ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of
DEVELOPMENT RESEARCH

International Journal of Development Research
Vol. 6, Issue, 03, pp. 7113-7118, March, 2016

Full Length Research Article

A GLANCE TO DIABETIC PERIPHERAL NEUROPATHY

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ARTICLE INFO

Article History:
Received 19th December, 2015
Received in revised form
28th January, 2016
Accepted 24th February, 2016
Published online 31st March, 2016

Key Words:
Neuropathic,
Duloxetine,
Hydrochloride and
Pregabalin,
Dysfunction
Unreported,
Neuropathic.

ABSTRACT

Neuropathic pain is defined as "pain initiated or caused by a primary lesion or dysfunction in the nervous system." Painful diabetic neuropathy (PDN) affects 16% of patients with diabetes, and it is frequently unreported (12.5%) and more frequently untreated (39%). Neuropathic pain is poorly managed by NSAIDs, and opioids have limited effectiveness because high doses are associated with adverse events. Treatments are needed for neuropathic pain that are effective but that cause a minimal risk of dependence or of other negative impacts on a patient's quality of life. Currently 2 medications are approved by the US Food and Drug Administration for the management of DPNP: Duloxetine hydrochloride and Pregabalin. Duloxetine is an antidepressant while Pregabalin is a chemical analogue of the mammalian neurotransmitter γ-amino butyric acid (GABA). Diabetic neuropathy is a common complication in diabetes mellitus and it compromises patient quality of life and often end up with hospitalization. In addition the condition may also cause a marked increase in total cost of illness

INTRODUCTION

Diabetes has emerged as a major healthcare problem in India. The Diabetes Atlas published by the International Diabetes Federation (IDF), has revealed that an estimate of 40 million peoples with diabetes live in India .The number of diabetes patients are predicted to rise in India, China and USA by 2030 (Gupta, 2008). It was estimated that every fifth person with diabetes will be an Indian. Almost 382 million people suffer from diabetes with a prevalence of 8.3% in 2013 globally. As per the International Diabetes Federation approximately 50% of people with diabetes are from China (98.4 million), India (65.1 million) and USA (24.4 million). Neuropathy is a common consequence of diabetes, affecting 60–70% of diabetic patients. The diabetes may not necessarily be the cause of the neuropathy in all patients, but other causes such as hereditary, inflammatory, and other metabolic neuropathies may also coexist.

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Diabetic neuropathies are nerve disorders which are classified as peripheral, autonomic, proximal, and focal.

Types of Diabetic Neuropathy

Autonomic Neuropathy

Autonomic Neuropathy is a group of symptoms which occur due to the damage of nerves which manage our everyday body functions such as blood pressure, heart rate, sweating, bowel and bladder emptying, and digestion. While diabetes is generally the most common cause of autonomic neuropathy, there are other health conditions even an infection can result in this condition. The usage of some medications may also cause nerve damage and based on the nerve damage the symptoms and treatment may vary (Vinik *et al*., 2003).

Proximal Neuropathy

The Proximal Neuropathy is a neurological disorder which occurs as a result of diabetic complication and is a type of diabetic neuropathy characterized by painful muscle wasting and weakness.

Though it can occur in both Diabetes type I and II; it is more common in type II diabetes and mainly affects the proximal muscles of lower limbs (Laino, 2004).

Focal Neuropathy

The Focal Neuropathy is less common than peripheral and autonomic neuropathy and the focal neuropathy is also called mono neuropathy, which affects a single nerve usually wrist, thigh or foot and occur mostly in elder diabetic patients (Boulton *et al*., 2005).

Peripheral neuropathy

The Peripheral Neuropathy is a common complication of diabetics and is the most common diabetic neuropathy, found to occur in 47% of diabetic patients were nerve conduction testing are used for diagnosis. Peripheral neuropathies manifest with painful or painless symptoms, and many diabetic patients experience both (Dyck *et al*., 1993). The peripheral neuropathies usually progress gradually and involve small and large sensory fibres. The symptoms are categorized by loss in ability to sense pain, loss of sensation to temperature and developing neuropathic pain followed by a "glove and stocking" distribution which begins from the lower limbs, first affecting the toes, and then progress upward (Greene *et al*., 1999).The primary cause of diabetic neuropathy was thought to be due to hyperglycaemia (Klein *et al*., 2001).

Diabetic peripheral neuropathy (DPN)

Diabetic peripheral neuropathy (DPN) is one of the main complications associated with diabetics. It is a heterogeneous group of disorders that can affect neuronal function throughout the body. Diabetic peripheral neuropathy is a common chronic complication which are present up to 50% of diabetic population with a long diabetic history. Approximately 16%-26% of all patients with diabetics are known to develop this condition (Tesfaye *et al*., 2013). The survey shows that 30% of hospitalized and 20% of community-dwelling diabetes patients have peripheral neuropathy and the annual incidence rate is approximately 2 % (Wong *et al*., 2007).

The pain associated with diabetic peripheral neuropathy may be in part due to failure of the endogenous analgesic mechanisms in the descending spinal pathways that control pain transmission to the brain (Tanenberg *et al*., 2011). The patients with PDN (Painful Diabetic Neuropathy) experience reduced mobility, fatigue, limitations in social activity, diabetic foot infections, sleep impairment, anxiety, and depression (Schmader, 2002; Gore *et al*., 2005). A study have reported that increased age, increased duration of diabetes, and poor glycaemic control increases the risk of PDN (Franklin *et al*., 1994). According to the International Association for the Study of Pain, DPN is defined as "pain arising as a direct consequence of abnormalities in the peripheral somatosensory system in people with diabetes." DPN is described as a burning, tingling, prickling, aching, sharp pain characterized by symptoms that are symmetric and distal, often worsening at night and sometimes associated with allodynia, hyperalgesia, and paresthesia (Boyle *et al*., 2012). Peripheral neuropathies manifest with painful or painless symptoms and many patients experience both.

Once diagnosed correctly, Painful Diabetic Neuropathy presents a unique challenge in patient management and should be considered as syndrome clinically distinct from diabetic peripheral neuropathy. PDN can have debilitating consequences with a significant impact on QoL and costs of management. Current therapies that reduce pain in PDN do not prevent progression of DPN (Veves *et al*., 2008). The main symptoms of Diabetic peripheral neuropathic pain (DPNP) are burning or shooting pain in the lower limbs and feet which exist for more than three months. Currently, there are no approved treatments that restore nerve function. The major goal in pharmacological treatment for DPNP is to control the pain.

Simple analgesic may provide partial, short term relief, but more specifically targeted drugs are normally required for sustaining the control of pain of neuropathic origin (Tesfaye *et al*., 2013). The pain associated with diabetic neuropathies can be severe and sometimes intractable. Studies have reported that there are two types of painful neuropathy, one is acute remitting and the other is chronic PDN. Although data regarding the natural history of PDN are limited, clinicians should be aware that pain symptoms can improve and completely resolve while progression of neuropathy continues and the diminution of pain can results in worsening of sensory function (Boulton *et al*., 1983).

Pathophysiology of DPN

The pathophysiology of DPN is complex and involves multiple pathways which include vascular factors and metabolic interactions, as well as neuro structural mechanisms. Some of the proposed mechanisms of DPN include changes in sodium and calcium channel distribution and expression, varied neuropeptide expression, peripheral sensitization, altered blood flow, axonal atrophy, small fiber damage, and glycemic flux (Smith and Argoff , 2011).Although various etiologies have been described for the pathogenesis of DPN, independent factors influencing the development and progression are duration of diabetes, level of glycemic control, and underlying cardiovascular risk factors such as hypertension, dyslipidemia, smoking, and body mass index. Therefore, treatment strategies should include these aspects in the overall management of DPN (Sheth and Tata, 2012) .

The current understanding of general mechanisms of neuropathic pain may provide insights into the abnormalities leading to pain in diabetic neuropathy. The damage to peripheral nerves leads to hyper excitability of primary afferent nociceptors (peripheral sensitization) leading to hyper excitability in central neurons (central sensitization) which further lead to the generation of spontaneous impulses within the axon as well as the dorsal root ganglion of these peripheral nerves (Baron, 2000).

This sensitization resolves when the nerve is able to repair; however, in chronic disease such as diabetes with ongoing damage, continued sensitization and altered processes in nociceptors lead to further generation of spontaneous symptoms. Sensitization are characterized by a lower activation threshold, increased response to a given stimulus and abnormal spontaneous activity (Scadding , 1981; Woolf *et al*., 1992).

Drug name	Therapeutic class	Dosage	Adverse events
Amitriptyline	TCA	25-100 mg at bedtime	Dry mouth, sweating, dizziness, orthostatic
Imipramine	TCA	25-150 mg at bedtime	hypotension,fatigue, constipation, urinary
Imipramine	TCA	25-100 mg at bedtime	retention, paresthesia, vertigo,confusion,hypomania, rash, tremor, insomnia, palpitations
Gabapentin	Anticonvulsant	300-1,200 mg 3 times daily	Dizziness, somnolence, headache, diarrhea, confusion,nausea, sedation, ataxia,confusion
Pregabalin	Anticonvulsant	300-600 m/d divided in 2-3 doses	Dizziness, somnolence, peripheral edema, headache, vision disturbances, ataxia. asthenia. weight gain, dry mouth, constipation, peripheral edema, weight gain, confusion,euphoria, diarrhea, flatulence, hyperglycemia, nausea/ vomiting
Sodium valproate	Anticonvulsant	500-1,200 mg/d	Nausea, drowsinesss, liver changes
Carbamazepine	Anticonvulsant	200-600 mg twice daily	Somnolence, dizziness, drowsiness, gait changes, urticaria, nausea, vomiting, diarrhea, paresthesia,anorexia
Lamotrigine	Anticonvulsant	Up to 400 mg/d	Rash, nausea, epigastric pain, headache, drowsiness,dizziness
Topiramate	Anticonvulsant	Up to 400 mg/d	Diarrhea, loss of appetite/anorexia, somnolence, nausea,URT infection, paresthesia,dizziness, fatigue, taste changes, sinusitis, difficulty with concentration/attention,injury, abnormal vision,constipation, hypoglycemia, nervousness, UTI
Lacosamide	Anticonvulsant	Up to 400 mg/d	Dizziness, nausea, fatigue, headache, tremor, diplopia, vertigo, URT infection, balance disorder, asthenia, back pain nasopharyngitis, ,influenza, tachycardia, anxiety,chest pain, ECG changes
Duloxetine	SNRI	60-120 mg/d	Nausea, somnolence, dizziness, constipation, dry mouth,increased sweating, decreased appetite, anorexia, weakness, hyperhidrosis, asthenia, erectile dysfunction
Venlafaxine	SNRI	75-225 mg/d	Anorexia, dyspepsia, flatulence, nausea, vomiting, myalgia, insomnia, somnolence,sweating, impotence
Lidocaine Patch	Local anesthetic/topical agent	3 patches/d	local irritation
Capsaicin	Local anesthetic/topical agent	0.075% cream 4 times daily	Stinging, burning
lidocaine intravenous	Antiarrhythmic	5 mg/kg over 30 min	Hypotension, arrhythmias,nausea
Mexiletine	Antiarrhythmic	675 mg/d	GI (heartburn, nausea, vomiting); neurologic (coordination problems, tremor, dizziness, light headedness); blurred vision/visual disturbance; feeling nervous
Dextromethorphan	Opioid	400 mg/d	Sedation, dry mouth, GI distress, anorexia, constipation,nausea/vomiting
Tramadol	Opioid	200 mg/d	Nausea, constipation, headache,
Oxycodone	Opioid	40 mg/d; max of 120 mg/d	somnolence,dyspepsia, pruritus, rash, fatigue, dizziness, vomiting, drymouth,
Morphine	Opioid	15-120 mg/d (titrated)	insomnia

ECG- electrocardiogram; GI- gastrointestinal; SNRI-serotonin nor epinephrine reuptake inhibitor; TCA- tricyclic antidepressant; UTI-urinary tract infection; URT- upper respiratory tract

Pharmacological Treatment

Several pharmacological treatments have been proved, which are efficacious in managing painful DPN, but only Duloxetine and Pregabalin are most used for treating neuropathic pain in diabetes approved both by the Food and Drugs Administration (FDA) of the U.S. and the European Medicines Agency.Historically, DPNP has been treated with tricyclic antidepressants (TCAs), opioid analgesics, and certain anticonvulsant agents. Although TCAs have been the standard treatment for DPNP, long term use lead to serious adverse effects like orthostatic hypotension, greater risk in cardiovascular system (Ray *et al*., 2004) and relative risk for the overall mortality (Cohen *et al*., 2000). Opioid analgesics will provide prompt pain relief, but their adverse effects and potential for abuse or addiction makes them less desirable for long-term treatment. Among anticonvulsant agents, Gabapentin are commonly prescribed medication for the management of DPNP and is considered to have safety profile with no clinically important drug interactions (Dworkin *et al*., 2007). The main disadvantage with anticonvulsant drug are it take several weeks to reach an effective dosage (Backonja and Glanzman , 2004).

The diabetic neuropathy is painful and common problem associated with diabetics. The complications associated with diabetic neuropathy are difficult to manage. The signs and symptoms consistent with PDN have been identified in patients with impaired glucose tolerance and new onset diabetes. The signs and symptoms can be better managed if detected earlier. Both peripheral and central mechanisms have been proposed to play a role in the genesis of the painful symptoms. Despite the evaluation of many pharmacologic and non-pharmacologic therapies, there are presently only two FDA approved treatments of PDN (Veves *et al*., 2008).

Recent guidelines for pharmacological treatment

The European Federation of Neurological Societies proposed that first-line treatments might comprise of TCAs, SNRIs, Gabapentin, or Pregabalin (Attal *et al*., 2010). The National Institute for Health and Care Excellence in UK has provided the guidelines for the management of neuropathic pain in non-specialist settings proposed that Duloxetine should be the first-line treatment with Amitriptyline as an alternative, and Pregabalin as a second-line treatment for painful DSPN (www.nice.org.uk). The recommendation of Duloxetine as the first-line therapy was not based on efficacy but rather cost effectiveness.

More recently, the American Academy of Neurology has recommended Pregabalin as the most effective and should be offered for relief of painful DSPN (Bril *et al*., 2011), whereas venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, opioids, and capsaicin are used for treatment of painful DSPN (Felice *et al*., 2011). This recommendations were primarily based on the achievements greater than 80% rate of clinical trial completion. The recommendation in turn may influence the length of the trials. Finally, the International Consensus Panel on Diabetic Neuropathy recommended TCAs, duloxetine, pregabalin, and gabapentin can be used as first-line agents after having careful review of all the available literature regarding the pharmacological treatment of painful DSPN (Tesfaye *et al*., 2011), the final drug of choice are based on particular patient's demographic profile and comorbidities.

FDA approved Drugs for DPN

Pregabalin

Pregabalin is a chemical analogue of the neurotransmitter Gamma Amino Butyric Acid (GABA) present in mammals. Pregabalin is inactive at GABA receptors and does not appear to mimic GABA physiologically. Pregabalin binds with α2δ subunit of pre synaptic, voltage dependent calcium channels (Fink *et al*., 2002) which probably contributes to its anticonvulsant properties because this activity correlates with a decrease in calcium channel function. The Pregabalin was developed as an antiepileptic drug but has been reported to have clinical efficacy as an analgesic for neuropathic pain and fibromyalgia and as an anxiolytic in patients with generalized anxiety disorder. Dizziness, somnolence, face edema, peripheral edema and weight gain are the most common adverse effects reported in the Pregabalin group (Moon *et al*., 2010).

Duloxetine

Duloxetine is one of the two drugs approved by the United States Food and Drug Administration for DPNP management. Duloxetine is a serotonin and nor epinephrine reuptake inhibitor (SNRI) which were proven safe, effective, and cost-saving in reducing DPNP symptoms at a dose of 60 mg/day. Duloxetine doses greater than 60 mg/day for DPNP management are not recommended as they are not much effective and increase incidence of side effects (Ormseth *et al*., 2011). The proposed mechanism of action of Duloxetine, an antidepressant, is the reuptake inhibition of both serotonin and nor epinephrine in the central nervous system, there by increases the activity of these neurotransmitters and subsequently reduces the perception for pain by modulating the pain signals (Wong *et al*., 1993; Bymaster *et al*., 2001). Side effects of Duloxetine are generally mild for the SNRI class including nausea, dizziness, somnolence, fatigue, sweating, dry mouth, constipation, and diarrhoea. The Duloxetine is a good choice for DPNP treatment in patients with coexisting depression, anxiety, fibromyalgia, or chronic musculoskeletal pain. Duloxetine treatment has no clinically significant effect on glycemic control and do not increase the risk of cardiovascular events in diabetes patients. The use of Duloxetine should be avoided in patients with hepatic disease or severe renal impairment. The safety, efficacy and tolerability of Duloxetine make it an excellent choice for DPNP treatment in wide number of patients (Ormseth *et al*., 2011).

Conclusion

From the extensive data and their beneficial effects, many treatment strategies are available for DPN.TCA such as amitryptylline can be considered as the standard care for DPN. But for patients who aged 60 yrs or older or who have glaucoma, urinary retention, benign prostatic hyperplasia, impaired liver function, thyroid disease, or cardiac conditions, TCAs should be avoided. So for patients with this condition, mainly in the case of diabetic population, anticonvulsants should be evaluated as second line therapy. Pregabalin is the mostly used anticonvulsant and have good evidence for treating DPN and also FDA approved drug for DPN.Patients who cannot tolerate or afford anticonvulsants, SNRI such as Duloxetine or Venalafaxine may be used. These medications are better tolerated than TC As, and like Pregabalin, Duloxetine is also approved by FDA. Due to the high potential risk for abuse and tolerance, opoids such as oxycodone and tramadol should be considered as last line therapy. For making a viable option for adjunctive therapy to systemic medication lidocaine 5% patch or capsaicin cream is beneficial due to the decreased risk of toxicities for DPN treatment.

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