Diabetic Peripheral Neuropathy-emerging Pharmacologic Options


Abstract
Diabetes mellitus (DM) affects more than 194 million adults worldwide. Diabetic peripheral neuropathy (DPN) is one of the common late complications of DM and is associated with decreased quality of life and increased morbidity. Pain of DPN is most distressing and difficult symptom to manage. The pathogenesis of DPN is believed to be multifactorial with hyperglycaemia being primary risk factor.

Prevention through strict glycaemic control remains the mainstay of therapeutic intervention because effective disease modifying therapies are yet not available. The risk of developing DPN increases with the duration of DM, degree of glycaemic control, age, BMI, smoking. Many pharmacological agents are used to treat painful DPN either alone or in combination, but results are far from satisfactory. The article reviews the various available options to treat DPN with special focus on newer agents, Pregabalin and Duloxetine which are recently approved by FDA for treatment of Diabetic peripheral neuropathy. However there still remains a need for safe, effective, better tolerated pharmacological agents capable of delaying or reversing Diabetic Neuropathy.

Introduction
Diabetic neuropathy (DN) is a common and debilitating symptom of DM leads to a significant morbidity. Approximately fifty percent of all the patients with diabetes will eventually develop DN over the course of their disease and roughly 11 to 20% of these patients will experience painful DPN, with significant decrease in their quality of life.

The risk of developing Diabetic peripheral neuropathy (DPN) increases with duration of the disease and degree of glycaemic control, and other contributing factors such as hypertension, dyslipidaemia, smoking, body mass index and hyperinsulinaemia. Distal symmetrical polyneuropathy is the most common type of DPN. It has an insidious onset and progress from most distal part of extremities in a symmetrical pattern that is generally described as “Glove and Stocking”.

Many pharmacological options are available to treat DN but still it is difficult for patients to obtain complete relief. Various pharmacological options available will be reviewed including newer agents-Pregabalin and Duloxetine.

Pathophysiology
DPN has three broad types of manifestations: Sensory, motor and autonomic. The most prevalent form is somatic or sensory motor neuropathy, which is often simply referred to as DPN. Symptoms often exhibit a distal symmetric pattern, beginning distally at the base of the toes and
ascending proximally up the lower leg as the disease progresses. These symptoms are often described as burning, tingling, stabbing or a pin-and-needle sensation in a stocking and glove distribution. Patients may also display muscle weakness, in coordination and ataxia. The paraesthesias often results in the loss of pain perception. The loss of protective sensation can lead to the formation of foot ulcerations, infections which often result in amputations and cause significant morbidity and mortality.

The pathogenesis of DPN is believed to be multifactorial with hyperglycaemia being the primary risk factor. Suggested theories that postulate the aetiopathogenesis of DN include abnormalities of protein glycation, sorbitol accumulation, polyol pathway flux, protein Kinase C activation, advanced glycation end products, receptor for advanced glycation end products, a decrease in neuronal nitric oxide synthase protein, and microvascular hypoxia, resulting in oxidative stress.

**Treatment**

**Pregabalin**

Pregabalin is the next generation drug in the same class of Gabapentin (binds to alpha-2 delta subunit of voltage sensitive calcium). It has a faster onset of action, linear pharmacokinetics and a very high bioavailability. Pregabalin also has an anxiolytic and anticonvulsant activity and it is the only anticonvulsant that was approved in DEC-2004 by FDA for management of painful DPN. As with Gabapentin, the exact mechanism of action of Pregabalin is unclear although researchers have postulated that it binds with high affinity to the alpha 2-delta subunit protein of voltage gated calcium channels and subsequently reduce the release of excitatory neurotransmitters.

Peak plasma levels occur approximately one hour after oral administration. Food does not significantly affect the extent of absorption of this drug and the oral bioavailability of Pregabalin is about 90%. It is completely absorbed and is not protein-bound and has a linear pharmacokinetics. Pregabalin exhibits a plasma half life of six hours. Hepatic metabolism is negligible and most of the oral dose is eliminated unchanged through the kidney.

Researchers have shown the efficacy of Pregabalin in treating painful DN in three randomized, double-blind, multi-centre studies with a total of 724 patients. They found that administering Pregabalin at a fixed dose of 300 and 600 mg per day demonstrated rapid and sustained improvement in pain with less pain related sleep interference. Study authors noted significant improvement in pain and sleep as early as first week, and these improvement were maintained in studies of up to 12 weeks in duration.

A recently published six-week, randomized, double-blind, multicentre study found Pregabalin to be effective and safe in the treatment of DPN. This study involved 264 patients with painful DPN who received Pregabalin (150 mg or 600 mg per day for a month) or placebo. The researchers noted that Pregabalin at a dose of 600 mg per day significantly decreased the mean pain score and pain intensity, and significantly reduced sleep interference. They found that Pregabalin at dose of 150 mg/day was no different than a placebo. The most common side effect was dizziness and somnolence.

Rosenstock, et al., evaluated the effectiveness of pregabalin 300 mg/day in alleviating pain associated with DPN in 146 patients in an eight-week multicentre, randomized, double blind, placebo controlled, parallel group trial. In comparison to placebo, pregabalin produced significant
improvements in pain reduction, reduced sleep interference and reduced mood disturbance. The authors concluded that pregabalin was safe and effective in decreasing pain associated with DPN with improvement in mood, sleep disturbance and quality of life.

For patients with painful DPN, the maximum recommended dose of pregabalin is 100 mg tid (300 mg / day). In patients with creatinine clearance of about 60 ml/ min, dosing should begin at 50 mg tid (150 mg/ day) and may be increased to 300 mg/day within 1 week based on tolerability and efficacy and repeat creatinine clearance levels. The dose for pregabalin should be adjusted for patients with reduced renal function. Pregabalin was well tolerated in patients with DPN. Most common adverse effects are dizziness, somnolence, and peripheral oedema. These are similar to those reported most often for gabapentin. Additional studies with pregabalin have demonstrated the effectiveness of flexible dosing with this agent, and high completion rates in clinical trials suggest that its use should promote high adherence in clinical practice.

**Duloxetine**

Duloxetine hydrochloride is a balanced selective serotonin and nor epinephrine reuptake inhibitor (SNRI) for the treatment of major depressive disorders, pain associated with DPN, and female stress urinary incontinence. Although it is not currently approved for all indications in all countries, Duloxetine is one of two drugs currently approved by the FDA for the management of neuropathic pain secondary to diabetes.

SNRI represent a class of antidepressant agents that help regulate and treat depressive emotions and neuropathic pain by sustaining balanced level of two neurotransmitters Serotonin and Norepinephrine. Serotonin and Norepinephrine are implicated in modulating descending inhibitory pain pathways in the central nervous system, and are known to help in regulating emotions as well as sensitivity to pain. Clinical evidence suggests that dual acting agents may better modulate pain than those agents that increase serotonin or noradrenalin alone. Absorption of Duloxetine begins about two hours after oral administration and reaches maximum plasma concentration in about six hours, with a half life of 12 hours. It is eliminated primarily in the urine after extensive hepatic metabolism by multiple oxidative pathways, methylation and conjugation.

In September 2004, Duloxetine became the first medication approved by the FDA for the treatment of DPN. In a double-blinded, placebo-controlled study, researchers showed that a 60 mg daily dose of Duloxetine was effective and well tolerated. Furthermore, they noted a rapid onset and sustained effect in reducing pain associated with DPN. The maximum dose approved for marketing is 120 mg per day, but the recommended dosage of duloxetine is 40 to 80 mg daily, depending on the indication, and preferably split into two doses per day.

A 12 week, multicentre, double-blind study found Duloxetine to be safe and efficacious in the management of DPN. In this study, researchers randomized 457 patients with symptomatic DPN into one of the four treatment arms to receive Duloxetine 20 mg OD, 60 mg OD, 60 mg BID or a placebo. Duloxetine at 60 mg and 120 mg per day doses demonstrated statistically significant improvement in comparison to the placebo on the average pain score. The improvement was noted one week after randomization and continued through the 12 week trial. Duloxetine was noted to be safe and well tolerated with less than 20% discontinuation rate due to adverse effects.
Similarly, in a multi-centre, double-blind, randomized, placebo-controlled trial that enrolled 348 patients with DPN. Patients were randomized to either receive Duloxetine 60 mg twice daily or placebo for 12 weeks.11 Both Duloxetine-treated groups improved significantly more on the 24-hour average pain score in comparison to patients in the placebo group.11 Duloxetine showed no adverse effects on the diabetic control and researchers noted that both Duloxetine 60 mg OD and Duloxetine 60 mg BID were safely administered and well tolerated.11

Duloxetine is safe and generally well tolerated with few reports of serious side effects.12 The side effects of Duloxetine are similar to those of traditional SNRIs. Nausea is common and has been cited as the primary reason for discontinuation of therapy. Researchers have noted mild increase in blood pressure so clinicians should exercise caution when considering this drug in patients with hypertension. Patient with a creatinine clearance of less than 30 ml/min and patients with hepatic impairment should avoid Duloxetine.9 Like SNRIs Duloxetine is contraindicated in patients taking nonselective, monoamine oxidase inhibitors or thioridazine, so also in patients with hepatic insufficiency, end-stage renal disease or uncontrolled narrow angle glaucoma.9,12

**Tricyclic Anti-depressants (TCAs)**

TCAs have traditionally been used as first line of therapy for DPN and hence have been studied extensively for treatment of DPN.13 The efficacy of TCAs in managing neuropathic pain is thought to be as a result of their analgesic action rather than their antidepressant effect and the proposed mechanism of analgesics is due to reuptake of 5HT and NE.14 Amitryptiline is the best studied TCAs in Diabetic neuropathy although Desipramine, Imipramine and clomipramine, oseipramine, have also demonstrated good efficacy. Two studies which have compared Desimipramine with amitryptiline and showed that Desimipramine was better tolerated.15,16 Their analgesic effect is independent of their anti-depressant effect.17 The newer selective serotonin reuptake inhibitors SSRIs selectively block reuptake of serotonin. This group includes fluoxetine, paroxetine, and sertraline. TCAs have a considerable adverse effect burden and are less well tolerated than the SNRIS or SSRIS. Despite their widespread use none of the TCAs have been approved by FDA for treatment and DPN due to lack of evidence of efficacy in DPN in clinical trials.18 Little difference in efficacy was seen among various TCAs in symptomatic relief and the agents with lowest risk of adverse events i.e. Desipramine should be considered first. While there is no absolute minimum effective dose for TCA, it is best to start low and go slow with these agents. Tertiary TCAs, including Amitryptiline should be used with caution in geriatric population. The commonest side effects of TCAs are dry mouth, constipation, dizziness, blurred vision and urinary retention and serious ones include cardio toxicity which includes slowing of AV node and orthostatic hypotension.

**Antiepileptic Drugs (AEDs)**

Similarities in the pathophysiology and biochemical basis of epilepsy and neuropathic pain have led to their increasing use in the management of neuropathic pain. AEDs are thought to raise the pain threshold and reduce neuronal hyper excitability involving mechanisms such as blockade of sodium channels, inhibition of glutamate, and enhancement of the inhibitory neurotransmitter gamma-amino butyric acid (GABA).19 AEDs play a very important role in the treatment of DN; Gabapentin and
Lamotrigine are currently the most frequently prescribed medications from this group for DPN.

**Gabapentin** is an alpha-2-delta calcium channel modulator, and has demonstrated efficacy in DPN. Gabapentin is approved by FDA for the treatment of peripheral neuropathy and partial seizures but not specifically for Diabetic peripheral neuropathy. In a large multicentre double blind randomized controlled trial, Gabapentin significantly reduced pain of DNP compared with placebo. Dosages used ranges from 900 mg/day to 3600 mg/day and pain relief was observed during the second week after the doses of gabapentin reached 1800 mg/day. The data also shows favourable actions of gabapentin in improving sleep disturbance, mood and quality of life.

In another randomized controlled trial, 25 patients with DPN were randomly assigned to receive gabapentin and or amitryptiline for 6 months. The mean dosage of gabapentin and amitryptiline were 1565 mg and 59 mg respectively. Pain relief with gabapentin and amitryptiline were almost same.

A recent study has shown that judicious use of gabapentine with morphine was more effective than either treatment alone and allowed use of lower doses of both the drugs. Another study compared Gabapentin with Amitryptiline and it was seen that Gabapentin was well tolerated with similar side effect profile to Amitryptiline.

The recommended dosage regimen for gabapentin in treatment of DPN is 300 mg dose on day 1 and increase to 300 mg bid and tid on day 2 and day 3 respectively. Then dose is increased gradually to 1800 mg/day by day 14. If patient is elderly it is recommended to commence at 100 mg/day interval dose and slowly increased. Common side effects are dizziness and somnolence. Gabapentin neither inhibits nor induces Cytochrome P450 isoenzyme hence minimizing potential for drug interactions. Since this is excreted unchanged in urine a dose adjustment is needed in patient with renal insufficiency.

**Lamotrigine** is an anticonvulsant with an antidepressant property and works by stabilizing neuronal membranes through voltage gated sodium channels and inhibit glutamate release. Lamotrigine has demonstrated efficacy in management of various types of neuropathic pain including DN, but not all results are favourable. Several small controlled trials have given conflicting reports of its efficacy in neuropathic pain. In one study Lamotrigine in dose of 200-400 mg/day appeared to give relief of pain but side effects of lamotrigine include high incidence of serious cutaneous reactions apart from headache, dizziness, epigastric pain. To minimize the possibility of cutaneous reactions strict titration regimen is needed and hence it may take several weeks to reach the analgesic dose.

**Carbamazepine** (CBZ) is thought to act both centrally and peripherally decreasing Na⁺ and K⁺ ionic conduction through membrane stabilization by inhibition of ionic conductance. It is one of the earliest drugs tried for neuropathic pain. In a recent study Carbamazepine was compared with nortryptiline-fluphenazine for treatment of DPN. Both therapies produced improvement in pain and paraesthesia but difference was not statistically significant.

**Oxcarbazepine** (OXC) is a chemically related and has a mechanism of action similar to that of carbamazepine and has shown to have a better adverse effect profile than carbamazepine. There are no published study examining oxcarbazepine for treatment of DPN but it has demonstrated efficacy comparable to that of CBZ in treatment of...
trigeminal neuralgia. CBZ use in clinical practice for pain associated with DPN is limited secondarily to its side effect profile (somnolence, dizziness, ataxia). OXC a newer AED structurally similar to CBZ, has been demonstrated in studies to offer a better side effect profile, not undergo auto-induction and has fewer drug interactions in its profile.25

**Topiramate, Vigabatrin, Levetiracetam** are new AEDs as potential therapies for DPN. These agents at present are being used primarily as therapy for refractory seizures. These novel antiepileptic offer both improved efficacy in the treatment of refractory seizures, reduction of neuropathic pain and the possibility of reducing or eliminating adverse effects as seen with the older AEDs.25 These are yet to be studied in controlled trials before they can be recommended for use in DPN.

**Zonisamide** is a newer antiepileptic and was used in open label studies to assess its effectiveness in DPN. Most patients withdrew from the study due to high rate of side effect profile. Another anti convulsant **Lacosamide** has shown some improvement but side effects of dizziness, headache, tremors are more seen. More studies are needed for any of the newer anti convulsant to be recommended for DPV at present.

**Opioid Analgesics**

Opioids till present time have played a limited role in treatment of neuropathic pain because the evidence base of its effectiveness in clinical trials is weak and limited by lack of good controlled studies.

**Oxycodone CR** (controlled release) has been studied in randomized control trials for relief of pain in DPN.26,27 The result show that it significantly reduces average pain intensity and at an average dose of 37 mg/day. It significantly reduced average pain intensity (p < 0.01) when compared to placebo. At a higher dose of Oxycodone CR, pain relief was better but at an expense of higher rate of adverse effects. Main side effects of oxycodone are constipation, somnolence, dry mouth, nausea and dizziness. Any potential benefit of opioids must balance the risk of adverse effects and risk of physical dependence. If they are decided to be used for long term then it is advisable for the physician to sign an opioid agreement with the patient.26

**Tramadol** is unusual in its mode of action. It is a centrally acting opioid analgesics as well as has a unique action of norepinephrine and 5-HT reuptake inhibition very much like TCAs leading to enhancement of endogenous pain inhibitory pathway.28 In randomized double blind placebo controlled studies Tramadol resulted in reduced pain and enhanced and social functioning.28 The side effects reported commonly were constipation and headache. Drug dependence and abuse are there but less than other opioid analogics.29

**Non Opioid Analgesics**

The non steroidal anti-inflammatory drugs (ibuprofen, diclofenac) are useful in many painful conditions but there is very little evidence that NSAID’s are effective to relieve pain of DPN. The dose at which they may be effective can lead to potential serious side effects of GI haemorrhage, especially in older individuals.30

**Topical Analgesics**

**Capsaicin** is an alkaloid derived from chilli pepper that is postulated to block pain signals by depletion of Substance P a neurotransmitter and activation of other receptors that may decreases pain.31 The capsaicin study group evaluated its use in treatment in DPN and found it to be effective in providing pain relief.32 A study comparing
its efficacy to TCA for DPN showed it is not only equally effective to TCA, but also a safer alternative to TCA, without any significant drug interaction. It is available as a topical preparation in strength of 0.05% and 0.075%. It has to be applied multiple times a day to be effective. Although well tolerated at its higher concentration of 0.075% but in this strength it causes a burning sensation in most of the patients.

**Topical lidocaine** patch is FDA approved for treatment of post herpetic neuralgia but is useful alternative in the treatment of DPN. In two open label design trials\(^{33,34}\) patients with DPN show significant improvement in pain and QOL measures during 3 week treatment from with 5% lidocaine patch applied daily (4 patches per day for max 18 hours).\(^{33,34}\) The 5% lidocaine patch appears to be well tolerated potentially effective in management of DPN.\(^{34}\) Larger controlled trials are necessary to confirm these results.

9) **Mecobalamin**

It is one of the two active co-enzyme forms of Vit. B\(_{12}\). It is the co factor in the enzyme methionine synthetase which functions to transfer regeneration of methyl groups of methionine from homocysteine and regeneration of mecobalamin promotes axonal transport, myelination and lecithin production.

**Other drugs being tried**

1) **Essential Fatty Acids** : Metabolism of essential fatty acids Linolenic acid is impaired in diabetes and this defect can be bypassed by the administration of GLA. This may be the rate limiting step for synthesis of biologically important Eicosanoids like PGE\(_1\), PGE\(_2\), and prostacyclins. Several studies have shown improvement in peripheral nerve function with these compounds.

2) **Vasodilators** : It is being increasingly recognized that increase in blood fluid is implicated. The most promising vasodilator agents α1 adrenergic antagonist, ACE inhibitors, vasodilator prostanoids.

3) **Acetyl-l-carnitine** : Acetyl-L-carnitine is a common, naturally occurring chemical that is used as a dietary supplement. In preclinical studies, substitution with ACL corrected perturbations of neural Sodium-Potassium ATPase, myoinositol, Nitric oxide (NO), Prostaglandins, and lipid peroxidation, all of which play early pathogenic role in DN.

In a randomized placebo controlled trial, 1000 mg of Acetyl-L-carnitine three times daily was efficacious in alleviating pain as well as improved vibration perception in patients with chronic diabetic neuropathy. Although this agent has shown promise as an agent to help delay in progression of DPN more studies are needed to examine its full effect in treatment of diabetic peripheral neuropathy.

4) **Alpha Lipoic Acid** : It is a natural antioxidant that has been suggested to improve symptoms of DPN.\(^{35,36}\) As with most dietary supplements Alpha lipoic acid has a highly favourable safety profile with no significant adverse reactions; although FDA has still not approved it for treatment of DN. The efficacy of orally administered alpha Lipoic acid will need to be confirmed with long term multicentre trials.

5) **Aldose Reductase Inhibitors (ARIs)** : Aldose reductase is the first enzyme in the pathway that results in higher levels of sorbitol in nervous tissue. ARIs slow the production of Sorbitol and have been demonstrated in animal models to reverse neuropathy if started early and used for sufficient time. Only one agent of this drug class-Epalrestat is currently available in Japan.\(^{37}\) Other ARIs in Phase III trials include Fidaerestat, Zenarestat, Zopolrestat,
Lidorestat, Tolrestat and Minalrestat. Aldolase converts sugar into sorbitol, and raised concentration results in depletion of Sodium-Potassium-ATPase, which in turn helps maintain conduction velocity. The suggested mechanism of action also include altered phosphoinositide metabolism of Na⁺K⁺ ATPase activity or through reduced glutathione levels or by vasodilatation and impaired blood flow to nerves. ARIs decreases production of sorbitol in animal studies and have shown to reverse neuropathy of early stage. However results of clinical trials in humans have not been convincing. Tolrestat has been found to improve autonomic nervous system function in patients of Diabetic Autonomic Neuropathy. Common limitation to their use includes hepatic and renal toxicity. ARIs are primarily been studied now to study their ability to prevent progression of neuropathy.

**Non-pharmacological Therapy**

Drugs continue to be most widely used treatment for pain of DPN but some alternative therapies show promise.

Because there is no entirely satisfactory pharmacotherapy of painful DN, non pharmacological treatment options such as psychological support, transcutaneous electrical nerve stimulation or physical measure (e.g. Cold water immersion) have been used.

**Electro stimulation:** - This has been shown to provide temporary relief of pain associated with DPN.

One study studied the effect of transcutaneous electrotherapy which consists of self administered mild intensity electric shock 30 minutes a day in patients with painful diabetic neuropathy. More than 83% patients reported reduction of pain. In another study percutaneous electrical nerve stimulation (PENS) was examined in patients with diabetic peripheral neuropathy and compared with placebo therapy. Acupuncture like needles are inserted 1-3 cm in muscle of front of the leg and alternate frequencies of electrical shock are applied. Patients expressed profound reduction in reduction pain (56% versus 14%), improved sleep quality (41% versus 13%) and increased physical activity when compared with placebo. Electro stimulation produces analgesic effect by inducing release of endogenous opioid like chemically but more controlled studies are needed before it can be recommended for routine use.

**Surgery** to decompress the lower extremity nerves is another relatively new therapy. Researchers have postulated that decompression of peripheral nerves at known sites of anatomical narrowing can help decrease pain and restore sensory function in DPN. In a retrospective study of 50 patients followed up to 4.5 years after surgical decompression of tibial and peroneal nerves, no ulcers or amputations occurred. At present surgical decompression is only considered if absolutely necessary and only in patients who have clearly defined areas of compression and follow on medical treatment.

**Acupuncture** has shown to have some analgesic effect with minimal side effects. One study showed that 77% of patients had a significant improvement in the symptoms. There is some evidence that spinal cord stimulation and frequency modulated electromagnetic neural stimulation may be helpful.

**Monochromatic near-Infrared treatment** system improves sensation and balance, and reduces pain in patients with DN. Static magnetic field (450G) is released by small flexible pads located in shoe in soles are applied to the skin and it is postulated...
that it stimulates the release of nitric oxide then the haemoglobin and surrounding tissue. The NIRE system is considered a CLASS II, non invasive medical device and has received FDA clearance to help improve circulation and decrease pain.

**Drugs in Experimental Stage**

1) *Neurotropic Factors*: NGF selectively promotes the survival, differentiation and maintenance of small fibre sensory and sympathetic neurons. It is expressed in the skin and other target tissues of responsive neuronal populations, binds to high affinity receptor (trk A) on nerve terminals, and exerts tropic effect after retrograde transport back to neuronal perikaryon. Animal studies have demonstrated their potential efficacy and clinical trials with Nerve growth factors suggest that it some what improves neuropathic sign and symptoms, although those findings have not been replicated in large scale trials. Present research is also focusing in small molecule drugs that induce natural expression of nerve growth factors. A large number of neurotropic factors have been discussed. Among them the brain derived neurotrophic factors; neurotropin(NT)-3 and NT 4/5, insulin like growth factor (IGF)-II and glial cell derived neurotropic factor. NGF and IGF’s have shown very promising results in animal studies. Recombinant human nerve growth factor (rhNGF) has been in phase III trials and results are encouraging.

2) *Gene therapy for neuropathy and neuropathic pain*: Peptide neurotrophic factors can be used, although nerve growth factor studies in animal models involved several orders of magnitude higher doses that have been tried in humans. Such levels of treatment could be attained by direct delivery of trophic factors to involved nerves, perhaps with gene therapy by injecting a vector from which the desired genes would be taken up directly. Potential vectors include liposomes, retrovirus and adenovirus. Fink noted that herpes simplex virus must be an ideal vector for such treatment, as it is naturally taken up in sensory neuronl nuclei, remaining in this location through the lifetime of the host and carried by retroaxonal transport from the nerve fibres to the nucleus. Deletion of the early viral protein gene abolishes replication and infectivity, further suggesting this to be a potentially useful approach.

3) *Protein Kinase C Inhibitors*: Roboxistaurin, a selective protein Kinase C (PKC)-beta inhibitors was in Phase III clinical trials and discontinued in 2005 due to lack of efficacy.

4) *Erythropoietin*: Studies have shown that Erythropoietin receptors are found on the nerve cells and that perhaps erythropoietin can function as nerve protecting agent. Recent trial has shown that erythropoietin can ameliorate neuronal damage in acute ischaemic stroke patients. Erythropoietin is still in an experimental stage and more studies are needed before its use in DN is established. An increase in haematocrit is a potential undesirable side effect and can predispose to CVA.

5) *Antioxidants*: There is evidence that free radical mediated oxidative stress is implicated in pathogenesis of DN by inducing neuronal defect that results in endoneural hypoxia and subsequent nerve dysfunction. Hyperglycaemia induced overproduction of super oxide may also be an important pathogenic mechanism of free radical mediated injury. Role of antioxidants in inhibiting oxidative damage is not yet established.

6) *Clonidine*: Clonidine a sympatholytic agent has some usefulness in painful DPN. A topical form of Clonidine is under investigation; acts as in local analgesic and
its effect is concentration dependent.  

7) Pancreas Transplant: Pancreas Transplantation currently represents the only clinical method, which reliably re-establishes long-term normoglycaemia in diabetic subjects (despite the major breakthrough accomplished by the introduction of the Edmonton protocol, islet transplantation still lags behind in this respect). PT is most frequently performed in type 1 diabetic patients in advanced stages of Diabetic Nephropathy and with other microvascular complications. Diabetic neuropathy, involving motor, sensory and autonomic nerves to a similar extent is very common and severe in these patients.

The long term effects of re-established normoglycaemia have been studied both in pancreas transplant alone (PTA) and uraemic patients given simultaneous pancreas and kidney transplant (SPK). Allen et al. followed 44 patients after a successful SPK for up to 8 years. Two distinct patterns of neurological recovery were observed. Rapid initial recovery in NCV was followed by stabilization whereas action potential amplitudes recovered in a slow monophasic pattern which persisted for the duration of the study.

To date no systemic study has documented nerve regeneration directly through morphological examination of peripheral nerves following a successful PT. Nonetheless in a single case report Beggs et al. identified signs suggestive of tissue repair and regeneration of some nerve components in sequential sural nerve biopsies following PTA in a type I diabetic patients.

In summary, data from patients undergoing PT seem to suggest some nerve regenerative tendency mainly in less severe cases. However no marked effect on neuropathic deficits has been demonstrated and the risk of diabetic complications persist in the post transplant patients.

Conclusion

Although our knowledge regarding pathogenesis of DN has grown significantly during last two decades but still identifying effective treatment regimen remain challenging. Current pharmacologic Armamentarium for DN is large and diverse but till date no agents are available to repair the damage of diabetic DN. Two new drugs have been recently approved by FDA for treatment of diabetic peripheral neuropathy. One is an anti-epileptic Pregabalin which shares with Gabapentin the same mechanism of action. The linear pharmacokinetic and lack of risk of important pharmacokinetic interactions makes it suitable agent for treatment of DPN. The other is Duloxetine, a well balanced SNRI which has shown to be effective in clinical trials for Diabetic neuropathy:

Other drugs like, TCAs, anti-epileptics, opiate analgesic etc. have been used for long time and patients have reported good relief; however controlled clinical trials do not support their efficacy. Some times a careful combination of available agents is required to achieve satisfactory results but all medications should be monitored for side-effects and drug interaction. The reliable disease modifying therapies are developed but glycaemic control remains the foundation of prevention and the prerequisite of adequate treatment of diabetic neuropathy.

References

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