Sleep Scores Improve With Neuropathy Treatment

BY KERRI WACHTER
Senior Writer

WASHINGTON — Not only does duloxetine appear to reduce the severity of pain, especially during the night, the drug may also help patients with diabetic peripheral neuropathy get a better night's sleep, according to a poster presentation at the annual meeting of the American Pain Society.

After 12 weeks of treatment, patients on 60 mg of duloxetine once or twice daily had improvements in average daily pain severity, night pain severity, and pain-related sleep interference, wrote Dr. David A. Fishbain, professor of psychiatry and behavioral sciences at the University of Miami, and his colleagues at Eli Lilly, maker of duloxetine (Cymbalta).

Although causality cannot be demonstrated between duloxetine and better sleep, the findings suggest that improvements in pain will be associated with less interference in sleep, the authors wrote.

The researchers pooled data from three double-blind, placebo-controlled trials of duloxetine in patients with diabetic peripheral neuropathic pain (DPNP). In the first study, 457 patients were randomized to receive 20 mg of duloxetine once daily, 60 mg of duloxetine once or twice daily, or placebo. In studies two and three, 334 and 348 patients, respectively, were randomized to receive 60 mg of duloxetine once daily, 60 mg of duloxetine twice daily, or placebo.

Although the primary efficacy measure for the studies was the reduction in the weekly mean of the 24-hour average pain score, secondary end points included average daily night pain severity (measured on an 11-point Likert scale) and the Brief Pain Inventory sleep interference item.

Patients were included in the trials if they were 18 years or older with pain due to bilateral peripheral neuropathy caused by type 1 or type 2 diabetes mellitus. Pain had to have begun in the feet with relatively symmetric onset. Diagnosis was confirmed by a score of at least three on the Michigan Neuropathy Screening Instrument. Daily pain had to be present for at least 6 months. Patients also had to have at least a 4 on the 24-hour average pain severity (11-point Likert) scale and stable glycemic control. Notably, patients with a current or recent (within the last year) diagnosis of major depressive disorder as defined by the DSM-IV were excluded from the studies.

The researchers identified a subset of nonsomnolent patients by excluding those who reported treatment-emergent somnolence or who were on concomitant sedating medications. Treatment-emergent somnolence included reports of daytime sleepiness, drowsiness, being drowsy upon awakening, excessive daytime sleepiness, a feeling of residual sleepiness, groggy, groggy and sluggish, groggy on awakening, hard to awaken, less alert on rising, sleepiness, sleepy, and somnolence.

In all three studies, 339 patients received placebo. Of these, 307 met the criteria for the nonsomnolent subset. A total of 685 patients received 60 mg or 120 mg per day of duloxetine in all three studies. Of these, 607 met the criteria for the nonsomnolent subset.

Patients in the nonsomnolent/nonsedating subgroup who were on duloxetine showed improvements in daily average pain and night pain severity, compared with those on placebo. The improvements started as early as 1 week and were maintained for 12 weeks. At 12 weeks, subset patients on 60 mg of duloxetine once and twice daily had improvements in daily average pain severity of 47% and 50%, respectively, compared with 29% for those on placebo.

Duloxetine also reduced pain-related sleep interference at 4, 8, and 12 weeks. At 12 weeks, patients on 60 mg of duloxetine once and twice daily had reductions in pain-related sleep interference of 55% and 57%, respectively, compared with 45% for those on placebo. ■

Baseline Data for Nonsomnolent Patient Subset

	Placebo (n = 307)	Duloxetine (60 or 120 mg/day) (n = 607)
Average age	60	60
Male	54%	57%
White	86%	86%
Type 1 diabetes	11%	12%
Type 2 diabetes	89%	88%
Duration of diabetic peripheral neuropathic pain	3.8 yr	4.0 yr
Mean 24-hr average pain severity score	5.8/10	5.8/10
Mean night pain severity score	6.1/10	6.1/10
Mean brief pain inventory sleep interference score	5.4/10	5.4/10

Source: Dr. Fishbain

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Giving Insulin at the Dialysis Center Improves Patients' Glycemic Control

BY FRAN LOWRY
Orlando Bureau

ORLANDO — For hemodialysis patients with diabetes who refuse to take insulin at home, delivering insulin during dialysis is a good way to improve glycemic control, researchers reported at a meeting sponsored by the National Kidney Foundation.

Patients with diabetes make up roughly half of the end-stage renal disease (ESRD) population in the United States, and good glycemic control is essential to slow the progression of both microvascular and macrovascular disease.

But sometimes, having to take insulin is just too much for these patients, said Dr. Kalyana Janga of Maimonides Medical Center, New York. "It's like the straw that broke the camel's back. Dialysis patients with diabetes can be very noncompliant. They have to take so many different medications and they can be very dissatisfied with the complexity of their treatment."

When such a patient came to his dialysis center, Dr. Janga and his associates decided to try a novel approach for delivering insulin. Postulating that Lantus, a long-acting insulin, would continue to exert its effect until the next dialysis treatment and thereby improve glycemic control, they persuaded the patient to allow the dialysis nurse to give him his insulin after his dialysis session.

The patient was 72 years old and had been on maintenance hemodialysis for 3 years. In addition to being hypertensive and having coronary artery disease, the patient had poor glycemic control despite being on maximum doses of two oral hypoglycemic agents. He had had type 2 diabetes for 20 years, Dr. Janga said.

"His fasting glucose was more than 200 mg/dL, and greater than 250 mg/dL prelunch. His hemoglobin A_{1c} was 13.3%. He refused to take insulin at home; he was afraid to take it."

The patient was placed on a regimen of Lantus three times a week post dialysis. Lantus was begun at 5 units and progressively increased to 17 units after each dialysis, based on fasting glucose levels which the patient measured at home, and on prelunch glucose levels measured at dialysis.

After 3 months, the fasting blood glucose levels dropped to 100-110 mg/dL and the prelunch glucose levels decreased to 125-135 mg/dL. After 4 months, hemoglobin A_{1c} levels decreased from 13.3% to 8.4%, and at 8 months, hemoglobin A_{1c} had decreased even further, to 7.9%, Dr. Janga reported.

So successful was this treatment regimen that the patient was actually able to come off dialysis and became a kidney transplant recipient. "His wife donated a kidney. He's surviving and doing very well. We are so happy to see him when he visits us at the clinic," Dr. Janga said.

He added that this type of regimen should be considered in all diabetics who are noncompliant with their insulin therapy. "Giving them their insulin when they show up at the dialysis center reduces the cost and complexity burden to these patients … If we can at least take care of their diabetes, we can do something of major importance" for them. ■

Caution Advised When Using Long-Acting Insulin Analogues

The long-acting insulin analogues glargine and detemir offer only minor, if any, clinical benefit, according to Dr. K. Horvath and associates in the Cochrane Library's collaborative review group on metabolic and endocrine disorders.

Given this negligible benefit and the current lack of long-term safety and efficacy data, "we suggest a cautious approach to treatment with [glargine or detemir]," they said in an online issue of the Cochrane Database of Systematic Reviews.

The researchers conducted a meta-analysis of eight studies that compared the new, long-acting analogues with NPH insulin, which they termed the current standard of treatment. These studies involved 2,293 patients with type 2 diabetes who were assessed for 24-52 weeks.

Unfortunately, the methodologic quality of all of these studies was rated low, which allows only "a cautious interpretation" of their results.

Glargine (Lantus) showed no superiority to standard insulin therapy in achieving metabolic control, and detemir (Levemir) showed only "clinically unimportant" superiority, Dr. Horvath and associates said (Cochrane Database Syst. Rev. 2007 April 18;DOI:10.1002/14651858.CD005613.pub3).

Nocturnal hypoglycemic events were less frequent in patients treated with either of the two long-acting analogues than in those on standard insulin therapy, but no statistically significant advantage was noted. Moreover, all the reviewed studies were prone to reporting bias concerning this symptom, and the frequency of hypoglycemia was very low, "making it unlikely to see an important clinical effect for the different treatments," the investigators noted.

None of the trials investigated possible long-term effects of treatment with the new insulin analogues, and the maximum observation period was 12 months. The meta-analysis therefore "cannot provide any further guidance on potential adverse properties, such as mitogenic effects or progression of microvascular complications."

Similarly, none of the reviewed trials reported data on quality of life or costs, so these factors could not be assessed, they added.

—Mary Ann Moon