Menopausal symptoms and adjuvant therapy-associated adverse events

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Abstract

Third-generation aromatase inhibitors (AIs) are replacing tamoxifen as adjuvant therapy in postmenopausal women with hormone-sensitive breast cancer due to their superiority shown in several recent head-to-head trials. Healthy postmenopausal women normally experience age-related side effects, and in postmenopausal women with breast cancer, these symptoms may be exacerbated by adjuvant endocrine therapy. This review evaluates the current literature regarding bone health, lipid metabolism, cardiovascular disease, gynecologic health, and cognition in postmenopausal women receiving adjuvant AI therapy. The AIs – anastrozole, exemestane, and letrozole – are generally well tolerated: most adverse events are mild to moderate and common to menopause. Common short-term AI-associated toxicities are hot flushes, musculoskeletal complaints/arthralgia, and bone loss, all of which can be effectively managed. AIs may lack the cardioprotective and lipid-lowering effects of tamoxifen but, in contrast to tamoxifen, do not increase the risk of serious life-threatening thromboembolic or cerebrovascular events or endometrial cancer. Every patient should be individually assessed with respect to therapy risks and benefits. Lifestyle, comorbidities, and concomitant medications must be considered, and the importance of compliance to adjuvant therapy should be discussed before selecting a treatment regimen. The superior efficacy of adjuvant AI therapy will in most cases outweigh the risk of bothersome side effects that can be prevented or easily managed.

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Introduction

In Europe, breast cancer is the most common cancer in females, and two-thirds of breast tumors occur in postmenopausal women aged 55 years and older who may also have age-related comorbidities (e.g., hypertension, arthritis, heart disease, osteoporosis, and diabetes) that could affect treatment decisions and prognosis (Yancik et al. 2001, Tyczynski et al. 2004). The adverse events (AEs) associated with a particular adjuvant therapy thus must be considered when making treatment choices.

The antiestrogen tamoxifen had been the standard adjuvant therapy in postmenopausal women with hormone-sensitive (hormone receptor- positive) early breast cancer hazard ratio (HR+EBC) for 20 years (Nolvadex Adjuvant Trial Organization 1983). Tamoxifen therapy not only reduced breast cancer recurrence and mortality but was also associated with an increased incidence of thromboembolic events and endometrial cancer, as well as other bothersome AEs, including vaginal discharge, fluid retention, and hot flushes (Fisher et al. 1996, Early Breast Cancer Trialists’ Collaborative Group 2005), which increase the likelihood of therapy discontinuation (Demissie et al. 2001).

Tamoxifen inhibits the action of estrogen at the estrogen receptor, whereas aromatase inhibitors (AIs) inhibit the aromatase enzyme that converts androgens to estrogen (Brodie et al. 2003). The AIs have a different mechanism of action and a different safety profile that does not include the increased risk of serious AEs, such as thromboembolic events and endometrial cancer (Brodie et al. 2003, Howell et al. 2005, Thürlimann et al. 2005, Coombes et al. 2007). These results come from several AI trials that varied in their safety evaluations. Some classified AEs according to COSTART definitions (Arimidex, Tamoxifen, Alone or in Combination; ATAC), while others used the National Cancer Institute common toxicity criteria (Breast International Group (BIG) 1–98, Intergroup Exemestane Study (IES), MA.17), and still others did not explicitly state the method for reporting and grading of AEs.
(Tamoxifen, Exemestane Adjuvant Multicenter (TEAM); Arimidex/Nolvadex (ARNO 95); Austrian Breast and Colorectal Study Group (ABCSG 8); International Breast Cancer Intervention Study (IBIS) II; ZO-FAST, the companion study of the Zometa/Femara Adjuvant Synergy Trial (Z-FAST); Italian Tamoxifen Anastrozole (ITA); and Adjuvant post-Tamoxifen Exemestane versus Nothing Applied (ATENA)).

Several guidelines now advocate the use of AIs in the adjuvant setting for the management of postmenopausal women with HR+ EBC (Goldhirsch et al. 2005, Winer et al. 2005). The third-generation AIs, letrozole, anastrozole, and exemestane, have been approved for the adjuvant treatment of HR+ EBC, are displacing tamoxifen as initial adjuvant therapy (Howell et al. 2005, Thürlimann et al. 2005), and are being used as adjuvant therapy following the completion of 2–5 years of tamoxifen (Boccardo et al. 2005, Goss et al. 2005, Jakesz et al. 2005, Coombes et al. 2007). Yet, as adjuvant AI therapy reduces estrogen levels in postmenopausal women even further, such therapy is expected to exacerbate some of the menopausal symptoms women experience as they grow older. Patients and their physicians must weigh the benefits and risks of each therapy and consider comorbidities when making treatment decisions (Theriault et al. 2006). In this review, we discuss some safety concerns associated with adjuvant endocrine therapy and how these AEs, if they develop, may be managed so that patients do not discontinue their therapy.

**Fractures and osteoporosis**

Osteoporosis is a very common condition in postmenopausal women that is associated with low bone density and an increased risk for bone fragility and fracture (Melton 2002, Tuck & Francis 2002). Regarding fractures, about one in two women over the age of 50 is likely to experience such an event in her lifetime (Melton 2002). Estrogen plays a critical role in bone health (Mackey & Joy 2005), which deteriorates with aging (Hadj et al. 2002) and accelerates after menopause because of decreased circulating estrogen (Devine et al. 2005). Substudies of the Women’s Health Initiative Observational Study (N=93 676) have shown that postmenopausal breast cancer survivors have significantly lower total body bone mineral density (BMD) and total hip BMD (Chen et al. 2005a), as well as an increased risk of clinical fracture, compared with women without a history of cancer (Chen et al. 2005b).

**Chemotherapy**

Chemotherapy-induced ovarian failure, surgical or medical ovarian ablation, and estrogen deprivation therapy in women with HR+ EBC have all been shown to result in bone loss (Bruning et al. 1990, Aapro 2004). This was confirmed in a large retrospective study of women with non-metastatic breast cancer (N= 14 604), which showed that anticancer therapy with chemotherapy and hormonal agents increased the risk of osteoporosis/osteopenia (Boyce et al. 2005). Other factors such as poor health status, history of smoking and alcohol abuse, low baseline BMD, prevalent fracture, family history of osteoporosis, tendency for falls, corticosteroid use, as well as the presence of bone metastases, may also influence treatment-related osteoporosis (Boyce et al. 2005, Garreau et al. 2006, Mouridsen 2006). Disease- and treatment-associated skeletal-related events included fracture, spinal compression, bone pain, and hypercalcemia of malignancy. Vertebral fracture risk markedly increased in women with breast cancer (Kanis et al. 1999).

Chemotherapy agents such as methotrexate and ifosfamide could potentially induce negative effects on bone metabolism (Pfeilschifter & Diel 2000). In a cross-sectional study (N= 27) to investigate lumbar spine BMD in patients with breast cancer previously treated with adjuvant chemotherapy, 16 patients experienced treatment-related amenorrhea and had 14% lower BMD than did those who maintained menses (Headley et al. 1998). Another study (N= 49) showed that the median percentage decrease of spine BMD was −4.0 between 0 and 6 months and −3.7 between 6 and 12 months in the 35 patients who experienced chemotherapy-induced ovarian failure compared with no significant decrease in BMD in the 14 patients who retained ovarian function (Shapiro et al. 2001).

In a study of premenopausal women with breast cancer (N= 73) treated with cyclophosphamide, methotrexate, 5-fluorouracil (CMF) chemotherapy, changes in BMD, 3 and 5 years after treatment were correlated with menstrual function; however, 3 years of bisphosphonate treatment significantly reduced bone loss in the lumbar spine (Vehmanen et al. 2001). Another study in CMF-treated premenopausal women (N= 148), showed rapid bone loss in women who developed amenorrhea after chemotherapy, compared with only marginal changes in BMD in those with continued menstruation; women older than 40 years of age were at especially high risk (Saarto et al. 1997).

**Serum estrogen receptor modulators (SERMs)**

**Raloxifene**

Results from the Multiple Outcomes of Raloxifene Evaluation trial showed that raloxifene, a selective
estrogen receptor modulator, prevents bone loss and reduces the risk for clinical vertebral fracture (relative risk (RR) 0.20; 95% confidence interval (CI) 0.03–0.90; \( P = 0.034 \); Qu et al. 2005). Absolute risk reduction (0.17%) was seen as early as 3 months in postmenopausal women with osteoporosis (Qu et al. 2005). In the Continuing Outcomes Relevant to Evista (CORE) trial, raloxifene significantly increased lumbar spine (4.3 and 2.2% from baseline and placebo respectively) and femoral neck BMD (1.9 and 3.0% from baseline and placebo respectively); however, it had no effect on non-vertebral fracture risk after 8 years compared with placebo (Siris et al. 2005). Currently, raloxifene is being investigated in the prevention of primary breast cancer in the Study of Tamoxifen and Raloxifene (STAR) trial; it has been shown to have a risk of fractures similar to tamoxifen and increased musculoskeletal problems compared with tamoxifen (Vogel et al. 2006).

**Tamoxifen**

While tamoxifen has repeatedly proven not to have bone-sparing effects in premenopausal women (Vehmanen et al. 2006), it has demonstrated beneficial effects on bone in postmenopausal women. Two randomized trials showed significant increases in BMD with tamoxifen compared with placebo. A 2-year trial in 140 postmenopausal women found that mean BMD of the lumbar spine increased by 61% per year in women receiving tamoxifen, compared with a 1% decrease per year in those receiving placebo (\( P < 0.001 \); Love et al. 1992). In another 2-year trial (\( N = 50 \)), lumbar spine BMD increased during the first year in tamoxifen-treated postmenopausal women and stabilized, compared with decreased BMD in the control group (\( P = 0.00074 \); Kristensen et al. 1994).

However, some bone loss also occurs naturally as women age or as a consequence of chemotherapy and concomitant medication, and some women on tamoxifen do experience bone loss. A recent study of 118 women who completed 5 years of tamoxifen therapy showed that 23.7 and 41.5% of women had osteoporosis and osteopenia respectively, and 25% of women required treatment with bisphosphonates (Wchannel et al. 2006). An international study of 746 women prior to randomization to tibolone found that 11% of women had osteoporosis and 43% had osteopenia after adjuvant endocrine therapy (chemotherapy, tamoxifen, AIs; Bundred et al. 2006a).

**Aromatase inhibitors**

Results of the Letrozole, Exemestane, and Anastrozole Pharmacodynamics (LEAP) trial showed that, in healthy women volunteers (\( N = 90 \)), all three AIs had similar effects on bone biochemical measurements, resulting in increased bone turnover (McCluskey et al. 2006a). Another study in healthy postmenopausal volunteers (\( N = 77 \)) showed that all three AIs increased levels of bone resorption markers (Goss et al. 2003). Likewise, in a retrospective longitudinal analysis of 1354 women with breast cancer, the prevalence of osteoporosis/osteopenia (8.7 vs 7.1%; \( P = 0.01 \)) and bone fracture (13.5 vs 10.3%; \( P = 0.001 \)) was significantly higher in the AI than non-AI group on univariate analysis; similarly, on multivariate analysis, the increase in risk of osteoporosis and fracture was 27 and 21% respectively (Mincey et al. 2006).

**BMD loss and the risk of fracture and osteoporosis in adjuvant AI trials**

In the ATAC trial (\( N = 6186 \)), fracture rates per 1000 woman-years were 22.6 and 15.6 for anastrozole and tamoxifen respectively, at a median follow-up of 68 months (\( P < 0.0001 \); Howell et al. 2005). A higher incidence of osteopenia/osteoporosis (11 vs 7%; \( P < 0.0001 \)) and fractures (11 vs 7.7%; \( P < 0.0001 \)), significant BMD loss, and increased bone turnover is also seen with anastrozole, whereas tamoxifen is associated with increased BMD and decreased remodeling. In the ATAC trial bone substudy (\( N = 167 \)), assessment of lumbar spine and total hip BMD at baseline and 1, 2, and 5 years using dual-energy X-ray absorptiometry (DEXA) showed that significant bone loss occurred throughout the treatment period, with a decline in the rate of loss in years 2 through 5 (Coleman 2006). Patients receiving anastrozole (\( n = 81 \)) experienced significant decreases in lumbar spine (−8.1%; \( P < 0.0001 \)) and total hip (−7.4%; \( P < 0.0001 \)) BMD compared with patients receiving tamoxifen (\( n = 86 \)), in whom small increases were observed (Coleman 2006, Eastell et al. 2006). Similarly, in the randomized, double-blind, phase III BIG 1–98 trial (\( N = 8010 \)), the incidence of fracture was higher in the letrozole arm compared with the tamoxifen arm (5.7 vs 4.0% respectively; \( P < 0.001 \)) after a median follow-up of 25.8 months (Thürilmann et al. 2005). A subset analysis restricted to the monotherapy arm (letrozole 5 years versus tamoxifen 5 years) analysis (\( n = 4922 \)) of BIG 1–98 at 51-month follow-up confirmed these findings (8.6 vs 5.8% respectively; \( P < 0.001 \); Coates et al. 2007).

The increased risk for bone loss and fracture is also seen when a steroidal AI (exemestane) is used in the switch setting. In the IES (\( n = 4724 \)), the incidence of fracture (7.0 and 4.9% respectively; \( P = 0.003 \)) and osteoporosis (9.2 and 7.2% respectively; \( P = 0.01 \)) was significantly higher with exemestane at a median
follow-up of 55.7 months (Coombes et al. 2007). In the IES bone substudy (n=206), patients who switched to exemestane had decreased BMD at the lumbar spine (2.7% reduction, 95% CI 2.0–3.4; P < 0.0001) and hip (1.4% reduction, 95% CI 0.8–1.9; P < 0.0001) within 6 months of switching, but no significant changes in BMD were observed in patients who continued on tamoxifen. At 2 years, the BMD decrease was 1.0% at the lumbar spine (95% CI 0.4–1.7; P = 0.002) and 0.8% at the hip (95% CI 0.3–1.4; P = 0.003; Coleman et al. 2007). Results of another recent study also showed that switching postmenopausal women from tamoxifen to exemestane led to marked increases in bone turnover markers and reduced BMD (Gonnelli et al. 2007).

Studies of AIs versus placebo also report increases in the incidence of fracture risk. At the time of the unblinding of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-33, a study evaluating extended adjuvant exemestane therapy after 5 years of tamoxifen, more fractures were reported in patients receiving exemestane (n=783) than in those receiving placebo (n=779; 28 versus 20 patients; P = 0.33; Mamounas et al. 2006). Likewise, in the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) MA.17 trial (N=5187), letrozole was associated with a non-significant increase in the incidence of fracture compared with placebo (5.3 vs 4.6%; P = 0.25), and a small but significant difference in patient-reported diagnosis of new-onset osteoporosis (8.1 vs 6.0%; P = 0.003; Goss et al. 2005; Table 1). In the MA.17 bone substudy (n=226), patients receiving letrozole showed a significant decrease in total hip (−3.6 vs −0.71%; P = 0.044) and lumbar spine (−5.35 vs −0.70%; P = 0.008) BMD at 24 months, but no patient dropped below the threshold for osteoporosis in total hip BMD (Perez et al. 2006).

### Musculoskeletal/joint symptoms

Arthralgia and musculoskeletal pain have been reported in postmenopausal women undergoing AI treatment (Morales et al. 2006). A recent survey reported that joint aches were reported as the fourth most troublesome symptom by both tamoxifen and AI users (12 and 23% respectively; P = 0.002), after hot flushes, weight gain, and insomnia (Garreau et al. 2006). Early morning stiffness and hand/wrist pain are other frequently reported musculoskeletal symptoms experienced by postmenopausal women receiving adjuvant AI treatment (Morales et al. 2006). Among patients reporting joint pain in a study of postmenopausal women receiving adjuvant AI therapy, 70% reported worsening of baseline pain after the initiation of AI therapy and 30% developed pain; 50% of patients reported worsening of baseline joint stiffness after the initiation of AI therapy and 50% developed joint stiffness (Crew et al. 2006a).

### Joint symptoms in adjuvant AI trials

In the ATAC trial, arthralgia was more frequently reported with anastrozole than with tamoxifen (35.6 vs 29.4%; P < 0.0001), however, 46% of patients considered such symptoms to be an exacerbation of a preexisting condition (Buzdar 2006a). Only 2.1% of patients receiving anastrozole and 0.9% of those receiving tamoxifen withdrew from the study because of a joint symptom. Carpal tunnel syndrome was more common with anastrozole (3 vs 1%; P < 0.0001), but muscle cramps were more common with tamoxifen (4 vs 8%; P < 0.0001). Patients in the BIG 1–98 trial receiving initial adjuvant letrozole also had a higher incidence of arthralgia than those receiving tamoxifen (20.3 vs 12.3%; P < 0.001; Thürlimann et al. 2005); and initial adjuvant exemestane has also been associated with more bone/muscle aches than tamoxifen (Asmar et al. 2005).

In IES, switching to exemestane was associated with a higher incidence of arthralgia (20.8 vs 15.1%; P < 0.0001) and carpal tunnel syndrome (2.8 vs 0.4%; P < 0.0001) when compared with continued tamoxifen therapy (Coombes et al. 2007). The increased risk of arthralgia is also seen in trials that compare AIs with a placebo. At the time of unblinding of the NSABP B-33, the most common grade 3/4 toxicities in patients receiving extended adjuvant exemestane or placebo were arthralgia (1.0 vs 0.5%), and bone pain (0.5 vs 0.7%; Mamounas et al. 2006). Likewise, in the MA.17 trial, women who received letrozole had a significantly higher incidence of arthralgia (25 vs 21%; P < 0.001) than women receiving placebo, while the incidence of arthritis

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<th>Table 1 Adverse events and toxicities in patients in NCIC CTG MA.17 trial (Goss et al. 2005)</th>
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NCIC CTG, National Cancer Institute of Canada Clinical Trials Group.

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**Notes:**

- Data are expressed as number (%). P values are from a chi-square test. Significant P values are indicated in bold.
- Adverse events were classified as grade 3 (moderate) or grade 4 (severe).
- The primary outcome of the study was the incidence of adverse events.
- The study population consisted of postmenopausal women with early-stage breast cancer who had undergone surgery.
- The study was conducted at multiple centers in Canada and the USA.
- The study was sponsored by the Canadian Cytokine Group and the National Cancer Institute of Canada Clinical Trials Group.
- The study was published in the Journal of Clinical Oncology in 2005.
was similar between the treatment arms (6 vs 5%; \( P=0.07 \); Goss et al. 2005).

**Clinical management of bone health**

The education of patients and health care professionals regarding effective treatment options for the adverse effects of AIs on bone health is critical (Guise 2006). A recent survey showed that patients treated with tamoxifen and AIs report different and significant side effects, and slight differences in the use of medications for effective symptom control, but the costs associated with symptom control were similar and not a major barrier to treatment (Garreau et al. 2006).

Arthralgia and joint pain can be bothersome and may lead to impaired mobility; patients need to be advised that constant exercising of joints and the use of exogenous estrogens may alleviate the problem (Chlebowski et al. 2006). AI-associated pain can generally be managed with over-the-counter analgesics and glucosamine (Presant et al. 2006): a recent study also suggests that acupuncture may be effective (Crew et al. 2006b).

A study \((N=147)\) investigating the potential deleterious effect of adjuvant exemestane on bone reported vitamin D deficiency in the majority of patients in both the placebo (56/62) and exemestane (52/59) groups, suggesting that vitamin D deficiency may play a role in the incidence of bone symptoms in postmenopausal women (Lønning et al. 2006). Yet, data from the IBIS II, a breast cancer prevention study of 6000 postmenopausal women at increased risk of breast cancer receiving anastrozole versus placebo, suggest that AI-induced arthralgia is not correlated with 25(OH) vitamin D levels (Singh et al. 2006a,b). Vitamin D deficiency has been shown to increase bone loss and fracture risk (Brazier et al. 1995, Prince et al. 1995), and patient comorbidities may influence treatment-related osteoporosis/osteopenia (Boyce et al. 2005). All patients receiving adjuvant AI therapy should be given calcium and vitamin D supplementation and encouraged to engage in weight-bearing exercise (Morandi et al. 2004).

Lifestyle modification and bisphosphonates can improve patient outcome (Guise 2006). Bisphosphonate therapy has shown great benefit in the management of cancer treatment-induced bone loss. In the Z-FAST, 602 postmenopausal women starting adjuvant therapy with letrozole were randomized to receive upfront or delayed zoledronic acid (ZA; Brufsky et al. 2007). The effectiveness and safety of ZA therapy on AI-induced bone loss seen at 12 months was continued at the 24-month assessment (Brufsky et al. 2006, 2007). At month 24, the upfront ZA group \((n=201)\) showed a mean increase of 1.37% in total hip BMD, while the delayed group \((n=190)\) showed a mean decrease of 3.24%. Greater changes were seen at the lumbar spine BMD, as the upfront ZA group \((n=200)\) demonstrated a mean increase of 3.06% and the delayed group \((n=191)\) showed a mean decrease of 2.89% (Brufsky et al. 2006). Results of ZO-FAST (a companion trial conducted in 28 countries outside North America) and a combined Z-FAST/ZO-FAST analysis also support the use of ZA to manage AI-induced bone loss (Brufsky et al. 2006, Bundred et al. 2006b). The Study of Anastrozole with the Bisphosphonate Risedronate (SABRE) trial is investigating the effect of the bisphosphonate risedronate sodium on BMD and serum lipid profile in postmenopausal women treated with adjuvant anastrozole (Van Poznak et al. 2006).

All AIs have been associated with accelerated bone loss and increased risk of fracture, but this should not limit their use. Patients at risk of BMD loss during treatment should be identified and managed according to evolving clinical guidelines (Lester et al. 2005, US Preventive Services Taskforce 2005, Winer et al. 2005, Mouridsen 2006). Current guidelines (American Society of Clinical Oncology) recommend that only women with osteoporosis \((T\text{-score }<−2.5)\) receive bisphosphonate therapy to increase BMD and reduce the risk of fracture. However, as BMD testing is not readily available to all patients, BMD should not be the sole criterion to assess fracture risk; a better approach is to consider other risk factors (Hadji et al. 2007). Postmenopausal women receiving AI therapy should undergo periodic BMD assessment to facilitate early diagnosis and intervention for treatment-related bone loss (Hillner et al. 2003, Winer et al. 2005). DEXA scans for BMD measurement and bone resorption markers (e.g., N-telopeptide, C-telopeptide) have been used to facilitate diagnosis (Brown & Coleman 2002, Coleman 2004). With DEXA scan results of a \(T\text{-score} < −2.0\), patients should take calcium and vitamin D supplementation and a bisphosphonate to prevent fracture. For any patient with a \(T\text{-score} < −1.5\) with at least one additional risk factor (age over 65, family history of hip fracture, low body mass index, personal history of fragility fracture after age 50, oral corticosteroid use longer than 6 months, smoker, and alcohol use), bisphosphonate therapy should be considered. When DEXA scan information is lacking, any patient receiving AIs who has two additional risk factors should receive bisphosphonate treatment to prevent bone loss.
Lipid metabolism

Obesity is increasing in the European population: more than 48 million adults in Europe and 23 million adults in the European Union have diabetes (Peterson et al. 2005). As breast cancer patients live longer, weight gain after therapy is a common problem that negatively affects serum lipid profiles and increases the risk of diabetes and cardiovascular disease (CVD) (Herman et al. 2005). Menopause also has a negative effect on lipid metabolism: increases in total cholesterol (Stevenson et al. 1993, Tremolieres et al. 1999, Kuh et al. 2005), low-density lipoprotein cholesterol (LDL-C; Matthews et al. 1989, Kuh et al. 2005), and triglycerides (Kuh et al. 2005) and decreases in high-density lipoprotein cholesterol (HDL-C) (Matthews et al. 1989, Kuh et al. 2005) tend to occur after menopause and are associated with an increased risk of coronary heart disease (Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults 2001).

Generally, SERMs such as tamoxifen have been shown to decrease LDL-C and increase HDL-C (Thangaraju et al. 1994, Mannucci et al. 1996, Herrington & Klein 2001), but the AIs have not been reported to have such effects (Mitsuyama et al. 2006). In the LEAP study of healthy postmenopausal women, no difference was found in lipid profiles for either letrozole or exemestane, compared with anastrozole, except for a higher increase in triglycerides with letrozole than anastrozole at 12 weeks (+9.6 vs −2.9%; P < 0.05) and a more marked reduction in HDL-C with exemestane than anastrozole at 24 weeks (−13 vs 0.3%; P < 0.001); additionally, the HDL:LDL ratio with exemestane was significantly higher than with anastrozole at 24 weeks (17.09 vs 4.6%; P < 0.05; McCloskey et al. 2006b).

Hypercholesterolemia in adjuvant AI trials

Adjuvant anastrozole therapy has been associated with weight gain (Hori et al. 2006), and an exploratory analysis of non-predefined AEs in the ATAC trial showed that patients receiving anastrozole, compared with tamoxifen, had a higher incidence of hypercholesterolemia (9 vs 3%; P < 0.0001) and hypertension (13 vs 11%; P = 0.04; Buzdar et al. 2006b). In the BIG 1–98 trial, hypercholesterolemia was measured more rigorously: total cholesterol was measured at baseline, every 6 months in the first 3 years, yearly for the next 2 years, and 1 year after treatment ended, and hypercholesterolemia appeared as a check-listed box on case report forms (Thürlimann et al. 2005). More patients in the letrozole arm experienced hypercholesterolemia at least once during treatment (43.6 vs 19.2% in the tamoxifen arm), but the majority of cases in both arms were grade 1 (35.1 and 17.3% respectively; Thürlimann et al. 2005). The median total cholesterol did not change significantly from baseline in patients in the letrozole arm but decreased by 13.5% in those in the tamoxifen arm (Thürlimann et al. 2005).

The same increase is seen if AIs are given in the switch setting. In the ITA trial, lipid disorders were reported in 9.3% of patients treated with anastrozole versus 4.0% of those receiving tamoxifen (P = 0.04; Boccardo et al. 2005). In the IES, the incidence of hypercholesterolemia was 8.8 and 7.6% in the exemestane and tamoxifen arms respectively (P = 0.14; Coombs et al. 2007). Another randomized study examining body composition and lipid profile in 55 postmenopausal women with primary breast cancer who switched to exemestane after at least 2 years of tamoxifen therapy found that although fat mass decreased significantly by month 12 in women receiving exemestane but not tamoxifen (P < 0.01), triglycerides and HDL-C decreased significantly (P < 0.01 for both), and LDL-C increased significantly (P < 0.01) in the exemestane group (Francini et al. 2006).

The AIs may lack the lipid-lowering properties of tamoxifen, but they do not seem to have any detrimental effects on lipid profiles (Monnier 2007). When compared with placebo, an increase in hypercholesterolemia has not been observed. Final results from the MA.17 study showed that hypercholesterolemia occurred at similar rates in both the letrozole and placebo groups (16% each; P = 0.79; Goss et al. 2005). These findings were confirmed in the lipid substudy (n = 347), which found that letrozole did not significantly alter lipid parameters in postmenopausal women who had completed 5 years of adjuvant tamoxifen therapy (Wasan et al. 2005). Of note, the HDL:LDL ratio decreased after the first 6 months of therapy in both the letrozole and placebo arms (no statistically significant differences were noted; Femara package insert 2005). Likewise, another study (N = 147) found that exemestane, compared with placebo, had no major effect on lipids, with the exception of a small decrease from baseline HDL-C (P < 0.001) and apolipoprotein A1 (P = 0.004; Lønning et al. 2005). Preliminary results of the ATENA substudy of patients treated with extended adjuvant exemestane, compared with placebo, showed that following 6 months of tamoxifen discontinuation, there were no significant differences between the exemestane and placebo groups for any lipid parameters, consistent with MA.17 findings (Markopoulous et al. 2005). Updated data from the IBIS II study (N = 141) showed no significant difference in mean

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change in HDL-C, total cholesterol, or triglycerides between the anastrozole and placebo groups (Singh et al. 2006a,b). Thus, all three AIs have a similar impact on lipid parameters and, when compared with placebo, the AIs are not associated with increased hypercholesterolemia or cardiovascular events (Monnier 2007).

Cardiovascular disease
In Europe, CVD accounts for more than 1.88 million deaths each year and is the main cause of death in individuals younger than age 75 (44% of deaths in women); stroke is the second most common cause of death, accounting for 1.28 million deaths per year (Peterson et al. 2005). Women with breast cancer are at risk of CVD, and the incidence increases significantly after menopause (Monnier 2007). Postmenopausal women with breast cancer may be more susceptible to certain risk factors associated with CVD, including aging (Coebergh et al. 1999), diabetes (Coebergh et al. 1999, Louwman et al. 2005), and hypertension (Franklin et al. 1997, Coebergh et al. 1999).

Tamoxifen
In a trial comparing 2129 patients who received 2 years versus 2046 patients who received 5 years of adjuvant tamoxifen, mortality due to coronary heart disease was significantly reduced in the 5-year group (HR) 0.67, 95% CI 0.47–0.94; P = 0.022; Nordenskjöld et al. 2005). A meta-analysis of published randomized controlled trials showed that tamoxifen significantly decreased death due to myocardial infarction (MI; RR 0.62, 95% CI 0.41–0.93; Braithwaite et al. 2003), and the cardioprotective effects of tamoxifen may confound comparisons of AIs with tamoxifen in assessing the effect of various agents on cardiovascular health.

Cardiovascular events in adjuvant AI trials
In ATAC, the incidence of ischemic cardiovascular events was higher in patients treated with anastrozole than in those treated with tamoxifen (4.1 vs 3.4%; P = 0.1; Howell et al. 2005). Angina was mostly mild to moderate and numerically occurred more often in patients receiving anastrozole (71 vs 51%; P = 0.07), while MI occurred in 1% of patients in each arm (P = 0.07; Buzdar et al. 2006b). The BIG 1–98 trial demonstrated a similar incidence of cardiac events in the letrozole and tamoxifen groups (4.1 vs 3.8%; P < 0.001; Thürlimann et al. 2005). More women receiving letrozole had grade 3, 4, or 5 cardiac events (2.1 vs 1.1%; P < 0.001), but these events were rare (Thürlimann et al. 2005). In the subset analysis restricted to the monotherapy arms of the BIG 1–98 trial, at 51-month follow-up, the incidence of cardiac events was comparable in the two groups: 134 events (5.5%) versus 122 events (5.0%) with letrozole and tamoxifen respectively. With longer follow-up in almost 5000 patients, the incidence of grade 3–5 cardiovascular events was low in both groups (Coates et al. 2007).

Vascular events (hot flushes, ischemic cardiovascular events, deep vein thrombosis, and ischemic cerebrovascular events) occurred more frequently in patients switching to anastrozole than in those who continued on tamoxifen (9.2 vs 8.8%; P ≠ reported) in the ARNO 95 trial (N = 979; Kaufmann et al. 2006). Similarly, in the IES, patients switching to exemestane reported more cardiovascular events (excluding venous thromboembolic events) than those continuing on tamoxifen (20.8 vs 18.9%; P = 0.09; Coombes et al. 2007). The incidence of MI was higher in patients receiving exemestane than in those receiving tamoxifen (1.3 vs 0.8%; P = 0.08; Coombes et al. 2007). Yet, when compared with placebo, the AIs do not significantly increase the risk of cardiovascular events, as was shown in MA.17, where the incidence of cardiovascular events was similar with letrozole and placebo (5.8 vs 5.6%; P = 076; Goss et al. 2005).

Clinical management
Several clinical trials have reported that although the overall incidence of cardiac events was numerically higher in patients receiving an AI than in those receiving tamoxifen, the differences between groups were not statistically significant (Howell et al. 2005, Jakesz et al. 2005, Thürlimann et al. 2005, Salgado & Zivian 2006, Coombes et al. 2007; Table 2). According to current guidelines, present knowledge is insufficient to fully determine the effect of AIs on CVD and coronary heart disease (Winer et al. 2005) and the risk of long-term side effects (Goldhirsh et al. 2005). The negative impact of cardiovascular risk factors typically seen in older postmenopausal women becomes more evident once adjuvant therapies reduce the rate of breast cancer-related deaths (Monnier 2007). Although AI may lack the lipid-lowering and cardioprotective effect of tamoxifen, the risk of cardiovascular events with AIs is well within the range seen in an age-matched, non-breast cancer population (Sourander et al. 1998). Other databases (UK General Practice Research Database, Swedish MI register) have reached similar conclusions (Medicines and Healthcare Products Regulatory Agency 2005). Clinical management includes monitoring cholesterol levels, eating a healthy diet, engaging in regular
exercise, and regulating preexisting hypercholesterolemia with medications (Grundy et al. 2004). All patients at risk of CVD and all patients with breast cancer should be routinely monitored for CVD; lipid-lowering medications may be prescribed (Grundy et al. 2004).

**Gynecologic health**

Hot flushes and night sweats are common menopausal symptoms (Bennett & Degeling 1995). Hot flushes may cause disturbed sleep, depressive symptoms, and significant reductions in quality of life (Bachmann 2005). Sexual dysfunction may also occur as healthy women age (Rosen et al. 1993, Ganz et al. 1999). In a study of 329 healthy women, some common sexual problems included inhibition or anxiety during sexual activity (38.1%), lack of sexual pleasure (16.3%), lack of lubrication (13.6%), and painful intercourse (11.3%), with the latter two problems being significantly more prevalent in postmenopausal women (Rosen et al. 1993). A study of 1134 breast cancer survivors showed that the most consistent and important predictors of sexual health were vaginal dryness, emotional well-being, body image, quality of the partnered relationship, and the presence or absence of sexual problems in the partner (Ganz et al. 1999).

**Hot flushes and vaginal symptoms in adjuvant AI trials**

In ATAC, the incidence of hot flushes was significantly lower with anastrozole than tamoxifen (35.7 vs 40.9%; \(P < 0.0001\)), as was vaginal bleeding (5.4 vs 10.2%; \(P < 0.0001\); Howell et al. 2005). Conversely, reduced libido (1 vs <1%; \(P = 0.0001\)) and dyspareunia (1 vs <1%; \(P = 0.002\)) was found in significantly more patients receiving anastrozole than tamoxifen (Buzdar et al. 2006b). In the BIG 1–98 trial, letrozole versus tamoxifen was associated with a lower incidence of vaginal bleeding (3.3 vs 6.6%; \(P = 0.001\)), hot flushes (33.5 vs 38.0%; \(P < 0.001\)), and night sweats (13.9 vs 16.2%; \(P = 0.004\); Thürlimann et al. 2005). The TEAM study also found that at 12 months, patients receiving tamoxifen, versus those receiving exemestane, had a significantly higher mean hot flush score (\(P = 0.0253\)) and more vaginal discharge (\(P < 0.0001\)), whereas patients receiving exemestane had more vaginal dryness (\(P = 0.0004\)) and decreased libido (\(P = 0.0343\); Asmar et al. 2005).

In the switch setting, the combined results of the ABCSG 8 and ARNO 95 trials showed no difference between anastrozole- and tamoxifen-treated patients in the incidence of hot flushes (50 vs 48%; \(P = 0.32\)), vaginal bleeding/discharge (17 vs 18%; \(P = 0.93\)), or endometrial cancer (<1 vs <1%; \(P = 0.069\); Jakesz et al. 2005). In the IES, at a median follow-up of 55.7 months, there was no significant difference in the incidence of hot flushes (42.4% vs exemestane versus 39.9% with tamoxifen; \(P = 0.08\)), and the incidence of vaginal bleeding was lower in the exemestane than tamoxifen arm (5.2 vs 7.6%; \(P = 0.002\); Coombs et al. 2007). Likewise, in the MA.17 trial, letrozole was associated with less vaginal bleeding than a placebo was (6 vs 8%; \(P = 0.005\)) but a greater incidence of hot flushes (58 vs 54%; \(P = 0.003\)), while the incidence of vaginal dryness was similar between groups (Goss et al. 2005).

**Cognition**

A decline in cognitive ability has been associated with aging. The European Community Concerted Action on the Epidemiology and Prevention of Dementia group calculated prevalence rates for women in nine age groups (30–59, 60–64, 65–69, 70–74, 75–79, 80–84, 85–89, 90–94, and 95–99) based upon pooled data on the prevalence of moderate to severe dementia in several European countries. The results clearly showed that prevalence increased with age (Hofman et al. 1991).

### Table 2 Cardiac events in patients receiving tamoxifen versus an aromatase inhibitor (AI)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Cardiac event</th>
<th>Al no. (%)</th>
<th>Tamoxifen no. (%)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intergroup exemestane group (Salgado &amp; Zivian 2006)</td>
<td>Cardiovascular disease other than myocardial infarction</td>
<td>Exemestane 984 (42.6)</td>
<td>913 (39.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>Updated intergroup exemestane group (Coombes et al. 2007)</td>
<td>Cardiovascular events (excluding venous thromboembolic events)</td>
<td>Exemestane 483 (20.8)</td>
<td>441 (18.9)</td>
<td>0.09</td>
</tr>
<tr>
<td>Combined results of ABCSG 8 and ARNO 95 (Jakesz et al. 2005)</td>
<td>Myocardial infarction</td>
<td>Anastrozole 3 (1)</td>
<td>2 (&lt;1)</td>
<td>1.0</td>
</tr>
<tr>
<td>ATAC (Howell et al. 2005)</td>
<td>Ischemic CVD</td>
<td>Anastrozole 127 (4.1)</td>
<td>104 (3.4)</td>
<td>0.1</td>
</tr>
<tr>
<td>BIG 1–98 (Thürlimann et al. 2005)</td>
<td>Cardiac event</td>
<td>Letrozole 162 (4.1)</td>
<td>153 (3.8)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

ABCSG, Austrian Breast and Colorectal Cancer Study Group; ARNO, arimidex-nolvadex; ATAC, arimidex, tamoxifen, alone or in combination; BIG, Breast International Group.
A more recent pooled collaborative analysis of European population-based studies found that, in individuals aged 65 years or older, the age-standardized prevalence of dementia (all-cause), Alzheimer’s disease, and vascular dementia was 6.4, 4.4, and 1.6% respectively, with the prevalence of Alzheimer’s disease 0.6% in the 65–69 age group and 22.2% at 90 years of age and older (Lobo et al. 2000). Another analysis reported the prevalence of Alzheimer’s disease in Europe to be very low at younger ages (<2% in the age group 65–70), but then increasing with age and female gender at older ages (up to 46% in French females above 90 years; Moise et al. 2004).

Data for the effects of adjuvant AI therapy on cognition are sparse, and more research is needed. In a study comparing patients from the ATAC trial with healthy controls, those receiving anastrozole were more impaired in a processing speed task ($P = 0.032$) and in a measure of immediate verbal memory ($P = 0.026$; Jenkins et al. 2004). Another pilot study found more severe cognitive impairment in women taking anastrozole versus those on tamoxifen (Bender et al. 2005), and exemestane was associated with more impaired word finding than tamoxifen ($P = 0.0057$) in the TEAM study (Asmar et al. 2005). Yet, in the prevention setting, the results from the cognitive substudy ($n = 179$) of the IBIS-II study found that anastrozole did not have a significant impact on cognitive functioning in postmenopausal women (Jenkins et al. 2006). More studies are needed to evaluate the long-term influence of AIs on cognition, dementia, and Alzheimer’s disease.

**Other AEs**

Some other minor AEs have been reported in adjuvant AI trials. In ATAC, non-predefined AEs (e.g., dry mouth, nail disorders, and fungal infection) occurred more often in patients receiving anastrozole than tamoxifen (Buzdar et al. 2006b). A recent analysis of the ATAC trial showed a significantly greater incidence of dry mouth in patients receiving anastrozole compared with tamoxifen (4 vs 2%; $P = 0.003$), as well as an increased incidence of diarrhea (9 vs 7%; $P = 0.02$; Buzdar et al. 2006b). In the IES, diarrhea (4.2 vs 2.7%; $P = 0.0002$), gastric ulcer (1.2 vs 0.3%; $P = 0.001$), paresthesia (9 vs 7%; $P = 0.02$), and insomnia (3.0 vs 1.2%; $P < 0.0001$) occurred more often in patients receiving exemestane than tamoxifen (Coombes et al. 2007). Some of the AEs reported with exemestane (e.g., diarrhea, visual disturbances) have not been reported with non-steroidal AIs (Aromasin package insert 2005, Coombes et al. 2007).

**Life-threatening AEs**

AIs are associated with fewer serious AEs compared with tamoxifen and lower discontinuation rates due to AEs (Table 3). In ATAC, there was a non-significant trend toward fewer serious AEs leading to death in the anastrozole than in the tamoxifen group (3 vs 4%; $P = 0.6$; Buzdar et al. 2006b). A similar observation was seen in the switch studies, with fewer incidences of serious or life-threatening AEs in patients who switched to anastrozole than in those who remained on tamoxifen (Boccardo et al. 2005, Kaufmann et al. 2006). In contrast, an excess of life-threatening AEs was observed with adjuvant tamoxifen therapy that occurred early in the first 2–3 years of treatment (Cuzick & Wale 2006, Duffy 2006).

Meta-analyses have demonstrated that tamoxifen is associated with significant increases in pulmonary embolism (RR 1.88; 95% CI 1.77–3.01), stroke (RR 1.49; 95% CI 1.16–1.90), and deep vein thrombosis (RR 1.87; 95% CI 1.33–2.64; Braithwaite et al. 2003) and a slightly increased incidence of mortality due to thromboembolic events (15 vs 8 patients; $P = \text{NS}$) and stroke (54 vs 29 patients; $P = 0.07$; Early Breast Cancer Trialists’ Collaborative Group 2005). The ATAC trial also showed that the incidence of venous thromboembolic events was significantly higher in patients receiving tamoxifen than anastrozole (odds ratio (OR) 0.61; 95% CI 0.46–0.80; $P < 0.0001$; Cuzick & Wale 2006). Trials of letrozole and exemestane showed similar findings (Goss et al. 2005, Jakesz et al. 2005, Thürilmann et al. 2005, Coombes et al. 2007). In the BIG 1–98 trial, the incidence of thromboembolic events was also significantly lower.

<p>| Table 3 Incidence of serious adverse events (AEs) and discontinuation due to AEs in aromatase inhibitor adjuvant therapy (Braithwaite et al. 2003, Goss et al. 2005, Thürilmann et al. 2005) |</p>
<table>
<thead>
<tr>
<th>Comparator</th>
<th>ATAC</th>
<th>BIG 1–98</th>
<th>IES</th>
<th>MA.17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of serious AEs</td>
<td>Anastrozole versus tamoxifen</td>
<td>Letrozole versus tamoxifen</td>
<td>Exemestane versus tamoxifen</td>
<td>Letrozole versus placebo</td>
</tr>
<tr>
<td></td>
<td>33 vs 36%</td>
<td>1.7 vs 1.7%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Discontinuation due to AEs</td>
<td>11 vs 14%</td>
<td>11.3 vs 10.4%</td>
<td>6 vs 5.2%</td>
<td>4.9 vs 3.6%</td>
</tr>
<tr>
<td></td>
<td>$P = 0.0002$</td>
<td>$P = \text{NR}$</td>
<td>$P = \text{NR}$</td>
<td>$P = 0.019$</td>
</tr>
</tbody>
</table>

ATAC, aniride, tamoxifen, alone or in combination; BIG, Breast International Group; IES, Intergroup Exemestane Study; MA.17, National Cancer Institute of Canada Clinical Trials Group letrozole study; NR, not reported.
with letrozole (1.5 vs 3.5%; \( P < 0.001 \); Thürlimann et al. 2005). Similarly, in the IES, switching to exemestane was associated with significantly reduced incidences of venous thromboembolic events (1.9 vs 3.1%; \( P = 0.01 \); Coombes et al. 2007).

Tamoxifen use is also associated with a significant increase in the risk of endometrial cancer (RR 2.70; 95% CI 1.94–3.75; Brathwaite et al. 2003). A prospective endometrial assessment in menopausal women demonstrated that AIs as upfront adjuvant therapy had no effect on endometrial thickening; however, if administered as switched therapy after tamoxifen, AIs may reverse tamoxifen-associated endometrial thickening (Garutti et al. 2006). In ATAC, anastrozole was associated with a significantly lower incidence of gynecologic events (endometrial hyperplasia, endometrial neoplasia, cervical neoplasms, and enlarged uterine fibroids; 3 vs 10%; \( P < 0.0001 \)) and endometrial cancer (5/3092 vs 17/3094) than was tamoxifen (Buzdar et al. 2006b). At a mean follow-up of 6 years, the ATAC endometrial sub-protocol found that anastrozole was associated with fewer endometrial abnormalities (most commonly polyp formation) than tamoxifen (27 vs 44%; \( P = 0.17 \); Duffy 2006). In BIG 1–98, letrozole versus tamoxifen was associated with fewer endometrial biopsies (2.3 vs 9.1%; \( P < 0.001 \)) and fewer invasive endometrial cancers (0.1 vs 0.3%; \( P = 0.18 \); Thürlimann et al. 2005). In IES, fewer serious gynecologic events occurred in women receiving exemestane than tamoxifen (7.0 vs 10.6%; \( P = 0.0001 \)), and no significant difference was noted in the incidence of endometrial cancer between treatment arms (Coombes et al. 2007).

Finally, safety analysis of the ATAC trial showed a surprisingly higher incidence of head and neck cancer with anastrozole than tamoxifen (10/3092 vs 3/3094), as well as a higher incidence of lung cancer (25/3092 vs 16/3094) and lung cancer deaths (15/3125 vs 8/3116; Buzdar et al. 2006b). The mechanism responsible for this increased incidence is unclear. These are very small absolute numbers that have little clinical significance; nonetheless, further analysis and follow-up are warranted.

**Efficacy and safety of adjuvant endocrine therapy in older patients**

Physicians may be hesitant to prescribe adjuvant AIs, because they may consider them no more effective than tamoxifen or possibly unsafe in this population (Mustacchi et al. 2007, Passage & McCarthy 2007); older patients are more likely to have serious comorbidities, as well as increased risk for CVD and dying of other causes. Older patients often receive less aggressive treatment than younger patients (Rao et al. 2007), but a study of 118 women aged over 80 years with breast cancer showed that the women treated with letrozole had better progression-free survival than those treated with tamoxifen (progression was 5/64 and 24/54 respectively; Garamella et al. 2006). In the BIG 1–98 trial, letrozole, compared with tamoxifen, significantly reduced the risk of recurrence by 21% in patients aged 65 years or older (HR 0.79; 95% CI 0.64–0.97; \( P = 0.02 \); Thürlimann et al. 2005), while in the ATAC trial, anastrozole reduced the risk of recurrence by only 7% in women aged 65 years and older (HR 0.93; 95% CI 0.80–1.08) when compared with tamoxifen (Arimidex package insert 2005). A recent analysis from the BIG 1–98 trial only on the patients in the monotherapy arms (\( N = 4922 \)) showed that letrozole provided consistent benefit over tamoxifen irrespective of age (\(< 65–75\) years and older; Crivellari et al. 2007).

In MA.17, letrozole reduced the risk of recurrence by 27% in women aged 50 years and older (HR 0.73; 95% CI 0.55–0.98; Goss et al. 2005). A follow-up MA.17 analysis showed that in patients aged 70 years and older who were in good health, letrozole yielded benefits in disease-free and distant disease-free survival similar to those seen in younger patients, without increased toxicity versus placebo (Muss 2006). Overall survival was significantly shorter in patients aged 70 years and older (perhaps due to non-breast cancer death), but patients in this age group with node-positive disease had a significant improvement in overall survival with letrozole (\( P = 0.04 \)). There was no difference in toxicity by age between letrozole and placebo in patients of 70 years old and older and, at 36 months, quality of life in these patients was similar in both letrozole and placebo groups (Muss 2006). The results suggest that older patients generally benefit from AI therapy and should be considered for letrozole after 5 years of tamoxifen (Muss 2006).

**Compliance with adjuvant endocrine therapy**

Compliance in patients with all chronic diseases is low, with about 50% of patients adhering to recommended treatment regimens (World Health Organization 2003). Two German studies found that mean compliance was low with daily and weekly bisphosphonate use (37.7 and 51.7% respectively) for patients with osteoporosis (Bartl et al. 2005), and about one-third to one-half of patients on weekly versus daily bisphosphonate therapy discontinued treatment after one prescription (31.3 vs 45.8% respectively; Bartl et al. 2006). Likewise, a retrospective cohort analysis found that statin use decreased over time, from 79% in the first 3 months to 42% after 120 months (Benner et al. 2002). A study showed that a greater belief in the necessity of treatment correlated with higher
reported adherence (RR 0.21; $P < 0.01$), whereas greater concern regarding dependence or long-term effects correlated with lower adherence (RR 0.33; $P < 0.01$; Horne & Weinman 1999). A meta-analysis has shown that therapy non-compliance was responsible for 5.5% of hospitalizations in the United States (Sullivan et al. 1990), illustrating that non-compliance can lead to serious health risks.

Tamoxifen is associated with poor tolerability; 23–40% of patients discontinue therapy (Demissie et al. 2001). A study of 462 women (65 years and older) with stage I–IIIA breast cancer showed that 31% of those who started tamoxifen therapy failed to complete the recommended 5-year course (Lash et al. 2006). Another study found that 50% (489/974) of women discontinued tamoxifen during 5 years of follow-up (Owusu et al. 2006). In a study of 516 women aged 65 years and older, tamoxifen discontinuation was more likely in women with neutral or negative beliefs about tamoxifen (OR 3.0; 95% CI 1.6–5.6; Fink et al. 2004). A study of 131 women with stable breast cancer found that women who disliked taking medication reported significantly less adherence ($P = 0.001$; Atkins & Fallowfield 2006). Self-reported non-adherence to tamoxifen was associated with the belief that nothing would be gained by taking the drug, whereas adherence was associated with the belief that tamoxifen would prevent breast cancer; side effects were the main reason reported for not taking tamoxifen (Grunfeld et al. 2005).

Tamoxifen adherence rates were significantly lower in the youngest, oldest, non-white, and mastectomy patients, whereas adherence rates were significantly higher in patients who saw an oncologist in the year before the initiation of tamoxifen (Partridge et al. 2003).

Noncompliance also occurs with adjuvant AI therapy. A study evaluating adherence to adjuvant anastrozole therapy ($N = 1498$) found that 20% of women may be suboptimally adherent during the first 12 months of therapy (Partridge et al. 2006). A smaller study of women with breast cancer receiving anastrozole ($n = 44$), letrozole ($n = 10$), or exemestane ($n = 2$) found that treatment-related arthralgia and/or bone pain was severe enough to cause 20% of patients to discontinue AI therapy (Presant et al. 2006). Yet, an investigation of adherence and persistence patterns in 16 900 patients treated with adjuvant endocrine therapies found that AI usage is increasing, and that individuals who switched from tamoxifen to an AI persisted longer on therapy (Martin et al. 2006). For example, a study of 104 postmenopausal women who were experiencing distressing side effects while taking adjuvant tamoxifen and then switched to letrozole found that, after 6 weeks, 66% of the women preferred to remain on letrozole (Thomas et al. 2006).

A retrospective observational study ($n = 128$) reported that of 51 patients switched from one agent to another, almost half (45%) did so because of AEs, and the majority (78.4%) switched from tamoxifen to an AI after a mean of 36 months (Schwartzberg et al. 2006).

AEs can be quite troublesome to patients and may result in treatment discontinuation. Physicians need to actively identify and treat AEs before patients decide to discontinue therapy, but patients should be informed of any therapy-associated AEs that may develop before treatment is initiated. Educating the patient beforehand will help manage patient expectations and beliefs about the benefits of therapy. Physicians also should emphasize the importance of compliance to therapy and how it affects the patient’s outcome before starting therapy. A recent study shows that increased duration of drug usage is associated with improved survival in breast cancer patients, so clearly, these drugs cannot be effective in patients who do not take their therapy (McCowan et al. 2007).

Conclusion

Clinical trials show that all AIs are superior to tamoxifen in terms of reducing recurrence risk, and some, like letrozole, are also superior to tamoxifen in terms of reducing the risk of distant metastases, especially early on in the course of therapy (Howell et al. 2005, Thürlimann et al. 2005, Coombes et al. 2007, Mauriac et al. 2007). The AIs are generally well tolerated and have similar safety profiles, with the majority of AEs being mild to moderate and common to menopause. Common short-term AI-associated toxicities included hot flushes, musculoskeletal complaints/arthralgia, and bone loss, which are all predictable and can be effectively managed. Results from the Z-FAST and ZO-FAST studies have shown that initial use of concomitant ZA with adjuvant AI therapy is a safe and effective way to prevent bone loss. Although AIs lack the cardioprotective and lipid-lowering effects of tamoxifen, they have not been determined to have a detrimental impact on cardiac health. In contrast to tamoxifen, the AIs also do not increase the risk of serious life-threatening thromboembolic and cerebrovascular events and endometrial cancer. Patients and doctors should engage in a dialogue about possible side effects and the importance of compliance to therapy before initiating AI treatment, so that fully informed decisions can be made (Salgado & Zivian 2006). Individual patient assessment with respect to therapy risks and benefits is critical. Lifestyle factors, comorbidities, and concomitant medications must all be considered. Proper management of AEs, if they develop, can greatly improve compliance and, ultimately, patient outcome.
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