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Objective: Review evidence to guide the management of menopausal signs and symptoms in women after breast cancer and make recommendations accordingly.
Evidence: Randomized controlled clinical trials, observational studies, evidence- based guidelines, and expert opinion from professional societies.
Background: Several symptoms and clinical problems associated with estrogen depletion — sleep disorders, vulvovaginal atrophy (VVA), vasomotor symptoms (VMS), mood changes, depressive symptoms, cardiovascular disease, osteopenia and osteoporosis— confront the estimated 9.3 million breast cancer survivors globally.
Recommendations: Following breast cancer, women should not generally be treated with menopausal hormone therapy or tibolone but should optimize lifestyle. Women with moderate to severe symptoms may benefit from mind-brain-behavior or non-hormone, pharmacologic therapy. The selective serotonin /noradrenaline reuptake inhibitors and gabapentenoid agents exert beneficial effects on VMS and quality of life. For osteoporosis, the panoply of non-hormonal agents is available. Treatment of VVA remains an area of unmet need. Low dose vaginal estrogen is absorbed in small amounts with blood levels remaining within the normal range but could potentially stimulate occult breast cancer cells, and although poorly studied, is not generally advised, particularly for those on aromatase inhibitors. Intravaginal DHEA and oral ospemiphene have been approved to treat dyspareunia, a symptom of VVA but safety after breast cancer has not been established. Vaginal laser therapy is being utilized for VVA but efficacy from sham-controlled studies is lacking. Therapies undergoing development for possible future use include lasofoxifene, neurokinin B inhibitors, stellate ganglion blockade, vaginal testosterone, and estetrol.
Conclusions: A variety of non-hormone options and therapies are available for treatment of estrogen –depletion symptoms and clinical problems after a diagnosis of breast cancer. Individualization of treatment is essential.

The number of breast cancer survivors worldwide is increasing and treatment of estrogen deficiency symptoms in these patients is important and complex as reviewed here. .

Introduction:

Early diagnosis and concomitant initiation of more effective cancer treatments have reduced the death rate from breast cancer by 38% from 1989 to 2014 (1;2). The five year survival rate in developed countries is now 99% for patients with localized disease (3). Accordingly, the number of breast cancer survivors is increasing and has now reached 3.1 million in the USA and is

estimated to be approximately 9.3 million worldwide (3;4).* In Western countries, approximately 43 % are ≥ age 65 and approximately 25 % ≤ age 50 at diagnosis. The numbers of survivors are increasing due to the reduction in disease specific death rates since 1989 . Early detection in developed countries has enhanced the number of women free of lymph node metastases; the 5 year survival rate for these women is 99% in comparison with 84% if lymph nodes are positive (3).

A large proportion of women experience menopausal symptoms or clinical manifestations of estrogen deficiency during treatment of their breast cancer or after completion of therapy (5;6). The specific symptoms and clinical challenges differ based on menopausal status prior to initiation of cancer treatment and therapeutic agents used. For example, pre-menopausal women treated with chemotherapy can develop ovarian insufficiency and severe menopausal symptoms as well as infertility resulting from toxic effects of chemotherapeutic agents on the ovary (7). Postmenopausal women treated with aromatase inhibitors (AIs) may experience arthralgia, accelerated bone loss, and an increased incidence of osteoporotic fractures as a result of markedly suppressed estrogen levels (i.e.< 2 pg/ml) (8-10). They may also experience a severe form of vulvovaginal atrophy (VVA) with significantly higher rates of vaginal dryness (16.3%) and dyspareunia (17.8%) compared to women taking tamoxifen (8.4% and 7.5% respectively) (11-13) .

The constellation of signs and symptoms related to estrogen deficiency has prompted a variety of studies of menopause management in breast cancer survivors (5;7;14-20). However, the lack of randomized placebo controlled trials (RCTs) in this population has limited the evidence upon which to base therapeutic decisions. Consequently, written guidelines to address menopause management in women during and after treatment of breast cancer have not sufficiently focused on treatment of this subgroup of women. To address this gap, the writing group (C.A,S, S.R.D, AG, M.A.L, J.V.P, and R.J.S) of the Endocrine Society Guidelines on management of menopausal symptoms (13) was prompted to write a review focusing on current and future approaches to management of menopausal symptoms and sequelae in women after breast cancer.

- Footnote The incidence of new breast cancers worldwide in 2008 was 1.38 million with an estimate of approximately 9.3 million survivors. This estimate is based on the ratio of new cases to survivors in the USA (231,000 new cases/3.1 million survivors) reduced by an estimated factor of 0.5 to account for higher mortality outside of North America and Western Europe.(3;4)

The prevalence of estrogen -deficiency symptoms in women after breast cancer ranges from 79% to 95% (6;21-27) and is higher than in women without breast cancer (6;22). Survivors report more sleep disturbance ($P<0.01$), difficulty concentrating ($P<0.01$), muscular/joint pain ($P<0.01$), crying ($P<0.01$) and irritability ($P<0.01$), and vasomotor symptoms ($P<0.01$) (28) .These differences may reflect the rapidity of the menopause transition and the magnitude of estrogen deficiency exacerbated by AI therapy. Illustrative data originate from a follow up study of women with breast cancer no longer on therapy and 6 years on average after diagnosis (6).In the group of women ages 50-59, 72.8% reported vasomotor symptoms, and 80.8% sexual symptoms (6). The prevalence of these symptoms was lower in women younger than age 50 and older than 59 but the symptoms were still frequent (i.e. 50-60%) (6) (19) The authors reported that breast cancer survivors had significantly higher vasomotor domain ($P \leq 0.002$) and sexual domain ($P \leq 0.004$) scores than community controls (6),indicating more bothersome symptoms. Weight gain is also a common problem associated with breast cancer therapy (29).

Specific components of the problem:

Both pre- and post-menopausal breast cancer survivors often experience moderate to severe VMS and sleep disturbances with related fatigue, mild depressive symptoms, and mood changes (26). Arthralgia, osteopenia, osteoporosis and related fractures occur predominantly in post-menopausal women as does VVA and associated dyspareunia (11;12;28;30;31). Less common problems include weight gain, symptomatic osteoarthritis and intervertebral disk degeneration, degenerative skin changes, radiation and chemotherapy-related cardiovascular disease and reduced quality of life (12) (11).

Strategies for Management:

Key principles are to determine (a) the severity of the signs and symptoms related to estrogen deficiency and (b) the degree of bother to the patient. This allows treatment to be individually tailored based on these assessments. For *mild symptomatology or maintenance of health*, lifestyle modifications or over the counter options may be sufficient. *Moderate or severe signs or symptoms* usually require pharmacological management.

Lifestyle modifications:

Amelioration of symptoms:

Women with mild VMS frequently do not need pharmacotherapy but do benefit from lifestyle changes (32). Simple behavioral measures such as lowering of room temperature, using portable fans, dressing in layers that can be easily shed, avoiding triggers (such as spicy foods and stressful situations) and likely exercise, may help reduce the number of hot flashes.(32;33) A Cochrane review provided supportive evidence that exercise results in a reduction in hot flashes but suggested that additional randomized trials are needed to resolve existing controversy (34). While a recent RCT provided evidence that exercise training decreases hot flashes, (35) a pooled analysis of 6 studies reported no benefit from aerobic exercise (36). Diet may modify the incidence of vasomotor symptoms (37). Loss of 10% or more of body weight, as part of a healthy dietary intervention may significantly reduce VMS (37). Use of non-pharmacologic agents such as soy, black cohosh , flaxseed, remifemin, equol in equol -producers, and vitamin E have been reported to be beneficial for VMS primarily when mild (13;38;39). However, RCT evidence of efficacy is mostly lacking and safety has not been firmly established in any population, much less in women who have had breast cancer . Of potential concern are products that may have some degree of weak estrogenic actions.

Recent research emphasis has been on the development of non-pharmacologic therapies of VMS. Cognitive behavioral strategies which include stress management, relaxation, deep breathing, and yoga have been tested in clinical trials with varying results (12;13;33).Hypnosis appears to be promising based on recent randomized trials (40). Another approach, stellate ganglion block with a local anesthetic provides improvement in hot flashes, but has more potential risks (41). Acupuncture may be another effective procedure although sham acupuncture is also effective (20;42;43)

Overall health and survival benefit:

Increased physical activity, weight reduction and cessation of smoking and alcohol are important for breast cancer survivors based on evidence that these steps may provide objective benefit (44). Specifically, physical activity improves postmenopausal women's balance, body composition, muscle strength, and bone health; improves mood (45) reduces cardiovascular risk (46;47); and

potentially, reduces falls contributing to osteoporotic fractures (47). As obesity, independent of treatment, is associated with a poorer prognosis after breast cancer, including women with early disease, normalization of body weight is to be encouraged (48). Smoking cessation reduces mortality and improves quality of life (49). These lifestyle improvements may also benefit the metabolic syndrome (50). Adherence to a Mediterranean diet has been shown to decrease the incidence of breast cancer, particularly estrogen receptor negative cancer, and could reduce the incidence of second breast cancers (51).

Another lifestyle modification is to optimize vitamin D levels so as to maintain bone health. (52). A Cochrane meta-analysis (53) concluded that supplementation of vitamin D and calcium in older patients reduces fracture risk (OR 0.89; 95% CI 0.80-0.99). An Institute of Medicine (IOM) report (54) (55) stated that raising low levels to normal are beneficial whereas no benefits accrue from increasing Vitamin D levels above 50 ng/ml. Disagreement exists as to what levels constitute vitamin D deficiency. As defined by the IOM, deficiency represents a level below which rickets or osteomalacia occurs, namely <10-20 ng/ml (25-50 nmol/l) and normal levels are 20 ng/ml and above (56). The Endocrine Society Guidelines consider deficiency to be <20ng/ml, insufficiency 20-29 and normal ≥30 ng/ml (57) .The IOM suggests daily supplementation of vitamin D with 600 IU for women < 70 years and 800 IU for those older. While vitamin D intoxication is rare unless supplementation exceeds 10,000 IU daily, a recent, detailed IOM report suggests that levels above 50 ng/ml may be associated with cardiac toxicity (56) . Selected recent data suggest that levels of vitamin D may correlate with overall survival (58). Calcium supplementation is currently controversial, but postmenopausal women need 1200 mg of calcium, ideally from diet, to maintain bone health during menopausal transition.

General Advice:

All breast cancer survivors should be advised to modify their lifestyles to include smoking cessation, weight loss (if indicated), limiting or avoiding alcohol, maintaining adequate levels of vitamin D and calcium, eating a healthy diet and regular physical activity (59).

Management of moderate or severe signs and symptoms:

Vasomotor Symptoms:

Hot flashes and night sweats have been categorized as mild, moderate or severely bothersome depending on presence of sweating or disruption of usual activity (32). Previous opinion held that hot flashes resolve within 5-10 years after menopause onset in most women. However, recent data suggest that this symptom can continue for 15 years or more in as many as 33% of women with natural menopause (60). Women taking tamoxifen may experience severe flushing which leads to stopping the treatment. While the most effective treatment of moderate to severe VMS is the use of menopausal hormone therapy (MHT)(12;13;13), clinical guidelines consider this approach contraindicated in women with a history of breast cancer based on existing, but limited RCT evidence. Early meta-analyses based on observational data reported this approach to reduce breast cancer recurrence in breast cancer survivors (61). Later, more critical assessments have suggested that selection bias may have confounded this conclusion (62). Specifically women thought to be cured of breast cancer were likely selected to receive MHT, and the women felt to harbor residual tumor were not. Accordingly, the recurrence rate in the women receiving MHT appeared to be reduced compared to the placebo group.

To address the “wellness bias”, three RCTs compared MHT to placebo in breast cancer survivors (63-66). Two, the Habits and Stockholm trials, compared estrogen with or without a

progestogen and were conducted in Stockholm. The trials differed with respect to the progestogen used, primarily norethisterone in Habits trial and medroxyprogesterone acetate in the Stockholm trial. The Habits trial with 898 women, reported an increased hazard ratio (HR) for breast cancer recurrence of 2.2 (CI 1.0-5.1) for those using MHT, whereas the other, the Stockholm trial with 844 women , reported no increased risk (HR 0.82 (CI 0.35-1.9)(63-65). Differences in the trials included continued use of tamoxifen and stage or histology or receptor status of the pre-existing breast cancer. Prior to completion of these studies, the decision was made to combine the data, resulting in an overall hazard ratio of 1.8 (CI 1.03-3.10)(64) . The third trial evaluated tibolone, 2.5mg/day, and also reported an increased risk of breast cancer recurrence (HR 1.40 [CI 1.14-1.70]). The results might have been influenced by the inclusion of women taking AIs in the study as tibolone can exert estrogenic effects (66). These three trials, while not definitive, have led the majority of guideline committees to consider MHT to be contraindicated in breast cancer survivors (13) (33;66-68).

Other non-hormonal pharmacological treatments of moderate to severe hot flashes are available which exhibit significant efficacy. RCTs demonstrate the efficacy of the SSRI/SNRI class of agents, transdermal nitroglycerin (69), and of gabapentin and pregabalin (figure 1) (36;70-74). In general, these agents result in an overall 70-80% reduction in hot flash number and severity. However, on average, approximately 30% of the reduction is due to placebo effects (75)(figure 1). From the patient's point of view, overall efficacy (including both drug and placebo effect) is the most important factor with respect to reduction of hot flash severity, sleep disruption, elevation in mood (76) and improvement in quality of life. Substantial clinical experience has been gained by the numerous trials of Charles Loprinzi and colleagues in breast cancer survivors (15;71;77). The first recommendation from this group is to try low dose antidepressants in women with moderate to severe hot flashes. Women taking tamoxifen should avoid potent CYP2D6 inhibitors as these agents reduce the levels of an active metabolite, endoxifene (73) . Higher CYP2D6 inhibitory potency is found with paroxetine and fluoxetine (avoid), weak to moderate with citalopram, and relatively low (better choice) with venlafaxine, desvenlafaxine, escitalopram, gabapentin and pregabalin (78-82).

Nighttime VMS may be associated with a greater risk of minor depression, fatigue, and mood changes than those occurring during the daytime. (83). On this basis, the first step in management is to ascertain whether the symptoms occur predominantly at night as the pattern of hot flash presentation can inform the specific therapy to be chosen. *For night time VMS or sleep disruption*, a single dose of gabapentin given one hour before sleep is associated with a reduction in night time hot flashes and a soporific effect on initiating sleep. The short half-life of this agent yields fewer side effects upon awakening. Clinical experience has shown that the gabapentin dose must be individually determined and ranges from 100 mg to 1200 mg given as a single dose one hour before bedtime. A formal dose escalation protocol in each patient determines the appropriate dose. *For VMS occurring both during the day and night*, an additional morning dose of gabapentin can be added.

For women with predominantly daytime hot flashes, the SSRI/SNRI class of agents has been shown to be effective. In the USA, only one agent, paroxetine salt 7.5 mg, is approved by the FDA for treatment of VMS, but others in this class are also effective (figure 1) and have been shown to be successful for symptom relief in breast cancer survivors (15;71;73;84). Another agent, clonidine, is somewhat effective, and can be a second line agent. Because of side effects with oral preparations, the long acting TTS (transdermal therapy system) preparation of clonidine is preferable, with titration of dose depending on symptom relief and effect on blood

pressure. With each of these approaches, approximately half of these women experience at least a 50% decrease in hot flash score (see Table 2 from reference (77).

In patients refractory to the above agents, intramuscular medroxyprogesterone acetate (MPA), 500 mg at 4-5 month intervals, has been suggested by the Mayo Clinic group to be as effective as estrogen therapy (77). Since this agent has been shown to be an effective therapy for hormone dependent breast cancer (85-87), these investigators consider it safe for breast cancer survivors. However, this conclusion is controversial because of concerns about the proliferative effects of a progestogen on occult breast cancer cells. Until more safety data are available, this agent is generally not recommended. An important side effect of MPA is the weight gain occurring from its glucocorticoid actions. Micronized progesterone 300 mg nightly also significantly decreases VMS and improves sleep when compared with placebo (88). Notably, observational studies in healthy postmenopausal women have suggested a lesser effect of progesterone/estrogen combinations on breast cancer risk compared to synthetic progestogen/ estrogen combinations (89-93), but these findings have not been confirmed in RCTs and no data are available in women with breast cancer.

A key question is whether or not MHT might be prescribed to breast cancer survivors refractory to the agents mentioned above. A multidisciplinary conference (94), recommended that MHT can be used in the lowest effective dose but only after obtaining full, written informed consent from the patient with attention to all potential risks and benefits (94). The Endocrine Society 2015 guideline also allows for individual women to accept a degree of risk that might otherwise be considered to outweigh the benefits of MHT (13). The guideline states, “A fully informed patient should be empowered to make a decision that best balances individual QOL benefits against potential health risks.” (13).

Vulvo-vaginal atrophy (VVA):

This common condition is a consequence of estrogen deficiency. Symptoms of VVA include vaginal dryness, irritation, itching, infection, discomfort and painful sex (dyspareunia). Dyspareunia in turn leads to diminished sexual desire, arousal difficulties, and relationship problems. Up to 25-50% of postmenopausal women, particularly those on AIs, have VVA, and thus many women with breast cancer are profoundly affected in a major way by this problem (25). Dyspareunia interferes with sexual intimacy and disrupts the quality of life and successful partnerships in women with VVA. With the growing awareness of quality of life issues in cancer survivors in general, the issue of VVA has been increasingly emphasized as a major problem. VVA has been recently included under the broader term “Genitourinary Syndrome of Menopause (GSM) “ which also includes urinary symptoms (urgency, dysuria, and recurrent urinary tract infections (95)

For mild symptoms, regular use of vaginal moisturizers may be effective in combination with lubricants proximate to intercourse. (Moisturizers are used continuously but not at the time of intercourse, as they may be irritating). Differences between lubricants used acutely prior to intercourse and vaginal moisturizers used chronically to improve vaginal pH and moisture should be emphasized to patients. There are many types of moisturizers and lubricants available, including preservative free if needed. For more severe symptoms, the measures described above are not sufficiently effective. A logical approach is to consider low dose vaginal estrogen therapy. However, high sensitivity mass spectrometry assays have demonstrated that all vaginal estrogen preparations result in a minor degree of systemic absorption but not exceeding normal postmenopausal levels (96). Whether a very small increase in estradiol exposure will stimulate quiescent, occult breast cancer cells or contribute to the development of a breast cancer

is not known. Pre-clinical data have shown that long term estrogen deprivation can result in a state of estradiol hypersensitivity, both to proliferation and apoptosis (97) but it is not clear which effect would predominate.

Low dose vaginal estrogen in women taking the anti-estrogens, tamoxifen or raloxifene, might be theoretically safer than in women not receiving these agents because of blockade of some possible effects of systemic estrogen absorption (98). Three studies (observational and case controlled) have examined the impact of vaginal estrogen administration in breast cancer survivors, and the results are reassuring, at least when vaginal estrogen is administered concurrently with tamoxifen (98-100). These studies, however do not provide robust evidence regarding the safety of vaginal estrogens in breast cancer survivors taking aromatase inhibitors, the efficacy of which is due to markedly suppressed estrogen levels (101). One observational study of breast cancer survivors using tamoxifen or an AI, however, found no increased breast cancer recurrence risk with low dose vaginal estrogen (vaginal ring or 10-mcg tablet) during a 3.5 year mean follow up (98). In general, the use of low dose vaginal estrogen in breast cancer survivors has been discouraged, particularly in those receiving A!s (13;68). If recommended following consultation with the attending oncologist, one should use the lowest effective dose of vaginal estrogen as recommended by ACOG, ASCO, the Endocrine Society (13), and NAMS (33;68;102).

The SERMs, tamoxifen and raloxifene, can exert mildly estrogenic effects on vaginal tissue. In the ATAC (anastrozole, tamoxifen and in combination) trial, 11.4% of women treated with tamoxifen reported vaginal discharge compared with 2.8% treated with an AI (103). In a chemoprevention trial comparing the effects of tamoxifen and raloxifene, vaginal discharge was reported more commonly by women taking tamoxifen than raloxifene (104;105). Ospemiphene, an oral SERM, has been approved in Europe and North America for the treatment of dyspareunia secondary to VVA in healthy postmenopausal women. Comprehensive studies of ospemiphene demonstrated an improvement in vaginal maturation index and relief of most VVA symptoms, as well as improvement in measures of sexual wellbeing (106;107). Safety evaluation showed a negligible estrogen effect on the uterus, and pre-clinical data suggested a predominantly anti-estrogen effect on breast cancer growth (106;107). Current FDA labeling in the US recommends against use of ospemiphene in women with a history of breast cancer which will need to await an adequately powered RCT of its effect on the breast.

A recently FDA approved (i.e. November 2016) therapy for dyspareunia secondary to VVA is intravaginal dehydroepiandrosterone (DHEA).This therapy has not yet been approved beyond the USA. Nightly vaginal application of a 6.5 mg DHEA ovule has been shown to significantly improve vaginal cell maturation indices and the most bothersome symptoms of VVA. As DHEA can be enzymatically converted into both estrogen and androgens locally, this therapy theoretically provides a non-systemic hormonal approach. Carefully conducted studies with highly sensitive and specific mass spectrometry assays suggest a slight but statistically significant increase in plasma estradiol and testosterone (108). Intravaginal DHEA has not been tested in breast cancer survivors; thus there is a warning about its use due to lack of testing.

A small, double blind RCT of women without breast cancer has shown that intravaginal testosterone may be efficacious when compared with a placebo and vaginal estrogen in terms of subjective and objective VVA measures (109). A preliminary, non-controlled trial suggested that intra-vaginal testosterone may provide an effective treatment option for women with breast cancer taking an AI and experiencing symptoms of atrophic vaginitis (110). Further data on safety and efficacy are needed before this approach is recommended.

An additional approach to treatment of VVA includes laser reduction of the vaginal mucosal lining using a fractional carbon dioxide laser (111). Although FDA approved for use on soft tissues, the specific indication for laser treatment of VVA is not included (112). ACOG currently recommends against this procedure due to lack of safety and efficacy data (112) . Although results appear promising in a number of observational studies, including one in women with breast cancer (113;114) no RCTs have compared this approach with sham treatment, and its efficacy and safety therefore remain unclear (115).

Depressive symptoms and mood changes:

The relationship between menopause, VMS and depressive symptoms and mood changes has been well established (116). Major depression should be identified and treated with specific pharmacologic agents and/or cognitive behavioral therapy. Recent experimental data support the concept that mild depressive symptoms and fatigue may in part result from sleep disruption with frequent awakening at night due to hot flashes (83;117). Further data are needed to confirm this conclusion in women with breast cancer.

Cognition:

Menopause appears to be associated with subtle changes in cognitive function, notably delayed verbal memory (118). Sleep disruption may contribute as sleep is important for the encoding and consolidation of memory (119) **.** However evidence that exogenous estrogen therapy improves cognitive function within the first few years after menopause is lacking except for those with early surgical menopause (120;121). Lower testosterone levels, as seen with age, surgical menopause or chemotherapy, have been implicated in cognition (122). As breast cancer survivors experience chemotherapy induced " chemo-brain" and sex-steroid deficiency related effects, further understanding and possible treatments of cognitive problems remain key goals at the present time.

Osteopenia, Osteoporosis, and Fractures:

Endocrine therapy for hormone dependent breast cancer impedes either estrogen synthesis or its action. Surgical oophorectomy or chemotherapy induced ovarian insufficiency in premenopausal women reduces estrogen levels and accelerates the rate of bone resorption as does tamoxifen in this population (11). On this mechanistic basis, an increased rate of osteopenia or osteoporosis and fracture has been reported (11). In post-menopausal women with breast cancer, AIs have become first line therapy in preference to tamoxifen. The substantial reduction of estradiol levels to sub-pg concentrations (i.e. 0.05 to 0.6 pg/ml) (8;10) markedly contributes to bone resorption. Quantitative data demonstrate a rapid and substantial increase in markers of bone resorption such as NTX or CTX and a subsequent reduction in bone density with aromatase inhibitors (11;123;124)(Figure 2 below). These effects are not sufficiently counteracted by a reflex rise in bone formation, demonstrated by measurements of osteocalcin and other markers. Accordingly, there is a net decrease in bone density and an increase in fracture rate. As recent data demonstrate the greater efficacy of 10 years vs five years of therapy with the AIs, this problem will become increasingly severe in the future (125). Interestingly, tamoxifen acts as a weak estrogen on bone in postmenopausal women and, as a SERM, increases bone density. On this mechanistic basis. tamoxifen, is associated with fewer fractures than use of AIs (11;126;127).

Minimal trauma fractures are common after a breast cancer diagnosis, with non-pathological rib fracture the most commonly reported fracture (30). In a 6 year follow-up study

of 1683 women after a diagnosis of breast cancer, minimal trauma fracture was not associated with radiotherapy, chemotherapy, treatment with an AI, or bilateral oophorectomy (30).

Several additional approaches have been developed to prevent osteoporosis and fractures in AI treated patients or in women after breast cancer with osteoporosis. Algorithms to guide decisions whether to use pharmacologic agents or life style changes have been developed (figure 3) (11;123). Prophylactic or treatment agents include oral and parenteral bisphosphonates and Denosumab (128). Both are effective but associated with serious, but uncommon (rare) toxicity such as osteonecrosis of the jaw (1 in 10,000 and 1 in 100,000 person years (www.asbmr.org) and atypical femoral fractures 3.2 to 50 cases/100,000 person years (www.asbmr.org). The disproportionate concern about these toxicities by the public has led to a 50% reduction in utilization by patients who are candidates for these agents (https://asbmr.org/call-to-action.aspx).

Published reviews have recommended such agents in all breast cancer survivors with osteoporosis and selective use depending on other risk factors in those with osteopenia (11;123).The algorithm in Figure 3 provides a roadmap for selection of which patients to treat with pharmacologic agents during therapy with tamoxifen, AI, or GnRH agonist. Effects of these agents beyond the bone may also be important in breast cancer survivors. Recent studies have shown that intravenous zoledronic acid and denosumab are associated with a decrease in breast cancer recurrence in postmenopausal but not pre-menopausal women (129) .For zoledronic acid, this represented a 34 % relative risk reduction of disease recurrence and for denosumab 19% ((130;131) Zoledronic acid also was associated with a 19% relative risk of death (123).

Cardiovascular disease:

With aging, the incidence of coronary artery disease, myocardial infarction, and acute coronary syndrome increase as does coronary plaque. Incomplete data address the increased rate of CV disease in premenopausal women < age 45 undergoing chemotherapy-induced premature menopause. Both chemotherapy (anthracycline, trastuzumab, and aromatase inhibitors) and radiation therapy (especially to the left breast and axilla) can contribute to development of ischemic coronary heart disease, valvular injury, pericardial injury, and cardiomyopathy (132;133). Statins are effective therapy in those with increased cardiovascular risk factors and represent a reasonable approach in breast cancer survivors (132). Emphasis on cessation of smoking, maintenance of a healthy body weight, nutritious dietary pattern, regular exercise, and aggressive treatment of traditional risk factors such as hypertension and glucose intolerance also represent appropriate approaches (13;33;68) .

Emerging Approaches for unmet needs in breast cancer survivors:

SERMS:

As VVA and the osteopenia/osteoporosis/fracture complex are common in breast cancer survivors, an approach targeting both conditions would be useful. A major goal of pharmaceutical development has been to create SERMs with three separate actions: (a) prevention of breast cancer (b) decrease of bone resorption and prevention of fractures and (c) improvement in the symptoms of VVA. Most SERMS increase VMS but not enough to cause discontinuation. While tamoxifen and raloxifene prevent breast cancer, these two agents have not been shown to exert sufficient vaginal effects to treat VVA. Ospemiphene objectively improves VVA by increasing vaginal maturation indices and reducing the most bothersome symptoms (106;107) and preclinical studies suggest a neutral effect on breast. No clinical data yet exist to demonstrate breast cancer prevention and reduction of bone resorption. With respect to

lasofoxifene (an unapproved SERM), the PEARL (Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene) studies indicate prevention of breast cancer and fractures, reduction of bone resorption, and improvement of VVA, suggesting that this agent shows promise for breast cancer survivors. As breast cancer survivors experience a 0.5 to 1.0% rate of contralateral breast cancer per year, an agent blocking growth of these lesions when too small to be detected clinically would be useful. (134) . Of note, VTE rates were higher with lasofoxifene than other SERMS, but this agent also significantly reduced both stroke and MI (135). .Lasofoxifene will be starting phase 2 trials for treatment of locally advanced and metastatic breast cancer.

Tissue selective estrogen complex (TSEC) therapy:

The concept of combining a SERM with an estrogen to create a TSEC has been studied intensively in the past decade, and one TSEC, pairing oral conjugated equine estrogen ,45mg, with bazedoxifene, 20 mg, has been approved in the USA, Canada and by the European Union (136-143). In a series of studies (142;143) this combination improves hot flashes, reduces bone resorption, and exerts no stimulatory effects on the uterus while highly effective for VMS and VVA (144). In 2 year clinical trials, the effect on breast tenderness and breast density was the same as placebo (145;146) with no increase in breast cancer cases but further testing is needed. Pre-clinical studies demonstrate that this TSEC blocks the growth of three separate breast tumor models (147-149) (MCF-7 xenografts, NMU induced tumors, and estrogen induced ACI tumors in rats). Confirmation of breast anti-tumor effects in women would support the use of this TSEC in breast cancer survivors.

Miscellaneous agents:

Recent data suggest that the KNDy neurons (kisspeptin, neurokinin B and dynorphin) in the arcuate nucleus of the hypothalamus— particularly neurokinin B, mediate hot flashes (150). On this basis, two randomized controlled trials have evaluated the effects of oral neurokinin B receptor antagonists on hot flashes (76;151;152). Both agents (*MLE 4901 and fezolinetant)* reduced hot flash frequency and severity by 40 to 50% over placebo in postmenopausal women with negligible side effects(151;152). As these inhibitors act on specific hot flash mediating pathways, they show promise as effective, non–hormonal agents to treat hot flashes. The pregnancy-associated natural estrogen, estetrol, is undergoing clinical trials in post-menopausal women as a candidate for hormone therapy. A rationale for use of this agent is that estetrol did not stimulate the hormone dependent DMBA tumors in rats and could potentially be safe for use in breast cancer survivors. (153-159).

Conclusions:

Lifestyle optimization may improve estrogen deficiency symptoms, improve quality of life, and possibly improve prognosis. Smoking cessation, weight loss (if indicated), limiting or avoiding alcohol , maintaining adequate levels of vitamin D and calcium, eating a healthy diet and regular physical activity are suggested for all women with prior breast cancer. Non-pharmacologic therapies for VMS such as cognitive behavioral therapy, hypnosis, and acupuncture may be helpful as may vaginal lubricants and moisturizers. For women with more severe symptoms or signs of estrogen deficiency, pharmacologic agents are available to relieve VMS and VVA, and to prevent and treat fractures. Therapy must be individualized based on each woman's needs and goals for therapy. Several emerging approaches such as SERMs, TSECs, estetrol, and neurokinin

B inhibitors show promise as useful agents to expand options for symptom relief with less breast cancer risk but not yet tested in women with prior breast cancer.
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Reference List

1. **Siegel RL, Miller KD, Jemal A** 2017 Cancer Statistics, 2017. CA: a Cancer Journal for Clinicians 67:7-30
2. **Dubrawsky N** 1989 Cancer statistics. CA: a Cancer Journal for Clinicians 39:399-Dec
3. **American Cancer Society** 2017 Cancer TGreatment and Survivorship Facts and Figures 2014-2015. Atlanta ,Georgia: The American Cancer Society; 1-45
4. **Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM** 2010 Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International Journal of Cancer 127:2893-2917
5. **Pinto AC, de AE** 2011 Improving quality of life after breast cancer: dealing with symptoms. [Review]. Maturitas 70:343-348
6. **Davis SR, Panjari M, Robinson PJ, Fradkin P, Bell RJ** 2014 Menopausal symptoms in breast cancer survivors nearly 6 years after diagnosis. Menopause 21:1075-1081
7. **Howard-Anderson J, Ganz PA, Bower JE, Stanton AL** 2012 Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. [Review]. Journal of the National Cancer Institute 104:386-405
8. **Santen RJ, Demers L, Ohorodnik S, Settlage J, Langecker P, Blanchett D, Goss PE, Wang S** 2007 Superiority of gas chromatography/tandem mass spectrometry assay (GC/MS/MS) for estradiol for monitoring of aromatase inhibitor therapy. Steroids 72:666-671
9. **Ingle JN, Kalari KR, Buzdar AU, Robson ME, Goetz MP, Desta Z, Barman P, Dudenkov TT, Northfelt DW, Perez EA, Flockhart DA, Williard CV, Wang L, Weinshilboum RM 2015** Estrogens and their precursors in postmenopausal women with early breast cancer receiving anastrozole. Steroids 99:A-8
10. **Klein KO, Demers LM, Santner SJ, Baron J, Cutler GB, Jr., Santen RJ** 1995 Use of ultrasensitive recombinant cell bioassay to measure estrogen levels in women with breast cancer receiving the aromatase inhibitor, letrozole. Journal of Clinical Endocrinology & Metabolism 80:2658-2660
11. **Santen RJ** 2011 Clinical review: Effect of endocrine therapies on bone in breast cancer patients. [Review]. Journal of Clinical Endocrinology & Metabolism 96:308-319
12. **Santen RJ, Allred DC, Ardoin SP, Archer DF, Boyd N, Braunstein GD, Burger HG, Colditz GA, Davis SR, Gambacciani M, Gower BA, Henderson VW, Jarjour WN, Karas RH, Kleerekoper M, Lobo RA, Manson JE, Marsden J, Martin KA, Martin L, Pinkerton JV, Rubinow DR, Teede H, Thiboutot DM, Utian WH, Endocrine Society** 2010 Postmenopausal hormone therapy: an Endocrine Society scientific statement. [Review] [511 refs]. Journal of Clinical Endocrinology & Metabolism 95:Suppl-Sus66
13. **Stuenkel CA, Davis SR, Gompel A, Lumsden MA, Murad MH, Pinkerton JV, Santen RJ** 2015 Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. Journal of Clinical Endocrinology & Metabolism 100:3975-4011

14. **Eden J** 2016 ENDOCRINE DILEMMA: Managing menopausal symptoms after breast cancer. [Review]. European Journal of Endocrinology 174:R71-R77

15. **Faubion SS, Loprinzi CL, Ruddy KJ** 2016 Management of Hormone Deprivation Symptoms After Cancer. [Review]. Mayo Clinic Proceedings 91:1133-1146

16. **Kuhle CL, Kapoor E, Sood R, Thielen JM, Jatoi A, Faubion SS** 2016 Menopausal hormone therapy in cancer survivors: A narrative review of the literature. [Review]. Maturitas 92:86-96

17. **Brennan ME, Houssami N** 2011 Overview of long term care of breast cancer survivors. [Review]. Maturitas 69:106-112

18. **Hickey M, Emery LI, Gregson J, Doherty DA, Saunders CM** 2010 The multidisciplinary management of menopausal symptoms after breast cancer: a unique model of care. Menopause 17:727-733

19. **Hickey M, Saunders C, Partridge A, Santoro N, Joffe H, Stearns V** 2008 Practical clinical guidelines for assessing and managing menopausal symptoms after breast cancer. [Review] [124 refs]. Annals of Oncology 19:1669-1680

20. **Lammerink EA, de Bock GH, Schroder CP, Mourits MJ** 2012 The management of menopausal symptoms in breast cancer survivors: case-based approach. [Review]. Maturitas 73:265-268

21. **Gupta P, Sturdee DW, Palin SL, Majumder K, Fear R, Marshall T, Paterson I** 2006 Menopausal symptoms in women treated for breast cancer: the prevalence and severity of symptoms and their perceived effects on quality of life. Climacteric 9:49-58

22. **Marino JL, Saunders CM, Emery LI, Green H, Doherty DA, Hickey M** 2014 Nature and severity of menopausal symptoms and their impact on quality of life and sexual function in cancer survivors compared with women without a cancer history. Menopause 21:267-274

23. **Conde DM, Pinto-Neto AM, Cabello C, Sa DS, Costa-Paiva L, Martinez EZ** 2005 Menopause symptoms and quality of life in women aged 45 to 65 years with and without breast cancer. Menopause 12:436-443

24. **Schultz PN, Klein MJ, Beck ML, Stava C, Sellin RV** 2005 Breast cancer: relationship between menopausal symptoms, physiologic health effects of cancer treatment and physical constraints on quality of life in long-term survivors. Journal of Clinical Nursing 14:204-211

25. **Biglia N, Cozzarella M, Cacciari F, Ponzone R, Roagna R, Maggiorotto F, Sismondi P** 2003 Menopause after breast cancer: a survey on breast cancer survivors. Maturitas 45:29-38

26. **Crandall C, Petersen L, Ganz PA, Greendale GA** 2004 Association of breast cancer and its therapy with menopause-related symptoms. Menopause 11:519-530

27. **Harris PF, Remington PL, Trentham-Dietz A, Allen CI, Newcomb PA** 2002 Prevalence and treatment of menopausal symptoms among breast cancer survivors. Journal of Pain & Symptom Management 23:501-509

28. **Seib C** 2017 Menopausea symtom clusters and their correlates inwomen with and without a history of breast cancer.

29. **Goodwin PJ, Ennis M, Pritchard KI, McCready D, Koo J, Sidlofsky S, Trudeau M, Hood N, Redwood S** 1999 Adjuvant treatment and onset of menopause predict weight gain after breast cancer diagnosis. Journal of Clinical Oncology 17:120-129

30. **Robinson PJ, Bell RJ, Zecena Morales CS, Fradkin P, Davis SR** 2015 Minimal-trauma fracture in women with breast cancer surviving for at least 5 years from diagnosis. Osteoporosis International 26:795-800

31. **Biglia N, Bounous VE, Sgro LG, D'Alonzo M, Pecchio S, Nappi RE** 2015 Genitourinary Syndrome of Menopause in Breast Cancer Survivors: Are We Facing New and Safe Hopes?. [Review]. Clinical Breast Cancer 15:413-420

32. **LoPrinzi C, Santen RJ** Management of Hot Flashes.

33. **Pinkerton JV** 2017 Hormone therapy: 2016 NAMS PositionStatement.

34. **Daley A, Stokes-Lampard H, Macarthur C** 2011 Exercise for vasomotor menopausal symptoms. [Review][Update in Cochrane Database Syst Rev. 2014;11:CD006108; PMID: 25431132], [Update of Cochrane Database Syst Rev. 2007;(4):CD006108; PMID: 17943886]. Cochrane Database of Systematic Reviews (5):CD006108, 2011CD006108

35. **Bailey TG, Cable NT, Aziz N, Dobson R, Sprung VS, Low DA, Jones H** 2016 Exercise training reduces the frequency of menopausal hot flushes by improving thermoregulatory control. Menopause 23:708-718

36. **Guthrie KA, LaCroix AZ, Ensrud KE, Joffe H, Newton KM, Reed SD, Caan B, Carpenter JS, Cohen LS, Freeman EW, Larson JC, Manson JE, Rexrode K, Skaar TC, Sternfeld B, Anderson GL** 2015 Pooled Analysis of Six Pharmacologic and Nonpharmacologic Interventions for Vasomotor Symptoms. Obstetrics & Gynecology 126:413-422

37. **Kroenke CH, Caan BJ, Stefanick ML, Anderson G, Brzyski R, Johnson KC, LeBlanc E, Lee C, La Croix AZ, Park HL, Sims ST, Vitolins M, Wallace R** 2012 Effects of a dietary intervention and weight change on vasomotor symptoms in the Women's Health Initiative. Menopause 19:980-988

38. **Caan BJ, Natarajan L, Parker B, Gold EB, Thomson C, Newman V, Rock CL, Pu M, Al-Delaimy W, Pierce JP** 2011 Soy food consumption and breast cancer prognosis. Cancer Epidemiology, Biomarkers & Prevention 20:854-858

39. **Newton KM, Reed SD, Uchiyama S, Qu C, Ueno T, Iwashita S, Gunderson G, Fuller S, Lampe JW** 2015 A cross-sectional study of equol producer status and self-reported vasomotor symptoms. Menopause 22:489-495

40. **Elkins GR, Fisher WI, Johnson AK, Carpenter JS, Keith TZ** 2013 Clinical hypnosis in the treatment of postmenopausal hot flashes: a randomized controlled trial. Menopause 20:291-298

41. **Guirguis M, Abdelmalak J, Jusino E, Hansen MR, Girgis GE** 2015 Stellate Ganglion Block for the Treatment of Hot Flashes in Patients with Breast Cancer: A Literature Review. [Review]. Ochsner Journal 15:162-169

42. **Lesi G, Razzini G, Musti MA, Stivanello E, Petrucci C, Benedetti B, Rondini E, Ligabue MB, Scaltriti L, Botti A, Artioli F, Mancuso P, Cardini F, Pandolfi P** 2016 Acupuncture As an Integrative Approach for the Treatment of Hot Flashes in Women With Breast Cancer: A Prospective Multicenter Randomized Controlled Trial (AcCliMaT). Journal of Clinical Oncology 34:1795-1802

43. **Kim DI, Jeong JC, Kim KH, Rho JJ, Choi MS, Yoon SH, Choi SM, Kang KW, Ahn HY, Lee MS** 2011 Acupuncture for hot flushes in perimenopausal and postmenopausal women: a randomised, sham-controlled trial. Acupuncture in Medicine 29:249-256

44. **Guldberg TL, Christensen S, Zachariae R, Jensen AB** 2017 Prognostic factors in early breast cancer associated with body mass index, physical functioning, physical activity,

and comorbidity: data from a nationwide Danish cohort. Breast Cancer Research & Treatment 162:159-167

45. **Stuenkel CA, Gass ML, Manson JE, Lobo RA, Pal L, Rebar RW, Hall JE** 2012 A decade after the Women's Health Initiative--the experts do agree. Menopause 19:846-847

46. Chomistek AK, Manson JE, Stefanick ML, Lu B, Sands-Lincoln M, Going SB, Garcia L, Allison MA, Sims ST, LaMonte MJ, Johnson KC, Eaton CB 2013 Relationship of sedentary behavior and physical activity to incident cardiovascular disease: results from the Women's Health Initiative. Journal of the American College of Cardiology 61:2346-2354

47. **Daly RM** 2017 Exercise and nutritional approaches to prevent frail bones, falls and fractures: an update. [Review]. Climacteric 20:119-124

48. **Robinson PJ, Bell RJ, Davis SR** 2014 Obesity is associated with a poorer prognosis in women with hormone receptor positive breast cancer. Maturitas 79:279-286

49. **Holahan CK, Holahan CJ, North RJ, Hayes RB, Powers DA, Ockene JK** 2013 Smoking status, physical health-related quality of life, and mortality in middle-aged and older women. Nicotine Tob Res 15:662-669

50. **Coviello JS, Knobf MT, Laclergue S** 2013 Assessing and managing metabolic syndrome and cardiovascular risk in midlife women. Journal of Cardiovascular Nursing 28:147-156

51. **van den Brandt PA, Schulpen M** 2017 Mediterranean diet adherence and risk of postmenopausal breast cancer: results of a cohort study and meta-analysis. International Journal of Cancer 140:2220-2231

52. **Karkkainen MK, Tuppurainen M, Salovaara K, Sandini L, Rikkonen T, Sirola J, Honkanen R, Arokoski J, Alhava E, Kroger H** 2010 Does daily vitamin D 800 IU and calcium 1000 mg supplementation decrease the risk of falling in ambulatory women aged 65-71 years? A 3-year randomized population-based trial (OSTPRE-FPS). Maturitas 65:359-365

53. **Avenell A, Gillespie WJ, Gillespie LD, O'Connell D** 2009 Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst RevCD000227

54. **Rosen CJ, Gallagher JC** 2011 The 2011 IOM report on vitamin D and calcium requirements for north america: clinical implications for providers treating patients with low bone mineral density. [Review]. Journal of Clinical Densitometry 14:79-84

55. **Institute of Medicine** 2011 Dietary reference intakes for calcium and vitamin D. Washington DC:

56. **Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS, Mayne ST, Rosen CJ, Shapses SA** 2011 The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. Journal of Clinical Endocrinology & Metabolism 96:53-58

57. **Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM, Endocrine Society** 2011 Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline.[Erratum appears in J Clin Endocrinol Metab. 2011 Dec;96(12):3908]. Journal of Clinical Endocrinology & Metabolism 96:1911-1930

58. **Yao S, Kwan ML, Ergas IJ, Roh JM, Cheng TD, Hong CC, McCann SE, Tang L, Davis W, Liu S, Quesenberry CP, Jr., Lee MM, Ambrosone CB, Kushi LH** 2017

Association of Serum Level of Vitamin D at Diagnosis With Breast Cancer Survival: A Case-Cohort Analysis in the Pathways Study. JAMA Oncology 3:351-357

59. **Anderson DJ, Seib C, McCarthy AL, Yates P, Porter-Steele J, McGuire A, Young L** 2015 Facilitating lifestyle changes to manage menopausal symptoms in women with breast cancer: a randomized controlled pilot trial of The Pink Women's Wellness Program. Menopause 22:937-945

60. **Tepper PG, Brooks MM, Randolph JF, Jr., Crawford SL, El Khoudary SR, Gold EB, Lasley BL, Jones B, Joffe H, Hess R, Avis NE, Harlow S, McConnell DS, Bromberger JT, Zheng H, Ruppert K, Thurston RC** 2016 Characterizing the trajectories of vasomotor symptoms across the menopausal transition. Menopause 23:1067-1074

61. **Col NF, Hirota LK, Orr RK, Erban JK, Wong JB, Lau J** 2001 Hormone replacement therapy after breast cancer: a systematic review and quantitative assessment of risk. [Review] [62 refs]. Journal of Clinical Oncology 19:2357-2363

62. **Col NF, Kim JA, Chlebowski RT** 2005 Menopausal hormone therapy after breast cancer: a meta-analysis and critical appraisal of the evidence.[see comment]. Breast Cancer Research 7:R535-R540

63. **Holmberg L, Anderson H, HABITS steering and data monitoring committees** 2004 HABITS (hormonal replacement therapy after breast cancer--is it safe?), a randomised comparison: trial stopped.[see comment]. Lancet 363:453-455

64. **Holmberg L, Iversen OE, Rudenstam CM, Hammar M, Kumpulainen E, Jaskiewicz J, Jassem J, Dobaczewska D, Fjosne HE, Peralta O, Arriagada R, Holmqvist M, Maenpaa J, HABITS Study Group** 2008 Increased risk of recurrence after hormone replacement therapy in breast cancer survivors.[see comment][erratum appears in J Natl Cancer Inst. 2008 May 7;100(9):685 Note: Maenpa, Johanna [corrected to Maenpaa, Johanna]]. Journal of the National Cancer Institute 100:475-482

65. **von SE, Rutqvist LE, Stockholm Breast Cancer Study Group** 2005 Menopausal hormone therapy after breast cancer: the Stockholm randomized trial.[see comment]. Journal of the National Cancer Institute 97:533-535

66. **Kenemans P, Bundred NJ, Foidart JM, Kubista E, von SB, Sismondi P, Vassilopoulou-Sellin R, Yip CH, Egberts J, Mol-Arts M, Mulder R, van OS, Beckmann MW, LIBERATE Study Group** 2009 Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial.[see comment]. Lancet Oncology 10:135-146;see erratum March 10 page 209

67. **Committee on Practice Bulletins-Gynecology** 2012 ACOG Practice Bulletin No. 126: Management of gynecologic issues in women with breast cancer. Obstetrics & Gynecology 119:666-682

68. **Runowicz CD, Leach CR, Henry NL, Henry KS, Mackey HT, Cowens-Alvarado RL, Cannady RS, Pratt-Chapman ML, Edge SB, Jacobs LA, Hurria A, Marks LB, LaMonte SJ, Warner E, Lyman GH, Ganz PA** 2016 American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. [Review]. Journal of Clinical Oncology 34:611-635

69. **Huang AJ, Cummings SR, Schembri M, Vittinghoff E, Ganz P, Grady D** 2016 Continuous transdermal nitroglycerin therapy for menopausal hot flashes: a single-arm, dose-escalation trial. Menopause 23:330-334

70. **Johns C, Seav SM, Dominick SA, Gorman JR, Li H, Natarajan L, Mao JJ, Su HI** 2016 Informing hot flash treatment decisions for breast cancer survivors: a systematic

review of randomized trials comparing active interventions. [Review]. Breast Cancer Research & Treatment 156:415-426

71. **Leon-Ferre RA, Majithia N, Loprinzi CL** 2017 Management of hot flashes in women with breast cancer receiving ovarian function suppression. [Review]. Cancer Treatment Reviews 52:82-90

72. **ShamsT FbHFAAABMMFM** 2014 SSRIs for hot flashes: a systematic review and meta-analysis of randomized trials. 29 ed.; 204-213

73. **Bardia A, Novotny P, Sloan J, Barton D, Loprinzi C** 2009 Efficacy of nonestrogenic hot flash therapies among women stratified by breast cancer history and tamoxifen use: a pooled analysis. Menopause 16:477-483

74. **Nelson HD, Vesco KK, Haney E, Fu R, Nedrow A, Miller J, Nicolaidis C, Walker M, Humphrey L** 2006 Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. [Review] [74 refs]. JAMA 295:2057-2071

75. **Freeman EW, Ensrud KE, Larson JC, Guthrie KA, Carpenter JS, Joffe H, Newton KM, Sternfeld B, LaCroix AZ** 2015 Placebo improvement in pharmacologic treatment of menopausal hot flashes: time course, duration, and predictors. Psychosomatic Medicine 77:167-175

76. **Sassarini J AR** 2017 New pathways in the treatment for menopausal hot flashes.

77. **Loprinzi CL, Barton DL, Sloan JA, Novotny PJ, Dakhil SR, Verdirame JD, Knutson WH, Kelaghan J, Christensen B** 2008 Mayo Clinic and North Central Cancer Treatment Group hot flash studies: a 20-year experience. Menopause 15:t-60

78. **Donneyong MM, Bykov K, Bosco-Levy P, Dong YH, Levin R, Gagne JJ** 2016 Risk of mortality with concomitant use of tamoxifen and selective serotonin reuptake inhibitors: multi-database cohort study. BMJ 354:i5014

79. **Binkhorst L, Bannink M, de BP, Ruit J, Droogendijk H, van Alphen RJ, den Boer TD, Lam MH, Jager A, van GT, Mathijssen RH** 2016 Augmentation of Endoxifen Exposure in Tamoxifen-Treated Women Following SSRI Switch. Clinical Pharmacokinetics 55:249-255

80. **Probst-Schendzielorz K, Viviani R, Stingl JC** 2015 Effect of Cytochrome P450 polymorphism on the action and metabolism of selective serotonin reuptake inhibitors. [Review]. Expert Opinion On Drug Metabolism & Toxicology 11:1219-1232

81. **Lash TL, Cronin-Fenton D, Ahern TP, Rosenberg CL, Lunetta KL, Silliman RA, Hamilton-Dutoit S, Garne JP, Ewertz M, Sorensen HT, Pedersen L** 2010 Breast cancer recurrence risk related to concurrent use of SSRI antidepressants and tamoxifen. Acta Oncologica 49:305-312

82. In brief: Tamoxifen and SSRI interaction 2009 Medical Letter on Drugs & Therapeutics 51:45

83. **Joffe H, Crawford SL, Freeman MP, White DP, Bianchi MT, Kim S, Economou N, Camuso J, Hall JE, Cohen LS** 2016 Independent Contributions of Nocturnal Hot Flashes and Sleep Disturbance to Depression in Estrogen-Deprived Women. Journal of Clinical Endocrinology & Metabolism 101:3847-3855

84. **Loprinzi CL, Sloan J, Stearns V, Slack R, Iyengar M, Diekmann B, Kimmick G, Lovato J, Gordon P, Pandya K, Guttuso T, Jr., Barton D, Novotny P** 2009 Newer antidepressants and gabapentin for hot flashes: an individual patient pooled analysis. Journal of Clinical Oncology 27:2831-2837

85. **Martoni A, Longhi A, Canova N, Pannuti F** 1991 High-dose medroxyprogesterone acetate versus oophorectomy as first-line therapy of advanced breast cancer in premenopausal patients. Oncology 48:1-6

86. **Pannuti F, Martoni A, Cilenti G, Camaggi CM, Fruet F** 1988 Adjuvant therapy for operable breast cancer with medroxyprogesterone acetate alone in postmenopausal patients or in combination with CMF in premenopausal patients. European Journal of Cancer & Clinical Oncology 24:423-429

87. **Santen RJ, Manni A, Harvey H, Redmond C** 1990 Endocrine treatment of breast cancer in women. [Review] [282 refs]. Endocrine Reviews 11:221-265

88. **Hitchcock CL, Prior JC** 2012 Oral micronized progesterone for vasomotor symptoms--a placebo-controlled randomized trial in healthy postmenopausal women. Menopause 19:886-893

89. **Fournier A, Fabre A, Mesrine S, Boutron-Ruault MC, Berrino F, Clavel-Chapelon F** 2008 Use of different postmenopausal hormone therapies and risk of histology- and hormone receptor-defined invasive breast cancer. Journal of Clinical Oncology 26:1260-1268

90. **Fournier A, Berrino F, Riboli E, Avenel V, Clavel-Chapelon F** 2005 Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort.[see comment]. International Journal of Cancer 114:448-454

91. **Fournier A** 2009 Estrogen-progestagen menopausal homone therapy and breast cancer:does delay from menopause onset to treatment initiation influence risks? online publication Sept 14, 2009 ed.

92. **Fournier A, Mesrine S, Dossus L, Boutron-Ruault MC, Clavel-Chapelon F, Chabbert-Buffet N** 2014 Risk of breast cancer after stopping menopausal hormone therapy in the E3N cohort.[Erratum appears in Breast Cancer Res Treat. 2014 Aug;147(1):225]. Breast Cancer Research & Treatment 145:535-543

93. **Cordina-Duverger E, Truong T, Anger A, Sanchez M, Arveux P, Kerbrat P, Guenel P** 2013 Risk of breast cancer by type of menopausal hormone therapy: a case-control study among post-menopausal women in France. PLoS ONE [Electronic Resource] 8:e78016

94. **Santen R, Pritchard K, Burger H** 1998 The consensus conference on treatment of estrogen deficiency symptoms in women surviving breast cancer. [Review] [0 refs]. Obstetrical & Gynecological Survey 53:Suppl-83

95. **Hormone Therapy Position Statement Advisory Panel** 2017 Position Staement:the 2017 hormone therapy position statement of The North American Menopause Society. 24 ed.

96. **Santen RJ** 2015 Vaginal administration of estradiol: effects of dose, preparation and timing on plasma estradiol levels. [Review]. Climacteric 18:121-134

97. **Song RX, Mor G, Naftolin F, McPherson RA, Song J, Zhang Z, Yue W, Wang J, Santen RJ** 2001 Effect of long-term estrogen deprivation on apoptotic responses of breast cancer cells to 17beta-estradiol.[see comment]. Journal of the National Cancer Institute 93:1714-1723

98. **Le R, I, Dell'Aniello S, Bonnetain F, Azoulay L, Suissa S** 2012 Local estrogen therapy and risk of breast cancer recurrence among hormone-treated patients: a nested case-control study. Breast Cancer Research & Treatment 135:603-609

99. **O'Meara ES, Rossing MA, Daling JR, Elmore JG, Barlow WE, Weiss NS** 2001 Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality. Journal of the National Cancer Institute 93:754-762

100. **Dew JE, Wren BG, Eden JA** 2003 A cohort study of topical vaginal estrogen therapy in women previously treated for breast cancer. Climacteric 6:45-52

101. **Wills S, Ravipati A, Venuturumilli P, Kresge C, Folkerd E, Dowsett M, Hayes DF, Decker DA** 2012 Effects of vaginal estrogens on serum estradiol levels in postmenopausal breast cancer survivors and women at risk of breast cancer taking an aromatase inhibitor or a selective estrogen receptor modulator. Journal of oncology practice/American Society of Clinical Oncology 8:144-148

102. **American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice, Farrell R** 2016 ACOG Committee Opinion No. 659: The Use of Vaginal Estrogen in Women With a History of Estrogen-Dependent Breast Cancer. Obstetrics & Gynecology 127:e93-e96

103. **Baum M, Budzar AU, Cuzick J, Forbes J, Houghton JH, Klijn JG, Sahmoud T, ATAC Trialists' Group** 2002 Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial.[Erratum appears in Lancet 2002 Nov 9;360(9344):1520]. Lancet 359:2131-2139

104. **Runowicz CD, Costantino JP, Wickerham DL, Cecchini RS, Cronin WM, Ford LG, Vogel VG, Wolmark N** 2011 Gynecologic conditions in participants in the NSABP breast cancer prevention study of tamoxifen and raloxifene (STAR). American Journal of Obstetrics & Gynecology 205:535

105. **Bevers TB** 2010 Breast cancer prevention: an update of the STAR trial. Current Treatment Options in Oncology 11:66-69

106. **Constantine G, Graham S, Koltun WD, Kingsberg SA** 2014 Assessment of ospemifene or lubricants on clinical signs of VVA. Journal of Sexual Medicine 11:1033-1041

107. **Constantine G, Graham S, Portman DJ, Rosen RC, Kingsberg SA** 2015 Female sexual function improved with ospemifene in postmenopausal women with vulvar and vaginal atrophy: results of a randomized, placebo-controlled trial. Climacteric 18:226-232

108. **Martel C, Labrie F, Archer DF, Ke Y, Gonthier R, Simard JN, Lavoie L, Vaillancourt M, Montesino M, Balser J, Moyneur E**, other participating members of the Prasterone Clinical Research Group 2016 Serum steroid concentrations remain within normal postmenopausal values in women receiving daily 6.5mg intravaginal prasterone for 12 weeks. Journal of Steroid Biochemistry & Molecular Biology 159:142-153

109. **Fernandes T, Costa-Paiva LH, Pedro AO, Baccaro LF, Pinto-Neto AM** 2016 Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on vaginal atrophy: a randomized controlled trial. Menopause 23:792-798

110. **Witherby S, Johnson J, Demers L, Mount S, Littenberg B, Maclean CD, Wood M, Muss H** 2011 Topical testosterone for breast cancer patients with vaginal atrophy related to aromatase inhibitors: a phase I/II study. Oncologist 16:424-431

111. **Hutchinson-Colas J, Segal S** 2015 Genitourinary syndrome of menopause and the use of laser therapy. [Review]. Maturitas 82:342-345

112. **Position Statement: the American College of Obstetricians and Gynecologists and the American Congress of Obstetricians and Gynecologists** 2016 Fractional laser treatment of vulvovaginal atrophy and U.S. Food and drug Administration Clearance.

113. **Gambacciani M, Palacios S** 2017 Laser therapy for the restoration of vaginal function. [Review]. Maturitas 99:10-15

114. **Gambacciani M, Levancini M** 2017 Vaginal erbium laser as second-generation thermotherapy for the genitourinary syndrome of menopause: a pilot study in breast cancer survivors. Menopause 24:316-319

115. **Gambacciani M, Palacios S** 2017 Laser therapy for the restoration of vaginal function. [Review]. Maturitas 99:10-15

116. **Worsley R** 2017 Moderate-Severe vasomotor symptoms are associated with moderate-devere depressive symptoms.

117. **Joffe H, Crawford S, Economou N, Kim S, Regan S, Hall JE, White D** 2013 A gonadotropin-releasing hormone agonist model demonstrates that nocturnal hot flashes interrupt objective sleep. Sleep 36:1977-1985

118. **Weber MT, Maki PM, McDermott MP** 2014 Cognition and mood in perimenopause: a systematic review and meta-analysis. [Review]. Journal of Steroid Biochemistry & Molecular Biology 142:90-98

119. **Straube B** 2012 An overview of the neuro-cognitive processes involved in the encoding, consolidation, and retrieval of true and false memories. [Review]. Behavioral & Brain Functions [Electronic Resource]: BBF 8:35

120. **Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de AM, Melton LJ, III** 2007 Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause.[see comment]. Neurology 69:1074-1083

121. **Shuster LT, Gostout BS, Grossardt BR, Rocca WA** 2008 Prophylactic oophorectomy in premenopausal women and long-term health.[see comment]. [Review] [73 refs]. Menopause International 14:111-116

122. **Ryan J, Scali J, Carriere I, Amieva H, Rouaud O, Berr C, Ritchie K, Ancelin ML** 2014 Impact of a premature menopause on cognitive function in later life. BJOG: An International Journal of Obstetrics & Gynaecology 121:1729-1739

123. **Hadji P, Body JJ, Aapro MS, Brufsky A, Coleman RE, Guise T, Lipton A, Tubiana-Hulin M** 2008 Practical guidance for the management of aromatase inhibitor-associated bone loss. Annals of Oncology 19:1407-1416

124. **Geisler J, Lonning PE, Krag LE, Lokkevik E, Risberg T, Hagen AI, Schlichting E, Lien EA, Ofjord ES, Eide GE, Polli A, di SE, Paolini J** 2006 Changes in bone and lipid metabolism in postmenopausal women with early breast cancer after terminating 2-year treatment with exemestane: a randomised, placebo-controlled study. European Journal of Cancer 42:2968-2975

125. **Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, Abraham M, Medeiros A, V, Badran A, Bonfill X, Bradbury J, Clarke M, Collins R, Davis SR, Delmestri A, Forbes JF, Haddad P, Hou MF, Inbar M, Khaled H, Kielanowska J, Kwan WH, Mathew BS, Mittra I, Muller B, Nicolucci A, Peralta O, Pernas F, Petruzelka L, Pienkowski T, Radhika R, Rajan B, Rubach MT, Tort S, Urrutia G, Valentini M, Wang Y, Peto R, Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group** 2013 Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 381:805-816

126. **Cuzick J, Powles T, Veronesi U, Forbes J, Edwards R, Ashley S, Boyle P** 2003 Overview of the main outcomes in breast-cancer prevention trials. [Review] [9 refs]. Lancet 361:296-300

127. **Nelson HD, Smith ME, Griffin JC, Fu R** 2013 Use of medications to reduce risk for primary breast cancer: a systematic review for the U.S. Preventive Services Task Force. [Review]. Annals of Internal Medicine 158:604-614

128. **Qaseem A, Forciea MA** 2017 Treatment of low bene density or osteoporosis to prevent fractures in men and women: a clinical practice guideline update from the American College of Physicians.; 1-22

129. **Mathew A, Brufsky AM** 2014 The use of adjuvant bisphophonates in the treatment of early-stage breast cancer. [Review]. Clinical Advances in Hematology & Oncology 12:749-756

130. **Gnant M** 2015 The impact of adjuvant denosumab on disease-ree survival: results from 3,425 postmenopausal patients of the ABCSG-18 trial.

131. **Dhesy-Thind S, Fletcher GG, Blanchette PS, Clemons MJ, Dillmon MS, Frank ES, Gandhi S, Gupta R, Mates M, Moy B, Vandenberg T, Van Poznak CH** 2017 Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. Journal of Clinical Oncology 35:2062-2081

132. **McSweeney JC, Rosenfeld AG, Abel WM, Braun LT, Burke LE, Daugherty SL, Fletcher GF, Gulati M, Mehta LS, Pettey C, Reckelhoff JF, American Heart Association Council on Cardiovascular and Stroke Nursing CoCCCoEaPCoHCoLaCHaCoQoCaO** 2016 Preventing and Experiencing Ischemic Heart Disease as a Woman: State of the Science: A Scientific Statement From the American Heart Association. [Review]. Circulation 133:1302-1331

133. **Yeh ET, Chang HM** 2016 Oncocardiology-Past, Present, and Future: A Review. JAMA Cardiology 1:1066-1072

134. **Hartmann LC, Degnim AC, Santen RJ, Dupont WD, Ghosh K** 2015 Atypical hyperplasia of the breast--risk assessment and management options. New England Journal of Medicine 372:78-89

135. **Cuzick J, Sestak I, Bonanni B, Costantino JP, Cummings S, Decensi A, Dowsett M, Forbes JF, Ford L, LaCroix AZ, Mershon J, Mitlak BH, Powles T, Veronesi U, Vogel V, Wickerham DL, SERM Chemoprevention of Breast Cancer Overview Group** 2013 Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data. [Review]. Lancet 381:1827-1834

136. **Pazhekattu R, Lau AN, Adachi JD** 2015 The Tissue-Selective Estrogen Complex: A Review of Current Evidence. [Review]. Rheumatology & Therapy 2:47-58

137. **Palacios S, Mejia RA** 2015 Bazedoxifene/conjugated estrogens combination for the treatment of the vasomotor symptoms associated with menopause and for prevention of osteoporosis in postmenopausal women. Drugs of Today 51:107-116

138. **Palacios S, Arias L, Lavenberg J, Pan K, Mirkin S, Komm BS** 2016 Evaluation of efficacy and safety of conjugated estrogens/bazedoxifene in a Latin American population. Climacteric 19:261-267

139. **Smith CL, Santen RJ, Komm B, Mirkin S** 2014 Breast-related effects of selective estrogen receptor modulators and tissue-selective estrogen complexes. [Review]. Breast Cancer Research 16:212

140. **Wardell SE, Nelson ER, McDonnell DP** 2014 From empirical to mechanism-based discovery of clinically useful Selective Estrogen Receptor Modulators (SERMs). Steroids 90:30-38

141. **Komm BS, Mirkin S, Jenkins SN** 2014 Development of conjugated estrogens/bazedoxifene, the first tissue selective estrogen complex (TSEC) for management of menopausal hot flashes and postmenopausal bone loss. [Review]. Steroids 90:71-81

142. **Mirkin S, Ryan KA, Chandran AB, Komm BS** 2014 Bazedoxifene/conjugated estrogens for managing the burden of estrogen deficiency symptoms. [Review]. Maturitas 77:24-31

143. **Pinkerton JV, Abraham L, Bushmakin AG, Cappelleri JC, Racketa J, Shi H, Chines AA, Mirkin S** 2014 Evaluation of the efficacy and safety of bazedoxifene/conjugated estrogens for secondary outcomes including vasomotor symptoms in postmenopausal women by years since menopause in the Selective estrogens, Menopause and Response to Therapy (SMART) trials. Journal of Women's Health 23:18-28

144. **Lobo RA, Pinkerton JV, Gass ML, Dorin MH, Ronkin S, Pickar JH, Constantine G** 2009 Evaluation of bazedoxifene/conjugated estrogens for the treatment of menopausal symptoms and effects on metabolic parameters and overall safety profile. Fertility & Sterility 92:1025-1038

145. **Harvey JA, Pinkerton JV, Baracat EC, Shi H, Chines AA, Mirkin S** 2013 Breast density changes in a randomized controlled trial evaluating bazedoxifene/conjugated estrogens. Menopause 20:138-145

146. **Pinkerton JV, Harvey JA, Pan K, Thompson JR, Ryan KA, Chines AA, Mirkin S** 2013 Breast effects of bazedoxifene-conjugated estrogens: a randomized controlled trial. Obstetrics & Gynecology 121:959-968

147. **Santen RJ, Song Y, Yue W, Wang JP, Heitjan DF** 2013 Effects of menopausal hormonal therapy on occult breast tumors. [Review]. Journal of Steroid Biochemistry & Molecular Biology 137:150-156

148. **Yue W, Wang JP, Santen RJ** 2017 Effects of tissue selective estrogen complex (TSEC) on growth of estrogen-dependent breast cancer in the ACI rat model Endo 2017 abstract Sunday 150

149. **Yue W,Wang JP, Santen RJ** 2015 Differential effects of conjugated equine estrogens and estradiol on breast cancer: implications for menopausal hormone therapy in women Endo 2015 Abstract

150. **Rance NE, Dacks PA, Mittelman-Smith MA, Romanovsky AA, Krajewski-Hall SJ** 2013 Modulation of body temperature and LH secretion by hypothalamic KNDy (kisspeptin, neurokinin B and dynorphin) neurons: a novel hypothesis on the mechanism of hot flushes. [Review]. Frontiers in Neuroendocrinology 34:211-227

151. **Prague JK** 2017 Neurokinin 3 receptor antagonism as a novel treatment for menopausal hot flushes: a phase 2, randomized, bouble-blind, placebor-controlled trial.

152. **Fraser GL DHea** 2017 Clinical evaluationof the NK3 receptor antagonists Fezolinet (a.k.a. ESN 364) for the treatment of menopausal hot flashes.

153. **Tskitishvili E, Pequeux C, Munaut C, Viellevoye R, Nisolle M, Noel A, Foidart JM** 2016 Use of estetrol with other steroids for attenuation of neonatal hypoxic-ischemic brain injury: to combine or not to combine? Oncotarget 7:33722-33743

154. **Coelingh Bennink HJ, Verhoeven C, Zimmerman Y, Visser M, Foidart JM, Gemzell-Danielsson K** 2016 Clinical effects of the fetal estrogen estetrol in a multiple-rising-dose study in postmenopausal women. Maturitas 91:93-100

155. **Mawet M, Maillard C, Klipping C, Zimmerman Y, Foidart JM, Coelingh Bennink HJ** 2015 Unique effects on hepatic function, lipid metabolism, bone and growth

endocrine parameters of estetrol in combined oral contraceptives. European Journal of Contraception & Reproductive Health Care 20:463-475

156. **Gerard C, Mestdagt M, Tskitishvili E, Communal L, Gompel A, Silva E, Arnal JF, Lenfant F, Noel A, Foidart JM, Pequeux C** 2015 Combined estrogenic and anti-estrogenic properties of estetrol on breast cancer may provide a safe therapeutic window for the treatment of menopausal symptoms. Oncotarget 6:17621-17636

157. **Gerard C, Blacher S, Communal L, Courtin A, Tskitishvili E, Mestdagt M, Munaut C, Noel A, Gompel A, Pequeux C, Foidart JM** 2015 Estetrol is a weak estrogen antagonizing estradiol-dependent mammary gland proliferation. Journal of Endocrinology 224:85-95

158. **Tskitishvili E, Nisolle M, Munaut C, Pequeux C, Gerard C, Noel A, Foidart JM** 2014 Estetrol attenuates neonatal hypoxic-ischemic brain injury. Experimental Neurology 261:298-307

159. **Abot A, Fontaine C, Buscato M, Solinhac R, Flouriot G, Fabre A, Drougard A, Rajan S, Laine M, Milon A, Muller I, Henrion D, Adlanmerini M, Valera MC, Gompel A, Gerard C, Pequeux C, Mestdagt M, Raymond-Letron I, Knauf C, Ferriere F, Valet P, Gourdy P, Katzenellenbogen BS, Katzenellenbogen JA, Lenfant F, Greene GL, Foidart JM, Arnal JF** 2014 The uterine and vascular actions of estetrol delineate a distinctive profile of estrogen receptor alpha modulation, uncoupling nuclear and membrane activation. EMBO molecular medicine 6:1328-1346

Figure 1 Hot flash frequency and composite score with non-hormonal prescription therapies for relief of VMS. Upper panel: Effect on frequency of VMS; lower panel: effect on composite score (severity times frequency; best representation of effect); open bars, placebo, colored bars therapies; length of bars, ranges in studies; horizontal bar, means. The horizontal lines without bars represent studies in which the means but not ranges were reported. Figure reproduced from Stuenkel CA et al "Treatment of Symptoms of the Menopause: an Endocrine Society Clinical Practice Guideline . JCEM 100:3975-4011, 2015 with permission of the Journal and authors.

Figure 2. Percentage changes from baseline of bone formation (upper panel) and bone resorption markers (lower panel) at the end of 24 month treatment with placebo or exemestane and for 3 to 6 months after treatment discontinuation (i.e. 27 and 30 months). FU, follow-up. Reproduced from reference 124 with the permission of the publisher

Figure 3 Algorithm to aid in decision making regarding patients starting aromatase inhibitors and considering use of agents to prevent bone loss. Reproduced from reference 123 with permission of the publisher

Fig. 1

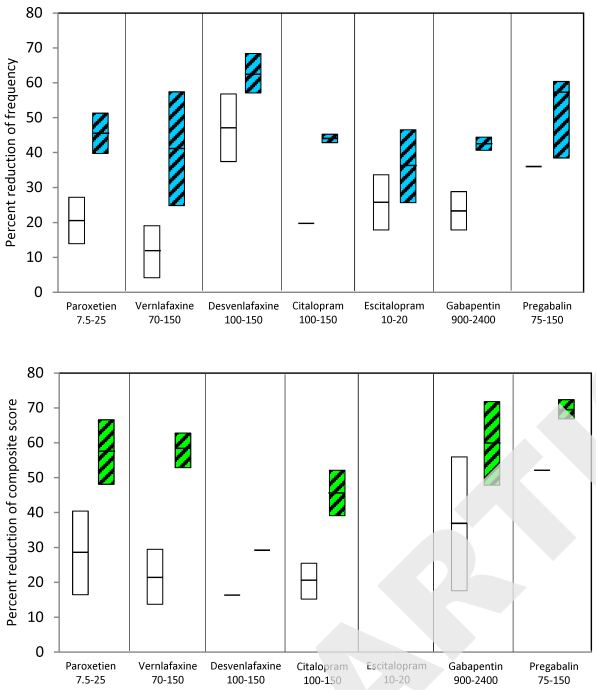

Fig 2

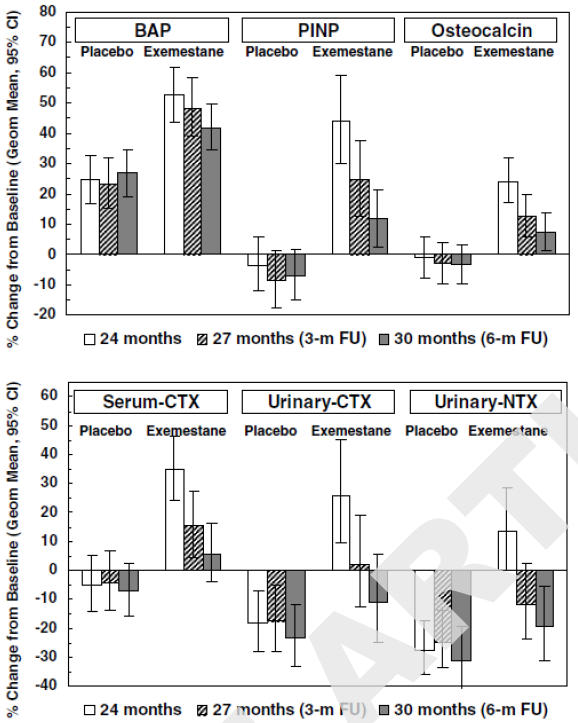

Fig 3