Medical News & Perspectives

Can Nonhormonal Treatments Dial Down the Heat During Menopause?

Julie A. Jacob, MA

Obstetrician-gynecologist Ruth Haskins, MD, estimates that fewer than 10% of the patients she treats in her Folsom, California, practice take systemic hormones to manage menopausal symptoms. Patients frequently ask about options to ease hot flashes and night sweats, but they don't want to take hormones, said Haskins, also president-elect of the California Medical Association.

"Since the WHI [Women's Health Initiative] study came out, women are so scared [to take hormones]," said Haskins, referring to the landmark 2002 clinical trial that determined hormone replacement therapy (HRT) increases the risk of breast cancer and coronary heart disease, among other conditions (*JAMA*. 2002;288[3]:321-333). After the findings splashed across newspaper headlines and dominated television news programs, women abandoned hormones in droves. By one account, HRT use for menopausal symptoms plummeted by 79% from 2002 to 2010 (Sprague BL et al. *Obstet Gynecol*. 2012;120[3]:595-603). As a result, surveys have reported that about 50% to 80% of menopausal women now turn to nonhormonal therapies (http://bit.ly/1PSpzxt). Largely in response to this shift, the North American Menopause Society (NAMS) recently published a position paper on the effectiveness of various nonhormonal options for managing menopausal vasomotor symptoms (http://bit.ly/1PSpzxt).

"The great news is that women [now] have more choices for management of menopausal symptoms [with a] critical mass of what works and doesn't work," said JoAnn E. Manson, MD, professor of medicine at Harvard Medical School, past president of NAMS, and a principal investigator in the WHI study.

According to the findings, some approaches commonly assumed to be helpful, such as avoiding hot beverages, exercising, or taking herbal supplements, don't have clinical evidence to support their effectiveness, while others that women may not have considered, such as cognitive behavioral therapy (CBT) and hypnosis, have been shown to be beneficial.

First Update in More Than a Decade

The NAMS last examined the efficacy of hormonal and nonhormonal interventions in a 2004 position paper, and it was time to review the evidence, said Janet Carpenter, PhD, RN, chair of the position statement advisory panel and associate dean of research at the Indiana University School of Nursing.

"Ten years is a long time in the health care field. [There has been] exponential growth in research in menopausal therapy, especially after the [2002] WHI findings," Carpenter said, noting that a 2008 National Institutes of Health initiative provided approximately $22 million over 5 years for research studying nonhormonal therapies to alleviate menopausal symptoms (http://1.usa.gov/1LWmgjF).

Most studies that the NAMS advisory panel reviewed to develop its new recommendations were published between 2005 and 2015. The panel determined that clinical studies support using CBT, hypnosis, and the selective serotonin reuptake inhibitor (SSRI) paroxetine salt to reduce the discomfort or frequency of hot flashes and night sweats.

The biggest shift from the 2004 to 2015 recommendations, Carpenter said, is that paced respiration therapy is no longer recommended as a first-line therapy for vasomotor symptoms. In the last 2 years, large studies have shown that it is not effective. Lifestyle cooling techniques, such as dressing in layers or avoiding hot food, which were cited in the 2004 paper as being effective based on anecdotal feedback from women,

are not recommended in the updated paper because of a lack of clinical evidence.

In support of CBT, the position paper cited 2 randomized, double-blind, controlled studies that showed 65% to 78% of women who participated in CBT programs reported a significant improvement in discomfort from vasomotor symptoms.

Cognitive behavioral therapy doesn't reduce the frequency of hot flashes, but rather helps women by "reframing how to cope with it," Carpenter said. Cognitive behavioral therapy also incorporates relaxation techniques. Yet CBT, while helpful, is not an option for every woman struggling with hot flashes, noted Wendy Molaska, MD, a family medicine physician with UW Health in Sun Prairie, Wisconsin. "It is a lot more time-consuming and can be more difficult for patients to see a therapist who is versed in [CBT]," said Molaska, who has recommended CBT to patients for other issues.

Two randomized clinical trials also supported the efficacy of hypnotherapy and self-hypnosis. Women who tried hypnosis, compared with women in the attention control group, reported fewer hot flashes (74% vs 17% reduction in frequency, respectively) and reduced scores of hot flash severity (80% vs 15% reduction, respectively) (Elkins GR et al. *Menopause*. 2013;20[3]:291-298). Like CBT, it's not a panacea for all women with vasomotor symptoms because hypnosis also requires time and practice, said Haskins.

What Works and Why

In addition to nondrug therapies, the NAMS advisory panel determined that several nonhormonal prescription drugs showed benefit, including paroxetine salt, which the US Food and Drug Administration approved as a treatment for hot flashes in 2013. Paroxetine salt has been shown to improve hot flashes and night sweats as well as sleep for up to 2 years, the position paper noted.

The NAMS also found that other SSRIs; selective norepinephrine reuptake inhibitors; the antiepileptic drug gabapentin; and the adrenergic agonist clonidine, commonly used to treat migraines, are effective in reducing vasomotor symptoms (http://1.usa.gov/1MiyFhc).

Antidepressants can help improve a woman's mood as well, said Molaska, noting that many of her menopausal patients also report feeling irritable.

Knowing which treatments are effective is important because hot flashes can't be dismissed as merely the punchline of a joke. "They affect a woman's work life and the overall quality of her life at a time when she is at the peak of her earnings," said Pauline Maki, PhD, professor of psychiatry and psychology at the University of Illinois at Chicago and a member of the NAMS advisory panel.

Weight loss, stellate ganglion block, mindfulness-based stress reduction, and S-equol soy derivatives were cited as potentially helpful interventions, but more research is needed to support their clinical use.

Stellate ganglion block, in which a local anesthetic is injected into the sympathetic nerves in the neck, is particularly intriguing, Maki noted, because it is a 1-time procedure, unlike daily medication. The NAMS statement noted that a randomized controlled trial found that the procedure reduced the frequency of vasomotor symptoms by 21% for at least 3 months. Although the precise mechanism by which this works in unclear, one study hypothesized that it might sever the connection between the central nervous system and sympathetic nervous system, thus resetting the body's ability to regulate temperature (Lipov ET et al. *Lancet Oncol*. 2008;9[9]:819-820).

The position paper does not currently recommend dietary supplements and herbal therapies, such as black cohosh, dong quai, flaxseed, and pine bark.

"There are a number of herbal supplements that are available, recommended, and touted, [but there is] a huge gap in research on their effectiveness," Carpenter said.

If a patient still wants to take an herbal supplement, despite the lack of clinical data supporting its effectiveness, she should proceed cautiously, Manson stressed.

"Some of those over-the-counter herbal remedies have been linked to adverse effects like liver damage and can interact with other medications," Manson said.

Other popular strategies for reducing hot flashes and night sweats, including exercise, yoga, and paced respiration, are also not recommended based on the NAMS evidence review.

That doesn't mean that women in their menopausal years should give up on their downward dogs, though.

"There are more than enough reasons for women to exercise and be physically active… so they certainly should go ahead and exercise and have a heart-healthy lifestyle," Manson said.

Common-sense approaches like cooling techniques and avoiding triggers such as alcohol and spicy foods are not currently recommended because of a lack of evidence, but the position paper notes that those approaches should be studied.

Root Cause Elusive

Even as numerous studies have been published on the efficacy of therapies to treat hot flashes and night sweats, the root cause of the intense warmth, flushing, perspiration, and chills that can occur anywhere from a few times a week to several times a day remains somewhat of a mystery. On average, a woman can expect to experience vasomotor symptoms for about 7 years (Avis NE et al. *JAMA Intern Med*. 2015;175[4]:531-539).

"The cause of vasomotor symptoms is the million dollar question," said Carpenter. "We don't fully understand what is causing them.… [There has been] work on the KNDy [kisspeptin, neurokinin B, and dynorphin] neurons in the brain, work on serotonin and estrogen, but how all these pieces fit together we are not exactly sure."

Vasomotor symptoms may be caused in part by a drop in estrogen and an increase in follicle-stimulating hormone. Changes in the way that a woman's body regulates her core temperature as well as genetic variations related to the metabolism of sex steroids have also been associated with vasomotor symptoms (*Obstet Gynecol*. 2014;123[1]:202-216). Hot flashes are more common in African American women than in women of other ethnicities and less common in Asian women, according to the American Congress of Obstetricians and Gynecologists (ACOG), possibly because of differences in cultural perceptions of hot flashes, physiological differences, or the amount of soy consumed. Women who are obese also experience more hot flashes, which ACOG states may be due to excess adipose tissue acting as insulation.

HRT Still Standard in Effectiveness

Despite the 2002 WHI study findings and their role in driving women away from hormones, HRT is still considered the most effective therapy for reducing vasomotor symptoms of menopause.

"There's been a great deal of confusion and fear surrounding hormonal therapy since

the results of the WHI, and it is important for women to understand, for those who are in early menopause and in generally good health and have moderate to severe night sweats, the benefits of hormone therapy are likely to outweigh the risks," Manson said.

In 2013, the WHI researchers published an update that called hormonal therapy for fewer than 5 years "a reasonable option" for easing vasomotor symptoms (Rossouw JE et al. *Obstet Gynecol*. 2013;121[1]:172-176). They noted that closer analysis of the original WHI data determined that "the absolute excess risks (and benefits) associated with hormone therapy were low and were even lower in women close to the menopause because of their low baseline risk."

Another 2013 study reaffirmed that the WHI data did not support the use of hormonal therapy for chronic disease prevention but could be appropriate for short-term management of menopausal symptoms (Manson JE et al. *JAMA*. 2013;310[13]:1353-1368). The analysis showed that for every 10 000 women taking estrogen and progesterone, there were 6 more coronary events, 9 additional pulmonary embolisms, 9 more strokes, and 9 additional incidents of breast cancer.

Word is filtering out to patients that hormonal therapy is a short-term option for managing menopausal symptoms, said Maki.

Yet many women still can't use hormonal therapy because they have risk factors for coronary heart disease or have had breast cancer, or they simply prefer not to take hormones. For these women, the new NAMS guidelines will help avoid wasting time and money on ineffective nonhormonal therapies.

"The buzz word is deimplementation," said Carpenter. "You can stop telling women to try [therapies not supported by clinical data] and have them come back frustrated when it doesn't work."

Manson suggested that women and their clinicians may want to try MenoPro, the NAMS free mobile app that can guide them in choosing among hormonal and nonhormonal options.

"The bottom line is that it is important to be knowledgeable about treatment options so you can make the most informed decision," Manson said. ■

The JAMA Forum

Campaign Wars: Health Policy in a Fantasy World

David M. Cutler, PhD

Watching national health reform debates reminds me of a night at the movies. On the one hand, there are true-life stories like "Apollo 13," that profile actual people and the problems they face. And then there are the fantasies, like "Star Wars," in which magical things happen and the rules of normal life don't apply. As I view the world of "Campaign Wars," I have developed the uneasy impression that Republican health care proposals exist only in a fantasy universe.

Insurance coverage is a central part of accessing the medical care system. On this criterion, the Affordable Care Act (ACA) is a huge success: More than 16 million people have gained coverage because of the ACA (http://1.usa.gov/1N7XGvZ). Past evidence suggests there will be positive changes in health as a result (http://bit.ly/1IlKTmNc).

In the world of the Republican candidates, in contrast, the ACA is an affront to "liberty." All of them have proposed repealing it. What would happen to health insurance for the 16 million who will lose coverage, and the millions more who still do not have it?

One of the frontrunners for the Republican nomination, businessman Donald Trump, has promised a health plan that will cover everyone (and added that "the government's gonna pay for it.") (http://cbsn.ws/1KZmhX9). However, he has released no details about how he would do it, how much it would cost, or how the government would get the money—other than implying that hospitals would be paid less. The other leading candidate, retired neurosurgeon Ben Carson, has suggested that everyone ought to be given $2000 per year for a medical savings account (http://bit.ly/1Iby7Oz). Given that per capita medical spending is nearly $10 000 per year and federal health spending per capita is at least $4000 per year, it is unclear whether a $2000 credit would buy any reasonable coverage. In any case, Carson has backed away from the idea that his plan would be universal (http://nyti.ms/1SlhReh).

Perhaps Carson and Trump are fumbling with the issue because they are new to politics. But even the Republican establishment feels no need to grapple with it. Sen Marco Rubio (R, Fla) and former Florida Gov Jeb Bush, from the establishment wing of the party, have each proposed a tax credit for health insurance, but both have declined to say how generous the credit would be or how many people it would cover (http://politi.co/1QoLWsy). In addition, both have also proposed reducing the generosity of private insurance, Medicare, and Medicaid, actions that would likely increase the number of uninsured.

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Least specific of all is Tea Party favorite Sen Ted Cruz (R, Texas), who has said nothing about coverage other than saying that Obamacare needs to be entirely repealed (http://1.usa.gov/1IhKiEq). I suspect the truest expression of Republican views about health care comes from former candidate