By Karen Roush, MSN, RN, FNP-BC

Managing Menopausal Symptoms

A review of the three most commonly reported symptoms: hot flashes, insomnia, and mood problems.

Overview: There are three major categories of symptoms peri- and postmenopausal women experience: vasomotor symptoms, sleep difficulties, and mood problems. This article reviews the literature on causes and treatments. This is part three of a four-part series on postmenopausal health.

Keywords: insomnia, menopause, mood disorders, vasomotor symptoms

The menopausal transition can be a rocky road for women. Some saunter along with barely a hot flash, but others have symptoms that range from mildly discomforting to life disrupting. A few factors can increase the likelihood that a woman will have hot flashes or disturbed sleep, but the associations aren't highly predictive. There's no way to foresee what symptoms will arise as a woman goes through menopause.

In this article I'll look closely at three categories of symptoms most commonly reported during peri- and postmenopause: vasomotor symptoms (hot flashes and night sweats), sleep disturbances, and psychological symptoms (depression and anxiety). (Other frequently reported symptoms include headache and joint pain, but they aren't often as distressing.) Changes in sexuality and urogenital function are a source of concern for many women, and I'll cover those in the final installment of this series on menopausal women's health.

VASOMOTOR SYMPTOMS

Hot flashes and night sweats are greatly distressing to many peri- and postmenopausal women. Hot flashes involve a sudden sensation of heat that can be mild to intense and that may be accompanied by anxiety, palpitations, sweating, and facial flushing. Night sweats are hot flashes that occur at night and are accompanied by excessive sweating, sometimes enough to warrant a change in bed linens.

It's believed that hot flashes originate in the hypothalamus, where estrogen withdrawal causes a dysfunction in the central thermoregulatory center. The trigger is thought to be *changing* levels of estrogen in the circulation, not lowered levels. Neurotransmitters, primarily norepinephrine and serotonin, also play a role in hot flashes. Shanafelt and colleagues describe the pathway as starting with estrogen withdrawal, which leads to a decrease in the release of endorphin and catecholestrogen, causing an increased hypothalamic release of norepinephrine and serotonin, which lowers the thermoregulatory set point.[1] As a result, subtle changes in core body temperature will set off heat-loss mechanisms such as sweating and sending blood to the peripheral circulation, close to the surface, where it can get cooled.

Studies indicate that 55% to 79% of women experience vasomotor symptoms to some degree during and after the menopausal transition.[2,3] The average duration of these symptoms ranges from five to 10 years, regardless of treatment,[4] with the severity and frequency of symptoms peaking during late perimenopause and early postmenopause.[5,6] A meta-analysis found that for most women vasomotor

symptoms didn't return to baseline until eight years after menopause, and in 10% of women it took as long as 12 years.[7]

Who will have hot flashes? The answer to that question isn't known. But there's strong evidence that race and ethnicity are factors. African Americans report the highest incidence of hot flashes and Asians report the lowest.[8-10] The reason is unclear, but it may be related to cultural influences or genetic factors.[11]

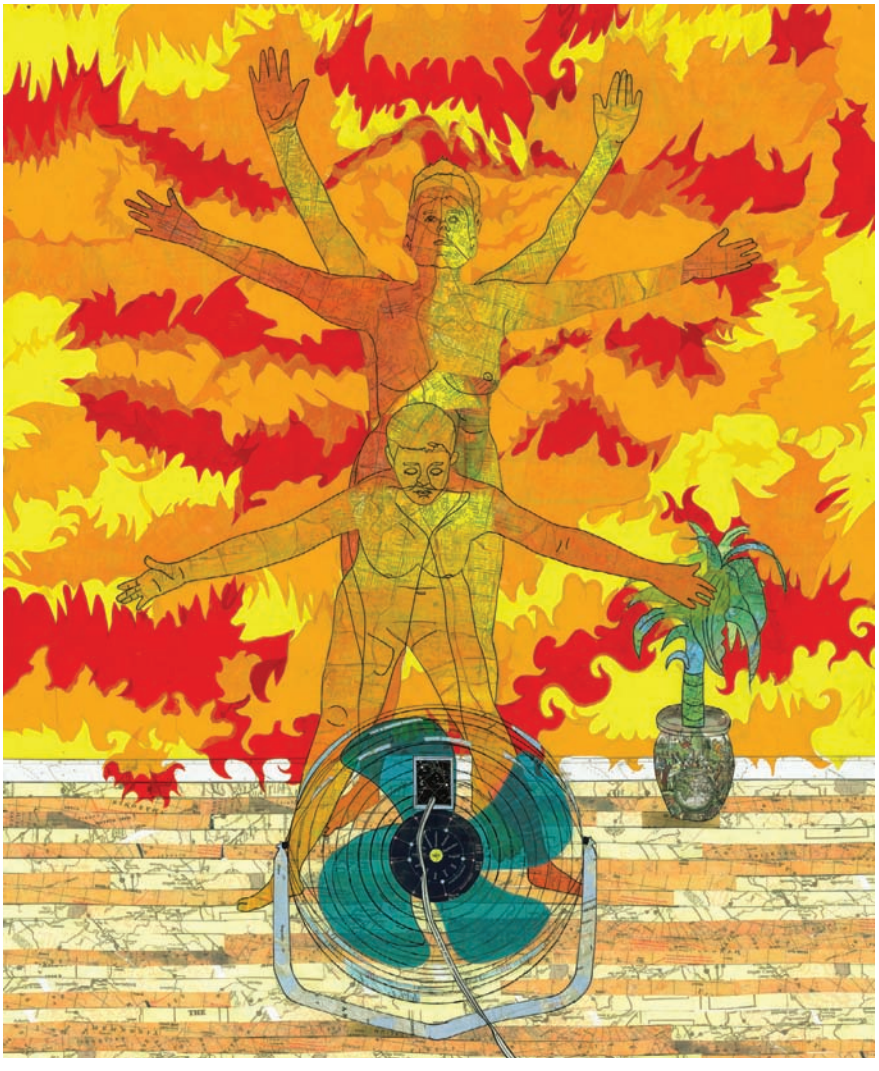
There appears to be an association between body mass index (BMI) and hot flashes—the underlying mechanism is believed to be the conversion of androgens to estrogen in body fat, resulting in endogenous estrogen at levels that vary according to a woman's body size—but study findings are conflicting. Some suggest that increased BMI lowers the risk of hot flashes while others indicate the opposite.[10] Recent studies that find increased hot flashes in women with higher BMIs, especially those with abdominal fat, challenge the prevailing belief that thin women have less endogenous estrogen and thus suffer more from hot flashes.[12, 13] The association could also be explained by an increased core body temperature in heavier women, whose body fat provides insulation.[14]

There's mixed evidence of the effects of physical activity on hot flash risk.[15] In a study of 1,427 women ages 45 to 64 years, sedentary subjects reported more vasomotor symptoms than physically active subjects did.[16] But a review of the literature on lifestyle factors and hot flashes found no relationship between physical activity and risk of hot flashes, although the authors note that small sample sizes and low incidence of hot flashes could have affected their findings.[17]

Genetics also likely plays a role. A study of a subsample of 174 women from the Seattle Midlife Women's Heath Study found that polymorphisms in the cytochrome P-450 (CYP) isoenzyme CYP19 11r allele were associated with more frequent and severe hot flashes.[18] A study of a multiracial and multiethnic group of women (N = 1,467) from the Study of Women's Health Across the Nation compared the prevalence of vasomotor symptoms to results of genotyping for single nucleotide polymorphisms in sex steroid–metabolizing genes and estrogen receptors.[19] The researchers found associations between certain polymorphisms and the prevalence of vasomotor symptoms that were specific to race and ethnicity and assert that more study is needed.

There's strong evidence that smoking increases the risk of hot flashes[10, 17] and some evidence that low socioeconomic level and stress are risk factors.[8, 14] Vasomotor symptoms are associated with increases in depression, anxiety, sleep disturbances, and somatic symptoms such as fatigue, pain, or dizziness.[20-22] Women with vasomotor symptoms are significantly more likely to suffer from depression, and that likelihood increases as symptoms increase in severity.[20, 23]

Managing vasomotor symptoms. Estrogen therapy is the most effective treatment for menopause-related hot flashes.[24] But its well-known risks related



to cardiovascular disease and breast cancer limit its use; many women prefer nonhormonal strategies. (See the first article in this series, "Menopausal Hormone Therapy: What We Know Now," June 2011). Other available treatments include nonhormonal pharmaceutical agents, complementary therapies, and exercise.

Nonhormonal pharmaceutical agents include selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and gabapentin (Neurontin). All three are effective in treating hot flashes, but efficacy varies among the SSRIs and SNRIs. In a pooled analysis of 12 studies the SSRI paroxetine (Paxil) and the SNRI venlafaxine (Effexor) decreased hot flash scores by 41% and 33%, respectively, compared with 18% for placebo, 13% for fluoxetine (Prozac), and 3% for sertraline (Zoloft).[25] The same analysis found that gabapentin decreased scores by 35% to 38%. The SSRI escitalopram (Lexapro) is also effective in decreasing the frequency and severity of hot flashes.[26]

The SSRIs and SNRIs are generally well tolerated, with discontinuation rates ranging from 5% to 21% in primary care.[27, 28] The most common adverse effects are sexual dysfunction, nausea, and weight gain; others include sleep disturbances, dry mouth, temporary nausea, fatigue, and constipation. Gabapentin is also well tolerated; in clinical trials, drop-out rates of 10% to 13% due to adverse effects, usually dizziness, have been reported.[29, 30] Adverse effects tend to be greater early in treatment and diminish after two to three weeks with both gabapentin and the SSRIs and SNRIs.

Complementary and alternative medicine (CAM). Many women turn to CAM for relief from hot flashes, despite scant evidence to support many of the most common strategies. Phytoestrogens, or plant-based estrogens, are among the most popular products, particularly isoflavones, one type of phytoestrogen often derived from soy. It's believed that the high soy content of many Asian diets accounts for the lower rates of hot flashes among Asian women. But little scientific evidence supports the use of phytoestrogens to reduce hot flashes. A 2007 Cochrane review found no evidence that phytoestrogens relieve hot flashes,[31] while a more recent meta-analysis found inconclusive evidence, with a significant positive trend.[32] Red clover, another source of isoflavones, hasn't been found effective against hot flashes.[33, 34]

Black cohosh, a plant in the buttercup family, is also popular, but evidence of its effectiveness is mixed. A 2008 systematic review found the evidence for efficacy to be inconclusive,[35] while a 2010 meta-analysis found some effectiveness (although the researchers noted a high degree of heterogeneity in the included studies).[36] Additionally, a National Institutes of Health randomized clinical trial found that black cohosh was less effective than placebo at reducing hot flashes (34% versus 63%, respectively).[33]

Acupuncture, a form of traditional Chinese medicine, has produced mixed findings but with a positive trend for effectiveness. A systematic review conducted in 2008 found no significant difference between true acupuncture and sham acupuncture—the placement of needles in placebo sites.[37] There's some debate, however, over whether sham acupuncture itself constitutes a treatment; needling regardless of site has produced known physiologic effects.[38] A recent study found that both sham and true acupuncture improved hot flashes and that women couldn't distinguish between the two.[39] Recent studies have also shown positive results when sham acupuncture isn't used as the control. The 2009 large multicenter Acupuncture on Hot Flushes Among Menopausal Women trial found that women who received 10 acupuncture sessions and advice on self-care had significantly fewer and less intense hot flashes after 12 weeks than women who received only self-care advice.[40] The benefits were only short-term, though; no differences were found at six and 12 months. A 2010 multicenter study also found significantly greater improvement with the use of acupuncture.[41]

Exercise is often recommended as a way to minimize hot flashes, but the evidence supporting it is weak. A 2009 Cochrane review concluded that evidence was insufficient to determine its effectiveness, although the researchers noted "a weak trend for exercise to be more effective than no intervention."[42] The researchers updated their review in 2011 and concluded that, although evidence continued to be weak, results of some newer trials showed the benefits of exercise among menopausal women, both those who did and did not suffer from hot flashes.[43]

INSOMNIA

Sleep disturbances are common during and after the menopausal transition. Overall, 40% to 48% of peri- and postmenopausal women report having difficulty sleeping.[44] A study by Tom and colleagues found that women in the menopausal transition were two-to-three-and-a-half times more likely than premenopausal women to report severe sleep difficulty.[45] There's a significant drop in sleep time in women after the age of 50,[46] and sleep quality and efficiency decrease as well.[47, 48]

Insomnia, defined as difficulty falling asleep or staying asleep that results in daytime impairment or distress,[49] significantly affects women's lives. It can cause daytime sleepiness, decreased concentration, mood disorders, decreased productivity, decreased quality of life, and job-related and motor vehicle accidents.[50, 51] A study of 5,781 postmenopausal women found that women experiencing night awakenings (n = 141) at least twice weekly had greater activity

impairment (including presenteeism) and poorer health-related quality of life than women who didn't have insomnia and the general population.[50]

Causes of insomnia. Women reporting sleep disturbances should be assessed for the presence of a primary sleep disorder, particularly sleep-disordered breathing (SDB) and periodic limb movement.[52] The prevalence of both of these disorders has been shown to increase during and after menopause. Assessment for SDB is especially important: studies show its serious health implications, including the risk of hypertension, cardiovascular disease, stroke, and death from any cause.[53, 54]

A 2001 sleep study by Bixler and colleagues included a one-night sleep laboratory evaluation of 1,000 men and women.[55] The prevalence of sleep apnea was 2.7% in postmenopausal women not taking hormone therapy and 0.5% in premenopausal women. A later examination of menopausal status and SDB in 589 women enrolled in the Wisconsin Sleep Cohort Study found that menopause was significantly associated with an increased risk of SDB (defined as repeated episodes of apnea–hypopnea during sleep) even after adjusting for age, smoking, and weight.[56] Postmenopausal women were two-and-a-half times more likely than premenopausal women to have five or more apnea–hypopnea episodes a night and three-and-a-half times more likely to have 15 or more episodes. A recent study of 93 women found that postmenopausal women were one-and-a-half times more likely than premenopausal women to have more than five apnea–hypopnea episodes an hour during sleep.[47]

Periodic limb movement, a parasomnia characterized by bilateral repetitive movements of the extremities (usually the legs but sometimes also the arms), disrupts sleep, and there's some evidence that it's more prevalent in postmenopausal women.[47, 57] This may be owing to estrogen's effect on dopamine.

Vasomotor symptoms can also disturb sleep in peri- and postmenopausal women. Studies consistently find significant associations between sleep difficulty, particularly nighttime and early morning awakening, and hot flashes or night sweats.[44, 58, 59]

Sedentarism has been found to be associated with sleep difficulties in menopausal women. In their study of 149 Ecuadorean women, Chedraui and colleagues found that sedentary women had more than three times the risk of daytime sleepiness than more active women did.[59] And in a study of 340 women, Arakane and colleagues found that sedentarism (15 minutes or less of twice-weekly activity) correlated positively with elevated scores on the Insomnia Severity Index.[58]

Managing insomnia involves drug, nondrug, and CAM therapies. If it's determined that SDB or periodic limb movement is present, a woman should speak with her provider about treatment.

Cognitive behavioral therapy (CBT) is the primary nonpharmacologic treatment and should be considered the first-line treatment for sleep problems during menopause. CBT aims at developing thoughts and behaviors that promote sleep and eliminating those that contribute to insomnia (see Table 1). There's strong support for CBT's effectiveness in treating insomnia when it's conducted by a behavioral specialist, such as a licensed therapist or psychologist.[60-62] Although I found no studies that looked at the effectiveness of CBT in improving sleep in otherwise healthy menopausal women, a meta-analysis that looked at its use in men and women ages 55 and older found moderate-to-large positive effects.[61] Sleep-hygiene behaviors, such as maintaining a quiet sleeping environment and avoiding caffeine, are sometimes considered CBT, but on their own they haven't been correlated with sleep improvement in people with sleep disturbances.[63]

Women who don't have access to CBT may find self-help methods useful. A meta-analysis found small-to-moderate improvements in sleep outcomes after use of self-help cognitive–behavioral methods such as audiotapes, online programs, and sleep diaries.[64] But the authors write of the strong possibility of publication bias in the studies reviewed, which may have led to an overestimation of the effect of these interventions.

Pharmacologic agents should be used only when nonpharmacologic strategies don't work. Those used most often are benzodiazepines, nonbenzodiazepines, antidepressants, and melatonin receptor agonists. A meta-analysis of 105 studies found that benzodiazepines and nonbenzodiazepines were effective treatments for insomnia, producing shorter delays in sleep-onset times (known as sleep-onset

Table 1. Cognitive Behavioral Therapy Strategies for Insomnia

Stimulus control
• Go to bed only when sleepy. • Get out of bed if unable to fall asleep. • Wake at the same time every day. • Resist naps.
Sleep restriction
• Limit the time in bed to the actual sleep time and gradually increase the time as sleep time increases.
Sleep hygiene
• Avoid caffeine and alcohol. • Reduce cognitive activity before bedtime. • Sleep in a cool, dark room.
Relaxation techniques
• Learn to meditate. • Use imagery techniques. • Reduce anxiety by using progressive muscle relaxation and biofeedback.

latency) and improvements in sleep as recorded in sleep diaries.[65] It also found that some of the older antidepressants, particularly doxepin (Sinequan) and trazodone (Desyrel and others), may help as well. But all of these drug classes were associated with significant risk of adverse effects: headache, dizziness, nausea, fatigue, and somnolence, among others.

In a relatively recent class of sleep medications, the melatonin receptor agonists, there's only one drug available, ramelteon (Rozerem). It has been shown to decrease sleep-onset latency and increase total sleep time.[49] But the improvement is small; sleep onset was less than 10 minutes sooner with ramelteon than with placebo and total sleep time was only 11 to 14 minutes longer, depending on the dose. It's usually well tolerated; the most common adverse effects, headache and somnolence, are similar to those associated with other sleep medications. Rare neuropsychiatric reactions have been reported with use of zolpidem (Ambien), more often in women than in men. These include driving, walking, and eating while asleep, usually without any memory of the event.

CAM. There's little scientific evidence to support the use of most CAM approaches in managing insomnia. Results of a recent meta-analysis were weakly positive for yoga, t'ai chi, and acupressure and mixed for acupuncture.[66] The results did not support the use of herbal medicines, while studies examining homeopathy, massage, and aromatherapy did not meet the inclusion criteria. An earlier systematic review also found no evidence that the use of homeopathy medicines or treatment by a homeopath were effective in treating insomnia.[67]

The evidence for the effectiveness of isoflavones is weak as well. Hachul and colleagues found a positive effect for isoflavones in their study; the percentage of women who reported moderate-to-severe insomnia decreased from 94% to 63% in women in the placebo group and from 90% to 37% in the group using isoflavones.[68] The sample of 38 women was too small, however, to place confidence in the results.

Melatonin may be an effective option for women who have difficulty falling asleep. A recent meta-analysis found that melatonin decreased sleep-onset latency by more than 23 minutes in both children and adults, although it didn't change the total sleep time or the awakening time.[69] The authors write that melatonin should be taken so that it works with the biologic clock, optimally three to six hours before the onset of endogenous melatonin, which usually occurs as natural light dims. Small doses help to prevent morning sleepiness.

PSYCHOLOGICAL SYMPTOMS

Most women will go through the menopausal years without significant mood changes. But a number of large studies have found that the menopausal transition is associated with increased rates of depression and anxiety.[70-74] The increased risk is highest in women with a history of mood disorders, but menopause raises the risk of depression and anxiety even in women without such a history. Symptoms tend to be worse in the perimenopausal period, when hormones are in the most flux and hot flashes are at their peak.[73] Studies have consistently found a strong association between vasomotor symptoms and both depression and anxiety.[20, 21] According to a retrospective chart review of 487 women, anxiety was more likely during perimenopause than postmenopause, and women with the most bothersome vasomotor symptoms were most likely to report anxiety.[23]

Women's vulnerability to depression and anxiety during menopause is thought to arise from the effect of erratic levels of estrogens on neurotransmitters, particularly serotonin and norepinephrine, and their brain receptors.[75] During perimenopause the cyclical response patterns developed during the reproductive

MENOPAUSE SYMPTOM RESOURCES

General Information and Vasomotor Symptoms

American Association of Clinical Endocrinologists
www.aace.com

Centers for Disease Control and Prevention
www.cdc.gov/reproductivehealth/WomensRH/Menopause.htm

North American Menopause Society
www.menopause.org

womenshealth.gov
www.womenshealth.gov

Insomnia

American Academy of Sleep Medicine
www.aasmnet.org

MedlinePlus: Sleep Disorders
www.nlm.nih.gov/medlineplus/sleepdisorders.html

Restless Legs Syndrome Foundation
www.rls.org

American Sleep Apnea Association
www.sleepapnea.org

National Center for Complementary and Alternative Medicine at the National Institutes of Health
http://nccam.nih.gov

Psychological Symptoms

American Psychological Association
www.apa.org

MedlinePlus: Mental Health
www.nlm.nih.gov/medlineplus/mentalhealth.html

Substance Abuse and Mental Health Services Administration
www.samhsa.gov

years no longer maintain hormonal homeostasis. As women reach postmenopause, the hormones stabilize at lower levels.

Menopause also represents a time of psychosocial upheaval in a woman's life. Children leave home, parents die or require care, intimate relationships shift, and job duties change. And signs of aging appear, bringing with them a sense of mortality as a woman enters her sixth decade. It's unclear whether and how much such factors contribute to mood changes.

Some women also report changes in cognitive functioning, particularly affecting memory, during menopause. Two large longitudinal studies found a small, transient cognitive decrement during perimenopause that's unrelated to sleep deprivation or depression, and that in postmenopause cognitive function returns to premenopausal levels.[11, 76]

A body of evidence suggests that there's a domino effect: changing estrogen levels trigger hot flashes, which then disrupt sleep, which leads to mood disturbances. The domino hypothesis was first posited by Campbell and Whitehead in their 1977 study of estrogen and menopausal symptoms, where they found that relief of symptoms led to improved psychological well-being.[77] This hypothesis has been supported by other studies that found strong associations between vasomotor symptoms, insomnia, and mood disorders.[78, 79] Results of other studies haven't been as clear-cut.[80, 81] For example, Joffe and colleagues found that sleep quality was worse in depressed women, not because of being awakened by vasomotor symptoms, but rather because of going to bed later, spending less time sleeping, and having problems falling asleep.[81] Burleson and colleagues did find some support for the domino hypothesis but concluded that it doesn't fully account for disordered mood in menopause.[80] Although both vasomotor symptoms and sleep problems caused same-day or next-day worsened mood, "Trouble sleeping is not the only, or perhaps even the most important, link between vasomotor symptoms and mood," the researchers write.

Managing depression and anxiety during menopause. The first step is to rule out an organic cause, particularly thyroid disease, which is common in older women,[82, 83] as well as factors unrelated to menopause, such as preexisting mental illness, significant loss, or family history of mood disorders.[74]

Interventions include exercise, CBT, and medication. A comparative study found an 18% to 22% improvement in depressed mood in postmenopausal women who engaged in a supervised program of moderate exercise for six months; those in the control group had no improvement.[84] There's also evidence that low-intensity aerobic activities such as yoga have a positive effect on mood in menopausal women.[42] CBT is considered first-line treatment for anxiety disorders. Group CBT has been found to be effective in menopausal women.[85]

Medication is the primary treatment for severe depression or anxiety or for moderate depression or anxiety that doesn't respond to nonpharmacologic strategies; the SSRIs and SNRIs are the agents of choice. The use of estrogen or estrogen combined with progestin hasn't been found to have any effect on major depression in menopausal women.[86, 87] There's no difference in the severity of depression in women taking estrogen and in those not taking it, nor does estrogen improve mood when given to postmenopausal women with mild-to-moderate depression. But it's been beneficial when given in combination with an SSRI, probably because of effects on vasomotor symptoms.[88]

Some CAM therapies may be helpful. A 2007 systematic review found that St. John's wort and black cohosh appeared to be effective in relieving depression and anxiety, and kava was effective in relieving anxiety, although there's a risk of liver damage with kava use.[33] Ginseng was shown to have a positive effect as well, but the authors note that results were based on only two observational studies. A 2010 study found that red clover also alleviated depression and anxiety in postmenopausal women.[89]

NURSING IMPLICATIONS

It's important that women be educated on what to expect as they approach the menopausal transition. Symptoms associated with menopause can cause women a great deal of distress over an extended period. Although some women will not respond to the treatments available, many will find significant relief. It's also important to help women distinguish the normal changes of aging from those that represent pathology. For example, subtle cognitive changes during perimenopause are to be expected, but great reductions in cognitive performance should be evaluated.

Nurses should also ask women about symptoms of anxiety and depression. The stigma of mental illness may prevent some women from volunteering information about new or worsened mood problems. Reassuring women that such symptoms often abate after menopause may help them cope; teaching them that the changes aren't likely indicative of a lifelong condition may help them accept antidepressant treatment.

Helping women to understand the myriad approaches to management of hot flashes and insomnia is important. The evidence of a possible connection between these symptoms and mood disturbances reinforces the importance of nurses reviewing good sleep-hygiene habits: having a consistent bedtime and bedtime routine, sleeping in total darkness, avoiding alcohol and caffeine for four to six hours before bedtime, and keeping the bedroom cool.

Unless physical activity is contraindicated, all women should be encouraged to engage in exercise; it has many benefits for menopause symptoms and

for overall health. The safety and efficacy of pharmacologic therapies should be reviewed. CAM therapies are very popular, but the research on these therapies for menopausal symptoms is weak and most studies have only short-term follow-up times.[90] There's a vast amount of information on CAM products on the Internet, and nurses should teach women how to distinguish the reliable from the questionable. Remind women to let their providers know about any CAM products they're using. Explain that botanical products and other supplements aren't always benign. Some, such as kava, have the potential to cause serious adverse effects or may interact with other medications they're taking. Providing women with up-to-date information allows them to make informed choices.

Finally, it's important that nurses help women find a balance between understanding menopause as a natural process and as one requiring treatment of distressing symptoms. ▼

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Karen Roush is the clinical managing editor of AJN*; a doctoral candidate at the New York University College of Nursing, New York City; and the author of* What Nurses Know . . . Menopause *(Demos Health; New York, 2011). She was not involved in the peer review of this article. Contact author: karen.roush@wolterskluwer.com.* *The author has disclosed no potential conflicts of interest, financial or otherwise.*

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