Diabetic polyneuropathy (DPN) remains one of the most challenging therapeutic areas for physicians, particularly neurologists, endocrinologists and primary care physicians. After years of intensive investigation, answers to some basic questions remain elusive; for example, what causes some patients to perceive unremitting pain and others to remain virtually asymptomatic despite similar durations of diabetes, levels of glycemic control and degrees of nerve fibre loss on pathological review. Specific interventions directed at the neuropathy are few: only intensive glycemic control helps reduce prevalence of neuropathy.1-4 The benefits for patients with Type 2 diabetes are far less certain.3 Multiple agents have failed phase 3 trials for various reasons and are unavailable for use in DPN.

This review focuses on the clinical trials of new treatments for DPN providing an update on the current status of investigation into this disorder. A discussion of symptomatic therapy for painful symptoms of diabetic polyneuropathy concludes this review.

Specific interventions directed towards DPN are based on presumed pathophysiological mechanisms which have been recently reviewed.5,6 Disordered nerve function in diabetes can be considered in several broad categories: metabolic, vascular, genetic, protein glycosylation, and neurotrophism. These are not mutually exclusive but tend to overlap and interact. Many nerve derangements demonstrated in animal models have not been shown in human subjects.7 The fundamental abnormality, other than hyperglycemia, leading to DPN in man is uncertain. For further details concerning pathophysiology of DPN, the reader is referred to recent reviews.5,8,9-15 Table 1 lists the specific interventions discussed in this paper.

Hyperglycemia

The evidence for the value of reducing hyperglycemia is strong in Type 1 diabetes.2 The Diabetes Control and Complications Trial proved conclusively that intensive glycemic control reduces the prevalence of confirmed DPN in young men by 64% as measured by clinical features, nerve conduction studies (NCS) and autonomic system testing.1,2,16 The effect was noted after five years of intensive intervention. Trials of intensive control in smaller numbers of patients treated for briefer durations, such as one year, have failed to demonstrate any alteration in symptoms, signs, NCS, vibration perception thresholds (VPT) and thermal thresholds.17 Other trials have shown electrophysiological improvements after shorter periods...
of intensive control. Presumably, the latter implies eventual clinical benefits if the positive therapeutic intervention is maintained. The UK Prospective Diabetes Study proves that better control for many years can improve neuropathic indices although limited end-points were performed in this study. After 15 years of intervention, no difference in ankle and knee reflexes, or erectile dysfunction was observed between groups, but vibration perception threshold was lower after nine years of therapy in the better controlled group. The relative risk of neuropathy as measured with the biothesiometer was 0.60 (95% confidence intervals: 0.39 - 0.90, p=0.0052) with better control. Navarro’s study showed that pancreatic transplant can help prevent progression of clinical, autonomic and electrophysiological parameters in both men and women. This cumulative evidence along with epidemiological studies, such as that by Pirart, which show more neuropathy in those with worse control after 25 years of diabetes, have changed practice patterns and recommendations for treatment in North America. Recent guidelines recommend that any patient with HbA1C > 8.4% should be subjected to “additional action”, and those with HbA1C between 7.1 and 8.4% have suboptimal control which may require action.

**Aldose reductase inhibitors**

The aim of aldose reductase inhibitor (ARI) therapy is to protect the nerve from the effects of overactivity of the polyol pathway caused by chronic hyperglycemia (Figure). In states of uncontrolled hyperglycemia, activation of this pathway results in accumulations of sorbitol and fructose and concomitant decreases in Na-K-ATPase. These changes are prevented by ARI administration in animal models and man. Unfortunately, none of the agents which were promising in the laboratory and early clinical trials proved effective in phase III trials for various reasons reviewed below. Currently, no aldose reductase inhibitor agent has proven effective for the therapy of DPN.

Sorbinil, the first agent extensively studied, was associated with toxic epidermal necrolysis as a complication in two patients. The methodology for measurement of the efficacy parameters in the pivotal neuropathy study was imperfectly defined and the results not monitored closely or expertly. The treatment interval lasted only 12 months. A single centre reporting results of pre- and post-treatment sural nerve biopsy parameters showed efficacy, but morphology was not a pivotal parameter in the overall study. The primary efficacy parameters from all study centres combined were negative. In another trial directed at retinopathy, neuropathy measures did not improve with sorbinil therapy.

However, the same problem with data quality control existed in that trial. Statil, a much safer ARI, was used for 18 months in a double-blind, placebo-controlled fashion. The methodology for measuring the efficacy end-points of NCS and quantitative sensory thresholds was carefully defined and the results monitored closely. The quality of the data was excellent. Unfortunately, the results were negative. No difference in nerve

---

**Table 1 Specific Interventions Investigated for the Treatment of Diabetic Polyneuropathy**

<table>
<thead>
<tr>
<th>Target</th>
<th>Intervention</th>
<th>Specific Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td>Intensive glycemic control</td>
<td>Insulin</td>
</tr>
<tr>
<td>Polyl pathway</td>
<td>Aldose reductase inhibitors</td>
<td>alredase</td>
</tr>
<tr>
<td>Polyl pathway</td>
<td></td>
<td>sorbinil</td>
</tr>
<tr>
<td>Polyl pathway</td>
<td></td>
<td>statil</td>
</tr>
<tr>
<td>Polyl pathway</td>
<td></td>
<td>FK-366/zenarestat</td>
</tr>
<tr>
<td>Polyl pathway</td>
<td></td>
<td>tolrestat</td>
</tr>
<tr>
<td>Polyl pathway</td>
<td></td>
<td>zopolrestat</td>
</tr>
<tr>
<td>Polyl pathway</td>
<td></td>
<td>epalrestat</td>
</tr>
<tr>
<td>Non-specific metabolic</td>
<td>Ubiquitous</td>
<td>alcar</td>
</tr>
<tr>
<td>Neurones</td>
<td>Neurotrophins</td>
<td>NGF</td>
</tr>
<tr>
<td>Vascular</td>
<td>Anti-oxidants</td>
<td>α-lipoic acid</td>
</tr>
<tr>
<td></td>
<td>Improved blood flow</td>
<td>γ-Linolenic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PKCi</td>
</tr>
</tbody>
</table>
conduction or quantitative sensory threshold parameters was found between groups treated with drug or placebo. After these disappointing results were found, further investigation revealed that statin did not penetrate human nerve. This compound demonstrated species differences in aldose reductase inhibitor activity as rat nerve showed the expected benefits with this intervention.\textsuperscript{27,28} Another study of statin therapy in diabetic autonomic neuropathy showed similarly disappointing results.\textsuperscript{29}

Tolrestat proved problematic in that some patients developed hepatic side-effects in an idiosyncratic manner on this medication. Severe elevations in hepatic enzymes were observed in a few patients. Furthermore, the interventions were limited to 18 months in the therapeutic trials; a very short time to show significant change in parameters of DPN. Small changes in motor nerve conduction velocities were observed but their meaning was questioned. Positive changes in nerve biochemistry and sural nerve morphology were observed in subjects treated with tolrestat in long-term, uncontrolled studies,\textsuperscript{30} but sural nerve parameters did not show sufficient change during the pivotal 12 month trials to establish therapeutic efficacy. Different research definitions of DPN emerged\textsuperscript{31} and modified requirements to prove therapeutic value. Longer study intervals may well have demonstrated true therapeutic benefits with this compound but development was halted due to the potential hepatic toxicity. Also, the degree of inhibition of the aldose reductase enzyme by tolrestat may not have reached levels now considered necessary to have the necessary effects in animal and human nerves.\textsuperscript{32}

FK-366 showed great promise in a phase 2 study in which both morphometry and electrophysiology showed benefits after 12 months of ARI intervention.\textsuperscript{33} Large-scale phase 3 trials of two years of treatment in the pivotal North American study (assessing endpoints of NCS and VPT) and five years of treatment in the foot ulcer prevention trial were terminated only recently in late 2000 due to unexpected dose-dependent elevations in creatinine levels in those on zenarestat. Clearly an agent having the potential to cause nephrotoxicity cannot be used to treat the complication of DPN since these patients are prone to develop nephropathy related to their diabetes and DPN will require chronic therapy. This drug showed 85-90% aldose reductase inhibition and a positive effect on the electrophysiological parameters at the time of termination, similar to those changes previously seen in the phase 2 study.

Zopolrestat is another ARI whose development was halted in 1999. The interim analysis of sural nerve fiber density after 18 months of treatment in a planned three year intervention program failed to demonstrate sufficient efficacy in this morphological parameter, one of two primary efficacy end-points. Although electrophysiology was also being measured, a single parameter is insufficient to demonstrate efficacy in any pivotal study in DPN. Although the phase 2 study was successful, the dose used was twice that used in the phase 3 study and likely accounts for the different results observed. One may speculate that the level of inhibition of nerve aldose reductase was weaker than expected with the lower dose, and hence insufficient to produce the hoped-for results in the phase 3 studies.\textsuperscript{32}

Epalrestat, another ARI, is available in Japan.\textsuperscript{34,35} However, the studies have not established sufficient efficacy for use in North America. The degree of aldose reductase inhibition may not be as high as currently considered efficacious.

More potent ARIs (fidarestat, IDD-676, AS-3201) are being investigated for efficacy. A phase 2 trial of fidarestat is underway and phase 2 trials of IDD-676 and AS-3201 should start later this year in North America. Whether these agents will prove sufficiently safe and efficacious for long-term treatment of DPN in human subjects remains to be determined.

**Other metabolic interventions**

Another therapeutic intervention which failed was acetyl-l-carnitine, Alcar. Based on results from animal studies, this drug had multiple potential benefits for human nerves including: effects on free fatty acid metabolism, nitric oxide synthase activity, mitochondrial function, membrane phospholipid structure, axonal transport, etc.\textsuperscript{36-39} Preliminary trials were positive. Then an excellent 12 month study which measured NCS and sural nerve morphology from pre- and post-treatment biopsies\textsuperscript{40} was carried out. Unfortunately, no effects on human nerve function and/or structure were observed after 12 months of therapy and further development was halted.

**Neurotrophins**

The roles of neurotrophins in neurological disorders are widespread.\textsuperscript{41} Those directed at peripheral nerve function are promising therapeutic targets for DPN.\textsuperscript{42} Nerve growth factor is particularly attractive, due to its name which implies the ability to stimulate nerves to grow. This agent has selective effects on sensory and autonomic neurons.\textsuperscript{43,44} A phase 2 trial showed surprisingly efficacious in parameters subdued by smaller fibers (pain perception and thermal thresholds) after six months of therapy\textsuperscript{44,45} but the phase 3 study was a resounding failure with the same efficacy parameters and 12 months of therapy.\textsuperscript{46} This is most likely due to the fact that the phase 2 trial was effectively unblinded as, in that trial, the NGF treatment consisted of painful injections compared to injections of a painless placebo. Approximately 90% of the patients and physicians guessed the treatment arm correctly. In the phase 3 trials, the placebo was designed to be uncomfortable, and the observers for the primary end-points (Neuropathy Impairment Score in the lower limbs [NIS-LL]\textsuperscript{47,48} and quantitative thermal thresholds) were kept blinded as to the treatment group for each subject but also all adverse events reported by the patients. Lack of efficacy in the US pivotal trial resulted in termination of the research program worldwide in 1999, including a study on the prevention of foot ulcers with three years of double-blind treatment.

Neurotrophin 3 (NT3) was another promising neurotrophin with selective effects on large nerve fibers. Recently a small six month phase 2 trial was completed but changes in VPT were not observed and further development has been halted, although NT3 did not produce any undue toxicity. Further development is not currently underway (personal communication).

Prosaposin is another neurotrophin occurring naturally in human milk and CSF. A synthetic form, Prosaptide\textsuperscript{59}TX14(A) has shown efficacy in animal models\textsuperscript{49,50} and symptomatic improvements in painful DPN in a phase 2 study (personal communication). Further clinical trials are necessary to confirm the efficacy of this intervention, both for painful symptoms and also for nerve function.
Vascular interventions

Anti-oxidant therapy

Alpha-lipoic acid (thioctic acid) has proved efficacious in phase 2 studies including small numbers of patients. This agent is a potent lipophilic free radical scavenger acting as an antioxidant and improving blood flow.\(^{51}\) It alleviates oxidative stress in diabetic nerve by multiple potential mechanisms as outlined in the review by Ziegler. A three-week intervention trial with intravenous therapy had questionable validity due to the high number of protocol violators withdrawn from study analysis. The results of this trial indicated more benefit with thioctic acid than one would expect even with intensified glycemic control.\(^ {17}\) After one year of intensive treatment of hyperglycemia, no improvements in clinical features, NCS, or quantitative sensory thresholds were observed.\(^ {17}\) These results cause some concern about the dramatic changes reported in the ALADIN study of thioctic acid administered by intravenous infusion daily for three weeks.\(^ {51,52}\) However, the results led to further development including a phase 3 trial of oral treatment (NATHAN Study) in North America and Europe. This four year intervention trial, designed to show slowing of progression of DPN as measured by clinical, electrophysiological and autonomic measures of neuropathy, is underway.\(^ {51}\) The results of another three month intervention trial with intravenous thioctic acid are not yet available.

Blood flow

The protein kinase C (PKC) pathway is activated by hyperglycemia resulting in reduced blood flow.\(^ {53,54}\) Inhibition of this pathway may normalize endoneural blood flow and improve neuropathy. Currently, a 12-month phase 2 study utilizing efficacy parameters of NIS-LL, NCS, and quantitative sensory thresholds is nearing completion. Further development will naturally depend on the outcome of the phase 2 study.

Other vascular interventions have been somewhat disappointing; such as pentoxyphylline, a smooth muscle relaxant, and sabeluzole, a calcium channel blocker, which have proven negative in phase 2 trials.\(^ {55,57}\) Gamma-linolenic acid plays a role in phospholipid structure and microcirculation. \(\omega-6\) essential fatty acid metabolism is altered with abnormal prostanoid synthesis which contributes to impaired nerve perfusion. These findings have led to clinical trials of \(\gamma\)-linolenic acid (GLA)-containing oils.\(^ {17}\) A phase 2 study of 111 patients following NCS and clinical signs showed large deteriorations in placebo patients and improvements in drug-treated subjects;\(^ {58,59}\) again unexpected given the lack of NCS changes in placebo subjects in one year observed in other trials.\(^ {60}\) The study may have been somewhat unbalanced with respect to distribution of patients across sites perhaps contributing to the results reported.

Others

Other prospective neuropathy treatments include stimulation of neurite outgrowth, activation of protective receptors such as with immunophilin ligand treatment and inhibition of abnormal excitatory activity. These interventions will need to be designed specifically for DPN to avoid bystander neurotoxicity with chronic use. None of these interventions is yet ready for phase 3 trials.

Summary of current status of specific therapies for DPN

To date, no specific intervention has proven effective for DPN other than intensive glycemic control. Even with major efforts to achieve optimal glycemic control, neuropathy is unlikely to be reversed. Furthermore, the prevalence of DPN does not drop to zero, as intensive control does not equate with euglycemia in more than 15% of highly motivated young males.\(^ {1}\) The associated cost is an increase in the incidence of serious hypoglycemic episodes. Several major trials of specific anti-neuropathy drugs have failed within the last two years: NGF and zopolrestat due to lack of sufficient efficacy, zanarestat due to unacceptable toxicity. However, newer, more potent ARIs with different toxicity profiles may prove efficacious and sufficiently safe for clinical use. Vascular interventions have been disappointing to date but others such as PKC inhibitors and thioctic acid are being investigated actively. Still, the only valid advice to offer patients currently is to intensify their glycemic control indefinitely to prevent progression. Reversal of neuropathy may be an unrealistic goal.

Clinical trials for DPN: Symptomatic interventions

Many patients with DPN have pain at some time during their neuropathy course. At least 10% of patients with DPN are affected at any one time.\(^ {51}\) The prevalence of painful symptoms in DPN is likely even higher as 34% of patients classified as having DPN, in a Toronto cohort of diabetic patients being screened for neuropathy,\(^ {52}\) reported painful symptoms referable to their neuropathy. A US National Health Interview Survey, published in 1965, reported that 22.5% of patients with diabetes experienced leg pain in the preceding month although it is unclear how many of these subjects had DPN.\(^ {63}\) Thus pain in the lower extremities is a frequent complaint in those with DPN.

These painful symptoms are highly variable in nature, and often debilitating and difficult to control but are amenable to therapy. The painful symptoms are variably described as burning, freezing, tingling, aching, cramping, shooting and electric shock-like. Some authorities advocate different symptomatic interventions based on the nature of the painful complaint.\(^ {64}\) Many patients have a mixture of all types of these painful symptoms and respond in a non-specific manner to interventions.

Many symptomatic interventions are available as shown in Table 2.\(^ {65}\) These are categorized as: analgesics and adjuvant analgesics, the latter drugs developed for other indications primarily but having analgesic potency. The major groups with demonstrated efficacy for DPN are: opioids, anticonvulsants, antiarrhythmics, and antidepressants. Many good clinical trials are available showing efficacy of these interventions in patients with painful DPN.\(^ {66-79}\) The trials are similar in that the response rate is incomplete and only about 60-70% of carefully selected patients achieve at least a moderate (\(\geq 50\%\)) reduction in pain. The response rate in the clinic is predictably lower. Thus expectations need to be realistic in that pain is rarely relieved completely and not every patient responds to intervention.

The therapeutic approach is similar with all symptomatic agents.\(^ {80}\) The dose is started at a low level, and slowly escalated to avoid undue toxicity. The interval between dose escalations
All of the TCA are providing another therapeutic option. The efficacy of TCA has been demonstrated in multiple trials. Of the TCA are helpful including amitriptyline, doxepine, imipramine, desipramine, nortriptyline and clomipramine. All have significant side-effects including orthostatic hypotension, arrhythmia, increased risk of hip fracture in the elderly, somnolence, weight gain, dry mouth, blurry vision, precipitation of acute angle-closure glaucoma, constipation, obstipation, urinary retention and delirium. Their analgesic potency is comparable and the choice of agent often depends on the clinical situation. Failure to respond to one agent should be the signal to try another within the class. Amitriptyline is frequently the first choice of TCA. The suggested starting dose is 10 mg at bedtime, which can be titrated upwards slowly until the patient achieves analgesia, or intolerable side-effects (often about 50-60 mg daily, although some patients achieve doses of 100-150 mg daily).

All antidepressant drugs are not equally effective in the treatment of painful DPN. Trazadone and fluoxetine have proven negative in controlled trials although inconsistent results have been reported.

Recently, venlafaxine has been reported to be efficacious for the treatment of DPN providing another therapeutic option although controlled trials need to be done. The starting dose recommended is 37.5 mg daily and increasing to 75 mg daily. Novel antidepressants are being tested in controlled clinical trials for this therapeutic intervention.

**Anticonvulsants**

The effective drugs in this category are carbamazepine and gabapentin. Carbamazepine may act by binding voltage-dependent sodium channels. By this action, neurons are able to fire at moderate rates but not more rapidly as might be observed in the ictus. Typically, a low starting dose of 100 mg daily and slow upward titration to a dose of 800-1000 mg daily in divided doses are suggested. The side-effects of carbamazepine are limiting and include: headache, drowsiness, ataxia, diplopia, agranulocytosis, hepatotoxicity and Stevens-Johnson Syndrome. Many patients do not tolerate sufficient drug to achieve analgesia.

Gabapentin is a novel anticonvulsant which has been shown in a recent study to have analgesic potency for DPN. The mechanism of action is unknown. It is much better tolerated than carbamazepine or the TCA and often is the drug of first choice for the therapy of painful DPN. Not all formularies allow use of gabapentin for this indication thus barring some patients from the benefits of this therapy. The starting dose of gabapentin is 400 mg once daily, with a slow titration up to 3600 mg daily in divided doses. The common side-effects are drowsiness, ataxia, anergy, facial swelling and dizziness. As typical of other adjuvant analgesics, gabapentin relieved pain in approximately 60% of patients by at least 50%. Strikingly, gabapentin also showed efficacy in multiple secondary end-points measured in the randomized, controlled clinical trial including: reducing sleep interference, improving mood, and improving the patient’s overall sense of well-being.

Other than carbamazepine and gabapentin, the proof for anti-epileptic drugs is limited and none of the other anticonvulsants are suggested for treating painful DPN at this time. Topiramate, another novel anticonvulsant agent, was effective in a preliminary study which was, however, questionably blinded due to mental status changes in the drug group as compared to the placebo group. The results were promising enough to lead to a further, large scale, phase 2/3 trial currently underway in the United States. Adequate therapeutic trials in DPN are not available for any of the other newer anti-epileptic drugs. Pregabalin, which has been shown effective for this indication in a controlled clinical trial, is not yet available.

**Other adjuvant analgesics**

Antiarrhythmics can be used but are problematic given that many of these patients have coronary artery disease and the potential for cardiac arrhythmias which induces reluctance to use mexiletine. Mexiletine, an antiarrhythmic with local anaesthetic properties and similar to lidocaine in structure and activity, blocks voltage-gated sodium channels but the mechanism of action in DPN is unknown. Studies have shown efficacy in relieving painful symptoms in DPN. Topical therapy with local anaesthetics or capsicain are also

---

**Table 2: Symptomatic Therapies for Painful Symptoms of Diabetic Polyneuropathy**

<table>
<thead>
<tr>
<th>Category</th>
<th>Class</th>
<th>Specific Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics</td>
<td>Non-steroidal anti-inflammatory agents, Acetaminophen, Opioids</td>
<td>First line</td>
</tr>
<tr>
<td>Adjuvant Analgesics</td>
<td>Anti-depressants</td>
<td>amitriptyline, doxepine, imipramine, desipramine, nortriptyline, clomipramine</td>
</tr>
<tr>
<td>Adjuvant Analgesics</td>
<td>Anti-arrhythmics</td>
<td>mexiletine, carbamazepine, gabapentin</td>
</tr>
<tr>
<td>Topical agents</td>
<td>Substance Pdeleter</td>
<td>capsaicin</td>
</tr>
<tr>
<td>Specific therapies</td>
<td>Local anaesthetics</td>
<td>lidocaine</td>
</tr>
<tr>
<td></td>
<td>Vasodilators</td>
<td>α-lipoic acid</td>
</tr>
<tr>
<td></td>
<td>Neurotrophins</td>
<td>Prospadite™TX14(A)</td>
</tr>
</tbody>
</table>
options for this challenging disorder.\textsuperscript{90,91} Ca...derivative of hot, red peppers depletes substance P from nerve terminals, and may provide relief in selected patients.

**Opioids**

Finally, some patients benefit from opioid therapy, although chronic intervention with this form of treatment is problematic and many patients fail to respond although remaining on chronic therapy. However, intervention with an appropriate opioid may provide relief without significant adverse effects.\textsuperscript{68,69} Tramadol has proven effective for painful DPN both in short-term and longer studies.\textsuperscript{68,92} Oxycodone is being investigated currently in a double-blind, placebo-controlled trial for this indication. The side-effects are those typical of opiates: nausea, constipation, headaches and somnolence.

**SUMMARY OF CURRENT STATUS OF SYMPTOMATIC THERAPIES FOR PAINFUL SYMPTOMS OF DPN**

In summary, many symptomatic interventions are available to the clinician for intervention in DPN. None are universally effective and all are associated with significant side-effects which must be weighed against potential benefit when prescribed for patients. Few of these agents have undergone direct comparison for efficacy in clinical trials, although statistical manipulation allows an estimate of relative efficacy of different symptomatic interventions.\textsuperscript{18} Novel agents are being investigated. In some patients the pain of DPN subsides after several years as the neuropathy progresses. However, many other patients complain of unremitting, severe pain, and others simply adjust to their symptomatology. The reassurance that symptoms subside as nerves die is hardly rewarding to the physician. In addition, caution is advised when discussing the benefits of improved glycemic control with these patients. Painful symptoms typically develop after about 10 years of hyperglycemia, and improved control will likely need to be maintained for many years prior to producing any significant benefit for patient’s symptoms. Nonetheless, successful control of painful symptoms of DPN can be achieved in many patients.

**REFERENCES**


