

Overview of diabetic neuropathy and review of FDA-approved oral therapies

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The Foot and Ankle Online Journal 13 (4): 2

Diabetic neuropathy is the most common complication of uncontrolled and chronic diabetes. Neuropathy is the result when the somatosensory system is compromised leaving patients with irreversible nerve damage. The continuity of this neuropathic pain may lead to disorders such as insomnia, depression, and anxiety. The cause of neuropathic pain cannot be treated, and current treatment management focuses on treating the symptoms. A review of current literature on diabetic neuropathy and of FDA approved oral therapies is performed to provide an extensive overview in order to reduce and prevent the progression of this disease. The epidemiology of diabetic neuropathy can be characterized by its prevalence and risk factors. Symmetric polyneuropathy is the most common type of diabetic neuropathy accounting for about 75% of affected patients and is divided into classes depending on the types of sensory fibers involved. Small fiber neuropathy is associated with burning, prickling pain due to non-painful stimuli or an exaggerated response to painful stimuli. Large fiber affected neuropathy involves numbness, tingling without pain, and loss of protective sensation. Besides lifestyle intervention and glucose control the first line medication for diabetic neuropathy is gabapentin, pregabalin and duloxetine. This literature review guide is dedicated to the millions suffering from diabetic neuropathy. Neuropathic pain is a chronic disorder that can impair a patient's quality of life. The results of this literature review demonstrate a need for long-term research with advancing technologies on new medications to understand their specific effects and risks to patients.

Keywords: diabetic neuropathy, gabapentin, duloxetine, cymbalta, FDA warning for gabapentinoids

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Diabetic neuropathy is the most common complication of uncontrolled and chronic diabetes. Neuropathy is the result of a compromised somatosensory system leaving patients with irreversible nerve damage [1,2]. The progression of this neuropathic pain may lead to disorders such as insomnia, depression, anxiety, and impaired quality of life [1,2]. This common complication of diabetes is correlated to increase doctor visits and increase prescription of medication [2]. Currently, treatment management for diabetic neuropathic pain focuses on treating the symptoms due to the irreversible nerve damage [1,2].

Our goal was to provide an overview of diabetic neuropathy and oral treatment options including a recent update of the new FDA warnings on gabapentinoids.

Methodology

Thorough research of literature via PubMed concerning (i) the etiology of diabetic neuropathy; (ii) symptom presentation (iii) FDA approved oral medications for patients with neuropathic pain was reviewed.

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Results

Epidemiology of Diabetic Neuropathy

The epidemiology of diabetic neuropathy can be characterized by its prevalence and risk factors such as lifestyle, comorbidities, and genetics. The prevalence of diabetes mellitus is 419 million adults worldwide (8.8% of the adult population), in which 50% of affected individuals will progress to develop polyneuropathy [3]. There is a high correlation of diabetic neuropathy in patients with obesity and increased waist circumference [3]. Clinical setting risks of diabetic neuropathy include comorbidities such as a high HbA1c, duration of diabetes disease, and poor glucose control [3]. For heredity causes, the opioid receptor gene (OPRM1) and sodium channel gene (SCN9A) showed significant association with diabetic neuropathy; it has been reported in one study that 56% of participants has reported a family member with diabetic neuropathy [3].

Signs and Symptoms of Diabetic Neuropathy

There are different types of diabetic neuropathy: symmetric polyneuropathy, autonomic neuropathy, and cardiovascular autonomic neuropathy [1,2]. Symmetric polyneuropathy is the most common type of diabetic neuropathy accounting for about 75% of affected patients [1]. The distribution of diabetic polyneuropathy includes a “stocking and glove” pattern because neuropathy typically affects the longest nerves of the body the most hence the feet, legs, hands, and forearms are the sites of the majority of symptoms [2]. Diabetic polyneuropathy is further divided into classes depending on the types of sensory fibers involved [1,2]. Small fiber neuropathy is associated with burning, prickling pain due to non-painful stimuli or an exaggerated response to painful stimuli. Clinical tests for small-fiber function include pinprick and temperature sensations [1]. Large fiber affected neuropathy involves numbness, tingling without pain, and loss of protective sensation. Due to the loss of protective sensations, large fiber affected neuropathy is associated as a high risk factor for foot ulcerations and amputations [1]. Clinical tests for large-fiber function include vibration perception with 128-Hz, proprioception, 10-g monofilament and ankle reflexes. Patients should be assessed for distal polyneuropathy starting at diagnosis of type 2 diabetes or five years after the diagnosis of type 1 diabetes with at least annual exams thereafter [1,2,3,4]. It is important to note that up to 50% of patients with diabetic neuropathy is asymptomatic which can put

these individuals at greater risk for injuries to their feet that lack sensation [1]. Prevention and early detection is an important medical practice for diabetic care due to not being able to restore underlying nerve damage.

FDA Approved Oral Medications for Neuropathy Pain

Diabetic neuropathy is hard to treat due to the underlying irreversible nerve damage. At this time there is no medication capable of restoring the nerve damage caused by neuropathy. Current methods of treatment focus on treating the symptoms of diabetic neuropathy supporting “unconventional analgesics” medications including antiepileptics, Gabapentin and Pregabalin, and antidepressant, Duloxetine [1,4,5,6]. It is important to note that the amount of patients who actually receive worthwhile pain relief from any oral listed medication, greater than 50% of pain relief, only occur in about 10% to 25% of the affecting population [4].

Gabapentin acts to bind to $\alpha 2\text{-}\delta$ calcium channels in the central and peripheral nervous system to reduce excitability of nerve cells [4]. Evidence shows patient’s who experience relief of symptoms report at least 50% reduction in pain [1,4]. It is important to note that effective oral dose is at least 1200 mg and noted high correlation with reported successful dosing as high as 3600 mg per day [1,4]. Due to the necessary high doses for the drugs effectiveness to alleviate neuropathic pain there has been numerous reported withdrawal and side effects noted in Gabapentin than other approved oral medications for neuropathic pain [4]. Common side effects seen in patients taking Gabapentin include dizziness, drowsiness, gait disturbances, and hypoventilation; the incidence rates of patients taking this medication who experience these negative side effects ranges 1.1% to 19% of the time [4,8].

Pregabalin also binds to $\alpha 2\text{-}\delta$ calcium channels inhibitory to reduce excitability of nerve cells [6]. Evidence suggests that patients who experience relief of symptoms report 30%-50% improvement in pain [1,6]. The effective dose of Pregabalin is 300 mg or 600 mg per day orally [1,6]. The benefits of Pregabalin include faster onset of action and less necessary dose for effectiveness when compared to Gabapentin [1]. Similar to Gabapentin reported side effects include dizziness, drowsiness, and gait disturbances; specific side effects to Pregabalin include edema and weight gain [1,6].

Antidepressant Duloxetine binds to norepinephrine and selective serotonin reuptake inhibitors that influence the pain pathway [1,5,6]. Evidence supports the efficacy of Duloxetine for relieving neuropathic pain when compared to Pregabalin and Gabapentin [6]. Effective dose 60 mg and 120 mg everyday orally [1,5,6]. Side effects of Duloxetine include increased blood pressure and lower leg edema [6].

New FDA Warning on Gabapentinoids

Common side effects of gabapentinoids already noted publically is drowsiness and dizziness. However, with the current opioid epidemic there has been a growing concern regarding the overprescribing gabapentinoids for neuropathic pain relief [7]. Additionally, there has been evidence of drug abuse and withdrawal symptoms noted with chronic use [7,8]. Most recently, there has been a new FDA warning label on gabapentinoids due to case reports of respiratory distress in patients with respiratory issues, like COPD, combined with other opioid pain relievers, and combined with other central nervous depressants [9]. Medical professionals should reassess their reliance on first line use of gabapentinoids for treatment of neuropathic pain in patients with respiratory issues.

Discussion

Neuropathic pain is a chronic disorder that can impair a patient's quality of life. Management of that pain should be addressed empathetically with a rational approach to manage the pain of neuropathy. The results of this literature review demonstrate a need for further research of the existing neuropathic pain medications to understand their specific effects and risks to patients. In closing, we should also continue to emphasize prevention of the progression of diabetic neuropathy with glucose control and lifestyle modifications.

Acknowledgments

The authors sincerely acknowledge the Temple University School of Podiatric Medicine, the Medicine Department, for their support.

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