

New Developments in the Management of Diabetic Peripheral Neuropathic Pain – Focus on Duloxetine

a report by

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Diabetic peripheral neuropathic pain (DPNP) is a manifestation of distal symmetrical sensorimotor polyneuropathy, the most common form of diabetic peripheral neuropathy. About 10% to 20% of patients with diabetes may experience neuropathic pain.¹ Now a new therapeutic advance makes it possible to offer patients significant symptom relief. In addition to pain, patients may experience diminished energy, mobility, and general enjoyment of life.

Clinical Manifestations and Impact on Quality of Life

The symptoms of DPNP typically begin in the feet and progress from distal to proximal over time.^{2,3} Patients frequently complain of pain, which may be described as burning, shooting, or stabbing. The discomfort is frequently exacerbated by activity and is typically worse at night, causing sleep difficulties. Paresthesias, allodynia, hyperalgesia, numbness, and loss of proprioception, causing impaired balance, may also be common among patients with DPNP.

In addition to pain, patients may experience diminished energy, mobility, and general enjoyment of life. A prospective survey study of 105 patients with DPNP showed that pain had the largest impact on sleep, enjoyment of life, and recreational activities. Pain also had an impact on general activity, mobility, work, and social activity – 53% of patients experienced pain on a constant, daily basis. For most, pain was found to be worse at night or when they were tired.⁴

The Role of Serotonin and Norepinephrine in Pain Relief

There are many theories to explain persistent pain states. For instance, central sensitization, hyperexcitability, and decreased inhibition may be involved in the mechanism of neuropathic pain states, including DPNP.

As part of the body's endogenous analgesic system, serotonin and norepinephrine are key modulatory neurotransmitters in descending inhibitory pain pathways. One of the most accepted theories is that both serotonin and norepinephrine modulate pain perception in the brain and throughout the peripheral nervous system.^{5,6} Targeting both serotonin and norepinephrine may promote central pain inhibition.

Cymbalta® (Duloxetine HCl) – A New Advance for Patients with DPNP

Duloxetine is the first US Food and Drug Administration (FDA)-approved agent for the management of DPNP. Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor with a relatively balanced effect on these neurotransmitters.⁷ The pain inhibitory effect of duloxetine is believed to be centrally mediated through potentiation of serotonin and norepinephrine activity in descending pain pathways in the central nervous system. Duloxetine has no *in vitro* affinity for opioid, glutamate, and gamma-aminobutyric acid (GABA) receptors and no significant affinity for dopaminergic, adrenergic,

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cholinergic, and histaminergic receptors. The FDA has also approved duloxetine for the treatment of major depressive disorder in patients who are 18 years and older. As part of the body's endogenous analgesic system, serotonin and norepinephrine are key modulatory neurotransmitters in descending inhibitory pain pathways.

Duloxetine Efficacy in DPNP

A total of 1,074 patients were treated with duloxetine in DPNP registration trials. On average, the patients studied in DPNP trials were 60 years old (range 22–88), had diabetes for 11 years, and a diagnosis of DPNP for four years. The majority of patients enrolled were male, caucasian, and had type 2 diabetes. All participants rated their pain at baseline as at least a four using an 11-point Likert scale. To assess the independent analgesic properties of duloxetine, patients with depression and other major psychiatric disorders were specifically excluded from these trials.

The efficacy of duloxetine was established in two double-blind, placebo-controlled trials lasting 12 to 13 weeks using doses from 20mg/day to 120mg/day.⁸ In both studies, duloxetine 60mg/day and 120mg/day produced a rapid and significant separation from placebo on the mean 24-hour average pain severity score as early as week one. The difference between duloxetine 60mg/day and 120mg/day was not statistically significant. The 20mg/day dose was not effective.

Duloxetine clinical trials prospectively assessed night pain experienced by DPNP patients. In pain reported at night, duloxetine significantly separated from placebo at week one and remained significant through week 12. Generally, a 30% or greater reduction in pain is considered clinically meaningful.⁹ Using this criterion, duloxetine demonstrated clinically meaningful reduction in mean night pain scores from week two through week 12. The difference between duloxetine 60mg/day and 120mg/day was not statistically significant.

Clinical trials prospectively assessed the degree to which pain interfered with patient functioning. The Interference portion of the Brief Pain Inventory measured seven domains – general activity, mood, walking ability, normal work, relationships, sleep, and enjoyment of life. Duloxetine 60mg once-daily and 120mg/day demonstrated significantly greater

reduction in average pain interference versus placebo at end-point. The 120mg/day dose was numerically superior to 60mg once-daily but this difference was not statistically significant.

Duloxetine Adverse Event Profile

The discontinuation rate due to adverse events was 14% for duloxetine (20–120mg/day) and 7% for placebo. Common adverse events reported as reasons for discontinuation and considered to be drug-related (i.e. discontinuation occurring in at least 1% of duloxetine-treated patients and at a rate at least twice that of placebo) were nausea (duloxetine 3.5% versus placebo 0.4%), dizziness (1.6% versus 0.4%), somnolence (1.6% versus 0%) and fatigue (1.1% versus 0%).

The most commonly observed adverse events for duloxetine (reported by >5% of patients and at least twice the incidence of placebo patients) were nausea (duloxetine 24% versus placebo 9%), somnolence (16% versus 5%), dizziness (13% versus 6%), constipation (11% versus 3%), dry mouth (9% versus 4%), hyperhidrosis (7% versus 2%), decreased appetite (6% versus <1%), and asthenia (5% versus 1%). Most of these were reported as mild or moderate in severity and were more common at higher doses of duloxetine. Nausea with duloxetine 60mg/day and 120mg/day generally occurred within the first week of treatment, with a median duration of six days. After one week, the incidence of new nausea reports was similar between duloxetine and placebo. Of patients who experienced nausea, 89% rated it as mild to moderate.

Because duloxetine has virtually no affinity for cholinergic receptors, the anticholinergic-like adverse events may be related to the potentiation of norepinephrine neurotransmission.

Summary

Duloxetine 60mg once-daily offers a significant advance for patients suffering from diabetic peripheral neuropathic pain. With duloxetine clinicians have an effective way to help patients with DPNP reduce their pain with a simple once-daily dosing schedule. ■

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