



Inside Bangladesh

Ketosis resistance in under thirty diabetic subjects.

Young onset diabetic subjects in tropical developing countries include a group of subjects who exhibits a characteristic ketosis resistance termed as Malnutrition Related Diabetes Mellitus (MRDM) by the WHO Study Group. The mechanism for this resistance to ketosis is still uncertain. To understand this mechanism we have studied the serum responses of glucose, non-esterified fatty acid (NEFA) and triglyceride (TG) to intravenous fat emulsion in newly diagnosed 8 fibrocalculous pancreatic diabetes (FCPD) and 11 low insulin secretory (LIS) subjects under 30 years of age along with 27 age-matched Non Insulin Dependent Diabetes Mellitus (NIDDM) subjects. Overnight fasting subjects were given a 90 min infusion of intralipos 10% (2.5 mg/kg body weight/min) and serum was collected at 0, 60, 90, 120 and 150 min. The fasting NEFA in the 3 groups were almost similar (micromol/l, M +/- SEM: 486 +/- 58, 564 +/- 76 and 559 +/- 34 in FCPD, LIS and NIDDM respectively). Fasting TG also showed a close similarity among 3 groups (mg/dl, M +/- SEM: 117 +/- 11, 110 +/- 22 and 123 +/- 4 in FCPD, LIS and NIDDM respectively). Intravenous fat caused a steady rise of NEFA as well as TG in all groups during the 90 minutes of infusion followed by a gradual fall. No two groups significantly differed regarding NEFA and TG at any time point. Fasting glucose was markedly higher in FCPD (22.9 +/- 2.5, mmol/l, M +/- SEM) and LIS (20.8 +/- 1.6) than NIDDM (11.0 +/- 1.0). In all the 3 groups glucose showed a slow but steady fall. Fasting C-peptide was very low in FCPD (0.42 +/- 0.08, ng/ml, M +/- SEM) and LIS (0.55 +/- 0.09) whereas it was within normal range in NIDDM patients (2.99 +/- 0.24). The results suggest the following: (a) Depleted body fat store do not lead to a decreased supply of NEFA in FCPD and LIS subjects at the fasting state; (b) Increased supply of NEFA in these subjects lead to a normal esterification response as evidenced by a parallel rise of TG; (c) In spite of markedly low level of the antilipolytic hormone insulin, FCPD and LIS subjects are capable to maintain NEFA and TG responses similar to NIDDM subjects. This may indicate that factor (s) other than substrate and esterification is (are) probably involved in the ketosis resistance of FCPD and LIS subjects; and (d) Although FCPD and LIS differ regarding generalized pancreatic damage (which raises the possibility of involvement of glucagon producing alpha-cells in the FCPD group) the two groups do not differ regarding the ketogenic substrate and esterification responses.

Source: Sutradhar SR, Ali L, Khan AK, Siddiqui NI, Sarker CB, Rahman S, Huq MH, Debnath CR. Mymensingh Med J. 2004 Jul;13(2):134-7.

Diabetescope

Alprazolam reduces glycated hemoglobin level

Anxiety is a common disorder and almost all diabetic patients suffer with various anxiety disorders. One of the main reasons for that is the fear regarding diabetes regulation. Besides the anti-diabetic products, surprisingly Alprazolam, which is mainly an anxiolytic, significantly improves glucose regulation in diabetic patients.

In a study (conducted by Department of Psychiatry, Washington University School of Medicine), Fifty-eight patients with poor glycemic control, 16 (27.6%) of whom had a symptomatic generalized anxiety disorder, were entered into a randomized, double-blind, placebo-controlled, 8-week trial using Alprazolam (up to 2 mg/day) as the active agent. The result was surprising! A statistically significant reduction in glycosylated hemoglobin level was observed in patients treated with Alprazolam compared with those receiving placebo (-1.1% vs. -0.3%, $P = 0.04$). Anxiety symptoms decreased in both Alprazolam and placebo-treated patients with generalized anxiety disorder, but reduction in glycosylated hemoglobin level was not dependent on alleviation of anxiety. They came in the conclusion that a short course of Alprazolam improved glucose regulation in patients with a history of poor diabetes control.

Source: Diabetes Care 1995, Vol. 18, Issue 8 1133-1139

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Higher Vitamin D Levels May Lower Type 2 Diabetes Risk

During a 17-year follow-up of a Finnish cohort of approximately 4,000 men and women, researchers demonstrated that individuals with a higher serum vitamin D level had a 40% lower risk of developing type 2 diabetes than those with lower values.

It has been suggested that vitamin D might be involved in processes leading to type 2 diabetes. Human evidence from population studies is, however, missing.

The mean serum 25-hydroxyvitamin D(25OHD) concentration measured in samples collected at baseline was 43.6 nmol/L. Adults in the highest serum 25OHD quartile had lower BMIs than those in the lowest quartile (26.0 vs 26.4).

During follow-up, there were 187 incident cases of type 2 diabetes. After adjusting for age, sex, and month when blood samples were obtained, a statistically significant inverse association was observed between serum 25OHD level and incidence of type 2 diabetes.

The relative risk between the highest and lowest serum 25OHD quartile was 0.60.

This association was attenuated (RR, 0.70) after further adjustments for potential risk factors for type 2 diabetes, including BMI, leisure-time exercise, and smoking.

This study is the first to demonstrate this association in a human population and therefore it has to be replicated in other populations before any firm conclusions can be made.

Vitamin D comes from the diet (mainly from fish) and sun exposure. Previous studies have suggested that high intake of fish fat is related to a reduced risk of coronary heart disease. This finding is thus in line with the suggestion of beneficial health effects of fish.

Source: Diabetes Care 2007;30:2569-2570.

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Diabetes Risk Increased in Hypertensive With Left Ventricular Hypertrophy

Hypertensive patients with persistent electrocardiographic left ventricular hypertrophy (LVH) have an increased risk of developing diabetes. Patients with hypertension and ECG LVH whose LVH does not regress with blood pressure lowering are at increased risk of developing new diabetes, as well as at increased risk of cardiovascular death, MI, stroke, AF and new HF.

In addition to following blood pressure response to antihypertensive therapy, physicians should consider following the response of ECG LVH to treatment, to better assess risk in their patients with hypertension.

In the Losartan Intervention for Endpoint reduction in hypertension (LIFE) study found that patients with resolution or continued absence of ECG LVH during antihypertensive therapy had a 38% lower incidence of new-onset diabetes than did patients with persistent ECG LVH.

The increased risk of diabetes in patients with ECG LVH during therapy persisted after adjusting for assignment to losartan or atenolol, history of prior antihypertensive treatment, baseline Framingham risk score and serum glucose level, HDL cholesterol, body-mass index, and other possible risk factors for diabetes.

The simple, widely available, and inexpensive routine ECG is a powerful noninvasive marker of risk when used in serial assessment of patients. In the LIFE Study, ECG was assessed for LVH at 6 months and then annually thereafter. This would seem like a reasonable approach until additional studies are done to examine optimal timing of assessment.

Researchers are now looking at echocardiographic measures of left ventricular structure and function that may shed additional insights into the relationship between changing levels of ECG LVH and new diabetes.

Source: Hypertension 2007;50:984-990,851-853.

Diabetescope

Exercise Training Improves Glycemic Control in Insulin-Treated Type 2 Diabetes

Combined endurance training and resistance-type training is beneficial and well-tolerated in patients with long-standing type 2 diabetes requiring insulin therapy, according to findings published in the October issue of Diabetes Care.

Regular exercise represents an effective strategy to prevent and/or treat type 2 diabetes. However, the clinical benefits of exercise intervention in a vastly expanding group of long-standing insulin-treated type 2 diabetic patients with comorbidities are less evident.

In this study, the researchers examined the feasibility and benefits of a 5-month low-impact exercise intervention program that combined endurance and resistance-type exercise in 11 male diabetic patients, with a mean age of 59 years. The mean duration of diabetes was 12 years, and the participants had been on exogenous insulin treatment for a mean of 7 years. All of the patients were sedentary and had a high cardiovascular risk profile.

All of the patients completed the exercise intervention and the attendance rate for the supervised sessions was 83%. The exercise training was associated with a decline in truncal fat mass and an increase in lean leg muscle mass. There was an improvement in glycemic control, and a significant decline in both fasting blood glucose concentration and A_{1C} (from 7.6% to 7.2%). The team found no change in exogenous insulin requirements throughout the training program.

Although selection bias and sample size should be acknowledged when generalizing the outcome of this study, we conclude that low-impact endurance and resistance-type exercise training should be prescribed in the vastly expanding population of long-standing insulin-treated type 2 diabetic patients.

Source: Diabetes Care 2007;30:2511-2513.

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Painful Diabetic Neuropathy: A Management-Centered Review

Diabetic neuropathy defined it as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes. There are many types of neuropathy with a variety of clinical presentations. This article focuses on one phenotype of neuropathy: painful diabetic neuropathy (PDN).

CLINICAL MANIFESTATIONS

The pain associated with PDN is often described as “tingling pain,” “numbness,” or “increased due to touch.” However, it may also be described as burning, electrical, or stabbing with parasthesia, hyperesthesia, and deep aching. The pain is typically greater at night. PDN typically develops in the feet and lower legs; however, it may also involve the hands. Neuropathy is chronic and progressive. The pain in PDN is usually excruciating but rarely may spontaneously revert. PDN greatly affects all areas of a patient’s life, including mood, sleep, self-worth, independence, ability to work, and interpersonal relationships.

Screening for neuropathy should be considered annually. Physical exam may reveal a decrease in pressure or vibratory sensation or altered superficial pain and temperature sensation. A simple vibratory sensation exam consists of a tuning fork placed on the bony prominence at the dorsum of the great toe. Pressure sensation is gauged with a 10-g monofilament. Superficial pain sensation is tested with a pinprick. A single test is sufficient. Patients’ mobility, gait, and balance should also be assessed.

The physical exam should also evaluate for signs of decreased arterial flow, altered reflexes, deformities, ulcers, or slow-healing wounds. Signs of decreased arterial flow may include absence of foot pulses, decrease in skin temperature, thin skin, lack of skin hair, and bluish skin color. Deformities include claw toes and Charcot’s arthropathy. Sweating is often diminished in peripheral neuropathy, and the skin may appear cracked and dry.

DIAGNOSIS

The diagnosis of PDN is a diagnosis of exclusion; all other etiologies of painful sensory neuropathy should be ruled out. Patients with diabetes are at an increased risk to develop other types of neuropathy, including chronic inflammatory demyelinating polyneuropathy, B₁₂ deficiency, hypothyroidism, and uremia. Patients with peripheral neuropathy should also be evaluated for these types of neuropathies. This evaluation should be dictated by the clinical scenario but would frequently include serum B₁₂, thyroid function tests, blood urea nitrogen, and serum creatinine. Tests for HIV and serum protein electrophoresis should be completed if HIV or monoclonal gammopathy are suspected. The presentation of typical pain description, decreased sensation, and absent reflexes is highly suggestive of PDN.

EPIDEMIOLOGY

Approximately 50% of patients who have had diabetes for >25 years will develop neuropathy. Approximately 50% will have pain as a symptom of neuropathy. Neuropathy is usually a late finding in type 1 diabetes; however, it can be an early finding in type 2 diabetes.

MANAGEMENT

Neuropathic pain is difficult to treat, and patients rarely experience complete pain relief. It is a frustrating problem for both providers and patients. The pain is often chronic and can be debilitating. There are no treatments that will relieve the pain completely; prevention remains the best strategy.

Prevention

Strict glycemic control is perhaps the single greatest prevention measure for neuropathy. Also, controlling hyperlipidemia and hypertension, taking daily aspirin, ceasing smoking, and consuming alcohol only in moderation may also be important in the prevention of PDN.

Treatment

The first step in the management of PDN is glycemic control and correction of any other metabolic derangements. In addition to controlling hyperglycemia, patients often require management of their pain symptoms. However, many patients are unable to achieve complete pain relief. A thorough understanding of therapeutic options and of the likely benefits and potential adverse effects of each option should be considered before starting a medication. This will help patients and providers set realistic goals for pain reduction.

Several agents, predominantly antidepressants and antiepileptics, have been used with varying degrees of success in the treatment of PDN. There are several limitations in the treatment of PDN and in determining the most appropriate medication to use in each patient. Often, patients expect 100% pain relief after the first dose. Unfortunately, there is no agent that will provide that type of relief. It often takes several weeks for the agents to become effective. To complicate the use of these medications, careful titration is needed to reduce adverse events and increase tolerability. It is easy to understand the aggravation patients often feel with therapies if they expect instant, complete pain relief.

Medications for Treatment of PDN

The major classes of drugs used to treat PDN are antidepressants, primarily tricyclic antidepressants [TCAs] and antiepileptics.

Many of the agents used to treat PDN have not been compared to each other. Also, the end points in many of the

Painful Diabetic Neuropathy

studies have varied, making it difficult to compare agents between studies. Although a randomized, controlled trial of all agents would be desirable to determine the most efficacious agents, such a study would be impractical. To increase the comparability, this article uses as a measure of efficacy the number needed to treat (NNT) to obtain one patient with 50% pain reduction. The NNT is the inverse of the absolute risk reduction.

TCAs

Amitriptyline and imipramine are balanced serotonin and noradrenaline reuptake inhibitors. They also block α -adrenergic, H1-histamine, muscarinic cholinergic, and N-methyl-D-aspartate receptors. Nortriptyline and desipramine are the metabolites of amitriptyline and imipramine, respectively, and are primarily noradrenaline reuptake inhibitors. They also block α -adrenergic, H1-histamine, muscarinic cholinergic, and NMDA receptors. TCAs act centrally to reduce the perception of pain.

TCAs generally have the lowest NNT of the medications used to treat PDN. In summarizing the trials performed for treatment of PDN with TCAs, ~ 30% of patients obtain 50% pain relief. The balanced serotonin and noradrenaline reuptake inhibitors amitriptyline and imipramine have an NNT of 2.1 to obtain one patient with a 50% pain reduction. The primarily noradrenaline reuptake inhibitor desipramine has an NNT of 2.5 to obtain one patient with a 50% pain reduction. No NNT can be calculated for nortriptyline because there have been no trials of monotherapy in the treatment of PDN, but it is considered to be similar to desipramine. Doxepin, which is similar in function to amitriptyline and imipramine, has not been evaluated in the treatment of PDN but likely has similar efficacy.

TCAs are often contraindicated. Also, there is a high incidence of adverse effects, and TCAs are often not tolerated by patients. TCAs should be used with caution in patients who have a history of cardiovascular disease or are > 65 years of age. Amitriptyline and nortriptyline are relatively contraindicated in patients with a history of ischemic cardiovascular disease, whereas doxepin is thought to be the least cardiotoxic of the TCAs. TCAs have been associated with orthostatic hypotension and should be used cautiously in patients with a history of orthostasis or frequent falls. Some side effects, such as dizziness and sedation, can be lessened by careful titration. Sedation also lessens after 3-4 weeks of use. TCAs have been associated with significant weight gain in the treatment of depression. Amitriptyline typically causes a rapid weight gain, whereas the other TCAs are usually associated with a slower weight gain.

Other antidepressants

Venlafaxine and its active metabolite are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak

inhibitors of dopamine reuptake. Venlafaxine is also thought to work centrally by decreasing the perception of pain. The calculated NNT from two of these trials is 5.5. Adverse events are less frequent with venlafaxine than with the TCAs and include somnolence, nausea, and sweating. When taking venlafaxine mean heart rate may increase by 4-9 bpm.

Duloxetine was the first agent approved by the FDA for the treatment of PDN. It inhibits both serotonin and norepinephrine transporters. The precise mechanism of the central pain inhibition of duloxetine is not known. It must be avoided in patients with any degree of hepatic insufficiency or substantial alcohol use.

Antiepileptics

Carbamazepine works peripherally by blocking the sodium channels on the Ad nerve fibers. Although carbamazepine has good efficacy in the treatment of PDN, it also is associated with serious adverse events, including aplastic anemia. Patients must be carefully monitored if placed on carbamazepine.

Lamotrigine also acts peripherally as a sodium channel blocker. It is less efficacious than carbamazepine and is associated with aplastic anemia and toxic epidermal necrolysis.

Valproate is another peripherally acting agent and is associated with thrombocytopenia, aplastic anemia, toxic epidermal necrolysis, and pancreatitis. Patients taking valproate must be monitored with serial liver function tests and complete blood count with platelets.

Topiramate is one of the few agents used in the treatment of PDN that is associated with weight loss. Unfortunately, topiramate has not been shown to be highly efficacious in the treatment of PDN, with a calculated NNT of 7.4, which is equivalent to placebo. It acts peripherally as a sodium channel blocker and at the GABA receptor. Topiramate requires careful titration during initiation and withdrawal.

Gabapentin is commonly used in the treatment of neuropathic pain. Like the other antiepileptics, it acts peripherally to decrease pain perception. The NNT for gabapentin is 3.9. Gabapentin is typically thought to have few side effects and interactions. Unlike the other antiepileptics, gabapentin is not hepatically metabolized, significantly decreasing its interaction with other medications.

Pregabalin is the second agent approved by the FDA for the indication of PDN. It acts peripherally at the GABA receptor to block the perception of pain. The NNT is 4.2. Pregabalin is relatively well tolerated and causes less sedation than gabapentin. However, it is associated with other rare but serious adverse events. Patients on pregabalin therapy must be monitored closely for myopathy and ocular complaints. Pregabalin is also significantly associated with peripheral edema and weight gain. This effect is intensified when given concurrently with thiazolidinediones.

Painful Diabetic Neuropathy

Table-1. Drugs in Treatment of PDN

Medication	Titration scheme	Adverse events	Contraindications for use	Recommended monitoring
Tricyclic antidepressants				
Amitriptyline Dosage: 100-150 mg/day (150 mg at bedtime or 75 mg twice daily) Time to effect: 6-8 wks	D 1: 12.5 mg/day D 2-7: 25 mg/day Wk 2: 50 mg/day Wk 3: 75 mg/day Wk 4: 100 mg/day Wks 5-8: 150 mg/day	Dry mouth, sedation, dizziness, confusion, orthostatic hypotension, constipation, urinary retention, blurred vision, weight gain, arrhythmias	Cardiovascular disease; with or within 14 days use of MAO inhibitors; concurrent use of cisapride	Blood pressure and heart rate before and during initiation; weight; EKG before and during initiation; mental status
Nortriptyline Dosage: 100–150 mg/day (50 mg three times daily) Time to effect: 6 Wks	D 1: 12.5 mg/day D 2-7: 25 mg/day Wk 2: 50 mg/day Wk 3: 75 mg/day Wk 4: 100 mg/day Wk 5-8: 150 mg/day	Dry mouth, sedation, dizziness, confusion, orthostatic hypotension, constipation, urinary retention, blurred vision, weight gain, arrhythmias	Cardiovascular disease; with or within 14 days use of MAO inhibitors; pregnancy	Blood pressure and heart rate before and during initiation; weight
Imipramine Dosage: 150 mg/day (75 mg twice daily) Time to effect: 4 Wks	Wk 1: 25 mg twice daily Wk 2: 50 mg twice daily Wk 3: 75 mg twice daily	Dry mouth, sedation, dizziness, confusion, orthostatic hypotension, constipation, urinary retention, blurred vision, weight gain, arrhythmias	Acute recovery phase of myocardial infarction; with or within 14 days use of MAO inhibitors; pregnancy	Blood pressure and heart rate before and during initiation; weight; EKG in
Desipramine Dosage: 200–250 mg/day (250 mg daily or 125 mg twice daily) Time to effect: 6 Wks	Wk 1: 50 mg/day Wk 2: 100 mg/day Wk 3: 200 mg/day Wk 4: 250 mg/day	Dry mouth, sedation, dizziness, confusion, orthostatic hypotension, constipation, urinary retention, blurred vision, weight gain, arrhythmias inhibitors	Acute recovery phase of myocardial infarction; with or within 14 days use of MAO inhibitors	older adults; mental status Blood pressure and heart rate before and during initiation; weight; EKG
Other antidepressants				
Venlafaxine Dosage: 150–225 mg/day (75 mg 3 times daily or extended release formulation daily) Time to effect: 4-6 Wks	Wk 1: 37.5 mg/day Wk 2: 75 mg/day Wk 3: 150 mg/day Wk 4: 225 mg/day	Headache, nausea, sedation, constipation, diarrhea, dizziness, dry mouth, sexual dysfunction, hypertension, seizures Rare: SIADH (syndrome of inappropriate antidiuretic hormone secretion), hyponatremia	With or within 14 days use of MAO inhibitors	Blood pressure; cholesterol; heart rate
Duloxetine Dosage: 60-120 mg/day (60 every day or twice a day) Time to effect: 4 Wks	Wk 1: 10 mg/day Wk 2: 20 mg/day Wk 3: 60 mg/day Wk 4: 120 mg/day	Nausea, somnolence, dizziness, dry mouth, constipation, sweating, weakness, headache, diarrhea	Hepatic insufficiency; alcohol use; creatinine enzymes clearance < 30 ml/min; with or within 14 days use of MAO inhibitors; uncontrolled narrow angle glaucoma; caution in delayed gastric emptying	Blood pressure; mental status; liver enzymes
Antiepileptics				
Carbamazepine Dosage: 600 mg/day (200 mg three times daily) Time to effect: 4 Wks	Wks 1-2: 100 mg 3 times daily Week 3: 200 mg 3 times daily	Agitation, dry mouth, sedation, ataxia, nausea, vomiting, blurred vision, confusion, fatigue, nystagmus Rare: aplastic anemia	Hypersensitivity to TCAs; bone marrow depression; with or within 14 days of MAO inhibitor use; pregnancy	CBC, reticulocytes, S.iron, lipid, LFT, urinalysis, BUN, carbamazepine levels, thyroid function tests, S.Na; ophthalmic (pupill reflexes); observe patient for excessive sedation, especially when instituting pacemaker

BUN-blood urea nitrogen; MAO-monoamine oxidase.

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Painful Diabetic Neuropathy

Table-1. Drugs in Treatment of PDN

Medication	Titration scheme	Adverse events	Contraindications for use	Recommended monitoring
Antiepileptics cont'd				
Lamotrigine Dosage: 200-400 mg/day (200 mg twice daily) Time to effect: 6-8 Wks	Wk 1: 25 mg/day Wk 2: 50 mg/day Wk 3: 100 mg/day Wk 4: 200 mg/day Wk 5: 400 mg/day	Dizziness, ataxia, sedation, headache, blurred vision, diplopia, nausea, confusion, nystagmus, rhinitis Rare: aplastic anemia, toxic epidermal necrolysis	Use with caution with valproic acid	Serum levels of concurrent antiepileptics; hypersensitivity reactions, especially rash
Valproate Dosage: 1,000-1,200mg/day (500 mg twice daily or 400 mg three times daily) Time to effect: 4 Wks	Wk 1: 600 mg/day Wk 2: 1,200 mg/day	Dizziness, somnolence, alopecia, insomnia, nausea, diarrhea, vomiting, thrombocytopenia, tremor, weakness Rare: aplastic anemia, pancreatitis, toxic epidermal necrolysis	Hepatic dysfunction, urea cycle disorders, pregnancy; concurrent use with topiramate	Liver enzymes; complete blood count with platelet count
Topiramate Dosage: 300–400 mg/day (200 mg twice daily) Time to effect: 12 Wks	Wk 1: 25 mg/day Wk 2: 50 mg/day Wk 3: 75 mg/day Wk 4: 100 mg/day Wk 5: 150 mg/day Wk 6: 200 mg/day Wk 7: 300 mg/day Wk 8: 400 mg/day	Dizziness, ataxia, psychomotor slowing, memory problems, speech difficulties, serum bicarbonate decreased, nausea, migraine, weight loss, anorexia Significant: metabolic acidosis, nephrolithiasis, hyperthermia, CNS effects, secondary angle closure glaucoma. Must be tapered to avoid withdrawal.	Use with caution in hepatic and renal impairment; concurrent use with valproic acid	Hydration status; electrolytes prior and periodically; acute acidosis, complications of chronic acidosis; ammonia for unexplained lethargy; symptoms of acute glaucoma
Gabapentin Dosage: 2,400-3,600 mg/day (1,200 mg three times daily or 900 mg four times daily) Time to effect: 4 Wks	Wk 1: 300 mg at bedtime Wk 2: 300 mg twice daily Wk 3: 300 mg 3 times daily Wk 4: 600 mg 3 times daily Wk 5: 900 mg 3 times daily	Somnolence, dizziness, ataxia, nausea, dry mouth, constipation, nystagmus, leucopenia, weight gain	Cautiously in patients with severe renal dysfunction	Serum levels of concomitant antiepileptic therapy
Pregabalin Dosage: 300–600 mg/day (300 mg twice daily or 200 mg three times daily) Time to effect: 4-6 Wks	Wk 1: 150 mg/day Wk 2: 300 mg/day Wk 3: 600 mg/day (Dosed twice or three times daily)	Peripheral edema, dizziness, somnolence, ataxia, tremor, blurred vision, diplopia, weight gain. Rare: rhabdomyolysis, acute renal failure, prolong PR interval, thrombocytopenia. Must be tapered to avoid withdrawal.	Cautiously in patients with congestive heart failure, hypertension; concurrent use of thiazolidinedione	Degree of sedation; symptoms of myopathy or ocular disturbance; weight gain/edema; creatine phosphokinase; skin integrity (in diabetic patients)
Others				
Capsaicin cream Dosage: 0.075% 4 times daily Time to effect: 8 Wks	No titration needed	Localized burning and itching, cough, sneezing	Open wounds	Skin breakdown
Tramadol Dosage: 200-400 mg/day (100 mg four times daily) Time to effect: 6 Wks	Wk 1: 50 mg/day Wk 2: 100 mg/day Wk 3: 150 mg/day Wk 4: 200 mg/day Wk 5: 300 mg/day Wk 6: 400 mg/day	Nausea, sedation, constipation, headache, dry mouth, urinary retention, confusion, tremor, seizures	Substantial alcohol use	Respiratory rate, blood pressure, heart rate; signs of tolerance or abuse
Mexilitine Dosage: 450-675 mg/day (225 mg three times daily) Time to effect: 1-4 days	Wk 1: 225 mg/day Wk 2: 450 mg/day Week 3: 675 mg/day	Dyspepsia, dizziness, tremor, ataxia, insomnia, diarrhea, constipation, headache, nervousness, hepatotoxicity, arrhythmia. Rare: agranulocytosis, toxic epidermal necrolysis	History of cardiogenic shock; second- or third-degree atrioventricular block (unless with functional pacemaker)	EKG prior to and during therapy; complete blood count with platelets; liver enzymes

Other agents

Capsaicin is an alkaloid derived from chillies. It acts peripherally by depleting the neurotransmitter substance P from sensory nerves. It is applied topically and is not absorbed significantly into the systemic circulation. The only adverse effects are local stinging and burning and sneezing or coughing during application. It must be applied while wearing gloves, and patients must be careful not to touch their face until after carefully washing their hands. The pain with application decreases after the 1st week of use.

Tramadol acts through both monoaminergic (like the TCAs) and opioid mechanisms and acts centrally to block pain perception. Tramadol has lower abuse potential than other opioids. The NNT is 3.5. Tramadol should be titrated so that the effects on the respiratory system may be monitored. Tramadol has side effects common to opioids, such as constipation, urinary retention, and central nervous system effects. It should be avoided in patients with substantial alcohol use or a history of opioid abuse.

Mexilitine is an oral analog of lidocaine. It is a class IB antiarrhythmic agent and acts peripherally as an ion channel blocker to prevent the perception of pain. Of all the agents used in the treatment of PDN, mexilitine has the fastest onset of pain relief, which is usually within 1-4 days. Mexilitine has been associated with agranulocytosis, hepatotoxicity, and toxic epidermal necrosis. It is absolutely contraindicated in patients with second- and third-degree atrioventricular block unless an artificial pacemaker is utilized.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have also been used in the treatment of PDN. However, great caution must be exercised when using NSAIDs in this population because this may worsen underlying renal dysfunction.

CONCLUSION

Different agents may be appropriate for different patients, and patients may try multiple agents before finding one that works for them. Combination therapies, especially those that combine centrally acting agents with peripherally acting agents, may provide increased pain relief.

Reference: Painful Diabetic Neuropathy: A Management-Centered Review, CLINICAL DIABETES, Volume 25, Number 1, 2007

Congratulations !

The Winners of diabetes Quiz Competition

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Editorial Note:

Dear Doctor, This issue of your *diabetes newsletter* is focused on "Painful Diabetic Neuropathy: A Management-Centered Review". We appreciate your comments and queries. Please participate in quiz competition & win prizes.

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