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Diabetic Neuropathy: Mechanisms to Management

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Abstract

Neuropathy is the most common and debilitating complication of diabetes and results in pain, decreased motility, and amputation. Diabetic neuropathy encompasses a variety of forms whose impact ranges from discomfort to death. Hyperglycemia induces oxidative stress in diabetic neurons and results in activation of multiple biochemical pathways. These activated pathways are a major source of damage and are potential therapeutic targets in diabetic neuropathy. Though therapies are available to alleviate the symptoms of diabetic neuropathy, few options are available to eliminate the root causes. The immense physical, psychological, and economic cost of diabetic neuropathy underscores the need for causally targeted therapies. This review covers the pathology, epidemiology, biochemical pathways, and prevention of diabetic neuropathy, as well as discusses current symptomatic and causal therapies and novel approaches to identify therapeutic targets.

1. Introduction

Neuropathy is a common and costly complication of both type 1 (T1DM) and type 2 diabetes (T2DM). The prevalence of neuropathy is estimated to be about 8% in newly diagnosed patients and greater than 50% in patients with longstanding disease (Boulton, 2005). There is increasing evidence that even pre-diabetic conditions are also associated with some forms of neuropathy (Franklin, 1990; Singleton, 2003). An estimated 15% of all patients with diabetes will develop foot ulcers (Gordois, 2003), and diabetic neuropathy is the leading cause of nontraumatic limb amputation (Thomas, 1999). The annual costs of diabetic neuropathy and its associated morbidities in the US have been estimated to exceed \$10.9 billion (Gordois, 2003).

In recent years, considerable progress has been made toward understanding the biochemical mechanisms leading to diabetic neuropathy, and as a result, new treatment modalities are being explored. This review will discuss the epidemiology and impact of diabetic neuropathy and the current understanding of its pathogenesis. This will be followed by a discussion of the diagnosis and evaluation of diabetic neuropathy, and conclude with an examination of current treatment options and anticipated new therapeutic approaches.

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Definition. Diabetic neuropathy is a descriptive term that encompasses a spectrum of clinical and subclinical syndromes with differing anatomical distributions, clinical courses, and possibly differing underlying pathogenetic mechanisms. Each is characterized by diffuse or focal damage to peripheral somatic or autonomic nerve fibers resulting from diabetes mellitus, although indistinguishable syndromes may occur idiopathically or in association with other disorders in nondiabetic individuals. Table 1 lists the most common clinical syndromes comprising diabetic neuropathy.

The syndromes may be grouped under two general headings: diffuse and focal neuropathies. The diffuse neuropathies, i.e., distal symmetrical sensorimotor polyneuropathy (DPN) and diabetic autonomic neuropathy (DAN) are common, usually chronic, and often progressive. The focal neuropathies are less common, usually acute in onset, and often self-limited.

In DPN, sensory deficits usually overshadow motor nerve dysfunction and appear first in the distal portions of the extremities and progress proximally in a “stocking-glove” distribution with increasing duration or severity of diabetes [Figure 1]. The signs and symptoms of DPN vary depending on fiber type involved, with large fiber disease impairing proprioception and light touch. Small fiber disease impairs pain and temperature perception, leading to paresthesias, dysesthesias, and/or neuropathic pain. Distal weakness occurs only in the most severe cases. Diminished or absent deep-tendon reflexes, particularly the Achilles tendon reflex, often indicates mild and otherwise asymptomatic DPN. More advanced asymptomatic neuropathy may first present with late complications such as ulceration or neuroarthropathy (Charcot’s joints) of the foot.

Diabetic autonomic neuropathy (DAN) is the other form of diffuse diabetic neuropathy. DAN often accompanies DPN and, as detailed in Table 2, can impair any sympathetic or parasympathetic autonomic function. Although DAN is highly prevalent and associated with a markedly reduced quality of life and increased mortality, it is among the least recognized and most poorly understood complications of diabetes (Freeman, 2005). Further, many of the clinical symptoms of DAN are common and may be due to causes other than diabetic neuropathy. Therefore, as will be discussed in a subsequent section on diagnosis and treatment, it is important to rule out non-diabetes related etiologies for the specific symptom(s) a diabetic patient is experiencing before making a final diagnosis.

The focal forms of diabetic neuropathy reflect damage to single (mononeuropathy) or multiple peripheral nerves (mononeuropathy multiplex), cranial nerves, regions of the brachial or lumbosacral plexuses (plexopathy), or the nerve roots (radiculopathy). The most common peripheral nerve mononeuropathies, medial and ulnar neuropathy, are essentially indistinguishable from entrapment neuropathies in nondiabetic subjects, suggesting that the diabetic nerve has increased susceptibility to compression. Indeed, carpal tunnel syndrome can be demonstrated electrophysiologically in 20 to 30% of diabetic patients, and presents as a clinically relevant problem in 5 to 10% of patients with diabetes (Dyck, 1993). Except for these mononeuropathies, the focal diabetic neuropathies are relatively uncommon, acute in onset, self-limiting, and tend to occur in older patients. The most common cranial neuropathy affects the third nerve, producing unilateral headache, diplopia, and ptosis with pupillary sparing (diabetic ophthalmoplegia) (Vinik, 2004b). Both lumbosacral plexopathy

and polyradiculopathy, sometimes referred to as diabetic amyotrophy, occur in diabetic patients, particularly elderly males with T2DM. These conditions usually present with pain, particularly of one thigh, involve L2 thru L4 innervated muscles and self resolve over time. Thoracic radiculopathy produces unilateral band like or abdominal pain that may be misdiagnosed as an acute intrathoracic or intra-abdominal emergency.

In summary, DPN and DAN are very common, generally diffuse, and progressive. The focal neuropathies, with the exception of median and ulnar neuropathies, are generally rare, sudden in onset, often self-limited, and tend to occur in older patients. The remainder of this module will focus on DPN and DAN. The reader is referred to a review by Vinik and colleagues for an extensive discussion of the focal neuropathies (Vinik, 2004a).

2. Epidemiology and Impact of Diabetic Neuropathy

Diabetic Polyneuropathy (DPN)

Estimating the prevalence, incidence, and risk of DPN depends on the criteria employed to identify the syndrome. The American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation published a consensus definition in 2005. Important points in the case definition include: 1) the combination of neuropathic symptoms, signs and abnormal electrodiagnostic studies is the strongest predictor of DPN, 2) symptoms alone are a poor predictor of disease, 3) electrodiagnostic studies are not required for the clinical definition of DPN, but are recommended to monitor disease in clinical research protocols (England, 2005). Thus, the definition of DPN may include a symptom score, a focused neurological examination and nerve conduction studies, or, optimally, all of these. Yet, regardless of the diagnostic criteria, it is clear that 1) DPN is highly prevalent in patients with diabetes, 2) its prevalence increases with the duration of diabetes and 3) strict glycemic control reduces the incidence and progression of diabetic neuropathy. Table 3 summarizes several reports on the prevalence of DPN in diabetic patients.

The prevalence of DPN increases with age, and tends to be more common in patients with T2DM than in those with T1DM. Figure 2 illustrates the prevalence of DPN as a function of disease duration and age interval observed in a cross-sectional study of 6,487 patients (~37% with T1DM). In the overall population the prevalence of DPN was significantly higher in patients with T2DM (32.1%) than in T1DM patients (22.7%, $P < 0.001$) and there was a highly-significant correlation between age and prevalence of neuropathy in both T1DM and T2DM (Young, 1993).

Similar rates of DPN were reported in the Rochester Diabetic Neuropathy Study (Dyck, 1993). In 1986, 380 patients were enrolled in this study; 102 (26.8%) had T1DM and 278 (73.2%) had T2DM. Patients were assessed for DPN by sign and symptom scores coupled to physiological assessments of nerve function, including nerve conduction studies and quantitative sensory testing. 54% of patients with T1DM with average disease duration of 14.5 years had DPN, while 45% of T2DM patients with average disease duration of 8.1 years had DPN.

The EURODIAB study examined 3,250 T1DM patients from 16 European countries. DPN was defined as the presence of 2 or more abnormalities in either symptoms, signs, quantitative sensory or autonomic function testing. The prevalence of DPN across Europe was 28%, with a strong correlation between duration of diabetes and level of glycemic control (Tesfaye, 1996).

The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive treatment in patients with T1DM significantly reduced both the incidence (The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group, 1993) and progression (The effect of intensive diabetes therapy on the development and progression of neuropathy. The Diabetes Control and Complications Trial Research Group, 1995) of neuropathy. Figure 3 depicts the prevalence of neuropathy in the primary prevention cohort of the DCCT after 5 years treatment with either a conventional or intensive insulin regimen in the DCCT.

HbA_{1c} levels in the intensive and conventional treatment groups were separated by about 2 percentage points throughout the follow-up (7.2% vs. 9.1%, respectively). Intensive treatment was associated with a 71% risk reduction for confirmed clinical neuropathy (abnormal history, physical examination, or both, confirmed by abnormal nerve conduction or abnormal autonomic function tests), a 54% risk reduction for clinical neuropathy, a 59% risk reduction for abnormal nerve conduction, and a 56% risk reduction for autonomic nervous system dysfunction. This figure also highlights the difference in prevalence estimates related to the stringency of criteria employed, as well as the lower prevalence of autonomic vs. peripheral neuropathy early in the disease.

In the United Kingdom Prospective Diabetes Study, 3,867 newly diagnosed T2DM patients were randomized into either intensive treatment with an oral hypoglycemic agent or insulin or conventional treatment with diet. After 10 years, intensive treatment resulted in approximately 1% lower HbA_{1c} vs. conventional treatment and was associated with a 25% risk reduction in microvascular endpoints (retinopathy, nephropathy and neuropathy) (Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group, 1998). However, most of this reduction was due to fewer patients in the intensive treatment arm requiring retinal photocoagulation compared to patients in the conventional arm. While there was a tendency toward a reduction in death from peripheral vascular disease and the prevalence of amputation, effects on these single endpoints failed to achieve statistical significance. Similarly, surrogate endpoints for neuropathy showed trends toward improvement in the intensive treatment group at year 10 and in a smaller group of patients followed for 15 years, the prevalence of impaired sensory perception in the lower extremities was significantly preserved by intensive versus conventional treatment (31.2% vs. 51.7%, $P = 0.0052$).

Height is another risk factor for DPN, suggesting that longer fibers are more vulnerable to injury. Other suggested risk factors for DPN include smoking (Tesfaye, 1996), excessive

alcohol use (Adler, 1997), hypertension (Forrest, 1997), low plasma insulin levels (Partanen, 1995), and co-morbid diabetic complications (Cohen, 1998).

The most common morbidities related to DPN are recurrent foot infections, ulcers and amputations, and Charcot's joints. It was estimated that upwards of 15% of patients with diabetes will develop at least one foot ulcer (Boulton, 2004b), and one recent study observed an annual incidence of nearly 2% (Ramsey, 1999). While vascular disease and ischemia contribute, it has been reported that 60 to 70% of diabetic foot ulcers are neuropathic in origin (Gonzalez, 2000). A significant proportion of neuropathic diabetic foot ulcers is accompanied by cellulitis or osteomyelitis (about 15%) and these conditions contribute to the annual incidence of lower extremity amputation in patients with diabetes, which has been estimated to be around 0.6% (van Houtum, 2004). In 1999, the attributable cost for a 40- to 65-year old man with a new foot ulcer was estimated to be \$28,000 for the 2 years after diagnosis (Ramsey, 1999) and in 2003, the total annual cost of DPN and its complications in the US was estimated to be between \$4.6 and \$13.7 billion – representing up to 27% of the direct medical cost of diabetes (Gordois, 2003). Furthermore, there are important quality of life issues for patients with DPN including pain and other forms of discomfort, decreased mobility, and a variety of psychosocial impairments (Vileikyte, 2003).

There are relatively few data available regarding the influence of DPN on mortality. However, in their study of diabetic foot ulcers, Ramsey and colleagues found that 3-year survival in patients with foot ulcers was ~ 17% less than in age- and sex-matched diabetic patients (Ramsey, 1999). Further, using a newly-developed accelerated failure time model which included alcohol consumption, proteinuria, race, retinopathy, sex, smoking, type of diabetes, BMI, duration of diabetes, HbA_{1c}, and “toescore” (an age-adjusted transformation of vibration perception threshold), it was found that toescore was the most significant contributor to mortality (Coppini, 2000). Thus, it is clear that DPN exacts an enormous toll.

Diabetic Autonomic Neuropathy (DAN)

Despite its negative impact on survival and quality of life in persons with diabetes, DAN remains poorly understood. Since all organs receive input from the autonomic nervous system (ANS), DAN can affect every body system. Most organs are dually innervated, receiving fibers from the parasympathetic and the sympathetic branches of the ANS. Because the vagus nerve (parasympathetic), the longest autonomic nerve, mediates approximately 75% of all parasympathetic activity (Low, 2004) and neuropathy is seen first in the longest fibers, the earliest manifestations of DAN tend to be parasympathetic and are usually widespread.

Although clinical symptoms of DAN may not appear until long after diabetes onset, subclinical neuropathy may be detected within a year of diagnosis in T2DM and two years of diagnosis in T1DM (Pfeifer, 1984). Such findings highlight the importance of screening for DAN. As for DPN, the reported prevalence varies greatly depending on the criteria used to identify DAN as well as the population studied. These range from as low as 2.5% of the primary prevention cohort in the DCCT (retinopathy and microalbuminuria-free patients with T1DM of 1 to 5 years duration) (The effect of intensive diabetes therapy on the

development and progression of neuropathy. The Diabetes Control and Complications Trial Research Group, 1995) to as high as 90% of patients with long-standing T1DM who were potential candidates for a pancreas transplant (Kennedy, 1995).

In 1988 the San Antonio Conference on Diabetic Neuropathy provided guidelines for standardized objective measurements of neuropathy based on clinical symptoms, clinical examination, electrodiagnostic studies (EDX), quantitative sensory testing (QST), and autonomic function testing for use in clinical research studies. It was further recommended that these measures be standardized to a normative control population (Asbury, 1988), and since that time, several studies have assessed the prevalence of DAN in defined populations. Like DPN, the diagnosis of DAN depends on specific clinical and physiological assessments. Most commonly, changes in heart rate with deep breathing, position change (lying to standing), and breathing out against pressure (Valsalva ratio) are measured in each patient. EKG leads are applied to the chest and the EKG recorded briefly while the patient inhales and exhales slowly and regularly 6 times per minute (E/I ratio, normal value 1.04), stands (30:15 ratio, normal value 1.08), or blows out against a closed tube (Valsalva ratio, normal value 1.26). Thus while DAN can involve many body systems, the cardiovascular system is most commonly tested, and frequently measures of DAN are, in reality, measures of cardiac autonomic neuropathy. In a community-based study, the overall prevalence of DAN assessed by heart rate variability was 16.7%, being somewhat more common in patients with T1DM (20.9%) than in those with T2DM (15.8%). Symptomatic DAN was much less common (2.5%) than that detected by autonomic function tests, but was significantly more frequent in patients with T1DM (5/43, 11.6%) than in patients with T2DM (1/202, 0.5%).

In a larger study (647 patients with T1DM, 524 patients with T2DM), Ziegler and colleagues defined DAN as an abnormality of 2 of 6 autonomic function tests. In addition to the 3 more standard tests discussed above, a spectral analysis of the EKG in the low- and mid-frequency bands and a vector analysis of deep breathing were performed to complete the battery of autonomic function tests. The investigators found that 25.3% of patients with T1DM and 34.3% of those with T2DM had abnormal findings in 2 of 6 autonomic function tests. If more restrictive criteria were used for diagnosis (3 of 6 abnormal autonomic function tests), the prevalence of autonomic neuropathy was 16.8% and 22.1% for patients with T1DM and T2DM (Ziegler, 1993). In another study of 110 children and adolescents with T1DM, abnormality of one or more of the 3 standard autonomic function tests was found in 42.7% of patients (Verrotti, 1995). In summary, DAN is a common form of neuropathy in diabetic patients. There is no convincing evidence for a difference in prevalence between T1DM and T2DM, but similar to DPN, the prevalence is highly dependent on the criteria used to define DAN.

Similar to DPN, the risk of DAN increases with inadequate glycemic control and with disease duration. For example, in the Appropriate Blood pressure Control in Diabetes trial, assessment of DAN was made in 869 patients with T2DM after washout of previous antihypertensive treatment. Stepwise logistic regression analysis of potential risk factors revealed that HbA_{1c} and duration of diabetes were independently associated with DAN (Cohen, 1998). The Diabetic Cardiovascular Autonomic Neuropathy study examined the

potential clinical correlates of cardiac autonomic neuropathy in 647 patients with T1DM and in 524 patients with T2DM. Stepwise regression analysis showed a significant association of cardiac autonomic neuropathy and HbA_{1c} in patients with T1DM, but not in those with T2DM (Ziegler, 1993). Other risk factors or significant correlates of DAN that have been reported include hypertension, female gender, LDL-cholesterol, HDL-cholesterol in patients with T1DM (Maser, 1990), retinopathy, DPN in patients with T1DM or T2DM (Ziegler, 1993), and albuminuria in patients with T2DM (Cohen, 1998).

Due to the importance of the autonomic nervous system in regulating virtually every body function, the consequences of DAN are many and varied, ranging from bothersome, to debilitating, to deadly. Cardiac autonomic neuropathy (CAN) is the most clinically important manifestation of DAN due to its association with several negative outcomes, including increased mortality. Early markers of CAN include resting tachycardia and loss of heart rate variation during deep breathing, whereas loss of heart rate response to mild exercise is indicative of nearly complete cardiac denervation. Impaired parasympathetic function causes loss of bradycardic responses to sleep and to deep inspiration. Impaired sympathetic function, which generally occurs as the syndrome progresses, can increase cardiac adrenergic sensitivity, which may predispose a patient to tachycardia and sudden death. A prolonged corrected QT interval (QTc) indicates an imbalance between right and left sympathetic innervation may increase risk for arrhythmias. Other common and potentially dangerous manifestations of cardiac autonomic neuropathy include exercise intolerance, orthostatic hypotension, and intraoperative cardiovascular lability (Vinik, 2003).

Another important syndrome associated with CAN is silent myocardial ischemia or “cardiac denervation syndrome.” Reduced appreciation of ischemic pain can impair timely recognition of myocardial ischemia or infarction and delay appropriate treatment. Many studies have compared the prevalence of silent myocardial ischemia, usually measured by exercise stress testing, in diabetic patients with and without CAN. Collectively these studies show cardiac autonomic neuropathy greatly increases the risk of silent myocardial ischemia. Conclusions from a large body of literature on cardiac autonomic neuropathy and various other diabetic cardiovascular morbidities make it abundantly clear that the presence of CAN greatly increases the risk of all-cause mortality, cardiovascular mortality, and major cardiovascular events, with relative risks ranging from 2 to > 4 (Freeman, 2005). There is also often an association between CAN and diabetic nephropathy, suggesting other co-morbidities likely contribute to the increased cardiovascular risk (Maser, 2003).

The most devastating outcome of DAN is the excess mortality associated with CAN. Many studies have explored the potential contribution of CAN to total mortality in patients with diabetes – both T1DM and T2DM. Of 15 studies included in a meta-analysis by Maser and colleagues (Maser, 2003), 14 reported increased mortality rates in patients with CAN; in those studies the risk ratio for all cause mortality in patients with CAN vs. those without CAN at baseline (follow-up = 0.5 to 16 years) ranged from 2.1 (Sawicki, 1996) to 9.2 (Jermendy, 1991). A statistically significant increase in mortality was reported in 12 of the studies.

As a whole there was a strong and consistent association between CAN and increased risk of mortality, however the association was much stronger ($RR = 3.45$, $P < 0.001$) in 10 studies where CAN was identified using 2 or more autonomic function tests than in studies that used a single test ($RR = 1.20$, $P = 0.03$). This difference could reflect the presence of more severe autonomic dysfunction in patients with CAN identified with multiple tests or a higher prevalence of co-morbid conditions. Alternatively, use of a single abnormal autonomic function test to identify CAN could allow a higher frequency of misclassification. Nonetheless, it may be concluded that CAN greatly increases the risk of mortality. Although symptoms of CAN may not appear until relatively late in disease progression, autonomic neuropathy has a profound impact, and regular screening for CAN in all patients with diabetes is advisable.

Gastrointestinal manifestations of DAN are diverse and can affect any portion of the gastrointestinal tract. Esophageal dysfunction resulting from vagal neuropathy may cause heartburn and dysphagia for solids (Freeman, 2005). Delayed gastric emptying (gastroparesis) was reported to occur in approximately 50% of patients with longstanding diabetes (Kong, 1999). Although diabetic gastroparesis is usually relatively benign, severe cases may cause nausea, vomiting, epigastric discomfort, and bloating which can last for extended periods or occur in cycles. Diarrhea, with or without intermittent constipation, is another common and often debilitating symptom of DAN (Low, 2004).

Genitourinary manifestations of DAN can include increased or decreased urinary frequency, bladder over distention, and urine retention or overflow incontinence. Patients with bladder dysfunction are predisposed to developing urinary tract infections, which may accelerate or exacerbate renal failure. Erectile dysfunction and retrograde ejaculation in men and decreased libido and decreased vaginal lubrication in women are also common and early findings in patients with DAN (Freeman, 2005; Low, 2004).

Autonomic sudomotor dysfunction can produce distal anhidrosis with a stocking-glove distribution similar to that of DPN. Although this manifestation of DAN is essentially asymptomatic, it can predispose a patient to heatstroke and hyperthermia and may produce a compensatory central hyperhidrosis (Freeman, 2005).

3. Clinical Evaluation of Diabetic Neuropathy

A consensus statement from the San Antonio Conference on Diabetic Neuropathy recommended that the diagnosis and classification of DPN for research and clinical trials be based on at least one standardized measure from each of the following categories: clinical symptoms, clinical examination, EDX, QST, and AFT (Ziegler, 1993). Many currently-used techniques are based on methods developed by Dyck and colleagues at the Mayo Clinic (Dyck, 1992). In the absence of neurological symptoms or clinically detectable neurological deficits indicative of a diffuse or focal neuropathy, subclinical neuropathy can be diagnosed and staged as outlined in Table 4. It is important to note that the diagnosis of subclinical or clinical DPN requires that signs (e.g., abnormal quantitative tests for subclinical neuropathy) and symptoms (for clinical neuropathy) are not attributable to a nondiabetic etiology. Because there are no distinguishing features unique to diabetic neuropathy, all other possible

causes of the observed neuropathic disorders must be ruled out by careful history and physical examination.

A simpler approach may be taken in an outpatient setting. In a recent statement by the American Diabetes Association, DPN is defined as “the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes” (Boulton, 2005). The diagnosis requires a careful history and clinical examination of the feet. Several instruments for this purpose have been developed and validated. One example is the Michigan Neuropathy Screening Instrument (MNSI) (Feldman, 1994), shown in Figure 4. This patient questionnaire consists of 15 questions about sensation, general asthenia, and peripheral vascular disease. A positive response on 7 of the questions is diagnostic of diabetic peripheral neuropathy and correlates well with neuropathy diagnosed by the Mayo Clinic criteria.

The MNSI questionnaire is followed by a simple 8-point clinical examination involving inspection of the foot, assessment of ankle reflexes, and semi quantitative determination of vibration perception (Figure 5). An MNSI score > 2 indicates the presence of neuropathy with a high specificity (~ 95%) and sensitivity (~ 80%) (Bax, 1996).

Patients with an abnormal MNSI score may undergo a more detailed examination such as that summarized by the Michigan Diabetic Neuropathy Score (MDNS), in which the severity of neuropathy is determined through a focused, 46-point neurological examination that includes measures of sensory impairment, muscle strength, and reflexes (Feldman, 1994). Other more complicated techniques to assess warm and cold perception thresholds, current perception thresholds, *etc.* have also been developed for research purposes. These are generally time-consuming and require specialized equipment, and thus are not routinely employed in a clinic setting.

Nerve conduction studies can be used to quantify the degree of nerve injury in DPN (Boulton, 2004c). While not usually required for the diagnosis, nerve conduction studies can help the patient and physician monitor DPN progression over a long period of time, particularly if the patient is asymptomatic. Nerve conduction studies are also useful to identify superimposed mononeuropathies, e.g., carpal tunnel syndrome. These superimposed mononeuropathies are a common problem in patients with DPN.

As for DPN, DAN is usually classified as either subclinical or clinical depending upon the presence of clinical manifestations of autonomic dysfunction. As mentioned previously, the clinical manifestations of DAN can be many and varied, but may not occur until long after DAN can be detected through autonomic function tests. Routinely, five simple, noninvasive cardiovascular reflex tests are used for diagnosis (partly described earlier): Valsalva maneuver, heart rate response to deep breathing, heart rate response to standing up, blood pressure response to standing up, and blood pressure response to sustained handgrip (Freeman, 2005). Abnormalities in these noninvasive tests of cardiovascular function show a strong correlation with symptoms (Low, 2004), and with autonomic dysfunction in other organs including pupillomotor function, gastrointestinal function, and norepinephrine production (Freeman, 2005; Vinik & Mehrabyan, 2004b). However, abnormalities in lower-

extremity sudomotor function and impotence may precede detectable impairment in the simple cardiovascular autonomic function tests (Freeman, 2005; Low, 1986; Vinik & Mehrabyan, 2004b). Table 5 lists several noninvasive tests of cardiovascular autonomic function and diagnostic values for CAN (Freeman, 2005).

Resting tachycardia and loss of heart rate variation in response to breathing or the Valsalva maneuver are primary indicators of parasympathetic dysfunction and are among the earliest signs of CAN. Orthostatic hypotension and loss of blood pressure responses to exercise or handgrip are signs of sympathetic dysfunction and tend to occur later in disease progression. Other more complex tests of cardiovascular autonomic function may be used for research purposes, including spectral analysis of 24-hour heart rate variability, measures of neurovascular flow with Doppler technology, and scintigraphic assessment of cardiovascular sympathetic innervation.

Because many prescription and non-prescription medicines, alcohol, and tobacco can influence autonomic nervous system activity, patients should be tested in an overnight-fasted state, having refrained from alcohol and tobacco for 24 hours, and they should omit even prescription drugs on the day of the test. Further, due to the influence of antecedent hypoglycemia on autonomic function (Dagogo-Jack, 1993), patients should not be tested within 24 hours of a hypoglycemic episode. As with DPN, it is important to rule out possible causes of abnormal AFTs other than DAN through patient history and physical examination. Abnormalities in two or more of the simple AFTs suggest a diagnosis of DAN. In a recent statement by the American Diabetes Association, it is recommended that patients with T1DM be tested five years after diagnosis of diabetes and be tested yearly thereafter. Patients with T2DM should be tested at diagnosis and yearly thereafter (Boulton, 2005).

4. Pathogenesis of Diabetic Neuropathy

There may be multiple etiologies which account for the various neuropathic syndromes seen in patients with diabetes. Hyperglycemia clearly plays a key role in the development and progression of diabetic neuropathy as well as the other microvascular complications of diabetes. Understandably, then, investigations into the molecular and biochemical pathophysiology of diabetic neuropathy have focused on glucose metabolic pathways. Over the past 25 years animal experiments and *in vitro* studies have identified biochemical pathways likely to be important in the development of diabetic complications and have led to possible approaches to treatment. All of these pathways are related to the metabolic and/or redox state of the cell. Pathways which are mainly driven by metabolism are: glucose flux through the polyol pathway; the hexosamine pathway; excess/inappropriate activation of protein kinase C (PKC) isoforms; accumulation of advanced glycation end-products. While each pathway may be injurious alone, collectively they cause an imbalance in the mitochondrial redox state of the cell and lead to excess formation of reactive oxygen species (ROS) (Kong, 1999; Vinik, 2003) (Figure 4). Increased oxidative stress within the cell leads to activation of the Poly(ADP-ribose) polymerase (PARP) pathway, which regulates the expression of genes involved in promoting inflammatory reactions and neuronal dysfunction. This section will discuss each of these mechanisms and the central role of ROS. This review will not discuss the proposed mechanisms underlying the focal neuropathies.

The reader is referred to the review by Vinik and colleagues for this discussion (Vinik, 2004a). Proposed mechanisms underlying DPN and DAN which will not be covered in detail include autoimmune mediation. For a thorough review of this topic, please also see Vinik and colleagues (Calcutt, 2008; Vinik & Mehrabyan, 2004b).

Diabetic neuropathy is thought to occur from both hyperglycemia-induced damage to nerve cells *per se* and from neuronal ischemia caused by hyperglycemia-induced decreases in neurovascular flow. Much of the basic science addressing the etiology/mechanisms of microvascular complications has used non-neuronal derived cells or cell lines, but studies in animal models of neuropathy, and/or human clinical studies with specific inhibitors of each pathway suggest that each mechanism can contribute to diabetic neuropathy.

4a. Polyol Pathway

The enzyme aldose reductase (AR) reduces glucose to sorbitol and sorbitol dehydrogenase (SDH) oxidizes sorbitol to fructose (Figure 6). Both of these enzymes are abundantly expressed in tissues prone to diabetic complications. Hyperglycemia activates the aldose reductase pathway primarily by mass action: Increased flux through the AR pathway causes increased intracellular sorbitol, a relative intracellular hypertonic state, and compensatory efflux of other osmolytes such as myo-inositol (MI, important in signal transduction) and taurine (an antioxidant) (Nakamura, 1999; Vincent, 2004b). Since NADPH is consumed by aldose reductase-mediated reduction of glucose to sorbitol (Brownlee, 2005; Jermendy, 1991) and NADPH is required for regeneration of reduced glutathione (GSH), this too contributes to oxidative stress. The second step in the polyol pathway oxidizes sorbitol to fructose via sorbitol dehydrogenase (Feldman, 1997). Formation of fructose promotes glycation as well as depletes NADPH, further augmenting redox imbalance. Activation of aldose reductase may also increase formation of diacylglycerol, which activates the deleterious PKC pathway (discussed below) (Uehara, 2004; Yamagishi, 2003).

4b. Hexosamine Pathway

In the late 1990's, the hexosamine pathway was implicated as an additional factor in the pathology of diabetes-induced oxidative stress and complications. Fructose-6 phosphate is a metabolic intermediate of glycolysis. However, during glucose metabolism some fructose-6-phosphate is shunted from the glycolytic pathway to the hexosamine pathway. Here fructose-6 phosphate is converted to glucosamine-6 phosphate by glutamine fructose-6 phosphate amidotransferase (Thornalley, 2005). Glucosamine-6 phosphate is then converted to uridine diphosphate-N-acetyl glucosamine (UDP-GlcNAc), a molecule that attaches to the serine and threonine residues of transcription factors (Brownlee, 2001). Hyperglycemic conditions create additional flux through the hexosamine pathway, ultimately resulting in excess GlcNAc and abnormal modification of gene expression (Brownlee, 2001; Kolm-Litty, 1998; Sayeski, 1996).

Specifically, hyperglycemic conditions and excess GlcNAc cause increased activation of Sp1, a transcription factor implicated in diabetic complications. Sp1 is responsible for the expression of many glucose-induced "housekeeping" genes including transforming growth factor- β 1 (TGF- β 1) and plasminogen activator inhibitor-1 (PAI-1) (Brownlee, 2001; Du,

2000). Overexpression of TGF- β 1 leads to increased collagen matrix production which promotes endothelial fibrosis and decreases proliferation in mesangial cells (Hirakata, 1996; Kolm-Litty, 1998). Overexpression of PAI-1 promotes vascular smooth muscle cell mitosis which plays a role in atherosclerosis (Sayeski & Kudlow, 1996). PAI-1 is not only upregulated via the hexosamine pathway but also the PKC pathway (Figure 6). Thus, two discrete pathways leading to diabetic complications converge through the same injurious mechanism. It has additionally been shown that GlcNAc impairs β -cell function by inducing oxidative stress; increased glutamine fructose-6 phosphate amidotransferase or glucosamine leads to increased hydrogen peroxide levels and reduced expression of insulin, glucose transporter 2, and glucokinase genes (Kaneto, 2001). Thus, increased flux through the hexosamine pathway has been causally implicated in multiple metabolic derangements in diabetes.

4c. PKC Pathway

The protein kinase C (PKC) pathway is an additional mechanism by which hyperglycemia causes injury in complications-prone tissues. Elevated glucose levels stimulate diacylglycerol (DAG), which in turn activates PKC. Increased production of the PKC β -isoform in particular has been implicated in overexpression of the angiogenic protein vascular endothelial growth factor (VEGF), PAI-1, NF κ B, TGF- β and the development of diabetic complications such as retinopathy, nephropathy, and cardiovascular disease (Figure 6) (Arikawa, 2007; Das Evcimen, 2007; Veves, 2001). Data on the effects of PKC- β and VEGF on diabetic neuropathy are less clear, but generally most support the concept that increased PKC pathway flux plays a roll in neuropathy as well (Arikawa, 2007; Das Evcimen & King, 2007). PKC pathway activation alters vasoconstriction and capillary permeability, and can cause hypoxia, angiogenesis, basement membrane thickening, and endothelial proliferation (Edwards, 1999; Williams, 1997). These changes in neurovascular blood flow are the likely source of PKC's role in neuropathy, though further studies are needed to establish a strong connection. PKC activation also alters function of the Na⁺-K⁺ ATPase pump and other enzymes crucial to proper nerve conduction. Activation of different PKC isoforms has been shown to decrease Na⁺-K⁺ ATPase activity in smooth muscle cells and normalize activity in peripheral nerves (Greene, 1987; Xia, 1995). The link of PKC to diabetic neuropathy is supported by studies in streptozotocin (STZ) induced diabetic rats, where PKC inhibition normalizes both sciatic nerve blood flow and nerve conduction velocity (Nakamura, 1999). Overexpression of PKC isoforms can also directly induce insulin resistance (Cortright, 2000; Naruse, 2006).

4d. AGE Pathway

Non-enzymatic reactions between reducing sugars or oxaldehydes and proteins/lipids result in advanced glycation endproducts (AGEs) (Ahmed, 2005; Toth, 2007). Three main pathways are responsible for the formation of reactive dicarbonyls (AGE precursors): 1) oxidation of glucose to form glyoxal; 2) degradation of Amadori products (fructose-lysine adducts); and 3) aberrant metabolism of glycolytic intermediates to methylglyoxal.

AGEs are heterogeneous modified intracellular and extracellular biomolecules. Inside cells, both protein and DNA adducts alter function and cellular transport. Methylglyoxal, a highly

reactive dicarbonyl, is shown to induce sensitivity to vascular damage in endothelial cells (Yao, 2007). Extracellular protein AGEs include plasma and matrix proteins that disrupt cellular adhesion and activate the receptor for AGEs (RAGE) (Ramasamy, 2007). AGE-RAGE interaction activates the transcription factor nuclear factor kappa B (NF- κ B) (Figure 6). NF- κ B regulates a number of activities including inflammation and apoptosis (Ramasamy, 2005). Activation of neuronal RAGE induces oxidative stress through NADPH oxidase activity (Vincent, 2007). Increased levels of AGE and RAGE are found in human diabetic tissue (Tanji, 2000). Diabetic RAGE knockout mice showed significant improvement in DPN and diminished expression of NF κ B and PKC compared to wild type diabetic model (Toth, 2007). While the NF κ B-PKC decrease in the knockout was present in dorsal root ganglion (DRG) and peripheral nerve, it was most pronounced in supporting Schwann cells. Collectively, the biochemical damage induced by AGEs results in impaired nerve blood flow and diminished neurotrophic support (Wada, 2005).

4e. PARP Pathway

PARP found in Schwann, endothelial cells, and sensory neurons is also implicated in glucotoxicity. PARP is a nuclear enzyme closely associated with oxidative-nitrosative stress: free radicals and oxidants stimulate PARP activation (Figure 6). Recent evidence also suggests that the two act in concert: PARP both causes and is activated by oxidative stress (Obrosova, 2005a). PARP acts by cleaving nicotinamide adenine dinucleotide (NAD⁺) to nicotinamide and ADP-ribose residues attached to nuclear proteins (Southan, 2003). The results of this process include NAD⁺ depletion, changes in gene transcription and expression, increased free radical and oxidant concentration, and diversion of glycolytic intermediates to other pathogenic pathways such as PKC and AGE formation (Du, 2003; Garcia Soriano, 2001; Ha, 2002; Obrosova, 2005a). Such PARP-implicated abnormalities manifest clinically as decreased nerve conduction velocity (NCV), small fiber neuropathy, neurovascular abnormalities, retinopathy, thermal and mechanical hyperalgesia, and tactile allodynia (Ilnytska, 2006; Li, 2005; Obrosova, 2005a; Obrosova, 2004; Pacher, 2002; Zheng, 2004).

4f. Oxidative Stress and Apoptosis

The AGE, polyol, hexosamine, PKC, and PARP pathways all contribute to neuronal damage. Figure 6 illustrates that the AGE and polyol pathways directly alter the redox capacity of the cell either through direct formation of ROS or by depletion of necessary components of glutathione recycling. The hexosamine, PKC, and PARP pathways exhibit damage through expression of inflammation proteins. The progression of diabetic neuropathy in a distal-proximal axon length-dependent manner suggests that damage is initiated in the axon (Leininger, 2006b). Axons are susceptible to hyperglycemic damage both due to their direct access to nerve blood supply and their large population of mitochondria (Mt). Mounting evidence suggests that the hyperglycemic environment coupled with a compromised blood supply overloads the metabolic capacity of the Mt, producing oxidative stress (Brownlee, 2001). This oxidative stress leads to Mt damage followed by axonal degeneration and death.

Mitochondrial damage occurs due to excess formation of ROS and reactive nitrogen species (RNS) (Nishikawa, 2000; Obrosova, 2007; Obrosova, 2005c). ROS, such as superoxide and hydrogen peroxide, are produced under normal conditions through the Mt electron transport chain and are normally removed by cellular detoxification agents such as superoxide dismutase, catalase, and glutathione (Figure 7)(Leininger, 2006b). Hyperglycemia leads to increased Mt activity, raising ROS production in the Mt. Peroxynitrite, the primary RNS, is formed by the reaction of superoxide and nitric oxide (NO). RNS induces a number of cytotoxic effects including protein nitrosylation and activation of PARP (Obrosova, 2005a; Obrosova, 2005b). Excessive ROS/RNS formation eventually overloads the natural antioxidant capacity of the cell, resulting in injuries to lipids, proteins, DNA. This damage ultimately compromises cellular function and integrity. As Mt are the origin of ROS/RNS generation, they are most susceptible to damage. While inhibitors of AR (Obrosova, 2002), PKC activation (The effect of ruboxistaurin on visual loss in patients with moderately severe to very severe nonproliferative diabetic retinopathy: initial results of the Protein Kinase C beta Inhibitor Diabetic Retinopathy Study (PKC-DRS) multicenter randomized clinical trial, 2005), AGE formation (Wada, 2001), and PARP (Ilnytska, 2006) can individually ameliorate hyperglycemia-induced nerve damage in animal models of diabetes, emerging evidence also suggests that these pathways converge to increase cellular oxidative stress (Figure 6). Cellular oxidative stress is further enhanced when excessive glucose leads to overproduction of superoxide as a byproduct of mitochondrial oxidative phosphorylation (Figure 7) (Vincent, 2004a). Overproduction of superoxide also markedly inhibits GAPDH, causing accumulation of upstream glycolytic intermediates. These intermediates further enhance AR, hexosamine, PKC, and AGE production, producing even more cellular injury. Experimental support for this unifying hypothesis derives from studies demonstrating that inhibition of superoxide accumulation by overexpression of superoxide dismutase prevents hyperglycemia-induced increases of AR (Nishikawa, 2000), hexosamine pathway products (Du, 2000), PKC activation, and AGE formation. Thus, there exists a vicious feed forward system in cells prone to diabetic complications, where glucose-activated metabolic pathways converge to produce cellular oxidative stress. Decreased nerve blood flow and ischemia, resulting from the processes described above, further exacerbate tissue injury. In summary, oxidative stress and ROS link the metabolic initiators and physiological mediators implicated in progressive nerve fiber dysfunction, damage, and loss in diabetic neuropathy. The generation of ROS may initiate a feed-forward cycle in which oxidative stress itself impairs anti-oxidative defense mechanisms.

In addition to their role in metabolism, Mt are involved in the determination of cell fate and viability. Oxidative stress not only damages Mt DNA, proteins, and membranes, it also initiates signaling pathways that result in localized mitochondrial destruction called mitoptosis. One pathway essential to mitoptosis, and subsequently apoptosis, involves Mt division via the dynamin related protein 1 (Drp1) (Frank, 2001; Lee, 2004b). Mt normally undergo an equilibrium-driven process of fission and fusion. In times of stress, Drp1 translocates from the cytosol to the Mt so as to increase Mt fission events (Arnoult, 2005). Aberrant Mt fission is associated with mitoptosis and implicated in apoptosis. Increased levels of Drp1 are found *in vitro* and *in vivo* models of diabetic neuropathy (Leininger,

2006a). This implicates Mt fission in diabetic neuropathy and renders Drp1 a potential therapeutic target.

Mt are pivotal components of metabolism, oxidative stress, and programmed cell death/apoptosis (Russell, 1999). As such, neurons in a hyperglycemic environment display signs of both oxidative stress and apoptosis (Russell, 1999). Diabetic models have shown either apoptosis in the cell body or neuroaxonal dystrophy. Some studies have shown an absence of apoptosis in high glucose treated sensory neurons (Cheng, 2003; Gummy, 2008). The current hypothesis that counts for these observations is that *in vivo*, recurrent injury occurs, activating cell death pathways; initially neurons with support from glia are able to undergo successful repair, however eventually cellular defense is overcome by recurrent activation of injury pathways, causing damage to the cell body. Over time, this cycle injures Mt, alters Mt distribution, and initiates axons dying back toward the cell body (Sullivan, 2005; Vincent, 2004b).

4g. Inflammation

Inflammatory agents including C-reactive protein and TNF- α are present in the blood of both T1DM and T2DM (Gomes, 2003; Gonzalez-Clemente, 2005). Higher levels of these proteins correlate with the incidence of neuropathy (Gonzalez-Clemente, 2005). Recent data from the Eurodiab prospective complications study demonstrates a correlation between diabetic neuropathy and plasma levels of hsp 27 (Gruden, 2008). Hsp 27 is a required intermediate in the pathway of TNF- α induction of the inflammatory mediators cyclooxygenase-2 (Cox-2), IL-6, and IL-8. The production of the initiating inflammatory mediators TNF- α and TGF- β results from several of the glucose-induced pathways already outlined (Brownlee, 2005; Vincent & Feldman, 2004a). As illustrated in Fig. 4, when excess glucose is shunted through alternative metabolic pathways such as the fructose-6-phosphate or diacylglycerol, the signaling intermediates and modified transcription factors lead to increases in TGF β and NF κ B (Brownlee, 2001). Similarly, breakdown of glycolytic triose phosphates forms methylglyoxal, an AGE, that covalently modifies transcription factors (Yao, 2007). One specific consequence of these modifications is decreased binding of a repressor of angiotensin II, known as Sp3. Thus, angiotensin II increases and leads to activation of vascular endothelial cells (Yao, 2007). In the endoneurium, this activation leads to inflammatory cell recruitment, local generation of cytokines, and reduced blood flow that leads to further generation of ROS (Coppey, 2006). Other extracellular AGEs that activate RAGE also lead to intracellular inflammatory signaling to upregulate NF- κ B (Toth, 2007).

Cox-2 is an important enzyme that is unregulated by NF- κ B (Lee, 2004a). This upregulation is observed in peripheral nerves and vascular tissues in experimental diabetes (Kellogg, 2005). Cox-2 activity appears to drive a feedforward loop since Cox-2 is upregulated by NF- κ B and in turn it generates prostaglandin E2 and ROS that activate NF- κ B. Pharmacological blockade or gene ablation of Cox-2 prevents diabetes-induced changes in peripheral nerves including depletion of GSH, increases in TNF- α , and blood flow and nerve conduction deficits (Kellogg, 2007; Matsunaga, 2007).

Another inflammatory enzyme regulated by NF- κ B is inducible nitric oxide synthase (iNOS) (Kim, 2008). Like Cox-2, iNOS both induces and is induced by NF- κ B, leading to a vicious cycle of inflammation (Hasnis, 2007; Kim, 2008). The NO generated by iNOS directly modulates the blood supply to nerves and participates in microvascular changes following injury (Levy, 2004; Zochodne, 2005). NO has direct roles in axon and myelin breakdown following an injury and also contributes to the development of neuropathic pain (Levy & Zochodne, 2004; McDonald, 2007). Excessive local levels of NO during inflammation may damage axons and growth cones (Zochodne & Levy, 2005).

All of the inflammatory mechanisms in diabetic neuropathy appear to converge upon the activation of NF- κ B. Because of chronic NF- κ B activation, blood vessels and nerve cells are more susceptible to injury in ischemia reperfusion (Wang, 2006). Subsequent to ischemia-reperfusion there is extensive infiltration of monocyte macrophages and modest infiltration of granulocytes in diabetic peripheral nerves (Wang, 2006). The cytokines induced by NF- κ B in endothelial cells, Schwann cells and neurons also lead to macrophage recruitment in diabetic nerves (Yamagishi, 2008). Macrophages promote diabetic neuropathy through a variety of mechanisms, including production of ROS, cytokines and proteases, which result in myelin breakdown and cellular oxidative damage (Conti, 2002; Kawamura, 2008; Tesch, 2007). Excessive macrophage recruitment likely impairs nerve regeneration in diabetic neuropathy (Conti, 2002; McDonald, 2007).

4h. Growth Factors

Growth factors promote the growth and survival of neurons and direct neurite outgrowth (Leininger, 2004). Given that diabetic neuropathy is characterized by neuronal degeneration and damage to supporting Schwann cells, perturbations in growth factors such as nerve growth factor (NGF), insulin like growth factor (IGF), and neurotrophin 3 (NT3) have been suggested to be involved in the pathogenesis of diabetic neuropathy. These factors bind to heterodimeric tyrosine kinase receptors. The receptors for the NGF family of growth factors consist of the p75NTR and a specific trk tyrosine kinase, which confers ligand specificity (although there is some overlap).

Expression levels of multiple growth factors are altered in animal models of DPN. NGF is the most studied growth factor in diabetic neuropathy. NGF is produced by muscle and keratinocytes, and its trkA receptor is expressed on sensory and sympathetic neurons (Averill, 1995; Fang, 2005; McMahon, 1994; McMahon, 1995). In multiple diabetic models, NGF levels are reduced as well as retrograde transport of NGF diminished (Hellweg, 1994; Kasayama, 1989). Interestingly, when glucose levels are returned to normal levels, NGF levels return to normal. This indicates that diabetes, either due to hyperglycemia or by lack of insulin, has the capacity to regulate growth factors (Hellweg, 1991). Some studies have generated conflicting results with regard to NGF expression levels (Arrieta, 2005; Delcroix, 1998; Delcroix, 1997; Fernyhough, 1994, 1995a; Fernyhough, 1995b; Hellweg, 1990; Hounsom, 1998). Despite these discrepancies, an observed decrease in the retrograde transport of NGF (both endogenous and exogenous) in diabetic rats is noteworthy in that the transport of NGF to the soma is required for its neurotrophic effects to occur (Arrieta, 2005; Fernyhough, 1995b; Hellweg, 1994; Schmidt, 1983; Schmidt, 1985). Similar to NGF, IGF I

& II are down-regulated under diabetic conditions, though administration of insulin restored expression (Migdalís, 1995; Olchovsky, 1991; Wuarin, 1994). NT-3 is expressed in muscle and skin. It can signal through trkA and B to some extent, and primarily signals through trkC, suggesting broad therapeutic potential (Barbacid, 1994; Lewis, 2006; Lindsay, 1996). Like trkB, trkC is found in motor neurons, and a population of large-diameter sensory neurons responsible for proprioception and tactile sensation (Barbacid, 1994; Lindsay, 1996). As with studies of other growth factors, changes in NT-3 expression in diabetes have not been consistently documented. NT-3 proteins levels are upregulated in diabetic sural nerve, though mRNA levels have been reported as both increased and decreased (Cai, 1999; Rodríguez-Pena, 1995).

5. Therapeutic Strategies for Diabetic Neuropathy

5a. Glycemic Control

Therapies for DPN and DAN may be divided into treatments that target the underlying pathogenetic mechanisms (Boulton, 2004a; Singh, 2005; Trotta, 2004) and those aiming to relieve symptoms (Adriaensen, 2005). In the latter category there are numerous established approaches; in the former, the only proven method currently available to prevent DPN and DAN or slow progression is strict glycemic control (Tesfaye, 2005).

5ai. T1DM

DCCT: As discussed previously, the DCCT compared intensive treatment (3 or more insulin injections or insulin pump) aiming to normalize HbA_{1c} with conventional treatment (1 or 2 insulin injections aiming to prevent hyperglycemic symptoms and hypoglycemia) in 1,441 patients with T1DM. After 5 years of follow-up, the prevalence of confirmed clinical neuropathy (defined by history or physical exam and confirmed by either abnormal nerve conduction or 1 autonomic function test) was 64% lower in patients receiving intensive treatment (HbA_{1c} = 7.2%) than in those receiving conventional treatment (HbA_{1c} = 9.1%). Further, nerve conduction velocities remained stable in patients receiving intensive treatment and declined significantly in those assigned conventional treatment (The effect of intensive diabetes therapy on the development and progression of neuropathy. The Diabetes Control and Complications Trial Research Group, 1995). The results of the DCCT agree with a similar study in Europe, the EURODIAB trial (Tesfaye, 1996).

It has been reported that the benefits of tight glycemic control in reducing microvascular complications are more far-reaching than originally determined. The Epidemiology of Diabetes Interventions and Complications (EDIC) study has followed the DCCT cohort for more than 7 years after the termination of the original study. EDIC has shown that despite convergence of mean HbA_{1c} in patients originally randomized to intensive vs. conventional treatment (due to institution of intensive treatment in 75% of the former conventional treatment group and a small proportion of the original intensive treatment group choosing to relax glycemic control), the rate of progression of retinopathy and nephropathy in patients originally randomized to intensive treatment remained significantly below those in the original DCCT conventional treatment arm (Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus, 2002). This benefit was also reported for

neuropathy. At the end of EDIC Year 1, mean HbA_{1c} levels were 7.9% and 8.3% in the former intensive and conventional DCCT arms, respectively. By EDIC Year 5 the HbA_{1c} levels were statistically indistinguishable (8.1 vs. 8.2%, $P = 0.09$). However, there continues to be a slower rate of acquisition and progression of DPN in the patients from the former intensive treatment arm, despite over 8 years of similar control (Martin, 2006).

Continuous Glucose Monitoring: Despite the evidence of the DCCT which suggest that HbA_{1c} levels are strong predictors for diabetic complications, factors other than average blood glucose levels have a profound influence on incidence of diabetic complications. Close examination of the DCCT has indicated that the prognosis of complications may need to go beyond the average blood glucose level as indicated by HbA_{1c} (Brownlee, 2006). Figure 8 shows that when the conventional therapy group of the DCCT was examined, the HbA_{1c} shows a general correlation with incidence of diabetic complications (Hirsch, 2005). In contrast, when the intensive therapy group was examined, HbA_{1c} holds only a slight relation to development of diabetic complications. As the difference between intense therapy and conventional therapy was multiple insulin injections and blood glucose monitoring, intensive therapy cohort patients are considered much less likely to undergo dynamic glycolytic flux. These studies suggest that glycemic *variability* rather than average glycemic control (HbA_{1c}) would be a better target for diminishing the onset and progression of complications.

In vitro studies now show that hyperglycemia-induced superoxide resulting in oxidative stress is the major causal agent of cellular injury. Work by Monnier *et al.* showed no correlation between oxidative stress and 24 h mean glucose concentration, fasting plasma glucose levels or HbA_{1c} (Monnier, 2006). On the other hand there was a direct correlation between oxidative stress and glycemic variability (as determined by mean amplitude of glycemic excursion). These data indicate that glycemic flux and variability lead to oxidative stress.

Glycemic variability is directly correlated to oxidative stress and is likely a better predictor of diabetes complications. Thus, the ability to reduce glycemic variability holds the potential of preventing complications. Until recently, real-time tracking and correction of glycemic flux was unattainable. Continuous glucose monitors (CGM) are now available which measure blood glucose levels every 1–5 min. Glucose self-monitoring is recommended 3 or more times per day. With the implantable CGM, >120 glucose levels per day are registered and stored (FreeStyle Navigator™ Continuous Glucose Monitoring System Use in Children with Type 1 Diabetes using glargine-based multiple daily dose regimens: Results of a Pilot Trial, 2007; Relative accuracy of the BD Logic and FreeStyle blood glucose meters, 2007; Wilson, 2005). Real time data from the CGM allows for the patient to adjust insulin or food intake before either hyper- or hypo-glycemia occurs. As such, glycemic variability may be reduced by modulating therapy (insulin/glucose intake) in response to glucose trends. Implantable CGM sensors are used for between 3 and 7 days. Widespread use of the CGM remains limited at present, likely due to the cost to the patient.

Islet Transplantation: Pancreas transplantations in T1DM patients are now at a sufficient success rate to assess potential therapeutic effects on diabetic complications. Pancreas/islet

transplantation re-established normoglycemia in T1DM patients. Compared to T1DM patients who received only kidney transplants, T1DM patients with successful pancreas transplants (as determined by normoglycemia and insulin independence) showed improvements in motor and sensory nerve conduction and clinical neuropathy (Navarro, 1997). These improvements were seen after 3.5 years for clinical examinations, between 1–5 yrs for sensory nerve conduction and after 10 years for motor nerve conduction. In fact, 50% of islet transplant patients with DPN exhibited stabilization or improvement of their neuropathy (Lee, 2005). Improvements were seen only for DPN and not for DAN.

5a ii. T2DM—Evidence that good glycemic control can delay or prevent progression of diabetic neuropathy in patients with T2DM is more limited. Neuropathy findings from the UKPDS were discussed previously. In brief, although it was clearly shown that intensive treatment significantly reduced the risk of an aggregate endpoint of microvascular complications, and single endpoints of retinal photocoagulation, and cataract extraction, there was only a trend for reduction in the risk of amputation ($P = 0.099$) in the intensively-treated patients (Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group, 1998). There was, however, a significant reduction in the risk of sudden death ($P = 0.047$) in which it is possible that autonomic neuropathy plays a role.

In the feasibility study for the Veterans Administration Cooperative Study on T2DM (VA CSDM), the effects of 2-year intensive treatment on clinical DPN and on DAN was examined in 153 men with T2DM (average duration = 7.8 ± 4 yrs) (Azad, 1999). Intensive treatment (stepwise introduction of multiple insulin injections plus daytime glipizide) achieved a separation in HbA_{1c} between intensive and conventional treatment of 2.1%, with intensively-treated patients at or below 7.3%. The baseline prevalence of clinical DPN was ~ 50% and of abnormal autonomic function tests, was ~ 35%. The prevalence of clinical DPN and abnormal autonomic function tests increased significantly and similarly in the two treatment groups, as did the prevalence of erectile dysfunction. Although there was a nearly-significant decrease in the prevalence of cranial neuropathy and more frequent preservation of touch sensation in the upper extremities in the intensive vs. conventional treatment group, this study provided only minimal evidence that good glycemic control improves neuropathic outcomes in patients with T2DM (Azad, 1999).

In summary, the interventional evidence relating hyperglycemia and neuropathy in patients with T2DM is less overwhelming than that in patients with T1DM. Yet, in view of the strong association between HbA_{1c} and the incidence, prevalence, and progression of neuropathy in all forms of diabetes, aggressive treatment aiming for normalization of both fasting and postprandial glucose levels remains the first and most important step in treating patients with any form of diabetic neuropathy.

There is an uncommon form of neuropathy that may occur in poorly-controlled diabetic patients shortly after instituting aggressive insulin therapy. This acute painful neuropathy has also been described in other situations, particularly in male patients following rapid weight loss (Windebank, 2001). This differs from DPN in that sensory loss is minimal and

weakness does not occur. In the cases arising from rapid weight loss, improving glycemic control and recovery of weight lead to symptomatic improvement, and temporarily relaxing glycemic control leads to symptomatic relief in those cases appearing to arise from instituting aggressive insulin therapy. In this form of neuropathy, complete resolution usually occurs over 6 to 24 months.

Other than strict glycemic control, disease modifying treatments for neuropathy are presently only experimental. Some have progressed to clinical trials and others, based on new findings from work on mechanisms of neuropathy, such as the central role of reactive oxygen species, are in earlier stages of development. These will be discussed at the end of this review.

Symptomatic Treatment of Peripheral Neuropathy. Foot Care: All patients with diabetes should receive at least an annual foot examination to identify high-risk conditions (Association, 2004; Boulton, 2005). Since DPN is one of the most important predictors of foot ulcers and amputation, the importance of preventative foot care in neuropathic patients cannot be overemphasized. Neuropathic patients should undergo a careful foot examination at every office visit and promptly be referred to a foot care specialist whenever necessary. Patient education on proper foot care including shoe selection, nail trimming, and daily foot inspection is essential, and patients with sensory loss should be advised to inspect their shoes three times daily to be sure that no sharp objects are present. Any signs of local infection should be treated by medical and surgical means if necessary (Boulton, 2004a; Singh, 2005).

5b. Symptomatic Therapies

5b1. Diabetic Polyneuropathy—Pain is an early manifestation of diabetic neuropathy and frequently precedes the diagnosis of diabetes (Boulton, 2005; Feldman, 2005). Several recent studies suggest that nearly one third of the patients with impaired glucose tolerance (pre-diabetes) seek medical attention for a pain syndrome identical to DPN (Singleton, 2005; Singleton, 2003). While DPN is a persistent symptom in epidemiological studies of patients with T2DM, it is less common in type 1 diabetes (Barrett, 2007; Clarke, 2002; Currie, 2007). Clinically, DPN includes burning, tingling, electric-like, achy pain beginning in the feet and extending upward over time. Patients with DPN also experience allodynia and hyperalgesia. Allodynia occurs when normally nonpainful stimuli become painful, whereas hyperalgesia is increased sensitivity to normally painful stimuli. DPN is a major factor in decreased quality of life for patients with diabetes (Dworkin, 2007a; Dworkin, 2005; Jensen, 2006a). While estimates vary, approximately half of all patients with diabetic neuropathy of T2DM experience pain, usually at the onset of their disease. Patients with DPN develop insomnia, depression and anxiety, decreased mobility, psychomotor impairment and inability to work (Dworkin, 2007a; Dworkin, 2007b; Dworkin, 2005; Jensen, 2006a; Jensen, 2006b). Over a period of time that could last several years, DPN subsides and the disabling pain is replaced by a complete loss of sensation, leading to the numb, insensate diabetic foot (Feldman E.L., 1999; Feldman, 2005; Feldman, 2002b).

Our lack of understanding of the pathogenesis of this disorder precludes the development of mechanism-specific therapies (Feldman, 2005; Feldman, 2002a). Therefore, currently accepted medical approaches are only partially successful and are often ineffective (Dworkin, 2007a; Dworkin, 2005). These include the use of anti-convulsants, antidepressants, topical agents, and opioid based therapies (Ziegler, 2006) that all have undergone placebo-controlled studies in patients with DPN (Table 10).

Antidepressants

Tricyclic and tetracyclic reagents: The tricyclic and tetracyclic antidepressants (TCA) are considered as the first line treatment for neuropathic pain. These antidepressants control pain and pain related symptoms such as insomnia and depression. The therapeutic actions of these agents are mediated by inhibition of the reuptake of norepinephrine and serotonin. In a study reported by Max et al., amitriptyline (150 mg/day) is superior to placebo in relieving DPN after 6 weeks of treatment (Max, 1992). However, amitriptyline is associated with significant side effects, including dry mouth, sedation, and blurred vision. Desipramine is better tolerated at 111 mg/day and is as effective as amitriptyline in alleviating DPN (Max, 1992). Randomized control trials for imipramine demonstrated that a dose of 50 and 75 mg/day significantly improves DPN (Sindrup, 1989; Sindrup, 1990b; Sindrup, 1999b). In addition, clomipramine relieves the symptoms of DPN (Sindrup, 1990c). Pooling the data from all of these trials suggests that approximately 1 in 3 patients experience at least 50% relief from pain by using these drugs (Collins, 2000). The use of TCA is limited by their side effects (Jann, 2007). Overall, secondary amines (nortriptyline, desipramine) are better tolerated than tertiary amines (amitriptyline, imipramine) (Dworkin, 2007b). TCAs are not well tolerated in older patients. The TCAs should be used with great caution (or avoided altogether) in patients with cardiac arrhythmias, congestive heart failure, orthostatic hypotension, urinary retention, or angle-closure glaucoma (Simmons, 2002). It is important to note that TCAs are contraindicated in patients taking monoamine oxidase (MAO) inhibitors. The usual dosage schedule for TCAs is 10 to 25 mg at bedtime initially, titrating as tolerated up to 100 or 150 mg as a single bedtime dose. In addition, their analgesic effects require several weeks to develop which limits their utility for acute pain (Max, 1987).

Selective Serotonin Reuptake Inhibitors and Serotonin-Norepinephrine Reuptake

Inhibitors: The selective serotonin reuptake inhibitors (SSRIs) are newer antidepressants that have largely replaced TCAs for the treatment of depression because they are better tolerated. However, in contrast to TCAs, the effects of SSRIs are limited in DPN. Fluoxetine, 40 mg/day, is not different from placebo (Max, 1992). In a crossover study with paroxetine and imipramine, significant benefits from paroxetine 40 mg/day are observed (Sindrup, 1990b). The improvement is less than imipramine 50 mg/day but better than placebo. Citalopram 40 mg/day has also been shown to be better than placebo for treating DPN (Sindrup, 1992). However, the numbers of patients involved in most of these studies are small and the trial periods are all short, limiting the interpretation of these data. Pooled data for SSRI treatment of DPN demonstrates no significant difference between SSRIs and placebo (Collins, 2000). In contrast, Tramadol is a weak μ -receptor agonist that inhibits reuptake of serotonin. A double blind, randomized, placebo controlled trial using an average dose of 210 mg/day for 6 weeks produced significantly reduced pain scores in patients with

DPN (Harati, 1998). Nausea, constipation, headache, and dyspepsia were common side effects. Another trial also demonstrated tramadol 200–400 mg/day significantly relieves DPN over placebo (Sindrup, 1999a). Tramadol is well tolerated with only mild side effects. In addition, a combination of tramadol/acetaminophen (37.5/325 mg) when taken as 1–2 tablets four times a day is effective in alleviating DPN (Freeman, 2007).

The serotonin-norepinephrine reuptake inhibitors (SNRI) have greater efficacy against DPN than SSRIs. Duloxetine has been approved by the Food and Drug Administration (FDA) for treating DPN following three large randomized placebo control trials (Goldstein, 2005; Raskin, 2005; Wernicke, 2006). In these trials, duloxetine 60 mg and 120 mg daily provided significant relief from DPN. The higher dose provides greater relief from DPN but is associated with increased side effects. In general, duloxetine is better tolerated, in terms of gastrointestinal and cardiac side effects, than other serotonin-norepinephrine reuptake inhibitors. Venlafaxine 150–225 mg/day alleviates DPN but produces unacceptable cardiac side effects with increased risk of electrocardiographic changes (Rowbotham, 2004).

Anticonvulsants—Anticonvulsants control neuronal excitability by blocking sodium and/or calcium channels (Wiffen, 2005). Originally developed for preventing seizures, they are in broad use for the treatment of neuropathic pain. Phenytoin and carbamazepine primarily block the voltage gated sodium channel. At doses between 200–600 mg/day, both reduce DPN compared to placebo. Due to side effects and newer improved therapies, these compounds are not recommended (Chadda, 1978; Gomez-Perez, 1996; Rull, 1969; Saudek, 1977).

Sodium valproate enhances GABA levels in the central nervous system, inhibits T type calcium channels, and increases potassium inward currents. Again, side effects, including hair loss, weight gain, hepatotoxicity, and cognitive dysfunction are not insignificant and increase with long-term use, although a dose of 500 mg/day decreases DPN (Kochar, 2004).

Lamotrigine is a new anticonvulsant which blocks voltage gated sodium channels, decreases presynaptic calcium currents to inhibit the release of glutamate, and increases GABA levels in the brain. Eisenberg and colleagues reported favorable results of lamotrigine (400 mg/day) against DPN (Eisenberg, 2001). Vinik *et al.* also reported two large scale (n=360) randomized double-blind, placebo-controlled trials. Although there is a reduction on the pain scale in one trial after 19 wk of duration with lamotrigine (400 mg/day), there is no difference between lamotrigine and placebo group at the end of the trial (Vinik, 2007). Lamotrigine is well tolerated but its efficacy against DPN is questionable.

Topiramate has multiple actions: 1) blocking activity-dependent voltage gated sodium channels; 2) inhibiting L-type voltage gated calcium channels; and 3) blocking postsynaptic kainite/ α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) excitatory amino acid receptors. Raskin *et al.* reported a randomized, double-blind, placebo-controlled study which involved 323 patients with DPN (Raskin, 2004). Topiramate 400 mg/day was usually well tolerated and significantly alleviated DPN in approximately 1 out of 6 patients.

Zonisamide blocks both voltage dependent sodium channels and T-type calcium channels. A randomized, double blind, placebo-controlled pilot study of 25 patients with a mean dose of 540 mg/day did not significantly reduce DPN after 6 weeks of titration and maintenance treatment (Atli, 2005). Common side effects were restlessness, GI discomfort, headache, and weight loss.

Oxcarbazepine is a keto-analogue of carbamazepine, which blocks sodium channels. In one study, 1800 mg/day oxcarbazepine significantly reduced DPN (Dogra, 2005), but in a larger study, no significant reduction of DPN was seen with 1200 and 1800mg/ day (Beydoun, 2006). Oxcarbazepine has a good side effect profile and is well tolerated. However, more studies are necessary to clarify its potential for treating DPN.

Calcium Channel $\alpha 2\text{-}\delta$ ligands—Gabapentin is widely used for neuropathic pain due to its effectiveness and relatively fewer side effects than TCA and other anti-convulsants. Gabapentin produces analgesia via binding to the $\alpha 2\text{-}\delta$ site of L-type voltage gated calcium channels and decreasing calcium influx. Gabapentin 2400 mg/day is effective in treating DPN compared to amitriptyline (90 mg/day) according to a randomized control trial of 165 patients (Backonja, 1998; Dallocchio, 2000). However, another study found no difference between gabapentin (900–1800 mg/day) and amitriptyline (25–75 mg/day) (Morello, 1999). Large head-to-head comparison studies are needed to demonstrate the superiority of gabapentin over amitriptyline. Gabapentin is usually well tolerated with slow titration. Common side effects of gabapentin include dizziness, ataxia, sedation, euphoria, ankle edema, and weight gain. Moreover, it usually takes weeks of titration to reach the maximal effective dose (Dworkin, 2007b) and a dosing of 3 per day is often necessary.

Like gabapentin, pregabalin also acts by binding to the $\alpha 2\text{-}\delta$ subunit of calcium channels. As demonstrated in four randomized placebo control trials, pregabalin (300–600 mg/day) is significantly more effective in alleviating DPN than placebo (Freynhagen, 2005; Lesser, 2004; Richter, 2005; Rosenstock, 2004). Unlike gabapentin, pregabalin has better GI absorption and can be administered twice per day. Its linear pharmacokinetics provide a rapid (< two weeks) onset of maximal pain relief (Dworkin, 2007b). However, side effects are similar to Gabapentin with dizziness, ataxia, sedation, euphoria, ankle edema, and weight gain. Among these side effects, weight gain is especially concerning for patients with T2DM. Like duloxetine, pregabalin is approved by FDA for treating DPN.

Mexelitine—Mexelitine is an anti-arrhythmia medication and has been used for treating a variety of painful neuropathic conditions including DPN (Jarvis, 1998). Several randomized placebo control trials have been performed, but none of the studies revealed greater than 50% reduction in pain scores. However, those patients with stabbing or burning pain, heat sensations, or formication benefit most by mexiletine therapy (Stracke, 1992).

Opiates—Slow release oxycodone 20 mg/day relieves DPN over a 6-week period (Gimbel, 2003). In a crossover design treatment strategy, slow release oxycodone was effective against DPN at a maximum dose of 80 mg/day (Watson, 2003). Although opioids are effective against DPN, long term use of opioids will result in side effects including constipation, urinary retention, impaired cognitive function, impaired immune function, and many other

issues associated with tolerance and addiction. Recently, trials used combination of therapies with opioid and Gabapentin has proven there is an additive effect of pain relieve in comparison to individual treatment. Gilron et al tested patients with neuropathic pain from DPN and postherpetic neuralgia using maximal tolerated doses of morphine, Gabapentin or both(Gilron, 2005a). The combinations of drugs achieve higher potency of pain relieve than individual treatment. However, the maximal tolerated dose of each drug is lower in the patient group with combination therapy, suggesting increased side effects with drug combination. The combination pharmatherapy have been used widely in clinical practice but more studies need to be performed to establish safety, compliance and cost-effectiveness and determine optimal drug combinations and dose ratios; comparing concurrent with sequential combination therapy; and combining more than two drugs(Gilron, 2005b).

Non-steroidal anti-inflammatory drugs—Non-steroidal anti-inflammatory drugs (NSAID) are a class of medications that inhibits cyclooxygenases, and thus prevent the formation of prostaglandins. Usually, NSAID are not recommended for the treatment of DPN due to their detrimental effects to GI, renal, and cardiac functions. Risk of overdose is also high in patients with chronic pain. However, a small, single blinded study demonstrated ibuprofen 2400 mg/day and sulindac 400 mg/day significantly reduced the paresthesia scores of DPN at 24 weeks (Cohen, 1987).

N-methyl-d-aspartate receptor antagonists—Two N-methyl-d-aspartate (NMDA) receptor antagonists, dextromethorphan and memantine, have been tested in DPN (Sang, 2002). These placebo controlled cross over studies involve 23 patients with diabetic neuropathy. The studies were designed with a 7-week titration period followed by a 2-week maintenance period for lorazepam, an active placebo, or one of the NMDA inhibitors. Both high and low doses of the inhibitors were assessed. Treatment with dextromethorphan but not memantine produced a significant dose-dependent decrease in DPN. However, the NMDA inhibitors have significant side effects, including sedation, dry mouth, and gastrointestinal distress.

Topical agents—Capsaicin is an extract of capsicum peppers. Capsaicin binds to TRPV1 receptor and exhausts substance P in the peripheral nerves to achieve it analgesic effects. In the study published by the Capsaicin Study Group, 0.075% capsaicin cream applied three times a day for 6 weeks was more effective in alleviating DPN than placebo (The Capsaicin Study, 1992). Burning was the most common side effects which tended to decrease as therapy is continued. The therapeutic effects of capsaicin started weeks after the cream application. Recently, a patch containing high concentrated capsaicin has demonstrated promising effects in treating diabetic pain.

Because impaired NO generation leading to reduced blood flow may be involved in DPN, a small trial using isosorbide dinitrate, an NO donor, was performed. In a 12 week, double blind, placebo controlled, crossover study with 22 patients, isosorbide dinitrate spray significantly relieved DPN (Yuen, 2002). Patients in the trial reported minor headaches and a larger sized study is necessary to evaluate the potential use of this treatment for DPN.

Topical lidocaine 5% patches have been reported by several studies to relieve DPN. In an open labeled study, up to four 5% lidocaine patches applied for up to 18 h/day are well tolerated in patients with painful diabetic polyneuropathy. Lidocaine patches significantly improved pain and quality-of-life ratings, and may allow tapering of concomitant analgesic therapy (Barbano, 2004). Given the open-label design of this trial, a randomized controlled trial is necessary to confirm these results.

Selection of a Drug Regimen for DPN—Recently, the data from most available placebo-controlled trials was used to generate an algorithm and a flow chart (Figure 9) for treating neuropathic pain (Dworkin, 2007b; Stokov, 2000). The consensual first line regimens are TCA, calcium channel α 2- δ ligands, topical lidocaine, and SNRIs. The recommended second line treatments are tramadol and opioids. The third line treatments include anti-epileptics, other antidepressants (SSRIs), NMDA receptor blockers, mexiletine, and topical capsaicin.

Non-drug treatments that have shown efficacy in controlling pain associated with DPN include transcutaneous electrical nerve stimulation (TENS) (Kumar, 1997) and acupuncture (Abuaisha, 1998). There is, however, a notable absence of controlled clinical trials of these treatments. Unfortunately for patients refractory to the stepwise approach to drug treatment as outlined above, the prognosis is poor with many patients requiring long-term care in a pain clinic.

Placebo Effect—Recent work by Tesfaye et al. has elucidated an interesting longlasting placebo phenomenon in DPN (Tefsaye, 2007). Two 1 yr placebo controlled DPN studies of ruboxistaurin were analyzed. After studying the DPN, all of which were characterized as mild for inclusion, progressive improvements in symptoms were demonstrated, whereas nerve conduction studies and heart rate deep breathing worsened over the course of 1 yr. This studying indicates a need to critically develop the timeframe and endpoints of clinical studies for DPN. To establish clinically significant worsening of DPN will require timeframes greater than 1 yr.

5b ii. Diabetic Autonomic Neuropathy—As discussed previously, the first step in the treatment of all forms of diabetic neuropathy is long-term improvement of glycemic control. However, there is little evidence to suggest that even strict glycemic control can reverse DAN, although it is necessary to prevent progression. Since the symptoms of DAN may be manifested in essentially any organ, symptomatic treatment is obviously aimed at the affected organ or body system. It should be reemphasized that a careful history and knowledge of all prescription and non-prescription medications is essential to rule out other causes other than diabetic autonomic neuropathy and identify any concomitant condition(s).

Orthostatic hypotension is notoriously difficult to manage because the standing blood pressure must be raised without causing hypertension when the patient lies down. Options for the treatment of orthostatic hypotension are listed in Table 7. Non-pharmacologic treatment should be the initial approach. To increase venous return, supportive stockings should be worn during the day and removed at bedtime. Patients should be advised to avoid

hot baths, to get out of bed or stand up slowly and if their diabetes is being treated with insulin, patients should administer insulin injections while lying down.

Pharmacologic approaches may also be employed. The mineralocorticoid, fludrocortisone, together with supplementary salt increases plasma volume. Unfortunately, it is generally ineffective until edema develops, which carries a risk of causing congestive heart failure and hypertension (Freeman, 2007). The mixed adrenergic agonist, ephedrine, the α -1 adrenergic agonist, midodrine, and the α -2 adrenergic agonist, clonidine have each been found to be effective in some patients, but it is important to begin with a low dose and titrate upward to minimize the various symptoms associated with their use (Freeman, 2007; Simmons, 2002). Finally, the somatostatin analog, octreotide may also help some patients who experience particularly refractory orthostatic hypotension after eating (Administration, 1997).

Many gastrointestinal symptoms may accompany DAN. Among the most common conditions is gastroparesis (Sawicki, 1996). Gastroparesis should always be suspected in patients with erratic glucose control. Table 8 addresses treatment of gastroparesis. As for all neuropathies, initial treatment should focus on improved blood glucose control. This is particularly important for gastrointestinal manifestations of DAN because good glucose control can improve gastric motor function. Eating frequent small meals is recommended, and patients should limit dietary fat to < 40 g/day and avoid excessive dietary fiber which can lead to formation of bezoars. Diabetic gastroparesis can be treated with a variety of prokinetic agents and recommended dose regimens are shown below. Unfortunately, it is often observed that tachyphylaxis develops after the first few doses. Periodic withdrawal may restore responsiveness and should be tried in apparently refractory cases. In severe cases, jejunostomy may allow the stomach to “rest” until it recovers function.

Diabetic diarrhea is also very common, usually characterized by an intermittent pattern. Table 9 provides approaches to evaluation and treatment of diarrhea in diabetic patients. The first step in treating diabetic diarrhea is excluding a treatable underlying cause. Drug-related diarrhea (due to metformin or acarbose treatment) and lactose intolerance should be considered. A hydrogen breath test can establish whether the diarrhea is due to bacterial overgrowth resulting from hypomotility. Diarrhea that resolves with fasting may be osmotic, caused by ingested substances, whereas diarrhea that continues when the patient is fasting suggests that a secretory process is involved, and neuroendocrine causes should be considered. Treatment, as with all manifestations of neuropathy should begin with good glycemic control. A broad-spectrum antibiotic such as metronidazole can be used to treat diarrhea resulting from bacterial overgrowth. Clonidine may improve diarrhea by reversing adrenergic overactivity. Cholestyramine may be used to chelate bile salts if the hydrogen breath test is normal and the patient fails to respond to antibiotics. Loperamide can be used to reduce the number of stools, but it should be used with caution due to risk of toxic megacolon. Diarrhea resistant to the aforementioned approaches may respond to octreotide.

DAN may also lead to bladder dysfunction. Diabetic cystopathy, or “neurogenic bladder” arises from loss of the afferent innervation of the bladder and accordingly, inability to sense a full bladder. As a result, voiding frequency is diminished and the patient may be unable to void completely. This predisposes a patient to recurrent urinary tract infections, overflow

incontinence, and dribbling. Treatment of neurogenic bladder should begin with scheduled voiding, often coupled with manual pressure on the bladder to initiate urination (Credé maneuver). The parasympathomimetic agent, bethanechol (10 mg, QID) may be helpful, and extended sphincter relaxation can be achieved with the α -1 adrenergic antagonist, doxazosin (1–2 mg, BID or TID) (Freeman, 2007). Self-catheterization can be very useful and reduces the risk of urinary tract infections. Occasionally, chronic catheterization or transurethral surgery of the bladder neck may be necessary (Simmons, 2002).

Erectile dysfunction is one of the most common and distressing manifestations of DAN. The prevalence of erectile dysfunction in men with diabetes is exceedingly high; recently reported to be 67% in normotensive men with diabetes and 78% in men with both diabetes and hypertension (Giuliano, 2004). Erectile dysfunction may be the presenting symptom of diabetes, and importantly, it is a marker for the development of generalized vascular disease and for premature death from myocardial infarction (Freeman, 2007). Since erectile dysfunction may presage future cardiovascular events, a thorough cardiovascular evaluation should be performed on all diabetic men with erectile dysfunction. Erectile dysfunction can result from a variety of factors other than or in addition to DAN and it is useful to distinguish organic from psychogenic causes. Maintenance of nocturnal tumescence suggests a psychogenic cause, and erectile dysfunction due to DAN is nearly always accompanied by loss of ankle reflexes and reduced vibration sensation in the large toes. Treatment of erectile dysfunction should begin with optimization of glucose control and abstinence from alcohol and tobacco. A variety of prescription drugs can cause erectile dysfunction, and thus the physician should be aware of all medications the patient is receiving and attempt to eliminate those that can cause erectile dysfunction, or seek a substitute with less propensity to cause sexual dysfunction.

Phosphodiesterase inhibitors are now available, with different pharmacokinetic and side effect profiles to treat erectile dysfunction (Anderson, 2004). Sildenafil (50 mg, 60 minutes before sexual activity) or tadalafil (5 to 20 mg, 60 minutes before sexual activity) are effective in treating erectile dysfunction in men with diabetes (Safarinejad, 2004). However, all of these agents are contraindicated in patients being treated with nitroglycerine or other nitrate-containing drugs. For many men, injection of prostacyclin into the corpus cavernosum produces satisfactory erections, and surgically implanted penile prostheses are also available. Thus there are now several effective approaches to treating erectile dysfunction in men with diabetes.

5c. Causal Therapies

Topics covered previously in this review discussed proven therapies which either prevent or slow diabetic neuropathy (glycemic control) or diminish its effects (symptomatic therapies). As the only proven approach to treating the cause of diabetic neuropathy is glycemic control, pharmacological and nutraceutical therapies which aim to reverse diabetic neuropathy are examined here. These potential therapies attempt to mitigate the biochemical aberrations which induce neuronal damage.

5C i. Polyol Pathway—The most common target of diabetic neuropathy therapies is sorbitol the first metabolic product of the polyol pathway, through the enzyme AR. AR converts cytosolic glucose to sorbitol by NADPH oxidation; SDH then converts sorbitol to fructose by NAD⁺ hydrogenation (Chung, 2005; Hers, 1956). Elevated sorbitol levels are thus indicators of hyperglycemia and good therapeutic targets for reducing oxidative stress resulting from excessive glucose metabolism.

Aldose Reductase Inhibitors: Aldose Reductase Inhibitors (ARIs) have historically been the primary target of diabetic neuropathy treatment, due largely to their success in reducing cataract-forming osmotic stress associated with polyol accumulation in the diabetic lens (Chylack, 1979; Kinoshita, 1968). Additionally, most studies of the human AR gene (*AKR1B1*) and its polymorphisms in diabetic patients indicate that the “high AR expression” genotype is correlated with elevated diabetic vascular complications and early diabetic neuropathy indicators, whereas the “low AR expression” genotype is correlated with diminished complications and indicators (Demaine, 2003; Donaghue, 2005; Thamothersampillai, 2006). Furthermore, ARIs have been successful in preventing and reversing nerve deterioration in rodent models (Cameron, 1986; Kato, 2000; Yagihashi, 1990). A variety of ARIs have entered the market; while most have effectively reduced nerve polyol levels, this result has not always translated to amelioration of diabetic neuropathy symptoms. Recent thinking posits that polyol levels themselves are not the best indicators of drug efficacy. Instead, the “Metabolic Flux Hypothesis” emphasizes cofactor turnover rate as a better marker of oxidative stress alleviation (Barnett, 1986; Cameron, 1994). This model suggests that much higher (~20–30 fold) doses of ARIs are needed to effectively decrease the rate of cofactor turnover and thereby alleviate common diabetic neuropathy symptoms (Oates, 2008, in press). Table 10 describes past and ongoing ARI trials and investigations.

Sorbinil: In 1981, Sorbinil was the prototype ARI to be developed solely for diabetic neuropathy treatment. Despite successfully reducing and preventing NCV deficits in rodent models, Sorbinil failed to produce noteworthy results in humans. While Sorbinil, a spiroimide, slightly improved in nerve fiber regeneration and human diabetic NCV (by 0.7–1.2 m/sec), it was associated with a high incidence of skin rash, and was withdrawn from the market in 1987 (Judzewitsch, 1983; Sima, 1988). However, Sorbinil’s moderate success paved the way for future ARI therapies.

Ponalrestat: Ponalrestat is a carboxylic acid that effectively lowers nerve sorbitol levels *in vitro* and in rats, but fails to do so in human diabetic nerves (Greene, 1993; Stribling, 1985). Ponalrestat is 99% plasma protein-bound in humans (~10-fold increase over rats), and most of the unbound acid is ionized at cellular pH. Such ions are slow to cross nerve plasma membranes, further diminishing Ponalrestat’s effectiveness.

Zopolrestat: Zopolrestat is a carboxylic acid analog of Ponalrestat that dose-dependently decreased diabetic rat nerve sorbitol and fructose levels. In human studies, low levels (250–500mg) of Zopolrestat decreased nerve sorbitol levels, but had no effect on fructose levels or symptom alleviation, and showed little NCV improvement. At higher levels (1000mg),

Zopolrestat was significantly more effective at increasing NCV, but was associated with a higher incidence (7%) of elevated liver enzymes and eventually withdrawn (Arezzo, 1996). These trials illustrate that nerve sorbitol level *per se* is not the best indicator of nerve health, and that elevated ARI doses are likely needed to achieve significant diabetic neuropathy symptom improvement.

Zenarestat: Zenarestat is a carboxylic acid ARI also showing a dose-dependant increase of NCV; notably, higher doses of Zenarestat continue to improve NCV, increase nerve fiber density and nerve health even after nerve sorbitol levels have stabilized (Greene, 1999). Though its development was terminated due to a high incidence of elevated serum creatine levels, the studies demonstrated nonetheless that sorbitol is not the best marker of drug efficacy, and provides hope that at high doses ARIs can be more effective than previously thought (Gabbay, 2004).

AS-3201: AS-3201, or Ranirestat, is a well-tolerated spirosuccinimide discovered in 1998. Phase 2 trials were promising, showing few side effects and marked improvement in both NCV deficit and diabetic neuropathy symptoms (Bril, 2006)(Eisai Co., 2007) However, definitive Phase 3 study conclusions could not be drawn as of July 2007 due to the trial's unusually high placebo effect. AS-3201 development is ongoing, and researchers hope that continued study and increased dosage of Ranirestat will prove effective in future diabetic neuropathy treatment (Oates, 2008, in press).

Epalrestat: In 1992, Epalrestat entered the Japanese market as a carboxylic acid ARI with minimum side-effects, but without conclusive evidence of efficacy backed by a randomized, double-blind placebo-controlled study. From 1997–2003 such a study was conducted, and at slightly elevated doses (150mg), Epalrestat delayed nerve deterioration and alleviated many common diabetic neuropathy symptoms such as limb numbness and cramping (Hotta, 2006). Though these results have not been replicated, Epalrestat is now the standard drug therapy for diabetic neuropathy in Japan.

Myo-inositol: Myo-inositol is a naturally occurring secondary messenger involved in proper nerve function. Myo-inositol depletion is associated with decreased $\text{Na}^+\text{-K}^+\text{-ATPase}$ function and decreased NCV, and has been implicated in early-stage diabetic neuropathy pathology (Sima, 1997). Evidence suggests that dietary myo-inositol supplements might slow diabetic neuropathy progression, though further study is needed to assess efficacy.

5c ii. Hexosamine Pathway—As described above, activation of the hexosamine pathway generates UDPGlcN-Ac, which modulates transcription factors and ultimately induces neurovascular insult. While ARIs directly target toxic pathways, modulation of the hexosamine pathway can redirect glycolytic flow away from subsequent deleterious pathways. This mode of action offers an intriguing possibility for altering pathways in metabolic disorders.

Benfotiamine: Benfotiamine is a fat-soluble analogue of thiamine/vitamin B1 that activates transketolase, an enzyme converting fructose-6 phosphate into pentose-5 phosphates (Figure 10). The reduced fructose-6 phosphate input decreases flux through the hexosamine pathway

(as well as flux through the advanced glycation end product (AGE) and the diacylglycerol (DAG) protein kinase C (PKC) pathways)(Hammes, 2003). The increased flux away from the hexosamine pathway and into the pentose-5 phosphate pathway may offer an additional benefit: increased redox capacity. One of the products of the pentose phosphate pathway is NADPH, a prime reactant in the formation of the antioxidant glutathione. Since NADPH is depleted in the polyol pathway, benfotiamine holds the speculative possibility of diminishing the effects of this pathway as well. Benfotiamine has successfully inhibited these pathways and prevented diabetic retinopathy in animal models (Hammes, 2003). In humans, Benfotiamine has been shown to improve pain associated with diabetic neuropathy and to improve NCV in conjunction with vitamins B6 and B12 (Haupt, 2005; Stracke, 1996; Winkler, 1999). Benfotiamine is currently available as a dietary supplement in the United States.

5c. iii PKC Pathway

Ruboxistaurin: Ruboxistaurin is a PKC- β competitive inhibitor that has effectively managed many complications of diabetes in clinical trials. It has been particularly successful in reducing the progression of diabetic retinopathy, endothelial vasodilation, and (to a lesser extent) nephropathy (Aiello, 2006; Beckman, 2002; Ishii, 1996; Tuttle, 2005). However, trials of Ruboxistaurin's effect on diabetic neuropathy have not shown significant improvement (Vinik, 2005). Ruboxistaurin was being developed for US marketing by Eli Lilly and was pending FDA approval as a pharmaceutical agent for diabetic retinopathy. However, the company withdrew its marketing application in March, 2007, and Ruboxistaurin's fate is currently unclear.

5c. iv AGE-RAGE Pathway—Clearly, glycemic control is the primary means for decreasing AGE formation. Given that this may be difficult to achieve, prevention of RAGE activation is an important alternative therapeutic goal for diabetic neuropathy (Figure 11). Two possible approaches are feasible: to prevent the formation of AGEs or to block RAGE. Numerous compounds have been investigated for anti-glycation activity but their use in humans is still debatable. The following section describes compounds that have been assessed for the ability to decrease activity of the RAGE axis in diabetic neuropathy.

Aspirin: As already mentioned, aspirin (acetylsalicylic acid-an NSAID) is a commonly used analgesic although long-term use in diabetic patients should be weighted against possible gastrointestinal side effects. In diabetic patients on high doses of aspirin, such as those with rheumatoid arthritis, the incidence of retinopathy is decreased compared with age-matched controls not taking aspirin, which suggested that aspirin may protect against glycation (Cotlier, 1981). Indeed, aspirin reduces glycation *in vitro*, and in animal experiments, potentially by acetylation of amino groups (Blakytyn, 1992). Other analgesics such as paracetamol and ibuprofen also protect against glycation but cannot acetylate proteins (Blakytyn & Harding, 1992). Alternatively, it is possible that aspirin does not directly alter glycation, but inhibits glycooxidation and AGE-cross-link formation; therefore its effects may be because of its antioxidant capacity (Fu, 1994). Besides the analgesic effects of aspirin, studies indicate a reduced risk of cardiovascular events for diabetic patients on low dose aspirin (Hennekens, 2004).

Aminoguanidine: Aminoguanidine (also called pimagedine) is a nucleophilic hydrazine compound and has received the most attention as a potential anti-glycation drug (Thornalley, 2003). Initially, it was thought that aminoguanidine prevented AGE formation by blocking carbonyl groups on Amadori products, although it is now known to react with carbonyl groups from reducing sugars or 3-DG (Edelstein, 1992; Lewis, 2006). In diabetic animals, aminoguanidine reduces nephropathy (Soulis, 1996), retinopathy (Chibber, 1994; Hammes, 1995), and neuropathy in some but not all studies (Birrell, 2000; Miyauchi, 1996). Preliminary studies in diabetic patients showed that aminoguanidine therapy for 28 days reduces hemoglobin-derived AGEs (Hb-AGE) but does not alter levels of Amadori products (Makita, 1992). Three other phase II and III trials of aminoguanidine have been completed with nephropathy endpoints but produced no benefit. The last was discontinued because of side effects in patients, which include flu-like symptoms, gastrointestinal disturbances, and anemia (Bolton, 2004). Despite the earlier promising results with aminoguanidine, it is unlikely to be used for therapeutic purposes. However, studies on anti-glycation compounds like aminoguanidine have provided evidence for the involvement of AGEs in the pathogenesis of diabetic complications.

Phenacylthiazolium bromide: Compounds capable of cleaving AGE cross-links have been described, opening up the exciting possibility of reversing diabetic complications. These compounds include *N*-phenacylthiazolium bromide (PTB), which can cleave AGE-cross-links by a mechanism which is still unclear. PTB has been used to cleave AGE cross-links between albumin and collagen *in vitro* and recent studies in diabetic rats have shown that PTB can prevent or reverse the accumulation of AGEs in blood vessels (Cooper, 2000). However, another study found that although PTB can reduce model AGE cross-links *in vitro*, it does not reduce AGE cross-links formed *in vivo* (Yang, 2003). Whether AGE-cross-link breakers are useful *in vivo* will also depend on their long-term toxicity. Due to the unstable nature of PTB, analogues such as alagebrium chloride, also known as ALT-711, have been developed. This compound provides renoprotection in diabetic mice (Coughlan, 2007; Peppia, 2006). Patient trials to date have found that ALT-711 is well tolerated and produces significant vascular benefit in the elderly through decreased blood pressure and increased vascular elasticity (Little, 2005; Ziemann, 2007). Effects on microvascular complications of diabetes including neuropathy are not yet completed.

Blocking RAGE: There is considerable interest in compounds capable of blocking the interaction between AGEs and RAGE. RAGE can be blocked by usage of soluble RAGE (sRAGE), which is the extracellular ligand-binding domain of RAGE or by use of antibodies capable of reacting with RAGE. Studies by Schmidt and coworkers have performed multiple studies in diabetic mouse models using RAGE knockout mice and mice treated with sRAGE or anti-RAGE (Hudson, 2004). They demonstrate: topical sRAGE improves wound healing (Wear-Maggitti, 2004), sRAGE decreases atherosclerosis in ApoE knockout mice (Bucciarelli, 2002), RAGE blockade prevents the final stages of diabetogenesis in non-obese diabetic mice (Chen, 2004), and that RAGE blockade prevented sensory deficits (Bierhaus, 2004). Therefore, blockade of RAGE may be an important mechanism to prevent diabetic complications and the Schmidt group is actively working on translation of sRAGE to a clinical trial.

5c. v PARP Inhibitors—As PARP mediates both neuronal dysfunction and inflammation, inhibition of PARP holds the potential of improving two aberrant causeways in diabetic neuropathy, making it a promising target. PARP inhibitors such as 1,5-isoquinolinediol and 3-aminobenzamide have successfully improved these PARP-mediated dysfunctions in STZ-induced diabetic rats (Ilnytska, 2006; Li, 2005; Obrosova, 2005a). Additionally, Nicotinamide (vitamin B₃) has been shown to act as both a PARP inhibitor and antioxidant in rodents, improving the complications of early diabetic peripheral neuropathy (Stevens, 2007). Nicotinamide is an attractive potential therapeutic due to its limited side effects and toxicity (Gale, 2004). A combination therapy for diabetic neuropathy including nicotinamide, the xanthine oxidase inhibitor allopurinol, and the antioxidant DL- α -lipoic acid is currently in trial.

5c. vi Antioxidants—Given the known mechanisms leading to diabetic neuropathy, a logical therapeutic approach is to prevent oxidative stress by increasing antioxidant defense. Antioxidant defense arises from (Hogan, 2003) antioxidant enzymes that catalyze the removal of ROS antioxidant molecules that prevent the oxidation of other molecules (Dworkin, 2007a), usually because they are readily oxidized molecules that chelate transition metal ions so they cannot catalyze the generation of ROS in a cell (Dworkin, 2005). A major portion of the body's antioxidant defense comes from dietary intake of micronutrient molecules that facilitate one or more of these three mechanisms. This makes oral antioxidants an attractive strategy for both prevention and treatment of diabetic neuropathy. Many clinical trials of antioxidant defense therapies have been completed, mostly using a high dose of a single antioxidant compound. The results of these trials have been largely negative, despite the strong rationale for this approach. We will discuss several of the lead candidate compounds and summarize other known trials in Table 11.

Vitamin E: Vitamin E is a fat-soluble compound that exists in 8 isoforms with varying biological activity (Traber, 1995). Blood levels of vitamin E can decrease under prolonged oxidative stress and in individuals who cannot absorb dietary fat (Triantafyllidis, 1998), are on a low fat diet, or are zinc deficient (Bunk, 1989). α -Tocopherol is the most active isoform and is the most common dietary supplement. This compound has been broadly tested for its ability to prevent chronic diseases involving oxidative stress including cancer and diabetes complications. While small studies have indicated that high intake of vitamin E may decrease incidence of certain cancers, large studies generally do not support the findings. One study found that regular intake of high doses of vitamin E for more than 10 years decreased the risk of death from bladder cancer (Jacobs, 2002). These studies demonstrate the safety of long-term use of vitamin E. In addition to potent antioxidant action, vitamin E can promote immune function, DNA repair, and metabolism (Traber, 1996; Wozniak, 2004). Chronic vitamin E administration improves the ratio of cardiac sympathetic to parasympathetic tone in patients with type 2 diabetes when given 600 mg/day for 4 mo (Manzella, 2001).

α -Lipoic Acid: Alpha-lipoic acid, also termed thioctic acid, is an antioxidant that is available for treatment of DPN in some countries (Ziegler, 1999b). It has the potent ability to scavenge ROS, regenerate other antioxidants, and chelate metal ions (Packer, 1997).

Some randomized controlled clinical trials have shown that intravenous infusions of α -lipoic acid (600 mg daily, 5 days/week for 3 weeks) significantly improved sensory symptoms of DPN or the Neuropathic Impairment Score (Ziegler, 1999a). In another small study of oral α -lipoic acid (800 mg, QD) a small (non-significant) trend toward improvement in measures of cardiac autonomic neuropathy was reported (Ziegler, 1997). In a more recent open-label trial of 10 days intravenous administration followed by 50 days of oral treatment, α -lipoic acid was found to improve several manifestations of autonomic neuropathy (Tankova, 2004). Other clinical trials have been completed with varying doses and either parenteral or oral administration of the drug. In 1995, a review of current evidence assessed trials that met specific requirements of randomization, double masking and placebo-controlled design (Foster, 2007). The study concluded that α -lipoic acid should be considered as a treatment for diabetic neuropathy since parenteral supplementation improves neuropathic symptoms over 3 weeks and oral treatment improves neuropathic deficits and potentially sensory symptoms. Another trial that was ongoing at this time was the Neurological Assessment of Thioctic Acid in Neuropathy (NATHAN) I. This was a 4-year oral treatment in 460 patients in a multicenter evaluation. The results have now appeared in abstract form and conclude that α -lipoic acid is tolerated long-term. It improves some neuropathic deficits and symptoms but does not improve nerve conduction in mild and moderate diabetic neuropathy. Despite many positive findings, α -lipoic acid remains broadly used in Europe and underutilized in the U.S.A., though commercially available as a nutritional supplement.

Botanicals: It has long been recognized that natural dietary products including red grapes, evening primrose, and cruciferous vegetables increase antioxidant status. In addition to many botanical extracts possessing antioxidant capacity, several compounds are known to increase the expression of antioxidant genes such as glutathione S-transferase and NAD(P)H:quinone oxidoreductase 1 (Halat, 2003). These enzymes belong to the class of phase 2 enzymes under the regulation of a specific promoter consensus region known as the antioxidant response element (ARE) (Itoh, 1999). Many compounds can activate the transcription factor, known as nuclear factor-E2-related factor-2 (Nrf-2), that binds this promoter. Oxidative stress can activate the promoter via phosphorylation of the Nrf-2 cytoplasmic chaperone protein Keap-1 (Tamasi, 2004). Botanical compounds may activate Nrf-2 either by inducing mild intracellular oxidative stress, by directly activating Nrf-2, or by causing recruitment of Nrf-2 co-activators, such as small Maf proteins (Dhakshinamoorthy, 2000; Kang, 2005; Venugopal, 1998). Several botanical compounds so effectively activate the antioxidant response they are used to treat diseases with an oxidative component, particularly cancer and Alzheimer's disease (Perry, 2007; Thimmulappa, 2002).

Resveratrol: The most widely assessed botanical compound is resveratrol, extracted from red grapes. Studies in STZ-treated rats demonstrated attenuation of thermal hyperalgesia and cold allodynia as well as decreases in oxidative stress DNA damage, and nerve conduction deficits (Kumar, 2007; Sharma, 2006). Similarly, in type 1 diabetic mice resveratrol prevents neuropathic pain (Sharma, 2007). Resveratrol is likely to provide additional therapeutic benefits in T2DM patients because it also activates the SIRT1 genes that regulate glucose metabolism and insulin sensitivity (Chen, 2007; Sun, 2007; Zang, 2006) Resveratrol was assessed in a trial examining aging and cardiovascular disease and produced positive

results (Labinsky, 2006). Although trials in diabetes are indicated by these findings, there are none on record to date. Other botanicals that activate the antioxidant response in experimental diabetes and in patients include extract of *Tinospora cordifolia* (Prince, 1999), curcumin (Osawa, 2005), garlic oil (Anwar, 2003), evening primrose oil (Ford, 2001; Halat & Dennehy, 2003), and sulphoraphane (Perry, 2007; Thimmulappa, 2002). A controlled diabetes patient trial has not been performed for any of these compounds.

5c. vii Targeting Vascular Disease—ARBs and ACE Inhibitors—Several drugs are in common use in T2DM for blood pressure, cardiovascular disease, and nephropathy. The first line of attack for these diabetes-related conditions is inhibition of angiotensin-converting enzyme (ACE) or of angiotensin receptor. Evaluation of the outcomes of clinical trials suggests that preventing one complication is likely to have a positive impact upon other complications (Podar, 2002). Specifically, prevention of cardiovascular disease is likely to prevent macro- and microvascular complications. Large-scale studies of the effects of ACE inhibitors or angiotensin receptor blockers, known as ARBs, have not been done, although some small studies and prospective assessments have been performed. In experimental diabetes, enalapril, an ACE inhibitor, or L-158809, an angiotensin II receptor blocker, decreases neurovascular deficits including blood flow and motor nerve conduction velocity (Coppey, 2006). Another ACE inhibitor, Perindopril, prevents photoreceptor loss, an indicator of neuropathy (Bui, 2003). In a small clinical study, the ACE inhibitor trandolapril produced a significant improvement in peripheral neuropathy (Malik, 2000). Another study treated long-term diabetic patients with DAN but not high blood pressure or arterial disease with the ACE inhibitor Quinapril and/or the ARB Losartan (Didangelos, 2006). Either drug alone improved DAN and cardiac function; in combination the improvement may have been greater.

5c. viii Neurotrophic factors—Peripheral nervous system injury in diabetes may be the result of both hyperglycemia and loss of neurotrophic support normally provided by insulin. This hypothesis is supported by reports of abnormal expression levels of growth factors in diabetes. Thus, there is growing interest in exploring the potential utility of NGFs, insulin, IGFs, and other neurotrophic factors in the treatment of diabetic neuropathy.

Insulin receptors are found in the PNS on Schwann cells, pericytes, endothelial cells, and neurons, especially sensory neurons (Brussee, 2004; Sugimoto, 2002; Sugimoto, 2000). Insulin-deficient rat models of diabetes appear to have more severely progressive neuropathy compared to T2DM models, suggesting insulin deficiency itself contributes to the development of neuropathy (Kamiya, 2005; Pierson, 2003). *In vitro*, insulin activates survival-promoting PI-3K/Akt signaling and neurite outgrowth in sensory neurons (Fernihough, 1993; Huang, 2005; Recio-Pinto, 1986). Local delivery of insulin to the spinal cords of STZ-treated rats improves nerve conduction velocity measurements, and low-dose systemic delivery at a level that does not reduce hyperglycemia is able to decrease signs of mitochondrial distress in sensory neurons (Brussee, 2004; Singhal, 1997; Toth, 2006).

C-peptide, long thought to be merely an inert peptide fragment byproduct of insulin synthesis, is now believed to have biological activity of its own, although little is known mechanistically as there is currently no identified receptor (Wahren, 2004). C-peptide

deficiency is concomitant with insulinopenia in T1DM. When C-peptide is replaced in diabetic rats, a number of measures of peripheral nerve function improve. Proposed mechanisms for these observations include potentiation of insulin signaling, vasodilation via nitric oxide release, and stimulation of the release of other neurotrophic factors (Cotter, 2003b; Kamiya, 2006; Pierson, 2003; Sima, 2004; Sima, 2001; Zhang, 2007).

Insulin-like growth factors (IGFs) I and II have profound effects on nervous system development and survival, mediated through activation of the IGF-I receptor (IGF-IR) (Fernandez, 2007; Leininger, 2005). IGFs and the IGF-IR are expressed throughout the developing and adult nervous system. IGFs have been reported to be reduced in some animal models of diabetes, although this varies and may be dependent upon the model, type of diabetes, and tissue examined (Craner, 2002; Ekstrom, 1989; Kamiya, 2006; Schmidt, 2003; Wuarin, 1994; Zhuang, 1997). A number of preclinical studies in diabetic rats suggest systemic or intrathecal IGF therapy can improve neuropathy (Brussee, 2004; Ishii, 1995; Lupien, 2003; Schmidt, 1999; Schmidt, 2000; Toth, 2006; Zhuang, 1997). Clinical use of IGFs may be complicated by their widespread systemic effects (Russo, 2005). Additionally, the complex system of IGF binding proteins (IGFBPs) may impact efficacy. The IGFBPs regulate IGF bioavailability, and studies attempting to establish the status of the IGFBPs in diabetes have been inconsistent (Busiguina, 2000; Crosby, 1992; Han, 2006).

The system of neurotrophins is critical for the development and maintenance of the PNS and CNS (Huang, 2003; Kaplan, 2000) and includes nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophins (NT) 3–6. NGF is not required for sensory neuronal survival in the adult PNS, but it does regulate axonal sprouting and the phenotype of sensory neurons (Chudler, 1997; Lindsay, 1988; Schwartz, 1982). Thus, preclinical studies of NGF in diabetic rats resulted in improvements in both signaling outcomes of the NGF system and PNS function, as well as positive effects on myelination (Apfel, 1994; Christianson, 2007; Christianson, 2003; Diemel, 1994; Elias, 1998; Fernyhough, 1995b; Sango, 1994; Unger, 1998). Clinical studies have not progressed past phase 3, however, and there is developing interest in small molecule activators of trkA as a potentially more viable alternative approach (Apfel, 2002).

BDNF is expressed by both peripheral neurons and muscle, and its receptor, trkB, is found on motor neurons and some sensory neurons (McMahon, 1994). Retrograde transport of endogenous, but not exogenous, BDNF to the neuron cell bodies is impaired in diabetic rats, suggesting there are problems with the local supply of BDNF at the peripheral nerve terminals (Mizisin, 1999). Exogenous BDNF is protective to large myelinated sensory fibers in STZ rats, but not smaller fibers, which is consistent with the distribution of trkB expression (Calcutt, 1998; Elias, 1998; Mizisin, 1997).

Preclinical studies of exogenous NT-3 therapy in diabetic rats have had mixed results. One study found improvement in large sensory fibers, but not motor fibers (Mizisin, 1998). Another study found effects on both large sensory and motor fibers (Mizisin, 2004). Intrathecal NT-3 increased myelinated fibers in the skin of diabetic mice, but without noticeable improvement of function (Christianson, 2007).

Ciliary derived neurotrophic factor (CNTF) is a cytokine with numerous neurotrophic properties (Vergara, 2004). It is only expressed in Schwann cells in the peripheral nervous system (Kobayashi, 2000), and levels of CNTF are reduced in diabetic rats (Calcutt, 1992). This deficiency can be improved by ARI therapy (Mizisin, 1997). Exogenous CNTF itself has therapeutic benefit in diabetic rats, improving function in both sensory and motor fibers, along with increasing regenerative capabilities (Calcutt, 2004; Mizisin, 2004). Therapeutic use of CNTF is complicated by its systemic effects, particularly on muscle, and thus more targeted delivery approaches are being considered (Bongioanni, 2004).

6. The Search for Novel Therapeutic Targets

While this review has discussed the fusion of over 30 years of research in diabetic neuropathy, glucose control alone still remains the only disease-modifying therapy for diabetic neuropathy (Leininger, 2006b; Little, 2007; Vincent, 2008). This lack of progress, despite intense research, suggests that a new paradigm is needed. We contend that a “discovery approach” using informatics to analyze genomic and proteomic data from animal models and patients with DPN may provide much needed insight into disease pathogenesis and identify viable targets for disease modifying treatments. To date, only one animal study (and no human studies) has addressed alterations in peripheral nervous system gene expression in response to diabetes. Price and colleagues performed microarray analyses on Wistar rat dorsal root ganglion neurons, 1, 4, and 8 weeks post STZ-induced diabetes (Price, 2006). Nerve conduction measures confirmed the presence of DPN in these animals at weeks 4 and 8 (Price, 2006). At week 1, genes involved in glucose metabolism were upregulated, and by week 4 glutathione transferase was upregulated as would be predicted secondary to conditions of oxidative stress (Price, 2006).

What is now required is a comprehensive effort to establish the molecular signatures of neural tissues from genome wide screening of RNA from different animal models without and with DPN and DAN (Sullivan, 2007; Sullivan, 2008). A discovery approach for diabetic neuropathy is presented in Figure 12. Genome wide expression profiling of sensory and sympathetic neurons and nerves from different animal models of DPN and DAN will yield differentially regulated transcripts. These expression profiles will provide the data needed to define categories of genes that are functionally regulated in diabetic neuropathy; possible examples would be genes involved in metabolism or mitochondrial function or nerve regeneration. Further analyses of these data can define shared promoter modules among members of different gene categories, providing one or more specific targets for disease regulation (Ashburner, 2000). In parallel, an informatics approach can also define relevant pathways related to functional gene categories, providing additional information on novel mechanisms of disease pathogenesis or identifying new disease targets (Dennis, 2003) (Figure 12). The feasibility, power, and utility of using a discovery/informatics approach to uncover disease mechanisms is well described in chronic kidney disease in a series of papers by Kretzler and colleagues (Cohen, 2006; Schmid, 2003a; Schmid, 2003b; Schmid, 2006). In these studies, human renal biopsies were examined by Affymetrix™ microarray analysis and real time RT-PCR. The genes that were found to be differentially expressed between healthy and diseased tissue were put into the context of cellular pathways and used to predict regulatory elements controlling the observed changes. Regulatory elements identified could

be used to identify drug targets and also to predict the downstream effects of gene expression, including the presence of biomarkers in chronic renal disease.

As emphasized above, we contend a similar comprehensive approach is needed in diabetic neuropathy to further advance our understanding of disease pathogenesis and our development of disease modifying therapies. Of special interest is how this approach can in parallel lead to biomarker discovery. As outlined in Fig. 12, the first step is to employ microarrays and confirmatory Q-PCR to analyze gene expression of relevant neural tissue and use validated techniques to detect enriched pathways. These data in turn provide the knowledge to predict proteins and macromolecules influenced by gene expression. By using clustering and classification analysis, while maintaining high standards of mathematical validation throughout, one could discover those targets most likely to serve as useful biomarkers, such as modified proteins or small molecule products of targeted pathways. The data can also be analyzed to see if there is a constellation of genes that cluster in a unique way, suggesting a target not observed by the gene selection or pathway enrichment approach. A flow diagram of this type of analysis plan is presented in Figure 13 and is complimentary to the approach presented in Fig. 12.

7. Summary

Neuropathy is one of the most prevalent, devastating and costly complications of diabetes. Distal symmetrical sensorimotor polyneuropathy (DPN) is the leading cause of nontraumatic limb amputation. Diabetic autonomic neuropathy (DAN) can affect virtually any body system and is associated with greatly increased morbidity and mortality and can have a profound influence on quality of life. Several biochemical mechanisms of nerve and neurovascular damage have been identified and excessive production of reactive oxygen species, or “oxidative stress”, is thought to be a common etiologic factor. Diabetic neuropathies can be diagnosed with relatively simple tests of peripheral and autonomic nerve function. Treatment of diabetic neuropathy should always begin with efforts to optimize glycemic control and with patient education. There are now many useful pharmacologic approaches to treating painful neuropathy and most manifestations of autonomic neuropathy, but disease modifying treatments other than strict glycemic control await a more complete understanding of the underlying mechanisms of diabetic neuropathy and the development of pharmacologic agents based on this emerging knowledge.

Some positive results from preclinical studies with inhibitors implicated in the pathogenesis of diabetic neuropathy have been reported, but only time will tell whether and how these will translate into therapeutics. Discovery of these therapeutic targets will require implementation of bioinformatics, biochemistry, cellular biology, and physiology. It may be anticipated that with further progress toward validation of the recently proposed “unifying hypothesis”, development of agents to prevent mitochondrial oxidative damage will be the focus of intense study (Green, 2004).

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Abbreviations

ACE	angiotensin-converting enzyme
AFT	Autonomic function tests
AGE	Advanced glycation endproducts
AR	Aldose reductase
ARB	angiotensin receptor blocker
ARI	Aldose reductase inhibitor
BDNF	Brain-derived neurotrophic factor
CAN	Cardiac autonomic neuropathy
CGM	Continuous glucose monitor
CNTF	Ciliary derived neurotrophic factor
COX-2	Cyclooxygenase-2
DAN	diabetic autonomic neuropathy
DCCT	Diabetes control and complications trial
DPN	diabetic polyneuropathy
DRG	Dorsal root ganglion
Drp1	Dynamin related protein 1
EDIC	Epidemiology of diabetes interventions and complications
EDX	Electrodiagnostic studies
HSP	Heat shock protein
IGF	Insulin like growth factor
IGFBP	IGF binding protein
MDNS	Michigan diabetic neuropathy score
MNSI	Michigan neuropathy screening instrument
Mt	Mitochondria
NCV	Nerve conduction velocity
NF-κB	Nuclear factor kappa B
NGF	Nerve growth factor
NMDA	N-methyl-d-aspartate

NO	Nitric oxide
NSAID	Non-steroidal anti-inflammatory drugs
NT-3	Neurotrophin 3
PAI-1	plasminogen activator inhibitor-1
PARP	Poly(ADP-ribose) polymerase
PKC	Protein kinase C
QST	Quantitative sensory tests
RAGE	Receptor for advanced glycation endproducts
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SDH	Sorbitol dehydrogenase
SNRI	Serotonin-Norepinephrine Reuptake Inhibitors
sRAGE	soluble RAGE
SSRI	Selective serotonin reuptake inhibitors
STZ	Streptozotocin
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TCA	Tricyclic and tetracyclic antidepressants
TGF-β1	Transforming growth factor β 1
VEGF	Vascular endothelial growth factor

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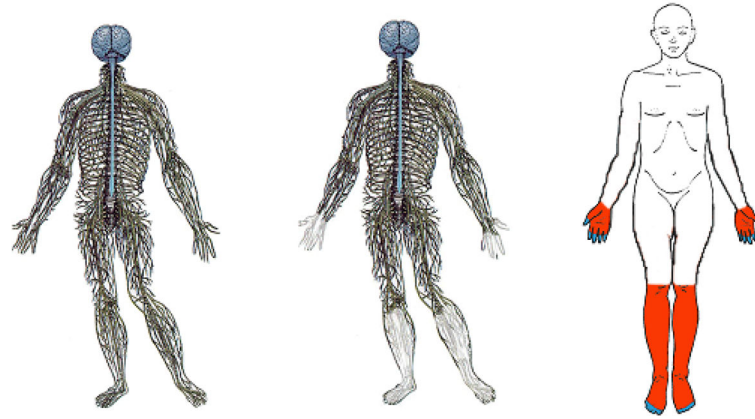
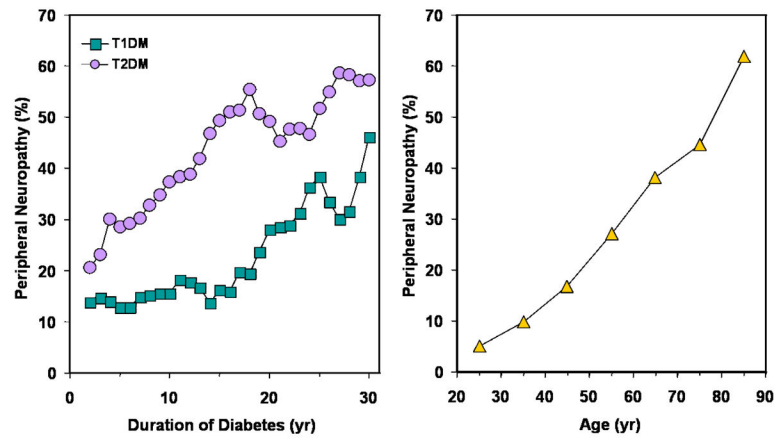


Figure 1. Stocking Glove Configuration of DPN

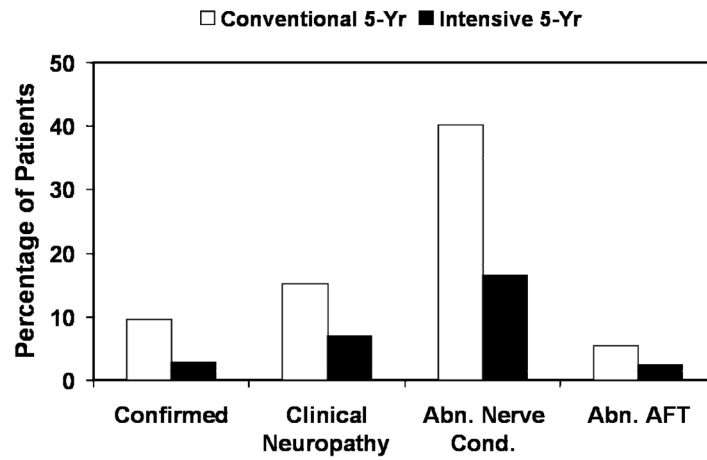
Diabetic neuropathy is dependent on axon length, initiating in the toes and progressing upward until reaching the calf. Neuropathy presents at the fingertips at this point.



Young MJ, et al., *Diabetologia* 36: 150-4, 1993.

Figure 2. Effect of Disease Duration and Age on Prevalence of Diabetic Neuropathy

For both T1DM and T2DM, duration of diabetes (left) as well as age of patient (right) is correlated to the incidence of diabetic neuropathy. Adapted from (Young, 1993)



The DCCT Research Group *Ann Intern Med* 122: 561-8, 1995.

Figure 3. Effect of Glycemic Control on Diabetic Neuropathy in DCCT

Intensive therapy cohort which showed better glycemic control, results in lower incidences of all forms of diabetic neuropathy compared to conventional therapy. Adapted from (The effect of intensive diabetes therapy on the development and progression of neuropathy. The Diabetes Control and Complications Trial Research Group, 1995)

Please take a few minutes to answer the questions below about the feeling in your legs and feet.
Check yes or no based on how you usually feel.

- | | | |
|---|---------------------------------|--------------------------------|
| 1. Are your legs and/or feet numb? | 1. yes <input type="checkbox"/> | 2. no <input type="checkbox"/> |
| 2. Do you ever have burning pain in your legs and/or feet? | 1. yes <input type="checkbox"/> | 2. no <input type="checkbox"/> |
| 3. Are your feet too sensitive to touch? | 1. yes <input type="checkbox"/> | 2. no <input type="checkbox"/> |
| 4. Do you get muscle cramps in your legs and/or feet? | 1. yes <input type="checkbox"/> | 2. no <input type="checkbox"/> |
| 5. Do you ever have prickling feelings in your legs or feet? | 1. yes <input type="checkbox"/> | 2. no <input type="checkbox"/> |
| 6. Does it hurt when the bedcovers touch your skin? | 1. yes <input type="checkbox"/> | 2. no <input type="checkbox"/> |
| 7. When you get in the tub or shower, are you able to tell the hot water from the cold water? | 1. yes <input type="checkbox"/> | 2. no <input type="checkbox"/> |
| 8. Have you ever had an open sore on your foot? | 1. yes <input type="checkbox"/> | 2. no <input type="checkbox"/> |
| 9. Has your doctor ever told you that you have diabetic neuropathy? | 1. yes <input type="checkbox"/> | 2. no <input type="checkbox"/> |
| 10. Do you feel weak all over most of the time? | 1. yes <input type="checkbox"/> | 2. no <input type="checkbox"/> |
| 11. Are your symptoms worse at night? | 1. yes <input type="checkbox"/> | 2. no <input type="checkbox"/> |
| 12. Do your legs hurt when you walk? | 1. yes <input type="checkbox"/> | 2. no <input type="checkbox"/> |
| 13. Are you able to sense your feet when you walk? | 1. yes <input type="checkbox"/> | 2. no <input type="checkbox"/> |
| 14. Is the skin on your feet so dry that it cracks open? | 1. yes <input type="checkbox"/> | 2. no <input type="checkbox"/> |
| 15. Have you ever had an amputation? | 1. yes <input type="checkbox"/> | 2. no <input type="checkbox"/> |

Figure 4. MNSI Patient Questionnaire
 Adapted with permission

			Yes (0)	No (1)
Appearance of feet	Right	Normal	_____	_____
			If no, check all that apply: _____ Deformed _____ Dry skin _____ Infection _____ Ulceration (1)	
	Left	Normal	_____	_____
			If no, check all that apply: _____ Deformed _____ Dry skin _____ Infection _____ Ulceration (1)	
		Present (0)	Present/reinforcement (0.5)	Absent (1)
Ankle reflexes	Right	_____	_____	_____
	Left	_____	_____	_____
		Present (0)	Decreased (0.5)	Absent (1)
Vibration perception at great toe	Right	_____	_____	_____
	Left	_____	_____	_____
			TOTAL	_____/8 pts.

Figure 5. 8 Point Clinical Examination for Diabetic Neuropathy
Adapted with permission

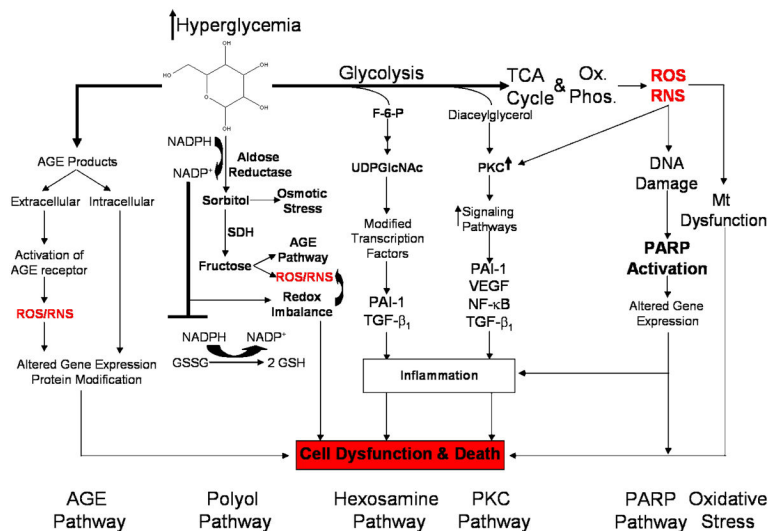


Figure 6. Schematic of Hyperglycemic Effects on Biochemical Pathways in Diabetic Neuropathy

Excessive glucose metabolism generates excess NADH and leads to overload of the electron transport chain causing oxidative stress, damage to Mt, activation of PARP. PARP activation by ROS acts in conjunction with the hexosamine and PKC pathway to induce inflammation and neuronal dysfunction. A combination of oxidative stress and hyperglycemia activate the detrimental pathways of AGE, polyol, hexosamine and PKC pathways which lead to redox imbalance, gene expression disturbances, and further oxidative stress. These pathways also induce inflammation and neuronal dysfunction. NF-κB :Nuclear factor kappa B; PARP: Poly(ADP-ribose) polymerase; PKC: Protein kinase C; AGE: Advanced glycation endproducts; RNS: Reactive nitrogen species; ROS: Reactive oxygen species, GSH: glutathione; GSSG: oxidized glutathione; UDPGlcNAc: UDP-N-Acetylglucosamine; VEGF: Vascular endothelial growth factor.

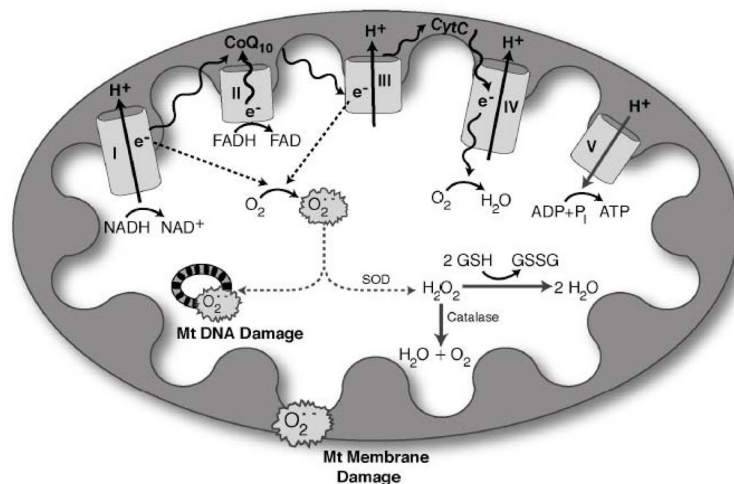


Figure 7. Oxidative stress and mitochondrial dysfunction(Leininger, 2006b)

Hyperglycemia increases production of reactive oxygen species (ROS) in mitochondria. NADH and FADH₂ produced from the tricarboxylic acid cycle transfer to the mitochondria, where they serve as electron donors to the mitochondrial membrane-associated redox enzyme complexes. The electrons (e⁻) are shuttled through oxidoreductase complexes I, II, III and IV (cytochrome c), until they are donated to molecular oxygen, forming water. The electron transfer into complexes I, III and IV by NADH (and FADH₂ via complex II to complex III) produces a proton gradient at the outer mitochondrial membrane, generating a potential between the inner mitochondrial membrane and outer mitochondrial membrane. This potential drives ATP synthesis, and is crucial for mitochondrial viability, function, and normal metabolism. As electrons are passed from complex II to complex III, however, ROS are produced as by-products. The levels of ROS produced during normal oxidative phosphorylation are minimal, and they are detoxified by cellular antioxidants such as glutathione, catalase and superoxide dismutase. The hyperglycemic cell, on the other hand, shuttles more glucose through the glycolytic and tricarboxylic acid cycles, providing the cell with an over-abundance of NADH and FADH₂ electron donors. This produces a high proton gradient across the inner mitochondrial membrane, which increases the turnover of the initial complexes, and thereby produces increased levels of radicals. Accumulation of these radicals, or ROS, is severely detrimental to mitochondrial DNA, mitochondrial membranes and the whole cell. Abbreviations: Cyto-c, cytochrome c; CoQ10, coenzyme Q10; e⁻, electrons; GSH, glutathione; GSSG, oxidized glutathione; H₂O₂, hydrogen peroxide; O₂⁻, superoxide; P_i, phosphate; SOD, superoxide dismutase.

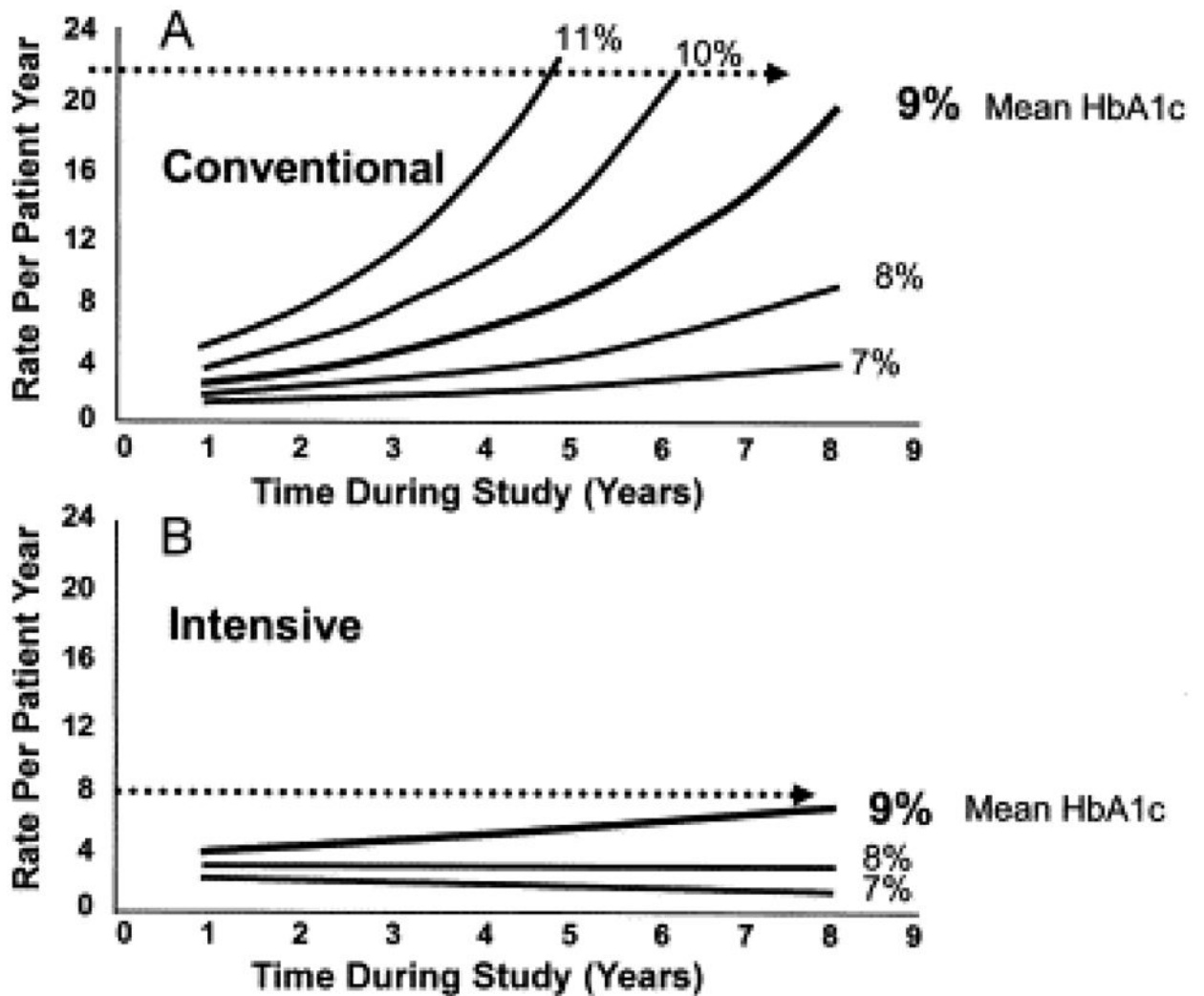


Figure 8. Risk of Diabetic Complications (Retinopathy) in Control vs. Intensive Therapy as related to Hb_{A1C}
 Absolute risk of sustained retinopathy progression as a function of updated mean A1C (percentage) during the DCCT and the time of follow-up during the study (years), estimated from absolute (Poisson) regression models. (A) Conventional treatment group. (B) Intensive treatment group. Results suggest that average glucose levels may be less important to prognosis of complications than fluctuations in glucose levels. Reprinted with permission from DCCT Research Group (1995) (Hirsch & Brownlee, 2005)

Stepwise pharmacological management of neuropathic pain (NP)

Step 1

- Assess pain and establish the diagnosis of NP; if uncertain about diagnosis, refer to pain specialist or neurologist
- Establish & treat cause of NP; if uncertain about availability of treatments addressing NP etiology, refer to appropriate specialist
- Identify relevant co-morbidities (e.g. cardiac, renal, or hepatic disease, depression, gait instability) that might be relieved or exacerbated by NP treatment, or that might require dosage adjustment or additional monitoring of therapy
- Explain diagnosis and treatment plan to patient and establish realistic expectations

Step 2

- Initiate therapy of disease causing NP, if applicable
- Initiate symptom treatment with one or more of the following:
 - Secondary amine TCA (nortriptyline, desipramine) or an SSNRI (duloxetine, venlafaxine)
 - Calcium channel $\alpha_2\text{-}\delta$ ligand, either pregabalin or gabapentin
 - For localized peripheral NP; topical lidocaine used alone or in combination with one of the other 1st line therapies
 - For patients with acute NP, neuropathic cancer pain or episodic exacerbations of severe pain, and when prompt pain relief during titration of a 1st line medication to an efficacious dosage is required, opioid analgesics or tramadol may be used alone or in combination with one of the 1st line therapies
- Evaluate patient for non-pharmacologic treatments and initiate if appropriate

Step 3

- Reassess pain and health-related quality of life frequently
- If substantial pain relief (e.g. average pain reduced to $<3/10$) and tolerable side effects, continue treatment
- If partial pain relief (e.g. average pain remains $>4/10$) after an adequate trial, add one of the other 1st line medications
- If no or inadequate pain relief (e.g. $<30\%$ reduction) at target dose after an adequate trial, switch to alternative 1st line medication

Step 4

- If trials of 1st line medications alone and in combination fail, consider 2nd and 3rd line medications or referral to a pain specialist or multidisciplinary pain center

Figure 9. Management of Neuropathic Pain

Stepwise instructions for treatment of the symptoms for painful diabetic neuropathy based on multiple levels of medications, pain scores and evaluations. Adapted from (Dworkin, 2007b)

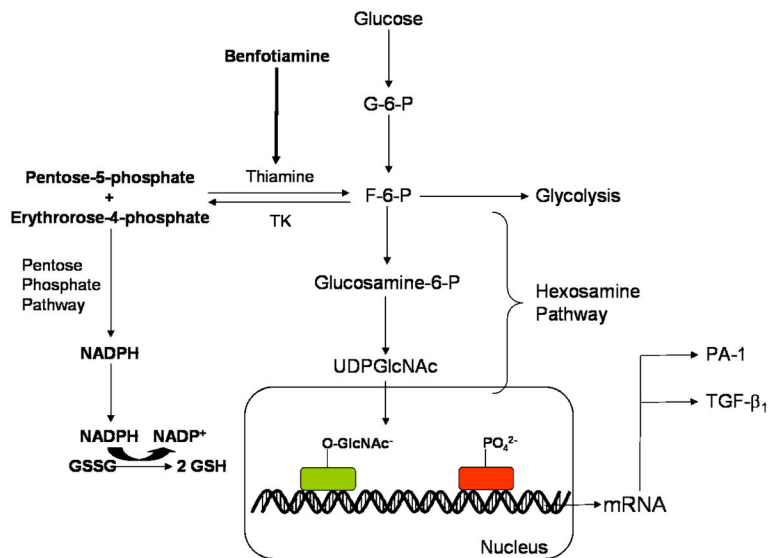


Figure 10. Diagram of Benfotiamine Effect on Biochemical Pathways in Diabetic Complications

Excess glucose activates flux through hexosamine pathway creating UDPGlcNAc from F-6-P. UDPGlcNAc modifies transcription factors which lead to inflammation. Addition of benfotiamine, a thiamine analog activates transketolase (TK) which diverts substrate away from the hexosamine pathway and into the pentose phosphate pathway. Adapted from (Hammes, 2003).

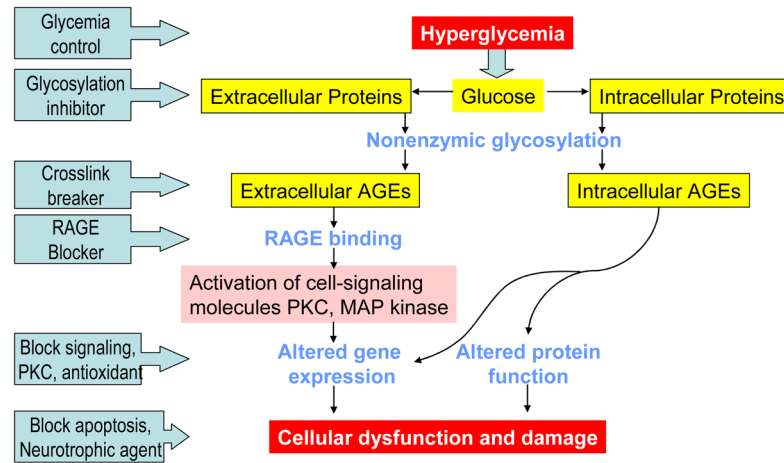


Figure 11. Therapeutic targets on the AGE-RAGE pathway to DN

The process of AGE damage and RAGE activation offer multiple approaches for preventing neuronal damage, from preventing AGE formation to blocking downstream signaling cascades.

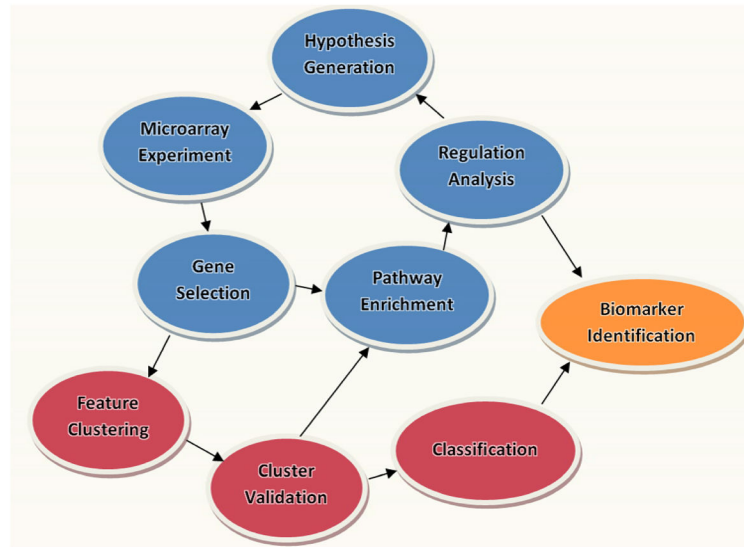


Figure 12.

Activities (in blue) are hypothesis driven and attempt to identify biomarkers based on the disequilibrium of identified targets in diabetic neuropathy, leading to an abnormal accumulation of products, such as modified proteins or small molecules. Activities in red are discovery oriented and seek to identify features of the data set that are predictive of diabetic neuropathy without necessarily corresponding to a single target.

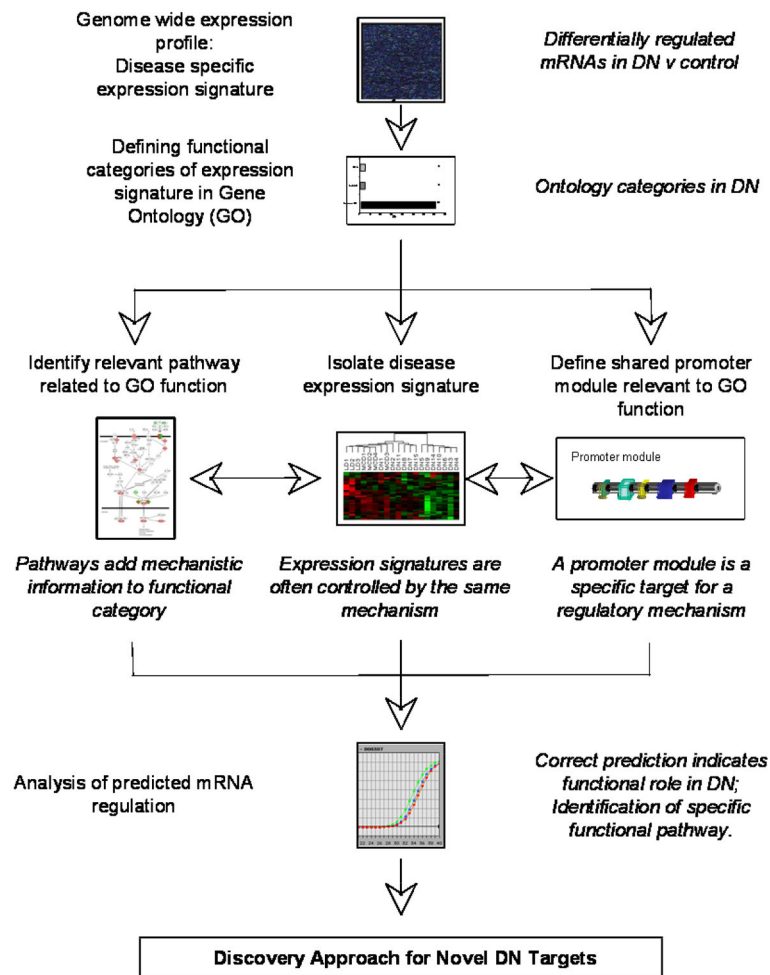


Figure 13.

Discovery Approach for Novel Targets in Diabetic Neuropathy (DN). Genome wide expression profiling of neural tissues from animal models with diabetic neuropathy (DN) will yield differentially regulated transcripts. Analyses of these data using Gene Ontology (GO) will provide the data needed to define categories of genes that are functionally related providing a molecular signature for diabetic neuropathy. Further analyses of these data can define relevant pathways related to functional gene categories and shared promoter modules among members of different gene categories, providing one or more specific targets for disease regulation. These targets can be verified at the mRNA level, confirming the identification of a novel disease target.

Table 1

Classification of Clinical Diabetic Neuropathy

Diffuse Neuropathy	Focal Neuropathy
Distal symmetrical sensorimotor polyneuropathy (DPN) <ul style="list-style-type: none"> • Small fiber • Large fiber • Mixed 	Mononeuropathy Mononeuropathy multiplex Plexopathy Radiculopathy Cranial neuropathy
Diabetic autonomic neuropathy (DAN) <ul style="list-style-type: none"> • Abnormal pupillary function • Sudomotor dysfunction • Genitourinary • Gastrointestinal • Cardiovascular • Hypoglycemia unawareness 	

Table 2

Clinical Manifestations of Diabetic Autonomic Neuropathy

<ul style="list-style-type: none"> • Pupillary <ul style="list-style-type: none"> - Decreased dark-adapted pupil diameter 	<ul style="list-style-type: none"> • Sudomotor <ul style="list-style-type: none"> - Anhidrosis - Heat intolerance - Gustatory sweating - Dry skin
-	<ul style="list-style-type: none"> • Gastrointestinal <ul style="list-style-type: none"> - Esophageal dysmotility - Gastroparesis - Constipation - Diarrhea, fecal incontinence
<ul style="list-style-type: none"> • Cardiovascular <ul style="list-style-type: none"> - Resting tachycardia - Exercise intolerance - Orthostatic hypotension - Silent myocardial ischemia 	<ul style="list-style-type: none"> • Genitourinary <ul style="list-style-type: none"> - Neurogenic bladder - Erectile dysfunction - Retrograde ejaculation - Female sexual dysfunction

Table 3

Reported Prevalence of Diabetic Peripheral Neuropathy

Reference	Diagnostic Criteria	Initial Prevalence (%)	Time of Initial Assessment	Later Prevalence (%)	Time of Later Assessment
(Pirart, 1978)	Neurological examination	7.5	At diagnosis	50	25 yr post-diagnosis
(Palumbo, 1978) T2DM	Symptoms and/or decreased vibratory sense	4	Within 5 yrs of diagnosis	15	20 yr post-diagnosis
(Young, 1993) T1DM, T2DM	Neurological examination and symptoms score	20.8		36.8	> 10 yr
(Dyck, 1993) T1DM, T2DM	Two or more abnormalities (symptoms, nerve conduction, QST*, AFT**)			T1DM: 54 T2DM: 45	Mean 14.5 yr Mean 8.1 yr
(Partanen, 1995)T2DM	Probable polyneuropathy Absent reflex	8.3 28	At Diagnosis	41.9 46	10 yr post-diagnosis
(The effect of intensive diabetes therapy on the development and progression of neuropathy. The Diabetes Control and Complications Trial Research Group, 1995)DCCT-T1DM	Confirmed clinical neuropathy Abnormal nerve conduction	2.1 21.8	Baseline (diabetes duration 1–5 yr)	9.6 40.2	5 yr post-baseline
(Tesfaye, 1996)T1DM	2 criteria	12	<7 yr duration	42	15 yr duration

* QST: quantitative sensory tests;

** AFT: autonomic function tests

Table 4

Classification and Staging of Diabetic Neuropathy

Class I: Subclinical Neuropathy	
Abnormal Electrodiagnostic Tests <ul style="list-style-type: none"> • Decreased nerve conduction velocity • Decreased amplitude of evoked potential (muscle or nerve) 	Class Ia: normal EDX, abnormal AFT or QST
Abnormal Quantitative Sensory Testing <ul style="list-style-type: none"> • Vibratory/Tactile • Thermal (warming/cooling) • Other 	Class Ib: abnormal EDX or abnormal AFT, and QST
Abnormal Autonomic Function Tests <ul style="list-style-type: none"> • Diminished sinus arrhythmia (beat-to-beat heart rate variation) • Diminished sudomotor function • Increased pupillary latency 	Class Ic: abnormal EDX and either abnormal AFT or QST, or both
Class II: Clinical Neuropathy – as detailed in Table 1	
AFT: autonomic function test EDX: electrodiagnostic tests, eg, nerve conduction and evoked potential QST: quantitative sensory testing	

Table 5

Diagnostic Tests for Cardiovascular Autonomic Neuropathy

Diagnostic Tests of CV Autonomic Neuropathy	
<i>Test</i>	<i>Diagnostic Value</i>
Resting heart rate	>100 bpm
Beat-to-beat HR variation (HRV) Abstain from coffee overnight Do not test after hypoglycemic episode Supine position, 6 breaths per minute	Difference < 10 bpm or expiration:inspiration R-R ratio > 1.17
Heart rate response to standing R-R interval measured at beats 15 and 30 after standing (normally tachycardia is followed by reflex bradycardia)	30:15 ratio > 1.03
Heart rate response to Valsalva maneuver Patient forcibly exhales into manometer mouthpiece, exerting 40 mmHg pressure for 15 seconds	Ratio of longest to shortest R-R interval < 1.2
Systolic BP response to standing Measure in supine position and 2 minutes after standing	Decrease > 30 mmHg (10 to 29 is borderline)
Diastolic BP response to isometric exercise Establish patient's maximum handgrip pressure Exert 30% maximum for 5 minutes	Increase < 16 mmHg in contralateral arm
Electrocardiography	QTc > 440 ms

Table 6

Pharmaceutical therapies for diabetic neuropathy

Drug	Number of patients	Daily Doses	Duration	Outcome	NNT	Reference
TCAs						
Amitriptyline	29	150mg	Cross over, 2X6 wks	Amitriptyline > placebo	2.1	(Max, 1987)
Desipramine	20	Average 201 mg	Cross over, 2X6 wks	Desipramine > placebo	2.2	(Max, 1992)
Imipramine	19	25-350 mg	Cross over, 3X2 wks	Imipramine > placebo	4	(Sindrup, 1990b)
Clomipramine	18	50-200 mg	Cross over, 3X2 wks	Clomipramine > placebo	4.5	(Sindrup, 1990c)
SSRIs						
Paroxetine	26	40 mg	Cross over, 3X2 wks	Paroxetine > placebo	5	(Sindrup, 1990a)
Citalopram	18	40 mg	Cross over, 3X2 wks	Citalopram > placebo	3	(Sindrup, 1992)
Fluoxetine	46	40 mg	Cross over, 2X6 wks	Fluoxetine = placebo	NA	(Max, 1992)
SNRIs						
Venlafaxine	244	150-225 mg	Parallel, 6 wks	Venlafaxine > placebo	4.5	(Rowbotham, 2004)
Duloxetine	457	20, 60, 120 mg	Parallel, 12 wks	Duloxetine (60mg, 120 mg) > placebo	60 mg: 4.3 120 mg: 3.8	(Goldstein, 2005)
Duloxetine	348	60 mg, 120 mg	Parallel, 12 wks	Duloxetine (60mg, 120 mg > placebo	60 mg: 11 120 mg: 5	(Raskin, 2005)
Duloxetine	334	60 mg, 120 mg	Parallel, 12 wks	Duloxetine (60mg, 120 mg > placebo	60 mg: 6.3 120 mg: 3.8	(Wernicke, 2006)
Anticonvulsants						
Carbamazepine	40	400 mg	Cross over, 2 wks	Carbamazepine > placebo	2.3	(Rull, 1969)
Lamotrigine	59	<400 mg	Parallel, 8 wks	Lamotrigine > placebo	4	(Eisenberg, 2001)
Oxcarbazepine	146	<1800 mg	Parallel, 16 wks	Oxcarbazepine > placebo	6	(Dogra, 2005)
Topiramate	323	<400 mg	Parallel, 12 wks	Topiramate > placebo	7.4	(Raskin, 2004)
Calcium channel α_2-δagonists						
Gabapentin	165	<3600 mg	Parallel, 8 wks	Gabapentin > placebo	4	(Backonja, 1998)
Pregabalin	146	300 mg	Parallel, 8 wks	Pregabalin > placebo	3.9	(Rosenstock, 2004)
Pregabalin	338	75, 300, 600 mg	Parallel, 5 wks	Pregabalin (300, 600 mg) > placebo	300 mg: 3.6 600 mg: 3.3	(Lesser, 2004)
Pregabalin	246	150, 600 mg	Parallel, 6 wks	Pregabalin (600 mg) > placebo	600 mg: 4.2	(Richter, 2005)

Drug	Number of patients	Daily Doses	Duration	Outcome	NNT	Reference
μ receptor agonists						
Tramadol	127	100–400 mg	Parallel, 6 wks	Tramadol > placebo	3.1	(Harati, 1998)
Oxycodone CR	159	10–100 mg	Parallel, 6 wks	Oxycodone > placebo	NA	(Gimbel, 2003)
NMDA antagonists						
Dextromethorphan	19	400 mg	Cross over, 9 wks	Dextromethorphan > placebo	3.2	(Sang, 2002)
Memantine	19	55 mg	Cross over, 9 wks	Memantine = placebo	NS	(Sang, 2002)
Topical agents						
Capsaicin cream	252	0.075% qid	8 wks	Capsaicin > placebo	NA	(The Capsaicin Study, 1992)

TCA: Tricyclic and tetracyclic antidepressants, SSRI: Selective serotonin reuptake inhibitors, SNRI: Serotonin-Norepinephrine Reuptake Inhibitors, NNT: number needed to treat, NA: not available. NS: not significant, Qid: four times a day.

Table 7

Approaches to Treatment of Orthostatic Hypotension

Treatment	Dose Regimen	Possible Side Effects
Support garments		
Behavioral advice Avoid sudden changes of body posture Avoid hot baths and predisposing medications Eat frequent small meals Take insulin injections lying down		
Fludrocortisone	0.1 mg titrated to 0.5 to 2.0 mg/day	May predispose to congestive heart failure, hypertension
Sympathomimetics Ephedrine Midodrine Clonidine	15 – 45 mg, TID 2.5 – 10 mg, TID 0.1 – 0.5 mg at bedtime	Sympathetic symptoms Fewer centrally-mediated side effects Hypotension
Octreotide	0.1 – 0.5 µg/kg/day	Injection site pain, diarrhea

Table 8

Approaches to Treatment of Diabetic Gastroparesis

Treatment	Dose Regimen	Possible Side Effects
Behavioral advice Improve glycemic control Eat frequent small meals Reduce dietary fat (<40 g/day) Reduce dietary fiber		
Metoclopramide	10 mg, 30–60 min ac	Galactorrhea, extrapyramidal symptoms
Erythromycin	250 mg, 30 min ac	Abdominal cramps, nausea, diarrhea, rash
Jujunostomy and liquid diet		

Table 9

Approaches to Treatment of Diabetic Diarrhea

Treatment	Dose Regimen	Possible Side Effects
Exclude other underlying causes: Bacterial overgrowth Drug-related (acarbose, metformin, lactose intolerance) Osmotic (resolves with fasting) Secretory (consider neuroendocrine tumors)		
Metronidazole	250 mg, TID, 3 wk	Fungal overgrowth
Clonidine	0.1 mg, BID or TID	Orthostatic hypotension
Loperamide	2 mg, QID	Toxic megacolon
Cholestyramine	4 g, 1 to 6 times daily	
Octreotide	50 µg, TID	Aggravated nutrient malabsorption

Table 10

Therapeutics for the Polyol Pathway

Compound	Trials/Notes	References
Sorbinil	Only slight improvement in NCV; high rate of skin rash, trial withdrawn	(Judzewitsch, 1983)
Tolrestat	Halted mild diabetic neuropathy progression; no significant improvements in NCV, trial withdrawn	(Boulton, 1990; Giugliano, 1993)
Ponalrestat	No effect due to poor pharmacokinetics & pharmacodynamics, trial withdrawn	(Greene & Sima, 1993; Stribling, 1985)
Zopolrestat	Low levels: slight NCV improvement High levels: significant improvement in NCV; elevated liver enzymes, trial withdrawn	(Arezzo, 1996)
Zenarestat	Dose dependent improvement of NCV	(Gabbay, 2004; Greene, 1999)
Lidorestat	Withdrawn at Phase 2 clinical trial	
Fidarestat	Similar to Sorbinil, suspended in phase 3 due to resource consolidation	(Giannoukakis, 2003)
AS-3201/ Ranirestat	Promising Phase 2 trials; Phase 3 underway. High placebo effect complicating study	(Bril & Buchanan, 2006; Oates, 2008, in press)
Epalrestat	Delayed progression of diabetic neuropathy, study not replicated	(Hotta, 2006)
Myo-inositol	Animal studies indicate beneficial effects, human studies needed	(Sima, 1997)

NCV=Nerve Conduction Velocity

Table 11

Antioxidant therapy in diabetic neuropathy

Compound	Trials/Notes	References
Coenzyme Q10	Cofactor that improves metabolism but also a potent antioxidant.	(Bonnetfont-Rousselot, 2004; Eriksson, 1999)
Nicotinamide	(AKA vitamin B3) is a weak PARP inhibitor, antioxidant, and calcium modulator. Effective in experimental diabetes and currently in a type 1 diabetes patient trial.	(Bonnetfont-Rousselot, 2004; Eriksson, 1999; Stevens, 2007)
Eugenol	From clove oil; both anti-inflammatory and antioxidant. Improves vascular and neural deficits in STZ-treated rats.	(Nangle, 2006)
Taurine	Plasma taurine is depleted in diabetic rats and replacement decreases hyperalgesia and other neural and vascular deficits.	(Li, 2006; Li, 2005; Pop-Busui, 2001)
U83836E	A synthetic ROS scavenger, effective against oxidative stress, and neurovascular deficits in rats.	(Sayyed, 2006)
Oleuropein	From olive leaf, decreases blood glucose as well as oxidative stress in alloxan-treated rabbit.	(Al-Azzawie, 2006)
Minerals	Metal ions including vanadium, chromium, magnesium, zinc, selenium, copper contribute to antioxidant defense. They may become depleted in diabetic patients and should be included in the diet.	(Bonnetfont-Rousselot, 2004)
Vitamin C	While vitamin C does not improve diabetes complications when given alone, it is used in combination with vitamin E or other antioxidants, since it facilitates effective antioxidant recycling.	(Dorchy, 1999; Jacobs, 2002; Will, 1999)
Quercetin	A flavonoid that attenuates thermal hyperalgesia and cold allodynia in STZ-induced diabetic rats	(Anjaneyulu, 2004)
Melatonin	Plasma levels decrease in diabetic patients with complications, supplementation reverses antioxidant status deficits and prevents complications. May both activate antioxidant response and scavenge ROS.	(Anwar & Meki, 2003; O'Brien, 1986; Tutuncu, 2005)
Apocynin	Decreases oxidative stress by inhibition of NAD(P)H oxidase	(Cotter, 2003a)
Rutin	A polyphenol that may activate the antioxidant response. Prevents oxidative stress in diabetic rats.	(Je, 2002)
Dimethylthiourea	A hydroxyl radical scavenger, prevents diabetes-induced mechanical and thermal nociceptive sensitivity and nerve blood flow deficits.	(Cameron, 2001)
Evening primrose oil	Initially used for therapeutic benefit of polyunsaturated fatty acids, also decreases oxidative stress. Efficacy further enhanced by conjugation with an antioxidant.	(Cameron, 1996; Ford, 2001)
Nitecapone	Catechol-O-methyltransferase inhibitor with potent antioxidant properties. Had some ability to prevent diabetic mechanical hyperalgesia, but essentially ineffective in preventing the development of diabetic neuropathy	(Pertovaara, 2001)
Troglitazone	Used as an insulin sensitizer in diabetic patients, but also operates as an antioxidant. May improve peripheral neuropathy in STZ-induced diabetic rats irrespective of blood glucose concentrations.	(Qiang, 1998)
N-acetylcysteine	Precursor of GSH that increases tissue GSH improves motor nerve conduction velocity and decreases oxidative stress in STZ-treated rats	(Sagara, 1996)