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ORIGINAL ARTICLE – BREAST ONCOLOGY

Endocrine Therapy for Surgeons: Practical Pearls for Managing Menopausal, Bone Loss and Sexual Adverse Effects

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ABSTRACT Breast cancer patients are living longer than ever before and as such the population of breast cancer survivors continues to grow. Approximately 80% of breast cancers are hormone receptor-positive (HR+) and most patients will receive neoadjuvant or adjuvant estrogen blockade, referred to as endocrine therapy. Although endocrine therapy reduces HR+ breast cancer recurrence by 30–50%, significant adverse effects pose a threat to treatment adherence. These adverse effects include vasomotor symptoms, colloquially referred to as hot flashes, bone loss, joint arthralgias, genitourinary syndrome of menopause (GSM), previously referred to as vaginal atrophy, and low libido. This review will present the evidence-based treatments available for each of these adverse effects, including clear treatment algorithms for GSM, which is often experienced by patients but overlooked by providers. The most important takeaway is to ask open-ended questions, encourage reporting of these symptoms, and refer patients to specialty providers as needed. Surgeons may be the first to encounter these symptoms, therefore it is critical to remain informed of the treatment options.

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With the advent of modern targeted therapies, breast cancer patients are living longer than before and the population of survivors continues to grow. Approximately 80% of breast cancers are hormone receptor-positive (HR+) and these patients will receive neoadjuvant or adjuvant estrogen blockade, referred to as endocrine therapy. Endocrine therapy includes tamoxifen, a selective estrogen receptor modulator (SERM), a competitive inhibitor of estrogen to its intracellular receptor, or aromatase inhibitors (Ais), which inhibit aromatase, the enzyme responsible for the peripheral conversion of androstenedione to estrone. For patients with non-metastatic HR+ breast cancer, the addition of appropriate adjuvant endocrine therapy, including tamoxifen and AIs, with or without ovarian function suppression in premenopausal women, affords a significant improvement in disease-free and overall survival.[1] For example, among low-risk HR+ breast cancer patients treated with tamoxifen, the 25-year distant recurrence-free interval is about 90%, emphasizing the longevity of survivors who will be taking endocrine therapy, and therefore facing significant, potentially life-altering adverse effects.[2]

Despite the improvements in disease-free and overall survival with the addition of adjuvant endocrine therapy, adherence to treatment outside of a clinical trial setting is as low as 66%,[3] and adherence is lowest among those who experience the most adverse effects.[4] Preparatory counseling

at the time of endocrine therapy prescription by the provider, along with proactive management of treatment sequelae when they arise, has the potential to improve treatment adherence, thereby optimizing oncologic outcome.

Both SERMs and Ais may lead to menopausal symptoms, including hot flashes, genitourinary syndrome of menopause (GSM), and sexual dysfunction. Both drugs also impact bone turnover through distinct mechanisms. Identifying and addressing the adverse effects of treatment is a critical component of survivorship. In the adjuvant setting, the surgeon may be the 'first responder' to a patient's concerns; indeed, the first step to treat sexual adverse effects is detecting the problem. Surgeons should therefore be equipped to elicit symptoms by trying the following steps: releasing any and all assumptions about the patient's sexual relationships, using inclusive language, normalizing the topic, asking open-ended questions and validating concerns. The surgeon should also be able to offer simple evidence-based mitigation strategies and appropriate referrals. Here, we summarize the prevention, detection, and management of common adverse effects of endocrine therapy for surgeons, who can improve a patient's treatment adherence and quality of life by tackling these issues head-on.

VASOMOTOR SYMPTOMS

Vasomotor symptoms, also known as hot flashes, are an adverse effect of estrogen deprivation affecting 35–40% of women receiving endocrine therapy.[5] Caused by a disruption in the hypothalamic perception of core body temperature leading to vasodilation, vasomotor symptoms can manifest as intense episodes of heat with perspiration and flushing, or as clamminess, anxiety, or episodes of palpitations. Vasomotor symptoms can also lead to chronic sleep disruption.[6]

Non-pharmacologic interventions for vasomotor symptoms include behavioral modifications such as exercise, avoiding triggers, and dressing in layers. Cognitive behavioral therapy, psychological treatment focused on changing thinking and behavior patterns, is effective in randomized controlled trials,[7] and acupuncture, real or sham, is also more effective at decreasing hot flash frequency and severity than no treatment.[8]

Many non-hormonal pharmacologic options are efficacious, but the choice of appropriate agent should take into account the adverse effect profile (Table 1). Clonidine, an alpha-agonist, and gabapentin, an antiepileptic medication, are centrally acting therapies shown to improve vasomotor symptoms,[9] although gabapentin may only be effective at large daily doses (300 mg three times daily or 900 mg/day).[10] Randomized trial data support the use of selective serotonin and serotonin-norepinephrine reuptake inhibitors for the treatment of hot flashes in otherwise healthy, non-depressed women.[11–15] Another effective non-hormonal option is oxybutynin, found to be effective at 2.5 and 5 mg twice daily and generally well-tolerated.[16] To date, cumulative evidence does not support the use of soy supplements, black cohosh, evening primrose oil, flaxseed, or ginseng for vasomotor symptoms.[15] Fezolinetant, a selective reversible neurokinin 3 receptor antagonist that slows GnRH pulse frequency, shows clinical promise for the treatment of VMS and is under investigation for approval by the US FDA.[17]

BONE HEALTH AND ARTHRALGIAS

Bone Health

Estrogen deficiency from menopause causes increased bone resorption, leading to a loss of bone density.[23] The exact mechanisms by which estrogen inhibits bone resorption are not fully elucidated, although some evidence suggests estrogen inhibits osteoclast function, osteoclasts being the cells responsible for breaking down bone, via effects on growth factors and cytokines.[23] Similarly, endocrine therapy for breast cancer treatment impacts bone health, and the mechanism differs based on the therapy and the patient's menopausal status.

In premenopausal patients, tamoxifen functions as an estrogen antagonist in a high estrogen environment and therefore results in a bone density loss of 2% per year. For those on ovarian function suppression with AI, bone density loss may be as high as 11%.[24–28] For both premenopausal patients whose ovaries are suppressed and postmenopausal patients, AI receipt leads to estrogen deficiency, which is associated with bone density loss through bone turnover as noted above, and increased risk of fracture, which is higher if treatment continues past 5 years.[29] In the postmenopausal population, endocrine therapy-related bone loss also appears to be greater in those receiving AI when compared with tamoxifen, which acts as an estrogen agonist in estrogen-low environments, and thus may improve or stabilize bone mineral density.[30]

Monitoring bone health and addressing treatment-related bone density changes can decrease the risk of osteoporotic fracture. For patients starting an AI, appropriate counseling on the risk of bone density loss, an assessment of osteoporosis risk factors, and a baseline bone density scan (dual x-ray absorptiometry [DEXA]) is standard, as well as closer monitoring with repeat testing approximately every 2 years (Fig. 1).[31] In addition to monitoring bone mineral density when indicated, non-pharmacological interventions include weight-bearing exercise and appropriate vitamin D and calcium supplementation.[32,33]

Pharmacologic treatments for osteoporosis can decrease the risk of bone loss and subsequent fracture. Bisphosphonates, which are available in intravenous and oral formulations, are the most common osteoporosis

TABLE 1 Behavioral and pharmacologic therapies for vasomotor symptoms (all drugs listed are oral formulations)

	Mechanism	Evidence	Dosing	Adverse effect profile
Cognitive behavioral therapy[7]	Psychoeducation, paced breathing, and relaxation	46% reduction in hot flush rating scale	90 min session every week for 6 weeks	None reported
Acupuncture[8]	11 acupuncture points: bilateral KI-3, SP-6, BL-23, HT-6, and KI-7, midline CV-4	40% reduction in hot flash frequency	Twice weekly for 8 consecutive weeks	None reported
Clonidine[9]	Centrally acting alpha-agonist	37% reduction in hot flash frequency at 4 weeks	0.1 mg/day QHS	Sleep disruption, dry mouth, constipation, sedation, elevation in blood pressure with abrupt cessation Caution in patients treated for hypertension (specifically MAOIs), or with symptomatic hypotension
Gabapentin[10]	Antiepileptic calcium channel modulator that augments neurotransmitter release	Only effective with larger cumulative doses (900 mg/day)	300 mg TID (total 900 mg daily dose)	Dizziness, sedation, loss of balance, peripheral edema
SSRIs[14]: Citalopram Escitalopram Paroxetine	SSRI, contraindicated with tamoxifen use (inhibitor of CYP2D6)	Reduction in hot flash frequency and severity varies from 27 to 61% [15]	CItalopram 20 mg/day Escitalopram 10 mg/day Paroxetine 7.5 mg/day (only FDA-approved non-hormonal therapy) Paroxetine ER 12.5 mg/day [18] Paroxetine ER 25 mg/day [18]	Nausea, fatigue, drowsiness, blood pressure increases Interaction with tamoxifen
SNRIs: Desvenlafaxine[19,20] Venlafaxine[21,22]	Selective serotonin and norepinephrine reuptake inhibitor, a weak inhibitor of CYP2D6 (little effect on plasma endoxifen)	Desvenlafaxine: Reduces hot flash frequency by 6.5 by week 4 [20] Venlafaxine 37.5 mg: 42% reduction in hot flash scores during weeks 1–4 [22] Venlafaxine 75 mg: 60% reduction in frequency after 4 weeks [21]	Desvenlafaxine 100 mg/day Venlafaxine 37.5 mg QD PO Venlafaxine 75 mg QD PO	Nausea, constipation, safer to use with tamoxifen than SSRIs
Oxybutynin[16]	Competitive acetylcholine antagonist, blocks muscarinic effect of acetylcholine peripherally	2.5 mg BID: 60% reduction in HF frequency 5 mg BID: 77% reduction in HF frequency	2.5 or 5 mg BID 5 mg ER QHS	Anticholinergic symptoms, dry mouth most common ER formulation may have a better adverse effect profile

CYP cytochrome P450, *MAOIs* monoamine oxidase inhibitors, *SSRIs* selective serotonin reuptake inhibitors, *SNRIs* serotonin-norepinephrine reuptake inhibitor, *BID* twice daily, *TID* three times daily, *ER* extended release, *QHS* at night, *QD* every day, *PO* oral, *HF* hot flashes

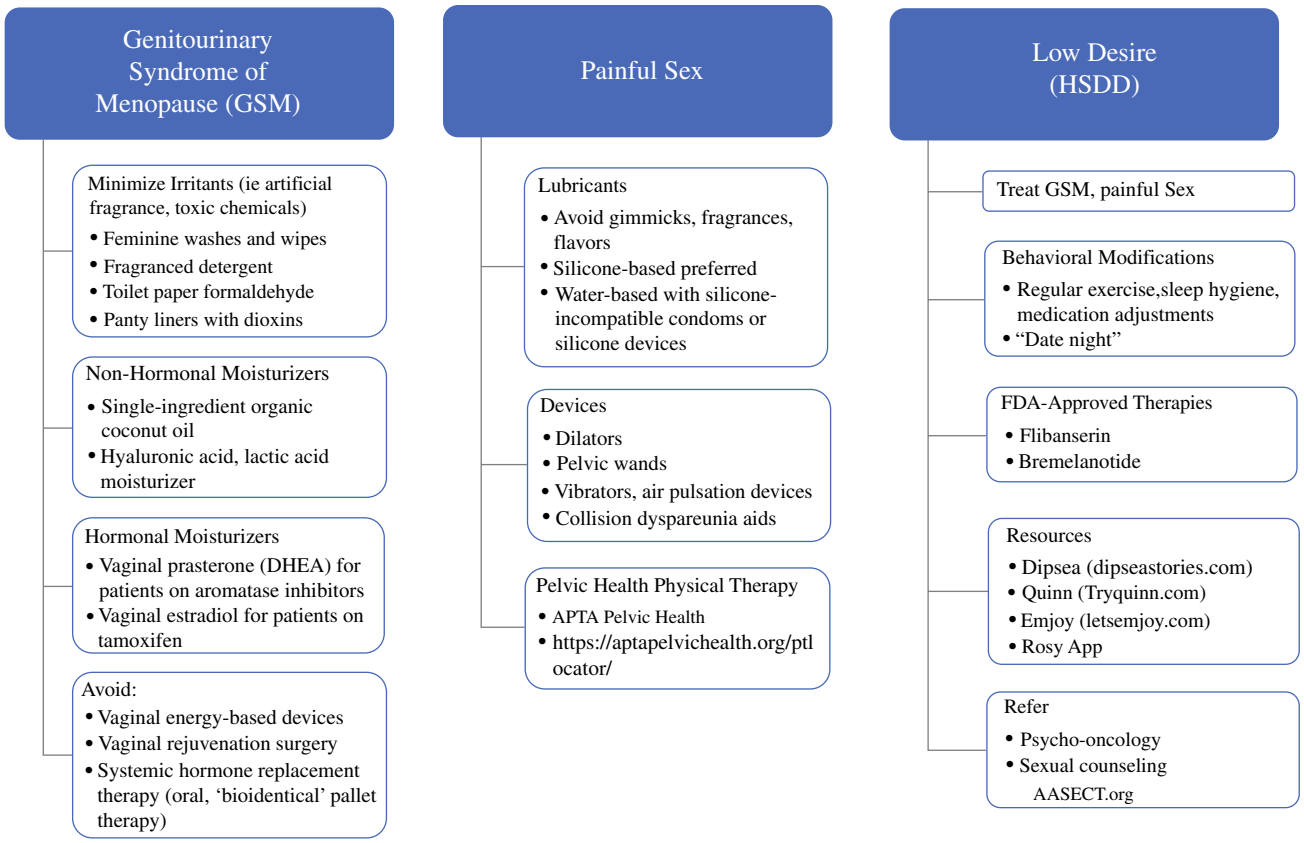

FIG. 1 Simple schema for the prevention, detection, and treatment of bone loss. In this schema, DEXA frequency applies to patients taking aromatase inhibitors, not tamoxifen. *DEXA* dual x-ray absorptiometry, *HSDD* hypoactive sexual desire disorder, *GSM* genitourinary syndrome of menopause, *DHEA* dehydroepiandrosterone

medications and principally work by inhibiting the resorption of bone by osteoclasts.[32] The National Comprehensive Cancer Network (NCCN) recommends considering the addition of adjuvant bisphosphonate therapy in postmenopausal patients (natural or induced) who are at an elevated risk of recurrence and are receiving adjuvant endocrine therapy. Specifically, zoledronic acid appears to decrease the risk of bone recurrence and breast cancer-specific mortality, but, of note, these findings were not statistically significant in premenopausal women.[34]

Another commonly utilized antiresorptive medication is denosumab, a monoclonal antibody that binds the cytokine RANKL (receptor activator of NFκB ligand), thereby blocking the activity of osteoclasts resulting in reduced bone resorption.[32] Denosumab reduces the risk of clinical fractures in postmenopausal patients receiving AIs, although the data are mixed with regard to its potential anticancer effect[31,35]

Arthralgias

Musculoskeletal symptoms, including arthralgias and myalgias, impact as many as one-third of patients being treated with AIs, the underlying mechanisms of which are largely unknown. In a prospective study of 100 women initiating AI therapy, the median time to musculoskeletal symptom onset was 1.6 months (range 0.4–10). These symptoms met the criteria for rheumatology referral in about 45% of enrolled women and led to discontinuation of the AI in about 10%.[36]

One of the most effective treatments of AI-related joint arthralgias is acupuncture. In a prospective multi-institution clinical trial, 226 postmenopausal or premenopausal women treated with gonadotropin-releasing hormone agonists were randomized to true acupuncture administered twice weekly for 6 weeks, followed by weekly for 6 weeks, versus sham acupuncture versus waitlist control. After 6 weeks, the

patients who underwent true acupuncture reported significantly less pain than those treated with sham acupuncture or waitlisted.[37]

An alternate treatment option for arthralgias includes duloxetine, which significantly reduced average joint pain scores compared with placebo in a prospective, randomized, double-blinded, placebo-controlled clinical trial. Although statistically significant, joint pain was only reduced by 0.82 points at 12 weeks and there were more adverse events in the duloxetine group (78%) than the placebo group (50%).[38] Although never compared head-to-head, in a choice between acupuncture and duloxetine most would recommend acupuncture as it led to a greater absolute pain score reduction. Lastly, nonsteroidal anti-inflammatory drugs, acetaminophen, omega-3 fatty acids, a mixture of aerobic and weight-bearing exercise, and yoga have all been proven at least somewhat effective in musculoskeletal symptom management.[39]

GENITOURINARY SYNDROME OF MENOPAUSE

Previously known as 'vaginal atrophy', the term genitourinary syndrome of menopause (GSM) encompasses a constellation of symptoms ranging from vaginal dryness and irritation to pelvic floor dysfunction, painful sex, and recurrent bladder infections. With estrogen deprivation, a loss of the superficial epithelial cells in the vulva and vagina (particularly the non-hair-bearing area) can become dry, thin, and less elastic, leading to tears, bleeding, and fissures. Furthermore, the vaginal pH alkalinizes, shifting the vaginal flora and increasing the risk of infection.[40] These vulvar and vaginal mucosal changes (irritation, sensitivity), and associated shortening or narrowing of the vestibule and vagina, impact the quality of life of both partnered and unpartnered women, and untreated adverse effects negatively impact endocrine therapy compliance. Therefore, patients should be informed about the potential sexual adverse effects of endocrine therapy and be given appropriate mitigation strategies at the time of prescription. Surveyed breast cancer patients reported that they desired information about potential disruptions in sexual function early and often through treatment.[41] As addressing these concerns may seem daunting for the busy surgeon, we have synthesized the available evidence and outline below four basic steps for the prevention and treatment of GSM: (1) eliminate irritants; (2) moisturize;

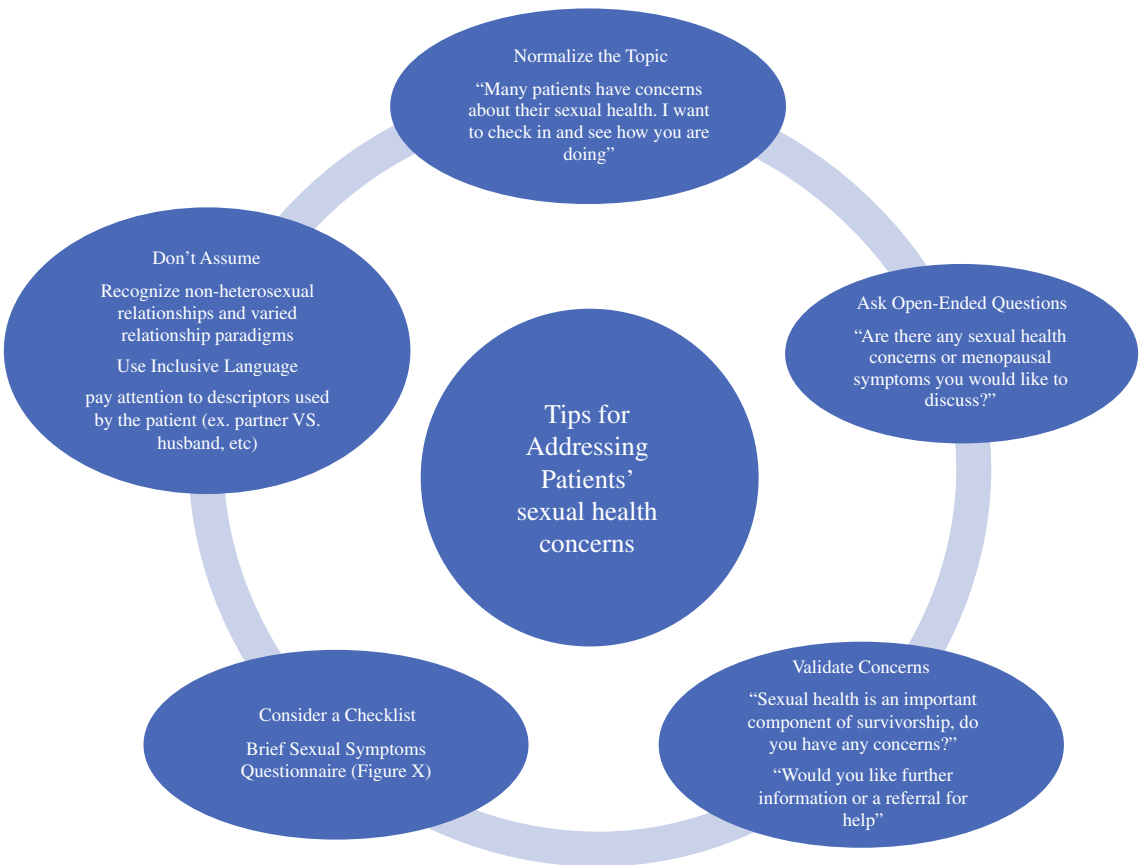

FIG. 2 Genitourinary syndrome of menopause, painful sex, and hypoactive sexual desire disorder treatment algorithms

(3) lubricate; and (4) address the pelvic floor/changes in anatomy (Fig. 2).

Eliminate Irritants

Vaginal dryness may progress to itching, burning, and stinging as a result of exposure of the delicate tissues of the vulva and vagina to irritants found in many over-the-counter feminine washes, alcohol-based wipes, or similar products. Patients should avoid products with potential offenders, including preservatives, parabens, petroleum, propylene glycol, glycerin, and artificial fragrances. Limiting the use of these products, avoiding intravaginal soap use, wearing cotton undergarments washed with fragrance-free detergent, and application of a bland emollient such as coconut oil can provide a barrier to the delicate skin to resolve irritation before moving on to a more 'high-tech' moisturizer regimen as explained below.

Moisturize

An explanation of the proper use of moisturizers (regular application) versus lubricants (PRN application with short-acting effect) can improve compliance with use and optimize symptom resolution. Both types of products have different properties and should be used in distinct ways. For patients with mild symptoms, single-ingredient organic coconut oil applied at least three times per week provides moisturization with natural antifungal and antimicrobial properties.[42–44] However, sexually active patients using condoms should be informed that some oil-based moisturizers may not be compatible with condoms. Once burning symptoms abate or with persistent symptoms, a moisturizer containing hyaluronic acid can be added, which is available in the form of creams, gels, or suppositories.

For patients with persistent symptoms after regular use of a non-hormonal moisturizer, the addition of a vaginal moisturizer with a hormone (either estrogen or androgen) can further reverse lactobacilli depletion, increase blood flow, improve mucosal thickness, and increase sexual response. Systemic hormone replacement therapy is not recommended for women with a history of breast cancer. Modern ultra-low-dose vaginal estrogen formulations (4 or 10 μg estradiol tablet, 1% estradiol cream) can be applied at less-frequent dosing schedules once or twice per week, or a 2 mg estradiol ring releasing 7.5 μg of estradiol per day can be changed every 90 days. The addition of vaginal estrogen after treatment for several weeks with a non-hormonal moisturizer may decrease the risk of systemic absorption by avoiding application of estrogen to thin, atrophic vaginal mucosa.

The use of vaginal estrogen for breast cancer patients, particularly those taking AIs, involves shared decision making with the patient and multidisciplinary collaboration. Overall, observational data have not shown an increased risk of breast cancer recurrence with the use of vaginal estrogen.[45–47] However, the controversy persists, as a 2022 Danish retrospective study reported a slightly higher risk of recurrence in a subset analysis of patients taking AIs (1.39, 95% confidence interval [CI] 1.04–1.85). The study findings are limited since many patients in the cohort treated between 1997 and 2004 did not receive contemporary standard adjuvant therapy (the study pre-dated HER2-targeted chemotherapy, and 37% were not taking endocrine therapy).[48]

Vaginal androgens are an attractive alternative to vaginal estrogen, with similar effects and less potential for systemic estradiol increases. Vaginal dehydroepiandrosterone (DHEA) is FDA-approved as a 6.5 mg vaginal prasterone tablet for treating painful sex. Topical application of DHEA works by *intracrinology*, converted to either testosterone or the more potent dihydrotestosterone (DHT) in the vulva and vagina, working locally to target androgen-specific pain receptors in the vulva and vagina before inactivation and elimination through the circulation.[49] The double-blind, randomized NCCTG-N10C Alliance trial found that patients taking AIs using an intravaginal preparation of DHEA did not have an increase in circulating estradiol, which may be related to the inhibition of peripheral aromatization of androstenedione to estrone.[50] In summary, vaginal estradiol or prasterone (DHEA) may be recommended to appropriately counseled patients with an incomplete response to non-hormonal therapies, according to a 2018 guideline summary published by the American Society of Clinical Oncology.[51]

Lubricate

Patients should be encouraged to choose their own lubricant for sexual activity or device use, and to avoid those with irritating ingredients listed above, flavors, glycerin, or any gimmicks such as warming properties. The optimal lubricant contains minimal irritants and minimizes friction and therefore postcoital spotting and vulvovaginal burning. For those not relying on condoms for pregnancy or infection protection, silicone-based lubricants are recommended due to longer duration of action. Water-based lubricants may be selected for patients using silicone non-compatible condoms or for use with some silicone sexual devices. Oil-based lubricants may also degrade latex condoms and certain devices.

Address the Pelvic Floor and Changes in Anatomy

Prolonged estrogen deprivation combined with a treatment-related hiatus in sexual activity may lead to changes in the width and length of the vagina, making the resumption of sexual activity painful, and for some, impossible. For patients with pelvic floor muscle dysfunction, including levator spasm and shortening or narrowing of the vagina

(stenosis), the addition of vaginal dilator therapy, particularly when combined with a hormonal moisturizer, can promote collagen remodeling and improve elasticity. Dilators may also function as a tool providing biofeedback during pelvic floor relaxation and stretching exercises. Established practice guidelines recommend placing the dilator in the vagina with a lubricant three times per week for at least 10 min.[52]

Sexual devices can be recommended as tools for increasing genitourinary blood flow (vibrators and air pulsation devices), vaginal dilation, pelvic floor relaxation, and biofeedback. Patients should be recommended devices only made with nonporous materials.[53] For patients with persistent deep dyspareunia with sexual activity, stackable silicone rings function as a collision dyspareunia device and can limit the depth of penetration (Ohnut.co). Pelvic floor muscle training (PFMT) provided by a specially-trained physical therapist may include an external and internal pelvic floor muscle assessment and utilize therapeutic exercise, manual therapy, dilator work, and biofeedback. PFMT can be a helpful adjunct for patients with painful sex, voiding dysfunction, and urinary incontinence, and has been shown to reduce symptoms of GSM and improve sexual function.[54]

Non-FDA-Approved Therapies: 'Bioidentical' Compounded Hormones and Energy-Based Vaginal Devices

The perception of limited treatment options to treat female sexual dysfunction has fostered an environment in which patients may seek alternative therapies. Compounded hormonal therapies containing combinations of estrogens, progesterone or synthetic progestins, and androgens, are advertised as 'bioidentical', which is a strategic marketing term. The term bioidentical encompasses both FDA-approved (estradiol) and compounded therapies, which are not FDA-approved. Compounded 'bioidentical' hormone formulations lack FDA oversight and there is no evidence they are safer than their FDA-approved counterparts. Compounded formulations can be prescribed in a variety of delivery vehicles, including pelleted hormone therapy, which involves the insertion of hormone pellets just under the skin, typically at the hip. In light of this increasing use of pelleted hormone therapy, in 2021, Jiang et al. compared a population of postmenopausal women receiving either pelleted therapy or FDA-approved formulations. They reported that adverse effects were higher among those receiving pelleted therapy and more than half of those with a uterus reported abnormal uterine bleeding. Notably, many women receiving pelleted therapy were found to have supraphysiologic levels of estradiol and/or testosterone. Mean peak estradiol levels were four times greater and mean peak testosterone levels were more than ten times greater in the pelleted group.[55] As FDA-approved hormonal formulations are sold with package inserts with detailed instructions and trial evidence of safety and efficacy, those who are recommended compounded therapies should be provided written warning of potential adverse effects, clearly stating that the formulation is not government-approved. Furthermore, the financial disclosures of prescribers, pharmacists, and pharmacies should be disclosed in this setting.[56]

Internal laser devices promising 'vaginal rejuvenation' advertise to treat a broad range of gynecologic conditions ranging from urinary incontinence and pelvic organ prolapse, to GSM and dyspareunia. One of the most popular CO2-based vaginal laser devices was cleared by the FDA in 2014 for "use in general plastic surgery and dermatology." However, the process under which these devices receive 'clearance', called 501(k), is not an 'approval', but a mechanism for manufacturers to register their devices. Notably, the FDA has not had to examine whether this technology, when used in the vagina, is either safe or effective. Treatment with CO2 vaginal lasers was not shown to be more effective than placebo for the treatment of GSM in two sham-controlled prospective trials that included either postmenopausal patients[57] or those taking AIs.[58]

Along with a lack of high-quality data showing effectiveness, there are also concerns regarding safety. Since 2018, the FDA has warned at least seven manufacturers against deceptive marketing tactics stating "these products have serious risks and don't have adequate evidence to support their use for these purposes. We are deeply concerned women are being harmed.".[59] Victims of harm from energy-based vaginal treatments are encouraged to report their experience to the FDA's Manufacturer and User Facility Device Experience (MAUDE) online database.[60]

Low Desire

Among female cancer survivors with sexual dysfunction, 36% report low desire as their most significant concern.[61] Treating dyspareunia, if present, is the first step to addressing low desire, also known as hypoactive sexual desire disorder (HSDD). Additional behavioral modifications include regular exercise, sleep hygiene (no screens in bed), and scheduled 'date night'. Patients may be referred to the American Association of Sexuality Educators, Counselors, and Therapists' (AASECT) website where a provider can be located using a zip code search function. Additional helpful online resources include audio erotica (Dispeastories.com, tryquinn.com), HSDD-focused mindfulness exercises (letsemjoy.com), and a patient-facing app of educational videos (Rosy App).

There are two FDA-approved therapies for premenopausal patients experiencing treatment-related HSDD. Flibanserin is a centrally acting serotonin receptor agonist taken once

daily that has been shown to increase the number of satisfying sexual encounters per month. A common adverse effect is sedation, and patients are advised to limit their alcohol intake by discontinuing drinking at least 2 h prior or to skip their dose that evening.[62] Both tamoxifen and flibanserin are metabolized by cytochrome P450 (CYP) 3A4 and therefore caution is advised with their concomitant use, although this subject is currently being investigated (ClinicalTrials.gov NCT03707340). Bremelanotide is a subcutaneous PRN injection that functions as a melanocortin receptor agonist, administered at least 45 min prior to sexual activity. Studies have reported an improvement in desire, arousal, and decreased sexual-related distress with its administration, although 40% of patients reported nausea in two randomized trials.[63,64]

A. Are you satisfied with your sexual function? Yes No
if no, please continue: _____

B. The problem(s) with your sexual function is: (mark one or all)
1. Problem with little or no interest in sex
2. Problem with decreased genital sensation (feeling)
3. Problem with decreased vaginal lubrication (dryness)
4. Problem reaching orgasm
5. Problem with pain during sex
6. Other: _____

C. Which problem is most bothersome? (circle 1 2 3 4 5 6)

D. Would you like to talk about it with your doctor? Yes No

FIG. 4 Brief sexual symptoms checklist (adapted from Latif et al. [65]).

CONCLUSIONS

Surgeons frequently prescribe endocrine therapy for the treatment of HR+ breast cancer, either in the prevention, neoadjuvant, or adjuvant setting. If not the prescriber, surgeons still have the opportunity to elicit patients' endocrine therapy adverse effects which, if left untreated, can lead to significant issues with non-adherence. For the treatment of vasomotor symptoms, cognitive behavioral therapy, acupuncture, and many non-hormonal pharmacologic treatment options are effective. One should take the adverse effect profiles into account when choosing the appropriate pharmacologic agent. For the treatment of bone loss, bisphosphonates are most common, with zoledronic acid as the typical treatment of choice because it also reduces the incidence of bone metastases, especially in postmenopausal patients. Arthralgias are most improved with acupuncture, although over-the-counter pain medications and duloxetine may also be helpful. The treatment of genitourinary symptoms of menopause includes the following steps: avoid irritants, moisturize, lubricate with intercourse, address pelvic floor dysfunction with pelvic floor physiotherapy, and avoid non-FDA regulated 'bioidenticals' and vaginal rejuvenation devices. Lastly, the treatment of HSDD includes addressing the aforementioned physical concerns, behavioral modifications, and two FDA-approved medications—flibanserin and bremelanotide. The most important first step to treat the sexual adverse effects of endocrine therapy is detection—we must address these issues head-on. The following simple steps can be taken to broach the topic: do not assume anything about patients' sexual relationships and use inclusive language, normalize the topic, ask open-ended questions, and validate concerns (Figs. 3, 4). Surgeons may be able to start the conversation addressing endocrine therapy adverse effects, introduce initial treatment strategies, refer to the appropriate specialist, and eventually make a significant impact on improving endocrine therapy adherence.

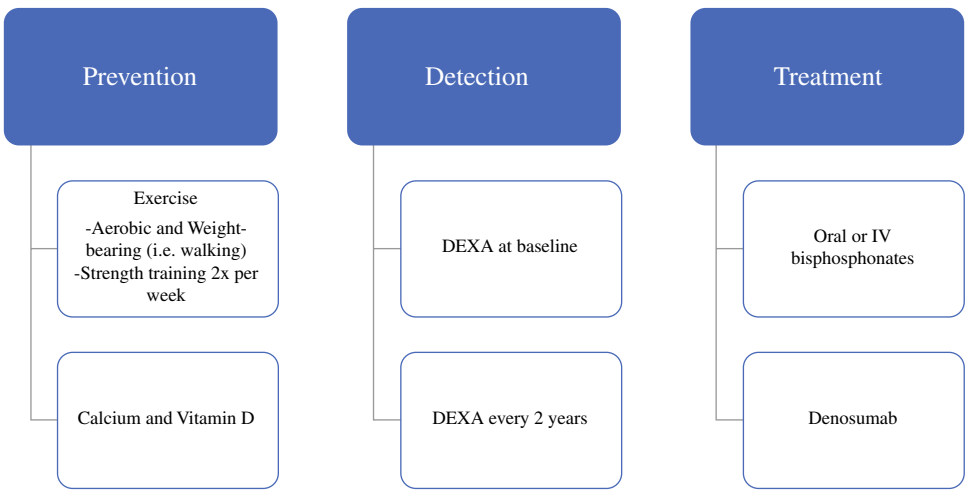

FIG. 3 Tips for addressing patients' sexual health concerns. *DEXA* dual x-ray absorptiometry, *IV* intravenous

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