ALTERNATIVE THERAPIES IN WOMEN'S HEALTH

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Insomnia in Women: Menopause and Melatonin

Part III of III-Part Series

By Susan T. Marcolina, MD, FACP, and Beth Rosenshein, BSEE

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When vasomotor events (VME) occur as a consequence of estrogen withdrawal, they respond to estrogen replacement.[1] Several randomized, placebo-controlled trials indicate that estrogen replacement significantly relieves hot flashes compared to placebo[2-4] and to other botanical interventions.[5] At the present time, however, the recommended treatment for moderate-to-severe VMEs is the lowest effective dose of hormone therapy for the shortest duration.[6] It is not universally understood what ovarian hormone replacement is and what the recommendations should be for women who continue to have long-term problems with VMEs and, by proxy, insomnia; therefore, consideration must be given to the option of long-term physiologic ovarian hormone replacement therapy.

Hormone Replacement Therapy and the Women's Health Initiative

Current recommendations regarding hormone replacement therapy come from the findings of the Women's Health Initiative, a prospective, randomized, controlled trial of hormone therapy involving more than 26,000 postmenopausal women (average age, 63 years), 10,739 of whom had a hysterectomy and were, therefore, randomized to CEE or placebo and 16,608 with a uterus who were randomized to CEE plus MPA or placebo. The arm of the trial assigned to the CEE plus MPA was terminated in 2002 due to an excess number of women with venous thromboembolism (VTE), coronary heart disease, stroke, breast cancer, and total mortality.[7] Subsequent secondary analyses of these findings and further recent clinical studies have uncovered several important factors to consider about hormone replacement therapy. Rousseau and colleagues concluded that there was a tendency, though statistically not a significant one, toward reduced CHD risk in younger subset of women

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(50-59 age group) beginning the replacement therapy closer to onset of menopause compared to those starting the hormone replacement therapy more than 10 years after climacteric onset.[8] This suggests a window of time for initiating hormone replacement wherein it may play a role in decreasing risk for CHD. It is important to keep in mind that the WHI was designed as a primary prevention trial and not as a symptom treatment trial. The results obtained in this trial were based upon the use of oral Premarin (CEE or conjugated equine estrogens) and Provera and, as such, may not be generalizable to different populations of women using different HRT formulations via different administration routes. CEEs are a complex mixture of at least 9 different estrogens, most of which are present only in horses.[9]

Since the WHI, the Estrogen and Thromboembolism Risk (ESTHER) study has shown that the route by which hormone therapy is administered, and the type of hormone replacement therapy used, can further attenuate the risks identified by the WHI. Scarabin and colleagues in a prospective, case-controlled trial, have shown that the odds ratio for VTE in current users of oral estrogen replacement therapy were 3.5 compared to .9 in current users of transdermal ERT. Most of the study subjects on transdermal estrogen used transdermal 17 beta estradiol, identical to the 17 beta estradiol produced by the functional ovary. Avoidance of the first pass effect of the liver with transdermal administration of hormones avoids the hepatic elaboration of prothrombotic species, such as prothrombin factors 1 and 2 and proinflammatory factors such as C-reactive protein (CRP) that is seen with oral estrogen therapy.[10,11] An elevation in CRP is an independent risk factor for coronary artery disease.[12,13]

Progestogen Considerations

Another important consideration in replacement therapy is the option for progesterone replacement. All women with a uterus must take a progestational agent if prescribed estrogen replacement for VMEs to prevent the risk of endometrial cancer associated with continuous unopposed estrogen.[14] The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, a placebo-controlled, double-blinded study with a 3-year follow-up examined the effects of different progestogens on 875 women (45-64 years of age) randomized to 5 treatment regimens: 1) placebo, 2) oral conjugated equine estrogen (CEE) .625 daily, 3) oral CEE plus Provera (medroxyprogesterone acetate) (MPA), 10 mgs days 1-12 of the month, 4) oral CEE plus MPA 2.5 mgs daily, and 5) oral CEE plus micronized progesterone (MP) 200 mgs days 1-12. All treatment groups had lower (LDL) low density lipoprotein levels, higher HDL levels (the CEE only and CEE plus MP regimen more than CEE plus MPA regimen), and higher triglyceride levels than placebo. The cyclic MP had the most favorable effect on HDL-C and LDL-C, preserving the effects of the CEE without risk of endometrial hyperplasia.[15]

Androgens in Ovarian Hormone Replacement Therapy

Heretofore, androgens have not been included as "hormone replacement therapy" despite the fact that women's bodies make approximately 71% of the androgens elaborated by men, one third of which are from ovarian sources with the other two thirds elaborated in the body's adipose stores and adrenal glands.[16] Standard hormone replacement has included estrogen and progestins in the oral forms and such routes of administration further reduce endogenous androgenic activity because oral estrogens both suppress gonadotropins, leading to reduced ovarian androgenesis and increase sex hormone-binding globulin (SHBG), which in turn diminishes bioavailability of androgens.[17] Animal studies have shown that testosterone protects breast tissues due to its effects on the two types of estrogen receptors, ER beta and ER alpha. The ratio of these two receptors plays an important role in breast cancer. Whereas estradiol increases ER alpha; testosterone decreases ER alpha, and increases ER beta. Prior to the onset of ovarian failure, ER beta is expressed to a greater extent than ER alpha, and this is

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reversed after ovarian failure due to the declining androgen levels. This decline in ovarian androgen production actually precedes the climacteric by approximately 10 years.[18-20] NIH-sponsored primate studies in 2000[21] and 2003[19] designed to investigate the effects of testosterone on the breast cancer gene MYC (implicated as a mediator of estrogenic tumorigenesis in the breast), and breast epithelial cell proliferation showed that androgen addition to estrogen treatment reduced mammary epithelial cell MYC expression. Testosterone treatment also reduced ER alpha and increased ER beta expression in estrogen-treated monkeys and, thus, had a protective effect on the estrogen-treated breast in the same way that progesterone has the protective effect of preventing hyperplasia in the estrogen-treated uterus. Their overall conclusion was that physiological estrogen/androgen hormone replacement might be beneficial to women and girls with ovarian failure.[22]

Hofling and colleagues demonstrated in a prospective, randomized, double-blind, placebo-controlled study of 99 postmenopausal women on continuous combined oral estradiol 17 beta and norethisterone acetate demonstrated that those who received a testosterone patch (Intrinsa Patch 300 micrograms testosterone /24 hours applied twice weekly) had no significant increase in breast cell proliferation form baseline through the 6-month study period. In contrast, the group treated with the oral estrogen/progestin and the placebo patch had more than a five-fold increase (*P* greater than .001) in total breast cell proliferation from baseline to 6 months. The tissue proliferation indices in this study were quantified from immunocytochemical staining of breast biopsies obtained by fine needle aspiration (FNA) taken before and after hormone therapy treatment. The information from this study is important because it provides a means by which to mitigate the increased risk of breast cancer seen with combined estrogen/progestogen therapy in randomized, controlled trials such as the WHI.[23]

There has been thoughtful concern that hormone therapy should be initiated for ovarian failure, and a discussion about what such treatment would involve.[24] With this in mind, all of the ovarian hormones, estrogen, progesterone, and testosterone, should be included in a hormone replacement regimen, and efforts should made to bring ovarian hormone replacement therapy into line with replacement therapy given for other hormone deficiency syndromes, such as insulin dependent diabetes, hypothyroidism, and growth hormone deficiency, where physiologic hormone replacement is the standard of practice.

Physiologic Hormone Products and Dosages for Postmenopausal Women

Since natural progesterone in powdered form is poorly absorbed via the oral route, due to gastric acid destruction, it must be micronized into smaller particles and dissolved in oils consisting of long-chain fatty acids, primarily peanut oil. The micronized progesterone is identical in chemical structure to endogenous progesterone, and is manufactured from the wild yam or soybean precursor diosgenin. It is available as Prometrium or through compounding pharmacists as oral micronized progesterone (MP).[25,26] The FDA recognizes a dose of 200 mgs for 12 sequential days per month for the prevention of endometrial hyperplasia in women taking estrogen replacement therapy.[27] Progesterone powder can be compounded, by a compounding pharmacy in a cream base, and applied topically. Generally, 60-100 mgs of progesterone is suspended per gram of cream (giving a 6-10% w/v suspension), which can be dispensed in syringes for ease of application. The dosage can be adjusted to achieve blood levels of 12,000-25,000 pg/mL, which is the average progesterone range over the course of the menstrual cycle. After one year, an endometrial biopsy should be done to assess progesterone effect, with subsequent biopsies yearly depending upon symptoms.

Several transdermal delivery systems for estradiol are available in the United States. Estradiol is released from an alcohol gel reservoir or directly from the adhesive matrix of a transdermally applied patch. *Table 1* provides examples of the available transdermal estradiol preparations. The most commonly used dosages are .05 and .1 mg patches, which are applied to the skin once to twice weekly depending upon the product.

The patches are designed to release .014-.1 mg of estradiol daily for 3.5-7 days. Menostar supplies the lowest dose of estrogen for prevention of osteoporosis. A patch is applied to the clean, dry, lotionless area of skin on the abdomen or buttock one or twice per week. The 7-day adhesive matrix patch produces similar mean estradiol levels to the 3.5 day patch, but with less variation in estradiol levels. The .1 mg estradiol patch can raise the serum level of estradiol from 17-195 pg/mL, which is a wide range not influenced by weight. Target blood levels of estradiol for replacement are 50-150 pg/mL, which is generally the average level measured during the course of the menstrual cycle. Since it takes only a day to reach a steady state level due to the short half-life of estradiol, a blood level of estradiol, two days after applying the patch, indicates how well the estradiol is absorbed transdermally. Dosages can be adjusted to keep the target blood levels in range.[29]

Table 1

Examples of Transdermal Estradiol Products (adapted from reference #28)

Name	Delivery System	Dosage (most common)	Comments
Climara®	Patch applied once/weekly	.025, .0375, .05, .06, .075, or .1 mg	Apply to clean, dry skin; apply firm pressure to place patch
Estraderm®	Patch applied once/weekly	.025, .05, or .1 mg	
Vivelle®	Patch applied twice/weekly	.025, .035, .05, .075, or .1 mg	.05 mg patch covers a surface area of 14.5 sq cm
Vivelle Dot®	Patch applied twice/weekly	.025, .0375, .05, .075, .1 mg	Each dose has a surface area of 2.5, 3.75, 5.0, 7.5, and 10 sq cm, respectively, which is the smallest patch available per dose
Alora®ETS	Patch applied twice/weekly	.05, .075, or .1 mg	
Estrasorb®	Topical emulsion suspended in soybean oil	2 pouches provide .05 mg/day	Large area of application on body
Menostar™	Patch applied once/weekly	.014 mg/day - only dose available	Indicated only for osteoporosis treatment; provides lowest estrogen dose of any patch
EstroGel®	Topical hydroalcoholic gel base in pump dispenser	1.25 gram unit dose contains .75 mgs estradiol	Apply from wrist to shoulder; pump dispenser needs priming prior to first time use

Intrinsa is a transdermal testosterone matrix patch, specifically developed for use in women with surgical menopause suffering from Hypoactive Sexual Desire Disorder (HSDD). Each patch contains 8.4 mgs of testosterone, and releases 300 µ over a 24-hour period of time. After patch application, average total testosterone levels are raised from 17 to an average of 79 ng/dL on the twice weekly Intrinsa patch. It can be obtained by ordering from www.atlanticdrugs.com, a company located in the United Kingdom. It is not currently FDA approved for use in the United States.[30] Patients on CEE (Premarin) should not use Intrinsa.[31]

Adverse effects:

Oral micronized progesterone or Prometrium is the only FDA-approved progesterone product available and, because it contains peanut oil, its use should be avoided in persons with nut allergies. It can also be sedating and, therefore, should be taken just prior to bedtime. If taken with food, absorption is increased, which can intensify its sedative side effects. Symptoms of bloating and breast tenderness are dose related.[27,32] For persons with peanut allergies or oral intolerance, transdermal preparations of progesterone can be formulated by compounding pharmacists with dosage guided by hormone blood levels and endometrial biopsies to assess the balance of secretory and proliferative effects on the endometrium. A major concern with progesterone creams is that serum progesterone levels achieved with the creams are too low to have an effect on the endometrium; however, antiprolif-

erative effects on the endometrium have been demonstrated even when circulating levels of progesterone are low. The status of the endometrium should be evaluated with an endometrial biopsy within a year of initiating hormone therapy. In its guidelines to the pharmaceutical industry, the US FDA recommends endometrial biopsies at the beginning and the end of an HRT trial.[33] Sonography of the uterus can provide additional useful information regarding endometrial thickness (should be less than 5 mm in postmenopausal women) and the presence of polyps or fibroids. Abnormalities identified either sonographically or by endometrial biopsy should be more completely assessed with a gynecologic referral.

Intrinsa is expensive at $16-$20/patch. The patch can cause mild erythema, inflammation, and itching at the site, which can be relieved by rotation of patch sites. Side effects of acne and hirsutism can be seen with supraphysiologic dosages, but are uncommon with the physiologic dosage provided by this patch.[34]

The use of estradiol patches is associated with mild skin erythema, itching, and irritation, which can be mitigated by frequent rotation of patch sites. Mild breast tenderness and irregular vaginal bleeding can be side effects, as with oral estrogen, but both symptoms can be attenuated by dosage adjustment.[35] If vaginal bleeding remains persistent, further evaluation is necessary.

Conclusions

Given the unique factors that contribute to insomnia in women with ovarian failure, including VMEs, sleep disordered breathing, and decreases in endogenous melatonin levels, it is difficult to predict the extent to which nonpharmacologic mind-body therapies would be efficacious if used alone, without consideration of ovarian hormone replacement therapy. The WHI has definitively demonstrated the risks posed by a standard nonphysiologic estrogen/progestin replacement regimen. Subsequent studies have shown that physiologic replacement, administered transdermally with regard to estrogen, testosterone, and progesterone can mitigate these VTE, breast cancer, and cardiovascular risks.

Since endogenous levels of melatonin decrease in temporal sequence to the drop in ovarian sex hormones, physiologic ovarian hormone replacement may positively impact melatonin levels, which are an important input to the quality of sleep, particularly in older individuals. Given the side effects of pharmacologic therapy for insomnia, which include decreasing endogenous melatonin levels and dangerous side effects such as complex, automatic sleep-related behaviors, it is important to get back to basics and consider physiologic replacement of ovarian hormone deficiencies with standardized, bioidentical products for women guided by periodic blood level determinations. It will be important to design randomized, controlled studies to evaluate the effect of these replacement therapies on validated indicators of sleep quality.

Recommendations

Women who present with complaints of insomnia in midlife should have a full endocrinologic evaluation to determine ovarian function. Depending upon their history and physical evaluation, consideration should be given to a polysomnographic evaluation to rule out sleep disordered breathing which may impose cardiovascular risk, and an appropriate work-up should rule out medical or psychiatric causes of insomnia which should be prioritized for treatment. A physician-patient discussion should include the topic of physiologic hormone replacement, with adjustment of the dosages of estrogen, progesterone, and testosterone determined according to measurements of plasma hormone levels. Estrogen and progesterone replacement have had salutary effects on quality of sleep in postmenopausal women. Animal and clinical studies suggest that maintaining physiologic blood levels of testosterone can mitigate the risk of breast cancer that has been seen in estrogen-progestogen replacement regimens. ❖

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CME Objectives

After reading *Alternative Therapies in Women's Health*, the health care professional will be able to:

1. evaluate alternative medicine and complementary therapies for women's health concerns;
2. identify risks and interactions associated with alternative therapies;
3. discuss alternative medicine options with patients;
4. offer guidance to patients based on latest science and clinical studies regarding alternative and complementary therapies.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity, you must complete the evaluation form provided and return it in the reply envelope provided at the end of the semester to receive a certificate of completion. Upon receipt of your evaluation, a certificate will be mailed.

CME Questions

19. The use of transdermal estrogens is associated with elevated levels of C-reactive protein.

a, True
b. False

20. Peanut allergy would be a contraindication to the use of Prometrium.

a, True
b. False

21. Side effects of transdermal hormone patches may include:

a, skin erythema
b. skin itching
c. Both A and B
d. None of the above

22. The Menostar transdermal patch provides the highest estradiol dose.

a, True
b. False

Answers: 19. (b); 20. (a); 21. (c); 22. (b)

News Briefs

Abbott recalls low-calcium/ vitamin D-free infant formula

Abbott has announced a voluntary worldwide recall of two lots of Calcilo XD® Low-Calcium/Vitamin D-Free Infant Formula with Iron powder in 14.1-ounce cans (400g). Only the 14.1-ounce (400g) cans are involved in this action. Calcilo XD® is a low-calcium and vitamin D-free infant formula that is specifically designed for the nutrition support of infants and children with hypercalcemia. It is only available by special order.

Abbott is voluntarily recalling two lots of product because small amounts of air may have entered the can, resulting in product oxidation. A common sign of oxidation is an off aroma. Consumption of highly oxidized foods can cause gastrointestinal symptoms such as nausea, vomiting, and diarrhea. If parents have questions or concerns they should contact a health care professional.

The problem is isolated to the lots of Calcilo XD Powder in 14.1-ounce (400g) cans, with stock code number 00378 and with lot numbers 39973RB or 47239RB6 printed on the bottom of the cans. No other Calcilo XD powdered infant formulas are affected.

The two lots were distributed in the United States, Canada, Malaysia, Korea, and Bahrain, between 06/06/06 and 04/17/08. Consumers who purchased Calcilo XD® Low-Calcium/Vitamin D-Free Infant Formula with Iron powder from either of the two lots mentioned above should contact Abbott Nutrition at (800) 638-6493.

Abbott is working with its distribution partners and the US FDA to execute this recall.

Obese adults no more likely to use CAM, study says

Although obesity is associated with higher health care costs, obese individuals are not more likely to turn to complementary and alternative medicine (CAM) than people of normal weight, says a study published May 1 on the website for the journal *Obesity*.

Researchers at Osher Research Center and Beth Israel Deaconess Medical Center at Harvard Medical School in Boston, MA, wanted to examine the relationship between obesity and the use of CAM. To do this, they analyzed data on CAM use from the 2002 National Health Interview Survey (NHIS) Alternative Medicine Supplement. They compared the use of CAM overall, within the past 12 months, between normal weight (BMI from 18 to < 25), overweight (from 25 to < 30), mildly obese (from 30 to < 35), moderately obese (from 35 to < 40), and extremely obese (> 40) adults.

For the primary analysis, the researchers' multivariable model was adjusted for sociodemographic factors, insurance status, medical conditions, and health behaviors. The researchers performed additional analyses to explore the association of BMI and the use of seven CAM modalities.

The analyses showed that adults with obesity have lower prevalence of yoga therapy use, and similar prevalence of use of several CAM modalities, including relaxation techniques, natural herbs, massage, chiropractic medicine, tai chi, and acupuncture, compared to normal-weight individuals. After adjustment for sociodemographic factors, insurance status, medical conditions, and health behaviors, adults with obesity were generally less likely to use most individual CAM modalities, although the differences often were modest, the researchers say. They concluded that additional research was needed to improve the understanding of CAM use by obese adults.

NCCAM names director of the Division of Extramural Activities

Martin H. Goldrosen, PhD, has been appointed director of the Division of Extramural Activities (DEA) at the National Center for Complementary and Alternative Medicine (NCCAM), part of the National Institutes of Health (NIH).

The division, through its Office of Scientific Review, coordinates the receipt, referral, and scientific review of grants, cooperative agreements, and research contracts. Its Office of Grants Management oversees the processing of grant, cooperative agreement, and contract awards. The division also coordinates meetings and directs committee management activities for the National Advisory Council for Complementary and Alternative Medicine.

Goldrosen began his NIH career in 1991 as a health scientist administrator within the Grants Review Branch of the Division of Extramural Affairs at the National Cancer Institute. Prior to joining NIH, he was a cancer research scientist at the Roswell Park Cancer Institute in New York. Concurrently, Goldrosen was a Research Professor of Experimental Pathology at the State University of New York in Buffalo. ❖

In Future Issues:

Acupuncture and Obesity

Ginger and Nausea