Polyneuropathy with Impaired Glucose Tolerance: Implications for Diagnosis and Therapy

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Opinion statement

Prediabetes is associated with a length-dependent polyneuropathy that typically is sensory predominant and painful. A diagnosis of prediabetes should be sought in patients with otherwise idiopathic sensory-predominant neuropathy by doing a 2-hour oral glucose tolerance test. Fasting plasma glucose of 100 to 125 mg/dL or 2-hour glucose 140 to 199 mg/dL (impaired glucose tolerance) constitutes prediabetes. Most patients with neuropathy associated with prediabetes (NAP) are obese and show metabolic manifestations of insulin resistance, including hyperlipidemia and hypertension. Appropriate treatment addresses hyperglycemia, insulin resistance, and neuropathic pain. Professionally administered individualized diet and exercise counseling (modeled on the Diabetes Prevention Program) has been shown to be more effective than glucose-lowering medications in preventing progression from impaired glucose tolerance to diabetes, and is the mainstay of treatment for all patients with NAP. The goals of this therapy should be a 5% to 7% reduction in weight and an increase to 30 minutes of moderate exercise five times weekly. Patients with prediabetes are at increased risk for myocardial infarction, stroke, and peripheral vascular disease. Therefore, risk reduction with control of hypertension and hyperlipidemia is essential. Neuropathic pain troubles nearly every patient with NAP, and often limits aerobic exercise. No trials have specifically addressed the patient population with NAP, and neuropathic pain treatment closely follows recommendations for diabetic neuropathy. Gabapentin, lamotrigine, and tricyclic antidepressants are well-validated first-line therapies. Adjunctive therapy with opioids, nonsteroidal anti-inflammatory drugs often are necessary. Diet and exercise seem to reduce neuropathic pain in patients with NAP.

Introduction

Eleven percent to 14% of asymptomatic Americans aged 50 to 75 years have prediabetes, as defined by the American Diabetes Association [1•]. Interest in prediabetes has escalated in the past decade as a marker for the insulin resistance syndrome (also called Syndrome X), which consists of hyperinsulinemia, hyperlipidemia, and hypertension. Patients with prediabetes are at increased risk for cardiovascular and peripheral vascular occlusive disease, independent of risk for diabetes [2, Class I; 3–6]. Because of these risks, the American Diabetes Association recommends screening for prediabetes in all patients older than 45 years, and in younger

patients with a body mass index more than 25 and additional risk factors for diabetes (family history). Screening can be accomplished with fasting plasma glucose or a 2-hour glucose tolerance test (OGTT), as described in Table 1.

Neuropathy is a common complication of chronic hyperglycemia. More than 50% of patients with diabetes develop clinical symptoms of neuropathy within 25 years of diagnosis [7,8]. However, nerve conduction studies are abnormal in 10% to 18% of patients at the time of diabetes diagnosis [9,10], suggesting that length-dependent nerve injury can predate the development of diabetes. Recent epidemiologic studies and case series establish a statistical association between neuropathy and prediabetes [11•,12–14]. Methodical prospective screening of patients with idiopathic neuropathy shows that 30% to 50% patients with otherwise idiopathic neuropathy have impaired glucose tolerance (IGT) [11•], three times the background rate [1•]. Similarly, a cross-sectional study using a combination of physical examination and focused history, and validated with vibration threshold measurement, found neuropathy in 26% of 279 patients with diabetes, 11.2% of 89 patients with IGT, and 3.9% of 577 age-matched normal control subjects [15]. It is important to understand that no study has yet established a causative link between prediabetes and neuropathy.

Most patients with neuropathy associated with prediabetes (NAP) have a symmetric, distal sensory neuropathy with neuropathic pain [11•,12,13,16]. Sensory loss in feet typically is accompanied by positive symptoms of uncomfortable tingling, lancinating, or burning paresthesias. Nocturnal foot pain often prevents sleep initiation. Patients describe allodynia from blankets and sheets, and sleep with their feet on top of the covers, or construct foot tents. Patients may have symptoms of leg restlessness at rest consistent with restless legs syndrome. Male patients often describe erectile dysfunction, but other clinical manifestations of autonomic neuropathy are rare. Distal weakness rarely is a first complaint, and may be absent or minimal after years of sensory symptoms.

The clinical history should particularly include childhood illness or foot deformities, and family history of neuropathy, sensory loss, foot pain, walking difficulties, foot deformities, and diabetes. Familial neuropathy is underdiagnosed, and may not be clinically apparent until late middle age [17•]. Examination often shows loss of foot intrinsic muscle bulk. Ankle reflexes often are diminished, but may be normal. Sensory deficits are most commonly recognized in response to pinprick, reflecting loss of small, cutaneous, pain-afferent fibers. Most patients with IGT neuropathy are moderately obese (mean body mass index, 32.4) [11•].

Initial diagnostic blood testing of idiopathic painful neuropathy should query the few common and treatable causes of sensory neuropathy. High yield testing includes serum vitamin B12, thyroid-stimulating hormone, serum protein electrophoresis, and 2-hour OGTT. Antigliadin antibodies associated with celiac disease have been reported in approximately 33% of patients with idiopathic neuropathy in a recent small series. OGTT is significantly more likely to detect a defect in glucose handling in patients with idiopathic neuropathy than fasting plasma glucose or hemoglobin A1c [11•,16]. Therefore, OGTT should be done in preference to other glucose tests.

Clinically suspected neuropathy should be confirmed using one of several ancillary tests. Nerve conduction studies and electromyography are most widely available. However, because NAP often affects predominantly small-diameter unmyelinated fibers, nerve conduction studies may be relatively insensitive as a confirmatory test. In one small series, nearly 25% of subjects with NAP had normal nerve conduction studies. Confirmatory tests more specific to small fiber function include quantitative sensory testing, quantitative sudomotor axon reflex testing, and skin punch biopsy with tabulation of intra-epidermal nerve fiber density [18].

Neuropathy associated with prediabetes is a newly recognized, yet unproven, clinical entity. As a consequence, Initial studies to characterize the natural history of NAP are ongoing, but dedicated treatment trials have not been reported. However, glycemic control must be regarded as the linchpin of effective treatment for NAP. The landmark Diabetes Control and Complications Trial conclusively showed that aggressive glycemic control reduces onset and progression of diabetic peripheral polyneuropathy, and that treatment early in the course of hyperglycemia is more effective [19••, Class I; 20].

Two recent, methodologically robust studies indicate that aggressive diet and exercise counseling for patients with IGT significantly reduces hyperglycemia and lowers the risk of progression to diabetes (Table 2) [21••,22•, Class I]. These studies establish a new standard of care for patients with IGT. Early recognition of prediabetes in patients with neuropathy should be regarded as an opportunity for intervention to forestall the development of diabetes and the recognized cardiovascular complications of insulin resistance [23]. The goals of the DPP are appropriate and achievable for most patients: a 7% reduction in weight, and 150 minutes of moderate exercise weekly. For those patients who are unable to exercise, glucose-lowering agents have proven efficacy, and should be considered.

As described previously, neuropathic pain is a reported almost universally by patients with NAP, and often is disabling. Recent preliminary studies indicate that compliance with diet and exercise counseling is associated with a reduction in foot pain in these patients [24, Class II]. However, neuropathic pain rarely responds to glycemic control. The mainstays of

Table 1. Prediabetes diagnostic criteria

	Plasma glucose value (mg/dL)		
Test	Normal	Prediabetes	Diabetes
Fasting plasma glucose	<100	100–125	>124
2 hour value in OGTT*	<140	140–199	>200

OGTT—Oral glucose tolerance test.
*For an OGTT, the patient should fast overnight after dinner, having fasting blood drawn before 8:30am, and then should receive 75 mg oral glucose. The patient should not exercise before having blood drawn again after 120 minutes. The American Diabetes Association has not issued guidelines for plasma values drawn before or after 120 minutes

therapy are anti-epileptic agents, tricyclic antidepressants, and opiates. In choosing therapy, it is important to consider efficacy, ease of dosing, side-effect profiles, and other factors specific to patients with NAP. A substantial minority of neuropathy patients have associated restless legs syndrome [25]. Tricyclic antidepressants have been reported to exacerbate this condition. Often, the patient's bed partner complains that the patient develops increased periodic leg movements during sleep after amitriptyline initiation. Conversely, gabapentin has proven efficacy in treatment of primary restless legs syndrome [26, Class I], though trials in patients with associated neuropathy have not been done.

Treatment

Diet and lifestyle

- Most patients with NAP are obese and sedentary, typically reporting essentially no weekly exercise. Individualized diet and exercise counseling should be prescribed for every patient with NAP, ideally modeled on the procedures and goals of the Diabetes Prevention Program (Table 2) [27, Class I]. It is important to recognize that the goal of this counseling is "lifestyle change"; a sustained modification in patients' daily activity that results in weight loss and altered dietary habits
- Standard goals are to reduce weight by 7%, and increase moderate exercise to 150 minutes weekly, (30 minutes, five times per week). Patients are encouraged to work toward these goals during a 6-month period.
- Moderate exercise is practically defined as aerobic exercise sufficient to make casual conversation slightly difficult.
- Certified nutritionists should administer diet counseling if possible.
- Although the DPP counseled patients 2 to 4 times monthly, this usually is impractical. Monthly counseling for 3 months followed by quarterly visits often is achievable.
- Patients with ataxia or a history of falls should receive physical therapy for gait training to minimize fall risk.
- Patients frequently have neuropathic foot pain that is exacerbated acutely by high-impact exercise such as jogging, and is reported to limit exercise tolerance. Low-impact exercise modes include swimming, water walking, and use of stationary bicycles and elliptical trainers.
- Patients should be encouraged to find one or more "exercise buddies" with similar conditioning. Buddies have been shown to increase exercise compliance.

Table 2. Efficacy of diet and exercise counseling in prediabetes [21••,22•, Class I]

	Diabetes Prevention Program [21••, Class I]	Finnish Diabetes Prevention Study Group [22•, Class I]
IGT patients enrolled	3234	522
Treatment groups	Placebo Metformin Intensive diet and exercise	General diet instructions Intensive diet and exercise
Diet and exercise goals	Reduced weight 7%, moderate exercise for 150 minutes/week	Reduced weight 5%, Moderate scheduled exercise
Follow-up	5 years (stopped at 3.5 years)	Mean, 3.2 years
Progression to diabetes during follow-up (%)	Placebo=29 Metformin=22 Intensive/exercise=14	General diet instructions=23 Intensive diet and exercise=11

IGT—impaired glucose tolerance.

- In a small prospective study of patients with NAP, diet and exercise compliance has been associated with a reduction in neuropathic pain, as measured by visual analogue scale.

Pharmacologic therapy

- Currently, pharmacologic therapy in NAP is applicable primarily for control of neuropathic pain. It is emphasized that trials of pain medications have not been done for patients with NAP. Recommendations for pharmacologic therapy are extrapolated from results of clinical trials for patients with diabetic neuropathy.
- Meta-analysis has established the number of patients with neuropathic pain (associated with diabetic neuropathy) necessary to treat to achieve a 50% pain reduction in one patient [28•, Class I]. These numbers necessary to treat are listed in Table 3.
- Patients unable to exercise because of pain, or who fail to comply with diet and exercise counseling should receive a glucose-lowering agent.

Pharmacologic agents for reduction in blood glucose

- The Diabetes Prevention Program and other trials have shown that treatment to reduce blood glucose inhibits progression from IGT to prediabetes [21••, Class I]. Changes in diet and exercise habits are difficult to sustain. In patients unable or unwilling to comply with diet and exercise counseling, or whether this counseling is unavailable because of travel distance or failure of insurance coverage, medication to lower blood glucose may be indicated. In the DPP, metformin reduced progression to diabetes by 31% [21••, Class I]. The insulin-sensitizing agent troglitazone reduced progression to diabetes by 50% in a randomized, placebo-controlled trial (133 subjects in each treatment arm) among Hispanic women with a history of gestational diabetes [29, Class I]. However, troglitazone has been withdrawn from the market because of liver toxicity. Active trials of other insulin sensitizing agents are being done. The Study to Prevent Non-insulin Dependent Diabetes Mellitus trial randomized 1430 patients with IGT aged 40 to 70 years to receive either placebo or acarbose (mean dose 194 mg/day) [30, Class I]. During the 3-year treatment period, 42% of placebo subjects and 32% of those taking acarbose progressed to diabetes, a reduction of 25%. However, in a 3-month placebo washout period, patients previously taking acarbose were more likely to progress to diabetes. Overall,

Table 3. Relative efficacy of pain medications for diabetic neuropathy [28•, Class I]

Drug	Number needed to treat*
Imipramine	1.4
Tricyclic antidepressants in aggregate	2.4
Tramadol	3.4
Gabapentin	3.7
Mexilitine	10

*Number of subjects receiving treatment to obtain 50% reduction in pain in one subject. A low number-needed-to-treat indicates greater efficacy.

metformin probably is the best validated of these agents for IGT. However, pharmacologic management of prediabetic hyperglycemia may go beyond the purview or interest of many neurologists.

Pharmacologic agents for control of neuropathic pain

Tricyclic antidepressants

- Tricyclic antidepressants (amitriptyline, nortriptyline, and desipramine) have been mainstays of neuropathic pain treatment, with efficacy proven in numerous well-designed studies [31, Class I; 32•, Class I]. A small, double-blind, crossover study found that amitriptyline had equal similar efficacy to gabapentin for treatment of neuropathic pain associated with diabetic neuropathy, and was as well tolerated [33, Class I]. Tricyclic antidepressants are inexpensive, and because of their long half-life, dosing is simple. When administered 2 hours before bedtime, amitriptyline may aid in sleep initiation, often at low doses. This sedative effect is durable, and is of significant benefit for patients who report that neuropathic pain increases with rest, and makes it difficult to fall asleep at night.

Amitriptyline

Standard dosage	50 to 200 mg, 2 hours before bedtime. To minimize side effects, patients should begin at 10 mg, and increase by 10 mg increments every 5 days to an initial plateau dose of 50 mg. Dosing increases then may proceed in 25 mg increments.
Contraindications	Partial or complete heart block. Older patients should have an electrocardiogram in evaluation of conduction defects. Patients taking monoamine oxidase inhibitors should not take tricyclics.
Main drug interactions	Monoamine oxidase inhibitors have a synergistic effect, resulting in hypertension, hyperpyrexia, confusion, seizures and rare deaths (serotonin syndrome). Similarly, SSRIs, verapamil, diltiazem, and phenothiazines inhibit tricyclic metabolism, resulting in possible toxicity. Beta agonists may increase the risk of cardiac arrhythmias.
Main side effects	Orthostatic hypotension, urinary hesitancy, fatigue and somnolence, confusion, and exacerbation of heart conduction defects.
Special points	A substantial minority of neuropathy patients have associated restless legs syndrome [25], and tricyclics have been reported to exacerbate this condition. Physicians should inquire about restless legs syndrome symptoms before choosing amitriptyline.
Cost/cost effectiveness	Very inexpensive. A daily dose of amitriptyline costs approximately $0.60. A daily dose of imipramine costs approximately $0.35.

Gabapentin

	Gabapentin is an anticonvulsant approved by the United States Food and Drug Administration for control of partial-onset seizures, with a recent indication for neuropathic pain associated with herpes zoster. Although structurally related to the pain modulating neurotransmitter gamma-aminobutyric acid, gabapentin acts neither as gamma-aminobutyric acid agonist or antagonist, and its mechanism of action is unclear. In several placebo-controlled, randomized trials including patients with painful neuropathies, gabapentin has been shown to significantly reduce neuropathic pain and improve sleep [34•, Class I].
Standard dosage	1800 to 3600 mg/day, divided into three daily doses. Begin dose escalation of gabapentin at 300 mg taken 2 hours before bedtime, increasing in 300 mg increments every 3 to 7 days to 600 mg three times daily. This conservative escalation schedule minimizes side effects. However, patients beginning gabapentin for partial-seizure prophylaxis routinely escalate by 300 mg daily, with dizziness as the only increased side effect compared to more conservative schedules [35]. A therapeutic trial should involve at least 4 weeks at a therapeutic dose, and many patients require more than 1800 mg daily in divided doses to achieve pain reduction.
Contraindications	Renal failure or insufficiency (relative).
Main drug interactions	Renal excretion results in no interaction with hepatic p450-metabolized drugs.
Main side effects	Dizziness and somnolence are the only side effects reported to occur more frequently in patients taking gabapentin than in those receiving placebo.
Special points	Although gabapentin has a relatively low number needed to treat (Table 3), it often is preferred as an initial treatment option because of its benign side effect and drug interaction profile. No routine blood monitoring is required. Gabapentin has proven efficacy in treatment of primary restless legs syndrome [26], though trials in patients with associated neuropathy have not been done.
Cost/cost effectiveness	Gabapentin is relatively expensive. One daily dose of brand name gabapentin currently costs approximately $6. Loss of patent rights and production as a generic will substantially reduce cost.

Lamotrigine

	Lamotrigine, an inhibitor of voltage-gated sodium channels, inhibits excitatory neuronal glutamate and aspartate release. Lamotrigine significantly reduced pain in sensory neuropathy associated with human immunodeficiency virus [36, Class I]. Trials specific to diabetic neuropathy have not been published.
Standard dosage	200 to 500 mg/day, usually divided into two daily doses. Start 50 mg/day for 2 weeks, then 50 mg twice a day for 1 to 2 weeks, then titrate to effect by increasing dose 50 to 100 mg every 1 to 2 weeks, divided into two daily doses.
Contraindications	Known allergy or hypersensitivity.
Main drug interactions	Valproic acid reduces lamotrigine metabolism, doubling bioavailable drug. If lamotrigine is started in patients taking valproic acid, ramp-up dosing should be halved, and drug monitoring is indicated. Other antiepileptic drugs have significantly less effect on lamotrigine biometabolism.
Main side effects	Headache, dizziness, nausea, and ataxia are common, especially with initial dosing. Most patients rapidly adapt to these transient side effects. Rash occurs in 2%, and serious rash occurs in 0.3% of patients. Life-threatening hypersensitivity reactions or multi-organ failure, and blood dyscrasias are rare, but serious, side effects.
Special points	Patients should be instructed to stop taking lamotrigine if any rash develops because serious rashes may evolve from mild rash unpredictably. A therapeutic plasma level has not been established for lamotrigine, and monitoring generally is not indicated unless the patient is taking valproic acid.
Cost/cost effectiveness	Treatment is expensive. A daily dose of lamotrigine costs approximately $7.

Other antiepileptic drugs

- In a crossover trial, carbamazepine compared favorably to nortriptyline for treatment of diabetic neuropathy [37, Class I], and is particularly effective in reducing painful lancinating paresthesias [38]. Clinical trials of phenytoin have produced equivocal results. Experience with newer anticonvulsants, including zonisamide, tiagabine, levetiracetam, oxcarbazepine, and topiramate is limited to anecdotal reports and small trials [39]. Newer antiepileptic agents typically are expensive.

Opiates

- Opiates have a defined role as adjunct treatment in poorly controlled neuropathic pain, but often are overlooked because of concerns for tolerance and addiction. Oral opiates have shown efficacy in the treatment of intractable neuropathic pain secondary to postherpetic neuralgia [40, Class I]. There have been no controlled trials of opiates in neuropathy associated with diabetes or prediabetes.

Oxycodone, hydrocodone, and morphine

Standard dosage	Immediate release oxycodone 2.5 to 10 mg can be given every 6 hours initially or for breakthrough pain. Sustained release oxycodone 5 to 10 mg should be given in the evening, or every 12 hours if necessary. Hydrocodone 5 to 10 mg can be given every 6 hours initially or for breakthrough pain. Controlled release morphine 15 to 30 mg can be given every 8 to 12 hours. Dosage typically starts with a short-acting agent, such as hydrocodone or oxycodone titrated slowly to efficacy or side effect. After an effective dose has been found, conversion to a long-acting ("time contingent") opiate such as extended-release morphine or oxycodone helps provide sustained pain relief with fewer side effects. A short-acting agent may be used for breakthrough pain or exacerbations.
Contraindications	Allergy or hypersensitivity and chronic ethanol or sedative use.
Main drug interactions	Ethanol and benzodiazepines synergize with opiates to cause respiratory depression and sedation. Patients should be counseled to avoid alcohol consumption.
Main side effects	Constipation is the most common side effect of low-dose oral opiate use. Prophylactic institution of a bowel control regimen helps prevent constipation. Sedation and central respiratory depression are of concern at higher doses, and may be more dangerous in obese patients with obstructive sleep apnea. Hypotension and negative cardiac inotropic effects. Long-term use causes variable tolerance and physical dependence.
Special points	Treating physicians often are reluctant to prescribe opiates because of the concern for risk of addiction. Although physical dependence occurs in many patients, it is rarely a problem. A prospective study in patients with diabetes suggests that psychologic dependence and addiction are rare when these agents are used for pain, even for long periods [41, Class II]. Patients should taper off of opiates rather than stopping them suddenly. Patients at higher risk of addiction, such as those with a history of drug or alcohol abuse may require referral to a pain specialist. In patients with an initial response to oral opiates but who subsequently become resistant, consideration of an intrathecal morphine pump is appropriate.
Cost/cost effectiveness	Inexpensive to moderately expensive, depending on dose and agent. A daily dose of oxycodone costs $1.50 to $2. A daily dose of hydrocodone costs approximately $3. A daily dose of sustained-release morphine sulfate costs approximately $5.

Other pharmacologic agents for neuropathic pain

- Tramadol, an agent that binds to opiate receptors and blocks reuptake of serotonin and norepinephrine, was significantly more effective than placebo in treating neuropathic pain in a 42-day double-blind, placebo-

controlled study of 131 subjects with diabetes [42, Class I]. Long-term use of tramadol in patients with diabetic neuropathy did not result in significant tolerance or dose escalation [41, Class II].

- Mexiletine is an orally active local anesthetic agent that showed statistically significant reduction in visual analogue scale pain ratings for diabetic neuropathy patients in two small trials at doses of 225 to 675 mg day. Nausea and other gastrointestinal complaints were the most common side effects [43, Class II].
- Capsaicin cream is applied topically, and acts to reduce pain sensation by depleting substance P from proximal terminals of cutaneous nociceptive c-fibers. Its use is well validated in patients with herpes zoster. In a study of 13 patients with painful diabetic neuropathy, capsaicin reduced pain visual analogue scale while improving heat pain perception threshold [44, Class II]. Capsaicin is practical only for patients with small areas of neuropathic pain. Pragmatically, few patients tolerate capsaicin therapy. The cream must be applied 3 to 4 times daily using rubber gloves to avoid affecting non-painful skin or mucosa. Failure to maintain treatment for even one dose allows substance-P regeneration and recrudescence of pain.

Surgery

- Surgery has no routine role in the treatment of NAP or diabetic neuropathy. Patients with diabetic neuropathy are more likely to develop compressive focal mononeuropathies (carpal tunnel syndrome or ulnar mononeuropathy at the elbow) that may be amenable to surgical decompression. The recently described practice of multiple lower extremity compressive-site decompression as a more generalized therapy for diabetic neuropathy has received no controlled evaluation. Bariatric surgery is effective for carefully selective patients with morbid obesity, but there is no published data regarding short-term or long-term effects on neuropathy.

Assistive devices

- Neuropathy associated with prediabetes typically presents as a mild, sensory predominant neuropathy for which assistive devices are not indicated. Some patients with gait ataxia may benefit from use of a cane to supplement foot proprioception. Foot dorsiflexion weakness sufficient to indicate use of ankle foot orthotics should strongly suggest an alternative or additional cause of peripheral neuropathy.

Emerging therapies

- Rational pharmacologic therapies targeted to the known pathogenesis of hyperglycemic neuropathy (aldose reductase inhibitors, free-radical scavengers, vasodilatory agents) have failed to slow or reverse neuropathy in diabetic patients [45]. In part, this failure may be attributable to the relatively advanced neuropathy present at the time of treatment for diabetic patients [46]. Patients with NAP typically exhibit a neuropathy that is mild clinically and electrodiagnostically. Therefore, patients with NAP may respond better to rationally targeted therapies. Agents that may be of value include alpha-lipoic acid, aldose reductase inhibitors, and growth factors.

Pediatric considerations

- Neuropathy associated with prediabetes is associated with insulin resistance that develops prior to the onset of type II diabetes. While type II diabetes (and thus prediabetes) has been recognized with increasing frequency in obese children, it remains rare. No studies have addressed glucose control or risk reduction in this population. Diet and exercise counseling modeled on the Diabetes Prevention Program is appropriate.

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