Nonhormonal Drug Eases Vasomotor Symptoms

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OTTAWA — A new, nonhormonal drug was safe and effective for reducing the incidence and severity of vasomotor symptoms of menopause in a series of three pivotal trials with a total of about 1,700 women.

If the drug, desvenlafaxine succinate, a serotonin-norepinephrine reuptake inhibitor (SNRI), is approved by the Food and Drug Administration, "it will be the first nonhormonal drug approved for treating hot flashes and nighttime awakenings," Dr. Margery Gass said at the annual clinical meeting of the Society of Obstetricians and Gynaecologists of Canada. She and her colleague, Dr. Sophie Olivier, presented the data in five separate reports at the meeting.

"Women and their physicians are seeking an alternative to estrogen. What's exciting is that this drug seems effective against hot flashes and mood, the things that trouble women during menopause," commented meeting attendee Dr. Jennifer Blake, chief of ob.gyn. at Sunnybrook Health Sciences Centre, Toronto.

Data from these studies were submitted by the drug's developer, Wyeth, to the FDA in June 2006, and—as of late June of this year—action by the FDA for the indication of moderate to severe menopausal vasomotor symptoms was still pending. Last January, the FDA told Wyeth that desvenlafaxine was approvable for the indication of major depressive disorder, but final approval for that use is also still pending. As of late June, a Wyeth spokeswoman said that the company plans to market the drug with the trade name Pristiq for both indications.

The largest of the three pivotal trials enrolled 689 women who reported having 50 or more moderate or severe hot flash episodes a week. Patients were randomized to daily desvenlafaxine dosages of 50, 100, 150, or 200 mg, or placebo, and were scheduled to receive 52 weeks of treatment. The primary efficacy end point was the number and severity of hot flashes after 12 weeks of treatment, and the number of nighttime awakenings. Hot flash episodes and nighttime awakenings were recorded in daily diaries. Efficacy data were available for 620 of the enrolled women.

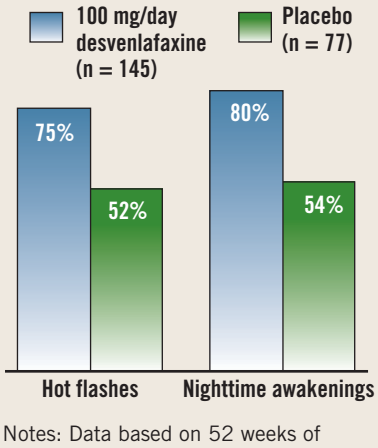
At baseline, these women had an average of about 11 hot flash episodes daily, with an average severity of 2.4 points (with measurements defined as severe [3 points], moderate [2 points], and mild [1 point]). They also reported an average of 3.7 awakenings a night.

Treatment with desvenlafaxine was most effective in this study at the 100-mg/day level. The 145 women on that dosage reported an average daily reduction of 1.76 hot flash episodes, compared with placebo, and an average drop in episode severity of 0.33 points, compared with the placebo effect. The frequency of nighttime awakenings fell by 0.56 episodes a night, compared with the placebo group. All of these changes were statistically significant compared with placebo, reported Dr. Gass, of the department of ob.gyn. at the University of Cincinnati. Dr. Gass disclosed that she receives compensation as a consultant to Wyeth. In Wyeth's submissions to the FDA, it has proposed 100 mg/day as the recommended dosage, she said.

The placebo effect was substantial. The 77 women in the placebo group reported an average reduction of 6.3 hot flash episodes a day compared with their baseline number, an average drop in hot flash severity of 0.5 points, and an average drop in awakenings of 2.2 episodes a night.

Significantly more women were satis-

Percentage of Patients Satisfied With Menopausal Vasomotor Symptom Relief



Notes: Data based on 52 weeks of treatment. Differences between desvenlafaxine and placebo were statistically significant.
Source: Dr. Gass

fied with treatment when taking 100 mg desvenlafaxine daily, compared with those in the placebo group. (See box, p. 26)

The researchers also evaluated the difference in treatment responses based on whether the women rated themselves as dissatisfied, neutral, or satisfied with their treatment response. The average increment in response between the women who self-rated themselves as neutral to the treatment, and those who were satisfied, was an additional reduction in hot flash episodes of 1.64 per day. Dr. Gass and her associates called this the "treatment satisfaction threshold." The difference between neutral and satisfied was an average drop in hot flash severity of 0.2 points, and an average decrease in awakenings of 0.42 episodes per night.

Notably, the 100-mg/day dosage of desvenlafaxine produced a drop in all three measures, compared with placebo, that exceeded all three of these treatment satisfaction thresholds, said Dr. Gass, who is also director of the Menopause and Osteoporosis Center at the University of Cincinnati Medical Center.

"They looked at patient satisfaction levels and showed a clinically meaningful difference from the drug compared with placebo," commented Dr. Blake, who is also a professor and associate chair of medicine at the University of Toronto.

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DR. GASS

The efficacy of the 100-mg dosage was confirmed in a second study that included 484 women who were randomized to either 100 mg or 150 mg desvenlafaxine daily or placebo, and were treated for 26 weeks. Again, the primary efficacy end points were measured after 12 weeks of treatment. The data from this second study were presented in a combined analysis with data from the first study, so that the total group included 843 women: 307 who received 100 mg/day desvenlafaxine, 281 who received 150 mg/day, and 255 who received placebo.

The findings for number and severity of daily hot flashes and number of nighttime awakenings were similar to the results from the first study. The analysis also included a more detailed look at the effect of treatment on sleep. Women who received either the 100- or 150-mg dosage had significant increases in the number of minutes slept and in their self-reported sleep quality, compared with placebo patients, reported Dr. Sophie Olivier, senior director for clinical research and development at Wyeth.

This report included data on mood, based on the Profile of Mood States (POMS) questionnaire. The lower the POMS score, the better a person's mood, and a normal score is about 20 points or lower. At baseline, women in the combined study had an average score of about 27.

After 12 weeks of treatment, the POMS scores had dropped by an average of about 19 points in the women treated with desvenlafaxine, compared with an average fall of about 12 points among women in the placebo group, a significant difference.

The ability of desvenlafaxine treatment to improve the POMS score is likely due to a direct antidepressant effect of the drug and to a secondary effect mediated by reduced vasomotor symptoms and improved sleep quality, Dr. Olivier said.

The third study involved 508 women who were randomized to daily treatment with 100 mg desvenlafaxine, 2.5 mg tibolone, or placebo and were treated for 12 weeks. Tibolone (Xyvion), a synthetic hormone that is a selective estrogen-receptor modulator, is not approved for use in the United States but is approved for use in Europe and elsewhere. In this study, the 100-mg dosage of desvenlafaxine was not significantly different from placebo for reducing the frequency and severity of hot flashes and nighttime awakenings, and this dosage of desvenlafaxine was significantly worse than tibolone.

In an analysis that combined the efficacy data collected in all three studies, the 100-mg/day and 150-mg/day dosages were each significantly better than placebo for reducing vasomotor symptoms. In addition, treatment with these dosages of desvenlafaxine produced the full treatment effect within 7 days of the start of treatment. In contrast, in the placebo group, the full effect of treatment was not seen until 4 weeks had elapsed.

The safety analysis involved a total of 1,131 patients treated with desvenlafaxine, including 495 treated for at least 12 weeks with the 100-mg/day dosage and 336 women treated with 150 mg/day. This analysis included 612 women assigned to treatment with desvenlafaxine for 52 weeks, including 155 women on 100 mg/day and 157 assigned to 150 mg/day. The results showed that desvenlafaxine was generally safe and well tolerated, with an adverse effect profile similar to those of other SNRIs. ■