

NEWS & Commentary

Note: The level of evidence indicated for each study is based on a grading system that evaluates the scientific rigor of the study design as developed by the U.S. Preventive Services Task Force. A synopsis of the levels is presented at the end of these items.

Gabapentin provides relief from hot flashes

Guttuso T Jr, Kurlan R, McDermott MP, Kiebertz K. Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. *Obstet Gynecol* 2003;101:337-345.

Gabapentin (Neurontin), an anti-epileptic drug, can reduce the frequency of hot flashes in postmenopausal women, according to this randomized, double-blind, placebo-controlled trial. A total of 59 postmenopausal women experiencing seven or more hot flashes per day received either 900 mg/day of gabapentin or a placebo. After 12 weeks of treatment, the 30 women in the gabapentin-treated group had a 45% reduction in hot flash frequency and a 54% reduction in a hot flash composite score (frequency and severity combined) from baseline. The difference was also significant when compared with placebo recipients, who had reductions of 29% and 31%, respectively. Adverse events were reported by 15 (50%) of gabapentin recipients compared with eight (28%) placebo recipients. Four women in the gabapentin group and one in the placebo group withdrew because of adverse events, primarily for somnolence and dizziness, which were the chief side effects of gabapentin seen in this trial. (They also were the most common

side effects observed in epileptic trials.) In an open-label extension of the study in which the dose could be increased to 2,700 mg/day, gabapentin recipients had reductions of 54% in hot flash frequency and 67% in hot flash composite scores from baseline.

Level I evidence

Comment. In this randomized, double-blind 12-week trial of gabapentin, 900 mg/day, authors reported hot flash reductions in both severity and frequency in excess of placebo. Notably, four of 30 women in the gabapentin group withdrew because of intolerable side effects. During the open-label continuation of the study, women were allowed to increase or reduce the dosage, and about 25% of them used 900 mg/day or less. Interestingly, assessments of mood or general health did not change with gabapentin administration, suggesting a selective effect on hot flashes. This small but carefully performed study implies that gabapentin may be a therapeutic alternative to current modalities to treat vasomotor symptoms, particularly in severely affected women.

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Mild to severe side effects seen with some dietary supplements

Palmer ME, Haler C, McKinney P, et al. Adverse events associated with dietary supplements: an observational study. *Lancet* 2003;361:101-106.

Some dietary supplements cause side effects that range from mild to severe,

including myocardial infarction, hepatic failure, bleeding, and seizures, according to a one-year nonintervention, observational study of data from 11 poison centers in the United States. Furthermore, these adverse events are voluntarily reported and ineffectively monitored. Investigators used a multiple-tiered review process including the toxic exposure surveillance system (TESS) data form to assess adverse events reported with dietary supplements. Supplements included botanical, nonbotanical products (eg, vitamins, minerals, glandulars, etc.), and traditional cultural remedies. Nearly one-third of the adverse events were considered either moderate (long-lasting or systemic) or severe (life-threatening); 1% resulted in death. In adults, the more severe reactions were associated with the use of multi-ingredient supplements and long-term use. The most common severe adverse events were coma, seizures, chest pain, conductive heart disturbances and arrhythmias, and dyspnea. The supplements most frequently associated with adverse events were the botanical products ma huang, guarana, ginseng, and St. John's wort and the nonbotanical products chromium, melatonin, and zinc. Associations between adverse events and specific dietary supplement ingredients were difficult to verify if the product had multiple ingredients.

Level II-3 evidence

Comment. This observational study points to several significant issues related to the lack of adequate surveillance of dietary supplement use. Supplements with multiple ingredients were more often associated with serious adverse outcomes, and they were used more often by symptomatic individuals who were attempting to treat disease. Family and friends (66%) were overwhelmingly the referral source for the use of supplements. That was much higher

than the recommendations of care providers, both traditional and complementary (12%). The high rate of unintentional ingestions (70%) in children younger than 12 years resulted in lower severity of adverse effects, but it illustrates the risks associated with packaging and home safety. This study has several limitations, which are acknowledged by the authors. Voluntary reporting of adverse effects of dietary supplements to the Poison Control Centers may not represent the scope of adverse effects experienced by consumers. Selection bias may have also affected results. Ingredients of supplements are not always reliably listed on the label confounding cause and effect. However, this study highlights the importance of screening and monitoring patients who choose to use supplements and identifying those who may be at risk for adverse events.

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Estrogen slows bone loss associated with depot medroxyprogesterone acetate contraception

Cundy T, Ames R, Horne A, et al. A randomized controlled trial of estrogen replacement therapy in long-term users of depot medroxyprogesterone acetate. *J Clin Endocrinol Metab* 2003;88:78-81.

Bone loss seen with the injectable contraceptive depot medroxyprogesterone acetate (DMPA) is closely associated with low endogenous estrogen levels but can be slowed by adding estrogen therapy, according to this randomized, double-blind, placebo-controlled trial. A total of 38 premenopausal women (mean age 37 years)

who had used DMPA for at least two years and had below average lumbar spine bone mineral density (BMD) received either oral estrogen (0.625 mg/day conjugated equine estrogens) or placebo. All women continued on DMPA. The primary outcome was changes in BMD, based on BMD testing conducted every 6 months during the 2-year study. At study end, lumbar spine BMD increased 1% among estrogen recipients while it decreased by 2.6% among the placebo recipients, a statistically significant difference. No differences in BMD were seen at the other sites measured, including the femoral neck, Ward's triangle, greater trochanter, and total body. No major adverse events were reported.

Level I evidence

Comment. Because use of DMPA, a highly effective and convenient long-acting progestin contraceptive, is associated with lowered endogenous estradiol levels, transient loss of BMD occurs in women using this method of birth control. This study confirms that such loss of BMD can be prevented by using a dose of estrogen (0.625 mg of conjugated equine estrogens) commonly employed for menopausal estrogen therapy. Clinicians should recognize, however, that use of DMPA contraception has not been demonstrated to cause postmenopausal osteoporosis or related fractures. Therefore, it is not clear which users, if any, would benefit from estrogen supplementation.

If clinicians or users have concerns about skeletal health with DMPA use, particularly if such concerns might prevent appropriate candidates from using or continuing this contraceptive, "add-back" estrogen supplementation could be considered for the following groups of DMPA users: slender women who have used injections for a year or more and who plan to continue use, and users with other risk factors for low BMD,

including cigarette smokers and perimenopausal women.

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Description of the level of evidence

- Level I:** Properly randomized, controlled trial.
- Level II-1:** Well-designed controlled trial but without randomization.
- Level II-2:** Well-designed cohort or case-control analytic study, preferably from more than one center or research group.
- Level II-3:** Multiple time series with or without the intervention (eg, cross-sectional and uncontrolled investigational studies); uncontrolled experiments with dramatic results also could be regarded as this type of evidence.
- Level III:** Opinions of respected authorities that are based on clinical experience; descriptive studies and case reports; reports from expert committees.

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