Managing the side effects of tamoxifen and aromatase inhibitors

AUTHORS: Suzanne D Conzen, MD, N Lynn Henry, MD, PhD
SECTION EDITORS: Daniel F Hayes, MD, William F Crowley, Jr, MD
DEPUTY EDITOR: Sadhna R Vora, MD

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INTRODUCTION

Tamoxifen and aromatase inhibitors (AIs) play a role in both breast cancer prevention and treatment.

Tamoxifen (as well as raloxifene) has antiestrogenic activity in breast tissue, reducing epithelial cell proliferation [1,2]. However, because tamoxifen and raloxifene modulate estrogen receptor (ER) metabolism in a tissue-specific manner, acting as either ER agonists or antagonists depending on the tissue, they have somewhat different side effect profiles. An important difference between the two drugs is their effect on the uterus, where tamoxifen has an estrogen-like effect while raloxifene acts as an estrogen antagonist. In apparent contrast to raloxifene, tamoxifen has been associated with endometrial hyperplasia [3,4], fibroids, polyps [4-6], and endometrial tumors (estrogen agonist effects) [7,8]. Tamoxifen is also associated with other side effects, including hot flashes (an estrogen antagonist effect), vaginal discharge, menstrual irregularities, sexual dysfunction, and blood clots. Although longer treatment with tamoxifen increases the risk of adverse effects, the reduction in breast cancer mortality associated with longer treatment often outweighs those risks. (See "Selective estrogen receptor modulators and aromatase inhibitors for breast cancer prevention".)

Raloxifene and tamoxifen are also metabolized differently in the liver. While tamoxifen is metabolized by the liver cytochrome P450 enzymes, raloxifene is metabolized by glucuronidation, and therefore avoids some of the potential issues with drug interactions that

apply to tamoxifen. (See "Mechanisms of action of selective estrogen receptor modulators and down-regulators", section on 'Patients taking SSRIs'.)

The AIs (letrozole, anastrozole, and exemestane) do not have tissue-specific effects because they suppress plasma estrogen levels globally, by inhibition of the enzyme aromatase. Aromatase is responsible for the peripheral conversion of androgens to estrogens. AIs are associated with loss of bone density, musculoskeletal pains and stiffness, and sexual dysfunction, among other side effects.

This topic review will cover management of the major side effects of tamoxifen and AIs. The use of these agents as hormonal treatment for breast cancer, both in the adjuvant setting and for advanced disease, and their use as chemopreventive agents in women at increased risk for breast cancer are discussed elsewhere. Raloxifene as a chemopreventive agent is also discussed elsewhere. (See "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer" and "Selective estrogen receptor modulators and aromatase inhibitors for breast cancer prevention".)

SIDE EFFECTS COMMON BOTH WITH TAMOXIFEN AND AIS

Hot flashes — Hot flashes are one of the most common and bothersome side effects both with tamoxifen and AIs; they are believed to be due to a central nervous system antiestrogenic effect causing thermoregulatory dysfunction [9]. Treatment typically includes nonhormonal strategies, including lifestyle modifications, selective serotonin or serotonin-norepinephrine reuptake inhibitors (SSRIs/SNRIs), or gabapentinoids, which are discussed in detail elsewhere. (See "Menopausal hot flashes", section on 'Women with breast cancer'.)

Some risk factors for endocrine therapy-induced hot flashes have been identified:

- Premenopausal women have a greater increase in hot flashes after starting tamoxifen compared with perimenopausal or postmenopausal women [10-13].
- Polymorphisms in drug-metabolizing enzymes (cytochrome P450 enzyme, CYP2D6) decrease the conversion of tamoxifen to its most active metabolite (endoxifen), and they may influence the likelihood of tamoxifen-related hot flashes, although the available data are conflicting [14,15]. (See "Mechanisms of action of selective estrogen receptor modulators and down-regulators", section on 'Tamoxifen resistance in breast cancer'.)
- Likewise, coadministration of drugs that inhibit the activity of CYP2D6, such as the SSRIs, reduce endocrine therapy-related hot flashes. However, strong CYP2D6 inhibitors have the

potential to adversely affect tamoxifen efficacy, in particular. Among SSRIs, there is a gradient of potency for inhibition of CYP2D6; for example, paroxetine and fluoxetine are strong CYP2D6 inhibitors, while sertraline and duloxetine are moderate inhibitors. However, the data to suggest that this issue decreases tamoxifen effect are very weak, at best. Therefore, the choice of which SSRI or SNRI is up to the individual clinician based on the agent's effectiveness in patient symptoms and their comfort with a specific agent. (See "Mechanisms of action of selective estrogen receptor modulators and down-regulators", section on 'Tamoxifen resistance in breast cancer' and "Menopausal hot flashes", section on 'Women with breast cancer'.)

- Inheritance of specific estrogen receptor and aromatase genotypes may also influence the risk and severity of endocrine therapy-induced hot flashes, although the findings have not yet been validated in independent cohorts [11,16].

- Hot flashes and night sweats occur with both tamoxifen and the AIs. However, studies suggest that for many women treated with AIs, vasomotor symptoms are less clinically bothersome [17-19].

While evaluation of genetic risk factors for tamoxifen-induced hot flashes such as these might hold promise for future selection of candidates for alternative therapeutic strategies when tamoxifen is indicated, genetic testing is not yet ready for clinical use.

Sexual dysfunction — Women on tamoxifen or AIs are at an increased risk for vaginal symptoms, including vaginal discharge and dryness, and sexual dysfunction. Women should be counseled about these potential adverse effects as part of their education before starting treatment and on methods that may help alleviate them. The approach to breast cancer survivors who complain of sexual dysfunction is covered separately. (See "Genitourinary syndrome of menopause (vulvovaginal atrophy): Treatment", section on 'Patients with breast cancer' and "Genitourinary syndrome of menopause (vulvovaginal atrophy): Treatment", section on 'Initial therapy with moisturizers and lubricants' and "Overview of long-term complications of therapy in breast cancer survivors and patterns of relapse", section on 'Menopausal symptoms'.)

Special considerations for premenopausal women receiving OFS — In the TEXT and SOFT trials, patients assigned exemestane plus ovarian function suppression (OFS) reported greater bone or joint pain, vaginal dryness, loss of sexual interest, and difficulties becoming aroused than patients on tamoxifen plus OFS; by contrast, patients assigned tamoxifen plus OFS were more affected by hot flashes and sweats than those on exemestane plus OFS [20].

In SOFT and TEXT, 24 percent of patients on exemestane plus OFS and 19 percent on tamoxifen plus OFS stopped protocol-specified treatment early [21], suggesting that approximately one-quarter of patients will have substantial endocrine symptoms.

Other side effects — Patients treated with endocrine therapy report a variety of symptoms. In one study, women on AIs and tamoxifen [22] reported higher rates of cognitive problems compared with women with breast cancer who did not take endocrine therapy; also, physical health scores one year after initiation of treatment were worse [23]. In another study, predictors of drug discontinuation at one year included fatigue, forgetfulness, and poor sleep hygiene [24]. Finally, both AIs and tamoxifen have also been associated with hair thinning, which is improved with topical minoxidil in the majority of cases [25].

TAMOXIFEN

Venous thromboembolism

- **Increased risks for venous thromboembolism (VTE)** – A number of studies have demonstrated that tamoxifen use is associated with an increased rate of **venous** thromboembolic events [26-28]. The relative risks (RRs) of VTE are increased two- to threefold in women receiving tamoxifen compared with those not taking tamoxifen. Additionally, while some elevated risk of thromboembolic events associated with tamoxifen appears to continue as long as the patient takes the drug, the RR decreases with time after initiation of therapy, with the first two years being the most hazardous [29].

  Nevertheless, more women experience pulmonary embolism (PE) when the treatment course of tamoxifen is extended to 10 years from 5 years (hazard ratio 1.87, 95% CI 1.13-3.07) [30].

Risk factors for tamoxifen-induced VTE include prior surgery, fracture, obesity, and immobilization. Atherosclerotic risk factors, including older age, elevated blood pressure, high total cholesterol, smoking, and a family history of coronary heart disease (CHD), also have been shown to increase the risk of VTE among tamoxifen users [31]. In addition, there is evidence that patients receiving tamoxifen who harbor a heterozygous Factor V Leiden mutation have a nearly fivefold risk of thromboembolism relative to those taking tamoxifen who do not have a mutation [32].

- **Decreasing the risk** – It is important to educate patients regarding the importance of modifying risk factors for deep vein thrombosis (DVT)/PE, including obesity, cigarette smoking, and hypertension. It is also important to educate patients about venous

thromboembolic disease so that they can seek medical evaluation promptly if they develop signs and symptoms concerning for DVT/PE. For patients with a family history of clots, we initiate a workup prior to initiating tamoxifen, in order to exclude known genetic causes of hypercoagulability. If a genetic cause of hypercoagulability is found, we do not use tamoxifen. Additionally, for those with a personal history of DVT, we typically avoid tamoxifen.

The data suggest that women receiving tamoxifen should discontinue use for several days to weeks prior to prolonged immobilization from anticipated surgery or travel, dependent upon the risks related to both the immobilization itself and patient-related factors [33]. Pharmacokinetics studies suggest that >90 percent of tamoxifen is cleared from plasma within three weeks; meanwhile, peak plasma concentration is reached within two weeks of restarting tamoxifen. Algorithms that account for patient age and duration of immobilization have been published to offer guidance [33].

Uterine bleeding, hyperplasia, and cancer — Tamoxifen has been associated with abnormal uterine bleeding as well as an increased risk of both endometrial cancer and uterine sarcoma. These risks, and their management, are discussed in detail elsewhere. (See "Abnormal uterine bleeding and uterine pathology in patients on tamoxifen therapy".)

Other tumors — An increased risk of nonuterine cancers has not been previously reported in women receiving tamoxifen. However, a modest but significantly increased RR of gastrointestinal tumors (RR 1.31, 95% CI 1.01-1.69) was suggested in a meta-analysis of 16 randomized controlled trials comparing a tamoxifen-containing treatment arm with a similar control arm, in which the incidence of gastrointestinal tumors was reported [8]. Most of this increased risk was derived from three individual Scandinavian trials; the majority of trials and the single largest study (NSABP P-1) did not report significant risk increases.

Although data are limited, tamoxifen may **reduce** the risk of ovarian cancer. This was illustrated in a retrospective study of 152 breast cancer patients undergoing oophorectomy, 44 of whom were receiving tamoxifen; nine had previously received tamoxifen, and 99 had never received tamoxifen [34]. There was no difference in the frequency of benign ovarian tumors or functional ovarian cysts based upon tamoxifen exposure. However, tamoxifen-treated women were less likely to have ovarian cancer (0 of 53 versus 10 of 99 patients in the tamoxifen and non-tamoxifen groups, respectively). Further studies are required to better define the effect of tamoxifen on ovarian cancer risk.

Eye problems — Use of tamoxifen has been associated with an increased risk of cataracts (3.7 percent), and less commonly with reversible corneal pigmentation, and irreversible retinal

deposits that have been associated with macular edema and vision loss.

Although these side effects are uncommon, ocular examination is recommended for any new visual symptoms. (See "Ocular side effects of systemically administered chemotherapy", section on 'Tamoxifen and toremifene'.)

Fatty liver disease — Based on imaging studies, use of tamoxifen has been associated with fatty liver disease in over one-third of patients [35], despite a favorable effect on cholesterol levels. Despite this high frequency, clinically significant steatohepatitis is uncommon. As such, in the absence of other indications, we do not typically monitor liver function tests or imaging for those on tamoxifen.

If fatty liver disease is detected incidentally, we typically continue tamoxifen, unless liver function tests are elevated to twice the upper limit of normal (in such cases, we hold tamoxifen and refer to a hepatologist for further evaluation). (See "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults" and "Management of nonalcoholic fatty liver disease in adults".)

Resumption of tamoxifen depends on the baseline risk of recurrence, how long tamoxifen has been administered, contraindications to AIs (which are an alternative in postmenopausal women), and degree of liver injury.

In a propensity score-matched cohort study of 328 women receiving either tamoxifen or an AI, incidence of fatty liver disease was higher in the tamoxifen group than in the AI group (128.7 versus 81.1 per 1000 person-years, or 37 versus 25 percent of patients), particularly within the first two years of therapy [35]. Risk factors for fatty liver disease included high baseline body mass index and triglycerides and low high-density lipoprotein cholesterol.

Does tamoxifen affect the risk of arterial thromboembolism?

Stroke — There are trials suggesting a modest increase in stroke risk with tamoxifen, but overall these data are conflicting. The possibility that tamoxifen may be associated with an increased incidence of arterial thromboembolism (ie, stroke) was raised in two NSABP randomized trials: P-1 (the breast cancer prevention trial) and NSABP B-24, a trial of tamoxifen for intraductal breast cancer. However, the available data are conflicting, and any increased risk of stroke may be counterbalanced by favorable effects on ischemic heart disease.

This was shown in the most recent overview analysis of randomized trials of adjuvant tamoxifen from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [28]. The nonsignificant excess of stroke deaths (three extra per 1000 women during the first 15 years) in women

treated with tamoxifen was exactly balanced by a nonsignificant reduction in cardiac deaths (three fewer per 1000 women during the first 15 years) [28]. Thus, there was little net effect of tamoxifen on overall vascular mortality.

Coronary heart disease — A lipid-lowering effect has been observed with tamoxifen [36], and several trials have noted beneficial effects from tamoxifen on CHD. However, the data are not consistent.

In a meta-analysis including 19 randomized trials, tamoxifen was associated with a 33 percent decreased risk of cardiovascular events compared with placebo or no treatment (RR 0.67, 95% CI 0.45-0.98) [37]. The results from extended adjuvant randomized controlled trials comparing tamoxifen with placebo showed a trend towards improved cardiovascular outcomes that did not reach statistical significance (RR 0.91, 95% CI 0.77-1.07).

By contrast, other data suggest that the use of tamoxifen is not associated with a beneficial cardiovascular effect:

- The NSABP P-1 trial (not included in the meta-analysis above) prospectively evaluated the occurrence of cardiovascular events [38]. Cardiovascular follow-up was available for 13,194 women, 1048 of whom had prior CHD. The rate of cardiovascular events (fatal myocardial infarction [MI], Q-wave MI, non-Q-wave MI, unstable angina, or severe angina requiring revascularization) was not significantly different in women assigned to tamoxifen compared with those receiving placebo, independent of pre-existing CHD. It has been suggested that the large proportion of younger women enrolled on this trial may have obscured the benefit of tamoxifen in terms of cardiovascular disease outcomes [39].

- A similar conclusion was reached in a case-control study of 11,045 women enrolled in a single health maintenance organization who developed breast cancer over a 20-year period, 134 of whom had a subsequent MI [40]. Compared with 262 control women who were MI free and matched for year of birth and breast cancer diagnosis, the use of tamoxifen was not associated with a lower risk of MI.

- As noted above, in the most recent overview analysis of randomized trials of adjuvant tamoxifen from the EBCTCG, there was a statistically nonsignificant reduction in cardiac deaths (three fewer per 1000 women during the first 15 years) in women treated with tamoxifen that was counterbalanced by a nonsignificant excess of stroke deaths (three extra per 1000 women) [28].

On balance, the available data support the view that in postmenopausal women both with and without CHD, the use of tamoxifen may result in a modest cardiovascular benefit.

AROMATASE INHIBITORS

Compared with tamoxifen, the AIs are associated with a higher risk of osteoporosis, fractures, cardiovascular disease, diabetes, and hypercholesterolemia [37,41-44]. By contrast, they are associated with a lower risk of venous thrombosis and endometrial cancer [42], and a lower risk of fatty liver disease [35].

While AIs are generally well tolerated, side effects may limit adherence in a number of women [24]. In the short term, some studies have suggested that the side effects associated with AIs are not detrimental to quality of life [45,46]. However, in one trial of adjuvant AIs, up to one-third of women may not complete an assigned five-year course of treatment [46]. Furthermore, the long-term effects of AIs (eg, bone loss) have not been fully characterized at this time. While data are available regarding the long-term risks of tamoxifen, and in particular that the risk persists for the duration of treatment but not afterwards [30], such data are limited for aromatase inhibition. Long-term risks of premature menopause, including osteoporosis and cardiovascular risk, which have been observed in noncancer patients, may apply to these patients as well. (See "Evaluation and management of aromatase inhibitor-induced bone loss" and "Overview of long-term complications of therapy in breast cancer survivors and patterns of relapse", section on 'Long-term adverse effects of primary therapy' and "Elective oophorectomy or ovarian conservation at the time of hysterectomy", section on 'Long-term health risks'.)

Musculoskeletal pains and stiffness — AIs are associated with musculoskeletal side effects including carpal tunnel syndrome as well as a constellation of symptoms including arthralgia, joint stiffness, and/or bone pain, which have been described as the AI-associated musculoskeletal syndrome (AIMSS) [47-51]. These symptoms may be severe in almost one-third of patients [49], and may be responsible for treatment discontinuation in 10 to 20 percent of patients [48-51]. No interventions have yet been identified that prevent development of AIMSS. Recognizing that there are few studies to inform the approach for patients with AIMSS, we suggest the following strategies, typically sequentially, although depending on patient preferences and severity of symptoms, this might not always be the case:

- **Exercise and NSAIDs** – The initial strategy for managing AIMSS includes exercise and nonsteroidal anti-inflammatory drugs (NSAIDs). In the HOPE trial, 121 physically inactive postmenopausal women with AI-associated arthralgias were randomly assigned to an exercise regimen or to usual care [52]. The exercise regimen consisted of twice-weekly supervised resistance and strength training plus moderate aerobic exercise for 150 minutes per week. Patients undergoing the exercise regimen had reduction in their worst pain score (20 versus 1 percent average score reduction, respectively) and pain severity (21

versus 0 percent reduction) compared with usual care. They also experienced more weight loss and improvement in their exercise capacity. In addition, a dose-response relationship between exercise and symptom severity was identified. Compared with women who attended fewer than 80 percent of the exercise sessions, those who attended 80 percent or more experienced a greater reduction in their worst pain score (25 versus 14 percent, respectively).

Beyond exercise, the primary treatment for AIMSS often begins with the administration of NSAIDs because these anti-inflammatory agents are a mainstay of treatment for pain. (See "Pharmacologic management of chronic non-cancer pain in adults", section on 'Nonsteroidal antiinflammatory drugs'.)

- **Temporary discontinuation of AI, followed by initiation of a different AI** – For women in whom conservative measures including exercise and NSAIDs have been unsuccessful, we discontinue treatment for two to eight weeks and then begin a different AI. In one prospective study, almost 40 percent of patients were able to continue on the alternate AI [53].

- **Duloxetine** – Duloxetine is an appropriate option for those preferring pharmacologic treatment. In the SWOG S1202 trial, among 299 patients with stage I to III breast cancer who developed AIMSS, those randomized to duloxetine (30 mg daily for one week, then 60 mg daily for 11 weeks, then 30 mg daily for one week) experienced improvement in joint pain through the 12 weeks of treatment relative to placebo [54]. After six weeks, 68 percent of patients treated with duloxetine had experienced at least a two-point improvement in pain, compared with 49 percent treated with placebo. However, 11 weeks after stopping treatment, average pain levels between the groups were similar. Duloxetine was relatively well tolerated; the most common adverse events were grade 1 or 2 fatigue (32 percent), xerostomia (24 percent), nausea (30 percent), and headache (21 percent). Grade 3 or 4 toxicities affected 8.7 percent of patients, with the most common ones being insomnia (2.9 percent) and extremity pain (1.4 percent).

- **Acupuncture** – Acupuncture offers a nonpharmacologic method of treating AIMSS. In a randomized trial of 226 patients with joint pain on AIs randomly assigned to 12 weeks of acupuncture, sham acupuncture, or waitlist control, those receiving acupuncture experienced a 1 point improvement in 52 week mean pain score on a scale ranging between 0 and 10, over the other groups [55,56]. Although the clinical significance of this small numerical improvement is unclear, some patients may desire a trial of this complementary form of therapy, particularly given its avoidance of systemic side effects.

- **Switch to tamoxifen, for those who are unable or unwilling to continue treatment with an AI.** (See "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer", section on 'Tamoxifen as alternative option'.)

Understanding the etiology of AIMSS is complicated because rheumatologic symptoms are present in a significant number of women before they initiate AI therapy. In one study, up to one-half of women who developed AIMSS had a pre-existing musculoskeletal disorder (eg, degenerative joint disease or morning stiffness) [51]. Risk factors for AIMSS have not been fully characterized, but the decrease in estrogen levels with aromatase inhibition may play a role [50,51,57,58].

Osteopenia/osteoporosis — AIs inhibit aromatase, the product of the *CYP19* gene, a member of the cytochrome P450 superfamily; this enzyme is responsible for the peripheral conversion of androgens to estrogens [59,60]. Treatment with AIs, therefore, results in bone loss due to estrogen deficiency [61]. These risks and their management are discussed in detail elsewhere. (See "Evaluation and management of aromatase inhibitor-induced bone loss".)

By contrast, tamoxifen and raloxifene improve bone mineral density in postmenopausal women, as discussed elsewhere. (See "Selective estrogen receptor modulators for prevention and treatment of osteoporosis".)

Ovarian reactivation in pre-/perimenopausal women — When premenopausal women are treated with chemotherapy, they can develop amenorrhea or biochemically confirmed ovarian failure that can be temporary or permanent. There is concern that their ovaries may resume estrogen production, thereby making AI therapy ineffective in reducing breast cancer risk. This issue is discussed in detail elsewhere. (See "Adjuvant endocrine therapy for premenopausal women with hormone receptor-positive breast cancer", section on 'Risk of ovarian function reactivation on an AI'.)

Do AIs increase risk of cardiovascular disease? — Some randomized controlled trials have associated AIs with an increased risk of cardiovascular outcomes, but studies on the topic have generated conflicting results [37,44,62]. It is likely that AIs are associated with an increased risk of cardiovascular disease relative to tamoxifen, but have a similar risk relative to placebo.

For example, in a meta-analysis including 19 randomized trials with over 62,000 patients, AIs were associated with a 19 percent increased risk of cardiovascular events compared with tamoxifen (relative risk [RR] 1.19, 95% CI 1.07-1.34) [37]. However, AIs were not associated with an increased risk compared with placebo in the extended-adjuvant setting (RR 1.01, 95% CI 0.85-1.20).

In a population-based cohort study of 17,922 women with breast cancer, the use of AIs was associated with increased risks of heart failure and cardiovascular mortality and trends toward increased risks of myocardial infarction and ischemic stroke compared with the use of tamoxifen [63].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Uterine cancer".)

SUMMARY AND RECOMMENDATIONS

- **Introduction** – Tamoxifen has antiestrogenic activity in breast tissue, reducing epithelial cell proliferation. However, it modulates estrogen receptor (ER) metabolism in a tissue-specific manner, acting as either an ER agonist or antagonist depending on the tissue. The aromatase inhibitors (AIs; letrozole, anastrozole, and exemestane) do not have tissue-specific effects because they suppress plasma estrogen levels globally, by inhibition of the enzyme aromatase. These differences lead to differences in side effects. (See 'Introduction' above.)

- **Side effects common to both** tamoxifen **and AIs** – Hot flashes and sexual dysfunction are among the most common and bothersome side effects of tamoxifen and AIs. Treatment typically includes nonhormonal strategies and is discussed in detail elsewhere. (See "Menopausal hot flashes", section on 'Women with breast cancer'.)

- **Side effects specific to** tamoxifen

  - The relative risks of pulmonary embolism and deep vein thrombosis are increased two- to threefold in older women receiving tamoxifen relative to those not taking it; the risk is higher in women who have inherited a Factor V Leiden mutation. Women receiving tamoxifen should discontinue use for several days prior to prolonged immobilization from anticipated surgery or travel. (See 'Venous thromboembolism' above.)

  - Tamoxifen has been associated with an increased risk of endometrial cancer, as discussed in detail elsewhere. (See "Abnormal uterine bleeding and uterine pathology in patients on tamoxifen therapy".)

- Further studies are required to better define the effect of tamoxifen on risk of other cancers, including gastrointestinal and ovarian cancer. (See 'Other tumors' above.)

- Some trials suggest a modest increase in stroke risk with tamoxifen, but overall these data are conflicting. Any increased risk of stroke may be counterbalanced by favorable effects on ischemic heart disease. (See 'Does tamoxifen affect the risk of arterial thromboembolism?' above.)

- **Side effects specific to AIs**

  - Compared with tamoxifen, the AIs are associated with a higher risk of osteoporosis, fractures, cardiovascular disease, and hypercholesterolemia. By contrast, they are associated with a lower risk of venous thrombosis and endometrial cancer, and a lower risk of fatty liver disease. (See 'Aromatase inhibitors' above.)

  - AIs are associated with musculoskeletal side effects including carpal tunnel syndrome as well as a constellation of symptoms including arthralgia, joint stiffness, and/or bone pain, which have been described as the AI-associated musculoskeletal syndrome. (See 'Musculoskeletal pains and stiffness' above.)

    - Initial treatment typically consists of conservative measures, including exercise and nonsteroidal anti-inflammatory drugs. A brief trial off treatment (typically two to eight weeks) and subsequent resumption of a different AI may be effective.

    - For patients with persistent symptoms, we suggest duloxetine (**Grade 2B**). Acupuncture is a reasonable nonpharmacologic alternative or adjunctive treatment.

    - For those in whom the above strategies have been ineffective, a switch to tamoxifen may be appropriate.

  - Treatment with AIs results in bone loss due to estrogen deficiency. These risks and their management are discussed in detail elsewhere. (See "Evaluation and management of aromatase inhibitor-induced bone loss".)

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