to other antiepileptic medications (carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid) for achieving pain relief in NP.(1)

**Opioids**

Neuropathic pain mechanisms are associated with poor opioid responses and resemble opioid tolerance. (4) Receptors may change phenotype in association with neuropathic pain. Morphine receptors are downregulated and dynorphin and cholecystokinin are released resulting in a reduced opioid responsiveness and relative opioid tolerance. Peripheral morphine analgesia is lost and central opioid analgesia blunted.(4). This central reorganization leads to resistance to peripheral acting analgesics such as sodium channel blockers, spinal analgesia and nerve blocks.(4) Data suggest that long term opioid treatment can also be associated with hyperalgesia.(12,13) While the stimulation of a  $\mu$ -opioid receptor initially hyperpolarizes neurons by activating inward potassium channels (clinically equivalent to analgesic effects), ongoing stimulation of the  $\mu$ -opioid receptor can result in upregulation of the intracellular messenger phosphokinase C, activation of the NMDA receptor system, and result in enhanced neuronal excitability (clinically equivalent to hyperalgesic effects).(14) Opioids have demonstrated some efficacy in patients with NP, but produce side effects, tolerance and

dependence more often than other treatments for various types of NP, and should be reserved for second or third line treatment. Long term opioid has rarely been associated with the development of immunologic changes and hypogonadism.(6)

**Tramadol**

Tramadol is a weak opioid agonist and a serotonin and norepinephrine reuptake inhibitor. It's metabolite is a strong opioid agonist. It is associated with abuse potential. In a systematic review of six trials, tramadol relieved paresthesias, allodynia, and touch-evoked pain.(4) It has good tolerability among the elderly (up to 250 mg/day), relatively few drug interactions, and low rate of constipation. It can cause serotonin syndrome if used in conjunction with SSRI's, lowers seizure threshold and can cause cognitive impairment.

**Topical Lidocaine**

Trials of lidocaine patch in treating neuropathic pain are inconsistent in showing a clear benefit .(1) It is recommended for patients with localized peripheral NP but not for patients with central NP.(6) Efficacy has been demonstrated in PHN and allodynia, but not in patients with HIV neuropathy. It should be avoided in patients receiving Class I antiarrhythmic drugs (mexiletine) and in patients with severe hepatic disease.(6)

**Topical Capsaicin**

Results comparing capsaicin with placebo in patients with DPH, PHN and post-mastectomy pain have been inconsistent (6). Topical application 3-4 times daily and local irritation contribute to unblinding and high drop out rates in studies.

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