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Medical Management of Diabetic Peripheral Neuropathic Pain: A Focused Review of Literature

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ABSTRACT

Diabetes is a global epidemic and one of the most leading complications of diabetes is peripheral neuropathy. Recent research and clinical practice focus is on symptomatic or painful diabetic peripheral neuropathy (PDPN). The objective of this review is to throw light on commonly used and well-established drugs and pharmacotherapy options in PDPN patients. The various drugs reported in controlled clinical trials in MEDLINE were searched independently and 118 suitable trials were identified. The selected studies are grouped under each drug and the drugs are described in alphabetical order in the review. The pharmacotherapy for PDPN patients includes Duloxetine (24 studies), Pregabalin (10 studies), capsaicin (6 studies), Oxcarbazepine (6 studies) and so on. The total number of drugs reviewed under pharmacotherapy for PDPN was 44. The review would facilitate clinicians and stakeholders to understand the established drug therapy options for symptomatic management of patients with painful diabetic peripheral neuropathy, and also facilitate researchers to develop better drugs in future.

Key words: drug therapy, diabetic neuropathy, neuropathic pain, management.

INTRODUCTION

The term diabetes mellitus describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both[1]. The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. The prevalence of diabetes is higher in men than women, but there are more women with diabetes than men. The urban population in developing countries is projected to double between 2000 and 2030[2]. The microvascular complications of diabetes are termed collectively as "triopathy" which includes retinopathy, neuropathy and nephropathy and the macrovascular complications include peripheral vascular disease, cerebrovascular disease and cardiovascular disease[3,4].

Diabetic peripheral neuropathy (DPN) is a common complication estimated to affect 30% to 50% of individuals with diabetes. Chronic sensorimotor distal symmetric polyneuropathy is the most common form of DPN. The prevalence of neuropathy in type 2 diabetes ranges from 27% to 63% and from 14% to 70% in diabetes mellitus in general.[4] The higher prevalence of neuropathy in type 2 diabetes patients is related to greater age,

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male gender, longer diabetes duration, higher levels of glycosylated hemoglobin, lower HDL cholesterol, smoking; peripheral vascular disease and insulin use[5].

Diabetic neuropathy has been defined as Peripheral somatic or autonomic nerve damage attributable solely to diabetes mellitus. It may be of two types- symmetrical and asymmetrical. The symmetrical type was the commonest and it affects the sensory and autonomic functions of mostly peripheral nerves whereas the asymmetrical type affects the cranial nerves in their sensory and motor functions.[6] The first description of "diabetic neuropathy as a presence of pain and paresthesiae in lower limbs" was done by Rollo in 1798.[7] The consensus of opinion at the San Antonio conference on diabetic neuropathy was that diabetic neuropathy was "a descriptive term meaning a demonstrable disorder, either clinically evident or subclinical that occurs in a setting of diabetes mellitus without other causes of neuropathy. The neuropathic disorder includes manifestations in both somatic and/or autonomic parts of the nervous system."

Diabetic peripheral neuropathic pain (DPNP) affects approximately 11% of patients with diabetic peripheral neuropathy (DPN). The most common type of neuropathy in DM is DPN, with up to 50% of patients experiencing some degree of painful symptoms and 10% to 20% having symptoms severe enough to warrant treatment. A classic population- based study found some degree of neuropathy in 66% of patients with DM. Among those with type 1 and type 2 DM, 54% and 45%, respectively, had DPN and 15% and 13%, respectively, were symptomatic.[8]

Pharmacotherapy for neuropathic pain in symptomatic patients with painful diabetic peripheral neuropathy (PDPN) include: antidepressants; first- and second-generation anticonvulsants; antiarrhythmic agents; topical agents; N-methyl-d-aspartate receptor antagonists; and the opioid analgesics.[9]

Step-wise approach to clinical decision-making involves: the first step in the diagnostic process is to identify the neuropathic origin of the pain; the second step is to evaluate the patient's medical history and make a rigorous baseline assessment of the neuropathic pain symptoms to determine an effective pain-management strategy; and in the third step, adequate and well-tolerated treatment directed towards a variety of painful symptoms is selected, taking into account other co-morbidities such as anxiety and depression.[10]

A broad approach to management comprising of lifestyle intervention and optimisation of glycaemic control are recommended as initial steps in management followed by use of either tricyclic antidepressants (TCAs), selective serotonin noradrenaline re-uptake inhibitor (SSNRI) or alpha-2-delta agonist, depending on patient co-morbidities and contra-indications. Occasionally addition of an opioid agonist may be required in the event of inadequate pain control.[11] Though a broad step-wise approach was propagated earlier by many, effectiveness of individual drugs provide a platform for clinical decision-making to include that drug as part of a therapeutic regime in patients with PDPN. The aim of this review is to identify and summarize the existing evidence on pharmacotherapy management in patients with PDPN through published studies in MEDLINE.

MATERIALS AND METHODS

Independent search was carried out by testers using a well-defined search strategy as follows; we searched the MEDLINE database using the key terms- pain AND diabetic AND neuropathy; management OR treatment; controlled AND clinical AND trial IN title OR abstract. A total of 240 studies were potentially identified by the authors. Studies published in English on effectiveness, safety, tolerability of drugs was included in our review; and studies on comparison of drugs (36 studies) or combined drug therapy (28 studies) with other treatments (32 studies) and reviews (26) studies were excluded. A total of 118 studies were finally identified that were published from 1954 to 2010 and then considered for review. To avoid search bias,

the testers performed independent searches and then disagreements were solved by consensus at various stages of the study.

MAIN FINDINGS OF THE REVIEW

The 118 included studies were grouped under 44 drugs studied for their effectiveness in PDPN patient population which is descriptively reported below, in alphabetical order;

ABT-594

ABT-594 is a neuronal nicotinic acetylcholine receptor (NNR) agonist that exhibits potent analgesic activity in preclinical models of acute, chronic, and neuropathic pain. There was only one controlled clinical trial by Rowbotham et al[12] who conducted a phase-2, randomized, multicenter, double-blind, placebo-controlled study to evaluate the safety and analgesic efficacy of ABT-594 in patients with diabetic peripheral neuropathic pain (DPNP). A total of 266 DPNP patients were randomized 1:1:1:1 to receive placebo, ABT-594 150 microg BID, ABT-594 225 microg BID, or ABT-594 300 microg BID. Patients were titrated to a fixed-dose of ABT-594 over 7 days and remained at this dose for another 6 weeks. The authors found positive benefits for the drug on pain relief in PDPN patients.

ACETYL-L CARNITINE

Acetyl-L-carnitine or ALCAR is an acetylated form of L-carnitine. It is a dietary supplement and naturally occurs in plants and animals. Only one clinical trial by Sima et al[13] which evaluated this drug from two 52-week randomized placebo-controlled clinical diabetic neuropathy trials testing two doses of acetyl-L-carnitine (ALC): 500 and 1,000 mg/day TID. Intention-to-treat patients amounted to 1,257 or 93% of enrolled patients. The results demonstrated that ALC treatment was efficacious in alleviating symptoms, particularly pain, and improved nerve fiber regeneration and vibration perception in patients with established diabetic neuropathy.

ALPHA-LIPOIC ACID (ALA) SUPPLEMENTATION

Lipoic acid (LA) is a dietary supplement which was described as an organosulfur compound derived from octanoic acid. It has antioxidant effects and is useful in aerobic metabolism.

Four studies were on efficacy of ALA supplementation in patients with PDPN. The first one was a systematic review[14] (Foster, 2007) that included five trials and other three studies[15-17] were clinical trials. Ziegler et al[15] studied 3-weeks intravenous administration of ALA and found it to be effective; Ziegler et al[16] found 3-weeks intravenous plus 6-months oral administration to be not more effective when compared to placebo; Hahm et al, 2004 found 8-weeks oral treatment with 600mg/day to be more effective than placebo. Overall the clinical trials showed mixed results against the positive benefits for the drug shown in the systematic review.

AMANTADINE (INTRAVENOUS)

Amantadine is the organic compound known formally as 1-aminoadamantane. The drug has antiviral and antiparkinsonian effects. Chemically it is a N-methyl-D-aspartate (NMDA) antagonist. Amin and Sturrock[18] studied the drug's effectiveness in 17 PDPN patients at 200mg daily infusion compared to placebo, and the authors found intravenous amantadine was beneficial in reducing the pain of painful peripheral neuropathy, with an effect sustained for at least 1 week after an infusion.

AMITRIPTYLINE

Amitriptyline is a tricyclic antidepressant (TCA) that acts primarily as a serotonin-norepinephrine reuptake inhibitor (SNRI), with strong actions on the norepinephrine transporter, and moderate effects on the serotonin transporter. Only one study tested this drug, which was by Max et al[19] who found

good pain relief in their 29 PDPN patients given 6-weeks drug versus 6-weeks active placebo in a cross-over methodology. The authors also found that this effect was independent of mood elevation in their patients.

AMPHETAMINES

Amphetamine or amfetamine is a psychostimulant drug that is known to produce increased wakefulness and focus in association with decreased fatigue and appetite. Amphetamine is chemically related to methamphetamine and lisdexamfetamine, a class of potent drugs that act by increasing levels of dopamine and norepinephrine in the brain, inducing euphoria. One study by Masor[20] found this drug to be effective in PDPN patients.

BENFOTIAMINE

Benfotiamine (S-benzoylthiamine O-monophoshate) is a synthetic S-acyl derivative of thiamine (vitamin B1). One study by Winkler et al[21] found high-dose (320mg/day) administration of this drug to be effective either alone or in combination with other drugs on 36 patients with PDPN in 6-weeks study duration.

CANNABIS-BASED MEDICINAL EXTRACT

Cannabis is other name for marijuana. The therapeutic effects of this drug are similar to opioids. Only one study by Selvarajah et al[22] found that this drug was no more effective than placebo in their study on 30 PDPN patients.

CAPSAICIN

Capsaicin is the active component of chili peppers, which plants are belonging to the genus *Capsicum*. It is an irritant for mammals, including humans, and produces a sensation of burning in any tissue with which it comes into contact. Of the total six studies[23-28] identified in MEDLINE, Capsaicin study group[23]; Scheffler et al[27]; Capsaicin study group[24]; Tandan et al[25]; Tandan et al[26]; Forst et al[28] evaluated the use of topical capsaicin (.075% 4 times per day) in the PDPN population and they all concluded in favor of the application, with minimal side effects.

CARBAMAZEPINE

Carbamazepine (CBZ) is an anticonvulsant and mood stabilizing drug. The two trials by Rull et al[29] and Badran et al[30] where the former used Tegretol, both found favorable results of pain relief with this drug in PDPN.

CEREBROLYSIN

Cerebrolysin is a peptide-based drug that exhibits unique neurotrophic and neuroprotective activity. One placebo-controlled study by Biesenbach et al[31] showed significant improvements in this drug therapy group compared to placebo where the effects were maintained for 6-weeks.

CLONIDINE

It is a direct-acting á2 adrenergic agonist. The two placebo-controlled trials by Byas-Smith et al[32] and Ziegler et al[33] on transdermal clonidine therapy showed positive results on pain in patients with PDPN.

DESIPRAMINE

Desipramine is a tricyclic antidepressant (TCA). It inhibits the reuptake of norepinephrine and to a lesser extent serotonin. Desipramine is an active metabolite of imipramine. Max et al[34] in their placebo-controlled study concluded that desipramine

relieved pain in many patients with painful diabetic neuropathy, offering an alternative for patients unable to tolerate amitriptyline.

DEXTROMETHORPHAN

Dextromethorphan (DXM or DM) is an antitussive (cough suppressant) drug under the category of N-methyl-D-aspartate (NMDA) receptor antagonists. Dextropmethorphan (Oral- 381mg/day) was studied in a single study of 6-weeks duration by Nelson et al[35] that showed promising results on pain in 14 patients with PDPN.

DULOXETINE

One of the most widely researched and studied drug among the selective

serotonin/norepinephrine reuptake inhibitors, Duloxetine was studied in two systematic reviews[36,37]- Smith and Nicholson[36]; Sultan et al[37]- and in 21 controlled clinical trials[38-58] by Hall et al[38]; Chen et al[39]; Skljarevski et al[40]; Wernicke et al[41]; Wu et al[42]; Fishblain et al[43]; Wasan et al[44]; Fishblain et al[45]; Beard et al[46]; Wernicke et al[47]; Armstrong et al[48]; Pritchett et al[49]; Ziegler et al[50]; Kajdasz et al[51]; Ziegler[52]; Wernicke et al[53]; Raskin et al[54]; Wu et al[55]; Raskin et al[56]; Raskin et al[57]; and Goldstein et al[58] and to a much larger surprise, the drug was shown to be effective across a range of doses, in patients with PDPN with some studies reporting long-term improvement in outcomes with maintenance of symptom relief for greater than 6-months duration.

INSULIN

Insulin is a hormone that is central to regulating energy and glucose metabolism in the body. Continuous subcutaneous insulin infusion was studied in two clinical trials Bertelsmann et al[59] and Boulton et al[60] which concluded clinical benefits on pain, nerve function and sensory parameters in patients with PDPN.

GABAPENTIN

Gabapentin is a pharmaceutical drug, specifically a GABA (gamma amino butyric acid) analogue. One study by Sandercock et al[61] evaluated and found efficacy for this drug with minimal side effects in patients with PDPN.

GLYCERYL TRINITRATE SPRAY

Glyceryl trinitrate (GTN) or nitroglycerine is a prodrug which must first be denitrated to produce the active metabolite- nitric oxide (NO). Only one clinical trial by Agarwal et al[62] evaluated this treatment method in their 10-weeks duration study and they reported positive benefits for the drug in their 4-weeks of drug therapy, 2-weeks washout period, 4-weeks active placebo in their cross-over study on 48 patients.

IMIPRAMINE

Imipramine is an antidepressant medication, a tricyclic antidepressant of the dibenzazepine group. Two trials[63,64] on Imipramine- Kvinesdal et al[63] on their 12 patients in 5-weeks plus 5-weeks cross-over with active placebo and Young and Clarke[64] found 150mg/day of the drug to be effective in 80 patients with PDPN in their step-wise intervention study.

ISOSORBIDE DINITRATE SPRAY

Isosorbide dinitrate (ISDN) (also known as Dilatrate) is a nitrate used pharmacologically as a vasodilator, whose short-term efficacy was reported in one study by Yuen et al[65]. In their study, after a 2-week run-in period, 22 diabetic patients were randomized to receive ISDN or placebo sprays for 4 weeks,

exchanging their treatment for a further 4 weeks after a 2-week wash-out period. The authors found relief of specific sensory symptoms in their patients compared to placebo.

LACOSAMIDE

Lacosamide or erlosamide is a functionalized amino acid, like antiepileptic drugs that are believed to act through voltage-gated sodium channels. Of the four trials; Rauck et al[66], Ziegler et al[67], Shaibani et al[68] and Shaibani et al[69], all of them concluded in favor of the drug at an average dose of 400mg/day at a study duration of 6-12 weeks.

LAMOTRIGINE

Lamotrigine is a novel antiepileptic agent that blocks voltage-sensitive sodium channels and inhibits the release of glutamate, in relieving the pain associated with diabetic neuropathy. Lamotrigine was studied in three controlled trials.

Eisenberg et al[70] randomly assigned 59 patients to receive either lamotrigine (titrated from 25 to 400 mg/day) or placebo over a 6-week period. The global assessment of efficacy favored lamotrigine treatment over placebo, and the adverse events profile was similar in both groups.

Eisenberg et al[71] in their another study, lamotrigine was administered at a dose of 25 mg/day for 1 week. The dose was doubled on a weekly basis up to 400 mg/day over 6 weeks. A long-term follow up of the 13 patients who completed the study showed that most patients were still using lamotrigine 6 months after the end of the study. The results of the study suggested that lamotrigine was potentially effective and safe in treating painful diabetic neuropathy.

Vinik et al[72] conducted two replicate randomized controlled trials where patients (n=360 per study) with painful diabetic neuropathy were randomized to receive lamotrigine 200, 300, or 400 mg daily or placebo during the 19-week treatment phase, including a 7-week dose-escalation phase and a 12-week, fixed-dose maintenance phase. The authors found compared with placebo, lamotrigine (300 and 400 mg daily) was inconsistently effective for pain associated with diabetic neuropathy but was generally safe and well tolerated.

LANEPITANT

Lanepitant is a drug classified under NK-1 receptor antagonists. Neurokinin-1 (NK_1) antagonists are a novel class of medications that possesses unique antidepressant, anxiolytic, and antiemetic properties. Goldstein et al[73] in their study after a 1-3 week lead-in period, was administered lanepitant 50 mg daily (n = 27), 100 mg daily (n = 27), 200 mg twice daily (n = 13), or placebo (n = 26) over 8 weeks. The authors found though it was well tolerated, lanepitant was ineffective in relieving pain of diabetic neuropathy.

LIDOCAINE-MEDICATED PLASTER

Lidocaine or xylocaine or lignocaine is a local anesthetic and an anti-arrhythmic drug. Only one systematic review on this method of topical application was available by Wolff et al[74] searched six databases in their meta-analysis of 38 studies for 5% lidocaine-medicated plaster (LMP) compared to other medical treatments and they concluded that 5% LMP was comparable in its therapeutic effects to other treatments (amitriptyline, capsaicin, gabapentin and pregabalin) and had comparatively lesser adverse events owed mainly to its non-systemic topical administration. DPN patients experienced a greater improvement in quality of life when using 5%LMP compared to pregabalin.

The three clinical trials studied intravenous administration of lidocaine[75,76] or lignocaine[77] which were as follows;

Kastrup et al[75] studied 8 patients with PDPN and 10 controls and found this drug infusion

to relieve patients' symptoms better which was also associated with decreases in plasma endorphin levels.

Kastrup et al[76] intravenous lidocaine (5 mg/kg body weight) versus placebo saline and significant positive benefits were observed at 1st and 8th days of therapy.

Viola et al[77] completed a double-blind, placebo-controlled crossover trial of two doses of intravenous lignocaine (5 and 7.5 mg/kg) versus saline on 15 patients. Infusions were administered in random order over 4 h at four weekly intervals.

MEXILETINE

Mexiletine is an orally active local anaesthetic agent which is structurally related to lidocaine (lignocaine) and has been used for alleviating neuropathic pain of various origins. It was studied in one systematic review[78] and four controlled clinical trials.[79-82]

Jarvis and Coukell[78] in their review of controlled trials included seven studies and concldued that Mexiletine is an alternative agent for the treatment of painful diabetic neuropathy in patients who have not had a satisfactory response to, or cannot tolerate, TCAs and/or other drugs.

Oskarsson et al[79] in their study of 216 patients randomized to three doses of the drug or placebo and found 675mg/day dose of the drug was significantly effective in symptomatic management.

Stracke et al[80] studied 95 patients in a multicenter trial and found mexiletine dose of 450mg/day was effective in symptomatic relief for patients with PDPN.

Dejgard et al[81] studied 16 patients in their randomised double-blind crossover trial to assess the effect of oral mexiletine (10 mg/kg bodyweight daily) on the symptoms and signs of chronic painful diabetic neuropathy. The authors found positive benefits with pain relief in the drug therapy group.

Wright et al[82] studied 29 patients who were randomized to receive mexiletine 600 mg/d or matching placebo for 3 weeks and the authors were unable to conclude in favor of the drug due to limited statistical power and small sample size.

NK1-RECEPTOR ANTAGONIST- TKA 731

Substance P is one of the neurotransmitters released by primary nociceptive neurons in the dorsal horn of the spinal cord and it binds post-synaptically to NK(1)-receptors. TKA731 is a non-peptide NK(1)-receptor antagonist, studied in only one trial. Sindrup et al[83] in their 2-weeks study of 81 patients given the drug vs placebo and reported no additional benefits of the drug in PDPN patients.

OPSITE™ FILM

Opsite is an adhesive-coated polyurethane film dressing. Only one study by Foster et al[84] assessed the effect of application of OpSite dressings on the pain and quality of life in 33 patients with chronic diabetic neuropathy. The effect of OpSite was compared with no treatment. After a run-in period of 2 weeks, OpSite was applied to one of the painful legs for 4 weeks. This was followed by another period of 4 weeks when OpSite was switched to the opposite leg. The authors found that this dressing was very effective to relieve symptoms.

OXCARBAZEPINE

Oxcarbazepine is an anti-epileptic drug, studied in six papers. One study was a review and other five were controlled trials. Beydoun et al[85] in their summative work of two earlier studies concluded and recommended this drug as an effective option for symptomatic management of patients with PDPN. Grosskopf et al[86] in their 16-week study of 141 patients (1200mg/day of the drug vs placebo) and they found no additional effect of the drug in their patients, whereas clinically meaningful but not statistically significant pain relief was

reported by Beydoun et al[87] for a dosage of 1200mg/day for the same duration. Erdemoglu and Varlibas[88] concluded in favor of the drug on their 38 patients for a 6-months study duration. Dogra et al[89] in their 16-weeks study on 146 patients (drug, n=69; placebo, n=77) with 300-1800mg/day dosage found clinically significant pain relief, and Beydoun et al[90] in their 9-week trial on 30 patients also reported similar positive results.

OXYCODONE

Oxycodone is an opioid analgesic studied in three trials. Jensen et al[91] compared the effects of controlled-release Oxycodone versus placebo on neuropathic pain scale scores take before, during and after treatment of 159 PDPN patients for a total study duration of 6 weeks. Relative to placebo, the opioid analgesic produced statistically significantly greater decreases in global pain intensity, pain unpleasantness, and sharp, dull, and deep pain sensations. Watson et al[92] studied 4-weeks intervention with 30mg-40mg/day every 12 hours of oxycodone versus placebo on 36 PDPN patients and found significant improvements in pain scores and quality of life in the drug therapy group. Gimbel et al[93] studied 159 patients randomized to either controlled-release oxycodone (30mg-60mg tablet/day every 12 hours for six weeks, n=82) or placebo (n=77) and found that the drug was effective in providing symptomatic relief, with few opioid-related side effects.

PONALRESTAT

Ponalrestat is an aldose-reductase inhibitor which was studied in two clinical trials. Krentz et al[94] studied 50 patients for 52 weeks given the drug (600mg/day) or placebo and found that it was clinically well tolerated and produced short-term relief of pain in patients with PDPN. Florkowski et al[95] studied 54 patients given the drug (300 or 600mg/day) or placebo for 24 weeks and found positive benefits on short-term.

PREGABALIN

Pregabalin is an anti-convulsant drug. This drug was evaluated and reported in eleven studies of which there were six systematic reviews and/or meta-analyses (Sharma et al,[96]; Tolley et al,[97]; Hurley et al,[98]; Freeman et al,[99]; Gutierrez-Alvarez et al,[100]; Frampton and Scott,[101] and five placebo-controlled clinical trials Hoffman et al[102] Arezzo et al[103] Richter et al[104] Rosenstock et al[105], Lesser et al[106] and all of them concluded in favor of this drug superior to placebo, with minimal reported side-effects. The reported positive benefits for this drug range from pain, neurological function, sleep, quality of life and mood and depression states.

QR-333

QR-333, a topical compound that contains quercetin, a flavonoid with aldose reductase inhibitor effects, ascorbyl palmitate, and vitamin D(3), was formulated to decrease the oxidative stress that contributes to peripheral diabetic neuropathy and thus alleviate its symptoms. QR-333 was studied in only one trial. Valensi et al[107]- found that QR-333 three times daily for four weeks versus placebo on 34 patients was effective in favor of the drug on pain measures and quality of life.

RUBOXISTAURIN

Ruboxistaurin (RBX) is an inhibitor of protein kinase C-beta. Tesfaye et al[108]- combined the data from two placebo-controlled trials on RBX and they found using logistic regression analyses that on 262 placebo-administered patients with PDPN, clinically meaningful worsening occurred after one-year follow-up in the placebo group.

Vinik et al[109]- studied Ruboxistaurin (RBX) on 205 PDPN patients (66 were assigned to the RBX 32 mg/d group, 71 to the RBX 64 mg/d group, and 68 to the placebo group) and

found at one-year, RBX group was symptomatically better than placebo in pain and neuropathy measures.

SODIUM VALPROATE

Sodium valproate or valproate sodium is the sodium salt of valproic acid and is an anticonvulsant drug. Kochar et al[110]- on their study on 38 patients, for 6 months study duration, found this drug to be effective on short-term and was superior to placebo on all subjective and objective symptoms of PDPN.

SORBINIL

Sorbinil is an aldose-reductase inhibitor that was studied in four trials. Jaspan et al[111] studied placebo-controlled study of sorbinil 250mg daily for 6-weeks versus placebo and they found better relief on pain and cardiac autonomic neuropathic symptoms in patients with PDPN. Young et al[112] in their placebo-controlled trial of 15 patients found benefits on pain and other neuropathic symptoms in PDPN patients with very few patients reporting adverse effects. Jaspan et al[113] studied 19 patients (11- sorbinil ; 8- placebo) and greater number of patients reporting pain relief was observed in the sorbinil group compared to placebo. Lewin et al[114] studied 200mg daily for 4-weeks on 13 patients given either placebo or drug and the authors were unable to detect any positive benefits for the drug treated group.

TOLRESTAT

Tolrestat, an aldose-reductase inhibitor, was studied in two controlled clinical trials.

Boulton et al[115] studied 219 patients randomized into tolrestat in four doses (maximum of 200mg once daily, n= 112) or placebo (n=107) for 52-weeks study duration.

MacLeod et al[116] studied 190 patients with PDPN prescribed tolrestat (200mg once/day for 6 months) versus placebo and found that the drug was effective and well tolerated in addition to glycemic control in such patients.

TOPIRAMATE

Topiramate is a centrally acting analgesic and an anti-convulsant, and was studied in one systematic review and in two controlled clinical trials.

Carroll et al[117] did a systematic review from PubMed, Ovid and International Pharmaceutical Abstracts databases, which included three clinical trials and found that topiramate was used successfully in symptomatic management of patients with PDPN.

Donofrio et al[118] assessed the long-term effectiveness and safety of topiramate (25-600 mg/d for 26 weeks) in an open-label extension of a clinical trial and found that pain relief was effective and durable in moderate and moderately severe PDPN patients.

Raskin et al[119] performed a 12-week, multicenter, randomized, double-blind trial included 323 subjects with PDN and pain visual analog (PVA) score of at least 40 on a scale from 0 (no pain) to 100 (worst possible pain). Topiramate (n = 214) or placebo (n = 109) was titrated to 400 mg daily or maximum tolerated dose. The authors found that Topiramate monotherapy reduced pain and body weight more effectively than placebo in patients with painful diabetic neuropathy.

TRAMADOL/ACETAMINOPHEN

Acetaminophen or paracetamol is a widely used over-the-counter analgesic and an anti-pyretic drug. Tramadol is a centrally acting analgesic. Freeman et al[120] examined the efficacy and safety of tramadol/ acetaminophen (APAP) for the management of painful diabetic peripheral neuropathy (DPN) in 313 adults with painful DPN involving the lower extremities. They were randomized to receive either 37.5 mg tramadol/325 mg APAP (160 subjects) or placebo (150 subjects), up to 1-2 tablets four

times daily, for 66 days. The authors concluded that Tramadol/APAP was more effective than placebo and was well tolerated in the management of painful DPN.

Harati et al[121] studied tramadol in 50-400mg/day doses on a sample of 56 former tramadol and 61 former placebo PDPN patients following a randomized trial into a 6-week open-label extension period where pain scores were assessed at 30, 90 and 180 days. The authors found tramadol was effective in its long-term effects for pain relief.

Harati et al[122] studied the effects of tramadol (210mg/day) in 163 PDPN patients randomized to either tramadol (n=65) or placebo (n=66) for a 42-day intervention period and found the drug to be effective and safe for pain relief in these patients.

TRAZODONE

Trazodone is an antidepressant of the serotonin antagonist and reuptake inhibitor (SARI) class. It is a phenylpiperazine compound. Trazodone also has anxiolytic, and hypnotic effects. One study by Wilson[123] studied low doses of 50-100mg/day oral administration of the drug in 31 patients and found symptomatic relief in 74.2% of patients after 2-weeks of therapy.

VENLAFAXINE HCL

Venlafaxine is an arylalkanolamine serotonin-norepinephrine reuptake inhibitor (SNRI) Kadiroglu et al[124] studied 60 PDPN patients for 8-weeks of venlafxine HCl compared to control- vitamin B-1 and vitamin B-6 and the authors found significant pain relief in the experimental drug group.

Rowbotham et al[125] studied 244 patients for 6-weeks on extended-release venlafaxine HCl compared to placebo and they concluded that the drug was effective and safe in relieving pain in diabetic neuropathy.

VITAMIN B-12

Vitamin B-12 is considered as a nutritional or a dietary supplement. Ever since Davidson[126] showed efficacy of vitamin B-12 as a treatment for PDPN patients, after numerous clinical trials published worldwide, Sun et al[127] reviewed 7 studies and the authors concluded that with both the vitamin B12 combination and pure methylcobalamin, symptomatic relief was greater than changes in electrophysiological results. Again, Ang et al[128] in their systematic review of the Cochrane collaboration reviewed 13 studies on 741 participants with alcoholic and/or diabetic neuropathy and they found vitamin-B was well tolerated and was slightly better than placebo. Overall the retrieved evidence was insufficient to draw conclusions.

ZONISAMIDE

Zonisamide is a sulfonamide anticonvulsant drug. Atli and Dogra[129] in their study randomized 25 PDPN patients to zonisamide (N = 13) or placebo (N = 12). The study drug was titrated over a 6-week period and continued at a fixed dosage for a 6-week maintenance period. The mean dosage of zonisamide for the maintenance phase was 540 mg/day. The authors found that pain scores on both the visual analog scale and the Likert scale decreased more for the zonisamide group compared with the placebo group that was not statistically significant.

RESULTS

Of the total 118 studies included in this review, 15 were systematic reviews and 103 were randomized controlled trials. Duloxetine was shown to be beneficial in 23 studies (19.65%); followed by pregabalin (10 studies-8.5%); capsaicin and oxcarbazepine (6 studies each- 5.12%); topiramate and mexiletine (5 studies each); alpha-liopic acid, sorbinil and lacosamide (4 studies each); vitamin B-12, venlafaxine HCl, Tramadaol, Oxycodone,

lamotrigine (3 studies each); tolrestat, ruboxistaurin, ponalrestat, intravenous lidocaine, imipramine, continuous subcutaneous insulin infusion, clonidine, carbamazepine and ABT-594 (2 studies each); other drugs had only one published study each.

DISCUSSION

This review was a clinically and scientifically applicable of its kind for use both by clinicians and researchers involved with patients of painful diabetic peripheral neuropathy. Some of the potential limitations of this review were the lack of meta-analysis and quality scoring of the included studies. We included studies which were either systematic reviews or randomized controlled trials (level-1 evidence) to keep us evidence-informed when we select a pharmacotherapeutic management of patients with PDPN. We also reviewed only studies from MEDLINE since it is the largest and comprehensive database commonly used for evidence synthesis. Considering the relatively lesser availability of studies on comparison of drugs and combined pharmacotherapy, future research could be on developing a comprehensive management involving other treatment methods as effective adjuncts like neurodynamic mobilization[130] in patients with painful diabetic peripheral neuropathy. The magnitude of tissue changes in chronic painful diabetic peripheral neuropathy shifts to mechanical from neurophysiological.[131] Mechanical changes were earlier observed in neural tissues and neurodynamic interventions like nerve sliders and nerve massage were extensively studied for peripheral neuropathic pain symptoms.[132] The effectiveness of treatment methods could also be evaluated using standardized multifaceted clinical assessment scales[133] to study the wholistic impact on pain, activity limitation, clinical examination findings and psychosocial issues.

CONCLUSIONS

Amitriptyline, nortriptyline, desipramine and imipramine are TCAs that have been shown to be effective for the symptomatic relief of PDPN. Serotonin noradrenaline reuptake inhibitors (SNRIs) such as venlafaxine and duloxetine have been shown to be very promising for the treatment of PDN with fewer adverse effects than TCAs. Selective serotonin reuptake inhibitors (SSRIs) were shown in a number of studies to have some efficacy in relieving PDN-related pain, yet other studies of the SSRIs have demonstrated conflicting outcomes. Most of the older antiepileptic studies were performed in patients with PDN. Carbamazepine, phenytoin and valproic acid were shown to be effective in ameliorating PDN-related pain. Other antiepileptic agents, including lamotrigine, oxcarbazepine and topiramate, have demonstrated some beneficial effects for the treatment of PDN, although they were also found to be ineffective in some PDN studies. alpha2delta Ligands such as gabapentin and pregabalin have been proven to be effective for the treatment of PDN in a number of large placebo-controlled trials. These drugs are useful not only in relieving pain but also in improving quality of life. Although the use of opioids for the treatment of neuropathic pain is controversial, a number of studies support the efficacy and safety of opioids in the treatment of neuropathic pain. Of these, oxycodone and tramadol have been shown to be superior to placebo for the treatment of PDPN. A number of small studies have shown that dextromethorphan was effective. Topical agents such as lidocaine 5% patches and topical capsaicin are useful in ameliorating pain in these patients but these agents are unsatisfactory for use as a sole agent. Although a number of drug treatments are available for the symptomatic relief of neuropathic pain symptoms, these agents do not provide satisfactory relief in all patients. For these patients, other treatment alternatives such as combination drug therapy that

produces pain relief via distinctly different mechanisms may be successful. Overall though duloxetine was extensively reported for its effectiveness, the larger number of systematic reviews in favor of pregabalin makes it the drug of choice as per our review.

We described the available drug therapy options for the most common yet most underestimated complication of the global epidemic which is further expected to rise due to our habits and lifestyle. The mentioned drugs were previously studied for their effectiveness, safety and tolerability but caution is warranted before interpreting the drug's efficacy or role in PDPN patients due to a large scope for conflicts of interest[134] from the funding pharmaceutical companies towards the researchers.

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