The treatment of painful diabetic neuropathy, particularly distal symmetrical polyneuropathy, continues to be a challenge to the podiatric physician.1-3 Numerous treatments have been reported, including topical capsaicin,4-6 tight diabetic control, 7,8 nonsteroidal anti-inflammatory drugs,9 anticonvulsants,10 clonidine,11 physical therapy,12 calcitonin, 13 pentoxifylline,14,15 vitamins,16-18 and antidepressants.19,20 Antidepressants, although not approved by the Food and Drug Administration for the treatment of diabetic neuropathy, are becoming increasingly popular for that purpose because of their efficacy. Of the antidepressants, the tricyclics have been most commonly used. The principal agents used are amitriptyline and nortriptyline.21 Although these are often effective, side effects are not uncommon and may limit their usefulness. Trazodone is an antidepressant whose side effect profile is superior to those of the tricyclics, and it has been successfully used to treat chronic pain conditions, including diabetic neuropathy.22 Only one study of the use of trazodone for the treatment of painful diabetic neuropathy has been reported, and this involved a small sample of six patients.23 The present study evaluates the efficacy of trazodone in the treatment of painful distal symmetrical polyneuropathy in a larger number of patients with long-term follow-up.

Materials and Methods
The subjects in this study were 31 adult diabetic patients treated in a podiatric medical office. All patients were treated for a primary diagnosis of painful distal symmetrical polyneuropathy, with the diagnosis based on clinical findings.

There were 13 women and 18 men. The duration of diabetes mellitus ranged from 1 to 40 years, with an average of 14.7 years. The duration of neuropathy symptoms ranged from 2 months to 20 years, with an average of 3.7 years. Seven patients had type 1 diabetes and 24 had type 2 diabetes; all of those with type 2 diabetes were taking oral hypoglycemic agents. The patients’ ages ranged from 40 to 82 years, with an average age of 64.9 years.

The neuropathy severity was evaluated according to the classification of Gudas.24 There were 23 patients classified as having type 1 neuropathy (mild-to-moderate hyperesthesia, burning, mild plantar hypoesthesia, and no motor dysfunction) and 8 patients classified as having type 2 neuropathy (moderate plantar hypoesthesia, mild motor dysfunction, forefoot deformities in some patients, and burning). All type 2 neuropathy patients were unable to feel the 5.07-g Semmes-Weinstein filament applied plantarly, suggesting significant neuropathy.25
Fourteen patients (45.2%) had been previously treated elsewhere for their neuropathy, all without improvement. Treatments consisted of nonsteroidal anti-inflammatory drugs (seven patients), capsaicin cream (four patients), amitriptyline (two patients), and nerve blocks (one patient).

All patients were instructed to take one 50-mg trazodone tablet at bedtime nightly for 2 weeks, at which time they were reevaluated. If significant side effects occurred, the medication was discontinued. If the patients had symptomatic relief, they continued on the same regimen for an additional 2 weeks, at which time they were again evaluated. If the patients had no relief but no side effects, or partial relief and no side effects, they were instructed to take a 100-mg tablet at bedtime. All patients were reevaluated at the end of the 4 weeks.

Results

Results of the trazodone therapy are summarized in Table 1. Subjective results were categorized as “no relief,” “some relief,” “considerable relief,” or “complete relief.” No objective criteria were measured on follow-up visits.

Results showed that 19 of 31 patients (61.3%) obtained at least some symptomatic relief with trazodone therapy, with 7 patients (22.6%) obtaining complete relief of all neuropathy symptoms. Only four patients (12.9%) who took the medication and experienced no side effects obtained no relief.

The side effect problem in this study was remarkable, with eight patients (25.8%) discontinuing the medication because of side effects. These side effects were dizziness (five patients), headache (two patients), and insomnia (one patient).

If the number of patients discontinuing the trazodone because of side effects (8 patients) is added to the number of patients obtaining no symptomatic relief (4 patients), a total of 12 patients (38.7%) were therapeutic failures. Thus the overall success rate of trazodone in providing at least some symptomatic improvement was 61.3% (19 patients).

All patients obtaining symptomatic relief continued to take the trazodone without deterioration of results or development of side effects. The duration of therapy has ranged from 2 to 13 years, demonstrating long-term efficacy and safety.

Discussion

Diabetic neuropathy is characterized by many different signs and symptoms, including severe pain. Clinical symptoms may be absent or nonspecific, and electrophysiologic testing often correlates poorly with symptoms. Neuropathy may occur in both type 1 and type 2 diabetes at any age, regardless of the duration of the disease or its other complications. Distal symmetrical polyneuropathy is the most common type of diabetic peripheral neuropathy, and it is often exacerbated by depression. This may partially explain why antidepressants are often helpful in treating it.

It has been reported that in chronic pain conditions, 50% of patients can expect to obtain at least 50% relief of pain with antidepressants. This finding was confirmed in the present study, with 61.3% of patients obtaining symptomatic relief.

Antidepressants are used at lower doses for chronic pain than for depression. Low doses are used initially, and the dose is gradually increased until symptoms improve or side effects intervene. The author’s findings suggest that the 100-mg daily dose of trazodone was more effective than the 50-mg dose. These findings support those of Khurana, who found that five of six patients experienced decreases in pain and numbness with daily trazodone doses of 100 mg.

The side effects of trazodone occurring in this study, although troublesome enough to cause eight patients to discontinue the drug, were relatively minor. These included some of the less common side effects reported in association with the drug; dizziness, headache, and insomnia have previously been reported as occurring in 6%, 3%, and 2% of patients, respectively. This side effect profile is superior to those of other antidepressants, such as imipramine and amitriptyline (Table 2). Priapism, a well-publicized but uncommon side effect of trazodone, did not occur in the patients in this study. This side effect occurs in only 1 in 8,000 male patients taking the drug.

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<th>Table 1. Subjective Results of Treatment</th>
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Trazodone produces selective inhibition of serotonin uptake by brain synapsosomes, and this is thought to be its mechanism of action in pain relief.\textsuperscript{22, 23} It relieves pain much more rapidly than the tricyclic antidepressants.\textsuperscript{22, 23}

The efficacy of trazodone in relieving diabetic neuropathy symptoms compares favorably with that of other antidepressants (Table 3).

**Conclusion**

Trazodone seems to be a good alternative to the trycyclic antidepressants because of its efficacy, safety, and rapid onset of action. It should be considered as a treatment option for patients with painful diabetic neuropathy.

**References**

27. KAPLAN WE, ABOURIZK NN: Diabetic peripheral neuropathies affecting the lower extremity. JAPA 71: 356, 1981.