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Outpatient Management of Neuropathic Pain in Diabetes Mellitus Patients

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Abstract

Diabetic neuropathy is one of the most frequent and severe chronic complications of Diabetes Mellitus (DM) affecting patients' quality of lif. The disease manifests in pain, decreased mobility, and amputations. Diabetic neuropathy consists of various types affecting the peripheral nervous system whose severity varies from pain to even death outcomes. Diabetic neuropathies can be of several types and the effect varies from mild pain to death due to the damage of the peripheral nerves. The oxidative stress in diabetic neurons through hyperglycemia contributes to the major neuronal damage in the patients. While there are medications for managing the symptoms of diabetic neuropathy, there are no effective treatments for the underlying causes. Moreover, a proper approach to treating neuropathic pain in patients with DM type 2 is necessary to reduce the patient's suffering and enhance their quality of life. The literature review to be presented in this paper has been designed to discuss the current approaches and recommendations concerning managing neuropathic pain in patients with DM through focusing on pharmacological treatment such as antidepressants, anticonvulsants, and opioid analgesics, non-pharmacological treatment such as aerobic exercise, and the patient education.

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1. Introduction

Neuropathic pain leads to abnormal hypersensitivity to stimuli and can result into issues such as metabolic disorders and autoimmune diseases that affect the central nervous system [1]. According to Saeedi and his colleagues, DM is a global health concern that is estimated to affect (9. 3%) 463 million adults in 2019 and is expected to reach (10. 9%) 700 million by 2045 [2]. Diabetes Peripheral neuropathy (DPN) is a common complication of diabetes and is estimated to affect 50% of diabetic patients, manifesting as neuropathic pain due to peripheral or central nervous system damage. It is characterized by burning, tingling, numbness or shooting sensation primarily in the limbs. Li and his colleagues. reported that neuropathic pain is relatively common in patients with DM, with an overall incidence rate of 57.2% in 25710 with T2DM reporting having painful diabetic peripheral neuropathy [3]. Therefore, assessment and management of neuropathic pain in the outpatient clinic are of paramount importance in enhancing the quality of life as well as the functional capacity of these patients because neuropathic pain can significantly affect many domains of a person's life including sleep, mood, and physical functioning. It is necessary to have an efficient management of this condition to reduce suffering and enhance the quality of life of patients with Diabetes.

2. Literature Review

2.1 Epidemiology

There is vast evidence highlighting the rising DPN prevalence which amplifies the need for outpatient management for neuropathic pain in DM patients. In one of the studies investigating DPN prevalence, Sun and his colleagues. systematically analyzed a total of 29 studies with 50,112 participants and found pooled DPN prevalence among the participants to be at 30% [4]. Upon breaking down the data, DPN prevalence for type 2 DM was 31.5% against 17.5% in type 1 DM patients [4]. This statistic implied that DPN prevalence is higher among type 2 DM patients and emphasized the need to target this population in outpatient management. In a similar study investigating DPN prevalence in type 2 DM in 2733 participants aged from 18-65 from different countries, Lu and his colleagues. found the prevalence to be 26.71% [5]. In another study, Akhtar and his colleagues. also researched DPN prevalence in diabetic patients among 8487 participants drawn from 19 studies [6]. The DPN prevalence in the entire population was 43.16% but varied depending on the duration of diabetes, with newly diagnosed patients having a DPN prevalence of 26.52% Reference [6]. The prevalence also varied depending on the location. In another study with 430 participants with type 2 DM, DPN prevalence was found to be 40.2% [7].

Researchers have also directed efforts towards understanding the risk factors associated with DPN in type 2 diabetes. Some risk factors identified are longer diabetes duration, poor glycemic control, depressive symptoms, cardiovascular disease and a history of hypertension [5]. Akhtar and his colleagues. findings provide concrete evidence on association between duration of diabetes and DPN prevalence [6]. While the total prevalence in all 8497 diabetic patients was 43.16% in their study, the authors determined that prevalence for newly diagnosed diabetic patients was 26.52%, implying that the longer the duration, the higher the DPN risk [6]. Oshitari offered more insights into how different risk factors are associated with neuropathic pain in DM patients. He asserted that

the high blood glucose level has an impact on the formation of AGEs and oxidative stress which cause nerve damage and neuropathy [6]. Oshitari indicates that poor blood glucose control shown by a high HbA1c level is tender to nerve damage and develops DPN and neuropathic pain [8]. As pointed out by Oshitari, this may be attributed to the fact that toxins resulting from chronic hyperglycemia and other metabolic derangements can progressively affect nerve functions [8].

Akhtar further claimed that individuals with diabetes who are obese or have a high body mass index (BMI) are at an increased risk of developing DPN and neuropathic pain (6). As is evident, obesity is accompanied by phenomena such as insulin resistance, dyslipidemia, and chronic inflammation, which can lead to nerve damage and neuropathy. The positive correlation between BMI and DPN is also attributable to fat deposition, mitochondrial dysfunction, and oxidative stress which are mechanisms for nerve damage [7]. It was also established that the participants with hypertension, dyslipidemia, and coronary artery disease were more likely to develop DPN and neuropathic pain (7). There are inconsistent findings on the association between DPN and gender, with some results showing that men are more susceptible to DPN than females [7]. Other modifiable risk factors that have been identified include smoking, alcohol use, vitamin deficiencies especially those of the B complex, the presence of other metabolic diseases, and autoimmune disorders [9]. Maintenance and regulation of these risk factors are central to minimizing or delaying the onset and progression of DPN and neuropathic pain Reference [10]. Interventions such as near-normal blood glucose level attainment, weight reduction, optimization of cardiovascular risk factors, and the institution of lifestyle modifications significantly reduced the risk of the development of this dreaded complication of DM [9].

2.2 Pharmacological Management

DPN can be managed using pharmacological and non-pharmacological approaches. The pharmacologic treatment of neuropathic pain in individuals with DM is imperative since several classes of drugs have proved useful in treating neuropathic pain, including antidepressants, antiseizure drugs, and opioids. Selective serotonin and norepinephrine reuptake inhibitors such as duloxetine, and tricyclic antidepressants including amitriptyline have gained prominence and are classified as first-line drugs for neuropathic pain. For example, in a systematic review and meta-analysis of seven randomized control trial, Wu and his colleagues. found that duloxetine medication was more efficacious in managing pain DPN than placebo [11]. They noted that when a dose of 60 mg fails, taking 120 mg of duloxetine can effectively alleviate PDPN symptoms as duloxetine, an SNRI, is expected to exert an influence on the descending pain pathways and relieve neuropathic pain by increasing the concentrations of these neurotransmitters in the CNS. The duloxetine drug further improved patients' quality of life, which was measured using Clinical Global Severity subscale, Patient Global Impression of Improvement scale and European Quality of Life Instrument 5D version [11].

Another medication for managing painful DPN is pregabalin, classified as a first line treatment in managing neuropathic pain [12, 13]. The medication was found effective in reducing the intensity of pain and in improving sleep in patients with diabetic neuropathy (12). Pregabalin is an alpha-2-delta ligand and it is believed that the mechanism through which it produces its analgesic effect includes inhibition of the release of excitatory neurotransmitters like glutamate and modulation of calcium channels in the CNS (12). More research is underway

to explore further the efficacy of these medications.

While pharmacological management approaches have shown effective in DPN management, researchers have also reported side effects among patients who used these drugs. In the research involving duloxetine, some side effects related to the drug included nausea, somnolence, constipation, decreased appetite and fatigue [11]. Similarly, side effects were reported among pregabalin users. The adverse effects included cormobid anxiety, sleep interference, dizziness and somnolence [12]. In both studies, it was reported that patients opted out of using the medication due to the associated side effects [11, 13]. Long term use of the drugs could also lead to withdrawal and cause drug misuse [13]. The negative impacts associated with pharmacological DPN management approaches have intensified the need for non-pharmacological methods.

2.3 Non-pharmacological Management

There are several non-pharmacological management approaches for neuropathic pain in DM patients. They include physical therapy and exercise, transcutaneous electrical nerve stimulation (TENS), and psychological therapies [14]. Exercise regimens, general and specific, can contribute to better circulation, less neuropathic pain, and better limb function. Another study by Seyedizadeh and his colleagues. concluded that a 12-week aerobic and resistance exercise training such as walking and cycling improved neuropathic pain intensity and quality of life by enhancing blood flow and stimulating the production of endorphin. Further, these exercise acted as a natural pain reliever, and increased physical fitness to manage pain more effectively [14].

Another non-pharmacological approach is use of Transdermal electrical nerve simulation (TENS). According to a controlled clinical trial by Bahram in 2020, TENS therapy showed a potential to decrease the neuropathic pain intensity in diabetics as this modality of therapy interfered with the release of endorphins and inhibited the signal transmission of pain [15]. Techniques like cognitive behavioral therapy (CBT) and mindfulness-based stress reduction (MBSR) are beneficial for treating chronic pain, including neuropathic pain in DM patients. Taguchi and his colleagues. reported that CBT supplemented with pharmacological intervention had beneficial effects on the intensity of pain and depression and the quality of life [16]. CBT is essential as it assists patients in modifying their coping skills, assessing and altering the distorted patterns of thinking regarding pain, and addressing maladaptive pain behaviors [16]. On the other hand, MBSR educates patients about mindfulness and various relaxation approaches aimed at enhancing pain coping and emotional functioning [16].

2.4 Patient Education and Self-Management

Researchers have also demonstrated that client education and self-management skills are key aspects in the outpatient management of neuropathic pain in patients with DM. For example, according to a systematic review conducted by Ernawati and his colleagues, it was concluded that diabetes self-management education interventions significantly contributed to lifestyle changes and self-care skills in T2DM patients [10]. Patient skills such as foot care, lifestyle changes such proper diet and exercise and medication compliance are among self-care components included in educational interventions. Also, a study by Kim and his colleagues,revealed that diabetic patients who underwent a self-management program noticed a decrease in neuropathic pain on the VAS and an

increase in the quality of life as opposed to the patients who only received standard care [17]. Therefore, there is evidence that self-management programs allow patients to become more involved in their treatment process as they gain knowledge how to handle neuropathic pain more effectively.

2.5 Multidisciplinary approach

Since neuropathic pain in DM type 2 patients is usually dangerous, treatment in outpatients usually requires an interdisciplinary approach involving a diverse healthcare team [18]. Members in the neuropathic pain care team can include physicians, nurses, pharmacists, physical therapists, psychologists, and dietitians depending on the complexity [19]. For instance, a doctor may recommend the necessary medications, and a physiotherapist may create a specific exercise regimen that will be suitable for the patient [20]. On the other hand, a psychologist may be required to offer CBT or MBIs to patients to help them in managing the emotional and psychological aspects of pain [21]. Moreover, a dietitian is needed in the care team to recommend healthy nutritional requirement to achieve better glycemic control, BMI and better general health.

Research offers evidence to support use of multiple strategies to address DPN in patients, which makes the need for a diverse team crucial. For example, in a study by Hange and his colleagues, it was demonstrated that diabetic patients with neuropathic pain who received integrated care, which included pharmacological therapy for pain relief, physiotherapy, CBT as well as health promotion and education, had significantly lower neuropathic pain intensity and better functional status than patients receiving current care as an integrated care model offers an individualized and holistic approach to the management of neuropathic pain [18]. Therefore, implementing pharmacological and non-pharmacological therapies, and patient education focused on patient-specific goals and strategies can positively influence pain management and patient's quality of life [15].

2.6 Limitations of the Study

The first limitation in the study is that there is lack of longitudinal studies to investigate the effectiveness of pharmacological and non-pharmacological interventions in long-term care. T2DM is chronic condition and the efficacy of management approaches may change with time and thus, the focus on short-term outcomes makes the studies inconclusive. Further the study is generalized as the management approaches do not consider T2DM patients with other conditions. There is need for further research to focus on the effectiveness of the approaches in T2DM patients with other comorbidities. Lastly, this research does not delve into the cost aspect which is critical for any treatment. Future research should integrate cost-effectiveness of management approaches when evaluating efficacy of treatment methods. Some approaches could be effective but not affordable, especially for underserved populations.

3. Conclusion

The management of neuropathic pain in diabetic patients is complex and necessitates a multimodal approach in the outpatient setting as treatments are often pharmacologic and include antidepressants like duloxetine, anticonvulsants like pregabalin, and opioids in some instances. However, non-pharmacological approaches for pain management have also to be included like physical therapy, TENS, and psychological approaches including

CBT. More specifically, patient education, self-management interventions, and an interdisciplinary model of care that includes many different healthcare practitioners are necessary to successfully manage neuropathic pain in DM. Through the use of research-based practices and being able to individualize the management that is given to the patient, physicians can improve the quality of life and functional capacity of such patients. For example, an individual care plan includes administering duloxetine as a pain reliever and pregabalin for neuropathic pain.

Simultaneously, the patient can also be advised to undergo an exercise program to improve blood circulation and functioning in general, as advised by the physical therapist, and may also be provided cognitive behavior therapy by the psychologist to cope with emotional problems related to chronic pain. Moreover, teaching patient responsibilities, including foot care, diet control, and medication compliance, may help diabetic patients deal with their disease effectively and reduce more severe outcomes. Further follow-ups and good collaboration between the patient and the medical team help to check on the progress made, modify the treatment processes when the need arises, and facilitate outcomes in relation to pain management. It is essential to point out that the therapy of neuropathic pain in patients with DM should be individual, because the effectiveness of the used approaches can differ from one patient to another. More importantly, continued research and clinical investigation are needed in order to find new and effective treatments for neuropathic pain and improve the lives of those who suffer from this condition.

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