

# Estrogen Alternatives Available for Hot Flashes

*Remedies such as progestins often are proposed, but few have been evaluated in controlled studies.*

BY ROBERT FINN  
San Francisco Bureau

SAN FRANCISCO — In the wake of the Women's Health Initiative, "It's easier to get OxyContin out of a doctor's office than Prempro," Melissa A. McNeil, M.D., joked at the annual meeting of the American College of Physicians.

The question then is how is a physician to manage the vasomotor symptoms of menopause? asked Dr. McNeil, who is women's health program director at the University of Pittsburgh. Although many remedies have advocates, few have been evaluated in controlled studies. She offered several evidence-based suggestions:

► **Time.** Tincture of time works for many women. Although 75% of menopausal women do experience hot flashes, for 30%-50% of them, the symptoms improve within months, and hot flashes resolve completely for most women within 4-5 years.

"That can be a very long 4 or 5 years," Dr. McNeil acknowledged. In addition, "A substantial minority will continue to have hot flashes for years beyond menopause."

The fact that women's hot flashes frequently resolve spontaneously leads to a

large placebo effect—in the neighborhood of 25%—in various studies of drugs and supplements.

► **Progestins.** There's good evidence from randomized, controlled trials for the efficacy of a number of progestins.

Medroxyprogesterone and megestrol (Megace) both were reported to result in a 74% reduction in hot flashes. Depo-Provera was reported in one study to result in a 90% reduction in hot flashes. Uterine

bleeding is a frequent side effect of progestin therapy, limiting its use in women who have uterine cysts. Furthermore, there are no long-term safety data available.

The most significant bar to progestin therapy, however, comes from Women's Health Initiative results, which suggest that progesterone supplementation may confer an increased risk of certain cancers or adverse cardiovascular events, compared with estrogen alone.

► **Clonidine and methyldopa.** Studies of antihypertensive agents such as clonidine

and methyldopa suggest a relatively small effect on hot flashes. Use of clonidine, in particular, is limited by side effects, including dry mouth, constipation, and drowsiness. Still, these drugs may be useful in women who need blood pressure treatment in addition to relief from their hot flashes.

► **Nonhormonal therapies.** Antidepressants, which are the most promising non-

hormonal therapies for hot flashes, have become the mainstay of treatment. Venlafaxine, fluoxetine, and paroxetine all appear to result in 50%-65% reductions in hot flashes in controlled trials, although some of

those trials studied breast cancer survivors, who may not be exactly representative of the entire population of menopausal women.

One advantage of antidepressants is that their effect on hot flashes seems to begin relatively quickly. Some patients have reported results in about 1-2 weeks, compared with about a month for their effects on depression. This allows for relatively rapid dose titration.

► **Gabapentin.** This drug appears to have a modest effect on hot flashes, with a reduction of about 50% in one small trial.

About half of the women who participated in that trial said they experienced at least one adverse event, including dizziness, somnolence, palpitations, or peripheral edema.

► **Nutritional supplements.** Although these supplements have received a lot of coverage in the lay press, scientific evidence of their efficacy in treating hot flashes generally is lacking. Soy phytoestrogens engendered a great deal of enthusiasm a few years ago, and several small studies seemed to indicate effectiveness. But more recently, a larger controlled trial found they had no effect on hot flashes.

Mixed evidence of effectiveness has been found for vitamin E and black cohosh, but most studies have been small and unblinded. Evening primrose oil, ginseng, and wild yam cream all have been shown to be ineffective.

In selecting a treatment for a patient's hot flashes, Dr. McNeil said that she always looks for a twofer. "If I'm treating depression, I'll go for an antidepressant," she said. "If they have chronic pain, I think about gabapentin. And if they have hypertension I might use clonidine. If they're straight out of the starting block, I'd think about venlafaxine as my starting point."

Dr. McNeil said she has no conflicts of interest with regard to her presentation at the meeting. ■

## Metformin, Reduced-Calorie Diet Improve CV Risk in PCOS Patients

BY HEIDI SPLETE  
Senior Writer

WASHINGTON — Metformin combined with a reduced-calorie diet reduced cardiovascular risk in a study of 791 women with polycystic ovary syndrome, Mofiz Haque, M.D., reported in a poster presented at the Clinical Research 2005 meeting.

The metformin-diet (MET-D) combination was effective in reducing weight, triglycerides, and LDL cholesterol, while increasing HDL cholesterol, reported Dr. Haque of the cholesterol center at the Jewish Hospital, Cincinnati, and his colleagues.

At baseline, the women had a median weight of 95 kg; 15% were overweight, 46% were obese, and 29% were severely obese. At baseline, the mean triglyceride level was 108 mg/dL, LDL cholesterol was 116 mg/dL, and HDL cholesterol was 46 mg/dL.

Women with a BMI less than 25 kg/m<sup>2</sup> were given a 2,000-calorie per day diet, and those with a BMI of 25 kg/m<sup>2</sup> or higher were given a 1,500-calorie diet. Each diet included 26% of calories from protein and 44% from carbohydrate, they noted at the meeting, sponsored by the American Federation for Medical Research.

Overall, metformin targeted to 2,500 mg/day in combination with dietary restriction was as-

sociated with significant reductions in weight, triglycerides, LDL cholesterol, and blood pressure levels.

The mean weight loss was 5 kg (5%), 6 kg (6%), and 5 kg (5%) for women who took medication for 12-18 months, 18-24 months, and more than 24 months, respectively. In those three groups, 13%, 14%, and 15% of the women lost at least 15% of their body weight.

Triglyceride levels dropped significantly—by 17 mg/dL—among the 65 women who followed the MET-D regimen for 18-24 months.

LDL cholesterol levels fell an average of 6 mg/dL (4%) and 9 mg/dL (7%), respectively, among the 102 women who followed the regimen for 12-18 months and the 210 women who followed the regimen for more than 24 months.

HDL cholesterol levels rose an average of 2 mg/dL

(6%) and 4 mg/dL (8%) among women who followed the regimen for 18-24 months and more than 24 months, respectively. Both increases were statistically significant.

In general, about 75% of women with polycystic ovary syndrome are obese, with unhealthy triglyceride and cholesterol levels. MET-D appears to be an effective strategy for helping such patients lose weight and reduce cardiovascular risk factors associated with overweight and obesity, the investigators noted. ■

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## Urge Incontinence Treated With Flexible Dosing of Oxybutynin

SAN FRANCISCO — Almost half of patients on flexible-dosing schedules of extended-release oxybutynin for urge incontinence chose a dose of more than 10 mg/day, the level employed in two fixed-dose trials of the medication, Peter K. Sand, M.D., and Scott A. MacDiarmid, M.D., reported in a poster presentation at the annual meeting of the American College of Obstetricians and Gynecologists.

In a combined analysis of 368 patients from three clinical trials employing flexible dosing schedules of 5-30 mg/day, 47% of participants chose a final dose of 15, 20, 25, or 30 mg/day.

At all selected final doses of oxybutynin, 77%-83% of the patients reportedly achieved a reduction of at least 70% in the number of urge incontinence episodes, according to Dr. Sand of Northwestern University, Chicago, and Dr. MacDiarmid of Wake Forest University, Winston-Salem, N.C.

At final doses of 5 mg to 25 mg/day, patients achieved a reduction of

about 85% in the number of urge incontinence levels.

But at 30 mg/day, the reduction in episodes was only 61%.

Given that the incidence of dry mouth (the most common side effect) was similar to that in the other groups, the investigators suggested that the finding of relatively low efficacy in the highest dose may be due to a relative insensitivity to anticholinergics among some of the patients.

Overall, 23.1% had moderate or severe dry mouth, but only 5 (or 1.4%) withdrew from their trial for this reason.

Ortho-McNeil Pharmaceutical Inc. sponsored the analysis.

—Robert Finn



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