

# Top Menopause Stories of 2006

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Just as we start each new year with plans and resolutions for the months ahead, the wise amongst us also take stock of the successes and shortcomings of the year just completed.

From the standpoint of the practice of menopause medicine, 2006 brought refinements to our knowledge about the risks and benefits of treatments for menopausal symptoms, new information about the safety and efficacy of selective estrogen-receptor modulators (SERMs), expanded therapeutic options for osteoporosis prevention and treatment and, via a lively debate, continued appreciation for the interface between traditional medicine and our regulatory agencies and the popular push for new alternatives. These findings, and more, contribute to a better understanding of menopause, and more effective tools for health promotion for women at midlife and beyond. Read on, and see how my list compares with yours!

## Estrogen and Heart Disease: The Beat Goes On

In January 2006, the media picked up and ran with the story that estrogen had finally been proven to reduce the risk of heart disease when taken by younger women close to the time of menopause. This was based on a report from the arm of the Women's Health Initiative (WHI) using unopposed

estrogen therapy (ET),<sup>1</sup> and a concurrent update from the Nurses' Health Study.<sup>2</sup>

What's the real story? The report from the WHI was certainly reassuring for women contemplating unopposed ET. Coronary heart disease (CHD) events (myocardial infarction and death) were not increased at any time point—a departure from the early risk reported

with combined hormone therapy (estrogen-progestogen therapy, EPT).<sup>3</sup> Neither was there a significant decrease in the primary endpoint overall. In subgroup analysis, there was a trend for benefit in younger women (*P* for trend, 0.07). Among women 50-59 years of age, assignment to ET was associated with 45% fewer coronary revascularization procedures (a secondary endpoint) (hazard ratio [HR], 0.55; 95% CI, 0.35-0.86). Composite outcomes (myocardial infarction, coronary death, coronary revascularization and confirmed angina) were also reduced by a third in this younger age group (HR, 0.66; 95% CI, 0.45-0.96).<sup>1</sup>

The Nurses' Health Study, an observational study, reported a reduced risk of CHD in women who started ET (relative risk [RR], 0.66, 95% CI, 0.54-0.80) or combined EPT (RR, 0.72; 95% CI, 0.56-0.92) near the time of menopause. For women who began EPT after age 60 or more than 10 years after menopause, there was no CHD benefit.<sup>2</sup>

What's the bottom line? Because of logistical challenges, the definitive clinical trial in young, recently menopausal women will probably never be

conducted. The low event rate in young women (about 1/5 of 1% per year in 50-54 year olds in the estrogen-only arm of the WHI) would require a trial of 17,251 completely adherent women for a trial to be adequately powered to detect a 30% treatment effect.<sup>1</sup> Several smaller trials measuring surrogate endpoints (such as progression of atherosclerosis measured by carotid intimal thickness or coronary artery calcification) are under way in younger women close to the time of menopause.<sup>4</sup> From a preventive standpoint, the risks of ET (increased stroke, venous thromboembolic events, and possibly breast cancer—with long-term use) exceed the known fracture benefit. Neither ET nor EPT should be prescribed for prevention of CHD at this time.

### Raloxifene Not Useful for the Heart

Raloxifene, a SERM currently FDA-approved for prevention and treatment of osteoporosis, significantly improved total and low-density lipoprotein (LDL) cholesterol and other cardiovascular risk factors in early clinical trials in postmenopausal women with osteoporosis or low bone mass. Raloxifene did not increase levels of C-reactive protein, as had been reported with oral estrogens. In a post hoc analysis of the Multiple Outcomes of Raloxifene Experience (MORE) trial, a fracture efficacy trial in women with osteoporosis, women with the highest risks for CHD who were

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assigned to raloxifene therapy had a 40% reduction in CHD events and a 60% reduction in stroke.<sup>5</sup> When the 4-year follow-up to the MORE trial—known as the Continuing Outcomes Relevant to Evista (CORE) trial—was concluded, cardiovascular benefit was not evident.<sup>6</sup>

The Raloxifene Use for The Heart (RUTH) trial,<sup>7</sup> initiated in 1998 (when cardiovascular benefits of estrogen were anticipated), enrolled 10,101 women (mean age, 67.5 years) with a history of CHD or risks for CHD. Participants were randomly assigned to 60 mg of raloxifene or placebo. Primary endpoints included death from coronary causes, nonfatal myocardial infarction, or hospitalization for an acute coronary syndrome. After 5.6 years, there was no significant increase or decrease in CHD risk between women assigned to raloxifene versus placebo.

Other findings in RUTH included an absolute increase of seven cases of fatal stroke (although no increase in total strokes) per 10,000 women treated for 1 year (22 cases in the raloxifene group versus 15 cases in the placebo group). As anticipated from previ-

ous trials, the risk of venous thromboembolism increased by 44%, an additional 12 cases for every 10,000 women taking raloxifene for 1 year. A 35% reduction in clinical vertebral fractures (13 fewer cases per 10,000 women treated for 1 year) was consistent with previous raloxifene trials in women with osteoporosis. As in the MORE trial, RUTH women assigned to raloxifene experienced a 55% reduction in the incidence of invasive estrogen-receptor-positive breast cancer (12 fewer cases per 10,000 women treated for 1 year).

The findings from RUTH do not appreciably alter the indications or safety profile of raloxifene for healthy postmenopausal women or women with osteoporosis who take raloxifene for bone benefits. In women with a history or strong risk factors for cardiovascular disease, the increase of fatal stroke may temper the use of raloxifene.

### Is there a Shining STAR for Breast Cancer Prevention?

In July 1999 the National Cancer Institute established the head-to-head Study of Tamoxifen and Raloxifene (STAR) trial. STAR was designed to determine whether raloxifene—shown in the MORE trial to reduce invasive breast cancer by 76% in women with osteoporosis,<sup>8</sup> and recently in the RUTH trial to reduce breast cancer by 44% in women with heart disease and risk factors<sup>7</sup>—was as effective as tamoxifen, which reduced

breast cancer by 49% in healthy women at increased risk for breast cancer.<sup>9</sup> A second goal was to compare the safety profiles of the two drugs. A total of 19,747 postmenopausal women (mean age, 58.5 years) with a mean 5-year breast cancer risk of 4.03% as determined by the Gail model were enrolled.<sup>10</sup>

By design, a final analysis was initiated when at least 327 cases of invasive breast cancer were diagnosed. After 3.9 years of follow-up, the rates of invasive breast cancer were equivalent in the two treatment groups (Table). There were fewer noninvasive cancers (lobular

carcinoma in situ and ductal carcinoma in situ) in the tamoxifen-treated women—a finding of uncertain clinical significance.

The rate of cardiovascular events (including stroke) and osteoporotic fractures did not differ between the two groups. Side effects tended to occur less frequently in the women assigned to raloxifene; thromboembolic events were 30% less likely. There were 38% fewer cases of endometrial cancer (not statistically significantly), 84% fewer instances of endometrial hyperplasia, and 56% fewer hysterectomies. Cataracts and cataract surgeries were 20% less common.

In an accompanying publication, patient-reported outcomes for physical health, mental health, and depression were not significantly different between women taking tamoxifen and raloxifene.<sup>11</sup> Women in the tamoxifen group reported more gynecologic problems, vasomotor symptoms, leg cramps and bladder control problems; women in the raloxifene group reported more musculoskeletal problems, dyspareunia and weight gain.

For women with an “average” breast cancer risk of 3.3 per

**Table. Study of Tamoxifen and Raloxifene (STAR) Clinical Outcomes**

| Outcome                | Tamoxifen<br>(Cases/1000 Woman-yr) | Raloxifene | RR*  | 95% Confidence<br>Intervals | P**  |
|------------------------|------------------------------------|------------|------|-----------------------------|------|
| Breast cancer          |                                    |            |      |                             |      |
| Invasive cancer        | 4.30                               | 4.41       | 1.02 | 0.82–1.28                   | .83  |
| Noninvasive cancer     | 1.51                               | 2.11       | 1.40 | 0.98–2.00                   | .52  |
| Endometrial conditions |                                    |            |      |                             |      |
| Cancer                 | 2.00                               | 1.25       | 0.62 | 0.35–1.08                   | .07  |
| Hyperplasia            | 4.69                               | 0.76       | 0.16 | 0.09–0.29                   |      |
| Hysterectomy           | 13.57                              | 6.04       | 0.44 | 0.35–0.56                   |      |
| Vascular conditions    |                                    |            |      |                             |      |
| Ischemic Heart Disease | 3.00                               | 3.29       | 1.10 | 0.85–1.43                   |      |
| Stroke                 | 1.39                               | 1.33       | 0.96 | 0.64–1.43                   |      |
| Thromboembolic events  | 3.71                               | 2.61       | 0.70 | 0.54–0.91                   | .01  |
| Fractures              |                                    |            |      |                             |      |
| Total                  | 2.73                               | 2.51       | 0.92 | 0.69–1.22                   |      |
| Eye conditions         |                                    |            |      |                             |      |
| Cataracts              | 12.30                              | 9.72       | 0.79 | 0.68–0.92                   | .002 |
| Cataract surgery       | 8.03                               | 6.62       | 0.82 | 0.68–0.99                   |      |

\* Raloxifene/tamoxifen

\*\* P value for cumulative incidence rates through 6 years.

1,000 (as reported in the placebo group of the WHI), one would expect 1.7 fewer cases of breast cancer per 1,000 women treated with raloxifene, a smaller absolute benefit than that of women in STAR with higher baseline risk.<sup>12</sup> Nevertheless, the breast cancer reduction in STAR is reassuring and might provide an added health benefit for women already taking raloxifene for osteoporosis prevention and treatment.

Tamoxifen is the only SERM currently FDA-approved for breast cancer prevention, and is the only SERM to have proven efficacy in premenopausal women. Yet, primary care physicians rarely prescribe tamoxifen for breast cancer prevention. If raloxifene also receives approval for prevention, the risks and benefits of these two SERMs should be carefully considered in light of each woman's risk profile and anticipated benefit.<sup>12,13</sup> Prevention trials comparing raloxifene to an aromatase inhibitor (AI) and an AI to placebo are under way. New SERMs in the pipeline might provide future alternatives for women seeking breast cancer chemoprevention.

### Breast Cancer Risk Varies by Hormone Therapy Type, Exposure Duration

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breast cancer.<sup>14</sup> In subgroup analyses of women who faithfully took study medication, a significant 33% *reduction* in the incidence of invasive breast cancer, specifically ductal carcinoma, was observed in women assigned to conjugated equine estrogens (CEE) compared with women assigned to placebo (HR, 0.67; 95% CI, 0.47-0.97;  $P = .03$ ).

Significant interactions between treatment assignment and baseline characteristics suggest an apparent protective effect of CEE on breast cancer incidence in low-risk groups (women with a 5-year Gail score < 1.25%, no history of benign breast disease [or biopsies for benign breast disease], and no first-degree relatives with a history of breast cancer). Invasive cancers that did occur in women assigned to estrogen were significantly larger (1.8 cm versus 1.5 cm;  $P = .03$ ), and more often node-positive ( $P = .07$ ), findings similar to those reported with combined therapy.<sup>15</sup>

More women assigned to estrogen than placebo required short-

interval follow-up mammograms (9.2% after the first year in women assigned to estrogen versus 5.5% in the placebo group;  $P < .001$ ). Over the course of the study, 36.2% of women assigned to estrogen and 28.1% of women assigned to placebo required follow-up ( $P < .001$ ).

Two separate publications described duration effects in users of both unopposed estrogen and combined therapy. The authors of the Harvard Nurses' Study reported findings from their observational study of 28,835 nurses followed for up to 2 decades.<sup>16</sup> In their population, the risk of breast cancer increased with increasing duration of estrogen use, yielding a 42% increase after 20 years of therapy ( $P$  for trend, < .001). The association of breast cancer with ET was stronger for receptor-positive cancers, and in women with a body mass index (BMI) < 25 (RR for breast cancer, 1.77; 95% CI, 1.26-2.48) compared with heavier women (RR, 1.25; 95% CI, 0.91-1.71).

In a second report from the WHI, prior combination EPT use was a significant modifier of breast cancer risk ( $P = .027$ ).<sup>17</sup> Among prior EPT users, the risk in women assigned to EPT was nearly double that of the placebo group (HR, 1.96; 95% CI, 1.17-3.27). In women reporting more than 2 years of prior combined hormone use, the HR was 2.61; 95% CI, 1.18-5.78. Among women who had never used hormones in the past, no effect of assigned EPT was seen (HR, 1.02; 95% CI, 0.77-1.36). Among the never users, Kaplan-Meier estimates of the cumulative incidence of breast cancer in women taking EPT versus

placebo appear to cross after 5 years, whereas for prior users the curves begin to separate at about 3 years.

The most important take-home lesson from these studies is that women who have undergone hysterectomy and who require ET alone can be counseled that breast cancer risk is not increased for short-term ( $\leq 7$  years) therapy. The paradox of possible early reduction of breast cancer risk followed by increased risk after long-term use of estrogen is intriguing and merits further study. For women considering combined therapy, breast cancer risk increases over time, possibly as early as 3 to 4 years after initiation of therapy in women who faithfully take their pills. Prior hormone exposure accelerates this risk.

### **Regulation of Compounding Pharmacies and Marketing of Bioidentical Hormones: Who's Minding the Store?**

Bioidentical hormones prepared by compounding pharmacies have become increasingly popular for women discouraged and disillusioned by negative findings reported from the WHI. In the lay press and online Web sites, claims of improved safety and enhanced efficacy of compounded bioidentical hormones abound.

In response to the growth of this federally unregulated industry, Wyeth Pharmaceuticals filed a Citizen's Petition with the FDA requesting that the Commissioner

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of Food and Drugs "take certain actions to address public health and other concerns resulting from the growing, unlawful manufacture and marketing of so-called bioidentical hormone replacement therapies (BHRT)."<sup>18</sup>

In November 2005 the FDA reported that the government had sent letters to about 50 firms and Web sites that market supplements and creams as alternatives to HT, warning them against making baseless claims that the treatments can help with serious diseases such as cancer, heart disease and osteoporosis.<sup>19</sup> The FDA also sent 16 letters to companies marketing alternative therapies, telling them that it considers the products (natural progesterone creams or dietary supplements) unapproved new drugs, which require FDA approval before they can be sold. Concurrently, the Federal Trade Commission sent warning letters to 34 Web site operators, warning that some claims made on the Web sites "may be false or unsub-

stantiated and therefore may violate the law."<sup>20</sup>

The American College of Obstetricians and Gynecologists and the Endocrine Society have produced formal statements to remind women and practitioners that compounded bioidentical hormones have not been proven to be more safe or more effective at preventing chronic diseases of aging than preparations studied in the WHI.<sup>21,22</sup> The reliability of salivary testing of hormone levels, an integral part of management in the bioidentical hormone realm, has also been questioned. The Executive Directors of both the American Society of Reproductive Medicine and The North American Menopause Society submitted letters to the FDA voicing similar concerns.<sup>23,24</sup>

In the year since Wyeth submitted its Citizen's Petition, the FDA has received more than 40,000 emails and letters from physician groups, pharmacy groups and women—so many that the FDA extended the comment period (originally scheduled to conclude April 4, 2006) by 1 month; to May 4, 2006. Wyeth submitted a supplemental filing to its original petition on April 4, 2006, countering that the FDA warning letters sent in November had not targeted the sale and marketing of BHRT drugs sold by prescription.<sup>25</sup>

A letter to the FDA from the American Pharmacists Association, dated May 3, 2006, opposes requests within Wyeth's petition because the petition fails to differentiate between compounding and manufacturing (compounding is regulated by state boards of pharmacy versus

the FDA), attempts to apply manufacturing standards to compounding (pharmacy compounding is exempt from meeting manufacturing standards, such as providing package inserts and warnings about safety) and directs the FDA to take enforcement action beyond its authority (currently, states regulate the practice of pharmacy compounding).<sup>26</sup>

In August 2006 the FDA issued warning letters to three compounding firms contending that custom-blended treatments are unapproved new drugs, giving the FDA jurisdiction over the compounding pharmacies.<sup>27</sup> By month's end, however, a federal court in Texas ruled that compounded medications are legal. In November 2006 the FDA held a teleconference titled "An Introduction to the Improved FDA Prescription Drug Labeling."<sup>28</sup> An FDA-sponsored public workshop on marketed unapproved drugs has been scheduled for January 9, 2007.

Whether or not the FDA will ultimately weigh in on this debate, it is important for each and every practitioner to be aware of the issues at-hand, and to explain clearly to women that evidence for safety and efficacy of compounded hormone preparations, as required for FDA-approved products, does not exist. For women interested in hormone preparations identical in composition to hormones produced endogenously, transdermal estradiol and micronized progesterone

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would fit the bill. These preparations have been tested in randomized controlled trials for relief of vasomotor and vaginal symptoms and endometrial safety.

### Tibolone Rejected for Menopause Treatment in the United States

Tibolone, a synthetic steroid, has been available and widely used in much of the world for nearly 20 years. It is prescribed for relief of menopausal vasomotor symptoms and prevention of osteoporosis. The tibolone molecule has no biological activity, but its metabolites are thought to act in a "tissue-specific" fashion with estrogenic, androgenic and progestogenic properties.<sup>29</sup> The estrogenic effect reduces hot flashes, bone loss and vaginal dryness. The progestational properties are thought to protect the endometrium. Some, but not all, studies have reported an increase in sexual arousal, possibly in response to the androgenic component.<sup>29</sup> Although breast effects were thought to be neutral, tibolone users had higher risks of breast cancer than women on estrogen-only therapy in the Million Women Study.<sup>30</sup>

Two recently completed clinical trials add new data to the safety and efficacy profile of tibolone. In the 3-year, placebo-controlled Osteoporosis Prevention and Arterial effects of tiboLone (OPAL) trial,<sup>31</sup> tibolone was associated with less vaginal bleeding and a comparable endometrial safety profile compared with CEE/medroxyprogesterone acetate (CEE+MPA). This was in contrast to the Million Women Study findings,<sup>32</sup> which had suggested that the risk of endometrial cancer was increased with the use of tibolone. Neither tibolone nor CEE+MPA had a favorable effect on atherosclerosis progression as measured by carotid intima-media thickness.<sup>33</sup>

In the 3-year Long-term Intervention on Fractures with Tibolone (LIFT) trial,<sup>34</sup> osteoporotic women assigned to tibolone experienced half as many vertebral fractures as those in the placebo group, but the incidence of stroke was doubled (RR, 2.59;  $P = .01$ ), with an increase of 2.62 cases per 1,000 woman-years of treatment.<sup>35</sup>

On June 2, 2006, the FDA determined that the New Drug Application submitted for tibolone was "not approvable."<sup>36</sup>

The new safety findings that may have contributed to the decision not to approve tibolone for use in the United States confirm the importance of adequately powered randomized clinical trials with clinical endpoints. Whether tibolone will be reconsidered for symptom relief in young,

healthy postmenopausal women who may have less risk of cerebrovascular disease than older women with osteoporosis remains to be determined.

### Emergency Contraception Approved for Nonprescription Access

On August 24, 2006, the FDA announced approval of Plan B as an over-the-counter option for women age 18 and older.<sup>37</sup> Plan B (levonorgestrel 0.75 mg) is taken in two oral doses, 12 hours apart, to prevent pregnancy after known or suspected contraceptive failure or unprotected intercourse. Taking both pills at the same time or each 0.75-mg pill 24 hours apart is still effective.<sup>38</sup> Plan B has been available for some time as a prescription drug, and has been available in a few states without a prescription. Early use is best; if taken within 72 hours of unprotected sex, Plan B can lower the risk of pregnancy by 85%.<sup>39</sup> (Emergency contraception is still moderately effective if taken up to 120 hours after intercourse).<sup>38</sup>

Women in the menopausal transition are at risk for unwanted pregnancy. According to abortion surveillance summaries published by the Centers for Disease Control and Prevention, in 2002 there were 310 abortions per 1,000 live births in women over 40 years of age.<sup>40</sup> The abortion ratio in women over 40 is second only to that in girls 15-19 years of age, with 368 abortions per 1,000 live births.

The most common adverse effects of Plan B include nausea (23%), abdominal pain (18%), fa-

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tigue (17%), headache (17%) and menstrual changes (16%).<sup>39</sup> There is no evidence to demonstrate that emergency contraception is unsafe for women with contraindications to oral contraceptives, or for those with any particular medical conditions.<sup>38</sup> The World Health Organization's "Medical Eligibility Criteria for Contraceptive Use" includes no conditions in which the risks of emergency contraception use outweigh the benefits.<sup>41</sup> Furthermore, no rationale exists for denying emergency contraception to women with undiagnosed vaginal bleeding; no clinical examination or testing is required before emergency contraception is provided.<sup>38</sup>

Women at midlife might be more vulnerable to unplanned pregnancy because menstrual cycle irregularity and the antic-

ipation of menopause engender a false sense of security. Additionally, separated, divorced or widowed women may practice sporadic contraception in response to sporadic sexual encounters. All perimenopausal patients at risk for pregnancy should receive contraception counseling. In the event counseling did not occur or recommendations were not put into practice, emergency contraception with Plan B provides an effective response to the threat of unwanted pregnancy.

### Intravenous Bisphosphonate Approved for Treatment of Postmenopausal Osteoporosis

Most clinicians are familiar with use of the IV bisphosphonates pamidronate and zoledronic acid for the indications of hypercalcemia of malignancy, Paget's disease and metastatic bone disease. IV bisphosphonates have been used "off-label" for osteoporosis treatment in patients unable to tolerate oral bisphosphonates or unable to comply with dosing regimens.<sup>42</sup> In a recent trial, IV pamidronate also relieved pain in patients who had experienced an osteoporotic vertebral compression fracture.<sup>43</sup>

In February 2006, the FDA approved ibandronate sodium as the first IV medication for treatment of postmenopausal osteoporosis. Oral ibandronate sodium reduces vertebral fractures and has been available for several years for daily or monthly dosing for prevention and treatment of osteoporosis. In

the Dosing IntraVenous Administration (DIVA) trial of 1,358 women with postmenopausal osteoporosis,<sup>44</sup> bone mineral density (BMD) increases over 1 year were greater with ibandronate 3 mg administered IV (over 15 to 30 seconds) every 3 months than with approved daily oral dosing ( $P < .001$ ). BMD benefits persisted during a second year of therapy.<sup>45</sup> In 3.7% of patients, acute-phase reaction-like events were reported after the first injection, but symptoms were transient in nature and resolved without treatment. After 2 years of therapy, there were no cases of osteonecrosis of the jaw.<sup>46-47</sup> Overall safety and tolerability of the two modes of administration were similar.<sup>44</sup>

Zoledronic acid infusions (over 15 minutes) administered at intervals of up to 1 year in postmenopausal women with low BMD produced effects on bone turnover and bone density similar to those of oral bisphosphonates.<sup>48</sup> In the Health Outcomes and Reduced Incidence with Zoledronic acid ONce yearly (HORIZON) trial, 7,736 postmenopausal women with osteoporosis (mean age, 73.1 years) were randomly assigned to an annual infusion of zoledronic acid 5 mg or placebo.<sup>49</sup> After 3 years, a 70% reduction in new vertebral fractures ( $P < .0001$ ) and a 40% risk reduction in hip fractures ( $P = .0032$ ) were reported in the treatment group.<sup>49</sup> Flulike symptoms occurred within the first 3 days of therapy, but usually resolved within a few days. Osteonecrosis of the jaw<sup>46,47</sup> occurred at the same frequency as in the placebo group.<sup>49</sup> Approval for osteoporosis treat-

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ment with zoledronic acid (re-named Reclast for this indication) is currently under review.

Intravenous therapies given at long (quarterly to annual) intervals will provide many patients who are currently unable to tolerate oral bisphosphonate therapy or who do not want to take daily, weekly or monthly pills with another option for bone preservation and fracture prevention.

### Alternative Treatments for Hot Flashes: Effective as Estrogen?

Relief of vasomotor symptoms is the primary indication for postmenopausal HT. Some women, however, are reluctant to initiate HT or have contraindications rendering HT unsafe. In a recent review of trials published through October 2005,<sup>50</sup> nonhormonal therapies for menopausal hot flashes, such as the selective serotonin-reuptake inhibitors or serotonin-

norepinephrine reuptake inhibitors (SNRIs) clonidine and gabapentin, were found to provide evidence for efficacy; however, effects were less than with estrogen. The authors concluded that adverse effects and cost might restrict the use of alternatives for many women, and while helpful for highly symptomatic women who cannot take estrogen, they are not optimal choices for most women.

Gabapentin is a gamma-aminobutyric acid analogue approved for treatment of seizures. In a head-to-head trial published this year,<sup>51</sup> gabapentin was found to be as effective as estrogen in reducing hot flashes. The trial included 60 symptomatic postmenopausal women (average age, 51 years) randomly assigned in equal groups ( $n = 20$ ) to CEE 0.625 mg per day, placebo, or gabapentin titrated to 2,400 mg per day. At the conclusion of the 12-week trial, both estrogen and gabapentin had reduced hot flashes by 72% and 71%, respectively—significantly more than placebo (54%). No differences were seen between groups in the Zung Depression Scale. Somatic complaints were significantly greater in the gabapentin arm than in the placebo arm; the Headache, Dizziness, and Disorientation cluster appeared with greater frequency in the gabapentin group, at a frequency of one in four women treated.

In response to this trial, Rochester-based PharmaNova Inc. exclusively licensed certain US patent rights to Depomed Inc. for development of an extended-release form of gabapentin specifically as a nonhormonal alternative treatment for vasomotor symptoms.<sup>52</sup> Other options for hot flash

relief are in the pipeline; a New Drug Application for desvenlafaxine succinate, a novel SNRI, was submitted by Wyeth to the FDA in June 2006.<sup>53</sup> Phase 2 studies are under way with MF101, an estrogen-receptor beta-selective drug developed by Bionovo, Inc. to treat vasomotor symptoms such as hot flashes and night sweats.<sup>54</sup>

Women and their providers can be guaranteed that the demographics of the menopausal population will continue to drive new drug development with indications for vasomotor symptom relief.

## Summary and Conclusions

Now that 2007 is under way, it will be exciting to follow the course of ongoing clinical trials, new drug development and enhanced modalities to encourage lifestyle improvements so women can make the most of the menopause transition and the years beyond. ■

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*This article includes discussion of off-label use of medications.*

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