Update on Therapies and Treatments in Women's Health

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KEYWORDS

• Women's health • Menopause • Postpartum depression • Contraception
• Osteoporosis • Vulvovaginal candidiasis • Urinary tract infection
• Hypoactive sexual desire disorder

KEY POINTS

- A number of new therapeutics have been approved in the past decade in nearly every clinical area of Women's Health.
- Many are first-in-class medications, including zuranolone/brexanolone for postpartum depression, bremelanotide for hypoactive sexual desire disorder, fezolinetant for vasomotor symptoms of menopause, and romosozumab for osteoporosis.
- Others are new agents in existing classes that enhance prior offerings, such as oteseconazole for vulvovaginal candidiasis or several new contraceptive formulations.
- There is also new evidence for older medications, such as methenamine hippurate for prevention of urinary tract infections.
- Ongoing work is needed to clarify how some of these agents fit into existing treatment algorithms.

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INTRODUCTION

Historic clinical research disproportionally represents male patients. The National Institutes of Health did not mandate inclusion of female individuals in clinical trials until 1994, and diseases that primarily impact this population remain understudied.[1] This general underrepresentation is counteracted by developing new treatments for conditions that primarily affect female patients. New therapies for vasomotor symptoms (VMS), postpartum depression (PPD), contraception, osteoporosis, recurrent yeast infections, acute and recurrent urinary tract infections (UTIs), and female hypoactive sexual desire disorder (HSDD) have notable benefits and side effects. Prescribers should be aware of and discuss novel treatment options with patients as appropriate.

FEZOLINETANT IS A NOVEL NONHORMONAL TREATMENT FOR VASOMOTOR SYMPTOMS

VMS are common, experienced by up to 80% of women during the menopausal transition.[2] About one-third of US women experience moderate-to-heavy symptom burden.[3] VMS may begin before the menopause onset, with a mean total duration of 7.4 years and median of 4.5 years following the final menstrual period. Approximately 10% of women have persistent VMS for up to a decade.[4] Importantly, VMS are associated with a decline in quality of life. Available treatments, such as menopausal hormone therapy (MHT) and available nonhormonal treatments (eg, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and gabapentinods), are not appropriate for all.

Fezolinetant, Food and Drug Administration (FDA) approved in May 2023, is a first-in-class selective neurokinin-3-receptor antagonist and alternative nonhormonal option for the treatment of moderate-to-severe VMS of menopause. Declining estradiol levels during the menopausal transition are associated with hypersecretion of neurokinin B, activation of the hypothalamic thermoregulatory center, and disruption of temperature control resulting in VMS. At a 45 mg dose, fezolinetant demonstrated a clinically meaningful reduction in moderate-to-severe VMS by about 2.5 hot flashes per day versus placebo.[5,6] VMS severity was improved, with a reduction of 0.2 to 0.3 (on a 3 point) scale compared to placebo. While no head-to-head studies have compared fezolinetant to other nonhormonal treatments, its effect size appears to be similar to other available nonhormonal options and smaller than that of MHT.

Overall, fezolinetant was well tolerated up to 52 weeks of follow-up.[5,6] It is recommended to monitor liver function tests (baseline, 3, 5, and 9 months) after initiation or with symptoms of liver dysfunction because elevated hepatic transaminases were deemed an adverse event of interest during clinical development (2.3% fezolinetant 45 mg and 0.8% placebo).[7] Fezolinetant is contraindicated in patients with cirrhosis, severe renal impairment or end-stage renal disease, and in patients on CYP1A2 inhibitors. Fezolinetant may be considered an alternative to other nonhormonal therapies for VMS when there is a contraindication, intolerance, or inadequate response.

ZURANOLONE AND BREXANOLONE: NOVEL, FASTER ACTING AGENTS FOR THE TREATMENT OF POSTPARTUM DEPRESSION

PPD is a prevalent mood disorder, estimated to be present with 12% of births. In 2021, the FDA-approved brexanolone, a neuroactive steroid γ-aminobutyric acid type A receptor modulator. Although a promising novel drug class, this 60 h continuous infusion was logistically challenging in a patient population for whom hospitalization presents a

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significant barrier to access. In 2023, the FDA evaluated and approved zuranolone, an oral agent in the same class.

The efficacy of zuranolone was evaluated in 2 industry-sponsored randomized, placebo-controlled, double-blind trials.[8,9] Participants were women aged 18 to 45 years with PPD, defined as a major depressive episode beginning in the third trimester or within 4 weeks of delivery. Only those with a Hamilton Rating Scale for Depression score of 26 or greater (severe depression) were included. The studies evaluated 14 day courses of once daily oral zuranolone, taken at night with fat-containing food to promote absorption. Patients had higher rates of remission starting at day 3 with zuranolone (19% vs 5% with placebo). Remission remained high throughout treatment and at 1 month after treatment conclusion (53% vs 30%). No evidence exists comparing zuranolone to usual treatment.

Zuranolone does have important safety considerations. Significant central nervous system (CNS) depressant effects were noted, although discontinuation rates were very low during the trial (1%). Patients should be counseled to avoid driving and may need assistance to care for infants or other children. Zuranolone is not recommended during pregnancy, and patients should be advised to use effective contraception during treatment. Zuranolone has been found in low levels in breastmilk, although there is no evidence on the effects of zuranolone on breastfed infants or milk production. CYP3A4 inducers should not be used concomitantly.

While oral zuranolone circumvents the logistical barriers of brexanolone infusions, the cost and lack of comparison to usual care make its incorporation into treatment algorithms challenging. At this time, we recommend case-by-case consideration for patients with severe PPD.

NEW CONTRACEPTIVES INCLUDE ORAL AGENTS, A DIFFERENT RING AND PATCH, AN ON-DEMAND GEL, AND EVIDENCE FOR USE OF 52 MCG LEVONORGESTROL INTRAUTERINE DEVICES FOR EMERGENCY CONTRACEPTION

All patients of childbearing age who desire contraception should be counseled about available options. Several updated and/or novel contraceptives have entered the market in the past several years: 2 novel oral contraceptives; a vaginal ring that can be used for 1 year; a lower systemic estrogen dose patch; a novel on-demand vaginal gel that works by lowering vaginal pH. In addition, there is evidence that the 52 mg levonorgestrol intrauterine device (IUD) has equal efficacy as the copper IUD for emergency contraception. Insurance coverage for novel methods is variable; coverage for new uses of old methods is typically not a problem.

Two novel oral contraceptives have gained FDA approval: drospirenone–estertrol 3 mg/14.2 mg (Nextstellis) and drospirenone 4 mg (Slynd). Drospirenone–-estertrol 3 mg/14.2 mg was approved in April 2021 and includes a novel estrogen. Other combined oral contraceptives contain estradiol that is clinically manufactured from pregnant mare's urine. Estertrol is synthetically derived from plant sources. In animal studies, it had a lower impact on hemostasis biomarkers, triglycerides, and breast tissue.[10] Compared to estradiol, less drug metabolite is excreted in the urine, which is motivating to some environmentally conscious patients. The efficacy and safety profile for drospirenone-estertrol is similar to other combined oral contraceptives. It had a Pearl Index (number of pregnancies per 100 woman-years of exposure) of 2.65 (95% confidence interval [CI]: 1.73–3.88) in a phase 3 trial of 1524 patients. The most common reported adverse events were metrorrhagia 4.4% and headache 3.5%.[11]

While drospirenone is not a new agent, a 4 mg drospirenone tablet was approved as a novel progestin-only pill in May 2019. Previously, the only available progestin-only

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pill was norethindrone 0.35 mg. The new drospirenone-only pill has better efficacy in the setting of delayed or missed pills, and a more favorable bleeding profile. The missed pill window for drospirenone 4 mg is 24 hours; for norethindrone 0.35 mg, it is 3 hours. In a phase 3 trial of 1864 participants, rates of unscheduled bleeding decreased and amenorrhea increased as the study progressed.[11] Less than 2% of participants discontinued due to bleeding. Drospirenone has mineralocorticoid effects. In studied patients, there were no adverse effects on blood pressure; 0.5% of participants developed asymptomatic hyperkalemia.[12] The Pearl Index was 4.0 (95% CI: 2.3–6.4). Approximately one-third of study participants were obese (body mass index [BMI] $\geq$30.0 kg/m^2); the Pearl Index was not affected by BMI. No cases of venus thromboembolism (VTE) were reported.[11,12] We recommend drospirenone 4 mg for patients with contraindications to estrogen who desire improved efficacy and more regular bleeding compared to norethindrone 0.35 mg. Patients should be monitored for hyperkalemia.

A new vaginal ring (Annovera) was FDA approved in 2018 and can be used for 13 cycles or 1 year. It contains segesterone and ethinyl estradiol and has no appreciable differences in side effect profile compared to monthly rings containing etonogestrel and ethinyl estradiol. The 13 cycle ring is approximately twice as thick (8.4 mm vs 4 mm) as the 1 cycle ring, both rings have a similar diameter. The 13 cycle ring is kept in place for 21 days, removed for 7, then reinserted. During the 21 day use period, it should not be removed for more than 2 hours. Although there is no evidence for 12 months of continuous use, some patients have begun to use it this way off label. The Pearl Index was 2.98 (95% CI: 2·13–4·06), similar to other hormonal contraceptives.[13] There is limited evidence for use in patients with BMI greater than 29 as enrollment for this group was halted after 2 participants had a VTE. There are no head-to-head trials comparing vaginal rings. The new ring may be a good choice for patients who struggle to refill medications at a pharmacy.

A new on-demand contraceptive, a lactic acid and potassium bitartrate vaginal gel (Phexxi) was approved in 2020 and lowers vaginal pH to reduce sperm motility. The nonhormonal, user-controlled gel is inserted into the vagina using a single-dose applicator up to 1 hour prior to intercourse; there is no evidence for use after sex. The Pearl Index was 27.5 (95% CI: 22.4%, 33.5%).[14] The most frequently reported adverse effect was vulvovaginal burning sensation (20.0%)[15]; partners may experience a similar sensation. It requires a prescription and expands options for patients seeking on-demand, hormone-free contraception. It can be used in combination with condoms and diaphragms.

A new ethinyl estradiol and levonorgestrel contraceptive patch (Twirla) entered the market in 2020. Previously, there was only one patch on the market, ethinyl estradiol and norelgestromin (Xulane, the generic of Ortho Evra). Serum levels of ethinyl estradiol for Twirla's are similar to those of a low-dose oral contraceptive; Xulane levels are about 60% higher.[16–18] While the 2 patches have not been compared head-to-head, both are less effective in patients with BMI greater than 30. Unfortunately, the risk of VTE with Twirla was in the same range as other combined hormonal contraceptive methods at 3 to 12 per 10,000 users.[17,19] While there is no current evidence to support it, this method may be used for patients who desire a patch and benefit from lower estrogen exposure.

For emergency contraception, the use of the 52 mcg levonorgestrol IUD was found to be non-inferior to the copper IUD in a study of 711 patients seen at 6 Utah clinics. In the modified intention-to-treat and per-protocol analyses, pregnancy rates were 1 in 317 (0.3%; 95% CI: 0.01–1.7) in the levonorgestrel group and 0 in 321 (0%; 95% CI: 0–1.1) in the copper IUD group.[20] Adverse events resulting in participants seeking

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medical care in the first month after IUD placement occurred in 5.2% of participants in the levonorgestrel IUD group and 4.9% of those in the copper IUD group. While not FDA approved for this use, clinicians have used this evidence to offer the 52 mcg levonorgestrol IUDs for emergency contraception.

ROMOSOZUMAB IS AN OSTEOPOROSIS TREATMENT FOR PATIENTS AT VERY HIGH FRACTURE RISK, OR WHO CANNOT TOLERATE TRADITIONAL THERAPIES

Romosozumab, a monoclonal anti-sclerostin antibody, is an osteoporosis medication that increases bone formation and decreases bone resorption. It was approved by the FDA in 2019. In an early study, 12 months of monthly subcutaneous romosozumab was compared with placebo in 7,180 women. All received denosumab for the following year. There was a reduction in radiologic vertebral fractures but not nonvertebral fractures in those treated with romosozumab.[21]

In a study of over 4,000 women with osteoporosis and a history of a fragility fracture, women were randomized to receive a monthly subcutaneous injection of romosozumab versus weekly oral alendronate for 1 year. After that year, all received alendronate weekly. After 2 years, among these women, whose median age was 74 years, romosozumab resulted in lower rates of new vertebral fracture, any clinical fracture, and hip fracture than did alendronate.[22]

Although there was no difference in overall serious adverse events, there was a higher rate of serious cardiovascular results among women who received romosozumab.[22] Romosozumab is FDA approved for use for 1 year for postmenopausal women at high fracture risk or in whom other treatments have failed, although the approval includes a warning about higher risk of myocardial infarction, stroke, and cardiovascular death.

The American College of Physicians recommends that bisphosphonates remain the first choice for the treatment of osteoporosis. Denosumab should be a second-line treatment for those who have contraindications to or are unable to tolerate bisphosphonates. Finally, the sclerostin inhibitor (romosozumab) or recombinant parathyroid hormone (PTH) (teriparatide or abaloparatide) followed by bisphosphonate should be used in patients with primary osteoporosis and very high risk of fracture.[23]

OTESECONAZOLE IS AN EFFECTIVE TREATMENT FOR RECURRENT VULVOVAGINAL CANDIDIASIS BUT SHOULD BE AVOIDED IN PATIENTS OF REPRODUCTIVE POTENTIAL

Approximately 75% of women develop vulvovaginal candidiasis (VVC) at least once in their lifetime, with around 5% to 10% developing recurrent vulvovaginal candidiasis (rVVC), defined as 3 or more symptomatic episodes in 12 months.[24] Oteseconazole is an azole metalloenzyme inhibitor for CYP51, a fungal enzyme required for cell-wall synthesis and fungal cell growth. Oteseconazole was approved by the FDA in 2022 after three phase 3 trials demonstrated efficacy in the treatment and prevention of rVVC.

In the 2 VIOLET trials (CL-011 and CL-012), participants received fluconazole induction consistent with current complicated VVC treatment, followed by randomization to either placebo or oteseconazole for maintenance.[25] To be included in the trial, participants had at least 3 acute VVC episodes in the past year. At week 48, 4% or 7% of participants in the oteseconazole arms of each of the 2 trials had recurrence of rVVC compared to 36% or 43% in the placebo arms ($P < .001$). The ultra VIOLET trial compared fluconazole and oteseconazole for induction, with induction failure rates in 4% and 7% of participants, respectively.[26] Rates of adverse events were similar between oteseconazole and placebo and included headaches (~7%) and nausea (~4%).

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These 3 double-blind, placebo-controlled randomized controlled trials demonstrated that oteseconazole for maintenance after fluconazole induction was superior to placebo, and oteseconazole induction was non-inferior to fluconazole. There is no evidence comparing fluconazole to oteseconazole for maintenance.

Animal studies suggest that oteseconazole is teratogenic, causing fetal ocular abnormalities. As the half-life is approximately 138 days, this drug is contraindicated in those of reproductive potential. In addition, oteseconazole is not recommended in those with moderate–severe hepatic impairment or with an estimated glomerular filtration rate less than 30.

In conclusion, oteseconazole is a promising new agent available to treat a common condition with low rates of adverse events. However, its potential teratogenic potential combined with its long half-life significantly limits the target population to postmenopausal women or those who have undergone permanent sterilization procedures.

SINGLE-DOSE FOSFOMYCIN MAY BE USED FOR PATIENTS UNABLE TO TOLERATE NITROFURANTOIN FOR ACUTE CYSTITIS

The 2010 IDSA guidelines incorporated nitrofurantoin and fosfomycin as first-line agents for the treatment of UTIs.[27] Fosfomycin is administered as a single dose and is attractive as a treatment option where adherence is of concern. In a recent clinical trial, 513 women with less than 1 symptom of UTI and a positive dipstick were randomized to receive a single 3 g dose of fosfomycin or nitrofurantoin 100 mg tid for 5 days (European dosing). The study found that 70% of patients treated with nitrofurantoin had clinical resolution at 28 days compared with 58% of women treated with fosfomycin, for a 12% absolute difference ($P = .004$). There was no difference in symptom duration or occurrence of pyelonephritis or adverse events.[28]

We recommend that given similar rates of adverse effects and higher rates of cure for nitrofurantoin, fosfomycin may be less efficacious than nitrofurantoin for the treatment of uncomplicated UTI in women. However, if a woman is unable or unwilling to take nitrofurantoin, and/or if adherence is a concern, fosfomycin is a reasonable treatment option.

METHENAMINE HIPPURATE IS A NONANTIBIOTIC ALTERNATIVE FOR TREATMENT OF RECURRENT URINARY TRACT INFECTION

Recurrence occurs in 25% of women after their first UTI. Guidelines recommend daily low-dose antibiotics as prophylaxis in women with recurrent UTI.[29] Although prophylactic antibiotic regimens vary, antibiotic resistance is a potential consequence of all regimens.

Methenamine hippurate is a urinary antiseptic and nonantibiotic alternative that has the potential benefit of not inducing antibiotic resistance. Although methenamine hippurate has been available for UTI prevention since 1967, it has not been commonly used, except in pregnancy.

Methenamine hippurate was compared to antibiotic prophylaxis in a randomized multicenter, open-label, non-inferiority trial.[30] Two hundred and forty adult women with recurrent UTI received methenamine hippurate 1 g twice a day or antibiotic prophylaxis (nitrofurantoin, cefalexin, or trimethoprim). The primary outcome was incidence of symptomatic, antibiotic-treated UTI over 12 months of follow-up. The absolute difference in UTI incidence after 12 month follow-up was 0.49 (015–0.84) episodes per person-year and met the prespecified non-inferiority margin (1 episode per person-year). Participants described the antibiotic regimen as more convenient (once a day vs twice a day dosing).

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We recommend methenamine hippurate as an acceptable alternative for antibiotic prophylaxis for recurrent UTI; however, it is not known how it compares to specific antibiotic regimens.

BREMELANOTIDE IS A NOVEL THERAPY FOR FEMALE HYPOACTIVE SEXUAL DESIRE DISORDER

HSDD is an absence or reduction of sexual fantasies or interest in sexual activity that causes significant distress for an individual. Low desire is the most common form of sexual dysfunction in women in the United States, with 10% reporting low desire that causes distress.[31] Despite its prevalence, limited pharmacologic treatment options are available for female HSDD.

Bremelanotide (Vyleesi) was approved by the FDA for the treatment of HSDD in premenopausal women in 2019. While the mechanism of action is not entirely understood, bremelanotide is a melanocortin receptor agonist that stimulates endogenous neuropeptides that are associated with the excitatory pathways in sexual response.[32]

Bremelanotide has been shown to improve sexual desire and decrease distress, but not significantly change satisfying sexual events. This medication was studied in two 24 week randomized, double-blind, placebo-controlled trials with extended open-label following for 52 weeks.[33,34] These studies included healthy, premenopausal women with HSDD for over 6 months. Individuals who were pregnant, nursing, or who had diagnoses of a mental health or substance use disorder were excluded. In surveys of participants, there was statistically significant improvement in self-reported sexual desire and a decrease in distress in the treatment compared to the placebo group after 24 weeks, which persisted in the open-label trial. There was no statistically significant change in the number of satisfying sexual events between the treatment and placebo groups.

Patients considering bremelanotide should be counseled about the delivery, potential side effects, and cost of this medication. Bremelanotide is recommended for use as needed at least 45 minutes (and up to 8–10 hours) before planned sexual activity (maximum 1 dose per 24 hours or 8 doses per month). Delivery is via a prefilled subcutaneous auto-injector (dose 1.75 mg per injection). The most commonly reported side effects include nausea (40%), flushing (30%), and headache (11%).[34,35] Less frequent side effects include transient blood pressure increase, fatigue, skin hyperpigmentation, and delayed gastric emptying. Bremelanotide is contraindicated in women with uncontrolled hypertension or who are at risk for cardiovascular disease.[35] Bremelanotide can decrease the serum concentration of naltrexone and indomethacin and should be used with caution in patients with hepatic and/or renal dysfunction. This medication should be avoided in pregnancy, and data are not available for lactation. Unlike the only other FDA-approved medication for female HSDD (Flibanserin [Addyi]), use of bremelanotide with alcohol is not limited. Cost can be substantial ($286 per auto-injector), although a coupon program is available through the manufacturer.

While bremelanotide is a welcome addition to the pharmacologic options to help women with HSDD, use remains limited by the balance of clinical impact with potential side effects and cost.

CLINICS CARE POINTS

- Fezolinetant is an alternative nonhormonal option for the treatment of moderate-to-severe VMS with similar efficacy to other nonhormonal treatments.

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- Zuranolone and brexanolone are a new class of agents to treat PPD.
- Updates in contraception include an estetrol/drospirenone combined oral contraceptive, a drospirenone-only pill, a 13 cycle vaginal ring, a new weekly patch, a pH-altering on-demand vaginal gel, and evidence for the 52 mg levonorgestrol IUD for emergency contraception.
- Romosozumab can be considered for patients with high fracture risk and low cardiovascular risk who cannot use bisphosphonates or denosumab.
- Oteseconazole treats recurrent VVC but should not be used in patients of childbearing potential.
- Single-dose fosfomycin treats cystitis but has a lower cure rate than nitrofurantoin. Methenamine hippurate is a nonantibiotic alternative for prevention of recurrent UTIs.
- Bremelanotide improves sexual desire but not sexually satisfying events in female HSDD.

DISCLOSURE

Dr S. Merriam writes content for ACP MKSAP and is compensated.

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