Nonhormonal Drug Eases Menopausal 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 Gynecologists 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; action by the FDA for the indication of moderate to severe menopausal vasomotor symptoms was pending when this report went to press. As of May 2007, the FDA told Wyeth that desvenlafaxine was approvable for the indication of major depressive disorder, but final approval for that use also is pending. If approved, the company plans to market the drug as Pristiq for both indications, according to a spokeswoman.

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 endpoint 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.

Tibolone, 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 hot flash severity of 0.33 points, compared with the placebo effect. The frequency of nighttime awakenings fell by 0.56 episodes a night, compared with placebo.

All of these changes were statistically significant compared with placebo, reported Dr. Gass, of the department of ob.gyn. at the University of Toronto.

The efficacy of the 100 mg dosage was confirmed in a second study that included 484 women who were randomized to either 100 mg of desvenlafaxine daily or placebo, and were treated for 26 weeks. Again, the primary efficacy endpoints 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 235 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.

The differences for the 100-mg dosage was confirmed in a second study that included 1,131 patients treated with desvenlafaxine, including 495 treated for at least 12 weeks with the 100 mg/day dosage and 336 treated with 150 mg/day. This analysis included 612 women assigned to treatment with desvenlafaxine for 52 weeks, including 155 as assigned to 100 mg/day and 157 assigned to 150 mg/day. Results showed that desvenlafaxine was generally safe and well tolerated, with an adverse effect profile similar to those of other SNRIs. The most common adverse events reported with desvenlafaxine were dizziness, headache, and nausea. Discontinuation related to adverse events occurred in 48% of the desvenlafaxine patients, compared with 23% of the placebo patients.

The safety analysis included a detailed assessment of the effect of desvenlafaxine on sexual function in the 689 women assigned to treatment for 52 weeks. Sexual function was scored for arousal, desire, orgasm, and overall measure; there was no statistically significant change in any of these measures, compared with placebo, Dr. Gass reported.

In addition, individual episodes of sexual dysfunction—abnormal orgasm, decreased libido, abnormal sexual function, or anorgasmia—were tallied for each of the treatment groups in this study. There was a suggestion of a dose-dependent relationship in the overall incidence of these events. (See box at left.) However, the rate of events in each treatment group was not significantly different from the rate of events in the placebo group, and there was no statistically significant trend in the dose-related incidence of these events.

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The clinical significance of the effect of desvenlafaxine was assessed by giving patients a questionnaire about their satisfaction with treatment. Significantly more women were satisfied with treatment when taking 100 mg desvenlafaxine daily, compared with those in the placebo group. (See box above.)

The researchers also ran another analysis to gauge the meaning of the treatment effect that they measured. They evaluated the difference in treatment responses based on whether the women rated themselves as depressed, 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 2.2 episodes a night.

The rate of adverse sexual events during desvenlafaxine treatment was very low. Only three women had episodes of anorgasmia—were tallied for each of the treatment groups in this study. There was a suggestion of a dose-dependent relationship in the overall incidence of these events. (See box at left.) However, the rate of events in each treatment group was not significantly different from the rate of events in the placebo group, and there was no statistically significant trend in the dose-related incidence of these events. (See box at left.)

No adverse sexual events were reported with desvenlafaxine in this study, with the exception of anorgasmia—were tallied for each of the treatment groups in this study. There was a suggestion of a dose-dependent relationship in the overall incidence of these events. (See box at left.) However, the rate of events in each treatment group was not significantly different from the rate of events in the placebo group, and there was no statistically significant trend in the dose-related incidence of these events.

Note: Based on data from 689 women who were treated for 52 weeks and reported episodes of sexual dysfunction.

Source: Dr. Gass

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