CURRENT THERAPEUTIC STRATEGY IN DIABETIC NEUROPATHY
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ABSTRACT
Diabetic neuropathy (DN) is a group of multifactorial disorder in diabetic patients, which affects neuronal function of the whole body and is accompanied by nephropathy and angiopathy. Its prevalence increases with duration of diabetes and hyperglycaemia which can induce oxidative stress resulting in activation of multiple pathways which can damage the neurons alone or in combination. Symptoms of DN are prominent early in type 2 than in type 1. Neuropathic pain which can occur continuously only in 20-30% of the patients, otherwise pain was not reported. The drugs available for DN were not able to cure the disease but provide only symptomatic relief and were also associated with major side effects. Current therapy provided in this review alleviates the symptoms in clinical trials and thus will be recommended in order to stop the progression of disease. Despite the recent understanding regarding the pathogenesis of disease, till date only two drugs were approved by FDA for DN, α-lipoic acid is available in several countries and epalrestat in Japan, which is also associated with side effects but they are tolerable.

KEYWORDS: diabetic neuropathy, hyperglycemia, neuropathic pain, pathogenesis

INTRODUCTION
Diabetes mellitus sometimes called “sugar diabetes”, affects an increasing percentage of our population each year. Diabetic Neuropathies (DNs) are among the most frequent complications of diabetes mellitus. DN are a heterogeneous group of conditions characterized by a progressive loss of nerve fiber function involving different components of the somatic and autonomic nervous systems. They can be focal or diffuse, proximal or distal. The prevalence of painful diabetic peripheral neuropathy (PDN) is about 20% in patients with type 2 diabetes and 5% in those with type 1. The progression of neuropathy is dependent on the degree of glycemic control in both Type 1 and Type 2 diabetes. Causative factors include persistent hyperglycemia, microvascular insufficiency, oxidative and nitrosative stress, defective neurotrophism, and autoimmune-mediated nerve destruction which may lead to pain. Neuropathic pain which significantly decreases a person’s quality of life can be described as a sensation of paresthesia, numbness and burning that is caused by the sustained, abnormal processing of CNS neuronal input. The constant pain, which affects 16–26% of people with diabetes, can lead to other health issues, such as constant fatigue, depression and anxiety which predominantly cause weakness, ataxia and incoordination predisposing to falls and fractures. Over a period of years nerve damage caused by diabetes may lead to complications of the digestive tract and sexual organs, which can cause indigestion, diarrhea or constipation, dizziness, bladder infections and impotence. The progression of neuropathy is also associated with potentially modifiable cardiovascular risk factors, including an elevated triglyceride level, a high body mass index and hypertension. Currently, there is no cure for this pain. Treatment of neuropathy should therefore focus on to reduce macrovascular risk factors including hyperglycemia, blood pressure, and lipid control and lifestyle modifications including exercise and weight reduction, smoking cessation, a diet rich in omega-3 fatty acids, and avoidance of excess alcohol consumption. Other known causes include genetic factors, damaging chemical agents such as chemotherapy drugs, and HIV.

Despite advances in the understanding of the metabolic causes of neuropathy, treatments aimed at interrupting the pathological processes have been limited. Thus, with the exception of tight glucose control, treatments are for symptomatic relief, that is reducing pain and other symptoms.

Diagnosis
Asymptomatic DN is still capable of leading to increased morbidity and mortality. The major morbidity is foot ulceration, which can lead to gangrene and ultimately to limb loss. Globally, an amputation occurs every 30 seconds. Even after its wide prevalence, neither endocrinologists nor non-endocrinologists have been trained to recognize the condition and even when patients are symptomatic, less than one-third of physicians recognize the cause or discuss this with their patients. A careful clinical examination is needed for the diagnosis because asymptomatic neuropathy is common. The importance of the skin biopsy as a tool for diagnosing DPN is increasingly being recognized. For quantifying neuropathic pain questionnaires or pain scales used are McGill Pain Questionnaire (frequently used), Brief Pain Inventory (BPI)15, The Neuropathic Pain Questionnaire (NPQ) and the Neuropathic Pain Scale for monitoring the effects of therapy are some commonly used for diabetic neuropathy.

When patients present with the "burning foot or hand syndrome," evaluation of glucose tolerance and features of the metabolic syndrome such as waist circumference, plasma triglyceride and high-density lipoprotein cholesterol levels as well as blood pressure become mandatory. Therapeutic lifestyle changes and the use of topiramate can reverse this form of neuropathy and alleviate symptoms with nerve-fiber regeneration

Initial Therapy Of Symptomatic Neuropathy
1. Exclude nondiabetic causes:
   - Malignant disease (e.g., bronchogenic carcinoma)
   - Metabolic
   - Toxic (e.g., alcohol)
   - Infective (e.g., HIV infection)
   - Iatrogenic (e.g., isoniazid, vinca alkaloids)
   - Medication-related (chemotherapy, HIV treatment)
2. Providing patients a full explanation of their condition, allaying their fears and misconceptions, and informing them that the pain may resolve in time and information on practical measures, e.g., bed cradle to lift bedclothes off of hyperaesthetic skin.

3. Assess level of blood glucose control and blood glucose profiles regularly.

4. Before trying a systemic medication, some doctors recommend treating localized diabetic periperal neuropathy with lidocaine patches.

**Treatment Based On Pathogenic Mechanisms**

Various pathogenic pathways are responsible for diabetic neuropathy. They contribute to oxidative stress and sometimes one pathway can stimulate other pathway leading to further nerve damage causing diabetic neuropathy. Hyperglycemia is the main contributing factor to DN, so appropriate glycemic control is the main therapeutic pathway in order to treat DN. The pathways responsible for DN are polyol pathway, PKC pathway, AGE pathway, PARP pathway and hexosamine pathway. Agents acting on these pathogenic pathways will be able to prevent and treat the further complications. Hyperglycemia induces an increased presence of markers of oxidative stress, such as superoxide and peroxyinitrite ions, and that antioxidant defense moiety is reduced in patients with diabetic peripheral neuropathy. Myo-inositol level is decreased and nerve blood flow is also reduced in DN (Figure No. 1).

Therapies known to produce symptomatic relief are therefore recommended. Therapies that are under investigation are as follows: -
- Aldose Reductase (AR) inhibitors,
- Antioxidants,
- Advanced Glycation End product (AGE) inhibitors,
- Protein Kinase C (PKC) inhibitors, and
- Glycemic control with Insulin
- Myoinositol

- Agents increasing nerve blood flow

**Aldose Reductase Inhibitors**

Aldose reductase inhibitors reduce the flux of glucose through the polyol pathway, inhibiting tissue accumulation of sorbitol and fructose. Increases in sorbitol concentrations result in cellular and organ injury. Additionally, excessive accumulations of sorbitol results in the decrease of myo-inositol in the peripheral nerves. When myo-inositol is decreased, there is a resulting decrease in Na⁺,K⁺-ATPase activity, which is essential for nerve conduction. As a result of the increased polyol pathway activity and the overutilization of NADPH by the enzyme aldose reductase, a number of other homeostatic mechanisms are compromised. NADPH depletion results in decreased nitric oxide (NO) and reduced glutathione production. Decreased in NO may lead to decreased vasodilation while decreased glutathione results in increased reactive oxygen species, leading to impaired endothelial cell function.

There exists a variety of structurally diverse aldose reductase inhibitors (ARIs) (Table 1). These compounds can be divided into two general classes, those containing a carboxylic acid moiety and those having a cyclic imide represented by a spirohydantion or related ring system. Recently, arylosulphonylnitromethanes have emerged as a new class. At present, only epalrestat is effective and is taken orally in a dose of 50 mg three times daily before meals.

**Antioxidants**

α-lipoic acid (thioctic acid), an anti-oxidant that is a non-prescription dietary supplement has shown benefit in a randomized controlled trial that compared once-daily oral doses of 600 mg to 1800 mg compared to placebo, although nausea occurred in the higher doses. The Symptomatic Diabetic Neuropathy 2 (SYDNEY 2) trial showed significant improvement in neuropathic symptoms and neurologic deficits in 181 diabetic patients with 3 different dosages of α-lipoic acid compared with placebo over a 5-week period.

**Protein Kinase C Inhibitors**

Protein kinase C is critical in the pathway to diabetic microvascular complications. It is activated by both hyperglycemia and disordered fatty-acid metabolism resulting in increased production of vasoconstrictive, angiogenic, and chemotactic cytokines in the skin, such as transforming growth factor-β, vascular endothelial growth factor, endothelin, and intercellular adhesion molecules. A multinational, randomized, phase-2, double-blind, placebo-controlled trial with ruboxistaurin (a protein kinase C inhibitor) failed to achieve the primary end point although significant changes were observed in many domains. Results from a smaller, single center study showed improvement in symptom scores, endothelium dependent skin blood flow measurements, and quality of life scores in the ruboxistaurin-treated group.

**Glycaemic Control with Insulin**

The main objective of treatment of diabetic neuropathy is glycemic control optimization. There is evidence that less frequent and less severe peripheral nerve complications is associated with good diabetic control. The Diabetes Control and Complications Trial (DCCT) in 1995 showed that diabetes neuropathy reduced by 64% with intensive glucose management by insulin pump or by three or more daily insulin injections in patients with type 1 diabetes mellitus at 5 years compared with conventional therapy. The DCCT also established that the occurrence or worsening of peripheral neuropathy is associated with poor glycemic control, but whether decreased in neuropathic pain intensity in glycemic control is still a matter of debate.

**Myo-Inositol**

As the polyol pathway gets activated, there is a depletion of myo-inositol, so it was given from outside will be able to restore the level of nerve myo-inositol.

**Agents Increasing Nerve Blood Flow**

Diabetic neuropathy lead to increase in nerve hypoxia and thus decrease in nerve blood flow was observed, therefore agents which will be able to increase nerve blood flow will proved to beneficial in neuropathy. These include vasodilators, such as ACE inhibitors and prostaglandin.
analogs which were effective up to phase II in randomized clinical trials. A compound called PVEGF165 gene transfer, phase III clinical trials are ongoing which leads to increase in angiogenesis.

**C-Peptide Replacement Therapy**
In animal models of type 1 diabetes mellitus, C-peptide replacement has shown improvement of nerve function. Moreover, it is known to enhance endoneural blood flow through stimulatory effects on endothelial nitric oxide synthase. Results concluded from humans have shown that C-peptide has significant improvement in sensory nerve conduction velocities, vibration perception, and autonomic nerve function. In a recent exploratory, multicenter, randomized placebo-controlled study including 6 weeks of treatment in 139 patients demonstrated improvement in sensory nerve conduction velocities, vibration perception, and neurologic impairment scores.

**Drug therapy for symptomatic relief in diabetic neuropathy**

**Analgesics**
Studies conducted on humans have demonstrated that these drugs [paracetamol, salicylates and non-steroidal anti-inflammatory drugs (NSAIDs)] are considered ineffective or poorly effective against neuropathic pain. Studies conducted in several controlled trials and thus are independent of antidepressant effect. Analgesics efficacy was similar across all of these drugs.

**Selective Serotonin Reuptake Inhibitors (SSRIs)**
Selective Serotonin Reuptake Inhibitors have been effective in treatment of pain in several studies and neurologic impairment scores.

These agents are effective in treatment of pain based on the significant role of norepinephrine in endogenous pain modulation through the descending noradrenergic pathway. Well-conducted studies have shown some efficacy with duloxetine in PDN. A significant improvement in sleep disturbance and Quality of Life (QoL) has also been reported. Duloxetine (30 or 60 mg tablets) is approved by FDA only for the pain associated with diabetic neuropathy. Liver disease, renal failure (creatinine clearance < 30 mL/min) and glaucoma are contraindications for duloxetine. Also, the drug can raise blood pressure, and must not be combined with inhibitors of CYP1A2 (fluvoxamine, ciprofloxacin, enoxacin). Venlafaxine has also shown efficacy in PDN, but is not approved for treating painful neuropathy.

**Selective Serotonin Reuptake Inhibitors (SSRIs)**
SSRIs such as fluoxetine, paroxetine, sertraline and citalopram are found to be no more efficacious than placebo in several controlled trials and thus are not recommended to treat painful neuropathy. Side effects are rarely serious and permanent disabilities did not occur. These drugs cause sedation and weight gain, which leads to worsen of diabetic's glycemic control. They can be used at dosages that also relieve the symptoms of depression, a common comorbidity of diabetic neuropathy.

**Anticonvulsants**
This class of drugs includes gabapentin, pregabalin and carbamazepine. A number of randomized controlled studies have shown effectiveness of gabapentin against neuropathic pain. An analgesic effect through decrease in the release of glutamate by gabapentin have probably related to its binding to the alpha-2-delta subunit of the voltage-gated calcium channels of the central nervous system. However, a recent double-blind randomized controlled trial showed that a slow-release formulation given once a day was equally effective for PDN. Only few interactions with concomitant pharmacological treatments occur as gabapentin is not significantly metabolized in humans. Dosage in renal impaired patients needs to be adjusted as gabapentin is only eliminated by the kidney as unchanged drug. The common side effects include somnolence, dry mouth, dizziness, weight gain, peripheral oedema, headache and gastrointestinal disorders.

Pregabalin a recently marketed, having mechanisms of action similar to gabapentin. The efficacy of pregabalin for neuropathic pain has been reported in several studies. Pregabalin is only eliminated by the kidneys so dosages need to be adjusted in patients with renal impairment. The reported side effects are somnolence, dizziness, gastrointestinal disorders, dry mouth, headache, weight gain and peripheral oedema. Recently pregabalin was approved for central as well as peripheral neuropathic pain.

Early studies on carbamazepine suggested that it might be effective in PDN and it is approved for neuropathic pain in adults in France. A number of dose-related side effects are reported including hepatitis, haematological complications (granulocytosis), severe dermatological reactions (Stevens–Johnson syndrome) and cognitive dysfunction. Carbamazepine is fully metabolized in the liver (CYP450, 3A4), thus multiple drug interactions occur and an active metabolite is produced.

**Opioids**
In PDN, extended-release oxycodone has proved its efficacy in several studies. Opioids must be only used when the patient does not respond to non-opioid therapy. The notable side effects include drowsiness, constipation, dizziness, nausea and dry mouth; the frequency of all these adverse events contributes to limit the continuation of treatment in fewer patients beyond 1 year.

Tramadol, agonist at the opioid receptors and the recapture of monoamines was inhibited by it. In several studies its efficacy was proven, with a possible effect on allodynia. It is available in the form of immediate or delayed-release capsule, although the tolerance of extended-release form is better. The main side effects include nausea, constipation, dizziness, headache, somnolence, dry mouth and urinary disorders. Increase in risk of seizure is reported when it is combined with tricyclic antidepressants, or in patients with epilepsy. (Table 5)

**NMDA Receptor Antagonists**
Agents including ketamine and dextromethorphan, have demonstrated effectively in reducing postoperative pain and analgesic consumption. Recently, a combination of dextromethorphan and quinidine in patients with PDN suggested a significant impact on pain intensity rating scale.
pain relief rating scale and patients’ diary assessments of sleep and pain intensity60.

Comparison of Treatment
A comparison between 2 or more drug in various studies was demonstrated and found to have great impact in PDN. In several good quality studies61-62, Amitriptyline was compared with gabapentin, it was that concluded that both these agents are similar in efficacy. In another study, amitriptyline and duloxetine were shown to be equally effective63. Another study of good quality, on a limited number of patients, found to have similar effectiveness between amitriptyline and lamotrigine with regards to pain64. However, drowsiness occurred notably with amitriptyline, although serious side effects were reported with lamotrigine. A meta-analysis for comparing the efficacy of pregabaline, duloxetine and gabapentin65 concluded that duloxetine was most effective among all the drugs.

Patients, who are unable to tolerate amitriptyline must be treated with desipramine, which is equally efficient as amitriptyline for relieving pain in diabetic neuropathy. The mechanism of action of these antidepressants having analgesic potential in diabetic neuropathy may be mediated through blockade of norepinephrine reuptake.

Non-Pharmacological Treatments
Patients unresponsive to pharmacological therapy may be referred to physical or invasive treatments, such as central neurostimulation. In patients with diabetes, physical therapy is found to effective66. This may be an alternate to reduce dependency on pain relieving drug treatment. Certain physiotherapy techniques can helpful in relieving symptoms with diabetic neuropathy such as deep pain in the extremities, tingling or burning sensation in lower portion, muscle cramps or weakness, sexual dysfunction, and diabetic foot67.

A painless electric current via electrical stimulation with low frequency current is done through Transcutaneous electrical nerve stimulation (TENS) and interferential current (IFC), to relieve neuropathic pain, reduce oedema, relieve stiffness, improve mobility and heal resistant foot ulcers68.

Patients with foot ulcers having diabetes neuropathy are trained through gait training or posture training, and teaching the basic principles of off-loading can help prevent and/or stabilize foot complications. Off-loading techniques can induce the use of crutches or foot splints. Individuals using prosthesis as they have lost their limbs due to diabetic neuropathy, gait re-training would also be beneficial for them69.

Muscle strength and reduced muscle wasting can be maintained by general muscle strengthening exercises69. Exercises which place excess pressure on feet such as walking long distance or running is contraindicated but aerobic exercise such as swimming and riding a stationary bicycle have impact in peripheral neuropathy70.

Various other methods including Heat, therapeutic ultrasound and short wave diathermy have been useful for treating diabetic neuropathy70. Sexual dysfunction occurred through neuropathy can be improved using Pelvic floor muscle exercises.

Now-a-days, Photo Energy Therapy devices are frequently used to treat neuropathic symptoms. These devices emit near infrared light (NIR Therapy) at a wavelength of 880 nm. Vasodilation of the capillaries and venules in the microcirculatory system occur as this wavelength stimulates the release of Nitric Oxide. This increase in circulation contributes to decrease pain intensity in diabetic and non-diabetic patients71. Photo Energy Therapy devices seems to overcome the root cause of neuropathies i.e. poor microcirculation, which cause pain and numbness in the lower extremities72-73.

Electrical Spinal Cord Stimulation
In 25 patients, three prospective case series and one retrospective cohort study were conducted. After 1 year of spinal cord stimulation (SCS), it was concluded that 50% pain relief occurred in 63% of patients and analgesics usage was also reduced (60% complete withdrawl) in most SCS-treated patients. No any major adverse events were reported. The pain-relieving effect of SCS in painful diabetic polyneuropathy is shown many studies and promising results were reported74.

General Measures
General measures include change in life style of the patient such as elevation of the head of the bed (by 15-25cm at night), increased salt (10-12 d/day) and water intake (>20 oz/day), eating more frequent small meals after 2-3 hours. Patients with a neurogenic bladder should be advised to a frequent urinal discharge, so as to reduce the amount of residual urine. It is advised to the patient for a healthy weight, quit smoking, taking antihypertensives and the use of natural remedies for diabetes. (Table 6)

Patient should be encouraged to daily inspection of the feet, regular pedicure and alertness to trivial injuries. Infections commonly occur in diabetes so proper skin care must be advised in patients with cutaneous sensory loss, impaired sweating, and vascular disease. These measures will decrease the risk of developing foot ulceration.

Therapy of dysfuncitoning organs
In diabetes, gastric emptying is delayed, nocturnal diarrhoea occur along with erectile dysfunction. Metoclopramide is used to treat delayed gastric emptying and with short courses of either tetracycline or erythromycin nocturnal diarrhoea can be treated. Erectile dysfunction may be corrected by either oral sildenafil or direct vasodilator injection into the copora cavernosa or penile implants. A urologist must be consulted during dysfunctioning of urinary bladder and erectile dysfunction.

Other Drugs In Clinical Trials

SB-509
SB-509 is recently in phase II trials for treatment of diabetic neuropathy.

SB-509 contains the gene (DNA) for a protein. When it was injected into legs, the drug enters the muscle and nerve cells around the injection site and promotes these cells to make a protein. This protein causes cells to increase production of another protein called vascular endothelial growth factor (VEGF), which may improve the structure and function of nerves. In addition, there are changes in the levels of 28 additional proteins in cells. These proteins function to promote the growth of cells, help synthesize products, affect immune cells and some have unknown functions. This increase in VEGF proteins may protect and repair the damaged nerves caused by diabetic neuropathy.

Quigley QR333
The Quigley Corporation (NASDAQ: QGLY) announced in 2009 that their recently completed Phase 2 double-blinded, placebo-controlled, clinical trial of diabetic peripheral neuropathy, demonstrated a significant improvement in two key measures of distal sensory nerve function in the group treated with QR333. The compound was applied topically to the feet of subjects suffering from painful diabetic neuropathy and over the course of 12 weeks, it significantly improved both maximal conduction velocity (p=0.05) and
compound sensory amplitude (p<0.05) in the sural nerve. These are well established, validated and objective electrophysiologic measures of the onset and progression of diabetic nerve damage. A positive finding was detected in subjects suffering from neuropathy.

**DRUGS APPROVED BY FDA**

The only two drugs approved by the FDA for diabetic peripheral neuropathy which have sufficient efficacy are the antidepressant duloxetine and the anticonvulsant pregabalin. Pregabalin is a highly potent and higher-effective analog of gabapentin. Evidence of its efficacy is derived from three pivotal clinical trials in diabetic painful neuropathy.²²

**CONCLUSION**

In diabetes mellitus, either insulin depletion or resistance to insulin occur, resulting in hyperglycaemia and abnormalities in carbohydrate protein and fat metabolism. This persistence hyperglycaemia often leads to microvascular and macrovascular complications such as neuropathy, nephropathy or retinopathy.

In diabetic neuropathy, there occurs altered neuronal structure and function due to oxidative stress through activation of several biochemical pathways. Treatment should emphasize on optimising glycaemic control and patient education. Till date, suitable treatment for controlling diabetic neuropathy still await except two drugs approved by FDA. Several drugs have been declined in clinical trials due to intolerable side effects and some are yet to be in some phase of clinical trial which will have great impact in diabetic neuropathy. A combination of treatment also serves as an effective means of therapy in many studies and provides hope in order to stop the progression of disease. Even though research is going on and fruitful result from preclinical studies have been reported, but whether these will be beneficial in therapeutics is still a matter of debate.

**REFERENCES**


70. Typpo, Omaha. Importance of Physical Activity in Neuropathy. Demand Media Inc 2010.


**Risk factors**
Hyperlipidemia, Smoking, Age, Hypertension, Insulin resistance

**Other causes**
Genetic factor, HIV, chemotherapeutic agents

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**Polyol pathway**
Glucose → Sorbitol → Fructose

**PKC pathway**
Glucose → PIP2 ↓ → DAG ↓ → PKC-α ↓ → Na+K+ATPase ↓ → Cellular injury & death

**AGE pathway**
Glucose → PIP2 ↓ → DAG ↓ → PKC-α ↓ → Na+K+ATPase ↓ → Cellular injury & death

**PARP pathway**
Glucose → PIP2 ↓ → DAG ↓ → PKC-α ↓ → Na+K+ATPase ↓ → Cellular injury & death

**Hexosamine pathway**
F-6-P → GFAT → Glu-6-P → UDP-N-Ac → Activation of TNF-α, PAI-1

**TABLE 1. ALDOSE REDUCTASE INHIBITORS (Oka and Kato, 2001)**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Classes</th>
<th>Agent</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Acetic acid Compounds</td>
<td>Epalrestat</td>
<td>Japan developed by Ono.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alrestatin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tolrestat</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zenarestat</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zopolrestat</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NZ-314</td>
<td>Agents were withdrawn due to adverse effect or ineffectiveness.</td>
</tr>
<tr>
<td>2.</td>
<td>Spirohydantoins</td>
<td>Sorbinal</td>
<td>Japan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fidarestat</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Succinimide</td>
<td>AS-3201 (ranirestat)</td>
<td>In Phase III trials in the US</td>
</tr>
</tbody>
</table>

**TABLE 2. RECENT PATENT AGENTS OF COMPOUNDS AS ALDOSE REDUCTASE INHIBITORS IN DIABETIC NEUROPATHY**

<table>
<thead>
<tr>
<th>Patent Number</th>
<th>Filing date</th>
<th>Inventor</th>
<th>Aldose reductase inhibitors</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>US 0131536</td>
<td>Nov, 2007</td>
<td>Ahmed Massoud</td>
<td>Flavonoids from licorice</td>
<td>Oral</td>
</tr>
<tr>
<td>US 0047370</td>
<td>Apr, 2008</td>
<td>Sam Schwartz</td>
<td>Alpha lipoic acid</td>
<td>Topical</td>
</tr>
</tbody>
</table>

**TABLE 3. RECENT PATENT AGENTS OF ALDOSE REDUCTASE INHIBITORS IN COMBINATION WITH OTHER AGENTS FOR DIABETIC NEUROPATHY**

<table>
<thead>
<tr>
<th>Patent Number</th>
<th>Filing date</th>
<th>Inventor</th>
<th>Aldose Reductase Inhibitor</th>
<th>Other Agents</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA 2690086</td>
<td>Jul, 2008</td>
<td>Tsuno</td>
<td>Ranistat</td>
<td>AMPA receptor antagonists</td>
<td>Oral</td>
</tr>
</tbody>
</table>
### TABLE 4. ANTIOXIDANTS IN CLINICAL TRIALS

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Drug</th>
<th>Sponsor</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Ascorbic acid (vitamin C)</td>
<td>Washington State University</td>
<td>Phase I</td>
</tr>
<tr>
<td>2.</td>
<td>N-acetylcysteine</td>
<td>University of Turin, Italy</td>
<td>Phase III</td>
</tr>
<tr>
<td>3.</td>
<td>Allopurinol, α-lipoic acid, nicotinamide</td>
<td>University of Michigan</td>
<td>Phase III</td>
</tr>
<tr>
<td>4.</td>
<td>Metanx (a medicinal food)</td>
<td>Pamlab, L.L.C., USA</td>
<td>Phase IV</td>
</tr>
<tr>
<td>5.</td>
<td>Hemoderivative of calf blood (Actovegin)</td>
<td>Nycomed, Denmark</td>
<td>Phase III</td>
</tr>
<tr>
<td>6.</td>
<td>Controlled nitric oxide releasing patch</td>
<td>Fundacion Cardiovascular de Colombia</td>
<td>Phase III</td>
</tr>
<tr>
<td>7.</td>
<td>BK-C-0701</td>
<td>Bukwang, Pharmaceutical</td>
<td>Phase III</td>
</tr>
</tbody>
</table>

### TABLE 5. ORAL SYMPTOMATIC THERAPY OF PAINFUL NEUROPATHY

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Drug Class</th>
<th>Drug [Daily Dose (mg)]</th>
<th>Advantages</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Tricyclics</td>
<td>Amitriptyline (25–150)</td>
<td>Low cost Antidepressant effect at high doses</td>
<td>Cardiac toxicity Anticholinergic effects Adrenolytic effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imipramine (25–150)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>SSNRIs</td>
<td>Duloxetine (30-60)</td>
<td>Easy and rapid dose titration Taken daily Antidepressant/antianxiety effects</td>
<td>Adverse effects Drug interactions</td>
</tr>
<tr>
<td>3.</td>
<td>Anticonvulsants</td>
<td>Gabapentin (900-1,800)</td>
<td>No major drug interactions Antianxiety effect</td>
<td>Adverse effects Titration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregabalin (160-600)</td>
<td></td>
<td>TID Cost</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lamotrigine (200-400)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carbamazepine (upto 800)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Opioids</td>
<td>Tramadol (50-400)</td>
<td>Beneficial effect on possibly associated inflammatory pain</td>
<td>Adverse events Physical dependence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oxycodone CR* (10-60)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All medications in this table have demonstrated efficacy in randomized, controlled studies. *Oxycodone controlled release (CR) may be useful as an add-on therapy in severe symptomatic neuropathy.

### TABLE 6. NUTRITIONAL TREATMENT FOR DIABETIC NEUROPATHY

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Treatment</th>
<th>Mechanism of action</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Gamma-linolenic acid (GLA)</td>
<td>Produce deformable RBCs, Regenerate veins/capillaries, over long period stimulate nerve growth</td>
<td>Stimulate COX 1 expression and production of PGI₂</td>
</tr>
<tr>
<td>2.</td>
<td>Vitamin E</td>
<td>Synergistic to GLA</td>
<td>Protects PGI₂, improve capillary permeability</td>
</tr>
<tr>
<td>3.</td>
<td>Niacin</td>
<td>Improve blood circulation, expand capillaries</td>
<td>Participates in glucose metabolism &amp; in nervous system</td>
</tr>
<tr>
<td>4.</td>
<td>Taurine</td>
<td>Dec. TNFα over expression</td>
<td>Increase insulin sensitivity</td>
</tr>
</tbody>
</table>