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This clinical e-newsletter from The North American Menopause Society (NAMS) presents questions and cases commonly seen in a menopause specialist's practice. Recognized experts in the field provide their opinions and practical advice. Mindy S. Christianson, MD, the Editor of *Menopause e-Consult*, encourages your suggestions for future topics. The opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or by Dr. Christianson.

Question

A 48-year-old woman came to me to discuss slightly irregular periods and weight gain. She states that she used to have periods every 26 to 28 days, but now they are occurring every 21 to 35 days. She does not have menorrhagia. She has had a tubal ligation. She states that over the last year, she has gained 20 lb and is thinking about going to a weight-loss program near her that "balances" her hormones in order to help lose weight. She states that the program uses a natural progesterone formula cream that is "safer and more effective" than traditional hormones and that hormone balancing is key to weight loss. She wants to know whether her hormone imbalance is the cause of her weight gain and whether this program will help. Are there any data on the use of hormones for weight loss?

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Commentary by

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The average age of natural menopause is approximately 52 years but can vary widely from 40 to 58 years. Although the hallmark symptoms of the menopause transition include vasomotor symptoms, mood swings, and sleep disturbances, weight gain is often one of the most common concerns in midlife women. Despite reports that women gain an average of 5 lb to 7 lb (2-3 kg) over the menopause transition,[1,2] it is not uncommon for midlife women to report weight gain in excess of 20 lb—much of which is in the form of increased abdominal adiposity.

To achieve sustained weight loss, a daily caloric deficit of 400 kcal to 600 kcal per day, regular physical activity, low fat intake, consumption of fruits and vegetables, and ongoing behavior support should be undertaken. Unfortunately, individualized weight loss prescriptions are lacking.

Furthermore, these recommendations do not account for differences in age, race, current weight, or stage of menopause (peri-menopause vs postmenopause). Despite the fact that various pharmacotherapies are recommended as adjuncts to caloric restriction and increased physical activity in women with a body mass index greater than 30 kg/m^2 (or >27 kg/m^2 with comorbidities), some women may not be ideal candidates for these therapies or prefer not to take

medications altogether. Many women do not consult a healthcare provider about their menopause-related concerns; therefore, this issue may go unaddressed.

Instead, women turn to the Internet, where there is an exorbitant amount of misinformation pertaining to both optimal weight loss strategies and the risks of hormone therapy (HT). Attention grabbing headlines such as "top-10 fat burners for women over 40," "how to activate your fat-burning hormones," or "control your weight gain naturally" are everywhere. In addition, it is difficult to truly know how all of these factors interact, likely making weight loss in midlife women even harder. Taken together, it is very easy to see why midlife women struggle to find effective, evidence-based strategies to lose weight.

Poor sleep is also a very common concern in midlife women, and its presence can further hinder a woman's ability to successfully lose weight. Indeed, sleep disruption is one of the primary reasons why midlife women seek medical care, with up to 60% of women reporting significant sleep troubles (ie, difficulty falling asleep, early morning waking, and interrupted sleep).[3]

Although vasomotor and psychological symptoms are strongly associated with sleep disruption, poor sleep quality can occur independently of vasomotor symptoms. And because poor sleep is linked to increased food intake, reduced physical activity, and reduced quality of life, sleep habits and the presence of sleep problems should be routinely assessed during clinic visits. Intervening with HT may help improve sleep quality and, therefore, increase the likelihood that a symptomatic woman maintains her regimented weight loss program.

Regarding the 48-year-old woman who is the subject of this case study, she is in the early stage of perimenopause, given the presence of slightly irregular periods and her reported weight gain of 20 lb. Although her irregular periods are a sign that her hormones are shifting, her weight gain (and increased fat gain) is likely not because of her reproductive hormone changes.

Important data from the Study of Women's Health Across the Nation (SWAN) demonstrate that body weight status was both an important predictor of sex steroid levels as well as the degree to which these sex steroids change across the menopause transition.[3,4] Specifically, women with obesity—especially black women—often maintain estradiol concentrations and have smaller increases in follicle-stimulating hormone with progress through the menopause.[3] These observations were confirmed in a smaller longitudinal cohort of women followed across the menopause transition.[2] Indeed, current weight status is more likely to dictate reproductive hormone changes across perimenopause and not the other way around.

So, would using a natural progesterone cream help a 48-year-old woman in early peri-menopause "balance her hormones" so that she would lose more weight? The short answer is no. The abovementioned data from SWAN simply do not support the use of HT (traditional or natural) to assist weight loss. There is also no quick fix that can promise weight loss, despite what the headlines say. The reality that some of this weight gain is inevitable is hard for many women to accept, in part because women are often told that their weight gain is under their control. All midlife women experiencing menopause-related symptoms or weight gain should consult with a menopause practitioner or a clinician they

trust to discuss use of HT (traditional or natural), weight loss medications, or before undertaking a weight loss program.

Behavioral-modification programs that incorporate both calorie restriction and exercise for at least 3 months do appear to have the greatest efficacy for weight loss (and fat mass) compared with calorie restriction or exercise alone.[5]

To ensure that calorie restriction is followed, successful programs often incorporate weekly or biweekly consultations with a trained dietician (either one-on-one or via telephone) to maximize adherence.

Furthermore, exercise training should be performed on an individualized, prescription basis and have the option of being offered in a group setting. And finally, regardless of the type of behavior-modification program used, it is of the utmost importance to ensure that the program is feasible for the individual woman—or the program will not be followed.

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Case

A patient came to my office complaining of low sexual desire. At 48 years old, she is still having regular menses, although her cycles now are every 26 to 27 days and lighter than they used to be. She denies current vasomotor symptoms, she has no current medical issues, and she is on no medications. She has noticed a decrease in her desire to have or initiate sex. She's not connecting this to any particular time point, but she thinks it's been going on for a while and has gotten a bit worse. She is able to be aroused, and she's able to orgasm, so she doesn't think it's a physical problem. She recently had her yearly examination, and she had no abnormalities, and she's had a negative current Pap test. She's married and has a good relationship with her husband, and he has no sexual performance issues. Their normal frequency of intercourse was several times a week, but now they haven't had sex in a couple of months. She's read that there may be a medication called Vyleesi for this and wants to know what it is and whether it can help.

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Commentary by

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This patient's history suggests that she may have hypoactive sexual desire disorder (HSDD). Controversially, this diagnosis was combined with sexual arousal disorder in the

most recent *Diagnostic and Statistical Manual of Mental Disorders* to form the single diagnosis female sexual interest/arousal disorder.[1] However, the basic diagnostic criteria are essentially unchanged—the presence for at least 6 months of decreased or absent sexual fantasies or interest in sexual activity that generates marked distress not related to a medical or psychiatric condition, medication, or relationship problem.[1-3]

Low desire is the most common sexual concern for women. Large population-based studies have found that approximately 38% of women endorse low desire, with 8% to 10% meeting the basic criteria for HSDD.[4,5]

Although your patient appears to have presented with this complaint, many women are uncomfortable bringing up the topic of sexual desire. Therefore, the first step in identifying HSDD is screening for sexual concerns. This can be accomplished by asking simple questions such as: Are you sexually active? If not, why not? Do you have any concerns about sexual desire, arousal, or orgasm?

The Decreased Sexual Desire Screener also may be helpful. It is a brief, 5-question validated tool that can be self-administered or used to guide discussions about HSDD.[6] Once a concern about desire has been identified, it is important to complete a more thorough evaluation including a review of medical conditions and medications, a psychosocial and sexual history, and physical examination in order to identify and treat contributing factors.

Women with HSDD benefit from treatment that encompasses the reality of the biopsychosocial nature of sexuality. The PLISSIT (Permission, Limited Information, Specific Suggestions, and Intensive Therapy) model can serve to guide discussions in an effective but efficient manner.[7] Once permission to discuss a sexual concern is given, the provider can offer limited information such as dispelling myths about sexuality, clarifying misconceptions about anatomy, or describing the importance of exercise and an overall healthy lifestyle to sexual function. Specific suggestions could include brief teaching about mindfulness or directing women to helpful websites, books, or other resources. If additional suggestions or counseling are needed, the provider can offer a referral to sex educators, counselors, or therapists.

In addition to education and counseling, there are now two FDA-approved pharmacologic options for treating women with HSDD. Both medications are thought to increase desire by correcting an imbalance between inhibitory and excitatory neurotransmitters in the brain.

Flibanserin, a daily oral medication, was the first drug approved for HSDD in premenopausal women. It is a 5-HT1A agonist and a 5-HT2A antagonist that is thought to increase dopamine and norepinephrine levels while decreasing levels of serotonin.[8] Flibanserin has been shown to be associated with a small but statistically significant increase in frequency of sexually satisfying events and an improvement in women's self-reported feelings of desire.

The most common adverse events of flibanserin are dizziness, somnolence, nausea, and fatigue. Although alcohol use had been an absolute contraindication to the use of flibanserin, this has been updated by FDA to state that flibanserin should not be taken within 2 hours of consuming alcohol to avoid hypotension and syncope.[9]

Bremelanotide (Vylessi) was approved in June 2019 to treat premenopausal women with

acquired, generalized HSDD.[10] Bremelanotide is a novel neuropeptide that is analogous to the endogenous hormone melanocyte-stimulating hormone, which stimulates melanocortin-4 receptors in the brain and is thought to increase sexual desire by ultimately increasing dopamine levels.[11] It is administered as a subcutaneous injection via auto-injector on an as-needed basis 45 minutes before sexual activity.

The two phase 3, randomized, controlled, double-blind, multicenter (RECONNECT) trials enrolled 1,267 women and found that bremelanotide was associated with a small but statistically significant increase in desire and reduction in distress related to low desire.[12]

Bremelanotide was not associated with an increase in the number of sexually satisfying events, but this end point has been questioned as an inaccurate measure of female sexual functioning.[13]

The most common treatment-related adverse events with the use of bremelanotide were nausea, flushing, and headache.[12] Nausea was very common, affecting 40% of women, but was noted to be mild to moderate in severity and led only to 8.1% of women to withdraw from the study.[12]

Bremelanotide does cause a transient increase in blood pressure (6 mm Hg systolic and 3 mm Hg diastolic) and a drop in heart rate (approximately 5%), which could be clinically significant for some patients.[14] Approximately 1% of patients who took up to eight doses per month of bremelanotide developed skin hyperpigmentation of the face, gingiva, or breasts; 38% of women who took bremelanotide for 8 days in a row developed focal hyperpigmentation. For this reason, it is recommended to avoid taking more than eight doses of bremelanotide per month.

Of note, 80% of the women who completed the RECONNECT trials opted to continue on in the open-label extension, which suggests that women were happy with the perceived effects of bremelonatide.[15] Women who continued on bremelanotide for an additional year had even further improvements in desire and additional reductions in distress. No new adverse events or safety concerns were identified.

If on further investigation, this patient meets the criteria for HSDD and has no modifiable risk factors, it would be appropriate to discuss the use of the FDA-approved medications flibanserin and bremelanotide to treat the biologic underpinnings that may perpetuate this condition. There are clear differences between these medications; some women may not prefer to take a daily medication, whereas others would not want to self-administer injections before sexual activity. Interestingly, no women dropped out of the bremelanotide trials because of the auto-injector, which suggests that it may be less bothersome in practice than in theory.[16]

Ultimately, these medications work in much the same way that antidepressants work to treat depression and can similarly be viewed as important biologic treatment modalities within the wider context of psychosocial education and counseling for low sexual desire in women. Discussions about these medications provide women the opportunity to explore all treatment options and choose therapies on the basis of their own personal preferences.

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Have you ever heard of or considered "hormone balancing" to achieve weight loss in a patient? Visit our Member Forum to discuss the March *Menopause e-Consult*.

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