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The Approach to the Management of the Patient with Neuropathic Pain

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Neuropathic pain occurs in about 6–7% of the general population and in 15–20% of people with diabetes. It is defined as a disease or disorder of the sensorimotor system and must be distinguished from nociceptive pain, which is a consequence of trauma, injury, or inflammation. A host of other conditions can mask neuropathy including entrapments, fasciitis, and claudication. Pain can derive from damage to unmyelinated C-fibers, Aδ fibers in the periphery, or from mechanisms within the spinal cord, brainstem, and cerebral cortex. A variety of excitatory and inhibitory neurotransmitters are involved and form the basis for targeted drug therapy. More important, however, is the pathogenesis of damage to the pain mechanism, which is multifactorial and includes metabolic disturbances such as hyperglycemia, even impaired glucose tolerance, dyslipidemia, oxidative and nitrosative stress, growth factor deficiencies, microvascular insufficiency, and autoimmune damage to nerve fibers. The approach to managing the patient with neuropathic pain is first to understand and recognize the cause of pain in a particular patient and to use monotherapies or drug combinations directed at the different types and sources of pain. Ultimately, therapy directed at the underlying pathogenesis of neuropathy is needed. The case presented in this report illustrates the complexity of resolution of pain in an individual and the need for a holistic approach to medicine, employing empathy, compassion, and understanding in the relationship between the doctor and the patient to succeed in alleviating pain. (J Clin Endocrinol Metab 95: 4802–4811, 2010)

Pain is the reason for 40% of patient visits in a primary care setting, and about 20% of these patients have had pain for longer than 6 months (1). Chronic pain may be nociceptive, which occurs as a result of disease or damage to tissue wherein there is no abnormality in the nervous system or there may be no somatic abnormality. In contrast, experts in the neurology and pain community define neuropathic pain as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” (2). Persistent neuropathic pain interferes significantly with quality of life, impairing sleep and recreation, and it significantly impacts emotional well-being of such patients, predisposing them to depression and noncom-
pliance with treatment resulting in a general worsening of the condition. Patients with chronic neuropathic pain report poor physical health and mental conditions compared with those with other causes of chronic pain even adjusting for pain intensity (3). Diabetic neuropathy pain is a difficult-to-manage clinical problem. It is often associated with mood and sleep disturbances, and patients with diabetic neuropathy pain are more apt to seek medical attention than those with other types of diabetic neuropathy. Two population-based studies showed that neuropathic pain is associated with a greater psychological burden than nociceptive pain (4) and is considered to be more severe than other pain types. Early recognition of psychological problems is critical to the management of pain, and physicians need to go beyond the management of pain per se if they are to achieve success. Patients may also complain of decreased physical activity and mobility, increased fatigue, and negative effects on their social lives. Providing significant pain relief markedly improves quality-of-life measures, including sleep and vitality (5). Because of its complexity, the presentation of pain poses a diagnostic dilemma for the clinician who needs to distinguish between neuropathic pain arising as a direct consequence of a lesion or disease of the somatosensory system and nociceptive pain that is due to trauma, inflammation, or injury. It is imperative to try to establish the nature of any predisposing factor, including the pathogenesis of the pain, if one is to be successful in its management. Management of neuropathic pain requires a sound relationship between patient and physician, with an emphasis on a positive outlook and encouragement that there is a solution, using patience and targeted pain-centered strategies that deal with the underlying disorder rather than the usual “Band-aid” prescription of drugs approved for general pain, which do not address the disease process. The inciting injury may be focal or diffuse and may involve single, or more likely, multiple mechanisms such as metabolic disturbances encompassing hyperglycemia, dyslipidemia, glucose fluctuations, or intensification of therapy with insulin. On the other hand, the injury might embrace autoimmune mechanisms, neurovascular insufficiency, deficient neurotrophism, oxidative and nitrosative stress, and inflammation (6). Because pain syndromes in diabetes may be focal or diffuse, proximal or distal, acute or chronic, each has its own pathogenesis, and the treatment must be tailored to the underlying disorder if the outcome is to be successful.

The Case

We first saw the patient—a 24-yr-old female with poorly controlled type 1 diabetes for the past 6 yr and an eating disorder with anorexia/bulimia syndrome—on May 19, 2009. She had been admitted to an eating disorder clinic from February 2009 through April 10, 2009. She had been on an insulin pump that she had manipulated to control her weight and was subsequently placed on an injectable combination of short- and long-acting insulin, Lantus (40 U in the morning) and NovoLog (1 U for every 15 g of carbohydrate for meals and snacks and 1 U for every 50 mg/dl of her blood glucose greater than 100 mg/dl). On this regimen, her blood glucose levels averaged 100 to 220 mg/dl without hypoglycemic episodes. Within 2–3 months of this therapy, she developed intractable pain and was referred for consultation. The pain was burning and ach- ing with tenderness bilaterally in the feet and the legs, as well as in the hips. A rheumatologist had diagnosed fibro-myalgia and prescribed Gabapentin [100 mg twice daily (BID), 200 mg at bedtime (HS) for 2 wk, increased to 200 mg three times a day for 1 week, and then increased to 300 mg BID and 600 mg at bedtime]. This had no real impact on the pain. She was very distressed and tearful, was confined to bed, and was unable to sleep. Advil two to three times per day eased the pain slightly. Her last hemoglobin A1c was 9.0.

She had exercised regularly, including Pilates, before the pain occurred, but she stopped because of pain. She had an eye exam in the fall of 2008, and there was no evidence of retinopathy. Her urine specimen contained no protein and was negative for ketones. She had developed grand mal seizures controlled with lamotrigine 150 mg daily (QD). She denied stress or phobia, although she had some difficulty with heights. She attended college and lived at home with her parents. Her family history revealed an older sister who suffered from some degree of anxiety; her mother had Hashimoto thyroiditis and also had rheumatoid arthritis, for which she was treated with Enbrel and methotrexate in small doses. Her father is disease free. Her paternal grandmother had Hashimoto thyroiditis with diabetes, and her grandfather had a myocardial infarction. On the paternal side, there was a history of lung cancer. The patient smoked a pack of cigarettes a day for 5 yr, but quit in November 2008. She did not consume alcohol or use illegal drugs. She had not been exposed to heavy metals, organotoxins, or other toxins. She was not intolerant to cold or constipated and had no voice change or hair loss.

**Physical examination**

Physical exam revealed an alert and oriented individual who, although tearful, communicated well. She had no pig- mentation change and no dry or brittle hair. She had a few psoriatic lesions at the back of her head, but not elsewhere.

Head, eyes, ears, nose, and throat were within normal limits. She had no lymphadenopathy. Her chest and lungs were clear. There were no breast masses. Her heart was normal without murmurs. Her abdomen was soft, non-
tender, and without masses. Her musculoskeletal system was intact. She had good dorsalis pedis and posterior tibial pulses. Application of pressure to her feet caused her to scream in agony. She weighed 120.4 pounds and was 5 feet 11 inches tall. Her body mass index was 16.7 kg/m². Her waist was 26 inches and hip measurement was 34 in, with a waist-hip ratio of 0.766. Supine blood pressure was 119/78 mm Hg with a pulse of 94 bpm, sitting blood pressure was 125/82 mm Hg with a pulse of 107 bpm, and standing blood pressure was 109/78 mm Hg with a pulse of 81 bpm.

**Neurological examination**
Cranial nerves were intact. Her pupils were large, reacted to light, and accommodated poorly suggesting autonomic dysfunction. She had no evidence of muscle weakness. Handgrip dynamometry was at the 10th percentile bilaterally. All her reflexes were present, and upper limb sensation was entirely intact. In the lower limb, she had a reduction of prickling pain perception to 15 cm on the right and 22 cm on the left, but she had marked hyperalgesic and hyperesthetic soles of her feet. Vibration perception was intact, there was some slight loss of joint position, but perception of 1- and 10-g monofilament was intact. Her total neuropathy scores were 5 on the right and 6 on the left, which indicated a mild degree of peripheral neuropathy (7). The use of simple clinical tools is illustrated in Table 1.

**Laboratory studies**
A quantitative sensory test done on May 12, 2009, showed normal vibration perception, touch/pressure, warm and cold thermal perception, indicating that her somatic nervous system was intact.

A cardiac autonomic function test revealed an expiration/inspiration ratio of 1.14, a Valsalva ratio of 1.05, and a 30:15 ratio of 1.05. This very abnormal result indicated autonomic nerve dysfunction. The QTc interval was 425 msec on electrocardiogram, which was normal. She had a sinus tachycardia syndrome of 100 bpm and appeared to have slight left atrial enlargement, but no other abnormalities.

Vitamin D level was 10.7 ng/ml, which is inordinately low. The remainder of the biochemistries were: urine protein microalbumin, 12.8 μg/ml; TSH, 1.329 μU/ml; glucose, 253 mg/dl (elevated); blood urea nitrogen, 18 mg/dl; creatinine, 0.5 mg/dl; electrolytes, within normal limits; serum glutamic oxaloacetic transaminase, 19; serum glutamic pyruvic transaminase, 25; alkaline phosphatase, 64; calcium and magnesium, within normal limits; estimated glomerular filtration rate, 59 ml/min; antinuclear factor antibodies, negative; C-reactive protein, 0.1; sedimentation rate, 12; glutamic acid decarboxylase antibody, 4.7 (elevated); and gastric parietal cell antibodies, 1.6. Serum protein electrophoresis revealed no gammopathy, and no motor or sensory nerve antibodies were detected; acetylcholine receptor antibodies in serum and antinuclear factor were negative. Serum folate and B12 were normal. Urine porphyrins and urine heavy metals were negative. Serum angiotensin-converting enzyme was normal. Lyme, HIV, and hepatitis screening tests were all negative.

Neuronal cells were incubated in culture with her serum. With control pooled human serum, 100,000 cells increased to 871,250 by the fourth day; with her serum, 100,000 cells fell to 11,250 by the second day and fell further to zero by the third and fourth days. There was no recovery of these cells, indicating that her serum was highly toxic to neuronal cells in culture and indicative of an autoimmune response (8).

**Clinical Considerations**
My impressions were that this young woman had type 1 diabetes for 6 yr, a seizure disorder, and anxiety, with claustrophobic panic disorder. She was an anorexic bulimic and was using an insulin pump to allow her to adjust the insulin doses down so that she could lose weight. When placed on a regular insulin regimen, monitored in an institution, she could no longer do this and within a few weeks of the intensification of insulin developed a severe, highly sensory form of neuropathy with autonomic manifestations, classic of the insulin neuritis syndrome. She had a long family history of autoimmune disease, and her serum was highly toxic to neurons in culture, suggesting the possibility of autoimmune disease. Neuropathic pain is not uncommon. A population-based survey of 6000 patients treated in family practice in the United Kingdom
reported 6% prevalence of pain predominantly of neuropathic origin (9). Similarly, a large population-based study in France showed that 6.9% of the population had neuropathic pain (4). Interestingly, in a Dutch population survey of more than 362,000 people, younger people with pain tended to be mostly women, but with advancing age the gender differences disappeared. Perhaps a little recognized fact is that mononeuropathies and entrapments were three times as common as diabetic peripheral neuropathy (DPN), and fully one third of the diabetic population has some form of entrapment (10), which when recognized is readily amenable to intervention (11). Even more salutary is the mounting evidence that even with impaired glucose tolerance, patients may experience pain (12–14). As a corollary, patients presenting with painful neuropathy have impaired fasting glucose or impaired glucose tolerance, and about 50% of the time, they are overweight and have autonomic dysfunction (12). Even in the absence of elevated fasting blood glucose (<100 mg/dl), pain may be the presenting feature of the metabolic syndrome and cosegregates with elevated triglycerides and a low high-density lipoprotein-cholesterol (15). Indeed, a risk factor for neuropathies in sensation, lack weakness or loss of reflexes, are electrophysiologically silent, and often lead to the erroneous diagnosis of hysteria or conversion reactions. Large fiber neuropathy presents with characteristic weakness, ataxia, loss of reflexes, and impaired nerve conduction. Pain is deep seated and gnawing in quality, “like a toothache” in the foot, or “a dog gnawing at the bones of the feet,” or “feet feel as if they are encased in concrete.”

In contrast, the nociceptive pain of arthritis does not have these qualities. It is localized to the joints; fasciitis is localized to the fascia; entrapment produces pain in a dermatome, and claudication is made worse by walking. Arthritic pain starts with morning stiffness and improves as the day wears on (18).

It is noteworthy that one third of patients with diabetes have some form of entrapment. In contrast with the mononeuropathies, the condition begins gradually and is made worse with repeated minor trauma or history of occupational exposure. The sensory disturbance often does not reflect the nerve distribution, and the pain can exceed the area of sensory innervation leading to incorrect diagnosis. Nerve conduction velocity is required to show impairment of conduction across the site of entrapment.

Evaluation of pain intensity is essential for monitoring response to therapy. There are a number of symptom-based screening tools, such as: Nerve Total Symptom Score-6, Brief Pain Inventory, Quality of Life Diabetic Neuropathy, Short Form-36, Visual Analog Scale for Pain Intensity, Neuro-QOL, and Norfolk Neuropathy Symptoms Score (7). With the visual analog scale, the patient marks the intensity of their pain on a scale from 0–10, allowing an assessment of the response to intervention. Simultaneously, the patient should complete a quality of life tool such as the Norfolk QOL-DN (17), which permits evaluation of the impact of the pain on quality of life, anxiety, and depression, known to be accompanying features of DPN.

The Clinical History

History taking is becoming an obsolete art. Without it, arriving at the correct diagnosis can be hazardous. Pain associated with a peripheral nerve injury has several distinct clinical characteristics. Neuropathic pain derived from small nerve fibers is often burning, lancinating, or shooting in quality with unusual, tingling, or crawling sensations referred to as formication. Some describe bees stinging through the socks, whereas others talk of walking on hot coals. The pain, worse at night, keeps the patient awake and is associated with sleep deprivation (17). Patients volunteer that they have allodynia or pain from normal stimuli, such as the touch of bedclothes, and may have hyperesthesias, increased sensitivity to touch, or hyperalgesia with increased sensitivity to painful stimuli or even altered sensation to cold or heat. These may be paradoxical with differences in sensation to one or other modality of stimulation. Unlike animal models of DPN, the pain is spontaneous and does not need provocation such as a hot plate or laser heat. It is a glove and stocking distribution. Small fiber neuropathies usually present with pain in the feet or hands, do not have abnormalities in sensation, lack weakness or loss of reflexes, are electrophysiologically silent, and often lead to the erroneous diagnosis of hysteria or conversion reactions.

The Clinical Examination

A careful evaluation of the nature of pain and its exact location and a detailed examination of the lower limbs are mandatory to ascertain alternate causes of pain (Table 1).

Laboratory Tests

These tests usually done for research: laser-evoked potentials; contact heat-evoked potentials, whereby brain signals evoked by peripheral heat stimulation can be quantified and amplitudes and conduction velocities of the slow conducting fibers measured; and quantitative sensory tests that measure the thresholds for various sensory modalities, such as vibration and heat and cold perception, and can be adapted to identifying hypoalgesia and hyposthesia. Also included are 3-mm skin biopsies to quantitatively assess the number of nerve fibers present in the epidermis. Paradoxically, these are reduced in number in DPN (19–21).
Conditions Mimicking Diabetic Neuropathy

There are a number of conditions that can be mistaken for painful diabetic neuropathy: intermittent claudication, in which the pain is exacerbated by walking; Morton’s neuroma, in which the pain and tenderness are localized to the intertarsal space, elicited by applying pressure with the thumb in the appropriate intertarsal space; osteoarthritis, in which the pain is confined to the joints and made worse with joint movement or exercise and is associated with morning stiffness that improves with ambulation; radiculopathy, in which the pain originates in the shoulder, arm, thorax, and back and radiates into the legs and feet; Charcot neuropathy, in which the pain is localized to the site of the collapse of the bones of the foot and the foot is hot rather than cold, as occurs in neuropathy; plantar fasciitis, in which there is shooting or burning in the heel with each step and there is exquisite tenderness in the sole of the foot; and tarsal tunnel syndrome, in which the pain and numbness radiate from beneath the medial malleolus to the sole and are localized to the inner side of the foot. These contrast with the pain of DPN, which is bilateral, symmetrical, covering the whole foot and particularly the dorsum, and worse at night, interfering with sleep.

Therapeutic Modalities for Neuropathic Pain

The growing knowledge about the neural and pharmacological basis of neuropathic pain is likely to have important treatment implications, including development and refinement of a symptom/mechanism-based approach to neuropathic pain and implementation of novel treatment strategies using the newer antiepileptic agents, which may address the underlying neurophysiological aberrations in neuropathic pain, allowing the clinician to increase the likelihood of effective management (Table 2). The neuropharmacology of pain is also becoming better understood. For example, recent data suggest that γ-aminobutyric acid, voltage-gated sodium channels, and glutamate receptors may be involved in the pathophysiology of neuropathic pain. Many of the newer agents have significant effects on these neurophysiological mechanisms. Hyperglycemia may be a factor in lowering the pain threshold. Pain is often worse with wide glycemic excursions. Paradoxically, acute onset of pain may appear soon after initiation of therapy with insulin or oral agents (22). In contrast, it has been reported that a striking amelioration of symptoms can occur with continuous sc insulin administration, which may reduce the amplitudes of excursion of blood glucose (22). This dichotomy is not well explained. There is a sequence in diabetic neuropathy, beginning when Aβ, and C nerve fiber function is intact and there is no pain. With damage to C-fibers, there is sympathetic sensitization, and peripheral autonomic symptoms are interpreted as painful. Topical application of clonidine causes antinociception by blocking emerging pain signals at the peripheral terminals via α-2 adrenoreceptors (23), in contrast with the central actions of clonidine on blood pressure control. With the death of C-fibers, there is nociceptor sensitization. Aβ fibers conduct all varieties of peripheral stimuli such as touch and these are interpreted as painful, e.g. allodynia. With time there is reorganization at the cord level and the patient experiences cold hyperalgesia and ultimately, even with the death of all fibers, pain is registered in the cerebral cortex, whereupon the syndrome becomes chronic without the need for periph-

### Table 2. Treatments for symptomatic diabetic polyneuropathy: dosing and side effects

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug</th>
<th>Dose (mg)</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclics</td>
<td>Amitryptyline</td>
<td>50–150 HS</td>
<td>Somnolence, dry mouth, tachycardia, dizziness, constipation, urinary retention, blurred vision</td>
</tr>
<tr>
<td></td>
<td>Nortriptyline</td>
<td>50–150 HS</td>
<td>Constipation, dry mouth, tachycardia, dizziness, constipation, urinary retention, blurred vision</td>
</tr>
<tr>
<td></td>
<td>Imipramine</td>
<td>25–150 HS</td>
<td>Confusion, dry mouth, tachycardia, dizziness, constipation, urinary retention, blurred vision</td>
</tr>
<tr>
<td></td>
<td>Desipramine</td>
<td>25–150 HS</td>
<td>Confusion, dry mouth, tachycardia, dizziness, constipation, urinary retention, blurred vision</td>
</tr>
<tr>
<td>SSRIs</td>
<td>Paroxetine</td>
<td>40 QD</td>
<td>Somnolence, dizziness, dry mouth, tachycardia, constipation, urinary retention, blurred vision</td>
</tr>
<tr>
<td></td>
<td>Citalopram</td>
<td>40 QD</td>
<td>Diarrhea, impotence, tremor, dizziness, constipation, urinary retention, blurred vision</td>
</tr>
<tr>
<td>SNRIs</td>
<td>Duloxetine</td>
<td>60 QD</td>
<td>Nausea, constipation, urinary retention, dry mouth, tachycardia, constipation, urinary retention, blurred vision</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Gabapentin</td>
<td>300–1200 TID</td>
<td>Somnolence, dizziness, dry mouth, tachycardia, constipation, urinary retention, blurred vision</td>
</tr>
<tr>
<td></td>
<td>Pregabalin</td>
<td>50–150 TID</td>
<td>Somnolence, dizziness, dry mouth, tachycardia, constipation, urinary retention, blurred vision</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine/oxcarbazepine</td>
<td>Up to 200 QID</td>
<td>Somnolence, dizziness, dry mouth, tachycardia, constipation, urinary retention, blurred vision</td>
</tr>
<tr>
<td></td>
<td>Topiramate</td>
<td>Up to 400 QD</td>
<td>Somnolence, dizziness, dry mouth, tachycardia, constipation, urinary retention, blurred vision</td>
</tr>
<tr>
<td>Opioids</td>
<td>Tramadol</td>
<td>50–100 BID</td>
<td>Nausea, constipation, urinary retention, dry mouth, tachycardia, constipation, urinary retention, blurred vision</td>
</tr>
<tr>
<td></td>
<td>Oxycodone CR</td>
<td>10–30 BID</td>
<td>Somnolence, constipation, urinary retention, dry mouth, tachycardia, constipation, urinary retention, blurred vision</td>
</tr>
<tr>
<td>Topical</td>
<td>Capsaicin</td>
<td>0.075% QID</td>
<td>Local irritation</td>
</tr>
<tr>
<td></td>
<td>Lidocaine</td>
<td>0.04% QD</td>
<td>Local irritation</td>
</tr>
<tr>
<td>Injection</td>
<td>Botulinum toxin</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

QID, Four times daily.
eral stimulation. Disappearance of pain may not necessarily reflect nerve recovery but rather nerve death. When patients volunteer the loss of pain, progression of the neuropathy must be excluded by careful examination.

**Adrenergic blockers**

Initially, when there is ongoing damage to the nerves, the patient experiences pain of the burning, lancinating, dysesthetic type often accompanied by hyperalgesia and allodynia. Because the peripheral sympathetic nerve fibers are also small unmyelinated C-fibers, sympathetic blocking agents (clonidine) may improve the pain.

**Topical capsaicin**

C-fibers use the neuropeptide substance P as their neurotransmitter, and depletion of axonal substance P (through the use of capsaicin) will often lead to amelioration of the pain. Prolonged application of capsaicin depletes stores of substance P, and possibly other neurotransmitters, from sensory nerve endings. This reduces or abolishes the transmission of painful stimuli from the peripheral nerve fibers to the higher centers (24). Recent analysis of randomized and controlled studies revealed that either a repeated application of low doses of capsaicin or single application of high doses affords pain relief (25).

**Lidocaine**

A multicenter randomized, open-label, parallel-group study of lidocaine vs. pregabalin with a drug washout phase of up to 2 wk and a comparative phase of 4-wk treatment periods of 5% lidocaine (n = 99 vs. pregabalin, n = 94) showed that lidocaine was as effective as pregabalin in reducing pain and was free of side effects (26). This form of therapy may be of most use in self-limited forms of neuropathy. If successful, therapy can be continued with oral mexiletine. This class of compounds targets the pain caused by hyperexcitability of superficial, free nerve endings (27).

**Tramadol and N-methyl-D-aspartate (NMDA) receptor antagonists**

There are two possible targeted therapies. Tramadol is a centrally acting weak opioid analgesic for use in treating moderate to severe pain. Tramadol was shown to be better than placebo in a randomized controlled trial (28) of only 6-wk duration, but a subsequent follow-up study suggested that symptomatic relief could be maintained for at least 6 months (29). Side effects are, however, relatively common and are similar to other opioid-like drugs. Another spinal cord target for pain relief is the excitatory glutaminergic NMDA receptor. Blockade of NMDA receptors is believed to be one mechanism by which dextromethorphan exerts analgesic efficacy (30). The NMDA receptors play an important role in central sensitization of neuropathic pain. Their use, however, has not been widespread due in part to dose-limiting side effects (31).

**Antidepressants**

Antidepressants are now emerging as the first line of agents in the treatment of chronic neuropathic pain (32). Clinical trials have focused on interrupting pain transmission using antidepressant drugs that inhibit the reuptake of norepinephrine or serotonin. This central action accentuates the effects of these neurotransmitters in activation of endogenous pain-inhibitory systems in the brain that modulate pain-transmission cells in the spinal cord (33).

**Tricyclic antidepressants (TCA)**

With the development of newer agents, this class is now being used less frequently due to cholinergic side effects of dysautonomia, dry mouth, and fatigue that can be troublesome. Caution needs to be exercised in patients with ischemic heart disease and arrhythmias. Amitriptyline and imipramine should be avoided in elderly patients because they can exacerbate cognitive impairment and gait disturbances, predisposing them to falls. Switching to nortriptyline or desipramine may lessen some of the anticholinergic effects of amitriptyline. The advantages of TCA are that they can be administered once daily and are inexpensive.

**Selective serotonin reuptake inhibitors (SSRIs)**

SSRIs inhibit presynaptic reuptake of serotonin but not norepinephrine, but are not effective.

**Selective serotonin norepinephrine reuptake inhibitors (SNRIs)**

There has been much focus on this group of drugs lately in treatment of diabetic neuropathic pain. Duloxetine has been studied in two doses of 60 and 120 mg for its effects of reducing diabetic neuropathic pain and for pain in fibromyalgia. To achieve an outcome of 50% pain relief over 12–13 wk, the number needed to treat was 6 (Table 3). Adverse effects include nausea, constipation, somnolence, decreased appetite, some increase in fasting blood sugar, and dry mouth (34, 35). There do not appear to be any significant cardiovascular risks. Venlafaxine is another SNRI that has mixed action on catecholamine uptake. At lower doses, it inhibits serotonin uptake, and at higher doses it inhibits norepinephrine uptake (36). The extended-release version of venlafaxine was found to be superior to placebo in diabetic neuropathic pain in non-depressed patients at doses of 150–225 mg/d, and when
added to gabapentin there was improved pain, mood, and quality of life (37).

**Antiepileptic Drugs (AEDs)**

Antiepileptic drugs (AEDs) have a long history of effectiveness in the treatment of neuropathic pain, dating back to case studies of the treatment of trigeminal neuralgia with phenytoin in 1942 and carbamazepine in 1962 (38). Principal mechanisms of action include sodium channel blockade (felbamate, lamotrigine, oxcarbazepine, topiramate, zonisamide), potentiation of \( \gamma \)-aminobutyric acid activity (tiagabine, topiramate), calcium channel blockade (felbamate, lamotrigine, topiramate, zonisamide), antagonism of glutamate at NMDA receptors (felbamate) or \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (felbamate, topiramate), and mechanisms of action as yet to be fully determined (gabapentin, pregabalin, levetiracetam) (39). An understanding of the mechanisms of action of the various drugs leads to the concept of “rational polytherapy,” where drugs with complementary mechanisms of action can be combined for synergistic effect. For example, one might choose a sodium channel blocker such as lamotrigine to be used with a glutamate antagonist such as felbamate. Furthermore, a single drug may possess multiple mechanisms of action, perhaps increasing its likelihood of success (e.g. topiramate). If pain is divided according to its derivation from different nerve fiber types (e.g. A\( \delta \) vs. C-fiber), spinal cord or cortical, then different types of pain should respond to different therapies.

In addition to providing efficacy against epilepsy, these new AEDs may also be effective in neuropathic pain. For example, spontaneous activity in regenerating small-caliber primary afferent nerve fibers may be quelled by sodium channel blockade, and hyperexcitability in dorsal horn spinal neurons may be decreased by the inhibition of glutamate release—two mechanisms of action possessed by the AED lamotrigine (40, 41). Clinical trials, however, have not been salutary (5). This was evident in our patient who was being treated with lamotrigine for seizures, and lamotrigine was ineffective in relieving pain. In addition, the “wind-up” phenomenon caused by nerve injury and the kindling that occurs in hippocampal neurons in patients with mesial temporal sclerosis both enlist activation of NMDA receptors (42, 43), which can be affected by felbamate (39). The evidence supporting the use of AEDs for the treatment of DPN continues to evolve (36). Patients who have failed to respond to one AED may respond to another or to two or more drugs in combination (44).

**Sodium Channel Blockers**

Voltage-gated sodium channels are crucial determinants of neuronal excitability and signaling. After nerve injury, hyperexcitability and spontaneous firing develop at the site of injury and also in the dorsal root ganglion cell bodies. This hyperexcitability results at least partly from accumulation of sodium channels at the site of injury (45). Carbamazepine and oxcarbazepine are most effective against “lightning” pain (46).

**Calcium Channel Modulators**

Five types of voltage-gated calcium channels have been identified, and the L- and N-types of channels have a role to play in the neuromodulation in the sensory neurons of the spinal cord. Gabapentin and pregabalin are medications that bind at the \( \alpha \)2\( \delta \) subunits of the channels. Unlike traditional calcium channel antagonists, they do not block calcium channels but modulate their activity and sites of expression. The exact mechanism of action of this group of agents on neuromodulation has yet to be clearly defined.

**Gabapentin**

Gabapentin was significantly superior to placebo in pain control, beginning at wk 2 and continuing through wk 8, and it significantly reduced sleep interference beginning at wk 1 and continuing through wk 8. The most common adverse events with gabapentin were dizziness and somnolence (47).

Gabapentin has the additional benefit of improving sleep (47), which is often compromised in patients with chronic pain (44). Over the long term, it is known to produce weight gain, which may complicate diabetes management (48). Combination therapy has been examined using gabapentin and morphine, indicating slight superiority of the combination (49).
Pregabalin
Several randomized, double-blind, placebo-controlled, multicenter studies have evaluated the effectiveness of pregabalin in a fixed dose with an open-label extension in alleviating pain associated with DPN. Forty percent of patients receiving pregabalin reported at least a 50% reduction in pain, compared with 14.5% of the placebo group ($P = 0.001$) (50).

Secondary measures that improved included a reduction in mean sleep interference scores on the SF-36 Bodily Pain subscale ($P < 0.0001$), total SF-MPQ score ($P < 0.05$), and total mood disturbance and tension-anxiety components of the Profile of Mood States ($P < 0.03$) (50). In this respect, the data appear to be not unlike the early reports on gabapentin.

Topiramate
Although topiramate failed in three clinical trials, due to the use of the wrong endpoint (51), it has been shown to successfully reduce pain and induce nerve regeneration (52), and has the added advantage of causing weight loss and improving the lipoprotein profile particularly useful in overweight type 2 diabetic patients.

Botulinum Toxin
Botulinum toxin has been tried for trigeminal neuralgia (53) and has been shown to have long-lasting antinociceptive effects in carpal tunnel syndrome with no electrophysiological restoration (54).

Guidelines

Figure 1 is an algorithm that we propose for the management of painful neuropathy in diabetes. This starts with identification of neuropathic pain being focal or diffuse.

Focal neuropathic pain is best treated with diuretics to reduce edema in the canal, splinting, and surgery to release entrapment. Diffuse neuropathies are treated with medical therapy and in a majority of cases, need multidrug therapy. Immune-mediated neuropathies are treated with iv Ig, steroid, or other immunomodulators.

Back to the Patient

Having reviewed the treatment options we return to the patient.

If this was insulin neuritis syndrome, it would simply be a matter of time and would recover spontaneously. However, the patient clearly had an eating disorder, anxiety/depression, evidence of autoimmunity, and autonomic nerve dysfunction. She was started on topiramate 15 mg QD for 1 month, increased to 25 mg, and then to 50 mg/d. Topiramate has been shown to induce nerve regeneration and also reduces body weight in contrast with gabapentin, which causes weight gain. We added NutriNerve (an over-the-counter combination of antioxidants) at a dose of two tablets BID because this contains α-lipoic acid, which has been shown to improve autonomic dysfunction (55). Thirdly, she was placed on topical lidoderm to reduce the allodynia and hyperalgesia. Because of the seizure disorder, we endorsed the use of gabapentin and lamotrigine.

June 16, 2009

Her legs and feet still hurt very badly. She was very weepy, and one could not touch her toes. She had a magnetic resonance image done bilaterally of the feet, and this was found to be negative for impending Charcot neuropathy. Her heart rate had returned toward normal, about 80 bpm.

Our impression of the effects of topiramate (25 mg/d), NutriNerve (two pills BID), and a 5% lidoderm patch was that the pain has lessened some, but was still bad at night. In light of the very intense autoimmune response with the apoptosis of neuronal cells in culture, we resolved to do the following: 1) give her a course of iv Ig at 1.0 g/kg/d on consecutive days (two per week) for 3 wk; 2) increase the dose of topiramate to 50 mg/d and possibly to 100 mg/d; and 3) replace the vitamin D with 50,000 U ergocalciferol every month.

July to November 2009

We were making slow progress and decided to give her a course of botulinum toxin into her feet. The pain soon started to improve, and a second course was given in December.

October 19, 2009

Her Lantus was changed to 13 U in the morning and 26 U in the evening. She was also to use Novolog coverage (1

FIG. 1. Treatment algorithm: neuropathic pain after exclusion of nondiabetic etiologies and stabilization of glycemic control.
U for every 12 g of carbohydrate for meals and snacks, along with 1 U for every 50 mg/dl of blood sugar >200 mg/dl. She is currently covering with 1 U for 10 g of carbohydrate and 1 U for every 50 mg/dl blood sugar greater than 150 mg/dl.

She checks her blood sugar “too much”—about 10–15 times daily. The range is usually 70–140 mg/dl. For the past couple of days, the results have been higher and she is upset. For anxiety/depression, Ativan 1 mg BID was increased to three times daily (TID). Ambien was also increased from 10 to 12.5 mg HS.

**November 16, 2009**

She was feeling better. Her hemoglobin A1c was 5.5, down from 8.8 in May 2009.

**January 2010**

Pain had resolved completely. Diabetes control remained superb. The patient had started to reduce the dosages of the medications, and she had returned to doing a full exercise program including Pilates and yoga! Repeat autonomic function tests showed improvement in the autonomic function, and the neuronal apoptosis assay had become negative.

**Conclusions**

Painful neuropathy is an important complication of diabetes, and our patient illustrates that pathogenesis is multifactorial and requires attention to detail of management if one is to achieve success. Two drugs have been approved for neuropathic pain in the United States, pregabalin and duloxetine, but neither of these afforded relief, even when used in combination. If we had neglected the evidence for an eating disorder, manipulation of insulin dosing, the presence of significant autoimmunity and autonomic dysfunction, as well as the huge psychological disturbance and not used a holistic positive approach to the patient we might have failed. Indeed, a sobering view is that few drugs achieve a greater than 30% reduction in pain in more than 50% of patients, dictating a need to use more than one drug with different mechanisms of action. Even in the class of AEDs, not all are created equal as shown here. There is a great need to understand pathogenic mechanisms more fully, particularly the differences in origin of peripheral and central pain. Our patient, when subject to traditional measures of nerve function, would have been labeled as hysterical because all nerve function studies are often normal with severe painful syndromes. A holistic approach is essential, and the doctor and patient need to generate trust and a positive attitude. One needs to be aware of the conditions that masquerade as painful neuropathy and the treatment directed toward the underlying disorder as suggested in the algorithm provided. As Winston Churchill said, “We need to go from failure to failure without losing our enthusiasm and ultimately we will succeed....”

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