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Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

What Are the Roles of the Combined Oral Contraceptive Pill and Metformin in the Management of Polycystic Ovary Syndrome?

By Robert W. Rebar, MD

Professor and Founding Chair Emeritus, Department of Obstetrics and Gynecology, Western Michigan University Homer Stryker M.D. School of Medicine, Kalamazoo

Dr. Rebar reports no financial relationships relevant to this field of study.

SYNOPSIS: This systematic review documents the effectiveness of combined oral contraceptive pills in treating hyperandrogenism and irregular menses, and of metformin in addressing the metabolic disturbances in women with polycystic ovary syndrome.

SOURCE: Teede H, Tassone EC, Piltonen T, et al. Effect of the combined oral contraceptive pill and/or metformin in the management of polycystic ovary syndrome: A systematic review with meta-analyses. *Clin Endocrinol (Oxf)* 2019;91:479-489.

In part, this systematic review was used as evidence for the development of the international evidence-based guidelines for polycystic ovary syndrome (PCOS) adopted across 38 societies and 71 countries.[1] A total of 56 randomized controlled trials identified from electronic databases prior to Jan. 11, 2017, were included in this systematic review. Researchers evaluated data about the effects of combined oral contraceptive pills (COCPs) and/or metformin alone or combined on hormonal and clinical features in PCOS. The length of treatment varied from three to 24 months in those included studies, and sample sizes varied from 10 to 253 participants. Fully 48 of the included studies were conducted in adults, six were in adolescents, and two did not report age. Mean body mass index (BMI) varied across studies, from the normal range (18.50-24.99 kg/m^2) to obese class III (≥ 40.00 kg/m^2). In general, side effects of therapy were inadequately detailed. Overall, the literature was found to be of poor quality, limiting the ability to draw firm conclusions.

In low-quality evidence in adults, meta-analyses indicated that metformin was better than placebo for reducing BMI ($P < 0.04$); metformin was better than COCPs with regard to fasting insulin levels ($P = 0.00001$); but COCPs were

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better than metformin for irregular bleeding ($P = 0.03$). COCPs alone were more effective than COCPs with an anti-androgen for BMI ($P = 0.01$). In low-quality evidence in adolescents, meta-analyses indicated that metformin was better than COCPs for controlling BMI ($P < 0.001$), but COCPs were better than metformin for menstrual irregularity ($P < 0.00001$). The studies documented that metformin typically was associated with mild gastrointestinal adverse events.

The authors concluded that COCPs have benefits for the management of hyperandrogenism and menstrual irregularity and that metformin combined with COCPs might be useful for the management of metabolic abnormalities. There was little evidence that anti-androgen added to COCPs provided additional benefit. Metformin alone benefited women for management of weight and metabolic features, particularly for women with BMI ≥ 25 kg/m^2. The authors were unable to reach any conclusions about the types and dosages of COCPs that were most appropriate or about the dosing and formulation of metformin that was most effective.

■ COMMENTARY

Quite frankly, this systematic review is neither very definitive nor informative, largely because of the poor quality of the studies. This is the case despite the fact that it has been noted that PCOS is the most common endocrine disorder in women of reproductive age, with a prevalence of 8% to 13%.[2] However, this less-than-perfect study provides me with the opportunity to offer some of my thoughts about the management of women with PCOS.

To my way of thinking, management has been complicated by the publication and widespread adoption of the diagnostic criteria developed at the Rotterdam consensus conference.[3] This viewpoint has been echoed by conclusions reached at a conference conducted by the National Institutes of Health in 2012, which I attended, but not formally published in the scientific literature.[4] The Rotterdam criteria did not separate women affected by PCOS by BMI or by the presence or absence of evidence of hyperandrogenism or irregular or absent menses. All the affected women are typically "lumped together," making it more difficult to assess what specific treatments are best for which phenotypes. The same is true of the randomized trials that formed the basis for the systematic review by Teede et al and served as the evidence for some of the published international guidelines. To be sure, this systematic review examined the effect of BMI, but it was unable to look in-depth at all of the individual features associated with PCOS.

In an international consensus workshop sponsored by the American Society for Reproductive Medicine and the European Society of Human Reproduction and Embryology in Amsterdam, it was noted that not all PCOS phenotypes have similar metabolic risk.[5] It was further appreciated that women affected with both hyperandrogenemia and oligomenorrhea are at most risk; this is the group most likely to benefit from metformin. Thus, it is important to remember that metformin need not — and I say should not — be administered to all women with a diagnosis of PCOS. It should be reserved for those in high metabolic risk groups, including those with diabetes risk factors, impaired glucose tolerance, or high-risk ethnic groups, as actually spelled out in the international guidelines. Administration of metformin is associated with the possibility of real and common side effects, including nausea and diarrhea. Lactic acidosis is an extremely rare but significant potential side effect as well. Consequently, judicious use is warranted. Over the years, I have had a significant number of women refuse to continue metformin for the long term because of the bothersome gastrointestinal side effects.

Treatment of women with PCOS aims to address the major complaints of those affected. First and foremost, lifestyle modification is advised and encouraged, but it alone is seldom effective therapy. Medically, COCPs provide first-line therapy for those complaining of menstrual irregularity and signs and symptoms of hyperandrogenemia. There is no evidence that any one low-dose COCP is better than another in women with PCOS. Although not addressed specifically in the study by Teede et al, the addition of an anti-androgen, most commonly spironolactone, has long been known to have a positive effect on the hyperandrogenism.[6] No anti-androgen should be administered to women with hirsutism who are not also using effective contraception because of the potential effect on any developing female fetus. Clomiphene citrate (Food and Drug Administration [FDA]-approved) or letrozole, not FDA-approved but with documented efficacy,[1,7] is first-line therapy for affected women with infertility.

It is important to remember that not all women who meet the diagnostic criteria for metabolic syndrome have PCOS, and not all women with PCOS have the features of metabolic syndrome. Metformin is not a miracle drug,

but merely one that belongs in the armamentarium of clinicians tasked with treating women with PCOS. ■

REFERENCES

1. Teede HJ, Misso ML, Costello MF, et al. Recommendations from the international-based guideline for the assessment and management of polycystic ovary syndrome. *Fertil Steril* 2018;110:364-379.
2. Bozdag G, Mumusoglu S, Zengin D, et al. The prevalence and phenotypic features of polycystic ovary syndrome: A systematic review and meta-analysis. *Hum Reprod* 2016;31:2841-2855.
3. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril* 2004;81:19-25.
4. National Institutes of Health. Final report. Evidence-based methodology workshop on polycystic ovary syndrome. Dec. 3-5, 2012. Available at: https://prevention.nih.gov/sites/default/files/2018-06/FinalReport.pdf. Accessed Dec. 4, 2019.
5. Fauser BC, Tarlatzis BC, Rebar RW, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): The Amsterdam ESHRE/ASRM-sponsored 3rd PCOS Consensus Workshop Group. *Fertil Steril* 2012;97:28-38.e25.
6. Cumming DC, Yang JC, Rebar RW, Yen SS. Treatment of hirsutism with spironolactone. *JAMA* 1982;247:1295-1298.
7. Legro RS, Arslanian SA, Ehrmann DA, et al. Diagnosis and treatment of polycystic ovary syndrome: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2013;98:4565-4592.

ABSTRACT & COMMENTARY

Tenaculum Placement Techniques and Effect on Pain

By Rebecca H. Allen, MD, MPH

Associate Professor, Department of Obstetrics and Gynecology, Warren Alpert Medical School of Brown University, Women and Infants Hospital, Providence, RI

Dr. Allen reports she receives grant/research support from Bayer and is a consultant for Merck.

SYNOPSIS: In this randomized controlled trial, there was no difference in pain score with tenaculum placement between the slow method of application and coughing with application (median pain score 44 vs. 32, $P = 0.16$).

SOURCE: Lambert T, Truong T, Gray B. Pain perception with cervical tenaculum placement during intrauterine device insertion: A randomised controlled trial. *BMJ Sex Reprod Health* 2019 Oct. 30; doi: 10.1136/bmjsrh-2019-200376. [Online ahead of print].

This is a randomized, controlled trial conducted at Duke University from January 2017 to March 2017. Inclusion criteria included English-speaking adult women who were having an intrauterine device (IUD) inserted. Women were excluded only if they were having another procedure in addition to an IUD insertion. Sociodemographic and clinical variables were collected, including age, obstetric history, body mass index (BMI), Generalized Anxiety Disorder-7 (GAD7) anxiety screen score, and any history of chronic pain or narcotic use. Procedures were performed by obstetrics and gynecology residents or attending physicians. Subjects were randomized to either the slow method of tenaculum placement (tenaculum closed on anterior lip of the cervix to the first ratchet over a five-second period) or the cough method of tenaculum placement (the participant was asked to give one strong cough first, then was asked to cough a second time, and the tenaculum then was placed on the anterior lip of the cervix). The study was not blinded. The primary outcome was the pain measured on a 0 to 100 mm visual analog scale at the time of tenaculum placement. The study had 90% power to detect a 16 mm difference on the visual analog scale between groups.

A total of 66 women, with a median age of 26 years and 50% of whom were nulliparous, were randomized. The median pain score in the slow placement group was 44 (interquartile range [IQR] 21, 63) and the median pain score in the cough group was 32 (IQR 19, 54), which was not statistically different ($P = 0.16$). The anxiety level was found to be associated with pain scores. Women with no/mild anxiety reported pain scores of 29 (IQR 18, 55), and women with moderate/severe anxiety reported pain scores of 54 (IQR 32, 67). There was no difference in pain scores between nulliparous and multiparous women or those with a history of chronic pain compared to those without. Provider assessment of optimal grasp of the cervix also did not differ between the two groups.

■ COMMENTARY

It is commendable that the authors took on this study to determine whether the tenaculum placement technique affects pain scores. The question of tenaculum placement and pain experienced by women is a topic of interest to most gynecologists. In most procedures involving uterine instrumentation, a tenaculum is used for stabilization and traction of the cervix and to decrease the flexion of the uterus to ease passage of instruments into the endometrial cavity. Common techniques that many believe decrease pain with tenaculum placement are closing the tenaculum very slowly to only one ratchet or instructing the patient to cough while the tenaculum is placed. While coughing has been found to decrease pain with cervical biopsy,[1] it has not been studied for tenaculum application. Previous studies comparing single-toothed and atraumatic tenaculums did not show any difference in pain with application.[2,3]

The authors did not find any difference in pain scores between the two groups. I wish they had compared these techniques to a third arm: placing the tenaculum on the anterior lip of the cervix quickly until it is completely closed. In this way, we would know whether ANY application technique reduces pain or whether the specific technique does not really matter. Other studied interventions to reduce pain with tenaculum placement include topical and injected local anesthetics; using a topical or local anesthetic does add a step to the procedure. A recent randomized, controlled trial among 70 women compared a 2 mL injection of 1% lidocaine and 1 mL of 2% lidocaine gel to the anterior lip of the cervix for tenaculum placement.[4] The tenaculum was placed immediately after medication administration. The results showed that women who received the injection had significantly less pain at the time of tenaculum placement compared to women who received the topical gel (12.3 vs. 36.6 out of 100, $P < 0.001$). The product label for 2% lidocaine gel states that the onset of action occurs in three to five minutes when used on mucosal surfaces.[5] Therefore, it is not surprising that the topical gel had no effect in this study. To this end, Rapkin and colleagues evaluated patient self-administration of 2% lidocaine gel vaginally five minutes prior to IUD insertion and found that mean pain scores for tenaculum placement were 32 in the lidocaine arm and 56 in the placebo group out of 100 ($P = 0.030$).[6] Because this technique does not require a speculum exam for gel application, it may be more acceptable to patients, but the gel would have to be stocked in the office.

In sum, injected lidocaine is effective in reducing pain with tenaculum placement and is convenient to perform when a paracervical block is planned. Otherwise, the type of tenaculum and whether it is applied slowly or with a cough does not seem to make a difference for most patients in terms of pain experienced. ■

REFERENCES

1. Schmid BC, Pils S, Heinze G, et al. Forced coughing versus local anesthesia and pain associated with cervical biopsy: A randomized trial. *Am J Obstet Gynecol* 2008;199:641.e1-3.
2. Doty N, MacIsaac L. Effect of an atraumatic vulsellum versus a single-tooth tenaculum on pain perception during intrauterine device insertion: A randomized controlled trial. *Contraception* 2015;92:567-571.
3. Speedie JMM, Mansour D, Landy R, et al. A randomised trial comparing pain and ease of use of two different stabilising forceps for insertion of intrauterine contraception. *J Fam Plann Reprod Health Care* 2016;42:241-246.
4. Goldthwaite LM, Baldwin MK, Page J, et al. Comparison of interventions for pain control with tenaculum placement: A randomized clinical trial. *Contraception* 2014;89:229-233.
5. McGee DL. Local and topical anesthesia. In: Roberts JR, Hedges JR, editors. *Clinical Procedures in Emergency Medicine*. 5th ed. Philadelphia, PA: Saunders; 2010.
6. Rapkin RB, Achilles SL, Schwarz EB, et al. Self-administered lidocaine gel for intrauterine device insertion in nulliparous women: A randomized controlled trial. *Obstet Gynecol* 2016;128;621-628.

ABSTRACT & COMMENTARY

Estrogen Replacement: Is Long Duration of Therapy Good for the Brain?

By Jeffrey T. Jensen, MD, MPH, Editor

SYNOPSIS: Longer lifetime exposure to endogenous estrogen and menopausal estrogen replacement were associated with better cognitive status in older adult women. Women who initiated estrogen therapy early (within five years of the onset of menopause) showed higher cognitive test scores than those who started later.

SOURCE: Matyi JM, Rattinger GB, Schwartz S, et al. Lifetime estrogen exposure and cognition in late life: The Cache County Study. *Menopause* 2019;26:1366-1374.

Several animal models and in vitro studies support a role for estrogen in memory.[1] Case control and other epidemiologic observational studies generally support a decrease in the risk of Alzheimer's disease (AD) associated with long duration use of postmenopausal hormone replacement therapy (HT).[2] However, the large prospective, randomized Women's Health Initiative (WHI) Memory Study found an increased risk of dementia and cognitive decline associated with oral conjugated equine estrogens (CEE) alone or in combination with medroxyprogesterone acetate (MPA).[3]

Matyi and colleagues used data from the Cache County Study on Memory in Aging (CCSMA) to study lifetime estrogen exposure and the risk of cognitive decline. The CCSMA surveyed residents of Cache County, Utah, age 65 years or older, without dementia, beginning in 1995. Researchers collected demographic information, including age, education, lifestyle factors (physical activity, smoking, and drinking), diet, and family history. They performed genotyping for apolipoprotein E (APOE) and cognitive and dementia screening. Reproductive health questions included age at menarche and menopause, number of pregnancies and live births, breastfeeding duration, and use of hormonal therapy. The authors used the 100-point modified Mini-Mental State Examination (3MS) to assess the outcome of dementia. To assess exposure to estrogen, they calculated lifetime: 1) endogenous estrogen exposure (EEE) as the reproductive window (menopausal age minus age of menarche), minus total duration of breastfeeding; and 2) exogenous estrogen exposure as the duration of hormone therapy used, type (none, estrogen only, estrogen/

progestogen), and timing (no HT; within one year of menopause; between one and five years; six years or more).

To evaluate the relationship between estrogen exposure and 3MS score, the researchers created a series of linear mixed effects models and adjusted the results for additional covariates of interest guided by prior studies, including age, level of formal education, APOE genotype (number of E4 alleles), body mass index (BMI), physical activity, overall health, and depression status. The first model examined only EEE; the second model examined EEE and duration of exogenous HT exposure (time varying); the third model examined EEE and type of HT (none, unopposed, opposed); and the fourth model examined EEE and timing of HT initiation relative to menopause. They also evaluated the effects of HT discontinuation.

A total of 2,147 women without dementia at the baseline visit comprised the study cohort for this paper. The women in the overall study sample had a mean age of 75 years and an average of almost 13 years of education. Almost all of the women were white and Mormon. The mean EEE was 33 years. Participants who reported ever using HT at baseline were significantly younger and better educated, and more physically active than never-users, and had higher baseline 3MS scores.

In the analysis evaluating the effect of EEE on cognition, the unadjusted model found that each additional year of EEE was associated with a 0.05-point higher score on the 3MS ($P = 0.008$). However, this result did not remain statistically significant in the fully adjusted mixed model. The researchers found a similar effect with respect to hormone therapy duration (each additional year was associated with a 0.02-point higher score). Both combined and estrogen-only therapies increased the 3MS scores. However, none of these relationships remained statistically significant after full adjustment.

All of the women who reported use of HT had higher 3MS scores than nonusers. However, in the fully adjusted model, women who used estrogen continuously or within five years of menopause scored significantly higher than those who initiated HT six or more years after menopause.

■ COMMENTARY

This study provides some additional evidence that menopausal hormone therapy may reduce the risk of cognitive decline. The results must be viewed with caution, as they represent a highly selected sample of older white women living in Utah. All of the effects are modest, and many of the outcomes lose statistical significance with adjustment. Despite those limitations, the results provide additional support for the timing hypothesis, and add to the body of work that refutes the WHI evidence suggesting cognitive risks associated with hormone therapy.

The Cache County study began in 1995. Zandi and colleagues published the first results from this cohort in the *Journal of the American Medical Association* in 2002.[2] I suspect most of you have seen the figures from this publication that show a dramatic difference between men and women in the risk of AD. The risk for women sharply increases beginning around age 80. Zandi and colleagues found a dose response for a reduction in the risk of AD associated with the duration of HT use. The risk associated with greater than 10 years of HT use approached the baseline risk observed in men. While these observations are consistent with the biologic mechanism of estrogen-induced synaptic connections, limitations of the Cache County study design deserve mention. The biggest concern is the healthy user effect. Women using HT had better 3MS scores at baseline, and as health declines (including mental health), many women may discontinue HT. Another problem is the effect of the WHI results in 2002 that led to a tremendous overall decline in HT use in the cohort.

Given that these limitations also apply to the new study by Matyi et al, how should clinicians use this information in counseling? The most interesting new results include the protective effect of EEE on cognitive decline. A late menopause is good for cognitive health, and early menopause is bad. Women who undergo premature ovarian failure or surgical menopause at a young age are at high risk for cognitive decline. I worry about these women, particularly if they receive care from a primary care clinician stuck in the post-WHI mindset of recommending HT at the "lowest dose" and for the "shortest duration." The Matyi paper also supports that early initiation of HT may result in the best protection.

While attractive, randomized trials have not confirmed the "timing hypothesis." The Elite-Cog[4] and KEEPS-Cog[5] studies explored the hypothesis of a critical window for HT initiation and found no treatment-related benefit of HT with respect to overall cognitive function. Although the outcome of these studies did not support the use of estrogen therapy to prevent subtle cognitive decline in postmenopausal women, this does not rule out a potential protective effect on the subsequent development of AD. In 2017, Finnish investigators published results from the Kuopio Osteoporosis Risk Factor and Prevention cohort, a population-based cohort followed for 20 years. They reported that a history of HT use did not change the risk of AD, but that a trend toward protection emerged with longer duration of self-reported use, with an approximately 50% reduction in risk seen in women reporting greater than 10 years of HT.[6] To restate, the consistent finding from both the Cache County and the Kuopio studies is that duration of treatment seems to matter for prevention of AD. At least 10 years of use represents an important goal of therapy. Current use of shorter duration may not reduce risk.

While most women remain interested in cognitive benefits, these are not approved indications for HT. Clinicians should always discuss the limitations of the data and the potential risks and benefits of treatment. However, I do not believe that HT increases the risk of dementia. While estrogen is not a panacea for age-related memory loss, a reduction in risk of AD development in women using HT for at least 10 years may come to pass as a hidden additional benefit. ■

REFERENCES
1. McEwen BS, Akama KT, Spencer-Segal JL, et al. Estrogen effects on the brain: Actions beyond the hypothalamus via novel mechanisms. *Behav Neurosci* 2012;126:4-16.
2. Zandi PP, Carlson MC, Plassman BL, et al. Hormone replacement therapy and incidence of Alzheimer disease in older women: The Cache County study. *JAMA* 2002;288:2123-2129.
3. Craig MC, Maki PM, Murphy DGM. The Women's Health Initiative Memory Study: Findings and implications for treatment. *Lancet Neurol* 2005;4:190-194.
4. Henderson VW, St John JA, Hodis HN, et al. Cognitive effects of estradiol after menopause: A randomized trial of the timing hypothesis. *Neurology* 2016;87:699-708.
5. Gleason CE, Dowling NM, Wharton W, et al. Effects of hormone therapy on cognition and mood in recently postmenopausal women: Findings from the randomized, controlled KEEPS-Cognitive and Affective Study. *PLoS Med* 2015;12:e1001833.
6. Imtiaz B, Tuppurainen M, Rikkonen T, et al. Postmenopausal hormone therapy and Alzheimer disease: A prospective cohort study. *Neurology* 2017;88:1062-1068.

SPECIAL FEATURE

CNS Agents Emerge as Frontrunners in FDA-Approved Treatments for Low Libido in Women

By Nicole Cirino, MD, CST, IF

Reproductive Psychiatrist, Associate Professor of Psychiatry and OB/GYN, Oregon Health & Science University, Portland

Dr. Cirino reports no financial relationships relevant to this field of study.

Low libido is the most common sexual complaint, affecting up to 38.7% of women, with up to 12.3% also reporting significant distress associated with this condition.[1] Debate continues in the scientific and clinical communities about how female desire disorders are characterized, diagnosed, and treated. The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) categorized this common female condition in women as hypoactive sexual desire disorder (HSDD). HSDD is characterized by deficient or absent sexual fantasies and desire for sexual activity lasting at least six months. Women must report significant distress and no other identifiable cause for HSDD, such as substance abuse or general medical conditions (that may affect sexual function).[2]

HSDD occurs in 8% to 19% of women and is associated with lower health-related quality of life, psychosocial distress, depression, anxiety, and increased total healthcare expenditures.[3] In the updated DSM-5, HSDD has been removed and replaced with an amalgamation of female sexual arousal disorder diagnoses termed female sexual interest/arousal disorder (FSIAD).[3] However, even though HSDD has been removed from the updated DSM-5, FSIAD has failed to gain clinical traction among the sexual medical community. HSDD remains the diagnosis used for studying new treatment modalities and developing algorithms of care. In the past five years, for the first time in history, we now have two Food and Drug Administration (FDA)-approved medications specifically for treating HSDD in women.

Thus far, FDA approval is for a specific population of HSDD: women who are premenopausal and have a generalized (vs. situational), acquired (vs. lifelong) form of the condition. Of note, both medications are central nervous system (CNS) agents. According to the FDA, both have pre- and post-menopausal designations, as is typical for sex steroids but atypical for CNS agents. The FDA Bone, Reproductive, and Urologic Drugs Advisory Committee (formerly Reproductive Health Drugs Advisory Committee), not a neuroscience committee,[4] approved the drug.

In fact, CNS-acting agents have emerged in sex-specific sexual medicine research as the newest treatment for this condition in women. The three main neurotransmitters in the brain implicated in sexual function are dopamine, serotonin, and norepinephrine. We have just recently begun to define how these neurotransmitters can inhibit or promote sexual desire. Generally speaking, both dopamine and norepinephrine are considered pro-sexual, while serotonin has anti-sexual properties and is considered to be a "sexual satiety" agent.[5] Because they are CNS agents, caution must be used in prescribing them to women already taking CNS medications for psychiatric or neurologic conditions.

It is fairly universally agreed upon that interventions for low libido start with a full medical and psychosexual evaluation. The first line of treatment is office-based counseling, as well as addressing modifiable factors such as untreated health conditions, medications, or relationship issues.[3] When this approach does not prove helpful, both physicians and patients alike start to wonder, "Is there a pill for this?" In 2020, it turns out, there are two — and perhaps three. Although two novel CNS agents have captured the elusive FDA approval for HSDD, one longtime antidepressant with wide use has led to three possible options for patients with HSDD: flibanserin, bremelanotide, and bupropion. *(See Table 1, available at: http://bit.ly/2QTatO9.)*

In 2015, flibanserin was approved by the FDA for HSDD in premenopausal women with generalized, acquired HSDD. It came with both controversy (since it failed

twice to be approved) and some trepidation, as it initially required a risk evaluation and mitigation strategies (REMS) certification and a black box warning limiting all alcohol consumption during the duration of the daily treatment because of concerns about hypotension and syncope. Recent updates have refined the limitation for alcohol and removed the REMS. Specifically, as of 2019, the boxed warning, contraindication, warnings and precautions, and adverse reactions sections of labeling are updated to reflect that women should discontinue drinking alcohol at least two hours before taking flibanserin at bedtime or skip the flibanserin dose that evening.[6]

Flibanserin is a CNS agent acting as a serotonin receptor agonist and antagonist that results in a transient decrease in serotonin with a downstream increase in dopamine and norepinephrine in certain regions of the brain. Initially, it was studied as a potential antidepressant, and although it was ineffective for depression, it appeared to increase sex drive.

A 2016 systematic review of flibanserin in pre- and post-menopausal women in the *Journal of the American Medical Association* found five published and three unpublished studies that included 5,914 women. Overall, the quality of evidence for efficacy was rated as "very low." The mean differences in sexually satisfying events (SSE) involved a 0.49-point increase in SSE per month with flibanserin vs. placebo and a 0.27-point increase in Female Sexual Function Index desire domain (FSFI-D). Women's mean global impression of improvement scores indicated minimal improvement to no change.[7] Although serious adverse effects were rare, adverse events in pre- and post-menopausal women included dizziness, nausea, fatigue, and somnolence in 29.9% to 36.5% for flibanserin vs. 12.7% to 15.8% for placebo.[7]

Bremelanotide, a melanocortin receptor agonist, was approved by the FDA in June 2019, also for treatment of generalized, acquired HSDD in premenopausal women.[8] The medication is administered as a subcutaneous injection (1.75 mg) at least 45 minutes before anticipated sexual activity. Bremelanotide works as a pre-melanocortin, accidentally discovered by experimenting with self-tanning agents. Its mechanism of action is considered to be a downstream increase in dopamine in the CNS system.

Two randomized, phase III trials involving a total of 1,247 premenopausal women with HSDD found that 24 weeks of bremelanotide compared with placebo resulted in more women with a meaningful increase in sexual desire using the FSFI-D (51% vs. 21%, $P < 0.001$) and improvement in sexual satisfaction using the Female Sexual Distress Scale desire/arousal/orgasm domain (FSDS-DAO) (57% vs. 26 %, $P < 0.001$). Women in the bremelanotide group showed an increase in FSFI-D scores of 0.35 points ($P < 0.001$) over placebo. Changes in the primary endpoint were observed at four weeks, which was the earliest evaluated time point. There was no statistically significant improvement in SSEs between treatment groups (bremelanotide 0.0 vs. placebo -0.1, $P = 0.630$) from baseline to the end of the study. The most common treatment-emergent adverse events, occurring in more than 10% of patients compared with placebo, are nausea, flushing, and headache.[9] Eighty-seven percent of participants rated administering the medication as "easy."[10]

Subsequently, a 52-week open label extension looked at the safety and efficacy of bremelanotide. The study concluded that no new safety signals were observed, and premenopausal women exhibited sustained improvements in HSDD with a higher reduction in distress over time (FSDS-DAO -1.7 and -1.4) from baseline to the end of open label testing, suggesting improvements in distress may lag behind improvements in desire.[11]

Bupropion is an antidepressant, known for a low sexual side effect profile, that has been widely used for depression and selective serotonin reuptake inhibitor (SSRI)-induced sexual dysfunction since its market release in 2006. Because it is widely used and has been on the market the longest, it has significantly more safety profile data and costs significantly less. Therefore, it is worth considering as an off-label CNS agent to treat HSDD. It is one of the few antidepressants that increases dopamine as well as norepinephrine. For HSDD, there is a single, randomized, placebo-controlled trial of four months duration in nondepressed women with HSDD. There were 75 premenopausal participants, with an average age of 36.1 years.

Statistically significant self-reported improvements in pleasure, arousal, and orgasm, according to the Changes in Sexual Functioning Questionnaire (CSFQ), occurred in the bupropion group.[12] Secondarily, blinded raters measured several sexual health variables, and although they showed improved "sexual responsiveness" in all rater-measured variables, many of them were not statistically significant. The effect was seen starting at 28 days of treatment.[12]

We now have two FDA-approved medications, and one off-label antidepressant, that can be considered in treating the most common sexual complaint in women — low libido. On one hand, this is groundbreaking, as we are beginning to see more research on how CNS agents may indeed be key in addressing sex-specific sexual dysfunction. However, each agent did not consistently show more than a modest improvement (if any) in the measurements used to assess sexual desire in their respective studies. Flibanserin, for instance, may increase SSEs by half an event a month, while no increase in SSEs was seen with bremelanotide. (SSEs were not studied with bupropion.)

Regarding the improvement in FSFI-D score, this was a statistically significant improvement in both the flibanserin and bremelanotide trials (0.27 points vs. 0.35 points). However, in the bremelanotide studies, this change in score did not transfer to significantly increase the women's global impression of improvement of their sexual function. While these medications may be options for some patients after behavioral approaches fail, it is unlikely that our current available medications for HSDD will change significantly the current landscape in our approach to the treatment of low libido. However, the press coverage (both positive and

negative) that these medications have received may bring the often-overlooked conversation on female sexual function back to the doctor's office to be addressed in a comprehensive way. ■

REFERENCES

1. Shifren JL, Monz BU, Russo PA, et al. Sexual problems and distress in United States women: Prevalence and correlates. *Obstet Gynecol* 2008;112:970-978.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. 2008, Washington, DC.
3. Goldstein I, Kim NN, Clayton AH, et al. Hypoactive sexual desire disorder: International Society for the Study of Women's Sexual Health (ISSWSH) expert consensus panel review. *Mayo Clin Proc* 2017;92:114-128.
4. FDA. Reproductive Health Drugs Advisory Committee Meeting Announcement. June 18, 2010. Available at: https://wayback.archive-it.org/7993/20170404150118/https://www.fda.gov/AdvisoryCommittees/Calendar/ucm210886.htm. Accessed Dec. 17, 2019.
5. Clayton AH. Epidemiology and neurobiology of female sexual dysfunction. *J Sex Med* 2007;4 Suppl 4:260-268.
6. FDA. FDA orders important safety labeling changes for Addyi. April 11, 2019. Available at: https://www.fda.gov/news-events/press-announcements/fda-orders-important-safety-labeling-changes-addyi. Accessed Dec. 17, 2019.
7. Jaspers L, Feys F, Bramer WM, et al. Efficacy and safety of flibanserin for the treatment of hypoactive sexual desire disorder in women: A systematic review and meta-analysis. *JAMA Intern Med* 2016;176:453-462.
8. FDA. FDA approves new treatment for hypoactive sexual desire disorder in premenopausal women. June 21, 2019. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-hypoactive-sexual-desire-disorder-premenopausal-women. Accessed Dec. 17, 2019.
9. Kingsberg SA, Clayton AH, Portman D, et al. Bremelanotide for the treatment of hypoactive sexual desired disorder: Two randomized phase 3 trials. *Obstet Gynecol* 2019;134:899-908.
10. Koochaki P, Revicki D, Wilson H, et al. 146 conversations with participants in the RECONNECT studies about their experiences with bremelanotide for treatment of hypoactive sexual desire disorder. *J Sex Med* 2019;16:S75.
11. Simon JA, Kingsberg SA, Portman D, et al. Long-term safety and efficacy of bremelanotide for hypoactive sexual desire disorder. *Obstet Gynecol* 2019;134:909-917.
12. Segraves RT, Clayton A, Croft H, et al. Bupropion sustained release for the treatment of hypoactive sexual desire disorder in premenopausal women. *J Clin Psychopharmacol* 2004;24:339-342.
13. GoodRX. Comparison of Drug Prices. 2019. Available at: https://www.goodrx.com/. Accessed Jan. 8, 2020.

CME/CE QUESTIONS

1. The relationship between hormonal therapy and Alzheimer's disease (AD) that appears most consistent across studies is that:
a. a short duration of therapy (< 3 years) provides the maximum protection against development of AD.
b. a long duration of therapy (> 10 years) provides the maximum protection against development of AD.
c. a short duration of therapy (< 3 years) increases the risk of development of AD.
d. a long duration of therapy (> 10 years) increases the risk of development of AD.

2. Which of the following is a true statement about hypoactive sexual desire disorder (HSDD)?
a. All current treatments are dosed on an as needed basis prior to sexual activity.
b. Buproprion is an FDA-approved treatment for HSDD.
c. The neurotransmitter serotonin is considered to have pro-sexual properties in women.
d. The shared mechanism of action for all FDA-approved medications for HSDD is believed to be an increase in dopamine in the central nervous system.

3. The major side effect of metformin involves:
a. renal failure.
b. lactic acidosis.
c. weight gain.
d. gastrointestinal disturbance.

4. First-line medical therapy for hirsutism in women with polycystic ovary syndrome (PCOS) is the use of:
a. spironolactone.
b. letrozole.
c. combined oral contraceptive pills.
d. medroxyprogesterone acetate.

5. First-line medical therapy for metabolic abnormalities in women with PCOS involves the use of:
a. spironolactone.
b. combined oral contraceptive pills.
c. metformin.
d. gonadotropin-releasing hormone agonists.

6. In the study by Lambert et al, pain scores with tenaculum placement were associated with:
a. depression.
b. anxiety.
c. slow placement method.
d. cough placement method.

CNS Agents Emerge as Frontrunners in FDA-Approved Treatments for Low Libido in Women

Table 1. CNS Agents for the Treatment of Hypoactive Sexual Desire Disorder

CNS Agent	FDA-approved for HSDD?	Pre-MP	Post-MP	Mode of Transmission	Cost	Efficacy	Onset	Mechanism of Action
Flibanserin	Yes	+	+/-	PO daily	$404/ month	Modest	Four weeks	Increase DA, modulate 5HT
Bremelanotide	Yes	+	-	SubQ PRN	$893/ three doses	Modest	45 minutes*	Increase DA
Buproprion	No	+	-	PO daily	$9/ month	Modest	Four weeks	Increase DA and NE

HSDD: hypoactive sexual desire disorder; CNS: central nervous system; MP: menopause; DA: dopamine; 5HT: serotonin; NE: norepinephrine
*Although studies showed improvement at four weeks, the earliest measured time point.