Pharmacotherapy of Painful Diabetic Neuropathy

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The scope of this review is to describe the epidemiology, physiology, symptomatology, and treatment of diabetic painful neuropathy, which is a common complication of diabetes with significant morbidity. This article focuses on treatment options. Various clinical trials of several classes of medications (eg, antidepressants, anticonvulsants, and topical medications) and alternative treatments (eg, acupuncture, electrostimulation, magnets) are reviewed. Physicians have a large panel of medications that can be used effectively solely or in combination at their disposal. However, a number of these treatments have significant side effects, which are noted, that limit their use. As the understanding of the pathophysiologic mechanisms of diabetic neuropathy improves, new medications are under investigation, which are reviewed in this article. There is great hope that the future may hold treatments that would prevent nerve damage.

Introduction

Diabetic neuropathy is one of the most common complications of diabetes. It affects the peripheral nervous system in several forms. Peripheral neuropathy can be acute, chronic, asymptomatic, or painful. The chronic distal form (distal symmetrical sensory or sensorimotor peripheral polyneuropathy) is the most frequent and is the focus of this paper. Although maintaining a normoglycemic state is the main prevention of neuropathy, it is often hard to achieve. Treatment of neuropathic symptoms (pain, paresthesia, numbness) is still problematic. Most medications used can have serious side effects. New therapies, which are based on the pathogenesis of diabetic peripheral neuropathy (DPN), target the prevention and treatment of nerve damage.

Epidemiology

Estimates of the prevalence, incidence, mortality, morbidity, natural history, and public health cost vary partly because of the lack of consistent criteria for the diagnosis of neuropathy (clinical or electrophysiologic), the use of different tests to assess its presence, and patients' cohorts. Because of these discrepancies, this review is limited to the largest studies conducted in the Unites States and in Europe.

Pirart [1,2] prospectively observed 4400 patients (mostly elderly patients with noninsulin-dependent diabetes mellitus [NIDDM]) between 1947 and 1973. He found that 7.5% of them had clinical neuropathy symptoms at the time of diagnosis and that this rate increased to 50% after 25 years.

In the Rochester Diabetic Neuropathy Study (RDNS) [3], a population-based, cross-sectional, and longitudinal epidemiologic study (380 patients with insulin-dependent diabetes mellitus [IDDM] and NIDDM who were free of neuropathic symptoms at the time of diagnosis) found a cumulative incidence of 4% 5 years after the diagnosis and 15% after 20 years for diabetic neuropathy; however, the prevalence of symptomatic neuropathy, including pain, paresthesias, orthostasis, and autonomic complaints, was 20%.

The EURODIAB IDDM Complications Study [4] examined 3250 randomly selected patients with IDDM from 31 centers in 16 European countries. The prevalence of DPN was 28%, with no difference in gender. A number of parameters were found to have a significant association with DPN including age, duration of diabetes, and metabolic control. Other studies have reported significant correlations with height, cigarette smoking, retinopathy, and reduced levels of high-density lipoprotein cholesterol [4,5].

Pathophysiology

The pathophysiology of diabetic neuropathy is far from known. In all likelihood, it is multifactorial, with various abnormalities being interactive and, at times, synergistic. Progression of DPN is dynamic, with nerve degeneration and regeneration potentially occurring simultaneously [6–10].

The hyperglycemic state induced by diabetes causes metabolic changes such as intracellular sorbitol accumulation, formation of advanced glucation endproducts (AGE), and oxidative stress, which consequently impairs neuron structure and function. It also damages endothelial cells and the basement membrane of endoneurial vessels, caus-

ing microvascular dysfunction. The resulting hypoxia/ischemia aggravates oxidative stress and nerve injury.

There also is evidence that nerve growth factor plays a role by decreasing the ability of the damaged nerve to regenerate and to defend against oxidative stress. Immune system abnormalities also have been implicated.

Diagnostic Issues

Sensory or sensorimotor neuropathy has an insidious onset. It generally involves the distal legs first and progresses proximally in a relatively symmetric manner.

Dyck [11] at the Mayo Clinic emphasized the importance of categorizing DPN to facilitate clinical practice and epidemiologic studies. The following categories consider the severity of clinical symptoms and of electrophysiologic abnormalities:

1. Stage 0 (no neuropathy): no symptoms and fewer than two abnormalities on testing (nerve conduction, neurologic examination, quantitative nerve testing of muscle strength, threshold of vibration, cooling or warming sensation, or autonomic function)
2. Stage 1 (symptomatic neuropathy): no symptoms and two or more abnormalities of functional testing
3. Stage 2: symptoms of a lesser degree than stage three and two or more functional abnormalities
4. Stage 3 (disabling neuropathy): disabling symptoms and two or more functional abnormalities.

Monitoring for DPN is extremely important in assessing the presence or progression of the disease and taking appropriate actions regarding treatment. It is known that tight control of diabetes and near normal levels of blood glucose can decrease the risks of developing and worsening DPN [12]. It is essential for any physician who is treating patients with diabetes to look for signs of change and to take action by using preventive or therapeutic measures, insisting on more rigorous glycemic control, improved foot care, or remedial pharmacologic intervention.

Diabetic peripheral neuropathy can be assessed clinically and by various tests, such as the nerve conduction study, quantitative sensory testing, and nerve biopsy (for study purposes).

Clinical symptoms

Polyneuropathy affects the limbs in a symmetric stocking or glove-like distribution. Signs often start in the feet as decreased sensation to vibration or temperature. Symptoms may be "positive" or "negative." Patients complain of numbness or pain that can be described as burning, shooting or stabbing, severe aching pain, or, less commonly, tearing, toothache-like, or itching. These symptoms are particularly worse at night. They also may experience dysesthesia and allodynia. "Negative" symptoms include a sense of distal "deadness."

Large-fiber degeneration results in loss of vibration and proprioceptive sensation, leading to sensory ataxia in severe cases. Small-fiber sensory loss results in the loss of temperature and pain sensation.

Ankle jerks are reduced and eventually lost. Motor weakness usually is restricted to foot intrinsics and ankle dorsiflexors.

Any patients who are asymptomatic or who are only minimally symptomatic may still suffer the consequences of this sensory neuropathy (*eg,* foot deformity). It is important to detect such a loss early with a careful physical examination, including vibration detection with a tuning fork, pinprick sensation, cold/warm sensation, 10 g monofilament perception, and strokes by cotton wool (Perkins *et al.* [13] found that 10 g monofilament, superficial pain, and vibration testing by the on-off method that can be used confidently for annual screening of diabetic neuropathy) [13].

Neuropathic pain is very difficult to treat, but its impact on quality of life, daily activities, and work warrants the efforts [14].

Nerve conduction studies

Nerve conduction studies are valid and reproducible measurements of the severity of the neuropathy and can be used to follow the course of DPN. Unfortunately, they do not correlate with clinical symptoms partly because they assess only motor and large sensory fibers.

Depressed conduction velocity usually signifies demyelination, affecting the fastest conducting fibers. Action potential amplitude is a measure of the number of nerve fibers capable of conducting impulses from the stimulating electrodes to the recording sites. It is useful for the assessment of axonal loss and is the most significant electrodiagnostic indicator of diabetic neuropathy, although there appears to be a clear component of conduction slowing [15].

Quantitative sensory testing

Quantitative sensory testing (QST) is non-invasive computer-based, psychophysical method to assess thermal sensations, which are carried by thinly myelinated α-δ fibers and unmyelinated C fibers, and vibration sensation carried by large myelinated α-β fibers. Cold sensation, warm sensation, cold and heat pain thresholds, and vibration sensations are measured. QST can be used to assess diabetic neuropathy when the clinical examination is normal despite neuropathic symptoms (early stage of the disease), to monitor progression of the disease, and to evaluate the response to therapy. This is of greater importance in a neuropathy that is predominantly sensory.

Biopsy

Nerve biopsies are characterized by fiber loss and atrophy of myelinated and unmyelinated fibers, degeneration and regeneration of fibers, specific fiber lesions (*eg,* axo-glial

dysjunction), swelling of the node of Ranvier, perinodal demyelination followed by remyelination, and microvascular abnormalities (basement membrane thickening, endothelial cell proliferation, vessels occlusion). The small C-fibers seem to be more susceptible to damage than the large fibers, and dysfunction of these small C-fibers is a typical early sign of neuropathy. In practice, biopsy is not needed often; it is reserved mostly for study purpose.

Skin biopsy employs punch biopsy or blister specimen to evaluate the density and morphology of epidermal nerve fibers. This technique has proven to be useful in the evaluation of the involvement of small fibers in neuropathies, including DPN, especially in the early stages. Because this technique is minimally invasive and uncomfortable, it has the potential for use in following progression over time or response to therapy.

Therapy

Pharmacotherapy of DPN can be divided in two goals: the relief of pain and unpleasant symptoms and the treatment of the nerve damage. Available medications for DPN are symptomatic and should be managed to achieve a balance between relief and side effects (the most limiting factor).

Symptomatic therapy

Tricyclic antidepressants

Amitriptyline and nortriptyline have been studied and used as a first-line therapy for neuropathic pain for approximately 30 years. They inhibit the reuptake of serotonin and norepinephrine, thus prolonging the inhibitory action of these neurotransmitters in the brain stem and spinal cord neurons involved in transmitting pain.

Amitriptyline is more effective than active placebo (benztropine used to mimic the anticholinergic side effects of the tricyclic antidepressants [TCAs] and diazepam to mimic the sedation caused by amitriptyline) for patients with DPN with or without depression after 3 weeks of treatment at a dose varying from 25 to 150 mg daily at bedtime [16]. Patients who could tolerate 150 mg of amitriptyline experienced the most pain relief. Max *et al.* [17] also compared the efficacy of desipramine and amitriptyline with placebo and found that they were more effective than placebo and that the efficacy of amitriptyline was superior to desipramine. Studies have also demonstrated that amitriptyline is effective for steady (*eg*, burning, cold) and lancinating pain.

Desipramine and maprotiline are relatively specific blockers of norepinephrine reuptake. They have been studied as alternative treatments to amitriptyline with fewer side effects. They also have studied so that the relative analgesic effects of serotoninergic or noradrenergic blockade could be understood. Desipramine, which does not block serotonin reuptake, was found to reduce pain significantly in DPN and to be as effective as amitriptyline in patients with DPN who are depressed and nondepressed [18]. In a study of 33 diabetic and nondiabetic patients involved in a trial of amitriptyline versus maprotiline, both agents were effective in relieving the pain, but the efficacy of amitriptyline was superior [19]. These results imply that the analgesic action of TCAs may be mediated by blockade of norepinephrine reuptake, with apparent synergy when accompanied by serotonin reuptake inhibition. This hypothesis is supported by the fact that fluoxetine (a serotonin selective reuptake inhibitor) has no effect on neuropathic pain [17].

Imipramine also was proven to be more effective than diazepam and placebo in the treatment of neuropathic pain [20,21].

The most common side effects of TCAs result from anticholinergic action and include constipation, dry mouth, blurred vision, cognitive changes, tachycardia, orthostatic hypotension, dizziness, and urinary hesitancy or retention.

Serotonin selective reuptake inhibitors

The use of TCAs may be limited by their side effects (especially sedation and cardiac contraindications). Therefore, more studies were done to assess the efficacy of "new" antidepressants with less sedation and fewer anticholinergic side effects. Fluoxetine was not efficacious in controlled trials of treatment for neuropathic pain [17] (some efficacy was shown in depressed, diabetic patients), although paroxetine showed efficacy for diabetic neuropathy [26].

Serotonin selective reuptake inhibitors are less effective than TCAs, but can be an alternative treatment for patients who do not tolerate the side effects of the heterocyclic agents.

Other antidepressants

Semenchuck *et al.* [27] studied the efficacy of buproprion SR and found significant improvement in pain and quality of life compared with placebo. Venlafaxine, a norepinephrine reuptake inhibitor, also was found to be effective [28,29], but a limited number of studies have been performed using these agents.

Anticonvulsants

Advances in the understanding of the pathophysiology of DPN have led to the conclusion that abnormal firing is a principle cause of neuropathic pain. Spontaneous activity of primary afferents neurons was found in diabetic rats and in the dorsal horn of rats with experimental peripheral neuropathy. Excitatory amino acids, such as glutamate, can play a key role in dorsal horn spinal hyperexcitability by acting as an *N*-methyl-D-aspartate receptor.

Carbamazepine

Carbamazepine decreases conductance in Na+ channels and inhibits ectopic discharges. It was found to be effective in a 6-week trial of 30 patients with diabetes, with 63% experiencing moderate to complete relief, compared with 20% of patients who were administered placebo [30]. Its

major side effects were vertigo, double/blurred vision, gastrointestinal upset/diarrhea, and cognitive impairment.

Phenytoin

Phenytoin also decreases sodium conductance. Saudek *et al.* [31] found no significant effect compared with placebo. One year later, Chadda and Mathur [32] extended the period of the study to 5 weeks and found that 74% of the patients had moderate to complete relief versus 26% who were administered placebo. In general, phenytoin is thought to be less effective than some of the other anticonvulsant medication.

Side effects of phenytoin are ataxia, gingival hyperplasia, and somnolence.

Gabapentin

Gabapentin is a relatively new anticonvulsant medication that has been used with increasing frequency for the relief of neuropathic pain. Many clinicians consider it to be a first choice of therapy. Its mechanism of action is still unclear, but it seems that gabapentin increases brain γ-aminobutyric acid (GABA) release without interacting with GABA receptors. It reinforces inhibitory controls that modulate the transmission of pain signal. Alternatively, it may reduce the synthesis of glutamate.

An early clinical trial by Gorson *et al.* [33] in 1998 involved a prospective trial that included 40 patients. They found that gabapentin was likely ineffective or only minimally effective at a dosage of 900 mg/d.

Backonja *et al.* [34] demonstrated significant efficacy in a multicenter study of 165 patients with type 1 and 2 diabetes (84 patients received gabapentin and 81 received placebo). Gabapentin, titrated at a dosage ranging from 900 to 3600 mg/d, significantly decreased the mean pain score and improved the profiles of mood states and quality of life (Short Form 36 Quality of Life Questionnaire and Profile of Mood States). Gabapentin appeared to be well tolerated, with 67% of the patients achieving the maximum dosage of 3600 mg/d.

The efficacy of gabapentin appears to be comparable with amitriptyline. In a double-blind study comparing gabapentin (titrated from 900 to 1800 mg) with amitriptyline (titrated from 25 to 75 mg/d), with a wash-out period of 1 week before cross-over, moderate or greater pain relief was experienced in 52% of the patients administered gabapentin and 67% administered amitriptyline. There were no significant period or carry-over effects [35].

Side effects are mild, but include somnolence, dizziness, headache, and diarrhea, making gabapentin a relatively well-tolerated medication.

Lamotrigine

More recently, the antiepileptic drug lamotrigine has been studied. It has at least two potential antinociceptive properties: it stabilizes the neural membrane through blocking activation of voltage-sensitive sodium channels and it inhibits the presynaptic release of glutamate.

In an open-label study and in a double-blind, placebo-controlled trial, Eisenberg *et al.* [36,37] showed that lamotrigine attenuates the pain of DPN at a daily dosage of 200 to 400 mg, and has a significantly superior analgesic effect compared with placebo. It also significantly reduced the intensity of spontaneous pain and cold allodynia. Comparing the magnitude of pain relief found in different studies for gabapentin and tramadol, they concluded that lamotrigine was equally effective.

In a larger-scale controlled study that was not limited to diabetic neuropathy, McCleane [38] did not find any efficacy when a daily dosage of 200 mg was administered. These results suggest that further investigation of lamotrigine, especially in diabetic neuropathy, is warranted.

Topiramate

Topiramate has in vitro activity against voltage-sensitive sodium, calcium channels, and GABAergic and antiglutamatergic properties. It was found to relieve pain in a double-blind, placebo-controlled study [39] and to be as effective as amitriptyline with less sedation [40]. Further studies are in progress. Side effects were asthenia, weight loss, and confusion.

Other treatments

Opioids

Opioids are used infrequently for diabetic painful neuropathy because of their side effects and risks of physical dependence, tolerance, and abuse potential. It had long been thought that opiates were ineffective in neuropathic pain; however, that dogma is being reconsidered. Several studies in the treatment of postherpetic neuralgia (PHN) have been conducted. It has been found that codeine was ineffective [41] and oxycodone [42] and intravenous morphine [43] were "modestly," but significantly effective (compared with placebo). Recently, a randomized, placebo-controlled trial of opioids versus TCAs for patients with PHN found that the two medications were equally effective [44].

However, more studies of the use of opioids are needed. Little is known about the long-term use of opiates; the risks and benefits need to be assessed.

Tramadol

The mechanisms of action of tramadol are related to its antidepressant activity (inhibition of reuptake of synaptic norepinephrine and serotonin) and opioid activity (low-affinity binding of μ-opioid receptors). Development of tolerance and dependence are uncommon. Tramadol can be an alternative to strong opioids. Harati *et al.* [45] found that tramadol relieved pain significantly in 65 patients compared with placebo. It seems to also relieve paresthesias and touch-evoked pain in patients with chronic painful neuropathy [46]. In an open-label follow-up study, tramadol was found to be effective in maintaining pain relief [47•]. Tramadol was well tolerated and 72.6% of

patients who entered the study completed the full 6 months; 11.3% of the patients discontinued the study because of intolerable side effects (nausea, constipation, and headache).

Lidocaine and analogs

Lidocaine is an anesthetic that has been tried in various pharmacologic forms. Intravenous administration has been found to alleviate diabetic neuropathy [48]. Oral administration of the lidocaine analog mexiletine, an antiarrhythmic medication, also has been investigated. In a small study of 19 patients, a reduction of pain during the mexiletine phase, but not the placebo phase, was found [49]. In a larger study, Stracke *et al.* [50] followed 95 patients treated with three different dosages of mexiletine. A global assessment of the Visual Analogue Scale among patients showed no differences between mexiletine and placebo; however, closer evaluation of the results of this study showed substantial advantages of mexiletine for stabbing or burning pain, heat sensation, or formication (as evaluated on the McGill scale). A medium dosage of 450 mg/d seemed to be appropriate; an increase in this dosage did not correlate with a better efficacy. In another study, 216 insulin-treated diabetic patients were observed during 3 weeks and administered three different dosages of mexiletine; pain level and sleep quality also were assessed [52]. A significant reduction in sleep disturbances and pain during the night was observed in the group of patients who were taking the highest dosage (675 mg/d) of mexiletine.

The topical form (Lidoderm patch, Endo Pharmaceuticals, Chadds Ford, PA) has been found to be effective in a double-blind, placebo-controlled trial in the treatment of PHN [53]. An open-label trial showed improvement in pain and quality of life of 30 diabetic patients after 3 weeks [54]. Patients did not need to discontinue prior concomitant medication. Further placebo-controlled studies will be needed to assess the efficacy of the topical form, but this can be an alternative or complement treatment for DPN when focal areas of significant discomfort can be identified. Side effects are mild, but include burning sensation and erythema at the site of application.

Capsaicin

Endogenous neurotransmitters, especially substance P, are important mediators of nociception in the peripheral nervous system. Capsaicin is known to deplete substance P from the terminals and central connections of type C fibers. Subsequent depletion of stored substance P is then considered to impair the transmission of impulses signaling pain to central pathways.

Anecdotal use [56] and efficacy of the capsaicin cream lead to controlled trials. The Capsaicin Study Group conducted a multicenter study [57,58] involving 277 patients who were applying capsaicin cream 0.075% or placebo 4 times daily during 8 weeks; 69.5% versus 53.4% of patients experienced a decrease in pain intensity, respectively; 58.4% versus 45.3%, respectively, noted improvement of pain relief. Biesbroeck *et al.* [59] compared the efficacy of this topical treatment with amitriptyline, which is a first-line treatment of diabetic painful neuropathy. During this 8-week double-blind study of 235 patients, topical capsaicin and oral amitriptyline produced equal and statistically significant improvement in pain during the course of the study. By the end of week 8, 76% of the patients in each group experienced diminished pain, with a mean reduction in intensity of more than 40%. Improvement in sleeping and walking also were significant.

The most common side effect of capsaicin is a burning sensation that is reported to decrease with continued treatment.

Invasive therapies

Decompressive surgery

The pathophysiology of diabetic neuropathy is unknown, but it is recognized that accumulation of sorbitol can be the cause of functional and structural change, which is associated with endoneural edema. Any swelling in the nerve would make it more vulnerable to localized ischemia at sites that are prone to nerve compression, such as tibial posterior and tarsal in the lower limb and carpal and ulnar in the upper limb.

Pain relief and, to a certain extent, restoration of sensation can be achieved by surgical decompression of the posterior tibial nerve. Several studies reported promising results (50% to 70% of the patients experienced a significant change) [61,62•]. This new surgical technique seems to be safe and effective; however, further investigation is needed.

Pancreas transplantation

Pancreatic transplantation cannot be a treatment per se of DPN, but by restoring a long-lasting normoglycemic state, improvement of electrophysiologic tests (increased amplitude and conduction velocities) occurs shortly after the transplant and continues many years after the surgery [63,64•,65]. Notes have not been made regarding the effects on subjective symptoms (*ie,* pain, numbness, paresthesia).

Alternative therapies

The general public has sought the use of complementary modalities for the treatment of many pain problems [66–72]. In recent years, several studies have been conducted to examine the use of alternative therapies to treat diabetic polyneuropathy symptoms. These modalities often include a variety of interventions such as acupuncture, use of magnet therapy, and laser therapy. Many of these interventions have been studied in Europe and the Far East where complementary therapies are more accepted as mainstream care. For many of these complementary therapies, the studies reflect a reduction in pain; however, the mechanism of action remains unknown. A summary of these studies is provided in Table 1.

Table 1. Complementary therapies with diabetic polyneuropathy

Study	Year	Modality	Type of study	Summary
Abuaisha *et al.* [66]	1998	Acupuncture	Experimental	44 subjects completed the 10-week study (n = 46); 34 patients (77%) improved in symptomatology and secondary symptomatalogy; seven patients (21%) ceased to experience symptoms
Armstrong *et al.* [67]	1997	Pulsed dose TENS	Experimental	Use-subjective burning; pain symptoms decreased significantly at 4 and 8 weeks
Goodnick *et al.* [68]	2000	Acupuncture	Case reports	Three male patients who were administered a combined therapy of nefazodone and six acupuncture sessions; decreases in visual analogue scale and paresthesia were noted for 6 months after intervention
Kalinina *et al.* [69]	1998	Laser therapy	Experimental	n = 20 patients received laser exposure and n = 24 patients were administered conventional therapy; there was a more pronounced restoration of functional state of nerve fibers with the administration of laser therapy
Kumar and Marshall [70]	1997	Amitriptyline vs TENS	Experimental, randomized	n = 26 patients were administered amitriptyline for 4 weeks; n = 23 patients with only partial relief were randomized to a control or an electrotherapy group; 85% of patients experienced symptomatic improvement
Rice *et al.* [71]	2001	Biofeedback for foot ulcers	Experimental, randomized	n= 32; 14 of 16 patients in the experimental group (87.5%) healed vs seven of 16 in the control group (43.8%)
Weintraub [72]	2000	Magnet therapy	Commentary; review of pilot studies (2 studies)	Placebo; randomized-controlled studies indicated a 75% to 90% reduction in dysesthetic and neuropathic pain with the use of magnetic footpads (475G)

TENS—transcutaneous electrical nerve stimulation.

Etiologic treatment

It has been proven that tight control of glucose blood level and early intervention in the course of the disease can prevent the development and worsening of neuropathy. The Diabetes Control and Complications Trial Research Group [12] demonstrated that intensive insulin therapy (three or more daily doses of intermediate and rapidly acting insulin) reduced a patient's risk of developing neuropathy by 60%. The main adverse effect was a two-fold increase in severe hypoglycemia and mild gain weight. For patients with NIDDM, normoglycemia should be sought with the help of diet, exercise, and oral hypoglycemic medication.

As noted previously, a pancreatic transplant also may be considered as a "preventive" treatment. Better understanding of the pathophysiologic mechanisms of DPN has led to trials of new therapies aimed at preventing DPN or ameliorating nerve function. Most of these new agents are unavailable outside of clinical trials. Results in animal studies have been promising, but applications in humans have been disappointing, with occasional improvement of nerve conduction, but not symptoms.

Aldose reductase inhibitors

Hyperglycemia results in an increased activity of the polyol pathway, leading to intracellular accumulation of sorbitol and, consequently, metabolic and structural abnormalities. Animal studies showed than aldose reductase inhibitors (ARIs) could reduce the level of intracellular sorbitol, correct peripheral nerve defects, and improve nerve conduction study results [73]. Most clinical trials focused on the electrophysiologic effects of ARIs, showing that there may be a beneficial effect for patients with DPN (zenerestat [74], fidarestat [75]).

More recent data suggest that ARIs also can significantly improve pain or subjective symptoms (*ie,* numbness, paresthesia, spontaneous pain). Hotta *et al.* [75] found fidarestat to improve nerve conduction velocity and subjective symptoms in a study including 279 diabetic patients. Unfortunately, zenerestat [74], alrestatin [76,77], sorbinil [78], and ponalrestat [79] did not prove to be useful in humans because of their adverse effects and inefficacy.

α Lipoic acid

Oxidative stress plays a major role in the pathophysiology of DPN; therefore, research trials turned to antioxidant

Table 2. Treatments for diabetic polyneuropathy

Medication	Study	Study design	Dosage	Side effects	Results
Zenerestat	Greene *et al.* [74]	Randomized, placebo-controlled, double-blind, multiple-dose; 208 patients were observed	150–699 mg/d	Renal insufficiency	Improvement in nerve conduction velocity slowing and small myelinated nerve fiber loss
Fidarestat	Hotta *et al.* [75]	Double-blind, placebo-controlled; 279 patients were observed	1 mg/d	None	Amerlioration of nerve conduction studies and subjective symptoms
Alrestatin	Handelsman and Turtle [76]	Single-blind, nonrandomized, placebo-crossover; nine patients were observed for 4 months	N/A	Photosensitivity	Subjective benefits were noted, but objective measures of conduction remained unchanged
	Fagius and Jameson [77]	Double-blind, placebo-controlled; 33 patients were observed	N/A	None	Significant difference was noted with the administration of placebo
Sorbinil	Sorbinil Retinopathy Trial Research Group [78]	Placebo-controlled; 497 patients were observed	N/A	None	No evidence of the effect of sorbinil on early clinical signs and symptoms of diabetic neuropathy was shown
Ponalrestat	Ziegler *et al.* [79]	Double-blind, placebo-controlled	600 mg once daily	Not significant	Showed no beneficial effects on symptom electrophysiologic parameters
α Lipoic acid	Ziegler *et al.* [80]	Double-blind, placebo-controlled; 509 patients were observed	600 mg intravenously during 3 weeks; 600 mg orally was then administered for 6 months	None	No significant differences between the administration of α lipoic acid and placebo

agents such as α lipoic acid (thioctic acid). In experimental animal diabetes (rats), this treatment has been shown to prevent nerve dysfunction. Human clinical trials are fairly recent and show some promising results. Ziegler *et al.* [80] conducted a 3-week trial (ALADIN) on 328 patients with NIDDM. After 19 days of intravenous administration of α lipoic acid (ALA) at different doses (ranging from 100 to 1200 mg), they observed a decrease of the total symptom score (Neuropathy Symptom and Disability Scores scales) of 58.6% for 1200 mg of ALA and 63.5% for 600 mg of ALA, compared with placebo (38.4%). No significant adverse reactions were observed.

The oral form of ALA also was assessed for its efficacy by the same authors [81]; 509 patients underwent 3 weeks of intravenous treatment of 600 mg of ALA or placebo, followed by oral treatment of 600 mg of ALA or placebo three times daily for 6 months. After 7 months, the Total Symptom Score for neuropathic symptoms (pain, burning, paresthesia, and numbness) was not significantly different than baseline. Further clinical trials are underway to assess the efficacy of oral ALA.

A complete list of etiologic treatments is offered in Table 2.

Conclusions

Diabetic painful neuropathy continues to be a therapeutic challenge for the physician. TCAs and anticonvulsant medications are the mainstay of treatment. Unfortunately, side effects are limiting and different classes of medications often are needed to be used concomitantly, without achieving complete relief.

A physician can only prevent neuropathy through early detection and metabolic control. As we better understand the pathophysiologic mechanisms of neuropathic pain, new medications have been tested and have shown promising results. Ideally, damage of the nerve should be treated or prevented. More research and studies are needed

because none of the medication has gained confirmation by clinical trials in humans.

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