Estradiol May Reduce Perimenopausal Depression

BY HEIDI SPLETE

FROM THE ANNUAL MEETING OF THE NORTH AMERICAN MENOPAUSE SOCIETY

NATIONAL HARBOR, MD. – Women who had a longer exposure to estradiol before menopause had a significantly lower risk of developing depression during the menopausal transition, based on data from 1,282 women.

"It is unclear why some women are at increased risk of depression while undergoing the menopausal transition," said Dr. Wendy Marsh of the University of Massachusetts, Worcester.

Data from previous studies have suggested that endocrine factors in general, and estrogen levels in particular, may contribute to a woman's susceptibility to depression during menopause, she noted.

Dr. Marsh and her colleagues reviewed data from 1,282 women participating in the Study of Women's Health Across the Nation (SWAN), a multisite, long-term epidemiologic study of women during midlife and through the menopausal transition. The women were premenopausal when they entered the study.

Each additional year of premenopausal estradiol exposure conveyed a 15% reduction in risk of experiencing depression during menopause (hazard ratio, 0.85) after confounding factors including premenopausal depression, baseline age, smoking status, education, antidepressant use, ethnicity, and length of time in the study were controlled for.

The average duration of estradiol exposure was 36 years. Longer exposure was significantly associated with a lower risk of having a score of 16 or higher on the Center for Epidemiologic Studies Depression (CES-D) scale.

VITALS

Major Finding: Each additional year of premenopausal estradiol exposure conveyed a 15% reduction in risk of depression during menopause (hazard ratio, 0.85).

Data Source: 1,282 women in the Study of Women's Health Across the Nation (SWAN).

Disclosures: The SWAN is supported by grants from the National Institutes of Health, the Department of Health and Human Services, the National Institute of Nursing Research, and the NIH Office of Research on Women's Health. Dr. Marsh reported having no relevant disclosures.

Estradiol has been shown to affect mood regulation, Dr. Marsh noted, but "it is unknown how such a modulatory effect during premenopausal years would lead to a protective effect against depression during the menopausal transition," she said.

Although these data are preliminary, they may provide a foundation for further research that may help clinicians identify and manage women at increased risk for depression during menopause.

"Additional analyses will further qualify and quantify other variables related to estrogen exposure, including use of oral contraceptives, pregnancies, and lactation," Dr. Marsh said. ■

Gabapentin Improves Hot Flashes, Sleep Post Menopause

BY HEIDI SPLETE

FROM THE ANNUAL MEETING OF THE NORTH AMERICAN MENOPAUSE SOCIETY

NATIONAL HARBOR, MD. – Extended-release gabapentin at daily doses of either 1,200 mg or 1,800 mg significantly reduced the number and severity of hot flashes and significantly improved sleep problems, compared with a placebo, in postmenopausal women.

Currently, hormone therapy is the only approved treatment for hot flashes in North America and Europe, said Dr. Mira Baron of Rapid Medical Research Inc., Cleveland, and colleagues.

In previous studies, gabapentin has shown effectiveness in reducing the frequency and severity of hot flashes, but its short half-life may limit its usefulness, the researchers said. However, an extended-release, once-daily dose of gabapentin was approved by the Food and Drug Administration in February 2011 to treat postherpetic neuralgia, she said.

In Breeze 2, a phase III, double-blind, placebo-controlled trial conducted at 45 sites, Dr. Baron and colleagues compared the effectiveness of 1,200 mg of extended-release gabapentin once daily vs. 1,800 mg twice daily (600 mg in the morning and 1,200 mg at night) on frequency and severity of hot flashes.

A total of 559 women completed 12 weeks of treatment and were included in the intent-to-treat population; 190 were randomized to once-daily treatment, 186 were randomized to twice-daily treatment, and 183 were randomized to a placebo.

The average age of the patients was 53 years, and the mean age at menopause was 44 years. The eligible participants reported at least seven moderate to severe hot flashes per day during a 1-week baseline period before they started the study.

Overall, the median daily number of hot flashes dropped significantly after 12 weeks of treatment in both treatment groups, compared with the placebo group. The number of daily hot flashes dropped to three in the placebo group and to two in the two treatment groups.

In addition, the severity of the hot flashes decreased significantly from baseline in both treatment groups, compared with the placebo group. The mean change in vasomotor severity score, compared with baseline, was –0.9 in the once-daily group, –0.8 in the twice-daily group, and –0.6 in the placebo group. The reduction in the severity of vasomotor symptoms was significant for both treatment doses, compared with the placebo. "However, the 1,800-mg dosage yielded more significant changes than the 1,200-mg dosage," the researchers noted.

In a second study, Dr. Risa Kagan of the Alta Bates Summit Medical Center, Berkeley, Calif., and colleagues studied the effectiveness of extended-release gabapentin on improving sleep problems commonly reported by postmenopausal women.

VITALS

Major Finding: The mean difference in the global PSQI sleep scores, compared with a placebo, after 4 weeks of treatment was –1.74 in women who took 1,200 mg of gabapentin daily and –1.68 in women who took 1,800 mg daily; the differences were significant for both doses, compared with a placebo.

Data Source: The Breeze 1 and Breeze 2 studies, which were phase III, double-blind, placebo-controlled trials conducted at multiple sites in the United States.

Disclosures: The studies were supported by Depomed. Dr. Baron had no financial conflicts to disclose. One study coauthor is an employee of Depomed. Dr. Kagan disclosed serving as a consultant or advisory board member for multiple companies, including Amgen, Bionovo, Depomed, Merck, Pfizer, and Shionogi. She disclosed receiving research support from Bionovo, BioSante Pharmaceuticals, Boehringer-Ingelheim, Depomed, and Pfizer, and serving on the speakers bureau for Amgen, Novogyne, and Novo Nordisk.

The researchers compared the effects of extended-release gabapentin vs. a placebo on sleep problems in postmenopausal women using data from the Breeze 1 study, which was a phase III, double-blind, placebo-controlled trial conducted at 48 sites. A total of 531 women made up the intent-to-treat population, and they were randomized to gabapentin 1,200 mg once daily, to 1,800 mg twice daily (600 mg in the morning and 1,200 mg at night), or to a placebo.

Overall, global scores on the PSQI (Pittsburgh Sleep Quality Index) improved significantly with both gabapentin doses, compared with the placebo, at three separate time points.

After 4 weeks, the mean difference in the global PSQI scores was –1.74 in the once-daily group and –1.68 in the twice-daily group. After 12 weeks, the mean differences in the global PSQI for the two treatment groups, compared with placebo, were –1.16 and –0.80, respectively. After 24 weeks, the mean differences in global PSQI scores for the two treatment groups, compared with placebo, were –0.77 and –0.93, respectively.

"The largest differences between the active arms and the placebo arm were observed at week 4," the researchers said. "The decrease in the magnitude of improvement over time likely resulted from the fact that the PSQI instrument requests reporting for the previous 4 weeks." However, the global scores did improve throughout the study, they noted.

Although the drug is not currently approved for this indication, the findings suggest that extended-release gabapentin might have potential as a treatment option for hot flashes and sleep disturbances in postmenopausal women who are reluctant to use hormonal therapies, the researchers said. ■

VIEW ON THE NEWS

A Reasonable Agent

Gabapentin is a very reasonable agent to study for hot flashes and sleep problems in postmenopausal women. Both of these problems are common concerns for midlife women. For women who cannot – or choose not to – take hormone therapy, a Food and Drug Administration–approved alternative is needed.

Small, randomized trials of non–extended-release gabapentin showed efficacy, compared with placebo. Side effects include drowsiness and sedation, so its use at bedtime often kills two birds with one stone. It's interesting that in these studies, daytime fatigue was not a side effect of this new extended-release formulation.

Gabapentin already is being used off label for night sweats and sleep problems in postmenopausal women. I discuss both gabapentin and SSRIs/SNRIs with my symptomatic patients who cannot – or choose not to – use hormone therapy, and they often elect a trial of gabapentin. If they're not depressed, many women do not like the idea of being on an antidepressant, and these agents have side effects as well. If daytime hot flashes are manageable, but night sweats and sleep disruption are a woman's principal concerns, then gabapentin is a very good off-label option.

JAN L. SHIFREN, M.D., *is associate professor of ob.gyn. and reproductive biology at Harvard Medical School, Boston. She reported having no relevant conflicts of interest.*