Menopause Management

1

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Key Points

1. Approximately 42% of women aged 60–65 will experience hot flashes and night sweats during menopause.
2. Approximately 50% of women will experience genitourinary syndrome of menopause (GSM): chronic, progressive genitourinary changes such as vulvovaginal dryness and atrophy, increased vaginal and urinary infections, as well as genitourinary discomfort and pain.
3. Hormonal and nonhormonal treatment options are available to treat older women in menopause.
4. Shared decision-making should be used to individualize treatment of symptomatic menopausal women.
5. Hormone therapy should not be used to prevent chronic disease, cancer, mood, or cognitive changes.

Case

Ann is a 57-year-old patient who presents with hot flashes and night sweats. She reports that menopause occurred at age 52, and she immediately began to experience bothersome hot flashes and night sweats. Her symptoms were relieved completely when her primary care provider prescribed combined

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hormone therapy containing estrogen and progesterone. After 2 years of hormone therapy, her primary care provider discontinued the hormone therapy out of concern for an increased risk of cancer and cardiovascular disease. She now has had a return of symptoms: severe hot flashes, approximately five to ten per day, sleep disrupted by night sweats, and uncomfortable sex, which she attributes to an increasingly dry vagina. She has tried over-the-counter herbs and supplements to relieve her symptoms; they have not helped. Glycerin and water-based lubricants did not help her vaginal symptoms.

Menopause results from the permanent cessation of ovarian function secondary to natural senescence of the ovaries or iatrogenic disruption of ovarian function secondary to surgical removal or damage from chemotherapy or radiation. Natural menopause is diagnosed after the cessation of menses for 1 year, and is on average diagnosed at age 51 in the United States. With an average life expectancy of 81.6 years, women in the United States can expect to spend more than 30 years in menopause [1]. The decline in ovarian function and hormone production—estrogen, progesterone, and testosterone—leads to a number of physiologic changes during the menopausal transition. Women frequently complain of vasomotor symptoms (VMS), also known as hot flashes and night sweats, genitourinary symptoms such as vaginal dryness, as well as changes in memory, mood, sleep, and weight. Vasomotor complaints are the most commonly discussed symptoms of menopause. The etiology of these hot flashes is incompletely understood, but is thought to be related to dysregulation of the thermoneutral regulatory zone in the hypothalamus. Hot flashes are thought to occur when the core body temperature is triggered to rise above the upper threshold of this narrow thermoneutral zone; shivering occurs when the core body temperature falls below the lower threshold. Recent research has implicated the KNDy—kisspeptin, neurokinin B, and dynorphin— neuron complex located in the arcuate nucleus as a mediator of estrogen signals to the thermoregulatory center [2].

Vasomotor symptoms are characterized by intense, recurrent episodes of warmth that begin centrally and progress to the upper body, culminating in flushing of the face followed by chills and sweating; 75–80% of menopausal women will experience bothersome hot flashes that may occur during waking hours or sleep [3, 4].

When these symptoms occur at night, they are referred to as night sweats; they often occur during and are disruptive to sleep. Vasomotor symptoms can vary in severity and frequency.

While vasomotor symptoms appear to be most intense during the menopausal transitions and early menopausal periods, these symptoms may continue and adversely impact the quality of life of older women. Nearly 20% of women visiting a menopausal consultation clinic at the Mayo Clinic were 60 years of age or older [5].

Forty-two percent of women aged 60–65 will experience moderate to severe hot flashes [6]. About 12% of women aged greater than 67 and ~20 years beyond the age of menopause report clinically significant vasomotor symptoms [7]. 16% of Swedish women older than age 85 report vasomotor symptoms several times per

Table 1.1 Conditions and medications that trigger or mimic vasomotor symptoms

Tumors/cancer: hypothalamic, pituitary gland, pheochromocytoma, carcinoid, pancreatic, renal cell
Diet: alcohol, spicy foods, monosodium glutamate (MSG)
Infections: tuberculosis or HIV
Medical conditions: thyroid disorder, mast cell disorders
Medications: chronic opioid use or opioid withdrawal, SSRIs, nitroglycerin, nifedipine, niacin, vancomycin, calcitonin, and antiestrogens (such as tamoxifen or aromatase inhibitors)
Anxiety disorders

week, though only 6% were using hormone therapy (HT) to treat these symptoms [8]. The presence of vasomotor symptoms has implications for poorer physical and psychological health: increased risk of coronary heart and cardiovascular disease, osteoporosis, and increased depression [9–11]. Women with hot flashes have increased visits for outpatient health care.

The costs, direct and indirect, associated with treating vasomotor symptoms is estimated to be hundreds of million dollars annually. Vasomotor symptoms are clinically diagnosed through patient report and history. Associated risks factors include: cigarette smoking, obesity, depressive symptoms, low educational attainment, and African American ethnicity [4, 12].

It is important to rule out other conditions as these symptoms can be provoked by medications, infections, endocrinopathies, and infections in older women (Table 1.1).

Laboratory measurement of hormone levels is often unnecessary to make a diagnosis of menopausal vasomotor symptoms. Women often report a sudden feeling of intense heat that begins centrally, radiates to the upper body and face, followed by increased sweating in the same areas. These hot flashes typically last about 2–5 min. The skin temperature may rise 1–7° and the heart rate may increase 5–7 beats/min. Following the resolution of the hot flash and sweating, women may also experience chills due to the rapid decline in skin and core body temperature.

Treatment

Estrogen therapy is the most effective treatment of vasomotor symptoms. For women with intact uteri, progestogen therapy is required for endometrial protection from the proliferative effects of systemic estrogen on the endometrium. A Cochrane review showed that estrogen alone, or combined with progestogen, is significantly more effective than placebo in reducing the severity of vasomotor symptoms and the frequency of symptoms by 75% [13]. Unfortunately, there has been a marked decline in the use of hormone therapy since the release of the Women's Health Initiative (WHI) study results in 2002. This randomized control trial was designed to assess the benefits of hormone therapy for chronic disease prevention and cancer in a healthy menopausal cohort. Patients who received estrogen alone had reduction in breast cancer risk, no increase in cardiovascular disease events, and a decrease in risk of fractures and colon cancer. Five years of estrogen–progestogen use resulted in a nominal increased risk of coronary heart disease (CHD), breast cancer, venous thromboembolic disease, and strokes.

The majority of the study population were older than age 60 and the oldest participants aged 79 [14]. Very few women in the trial reflected the population for whom hormone therapy is typically prescribed, women who are within 10 years of the final menstrual period and less than 60 years of age. These results have been overgeneralized to women of all age ranges and hormone therapy formulations, despite utilizing one route of administration, oral, and one formulation of estrogen: conjugate equine estrogen (CEE) or medroxyprogesterone acetate (MPA). More recent hormone therapy trials and follow-up reanalysis of the WHI results provide additional perspectives and guidance about the safe use of hormone therapy to treat menopausal symptoms. Moreover, 18-year follow-up data from the WHI show that the use of CEE with MPA for 5.6 years or CEE alone for 7.2 years was not associated with an increased risk of all-cause, cardiovascular, or total cancer mortality [15].

Based upon the best available data, hormone therapy is safe to use for the treatment of moderate to severe vasomotor symptoms and the genitourinary syndrome of menopause (GSM). Hormone therapy, however, should not be used to prevent chronic disease.

The Bottom Line on Hormone Therapy from the Women's Health Initiative and observational studies:

- The benefits of hormone therapy exceed the risk in most women.
- For women younger than age 60 or who are within 10 years of menopause and without contraindications, hormone therapy has a favorable benefit–risk ratio when used to treat moderate to severe vasomotor symptoms.
- The benefit–risk ratio is less favorable for women who *initiate* hormone therapy more than ten years after onset of menopause or who are older than age 60 due to the increased age-related risk of coronary heart disease, stroke, venous thromboembolism, and dementia.
- In 18 years of follow-up data, hormone therapy with conjugate equine estrogen plus medroxyprogesterone acetate for ~5 years or with conjugate equine estrogen alone for ~7.2 years, was not associated with risk of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up of 18 years.
- Annual evaluation of symptoms and documentation of persistent symptoms as well as the shared decision-making process should occur in the setting of extended duration of use for persistent vasomotor symptoms [15, 16].

Hormone therapy (HT) is available in various formulations—oral, transdermal, and vaginal—and dose preparations—standard and low dose—all of which may yield variable response. The risks of HT differ depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used.

Table 1.2 Combined hormone therapy

Product name(s)	Estrogen	Progestogen
Prempro	0.625 mg conjugated estrogens	2.5 or 5 mg medroxyprogesterone acetate
	0.3 or 0.45 conjugated estrogens	1.5 mg medroxyprogesterone acetate
Femhrt	5 μg ethinyl estradiol	1 mg norethindrone acetate
	2.5 μg ethinyl estradiol	0.5 mg norethindrone acetate
Activella	1 mg 17β-estradiol	0.5 mg norethindrone acetate
	0.5 mg 17β-estradiol	0.1 mg norethindrone acetate
Angeliq	0.5 mg 17β-estradiol	1 mg drospirenone
	0.25 mg 17β-estradiol	0.5 mg drospirenone
Climara Pro	0.045 mg 17β-estradiol	0.015 mg levonorgestrel
CombiPatch	0.05 mg 17β-estradiol	0.14 mg norethindrone acetate
Duavee	0.45 mg conjugated estrogens + 20 mg bazedoxifene	

Treatment should be individualized to identify the most appropriate HT type, dose, formulation, route of administration, and duration of use, using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation of the benefits and risks for continuing or discontinuing HT. Individualization is likely to improve *symptom relief, optimize patient adherence and satisfaction, and minimize associated risks.*

Commonly prescribed hormonal therapies may be found in Tables 1.2, 1.3, and 1.4.

Commonly Prescribed Hormone Therapies

A list of updated government-approved drugs for the treatment of menopausal symptoms may be found at http://www.menopause.org/docs/default-source/professional/nams-ht-tables.pdf [17]

MenoPro is a mobile app (https://www.menopause.org/for-professionals/-i-menopro-i-mobile-app) [18] produced by The North American Menopause Society (NAMS) that can be used by both clinicians and patients to individualize and personalize treatment decisions. It considers patients' personal treatment preferences, medical history, and underlying risk factors. Nonhormonal and hormonal treatment options are imbedded in the app.

Caution must be taken when considering the use of systemic hormone therapy to treat women more than 10 years from the diagnosis of menopause or those who are over the age of 60. Hormone therapy initiated between the age of 50 and 59, and within 10 years of the onset of menopause may be associated with a reduced risk of CHD [19]. However, initiating hormone therapy in women older than age 60 and in those women who are more than 10 years from the onset of menopause increases the risks of stroke, venous thromboembolism (VTE), and pulmonary embolism (PE) [20] for women who have age-related risks for these conditions. The NAMS,

Table 1.3 Estrogen-only therapy

Oral products		
Composition	Product name(s)	Range of available dose strengths
Conjugated estrogens	Premarin	0.3–1.25 mg
Synthetic conjugated estrogens, A	Cenestin	0.3–1.25 mg
Synthetic conjugated estrogens, B	Enjuvia	0.3–1.25 mg
Esterified estrogens	Menest	0.3–1.25 mg
17β-estradiol	Estrace, various generics	0.5–2.0 mg
Estradiol acetate	Femtrace	0.45–1.8 mg
Estropipate	Ortho-Est	0.625 mg (0.75 mg estropipate, calculated as sodium estrone sulfate 0.625 mg) to 5.0 mg (6.0 mg)
Transdermal products		
17β-estradiol matrix patch	Alora, Climara, Esclim, Fempatch, Menostar, Vivelle, Vivelle-Dot, various generics	0.014–0.1 mg delivered daily; applied once or twice weekly
17β-estradiol reservoir patch	Estraderm	0.05–0.1 mg delivered daily; applied twice weekly
17β-estradiol transdermal gel	EstroGel, Elestrin, Divigel	Applied daily via metered pump or packet delivering 0.52–0.75 mg of 1/β-estradiol in gel
17β-estradiol topical emulsion	Estrasorb	2 packets applied daily
17β-estradiol transdermal spray	Eva mist	1 spray/d, up to 2–3/d if needed
Vaginal products		
Estradiol acetate vaginal ring	Femring	Device containing 12.4 or 24. 8 mg estradiol acetate releases 0.05 mg/d or 0.10 mg/d estradiol for 90 days (both doses release systemic levels for treatment of vulvovaginal atrophy and vasomotor symptoms)

Table 1.4 Progesterone only therapy

Product name(s)	Composition	Dosage (mg/d)
Provera (generic(s) available)	Medroxyprogesterone acetate	5, 10 (administer cyclically 12–14 d/mo)
Prometrium	Micronized progesterone	200 (administer cyclically 12 d/28-d cycle)
Levonorgestrel IUD[*]	*Levonorgestrel IUD*	*52 mg over a 5 year period*

[*]Indicates off label use of the the Levonorgestrel IUD for endometrial protection

Endocrine Society, and American College of Obstetricians and Gynecologists (ACOG) advise against arbitrary age-related treatment discontinuation. Treatment decisions should be individualized through a shared decision-making framework that accounts for symptom severity, an analysis of risks and benefits of HT, and the patients' treatment goals. Annual evaluation of symptoms and treatment continuation is recommended [16, 21, 22].

For women who present with new onset vasomotor symptoms (VMS), it is important to evaluate for medications or other conditions that may contribute to VMS.

Systemic hormone therapy use is contraindicated in the setting of unexplained vaginal bleeding, severe active liver disease, prior estrogen-sensitive breast or endometrial cancer, coronary heart disease (CHD), stroke, dementia, personal history or inherited high risk of thromboembolic disease, porphyria cutanea tarda, or hypertriglyceridemia.

Many menopausal women report distressing sleep disruptions, mood instability, and cognitive impairment. All of the changes may be attributable to the general effects of aging. While these concerns should be fully evaluated, there is no clear benefit to using hormone therapy to treat sleep, mood, memory, dementia, or cognitive changes in women. Please see the chapters on sleep and depression for more guidance on evaluation and treatment.

Case (Continued)
Following a discussion of her symptoms and hormonal treatment options, Ann and her provider determine that she is a good candidate for hormone therapy; however, Ann wants to explore nonhormonal options as well.

For women who are not candidates for or elect to not use hormone therapy, there are many nonhormonal options. SSRIs and SNRIs are frequently used to treat vasomotor symptoms (Table 1.5). Paroxetine salt 7.5 mg is the only nonhormonal pharmacologic treatment approved by the FDA for moderate to severe vasomotor symptoms. The frequency and severity of vasomotor symptoms and sleep disruptions improve typically within 2 weeks, without increasing weight gain or diminishing libido. Off-label use of other SSRIs and SNRIs leads to mild to moderate improvement in VMS; these include escitalopram, citalopram, venlafaxine, desvenlafaxine, and paroxetine. Paroxetine and fluoxetine should be avoided in patients using tamoxifen as these drugs inhibit the CYP2D6 enzyme that converts tamoxifen to its active metabolite. SNRIs are safer, more effective options for these patients.

The gabapentinoids, gabapentin and pregabalin, are effective at improving hot flashes. Gabapentin may also improve sleep patterns in symptomatic patients. Suggested dosing for off-label use of gabapentin is 300 mg three times daily, 900 mg/day. Consider titrating slowly to reduce adverse side-effects such as dizziness, unsteadiness, and drowsiness. These side-effects typically improve in 1–2 weeks and resolve in 4 weeks.

Weight loss, mindfulness-based stress reduction, soy isoflavones derivatives and extracts, and stellate ganglion blockade are recommended with caution as there is evidence to suggest that these options may be beneficial in some circumstances; however, more evidence is needed. While lifestyle practices and modifications such

Table 1.5 Suggested dosing ranges for nonhormonal prescription therapies

SSRIs		
Paroxetine salt	7.5 mg	Single dose, no titration needed
Paroxetine	10–25 mg/d	Start with 10 mg/d
Citalopram	10–20 mg/d	Start with 10 mg/d
Escitalopram	10–20 mg/d	Start with 10 mg/d (for sensitive or older women, start with 5 mg/d for titration, but this dose has not been tested for efficacy)
SNRIs		
Desvenlafaxine	100–150 mg/d	Start with 25–50 mg/d and titrate up by that amount each day
Venlafaxine	37.5–150 mg/d	Start with 37.5 mg/d
Gabapentinoids		
Gabapentin	900–2,400 mg/d	Start with 300 mg at night, then add 300 mg at night, then a separate dose of 300 mg in the morning (start 100 mg if concerned about sensitivity)
Pregabalin	150–300 mg/d	

Abbreviations: *SNRIs* serotonin-norepinephrine reuptake inhibitors, *SSRIs* selective serotonin reuptake inhibitors

as exercise, yoga, cooling, and avoidance of triggers that may provoke vasomotor symptoms (spicy foods, alcohol, hot foods, or liquids) are reasonable and may be beneficial to overall health, there is good evidence that they are unlikely to alleviate quality of life. Herb and supplements, black cohosh, evening primrose oil, omega-3s, ginseng, vitamins, among other over-the-counter products, should not be recommended until higher-quality trials are performed that demonstrate their efficacy.

Case (Continued)
Prior to making a final decision about treating her vasomotor symptoms, Ann wishes to learn more about treatment for vaginal dryness and sexual discomfort.

Genitourinary Syndrome of Menopause (GSM)

The lack of estrogen following menopause directly impacts the urogenital and vulvovaginal tissues. Estrogen receptors are highly concentrated in the urogenital tract along the bladder trigone, the vulvar, and vaginal tissues. The loss of estrogen then results in numerous physical changes to these tissues: decreased collagen, elastic and vascular flow, and increased alkalization of the vagina. The decreased estrogenic state results in thinning, inflammation, keratinization, and atrophy for the vulvovaginal tissue [23].

As the vaginal pH becomes more basic causing shifts in the vaginal flora, the risk for vaginal infections increases. The vulvovaginal tissue becomes less flexible and elastic. The labia minora and vaginal epithelium become thin and the vaginal rugae

Table 1.6 Genitourinary syndrome of menopause: symptoms and signs

Symptoms
Vulvar pain, burning, or itching
Vaginal dryness or discharge
Dyspareunia
Spotting or bleeding after intercourse
Urinary pain or discomfort, frequency, urgency, or recurrent infections
Signs, external genitalia
Decreased labial size
Loss of vulvar fat pads
Vulvar fissures
Receded or phimotic clitoris
Prominent urethra with mucosal eversion or prolapse
Signs, vagina
Introital narrowing
Loss of elasticity with constriction
Thin vaginal epithelial lining
Loss of mature squamous epithelium
Pale or erythematous appearance
Petechiae, ulcerations, or tears
Alkaline pH (>5.5)
Infection (yellow or greenish discharge)

Source: Adapted from Ref. [28]

diminish. The introital tissues retract leading to a more prominent urethra meatus, which is subject to increased irritation and trauma. Acute and recurrent urinary tract infections (UTIs) may become more prevalent [24].

Collectively, these changes (Table 1.6) are termed the genitourinary syndrome of menopause (GSM) and are experienced by as many as 50% of menopausal women [24–26].

Women may report vaginal dryness, burning, itching, and irritation; and urinary frequency, urgency, and dysuria. Patients may experience these symptoms in the absence of sexual activity; those who are sexually active may experience dyspareunia and postcoital bleeding due to decreased lubrication of the vagina and vulvar tissues. Many women report that these symptoms affect their quality of life. Despite the impact and prevalence of vulvovaginal symptoms, the GSM is often underdiagnosed and undertreated by many health care providers. Less than 5% of menopausal patients recognize these symptoms as being related to menopause [27].

Treatments for Sexual Dysfunction Related to Genitourinary Syndrome of Menopause

Unlike vasomotor symptoms, GSM symptoms are chronic and progressive and do not improve over time unless they are treated, and will only get worse if not treated. First-line treatment for mild GSM includes *vaginal moisturizers and lubricants* (Table 1.7). Moisturizers do not cure atrophic conditions; however, using them two to three times weekly can provide temporary relief by reducing pain, itching, and

Table 1.7 Commonly recommended lubricants and moisturizers

Lubricants
Water based
Astroglide Liquid, Astroglide Gel, Liquid Astroglide
Just Like Me, K-Y Jelly, Pre-Seed, Slippery Stuff, Liquid Silk
Silicone based
Astroglide X, ID Millennium, K-Y Intrigue Pink, Pjur, Eros
Moisturizers
Replens, Me Again, Vagisil, Feminease, K-Y SILK-E, Luvena, Sliken Secret

Table 1.8 Nonpharmacologic therapies for GSM management

Education and normalization
Lubricants
Moisturizers
Painless stimulation or sexual activity
Vaginal dilators
Pelvic floor physical therapy
Psychotherapy/behavior counseling and/or sex therapy

irritation [24]. Moisturizers containing hyaluronic acid have been found to normalize vaginal pH, reduce itching, dryness, dyspareunia, and improve symptoms of vaginal atrophy equivalent to local estrogen in some studies [29].

The options for over-the-counter lubricants and moisturizers are endless, though not all are created equally.

Many water-based lubricants have been found to be hyperosmolar with the potential to cause more damage to fragile vaginal tissue. The World Health Organization recommends lubricants not exceeding 380 mOsm/kg, though a maximum of 1200 mOSm/kg is acceptable. Recommended iso-osmolar products that fall within the pH range of a healthy vagina, 3.8–4.5, or those that are silicone based are ideal to prevent further tissue damage and recurrent UTIs, yeast infections, and bacterial vaginosis. Patients should avoid products containing flavors, warming properties, parabens, glycerin, and spermicides because they too may further irritate the vaginal and vulvar tissues. Natural oils (e.g., olive, coconut) may promote vaginal infections.

Vaginal dilators and pelvic floor physical therapy may be utilized to improve and maintain vaginal patency and caliber for women who experience vaginismus associated with decreased elasticity of the introitus and pelvic floor hypertonicity that may result in dyspareunia. (See also Chapter 12). A list of nonpharmacologic therapies for GSM management is provided in Table 1.8.

There are a number of pharmacologic treatment options for treating GSM (Table 1.9).

Low-dose vaginal estrogen is the most effective local treatment for GSM and is the preferred treatment option for sexual dysfunction related to genitourinary

Table 1.9 Pharmacologic treatments for GSM

Treatment	Product name(s)	Initial dose	Maintenance dose
Vaginal products			
Creams			
17β-estradiol	Estrace Vaginal Cream	0.5–1 gm/d for 2 wk	0.5–1 gm/d × 1–3 per wk
Conjugated estrogens	Premarin Vaginal Cream	0.5–1 gm/d for 2 wk	0.5–1 gm 1–3 per wk
Vaginal ring			
17β-estradiol vaginal ring	Estring	2 mg releases 7.5 μg/d for 90 days	Change q 90d
Vaginal inserts			
Estradiol hemihydrate vaginal tablet	Vagifem, Yuvafem, generic	10 μg insert 1/d × 2 wk	1 tablet twice per wk
17β-estradiol soft gel ovule	Imvexxy	4 or 10 μg 1/d × 2 wk, followed by 1 ovule twice weekly	1 gel ovule twice per wk
Prasterone (DHEA)	Intrarosa	6.5 mg insert 1/d (DHEA)	6.5 mg insert 1/d
Vulvar products			
Lidocaine	4% Aqueous lidocaine	Applied to vestibule before sexual activity	
Oral products			
Ospemifene	Osphena	60 mg/d orally	60 mg/d orally

symptoms of menopause. Estrogen is important for the maintenance and functioning of the vaginal epithelium, thickens the basalis layer, and plays an important role in vasodilation to increase vaginal, clitoral, and urethral blood flow [30].

Improvement in the vulvar and vaginal tissue may be seen within 6–8 weeks. Prior to the use of estrogen, a physical exam should be performed to confirm a hypoestrogenic state and to rule out other pathologies. Local vaginal estrogen is available in many forms: cream, tablet, soft gel ovule, vaginal ring. Most have similar efficacy; thus, patient preference, cost, and ease of administration should be discussed with patients when choosing a method.

Progesterone is not generally indicated for endometrial protection with the use of local estrogen, though safety data for >1 year are not available [16]. Long-term follow-up data are not available to provide guidance about the optimal duration of use of vaginal estrogen, especially in those women who are breast cancer survivors. Low-dose vaginal estrogen use for 1–18 years did not appear to be associated with changes in breast density or Bi-RADS breast cancer risk scores in a small cohort of women, which included three breast cancer survivors [31].

For women who simultaneously experience systemic vasomotor symptoms and GSM and vasomotor symptoms, *low-dose transdermal estradiol* has demonstrable benefit in increasing frequency of sexual activity, sexual fantasies, and degree of enjoyment, and causing decrease in pain during intercourse. However, arousal and orgasm were not enhanced by transdermal estradiol treatment [32].

Ospemifene is a selective estrogen receptor modulator (SERM) that has demonstrated statistical and clinical improvements in the vaginal maturation index, vaginal

pH, and subjective vaginal dryness up to 1 year. With agonistic function at the genital tract and antagonistic properties on the breast and endometrial tissue, it has favorable effects on breast tissue and the endometrium, making it a safe option for current breast cancer patients or survivors or those in whom using an estrogen product is not ideal or desired. Clinical evidence shows decrease in palpable and abnormal mammographic findings, and the endometrium remains atrophic after 1 year of use [33].

In a review of preclinical and clinical studies, there were no reported cases of endometrial or breast cancer with ospemiphene use [34].

Ospemifene is dosed orally, 60 mg daily, and is a good option for those who cannot or prefer not to use a vaginal product. Patients may require a 6-month trial before noticing an improvement in dyspareunia. Ospemifene should be avoided in patients with undiagnosed vaginal bleeding, estrogen-dependent neoplasia, and inpatients with venous or arterial thromboembolic disease.

Intravaginal dehydroepiandrosterone (DHEA), *prasterone*, is FDA-approved for treatment of moderate to severe dyspareunia associated with GSM. Prasterone binds to both estrogen and androgen receptors and is aromatized to estrone and estradiol. Daily use is associated with clinically and statistically proven benefits in the vaginal maturation index, vaginal pH, vaginal dryness, and dyspareunia. While estrogen therapy is effective in the superficial mucosal layer, DHEA improves all three layers of the vaginal epithelium, improving the density of collagen fibers in the intermediate layer and stimulating the muscular third layer. Maximal benefits are seen after 2 weeks of daily dosing.

Currently, *no hormonal formulation has been FDA-approved for use in women with a history of hormone receptor positive breast cancer*. Nonhormonal therapy is first-line therapy for GSM symptoms in estrogen-sensitive breast and gynecologic cancer survivors. Prasterone, an estrogen precursor, has not yet been studied with breast cancer population. Use of vaginal estrogen or prasterone is considered off label and should be used with caution in estrogen- sensitive cancer survivors. The American Society of Clinical Oncology (ASCO) Sexual Health Guideline advises that clinicians may offer prasterone for women with a current or history of breast cancer who are on aromatase inhibitors and have not responded to previous treatment [35].

Use of estrogen and other hormone therapy in this population requires shared decision-making. Treatment should focus on the lowest effective dose for the least amount of time to enable function and alleviate symptoms [36]. The patient's oncology team should be consulted prior to initiating hormone therapy. Ospemifene use in breast cancer survivors is considered off label. While initial studies show promise in using CO_2 laser therapy therapy to improve GSM symptoms, the FDA has issued a warning against its use for these symptoms until further studies are conducted.

Numerous effective pharmacologic and nonpharmacologic options are available to treat both menopausal vasomotor and genitourinary symptoms for older women.

These include hormonal and nonhormonal treatment options. Shared decision-making and individualization are important to address the menopausal concerns of older women.

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