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A clinical guide to the management of genitourinary symptoms in breast cancer survivors on endocrine therapy

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***Abstract*:** There is increasing attention and concern about managing the adverse effects of adjuvant endocrine therapy for women with early breast cancer as the side effects of therapy influence compliance and can impair quality of life (QoL). Most side effects associated with tamoxifen (TAM) and aromatase inhibitors (AIs) are directly related to estrogen deprivation, and the symptoms are similar to those experienced during natural menopause but appear to be more severe than that seen in the general population. Prolonged estrogen deprivation may lead to atrophy of the vulva, vagina, lower urinary tract and supporting pelvic structures, resulting in a range of genitourinary symptoms that can in turn lead to pain, discomfort, impairment of sexual function and negatively impact on multiple domains of QoL. The genitourinary side effects may be prevented, reduced and managed in most cases but this requires early recognition and appropriate treatment. We provide an overview of practical clinical approaches to understanding the pathophysiology and the management of genitourinary symptoms in postmenopausal women receiving adjuvant endocrine therapy for breast cancer.

Keywords: atrophy, breast cancer, endocrine therapy, estrogen, genitourinary symptoms, management, menopause, oncology

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Introduction

The majority of women with hormone receptor-positive early breast cancer will be offered adjuvant endocrine therapy, including tamoxifen (TAM) and aromatase inhibitors (AIs), for at least 5 years to reduce the risk of recurrence and death. Practice guidelines now recommend up to 10 years of endocrine therapy and this has significant implications for compliance with treatment and ensuring that the adverse effects of treatment are adequately managed [Burstein *et al.* 2014]. The side effects of adjuvant endocrine therapy are essentially due to estrogen deprivation.

The female genitourinary tract (vulva, vagina, lower urinary tract and supporting pelvic structures) is particularly sensitive to the effect of estrogen as these tissues are rich in estrogen receptors [Kelley, 2007]. Decline in estrogen concentrations may culminate in genitourinary atrophy, resulting in a variety of symptoms that are now collectively termed as genitourinary syndrome of menopause (GSM) [Portman and Gass, 2014]. This new terminology covers a range of symptoms including (but not limited to) vaginal dryness, burning, irritation, itching, frequency, urgency, dysuria, urinary incontinence (UI), recurrent urinary tract infections (UTIs) and pain during sexual intercourse. This in turn can complicate the process of sexual arousal and achievement of orgasm, thus, leading to sexual dysfunction [Burich and Degregorio, 2011].

There is increasing awareness of the prevalence of genitourinary side effects of endocrine therapy and their potential impact on sexual functioning [Chin *et al.* 2009; Baumgart *et al.* 2013; Baumgart *et al.* 2011; Schover *et al.* 2006; Donovan, 2012]. It has been reported that up to 50–75% of breast cancer survivors experience one or more genitourinary symptoms [Ganz *et al.* 1998; Trinkaus *et al.* 2008]. It is also evident that genitourinary

and sexual concerns are often overlooked or not fully addressed with patients in clinical practice [Hordern and Street, 2007]. Many women are reluctant to mention their concerns related to genitourinary atrophy and, unless specifically raised by clinicians, the topic is rarely discussed [Lester and Bernhard, 2009]. Many clinicians are uncertain about how to treat these symptoms in breast cancer survivors [Rippy and Marsden, 2006; Lester and Bernhard, 2009].

The genitourinary side effects of endocrine therapy can be prevented, reduced and managed in many women but this requires early recognition and appropriate treatment [Lu and Serrero, 2001; Vincent, 2015]. The primary goal of treatment of genitourinary symptoms is to improve or alleviate symptoms and to reverse the atrophic changes from estrogen deprivation [Kingsberg *et al.* 2009; Palacios *et al.* 2015]. Ideally, the optimal therapy for estrogen-deficiency symptoms is systemic or topical (e.g. vaginal) estrogen administration. However, estrogen may be contraindicated in women with a history of hormone receptor-positive breast cancer [Lu and Serrero, 2001] and currently, there are no safety data of vaginal estriol (a less potent estrogen which cannot be converted to estradiol and blocks but does not activate the estrogen receptor) in patients on AIs or TAM. As a result, patients and their clinicians are sometimes reluctant to use topical estrogens [Sinha and Ewies, 2013] and effective alternative approaches, with nonhormonal lubricants and moisturizers, are needed. The major disadvantage of nonhormonal agents is that they only partially or temporally relieve local symptoms and are not as effective as vaginal estrogen. This manuscript provides an overview of practical clinical approaches to understanding the pathophysiology and management of genitourinary symptoms in postmenopausal women receiving adjuvant endocrine therapy for breast cancer.

Lifestyle advice

As an initial approach, women experiencing bothersome genitourinary symptoms should be educated and counselled about simple lifestyle changes, which may improve and prevent the onset of new symptoms [Trinkaus *et al.* 2008]. For example, smoking cessation and weight control should be encouraged. Cigarette smoking is associated with a three-fold increase in risk of urgency and frequency [Tahtinen *et al.* 2011], and accelerated vulvovaginal atrophy (VVA) [Karamanidis *et al.* 2001], while weight loss of 5–10% of total body weight has been shown to improve UI [Altman *et al.* 2009]. For a sustained weight loss in midlife women, the North American Menopause Society (NAMS) and International Menopause Society (IMS) recommend a combination of reducing daily caloric intake by 400–600 Kcal, performing regular physical exercises, limiting total intake of fats and oils (olive oil consumption is encouraged) and increasing servings of fruits and vegetables/day [Shifren and Gass, 2014; de Villiers *et al.* 2013]. In addition to promoting a healthy lifestyle, regular sexual stimulation should also be encouraged as it can increase blood flow to the genital area, helping keep this tissue healthy (i.e. non-atrophic) [Goldstein and Alexander, 2005; Lester *et al.* 2015].

Control of underlying medical conditions

Women with a number of pre-existing comorbidities are more likely to develop UI, vaginal atrophy, and sexual dysfunction [North American Menopause Society, 2007]. Thus, optimal management of coexisting diabetes, obesity (body mass index > 30) and hypertension may also help to improve genitourinary and sexual health [Johnston *et al.* 2004; North American Menopause Society, 2007]. Furthermore, underlying depression and distress should be investigated and treated as it has been shown to improve both sexual functioning [Trinkaus *et al.* 2008] and quality of life (QoL) in breast cancer patients [Park *et al.* 2012]. If an antidepressant is prescribed, then clinicians should discuss potential adverse sexual side effects and drug-drug interactions [Dauchy *et al.* 2013]. There is evidence that some psychotropic medications, such as selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants, are associated with decreased libido [Reichenpfader *et al.* 2014], delayed orgasm [Montejo *et al.* 2001], continence and flow dysfunction [Pollack *et al.* 1992]. Furthermore, antidepressants that are strong CYP2D6 (cytochrome P450 2D6) inhibitors may decrease the efficacy of TAM and are relatively contraindicated [Sideras *et al.* 2010]. A treatment option that may be appropriate for TAM users is the SNRI venlafaxine, which increased libido in women with early breast cancer without interfering with the metabolism of TAM [Sideras *et al.* 2010]. Similarly, desvenlafaxine has been shown to have a low potential for drug interaction and may be another option in TAM users [Cusack *et al.* 2013]. Finally,

mirtazapine and agomelatine may also represent a treatment alternative in these population group, particularly given their minimal effect on sexual function [Kennedy and Eisfeld, 2007; Atmaca *et al.* 2011] and no appreciable inhibitory effect on CYP2D6 [Spina *et al.* 2012].

Nonhormonal treatment options

Several over-the-counter vaginal moisturizers, as well as water-, oil- and silicone-based precoital lubricants are widely used first-line nonhormonal therapies to alleviate symptoms such as vaginal dryness, dyspareunia, itching and burning [Lester *et al.* 2015], particularly for women with mild symptoms and those who want to avoid, or are concerned about local estrogens (i.e. the majority of breast cancer patients) [North American Menopause Society, 2013; Rahn *et al.* 2014; Lester *et al.* 2015]. Nevertheless, the evidence to support the efficacy of these formulations is limited (level II); recent findings suggested that silicone-based lubricants may be more effective than water-based to treat discomfort during sexual activity in postmenopausal women with breast cancer but both therapies were unlilkely to reduce sexually-related distress [Hickey *et al.* 2016]. Moreover, in a double-blind, crossover randomized controlled trial (RCT) assessing 45 breast cancer survivors with a history of vaginal complaints (dryness or itching), a polycarbophil-based vaginal moisturizer was no more effective than placebo in relieving vaginal dryness and dyspareunia [Loprinzi *et al.* 1997].

Clinicians treating breast cancer patients need to inquire about type and severity of their symptoms and the individual women's expectations of treatment. For example, if the most important concern for a woman is pain during intercourse, lubricants applied before and after sexual intimacy [Tan *et al.* 2012] may be recommended to promote temporary relief of friction-induced vaginal discomfort for the patient [Sinha and Ewies, 2013]. Lubricants and moisturizers may also be used effectively in combination. An intervention to improve genitourinary symptoms and related sexual issues used a combination of olive oil as a lubricant, pelvic floor muscle relaxation exercises and a vaginal moisturizer, reported improvements in dyspareunia and sexual function in women with breast cancer [Juraskova *et al.* 2013]. Additionally, use of vaginal moisturizers on a regular basis may promote hydration of the epithelium and consequently lubrication of the vaginal wall thus, providing more long-term (2–3 days) relief of symptoms such as itching, irritation and dyspareunia [van der Laak *et al.* 2002]. However, these therapies may not completely solve the problem, especially in women with severe symptoms. If nonhormonal methods failed in symptomatic survivors, short-term hormonal therapy may be considered, following appropriate counselling and assessment of risk-benefits [ACOG Committee on Practice Bulletins-Gynecology, 2012].

A randomized, double-blinded, placebo-controlled study investigated the effect of a vaginal pH-balanced gel (containing lactic acid) on vaginal symptoms and atrophy in breast cancer survivors [Lee *et al.* 2011]. Vaginal pH-balanced gel improved both vaginal dryness and dyspareunia, lowered vaginal pH and enhanced vaginal maturation index with minimal side effects (mild irritation during the first four weeks of therapy administration) [Lee *et al.* 2011]. These findings suggest that vaginal pH-balanced gel is an alternative option to alleviate vulvovaginal symptoms in symptomatic patients and can ultimately protect against vaginal colonization by nonvaginal microflora, which predispose women to vaginal infections and UTIs.

Finally, it is important to acknowledge that there are available resources for vaginal health promotion in cancer survivors. Carter and colleagues have developed a patient handout, which summarizes how to best use vaginal lubricants, moisturizers and pelvic floor exercises [Carter *et al.* 2011].

Complementary and alternative therapies

Complementary and alternative therapies (such as 'natural' products, acupuncture and mind-body practices) are being used by breast cancer survivors [Lee *et al.* 2014] with an estimated 48% [Greenlee *et al.* 2014] to 83% [Wanchai *et al.* 2010] of patients using at least one type of these therapies following diagnosis. This is despite limited evidence of the effectiveness (and toxicity) of these therapies in managing GSM in breast cancer survivors [Mac Bride *et al.* 2010; Cusack *et al.* 2013]. This is concerning, particularly as at least half of breast cancer patients do not discuss their use of an alternative therapy with their clinicians [Cassidy, 2003; Greenlee *et al.* 2014].

Vitamin E and D

Anecdotal evidence suggests that vaginal application of oil from vitamin E capsules before intercourse increases vaginal lubrication and provides some atrophic-related symptom relief [North American Menopause Society, 2007; Mac Bride *et al.* 2010], while vitamin D supplementation may help squamous maturation of the vaginal epithelium [Abban *et al.* 2008; Calleja-Agius and Brincat, 2009]. However, there were no significant improvements in vulvovaginal symptoms or pH [Yildirim *et al.* 2004]. Therefore, the available evidence does not support the use of vitamin D for relief of genitourinary symptoms [Burich and Degregorio, 2011].

Dietary and 'natural' products

The use of dietary supplements with 'natural' products, such as soy, black cohosh, and some other herbs did not show any superiority over placebo in relieving a range of genitourinary symptoms, in clinical trials [Shifren and Gass, 2014]. Despite this, breast cancer patients are still very attracted to 'natural' products and generally convey the impression that they are less toxic than conventional medicine [Deng *et al.* 2010; Lammerink *et al.* 2012]. As per current data, the safety of many of these products is unknown [Roberts, 2010] and there may be possible interactions with TAM and unknown effects on breast cancer cells [Deng *et al.* 2010; Lammerink *et al.* 2012]. Furthermore, important side effects such as facio-oral edema, cutaneous vasculitis and liver failure have been described with the use of 'natural' products [Hickey *et al.* 2005; Leach and Moore, 2012]. Indeed, there is increasing concern about the lack of rigorous quality-control measures with regard to purity and levels of 'active compound' by some manufactures of herbal medicines as pointed out by the NAMS [Shifren and Gass, 2014]. Clearly, there is the need in the long-term to investigate adequately designed RCTs to determine whether these products are of any help to breast cancer patients experiencing GSM-related symptoms. Most importantly, a risk assessment should be performed to help define their safety. Until such evidence-based data are available, their use merits caution [Cassidy, 2003].

Acupuncture and behavioral interventions

There are very limited clinical data for the efficacy of acupuncture and behavioral interventions in the management of genitourinary symptoms and most of the published literature has been done on healthy women. The data on acupuncture suggests it can improve bladder capacity, urgency and frequency [Emmons and Otto, 2005] and a significant decrease in the urogenital subscale scores on the Menopause Rating Scale has been described [Chiu *et al.* 2015]. Despite these reports, the benefits of acupuncture remains 'unconvincing' without evidence-based data [Borrelli and Ernst, 2010].

Cognitive behavioral therapy, physical exercise and a combination of both significantly lessened urinary symptoms and increased sexual activity in patients with breast cancer experiencing treatment-induced menopausal symptoms, compared with controls, in a RCT [Duijts *et al.* 2012]. Interestingly, women who did not report reduction in the frequency of symptoms reported symptoms as less burdensome [Borrelli and Ernst, 2010]. Further studies should confirm the efficacy of these techniques on GSM in breast cancer survivors. In the interim, the use of cognitive behavioral therapy for GSM-related symptoms can only be tentatively recommended as per current scientific evidence.

Hormone therapy

Estrogen-containing treatments have been shown in many studies to alleviate symptoms of vulvovaginal dryness, irritation, pruritis, and dyspareunia [Ewies and Alfhaily, 2010]. Estrogen restores vaginal pH, improves elasticity of vaginal tissues, increases maturation of the vaginal and urethral epithelium [Shulman *et al.* 2008], enhances genitourinary blood flow and improves lubrication [Simon *et al.* 2008]. According to the position statement by the NAMS on the treatment of VVA, vaginal preparations of estrogen are well tolerated and are considered to be the best treatment for isolated, moderate-to-severe atrophic symptoms in the general healthy female population [North American Menopause Society, 2013].

Although the role of estrogen therapy for vulvovaginal concerns in healthy postmenopausal women has been well established, the evidence to support a role of systemic estrogen therapy in the management of urinary tract symptoms is conflicting [Grady *et al.* 2001; Hendrix *et al.* 2005; Robinson *et al.* 2014]. According to a 2012 Cochrane review [Marjoribanks *et al.* 2012],

systemic (oral) hormone therapy (HT) with unopposed estrogen results in worse incontinence symptoms than placebo [risk ratio (RR) 1.32; 95% confidence interval (CI): 1.17–1.48]. Similar worsening effects on incontinence were seen for combined regimens (estrogen and progestin) compared with placebo (RR 1.11; 95% CI: 1.04–1.18) [Marjoribanks *et al.* 2012]. In addition, one of the large trials analyzed in the review reported that women who were continent at baseline were more likely to develop incontinence after 1 year of HT compared with women on placebo [Hendrix *et al.* 2005; Marjoribanks *et al.* 2012]. The authors, however, suggested that the use of local (vaginal) estrogen therapy (e.g. creams or pessaries) for incontinence may be beneficial (RR 0.74; 95% CI: 0.64–1.48), and less frequency and urgency was also reported [Marjoribanks *et al.* 2012]. Several limitations of the studies included in the review were noted, these included heterogeneity in regards to type, dose and duration of exposure to estrogens between trials as well as the length of follow up [Marjoribanks *et al.* 2012].

A systematic review on the impact of estrogens in preventing recurrent UTIs suggested that vaginal estrogen reduced the incidence of UTI and prolonged the time to UTI recurrence [Suckling *et al.* 2006]. Estrogen use has also been recommended for the treatment of symptoms of overactive bladder (OAB) in postmenopausal women with vaginal atrophy [Ewies and Alfhaily, 2010; Robinson *et al.* 2014]. Further, local estrogen has been shown to improve sexual desire, arousal, coital satisfaction and orgasm by increasing blood flow to the genital area, and consequently, improving vaginal lubrication and sensation in the vaginal tissues [North American Menopause Society, 2012; Goldstein and Alexander, 2005].

Despite the indications of the benefit of HT for some genitourinary symptoms, since 2002 the evidence base regarding its use has changed significantly [de Villiers *et al.* 2013]. Concerns about the use of HT increasing risk of breast cancer recurrence mean that it is generally contraindicated after breast cancer [Von Schoultz and Rutqvist, 2005; Hickey *et al.* 2010, 2012]. Nonetheless, QoL concerns, magnitude of symptoms and endocrine therapy compliance may justify the use of HT in selected cases [Hickey *et al.* 2010, 2012]. Patients who wish to consider HT after a diagnosis of breast cancer should be informed that definitive evidence on its influence in prognosis of breast cancer is lacking. The results of observational studies (which are fraught with potential biases) [Biglia *et al.* 2010; Manson *et al.* 2014; Santen *et al.* 2002; Cold *et al.* 2015] and a recent phase II RCT (evaluating use of estradiol-releasing vaginal ring 7.5 μg/d for 12 weeks) have been reassuring with respect to safety [Melisko *et al.* 2016]. However, a single RCT suggested that HT in breast cancer survivors may increase breast cancer recurrence or new breast cancers by 2–3-fold [Holmberg and Anderson, 2004]. Alternative nonhormonal options should always be considered first option in these patients, but if symptoms persist and QoL is seriously impaired, then individual women with a low risk of tumor recurrence may wish to explore the option of HT [Loibl *et al.* 2011; Pfeiler *et al.* 2011; Hickey *et al.* 2010; Hickey *et al.* 2012]. In these selected cases, management of symptoms should take both women's needs and the recommendations of their oncologists into consideration [ACOG Committee on Practice Bulletins-Gynecology, 2012]. The American Cancer Society has no position or guideline regarding HT [The American Cancer Society, 2014]. Nonetheless, they mention that like any other medicine, it is best to use HT at the lowest dose for the shortest time possible.

Androgens

Researchers have looked for safer and effective alternative approaches to improve GSM-related symptoms. Androgens, such as dehydroepiandrosterone (DHEA) and testosterone, have provided some hope with studies evaluating androgen therapy suggesting improvements in vaginal atrophy with concomitant improvement in sexual function in postmenopausal women [Shulman, 2009; Hubayter and Simon, 2008; Raghunandan *et al.* 2010].

The basis for the potential genitourinary effect of DHEA is its role in the androgen metabolism [Labrie, 2010]. DHEA is one of the main precursors of androgens, which in turn are converted to estrone (by aromatization) and testosterone (by 5-alpha reduction) [Labrie, 2010]. There is supporting evidence for its efficacy in improving genitourinary symptoms. Studies have shown intravaginal DHEA to increase the vaginal maturation index and decrease vaginal pH without increasing the serum levels of estrogen above the postmenopausal range [Ibe and Simon, 2010; Witherby *et al.* 2011]. In addition, results from two randomized double-blind placebo-controlled phase III clinical trial reported this therapy to

exert beneficial effects across all four aspects of sexual function, including desire/interest, arousal, orgasm [Labrie *et al.* 2009] and pain at sexual activity in postmenopausal women [Labrie *et al.* 2016]. A Cochrane review [Scheffers *et al.* 2015] analyzed the effectiveness and safety of administering DHEA to women with menopausal symptoms and found that it was associated with improvements, albeit small, in sexual function by contrast with placebo and HT. However, only a small subset of the 28 trials included in the review analyzed sexual function outcomes and there were insufficient data available from the included trials to compare the effects of DHEA with HT for menopausal symptoms, mostly due to discrepancy in measurements between studies [Scheffers *et al.* 2015]. The United States (US) Food and Drug Administration (FDA) recently approved the use of prasterone (DHEA) in healthy postmenopausal women experiencing moderate-to-severe dyspareunia. However, there are no data on the safety of this in breast cancer survivors and hence, cannot be routinely recommended for the management of genitourinary and sexual-related disorders [Shifren and Gass, 2014].

Testosterone has also been a proposed treatment for genitourinary atrophy [Raghunandan *et al.* 2010; Shulman, 2009] with some studies showing this therapy to be associated with higher frequency of sexual activity, and increased interest, desire, enjoyment, arousal, and pleasure [Castelo-Branco *et al.* 2005]. Furthermore, vaginal administration of testosterone has been evaluated for the treatment of symptomatic genitourinary atrophy in postmenopausal women with breast cancer [Derzko *et al.* 2007; Witherby *et al.* 2011; Melisko *et al.* 2016]. Witherby and colleagues reported results of a phase I/II pilot study on the effect of intravaginal testosterone (cream containing either 150 μg or 300 μg of testosterone) in breast cancer patients taking AIs [Witherby *et al.* 2011]. The severity of vaginal dryness and dyspareunia improved significantly with treatment and was sustained 1 month after completion of treatment. The study also documented that the vaginal maturation index improved, pH decreased and that lubrication was increased [Witherby *et al.* 2011]. Similarly, 12 postmenopausal women with breast cancer who were receiving an AI and were experiencing sexual dysfunction, were assigned to 300 μg testosterone vaginal cream daily for 4 weeks [Dahir and Travers-Gustafson, 2014]. Results described significant improvement on sexual health (desire, arousal, lubrication, orgasm, satisfaction and pain) and QoL [Dahir and Travers-Gustafson, 2014]. Most recently, Melisko and colleagues published the results of a phase II RCT comparing 12 weeks of intravaginal testosterone (IVT) cream 1% (5000 μg 3 times/week) with an estradiol-releasing vaginal ring (7.5 μg/d) for genitourinary symptoms in postmenopausal women with early breast cancer receiving an AI [Melisko *et al.* 2016]. The results showed that both therapies were effective in treating vaginal atrophy and improving sexual interest and desire in this group. Sustained estradiol elevations were reported in a small sample of patients on IVT (4 out of 34) but elevations in testosterone levels (above the normal postmenopausal range, 2–45 ng/dl) were obsverved in the majority of patients on IVT (24 out of 27) [Melisko *et al.* 2016].

As AIs inhibit the aromatase enzyme from converting androgens to estrogens, circulating testosterone should not be converted to estradiol in women receiving AIs [Witherby *et al.* 2011]. Anecdotally, the use of vaginal testosterone has been reported to be a potential alternative to vaginal estrogen treatment in women with breast cancer on AIs [Dahir and Travers-Gustafson, 2014]. However, data on the effects of increased serum levels of testosterone is still lacking and its efficacy and safety have not been well established in healthy women or women with a cancer diagnosis [Hickey *et al.* 2008; von Schoultz and Rutqvist, 2005]. Testosterone or other androgens cannot be recommended in women with a history of breast cancer [Shifren and Gass, 2014].

Tibolone

Tibolone is a synthetic steroid that after absorption is rapidly converted to its active form which has weak estrogenic, progestagenic, and androgenic properties [Biglia *et al.* 2010]. It is classified as a selective tissue estrogenic activity regulator [Indhavivadhana *et al.* 2010; Biglia *et al.* 2010], and has been shown to improve vaginal dryness [Nappi *et al.* 2006; Saeideh *et al.* 2010] and may have a favourable effect on sexual function [Modelska and Cummings, 2002].

The most important findings for breast cancer survivors are the results of the LIBERATE trial which was the first trial to study tibolone effects in a large breast cancer population compared with placebo [Kenemans *et al.* 2009; Sismondi *et al.* 2011]. The study showed that tibolone (2.5 mg)

is effective in improving menopausal symptoms including vaginal dryness and enhanced QoL, but was associated with a significantly increased risk of breast cancer recurrence (HR: 1.40; CI 95%: 1.14–1.70) and is contraindicated after breast cancer, with the authors warning that any off-label use incurs a proven risk [Sismondi *et al.* 2011]. This recommendation has been endorsed by the IMS [de Villiers *et al.* 2013].

Selective estrogen receptor modulators

Selective estrogen receptor modulators (SERMs) were identified over 50 years ago and have been used clinically for over three decades [Wardell *et al.* 2014]. The understanding of their pharmacological profile is still evolving and they are currently used in several different settings with regulatory approval varying dependent on geographical location. As prescription rules are not yet the same worldwide, clinicians should check their local or national guidelines when prescribing SERMs for genitourinary symptoms in women with a history of breast cancer.

In the US, ospemifene is the only SERM approved for the treatment of moderate-to-severe dyspareunia due to postmenopausal VVA in healthy women [Portman *et al.* 2014]. In Europe, it is indicated for treatment of moderate-to-severe symptomatic VVA in postmenopausal women who are not candidates for local vaginal estrogen therapy [European Medicines Agency, 2015]. Daily dose of ospemifene 60 mg was reported to improve vaginal maturation index, vaginal pH and vaginal dryness in subjective and objective evaluations [Portman *et al.* 2013]. In a randomized double-blind 40-week safety extension study, ospemifene demonstrated no clinically significant endometrial changes and was not associated with carcinoma; however, an increased incidence of vasomotor symptoms was observed [Simon *et al.* 2013]. Ospemifene has not yet been formally studied in women with or at risk of breast cancer. Although the available safety data did not reveal a special safety concern [European Medicines Agency, 2015], the US FDA does not recommend its use in this group [Glaser and Dimitrakakis, 2013; Pinkerton and Kagan, 2015] and the European Medicines Agency (EMA) contraindicates its use in patients with suspected breast cancer or patients undergoing active treatment (including adjuvant therapy) for breast cancer [European Medicines Agency, 2015]. As no data are available on the concomitant use of ospemifene and therapies for breast cancer, the EMA recommends it should be used for the treatment of VVA only after completing treatment for breast cancer (including adjuvant therapy) [Pinkerton and Kagan, 2015; European Medicines Agency, 2015]. Future studies defining the safety profile of ospemifene in breast cancer patients and safety of prolonged used (i.e. more than 1 year) are eagerly awaited.

Although not approved for treatment of VVA symptoms of menopause, recent studies investigating the use of bazedoxifene combined with conjugated estrogens (BZA/CE), namely tissue-selective estrogen complex have suggested that BZA/CE may offer some vaginal benefits. Findings from two large clinical trials recorded that bazedoxifene 20 mg/CE (0.45 mg or 0.625 mg) significantly improved vaginal atrophy with no endometrial safety signals (low rates, $<1\%$, of endometrial hyperplasia which was similar to placebo) [Pickar *et al.* 2009; Lobo *et al.* 2009]. Other trials also supported the benefits of bazedoxifene in improving vaginal maturation index, vaginal pH, vaginal dryness and reduction of most bothersome vaginal symptoms ($p < 0.05$) [Kagan *et al.* 2010]. Despite these findings BZA/CE has not been registered for the treatment of VVA associated with menopause and no studies have investigated drug safety in breast cancer survivors; therefore, it should not be recommended in women with breast cancer.

Data on the effects of SERMs on the urinary tract are limited. A recent literature review suggested that ospemifene may have a neutral effect on the female urinary tract compared with raloxifene, bazedoxifene and TAM [Archer *et al.* 2015]. Another review suggested that more clinical studies are crucial to delineate the effect of ospemifene in the prevention or treatment of lower urinary tract symptoms (LUTSs) [Pinkerton and Kagan, 2015].

Laser

Laser therapy has gained interest as a non-invasive treatment option for GSM [Palacios *et al.* 2015; Hutchinson-Colas and Segal, 2015]. It has been reported that fractional CO_2 laser stimulates the production of new collagen and elastic fibers [Biglia *et al.* 2015], alleviating symptoms of vaginal dryness, burning, itching, dyspareunia and dysuria, resulting in improved sexual function and satisfaction with sexual life [Salvatore *et al.* 2014; Salvatore *et al.* 2015; Lee,

2014]. Nonetheless, available data are short-term and efficacy and safety of repeated applications is not clear [Hutchinson-Colas and Segal, 2015], nor are there published clinical trials in women with breast cancer. While this therapy appears a feasible option, further controlled studies are needed to better outline its indications and specific applications for GSM.

LUTS management

Treatments for LUTSs are related to the underlying cause of the particular pelvic/urinary disorder and range from conservative options to surgery [Committee on Gynecologic Practice and American Urogynecologic Society, 2014]. Importantly, most LUTSs can often be managed in the primary care setting [Newman *et al*. 2009]. Clinicians are encouraged to indicate nonpharmacological treatments as first-line therapy, where possible, and use their clinical judgment when deciding whether a referral to a specialist is needed for further investigation or treatment [Committee on Gynecologic Practice and American Urogynecologic Society, 2014]. A multidisciplinary approach for breast cancer survivors who are experiencing symptoms may also be beneficial, including the involvement of counselling professionals or psychologists to help minimize the negative impact of LUTSs on wellbeing [Wengstrom, 2008].

The conservative treatment options include: lifestyle interventions and behavioral therapy (bladder training, exercises, fluid and dietary modification, weight control), electrical stimulation, pelvic floor muscle training (PFMT), watchful waiting therapy and anti-incontinence/vaginal supporting devices (e.g. vaginal pessaries, vaginal cones and urethral inserts). Pharmacological therapy is more commonly used for urgency UI and includes: anticholinergics, possibly vaginal estrogens in selected cases (and with patient's informed consent), and more recently the use of botulinum toxin injection into the detrusor muscle. SRNI has also been indicated for stress UI [Lins *et al*. 2014].

Surgical treatment options can include: anti-incontinence procedures (e.g. retropubic urethropexy, autologous fascial slings, urethral bulking agents, and synthetic mid-urethral slings), pelvic organ prolapse (POP) corrective surgeries (e.g. sacral colpopexy, transvaginal mesh uterosacral colpopexy). Several different surgical procedures have been described and no single one is optimal for all patients [Rovner and Wein, 2004]. Hence, multiple factors should be considered such as safety, cost-effectiveness, invasiveness, surgeon's personal experience in order to tailor a therapy to the desires and needs of the individual patient [Rovner and Wein, 2004]. As it is not in the scope of this paper to describe each of the several available surgical procedures, emphasis will be given to the conservative approaches.

Finally, it should be noted that guidelines for the management of urinary symptoms in women with breast cancer are currently not available, therefore, all recommendations provided in this section (unless otherwise stated) is based on current practice in women in the general population and during midlife. As such, it is important to use clinical judgment and individualized approach to treating symptomatic breast cancer survivors.

PFMT, pelvic floor muscle control, bladder training and behavioral modification techniques

PFMT is recommended by the International Continence Society [Newman *et al*. 2009] as first-line therapy in women with stress, urge, or mixed UI [Dumoulin and Hay-Smith, 2010]. The main purposes of PFMT are to improve strength of the pelvic organ support, as well as increase intraurethral pressure during effort thus, maximizing women's ability to maintain continence [Lins *et al*. 2014]. A 2014 Cochrane review comparing 21 trials evaluating PFMT with no treatment for UI concluded that, overall, women who performed PFMT were 17 times more likely to report resolution or improvement of incontinence symptoms (RR 17.33, 95% CI: 4.31–69.64), have fewer urinary leakage episodes per day and have less leakage than controls [Hay-Smith *et al*. 2011]. In addition, PFMT had a positive impact on QoL [Dumoulin and Hay-Smith, 2010]. Importantly, it was noted that women under regular supervision relating to PFMT were more likely to report improvement than those who received little or no supervision [Hay-Smith *et al*. 2011]. PFMT has been highly recommended (high quality evidence) as a first-line management for women with UI [Hay-Smith *et al*. 2011] with the NAMS also endorsing behavioral therapies and pessaries as alternative options for UI [Shifren and Gass, 2014]. Furthermore, promising results for the use of PFMT for prolapse symptoms and severity were reported using pooled data from six trials

[Hagen and Stark, 2011]. A 17% higher chance of improvement in prolapse stage was reported with PFMT compared with no intervention [Hagen and Stark, 2011]. Thus, PFMT is a viable option for breast cancer patients reporting UI and prolapse.

Bladder training and behavioral modification techniques may help urgency and OAB as these interventions are focused on improving voluntary control of the bladder function by gradually increasing time interval between toilet stops, aiming to reduce the number of voids per day (up to approximately 4–6 voids during the day and 1–2 voids at night) [Burgio, 2002, 2004]. These techniques may help urgency and OAB, and early studies suggest that UI may also be improved; however, there are limited data and further studies are needed to confirm this observation [Wallace *et al.* 2004]. In the meantime, the recommendation is that all patients with suspected OAB should be educated regarding bladder training [Newman *et al.* 2009].

Electrical stimulation

Electrical stimulation is a treatment option for urinary urgency and urge incontinence; however, it is not commonly indicated as it is invasive and not without risk [Hajebrahimi *et al.* 2015]. Vaginal or anal transducers can be used to administer electrical stimulation, where the physiological objectives are to produce muscle hypertrophy, normalize the reflex activity of the lower urinary tract (i.e. inducing reflex contraction of the periurethral muscles and reflex inhibition of the detrusor muscle) and to increase blood flow to pelvic muscles [Ghaderi and Oskouei, 2014]. According to some reviews, electrical stimulation was associated with 30–50% clinical success rate [Hajebrahimi *et al.* 2015], however, it was shown to be similar to PFMT in improving UI [Ghaderi and Oskouei, 2014].

Vaginal/urethral support devices

Mechanical devices (vaginal or urethral) are also described as an easy-to-insert and cheap option for women who want to delay/avoid surgery for UI [Lipp *et al.* 2014]. However, the latest Cochrane review [Lipp *et al.* 2014] on the topic concluded that there is no evidence to suggest that one device is better than another and, most importantly, there is insufficient evidence to claim that mechanical devices are better than no treatment [Lipp *et al.* 2014]. Similarly, another systematic review assessing the use of pessaries to treat POP, could not draw conclusions on the use of different types of devices, the indications or the pattern of replacement and follow-up care as only one trial was included in the analysis and methodological flaws were noted in the study [Bugge *et al.* 2013]. Finally, weighted vaginal cones for UI were also reviewed [Herbison and Dean, 2013]. Again, the lack of larger, high quality trials, made it difficult for the authors to be conclusive. There were suggestions, however, that weighted vaginal cones were better than no active treatment (RR for failure to cure UI 0.84, 95% CI: 0.76–0.94) in women with stress UI and may be as effective as PFMT (RR 1.01, 95% CI: 0.91–1.13) and electrostimulation (RR 1.26, 95% CI: 0.85–1.87) [Herbison and Dean, 2013]. Therefore, vaginal cones may constitute an alternative option for management of stress UI, although the evidence of its effectiveness is weak.

Pharmacological interventions for UI

Duloxetine is a SNRI recommended for treatment of stress UI [Mariappan *et al.* 2007]. It increases the urethral sphincter tone resulting in a decrease in stress-induced leakage. Results from a systematic review conducted by Mariappan and colleagues found that duloxetine 80 mg/daily was superior to placebo with respect to subjective perception of symptom resolution and improvement in incontinence [Mariappan *et al.* 2007]. However, nausea was a common side effect and about one in eight women discontinued therapy because of side effects [Mariappan *et al.* 2007]. Duloxetine has been described as well tolerated in breast cancer patients [Henry *et al.* 2011], and a placebo-controlled phase III trial is now investigating its use to treat musculoskeletal pain caused by AIs [Henry *et al.* 2014]. To date, the most common adverse events described so far were fatigue, dry mouth, nausea and headache [Henry *et al.* 2011].

Anticholinergic medications such as darifenacin, fesoterodine, oxybutynin, solifenacin, propiverine, and tolterodine have demonstrated positive effects on urgency UI and mixed UI compared with placebo in the general population [Qaseem *et al.* 2014], with less episodes of leakage and reduced number of voids in 24 h [Nabi *et al.* 2006]. These drugs suppress bladder contractions *via* muscarinic receptors of the bladder wall, where acetylcholine is the transmitter substance [Yoshimura and Chancellor, 2003]. Side effects

such as dry mouth are commonly reported, tolerability is good and discontinuation of therapy is not significant [Nabi *et al.* 2006]. Therapy combining anticholinergics and bladder training was shown to be more effective than bladder training alone in one review, but it remains unclear if it is more effective than medication alone [Rai *et al.* 2012].

The American College of Physicians recommends that selection of pharmacological interventions for urgency UI should be based on drug tolerability and cost-effectiveness, and should be considered when bladder training is unsuccessful [Qaseem *et al.* 2014]. In the same way, the European Association of Urology (EAU) recommends lifestyle advices, individualized behavioral and physical therapies including PFMT and the use of drugs as an adjunct to conservative therapy [Thuroff *et al.* 2011; Lucas *et al.* 2012].

Sexual concerns

Although sexual issues may not be a patient's main concern during her diagnosis and primary treatment of breast cancer, it may become more of an important concern after this stage of her treatment [Lammerink *et al.* 2012]. It is also evident that sexuality and intimacy are often overlooked or not properly addressed with breast cancer patients in clinical practice [Hordern and Street, 2007]. Studies suggest that initiating the discussion about sexual-related side effects of cancer therapy with patients early on their treatment may make them more willing to be open about any issues they may experience in the future [Lammerink *et al.* 2012].

Treatment of sexual complaints may require a multi-modal treatment approach [Vincent, 2015], including the use of lubricants [Hickey *et al.* 2016] and moisturizers, liquid lidocaine [Goetsch *et al.* 2015], ultralow concentration of vaginal estrogen (usually as a last resort, and only upon risk assessment and informed consent from patient) [van Londen *et al.* 2013], counselling and sex therapy (alone or couple-based), PFMT and use of vaginal devices such as dilators or pessaries [North American Menopause Society, 2013] in addition to treatment of underlying depression and anxiety [North American Menopause Society, 2013]. Topical use of testosterone has been suggested but more research in breast cancer patients are needed [North American Menopause Society, 2013]. Most importantly, it is essential to encourage women to maintain regular sexual activity, which results in improved blood flow to the vagina, reducing further atrophy [North American Menopause Society, 2013].

Recent findings from a randomized, double-blind, crossover trial suggested that silicone-based lubricants are more effective than water-based for discomfort during sexual activity in postmenopausal women with breast cancer [Hickey *et al.* 2016]. Nonetheless, the study also highlighted that such therapies are unlikely to reduce sexually-related distress [Hickey *et al.* 2016]. In a systematic review specifically addressing interventions for sexual problems following breast cancer, it was suggested, that the most effective intervention for this issue was couple-based psycho-educational interventions that include an element of sexual therapy, although this was based on moderate evidence of its effectiveness [Taylor *et al.* 2011]. A new approach to dyspareunia involves the application of aqueous lidocaine prior to penetration, which potentially acts on reducing pain in the vulvar vestibule (i.e. entryway to the vagina) [Goetsch *et al.* 2015]. The application of 4% topical liquid lidocaine to the vulvar vestibule for 4 weeks reduced sexual distress and allowed for comfortable intercourse in postmenopausal women with breast cancer reporting severe dyspareunia in a proof-of-concept double-blind RCT involving 46 breast cancer patients [Goetsch *et al.* 2015]. New studies focusing on the physiopathology of the coital pain may shed some light and bring hope to the many survivors experiencing pain with intercourse.

Conclusion and recommendations

Appropriate and timely management of the adverse side effects of antiestrogens, including genitourinary symptoms is critically important to all postmenopausal women who are on long-term adjuvant endocrine therapy after the diagnosis of breast cancer. The side effects of treatment may negatively impact on QoL and also result in early discontinuation and poor compliance. Many women are recommended 10 years of adjuvant endocrine therapy and unless the side effects are adequately managed they will either stop treatment early or suffer with multiple symptoms for years. This manuscript paper has focused on the management of genitourinary symptoms and outlined the possible management options in women with breast cancer. HT is not recommended in women with a history of breast cancer, but there is a wide range of other management options

available that can improve genitourinary symptoms in these women. They include lifestyle and behavioral changes, lubricants, moisturizers, and nonhormonal pharmacological interventions, among others.

Topical estrogens are controversial given safety concerns, but while the limited evidence on the effect low-/ultralow-dose vaginal estrogen is promising additional evidence regarding safety is required. Topical estriol formulations theoretically should be safe but again more clinical data on their safety and effectiveness are needed. There is inconclusive evidence on whether systemic absorption after topical use of estrogens increases the risk of breast cancer recurrence. If topical estrogens are prescribed, the lowest possible dose should be used after discussing the potential risks.

Future studies to define the safety and efficacy of ospemifene, as well as topical testosterone are needed as they do appear to offer some benefit. Clinicians should actively question breast cancer patients on adjuvant endocrine therapy about signs or symptoms of genitourinary atrophy as well as about any sexual concerns or problems. These topics are frequently not discussed and early interventions are much more likely to be effective than treatment after years of estrogen deprivation. A multidisciplinary team approach is often required and treatment needs to be tailored to the individual patients' specific needs and circumstances.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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