

CLINICAL DIVERSIFICATION OF AROMATASE INHIBITORS BEYOND ONCOLOGY: SEX-BASED PHYSIOLOGY, BENEFITS, AND ADVERSE EFFECTS

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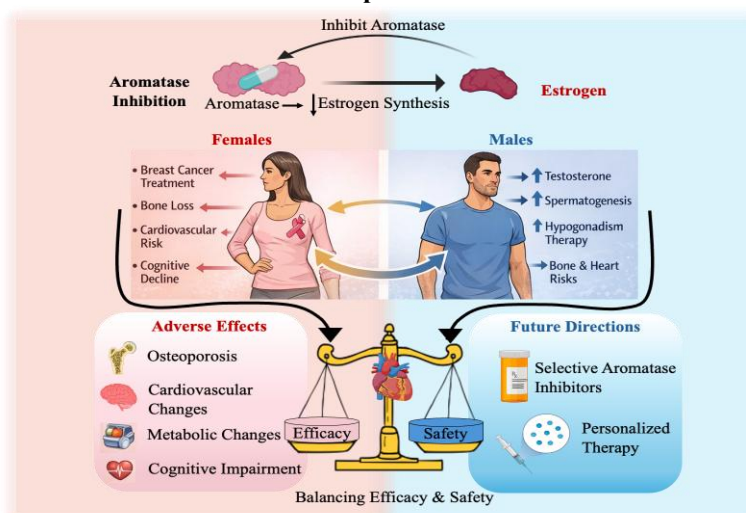
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ABSTRACT

Aromatase inhibitors (AIs) are potent endocrine agents that suppress estrogen biosynthesis by inhibiting aromatase, the enzyme catalyzing the conversion of androgens to estrogens. Originally developed for hormone receptor–positive breast cancer in postmenopausal women, their use has expanded to male endocrine disorders, including hypogonadism, infertility, and conditions with altered testosterone–estrogen balance. Due to fundamental differences in hormonal regulation, tissue-specific aromatase expression, and estrogen-dependent physiology, AIs produce distinct systemic responses in males and females. In women, AI-mediated estrogen suppression exerts therapeutic benefit in breast cancer but is associated with adverse skeletal, cardiovascular, metabolic, and neurocognitive effects during long-term therapy. In men, aromatase inhibition enhances gonadotropin secretion and testosterone synthesis; however, prolonged estradiol depletion may impair bone integrity, lipid metabolism, and cardiovascular function. This review synthesizes the pharmacology, clinical benefits, and sex-specific risks of AIs across generations and highlights the need for precision-based dosing and selective aromatase modulation to optimize efficacy while minimizing systemic toxicity in both sexes

KEYWORDS: Aromatase inhibitors, estrogen suppression, sex differences, bone metabolism, cardiovascular risk, endocrine therapy.

1. Graphical Abstract:



INTRODUCTION

The enzyme aromatase (CYP19A1), which is responsible for converting androgens like testosterone and androstenedione into Estrogen (oestradiol and estrone), is blocked by a significant class of drugs called Aromatase inhibitors (AIs). AIs are an essential treatment option for ER-positive breast cancer because they restrict the production of estrogen, which is the primary source of circulating estrogen in postmenopausal women due to peripheral aromatization [1]. Exemestane, letrozole, and anastrozole are common AIs (Figure 1). These steroidal and nonsteroidal drugs function by either irreversibly or reversibly inhibiting the aromatase enzyme. By blocking Estrogen-dependent signalling pathways that promote tumour growth, aromatase inhibition

significantly reduces tumour recurrence and improves disease-free survival in females, especially those with postmenopausal breast cancer but estrogen deficiency also has systemic effects, such as a decrease in bone mineral density (BMD), musculoskeletal discomfort, and an increased risk of cardiovascular disease. As a result, throughout the past 10 years, a great deal of research has been done on the benefit–risk ratio of long-term AI treatment [2]. However, systemic effects of estrogen deficiency include a reduction in bone mineral density (BMD), musculoskeletal pain, and an elevated risk of cardiovascular disease. The benefit–risk ratio of long-term AI treatment has thus been the subject of extensive research over the last ten years [3]. Aromatase is essential for maintaining bone homeostasis, controlling spermatogenesis, and controlling the male testosterone-to-estrogen ratio. Although AIs have not been officially approved for use in males, they are being used off-label to treat gynecomastia, obesity-related low testosterone, late-onset hypogonadism, and idiopathic infertility. Their ability to normalize testosterone levels by lowering excessive estrogen feedback at the hypothalamic-pituitary-gonadal axis has been studied recently [4]. However, little is known about the long-term metabolic, skeletal, and cardiovascular safety in males because of a dearth of clinical trial data [5]. Sex-specific pharmacological and physiological differences significantly influence AI response and adverse outcomes. Differences in hepatic metabolism, estrogen receptor subtypes, aromatase tissue distribution, and hormonal feedback pathways are the causes of these disparities [6]. Furthermore, variations in drug efficacy and toxicity that are sex-dependent and interindividual may be caused by genetic variations in CYP19A1 and drug-metabolizing enzymes. Understanding these differences is essential for optimizing AI therapy, modifying treatment duration, and reducing side effects [7].

Given their increasing use in both sexes, a comprehensive evaluation of the relative pharmacological effects, therapeutic outcomes, and safety profiles of AIs is essential. This review fundamentally examines recent research on the effects of AIs in males versus females, emphasizing molecular causes, clinical efficacy, and novel findings on the risks and benefits specific to each sex. The goals are to highlight knowledge gaps and guide future research toward safer, more individualized endocrine therapy [8].

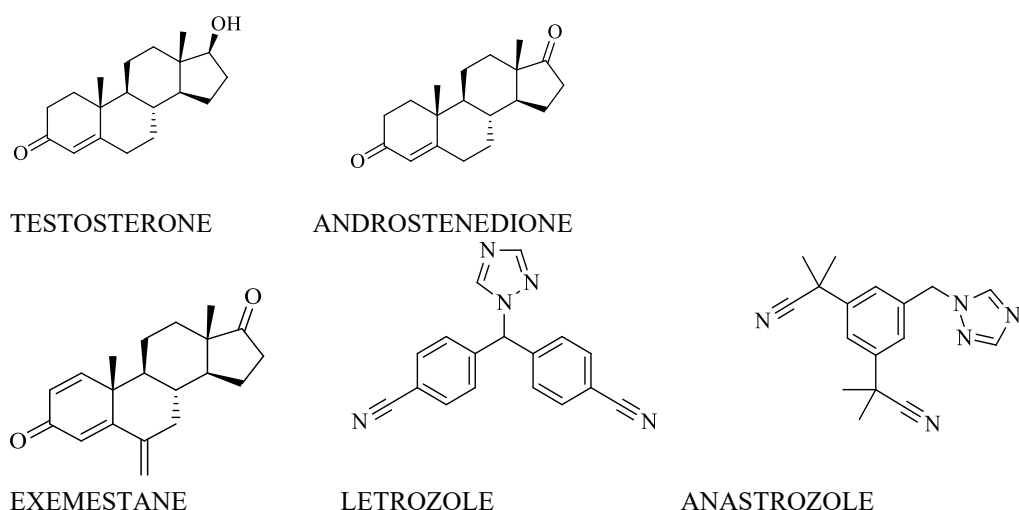


Figure 1: Currently available AIs

The aromatization of androgens' A-ring is catalyzed by the cytochrome P450 enzyme aromatase (CYP19A1), which converts androstenedione into estrone and testosterone into estradiol (Figure 2). It is expressed in the brain, liver, adipose, and gonadal tissues and is crucial for maintaining both local and systemic estrogen levels. Estrogens in turn regulate the reproductive, neuroendocrine, skeletal, and cardiovascular systems. As a result, aromatase inhibition has systemic metabolic effects that extend beyond the reproductive organs [9].

The distribution of aromatase is sexually dimorphic; females express it more in ovarian, adipose, and breast tissue, while males exhibit strong enzymatic activity in testicular Leydig and Sertoli cells, adipose tissue, and the brain [10]. This accounts for many of the pharmacodynamic differences between the sexes when taking AIs [11].

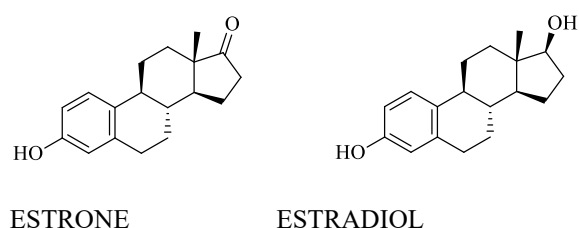


Figure 2: Structural Depiction of Estrone and Estradiol

AIs are classified based on chemical structure and mechanism of inhibition. Nonsteroidal inhibitors including anastrozole and letrozole, acts reversibly by attaching themselves to the heme-moiety of the aromatase enzyme and compete with the substrate androgen. Together with the heme iron, their triazole rings prevent oxygen from activating, which is necessary for aromatization [12]. Steroidal inhibitors like Exemestane, an androgen analog that permanently deactivates aromatase through "suicide inhibition." By creating a covalent bond with the enzyme's active site, Exemestane permanently deactivates the enzyme until new enzyme production occurs [13]. These medications have broad tissue penetration and oral bioavailability due to their tiny, lipophilic chemical makeup. Their structural diversity contributes to different metabolic fates and half-lives [14].

AIs prohibit androgens from changing into estrogen by interfering with the culminating phase of estrogen production [15]. As a result, postmenopausal women experience a significant ($\geq 95\%$) decrease in their circulating levels of estradiol and estrone, while men experience a moderate decrease. Suppressing both systemic and intracrine estrogen production within tumours or adipose depots, the mechanism also affects peripheral tissues [16]. When ovarian production ceases, women, especially those who have experienced menopause, rely on peripheral aromatization as their main source of estrogen. By obstructing this pathway, growth stimulation is denied to estrogen receptor-positive breast cancers, thereby preventing their proliferation and recurrence [17]. In males, aromatase regulates the ratio of testosterone to estradiol. Inhibition leads to increased testosterone through feedback stimulation of the hypothalamic-pituitary-gonadal (HPG) axis [18]. This can help men regain their libido and reproductive factors if they are hypogonadal or obese. The fact that prolonged estradiol reduction may have negative effects on mood, lipid profile, and bone metabolism emphasizes the need for cautious dosage [19].

Each of the three AIs is orally active and has a bioavailability of over 85%. Exemestane takes 2-4 hours to reach peak plasma concentrations, while anastrozole and letrozole take 1-2 hours. They are widely distributed throughout tissues due to their high lipophilicity and moderate plasma protein binding (roughly 40–70%). The volume of distribution varies between the sexes because of variations in body fat percentage and total body water [20].

The main hepatic cytochrome P450 enzymes that extensively metabolize letrozole and anastrozole are CYP3A4 and CYP2A6 [21]. Aldo-keto reductases reduce exemestane, and CYP3A4 oxidizes it to create active metabolites like 17-hydroexemestane, which still has some androgenic potential. Sex-based differences in hepatic enzyme expression and activity affect AI clearance. Women's hepatic metabolism is frequently slower for lipophilic drugs than men's, who may need higher or more frequent dosages for equal estrogen suppression because of increased hepatic blood flow and enzyme activity [22].

The half-lives of anastrozole, letrozole, and exemestane are approximately 46, 48, and 27 hours, respectively. The majority of inactive metabolites are eliminated by hepatic metabolism, with only a small quantity being eliminated by the kidneys. It takes 7–10 days to reach a steady state with a daily dosage. They accumulate little and have linear pharmacokinetics [23].

Recent pharmacokinetic models indicate that obesity and hepatic enzyme polymorphisms significantly affect AI clearance. Although even partial suppression may cause discernible hormonal changes in males with lower baseline estrogen levels, sequestration in adipose tissue may reduce effectiveness in obese individuals (mostly women) [24].

1. Effect of AIs on Endocrine system, Bone and Lipid Metabolism

AIs lower plasma estradiol by 85–97% in women and 40–60% in men. This results in a compensatory increase in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) through feedback mechanisms [25]. In women, AIs increase the efficacy of treatment for premenopausal women with ovarian suppression, while estradiol suppression in postmenopausal women increases gonadotropin secretion without restoring ovarian function [26] while in men, testosterone levels typically rise by 30 to 50% while estradiol levels marginally decline, increasing the T/E2 ratio. This promotes spermatogenesis in some infertile men [27]. A lack of estrogen brought on by AI accelerates bone resorption. Longitudinal studies show that the bone mineral density of women's lumbar spines decreases by 2–4% annually. Smaller studies conducted on males after a year of AI use show comparable effects, necessitating bone-protective measures. AI-induced estrogen deficiency speeds up bone resorption. According to longitudinal studies, women's lumbar spines lose 2–4% of their bone mineral density every year. Similar effects are shown in smaller studies on males after a year of AI use, requiring bone-protective measures [28].

1.1 Sex-Specific Pharmacological Considerations of AIs

While aromatase activity is more evenly distributed across the adipose, brain, and gonadal compartments in males, it is higher in females' adipose and breast tissue, according to molecular imaging and gene expression studies. Systemic hormonal feedback and local estrogen availability are impacted by this unequal distribution [29].

While ER α is more highly expressed in the breast, uterus, and bone in females, ER β is more widely distributed in the testis and vascular endothelium in males. Therefore, tissue-specific effects of AI-induced estrogen depletion include tumour suppression in women and skeletal or vascular changes in men [30].

Polymorphisms in the CYP19A1 gene change the inhibitor response and aromatase activity. Recent genome-wide studies have identified variants such as rs700519 and rs4646 as markers of AI toxicity and efficacy. Additionally, the effects of CYP3A422 and CYP2A69 alleles on metabolism and clearance result in different

exposures between the sexes [31].

Because AIs are CYP3A4 substrates, using them in combination with strong inducers like rifampicin or carbamazepine may reduce their effectiveness. However, inhibitors (ketoconazole, verapamil) may increase exposure [32]. Because of its steroidal makeup, which lowers the risk of pharmacokinetic interactions with tamoxifen or other medications, exemestane is used in combination regimens.

According to recent pharmacovigilance studies, long-term use of proton pump inhibitors may alter stomach pH, which reduces AI absorption; however, the therapeutic significance of this finding is still being investigated [33].

Clinical pharmacology information on women is abundant. Near-complete estrogen suppression is achieved by AI treatment in postmenopausal women, which significantly lowers the risk of breast cancer recurrence [34]. However, long-term inhibition of estrogenic pathways affects a number of organ systems. Potential risk of fracture and bone turnover has been reported in skeletal system [35] while loss of protective effects of estrogen on the vascular endothelium has been reported by Xing, D., et al., [36]. Lower levels of estrogen also precipitate neurological changes in mood affecting central nervous system [37].

In men, aromatase inhibition raises serum testosterone and lowers serum estradiol without altering gonadotropin secretion dynamics. Letrozole and anastrozole have been shown to improve fertility in men with elevated estradiol or hypogonadism brought on by obesity. Long-term suppression of estradiol below physiological levels (<10 pg/mL) is linked to lower BMD, lower HDL, and possibly endothelial dysfunction [38]. Low-dose or intermittent regimens are therefore recommended. Pharmacokinetic studies show that males obtain similar plasma concentrations at standard dosages. Males, however, exhibit a faster decline in estradiol due to lower baseline levels, necessitating close observation to avoid severe suppression [39].

1.2 Comparative Pharmacology of Major AIs

The potency gradient, letrozole > anastrozole > exemestane, reflects differences in enzyme binding affinity and turnover rate (Table 1). Because letrozole is so effective at suppressing estrogen to the greatest extent possible, it is the recommended treatment for high-risk breast cancer. Exemestane, an androgenic metabolite, helps people with osteopenia by reducing bone loss to some extent [40].

Table 1: Pharmacology of Major AIs

Property	Anastrozole	Letrozole	Exemestane	Ref
Class	Nonsteroidal (Type II)	Nonsteroidal (Type II)	Steroidal (Type I)	[41]
Binding	Reversible	Reversible	Irreversible	[42]
Half-life (h)	~46	~48	~27	[43]
Estrogen suppression	~85–95%	~95–98%	~85–90%	[44]
Metabolism	CYP3A4, CYP2A6	CYP3A4, CYP2A6	CYP3A4, aldo-keto reductases	[45]
Unique features	Minimal drug interactions	Highest potency	Mild androgenic metabolite	[46]
Clinical niche	Adjuvant breast cancer	Extended therapy; fertility modulation	AI failure cases; bone-sparing tendency	[47]

1.3 Toxicological and Off-Target Considerations

AIs have high therapeutic indices and low acute toxicity. However, long-term use causes effects of tissue-specific estrogen deprivation are cortical thinning and elevated osteoclast activity in bones [48], poor synthesis of nitric oxide and endothelial dysfunction [49] and mood-influencing changes in serotonin and dopamine pathways [50]. Long-term exposure to AI has also been linked to altered hippocampus neurogenesis in animal studies, which raises concerns about potential cognitive effects, particularly in women. Less than 1% of patients experience a brief increase in liver enzymes; hepatotoxicity and nephrotoxicity are uncommon. The androgenic metabolite of exemestane may result in hair loss or mild acne [51].

1.4 Emerging Pharmacological Comprehensions

Recent investigations have refined our understanding of aromatase inhibitor (AI) pharmacodynamics, highlighting several innovative strategies to improve therapeutic precision and safety. Emerging approaches in selective aromatase modulation aim to achieve partial enzyme inhibition while preserving physiological estrogen levels, thereby reducing skeletal toxicity and other estrogen-deprivation-related adverse effects. In parallel, tissue-selective inhibition through advanced drug-delivery platforms, such as liposomal formulations of letrozole and other nanocarrier-based systems, has demonstrated enhanced tumor targeting with diminished

systemic exposure and side-effect burden [52]. Furthermore, pharmacogenomic-guided dosing, particularly based on CYP19A1 polymorphisms, offers the potential for individualized treatment regimens that optimize estrogen suppression while minimizing interindividual variability and toxicity, paving the way for more personalized AI therapy [53].

2. Effect of AIs in Females

2.1 Endocrine and Reproductive System Effects

AIs are a cornerstone of treatment for postmenopausal women with estrogen receptor-positive (ER⁺) breast cancer. Their approach, which involves blocking the enzyme aromatase (CYP19A1), which catalyses the conversion of androgens into estrogen, results in significant estrogen suppression. Blocking peripheral aromatization in adipose and extra-gonadal tissues, which is the main source of estrogen after menopause, has a significant effect on endocrine regulation in several organ systems [54]. Our understanding of the systemic impacts and therapeutic efficacy of AI use in women has improved as a result of numerous studies carried out during the last five years. This section provides a comprehensive analysis of these findings across the endocrine, skeletal, cardiovascular, metabolic, and neuropsychological systems with an emphasis on molecular and clinical correlates [55].

2.1.1 Hormonal Modulation

AI therapy reduces circulating levels of estradiol and estrone in postmenopausal women by 95–98%. According to clinical research, letrozole and anastrozole almost completely prevent the synthesis of estrogen. The feedback effect causes a slight increase in luteinizing hormone (LH) and follicle-stimulating hormone (FSH), but permanent ovarian senescence keeps ovarian function dormant [56].

2.1.2 Fertility and Ovarian Response in Premenopausal Women

AIs are not recommended as monotherapy for patients with premenopausal breast cancer; however, their combination with ovarian suppression medications, like goserelin, has been shown to increase disease-free survival [57]. Outside of oncology, short-term AI treatment (letrozole 2.5–5 mg daily for 5 days) can induce ovulation in women with anovulatory infertility, particularly those with polycystic ovarian syndrome (PCOS). By momentarily reducing estrogen-mediated negative feedback, artificial intelligence (AI) increases follicular recruitment and FSH production. Randomized trials revealed a lower risk of multiple gestations and higher ovulation rates when compared to clomiphene citrate [58].

2.1.3 Menstrual and Hormonal Recovery

The menstrual recovery of cancer survivors of reproductive age is slowed by prolonged exposure to AI. Clinical follow-ups indicate that the causes of the chronic amenorrhea that lasts 6–12-month after medication are hypothalamic suppression and decreased endometrial proliferation. This highlights the importance of fertility counselling for younger women prior to starting AI [59].

2.2 Effects on Breast and Reproductive Tissues

AIs reduce intratumoral estrogen levels by inhibiting the expression of local aromatase in breast tissue. Estrogen promote proliferation by producing growth-promoting genes like cyclin D1, BCL2, and VEGF, which are controlled by Erα [60]. AIs block this signalling, which results in tumour regression and apoptosis. Studies have shown that AIs also improve anti-proliferative efficacy by suppressing MAPK and PI3K/AKT signalling [61]. Between 2021 and 2025, multiple phase III clinical trials and large-scale meta-analyses have reaffirmed the superiority of AIs (AIs) over tamoxifen in the management of postmenopausal estrogen receptor-positive (ER⁺) breast cancer. In the adjuvant setting, letrozole and anastrozole have been shown to improve 10-year disease-free survival by approximately 3–5% compared with tamoxifen [62]. Evidence from extended-therapy studies further indicates that continuation of AI treatment beyond five years confers an additional 2–3% reduction in recurrence risk, as reported by Sestak et al., albeit at the cost of increased skeletal toxicity, particularly osteoporosis and fracture risk [63]. In the neoadjuvant context, AIs effectively downstage primary tumours, leading to higher rates of breast-conserving surgery and improved surgical outcomes [64].

2.3 Resistance Mechanisms

According to recent genomic data, CYP19A1 expression upregulation, alternative growth pathway activation (HER2, mTOR), or ESR1 mutations that result in ligand-independent activation are the three main ways that adaptive resistance develops. Increased efficacy has been demonstrated in trials of combined therapy with either CDK4/6 inhibitors (Ribociclib) or mTOR inhibitors (Everolimus) [65].

2.4 Skeletal System Effects

2.4.1. Pathophysiology

Estrogen is crucial for preserving bone homeostasis because they reduce osteoclast activity and promote osteoblast survival. Osteoporosis and osteopenia result from the rapid bone turnover caused by an estrogen deficiency brought on by AI [66].

2.4.2. Clinical Findings

The decline in bone mineral density (BMD) is one of the most extensively studied adverse effects of AIs. Longitudinal studies show that AI treatment lowers BMD at the femoral neck and lumbar spine by 2–4% per year. Compared to age-matched controls, the risk of fracture increases by 20–35% when taking tamoxifen. The ATAC extension trial (2023) showed that fracture risk persisted even after treatment was stopped [67].

2.4.3. Prevention and Management

AI-induced bone loss is effectively prevented by denosumab and bisphosphonates (zoledronic acid,

alendronate). Current guidelines recommend baseline DEXA screening and calcium/vitamin D supplementation for all women taking AIs. Exercise and weight-bearing activities can lower risk. Recent research suggests that exemestane's low androgenic metabolite may make it less detrimental to bone density than nonsteroidal AIs [68].

2.5. Cardiovascular and Metabolic Effects

2.5.1. Lipid Metabolism

Estrogen positively regulates HDL production and maintains LDL receptor expression. AI-induced suppression may negatively impact lipid profiles. Several observational studies showed decreased HDL and increased LDL after 12–24 months of treatment. Letrozole had the most pronounced dyslipidemic effects, while the androgenic properties of exemestane had a neutral or slightly favourable effect [69].

2.5.2. Endothelial Function and Hypertension

Endothelial estrogen receptors (ER α and ER β) mediate vascular relaxation and nitric oxide (NO) release. AI-induced estrogen deficiency impairs this function. Vascular reactivity decreased by 20% within six months of treatment, according to endothelial flow-mediated dilatation experiments AI use is also associated with modest increases in systolic blood pressure (~5 mmHg). Reduced NO bioavailability and altered renin-angiotensin activity are the mechanisms [70].

2.5.3. Morbidity of the Heart

A meta-analysis found that compared to tamoxifen, long-term AI treatment slightly increases the incidence of cardiovascular events (hazard ratio 1.18). However, absolute risk remains low, particularly for women who have never experienced heart disease. This can be effectively decreased with lipid-lowering drugs and lifestyle modifications [71].

2.5.4. Metabolic Syndrome and Glucose Homeostasis

Recent evidence suggests that estrogen suppression is associated with increased visceral adiposity and insulin resistance. Cross-sectional studies have shown that AI users have higher fasting glucose and HOMA-IR scores than controls. Mechanistically, reduced Estrogen signalling lowers insulin receptor substrate-1 activity and modifies adipokine profiles (higher leptin, lower adiponectin). However, weight gain pales in comparison to the metabolic changes caused by chemotherapy [72].

2.6 Neurological and Cognitive Effects

2.6.1. Estrogen and Brain Function

Estrogen supports synaptic plasticity, neurogenesis, and cerebral blood flow. It modifies neurotransmitters such as acetylcholine, dopamine, and serotonin, which are critical for mood and cognitive functions [73].

2.6.2. Cognitive Results

Clinical neuropsychological studies have shown that women receiving AI treatment experience moderate impairments in verbal memory, processing speed, and executive function, especially after more than two years of use. Functional MRI imaging shows that a decrease in estradiol is linked to a decrease in hippocampal activity. However, the effects are typically mild and short-lived after treatment [74].

2.6.3. Emotion and Life Quality

Estrogen deficiency aggravates symptoms of depression, anxiety, and vasomotor instability. The prospective HOPE study found that AI users reported higher rates of fatigue and mood disturbance than those who received tamoxifen. Quality-of-life measures were significantly improved by exercise therapy or the concurrent use of selective serotonin reuptake inhibitors (SSRIs) [75].

2.7. Pain and Musculoskeletal Conditions

2.7.1. Both myalgia and arthritis

Up to 50% of women on AIs may experience joint or muscle pain, which is known as AI-associated musculoskeletal syndrome (AIMSS). It is characterized by morning stiffness, knee and hand arthralgia, and tendon soreness. Mechanistically, the removal of estrogen alters the metabolism of cartilage and increases proinflammatory cytokines (TNF- α , IL-6) [76].

2.7.2 Clinical Management

Nonsteroidal anti-inflammatory drugs (NSAIDs), exercise, and vitamin D optimization have all shown promise. According to recent research, omega-3 fatty acids and duloxetine are beneficial supplements (Hershman et al., 2023). The need for supportive care strategies is underscored by the fact that pain-related discontinuation rates remain between 10% and 15% [77].

2.8. Dermatologic, Gynaecologic, and Sexual Health

2.8.1. Vaginal and Vulvar Atrophy

The vaginal epithelium shrinks and becomes less lubricating when estrogen levels are low. The symptoms include pruritus, dyspareunia, and recurrent UTIs. Topical moisturizers and selective estrogen receptor modulators, like ospemifene, relieve symptoms without exposing the body to estrogen [78].

2.8.2. Impact on Skin and Hair

A lack of estrogen causes the vaginal epithelium to thin and become less lubricated. Symptoms include dyspareunia, pruritus, and recurrent UTIs. Topical moisturizers combined with ospemifene and other selective estrogen receptor modulators relieve symptoms without exposing the body to estrogen [79].

2.8.3. Sexual Activity

Arousal problems and decreased libido are common among AI users. Sexual dysfunction is associated with

hormonal and psychological problems. Interventions include vaginal lubricants, psychotherapy, and, experimentally, local DHEA formulations [80].

2.9. Inflammatory and Immunologic Routes

Estrogen controls immunological responses by influencing T-cell differentiation and cytokine balance. When it is suppressed, the expression of proinflammatory cytokines rises [81]. Recent studies found that AI users had higher levels of TNF- α , IL-6, and IL-1 β in their blood, which could explain their fatigue and joint pain. Conversely, lower estrogen levels may provide protection against autoimmune conditions like lupus, which are brought on by estrogen [82].

2.10. Effects on the Liver and Renal System

Hepatotoxicity is rare, even though transaminase elevations are mild in fewer than 1% of people. Exemestane's steroidal metabolism can result in benign cholestasis in susceptible individuals. Renal clearance is not significantly altered by dehydration during medication, although it may increase AI concentration and cause unpleasant side effects [83].

2.11. Compliance and Quality of Life

According to patient-reported outcomes, side symptoms such as fatigue, hot flashes, and arthralgia are often blamed for poor adherence. Real-world adherence rates are only 70–80% at three years. Results and continuation are improved by structured follow-up, lifestyle modifications, and psychological support [84].

3. Effect of AIs in Males

The male hypothalamic-pituitary-gonadal (HPG) axis is known to be significantly regulated by AIs (AIs). By changing testosterone and androstenedione into estradiol and estrone, aromatase (CYP19A1) regulates the delicate balance of sex hormones [85]. AIs are primarily used off-label to treat idiopathic infertility, gynecomastia, hypogonadism, and low testosterone brought on by obesity in men, but they are also widely used to treat estrogen-dependent breast cancer in women. Over the past five years, a growing body of research has examined the safety and efficacy of AI treatment in males, revealing complex endocrine, metabolic, skeletal, and cardiovascular effects. This study provides a thorough analysis of the pharmacology and effects of AI in men while summarizing recent findings [86].

3.1. Endocrine Effects

3.1.1. Testosterone and Estradiol Modulation

AIs raise circulating testosterone and lower levels of estradiol by preventing testosterone from aromatizing to estradiol [87]. In hypogonadal men, testosterone levels rise by 25–50%, and in 60–80% of cases, they return to normal. A 40–60% decrease in estradiol improves the ratio of testosterone to estradiol (T/E2) [88]. These modifications enhance mood, libido, sexual performance, and androgenic function. Crucially, excessive suppression of estradiol (<10 pg/mL) can lead to cardiovascular and bone problems [89].

3.1.2. Hypothalamic–Pituitary–Gonadal Axis Feedback

By lessening negative feedback in the pituitary and hypothalamus, reduced estradiol promotes the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). By encouraging Leydig cells to produce more testosterone, this could enhance spermatogenesis. Clinical studies reveal a 20–30% rise in LH/FSH following three to six months of AI medication [90].

3.1.3. Impact on the Activity of Aromatase

Male aromatase expression is highest in the brain, Leydig cells, and adipose tissue, according to molecular research. Obesity and insulin resistance increase aromatase activity, which decreases testosterone. By specifically blocking peripheral aromatization, AIs raise circulating androgen levels without directly affecting testicular steroidogenesis [91].

3.2. Reproductive System Effects

3.2.1. Spermatogenesis

AIs improve sperm parameters in men with idiopathic infertility and elevated estradiol/testosterone ratios. According to meta-analyses, there is a 30–40% increase in the total sperm count. A rise in sperm morphology and motility leads to higher rates of pregnancy among partners. Mechanistically, spermatogenesis is aided by increased intratesticular testosterone and decreased estradiol, which support Sertoli cell function [92].

3.2.2. Obesity and Male Fertility

In obese men, overexpression of aromatase in adipose tissue reduces the amount of testosterone in the blood. AI treatment increases fertility indices by reestablishing T/E2 equilibrium. Randomized experiments show improved sperm DNA integrity and decreased oxidative stress indicators [93].

3.2.3. Gynecomastia and Breast

Tissue By inhibiting estrogen-mediated breast tissue growth, AIs can aid in the treatment of gynecomastia in adult males. Clinical studies show that long-term medication reduces glandular tissue to some extent. However, surgery is often required in more severe cases [94].

3.3. Effects on the Skeletal System

Osteoclast-mediated resorption is inhibited by estrogen, which is essential for maintaining bone homeostasis in males. Bone turnover is increased by AI-induced estrogen suppression [95]. Bone resorption markers (CTX, NTX) increased by 30 to 50% after 12 months of AI treatment, and BMD at the lumbar spine and femoral neck decreased by 2 to 3%. Prolonged treatment results in trabecular microarchitecture degradation [96]. DEXA scan monitoring, calcium and vitamin D supplements, and weight-bearing exercise are recommended. Intermittent or

low-dose AI therapies lower skeletal risk while maintaining androgenic benefits [96].

3.4. Impact on the Heart and Metabolism

3.4.1. Profile of Lipids

Men who are estrogen deficient have higher LDL and lower HDL. According to clinical trials (Ho et al., 2024), there is a slight rise in LDL cholesterol (10%) and a decrease in HDL (~5-8%) and triglycerides did not significantly change [97].

3.4.2. Adiposity and Insulin Sensitivity

AIs may indirectly improve body composition by raising testosterone, which raises lean mass and lowers visceral fat. However, a decrease in estrogen may impair insulin sensitivity. Recent studies that demonstrate modest increases in fasting glucose and HOMA-IR with long-term treatment highlight the need for metabolic monitoring [98].

3.4.3. Cardiovascular Safety

Estradiol helps with endothelial function and nitric oxide synthesis. Prolonged AI treatment may hinder endothelial-dependent vasodilation. Despite small studies demonstrating slight reductions in flow-mediated dilatation, there is insufficient large-scale evidence of increased cardiovascular events in males [99]

3.5. Neurocognitive -Psychological Effects & Sexual Health

The neurotransmitter systems of serotonin, dopamine, and acetylcholine are all impacted by estradiol. The following are possible outcomes of AI-induced estradiol suppression: • Mood changes (mild depressive symptoms) [99]. Increased testosterone improves libido and erectile function. However, severe estrogen suppression can cause erectile dysfunction and a paradoxical decrease in sexual pleasure in a small percentage of people [100].

3.6. Musculoskeletal and Pain Effects

Males are less likely than females to experience myalgia or arthralgia during prolonged AI treatment. Among the mechanisms are alterations in muscle metabolism and proinflammatory cytokines (TNF- α , IL-6). Exercise and NSAIDs can help with the typically mild pain [101]. Generally speaking, an increase in testosterone promotes muscle growth. Thus, hypogonadal males can benefit from AI treatment by gaining lean body mass and functional strength [102].

3.7. Effects on the Skin and Hair

Elevated testosterone levels and an increased testosterone-to-estradiol (T/E2) ratio associated with aromatase inhibition may give rise to mild androgenic dermatological effects, including seborrhoea and acne [103]. In rare cases, a pronounced hormonal imbalance can accelerate the progression of androgenetic alopecia, particularly in genetically predisposed individuals. Conversely, enhanced androgen availability may also promote increased terminal hair growth in some men, reflecting the peripheral androgenic action on hair follicles [104].

3.8. Endocrine and Metabolic Safety Considerations

Prolonged suppression of estrogen synthesis may adversely influence endothelial function, lipid metabolism, and skeletal integrity, thereby increasing long-term cardiometabolic and osteoporotic risk. Accordingly, clinical guidelines recommend monitoring bone mineral density at 12–24-month intervals and periodically assessing serum glucose and lipid profiles to enable early detection and management of metabolic and vascular complications associated with aromatase inhibitor therapy[105]. Recent research indicates that low-dose or intermittent AI regimens (e.g., 1 mg of anastrozole every other day) optimize testosterone increase while minimizing systemic side effects and estradiol depletion [106].

3.9. Personalized Therapy and Pharmacogenomics

Men's AI response is significantly influenced by CYP19 A1 and CYP3A4 gene polymorphisms, and new studies have indicated that individuals with high-activity CYP19A1 alleles may require higher dosages to achieve the desired elevation of testosterone. It is expected that pharmacogenomic data integration will increase efficacy and lower risks [107].

3.10. Clinical Applications

AI therapy restores physiological testosterone without the need for exogenous androgen treatment; advantages include preventing HPG axis suppression and maintaining fertility [108]. AIs increase the T/E2 ratio and decrease the aromatase activity of adipose tissue to improve body composition [109]. Sperm motility, morphology, and count have been shown to improve, particularly in males with elevated estradiol or a modified T/E2 ratio [110]. In severe cases, surgery is still necessary because the glandular breast tissue has partially regressed [111].

4. Comparative Effects of AIs in Males vs Females

AIs target CYP19A1, the main enzyme that transforms androgens into estrogens. While AI has been thoroughly studied for breast cancer in postmenopausal women, it is primarily off-label for gynecomastia, hypogonadism, infertility, and hormone imbalances associated with obesity in males. Recent research highlights notable sex-dependent differences in pharmacodynamics, pharmacokinetics, treatment outcomes, and side effects [111]. Reducing adverse effects, optimizing dosage, and providing individualized treatment all depend on an understanding of these differences. This section systematically compares the effects of AI in males and females across organ systems, emphasizing the molecular, clinical, and systemic effects [112].

4.1. Pharmacokinetic and Pharmacodynamic Differences

In both sexes, AIs exhibit high oral bioavailability (>85%); however, sex-specific differences in body

composition influence their distribution. Women generally have a higher proportion of adipose tissue, which serves as a reservoir for lipophilic agents such as letrozole and anastrozole, potentially leading to greater tissue sequestration and prolonged drug retention [113]. In contrast, men typically possess relatively higher lean muscle mass and lower fat content, a profile that may result in higher active plasma concentrations per kilogram of body weight and reduced adipose storage of these compounds, thereby modifying pharmacokinetic behavior and systemic exposure [114]. The Process of Metabolism of steroidal AIs, particularly exemestane, are primarily metabolized by CYP3A4 and aldo-keto reductases, whereas nonsteroidal AIs such as letrozole and anastrozole are mainly biotransformed by CYP3A4 and CYP2A6 [13]. Sex-related differences in hepatic enzyme activity contribute to variability in AI clearance. Women generally exhibit slower hepatic metabolism, resulting in longer drug half-lives and more sustained suppression of estrogen synthesis [115]. In contrast, men tend to have higher metabolic rates, which may necessitate careful dose titration to achieve comparable levels of aromatase inhibition and estrogen suppression [116]. In women, profound aromatase inhibition resulting in $\geq 95\%$ suppression of estrogen is associated with effective tumor control but also leads to systemic estrogen depletion and its related adverse effects [117]. In men, a more moderate degree of aromatase inhibition, typically achieving 40–60% reduction in estradiol levels, is sufficient to enhance endogenous testosterone production and improve spermatogenesis; however, excessive suppression below physiological estradiol thresholds may predispose to bone loss and other hypoestrogenic complications [66]. The Endocrine and Hormonal Effects of these hormones is given in table 2.

Table 2: Endocrine and Hormonal Effects

Parameter	Females	Males	Comparative Notes	Ref
Estradiol suppression	95–98%	40–60%	Greater suppression in women due to reliance on peripheral aromatization	[118]
Testosterone levels	Slight decrease or unchanged	25–50% increase	Men benefit from HPG axis feedback; women have minimal ovarian response	[119]
Gonadotropins	Mild rise in LH/FSH	Significant rise in LH/FSH	Feedback more pronounced in men, enhancing testicular steroidogenesis	[120]
Fertility	Potential suppression in premenopausal women	Often improved in hypogonadal men	Sex-specific HPG regulation	[121]
Reproductive tissue effects	Tumor regression in breast, atrophy in reproductive tissues	Sperm count improvement, gynecomastia reduction	AI effect adaptive to tissue-specific estrogen roles	[122]

Men benefit therapeutically from hormone restoration (an elevated T/E2 ratio), whereas women undergo therapeutic estrogen suppression for cancer causes [123].

4.2. Skeletal Effects

In females receiving AIs, an annual decline in bone mineral density of approximately 2–4% is observed, most prominently at the lumbar spine and femoral neck, accompanied by a 20–35% increase in fracture risk [124]. In males, a more modest reduction in BMD of about 1–3% within the first year of therapy has been reported; however, the risk of clinically significant bone loss escalates with prolonged treatment duration and with profound suppression of estradiol below physiological levels, underscoring the importance of hormonal balance in maintaining skeletal integrity in both sexes [125]. Estrogen is crucial for stopping osteoclast-induced bone resorption in both sexes. AIs exacerbate bone loss because postmenopausal women have lower baseline estrogen levels. Some protection is provided by estradiol residue in men; the risk varies with dosage and duration [126]. In women receiving AIs, preventive and therapeutic strategies for skeletal protection include regular weight-bearing exercise, adequate vitamin D supplementation, and pharmacologic interventions such as denosumab and bisphosphonates. In men, management focuses on calcium and vitamin D supplementation, periodic bone mineral density monitoring by DEXA, and the use of low-dose or intermittent AI regimens to avoid excessive estradiol suppression [127]. From a comparative perspective, maintenance of estradiol within critical physiological thresholds appears to confer a more favorable risk–benefit profile in men, who generally tolerate AIs with less pronounced skeletal toxicity, whereas women experience more substantial and clinically evident bone loss as a consequence of profound and sustained estrogen deprivation [128].

4.3. Cardiovascular and Metabolic Effects

Aromatase inhibitor–induced estrogen suppression has important implications for cardiovascular and metabolic health. Estrogen exerts vaso protective effects by enhancing endothelial nitric oxide production, improving lipid profiles, and modulating glucose homeostasis; thus, its depletion may predispose to endothelial dysfunction, dyslipidaemia, and insulin resistance. Clinical studies have reported modest increases in total cholesterol and low-density lipoprotein levels, along with potential reductions in high-density lipoprotein, in patients receiving

long-term AI therapy, which may translate into an elevated risk of atherosclerotic cardiovascular disease. In addition, alterations in body fat distribution and impaired glucose tolerance have been observed, particularly in postmenopausal women. In men, partial estrogen suppression can also influence vascular function and lipid metabolism, although the effects appear more heterogeneous and dose dependent. Consequently, periodic monitoring of blood pressure, serum lipids, and glucose levels is recommended during prolonged AI treatment to enable early identification and management of cardiometabolic complications. (Table 3)

Table 3: Cardiovascular and Metabolic Effects

Parameter	Females	Males	Notes	Ref
Lipid profile	↑LDL, ↓HDL	↑LDL, ↓HDL	Both sexes affected, women slightly more due to higher suppression of estrogen	[129]
Blood pressure	Mild ↑	Mild ↑	Comparable, mainly due to endothelial estrogen deprivation	[130]
Insulin sensitivity	Slight insulin resistance	Slight insulin resistance	Men may benefit from increased testosterone on body composition	[131]
Cardiovascular events	Slightly increased in long-term therapy	Minimal evidence	Absolute risk remains low in men	[131]

In both sexes, estrogen plays a crucial role in maintaining lipid homeostasis and preserving endothelial function. Consequently, the near-complete suppression of estrogen achieved with aromatase inhibitor therapy renders women particularly susceptible to disturbances in lipid metabolism and to an increased risk of cardiovascular complications, reflecting the loss of estrogen's vaso-protective and anti-atherogenic effects [132].

4.4. Reproductive System Effects

In females, aromatase inhibitor therapy does not influence fertility in postmenopausal women; however, in premenopausal women, profound estrogen suppression may disrupt the hypothalamic–pituitary–ovarian axis and adversely affect ovulation [133]. In contrast, in males, aromatase inhibition can enhance spermatogenesis, particularly in those with hypogonadism, by increasing the testosterone-to-estradiol ratio, leading to improvements in sperm concentration, motility, and morphology [134]. In breast tissue, aromatase inhibition exerts sex-specific effects. In females, targeted suppression of estrogen synthesis directly limits estrogen receptor signalling, thereby promoting tumour regression and improving control of hormone-dependent breast cancers [135]. In males, reduction of peripheral estrogen production decreases the hormonal stimulus for breast tissue proliferation and can prevent further progression of gynecomastia; however, established glandular enlargement is often irreversible, making surgical intervention necessary for definitive management despite ongoing AI therapy [135].

4.5. Neurological and Cognitive Effects

Estrogen plays an important neuromodulatory role in synaptic plasticity, cerebral blood flow, and neurotransmitter regulation; therefore, its suppression by AIs may influence cognitive and neurological function. In women, particularly those receiving long-term therapy, AI use has been associated with complaints of memory impairment, reduced processing speed, mood changes, and sleep disturbances, which are thought to reflect central hypoestrogenic effects. In men, partial estrogen depletion may also affect cognitive performance and emotional regulation, although findings are less consistent and appear to be dose dependent. Overall, while most effects are mild and reversible, the potential impact of profound or prolonged estrogen suppression on brain function warrants clinical awareness and monitoring, especially in patients with pre-existing cognitive vulnerability. The Neurological and Cognitive Effects is provided in table 4.

Table 4: Neurological and Cognitive Effects

Domain	Females	Males	Comparative Insights	Ref
Mood	Fatigue, mild depression, anxiety	Mild mood changes	More pronounced in women due to abrupt estrogen depletion	[136]
Cognitive function	Mild verbal memory and processing deficits	Mild, reversible changes	Both sexes show subtle effects; duration and degree of estrogen suppression matter	[137]
CNS estrogen receptor modulation	ER α predominant in hippocampus; ER β in cortex	ER β prominent	Tissue distribution may explain sex-specific cognitive patterns	[138]

4.6. Musculoskeletal and Pain Syndromes

In females, aromatase inhibitor therapy rarely causes alopecia but is frequently associated with hypoestrogenic genital changes, including vaginal atrophy, dyspareunia, and reduced sexual satisfaction. In males, partial estrogen suppression often leads to a relative increase in testosterone, which can enhance libido, though mild

acne, increased hair growth, and, in some cases, accelerated androgenetic alopecia may occur (table 5). Comparatively, when estradiol levels are maintained above physiological thresholds, men generally experience improved sexual function due to elevated testosterone, whereas women are more susceptible to AI-related sexual dysfunction, reflecting the critical role of estrogen in female genital and musculoskeletal health [139].

Table 5: Comparative Musculoskeletal and Pain Syndromes in Men and Women on AIs

Feature	Females	Males	Comments	Ref
Arthralgia/Myalgia	40–50% incidence	10–20%	AI-induced cytokine elevation (IL-6, TNF- α) mediates pain; more severe in females	[140]
Muscle mass	Minimal loss	Increased lean mass (due to $\uparrow$ T)	Testosterone rise in males counteracts musculoskeletal effects	[141]
Functional mobility	Reduced in prolonged therapy	Preserved	Sex differences in hormone-driven muscle metabolism	[142]

4.7. Immune System and Inflammation

Aromatase inhibitor–induced hormonal changes exert distinct musculoskeletal and sexual effects in men and women. In women, profound estrogen depletion negatively impacts sexual function and increases susceptibility to musculoskeletal pain and inflammation, including arthralgia and cytokine-mediated tissue stress. In men, partial estrogen suppression often elevates testosterone levels, which can enhance libido, while arthritis and overt musculoskeletal inflammation remain uncommon, with only modest increases in circulating proinflammatory cytokines. Overall, these differences highlight the protective role of estradiol in mitigating pain and inflammatory responses, making women more vulnerable to AI-related musculoskeletal and sexual dysfunction. [143].

4.8. Hepatic and Renal Effects

Aromatase inhibitor therapy is generally well tolerated with respect to hepatic and renal function. In females, mild hepatotoxicity has been reported rarely, without any significant impact on renal function. In males, elevations in hepatic enzymes are uncommon, and renal effects are minimal. Overall, both hepatic enzyme elevations and renal complications are infrequent, indicating a generally favourable hepatic and renal safety profile for AIs across sexes [144].

4.9. Clinical Applications and Implications

AIs have broad clinical applications, with implications that differ between sexes due to their effects on estrogen and androgen balance. In postmenopausal women, AIs are a mainstay for the treatment and prevention of estrogen receptor–positive breast cancer, providing significant improvements in disease-free survival and reducing tumour recurrence. Extended and neoadjuvant use further enhances therapeutic outcomes but requires careful monitoring for bone loss, cardiovascular risk, and musculoskeletal symptoms. In men, AIs are employed primarily to manage conditions such as hypogonadism, infertility, and certain estrogen-dependent disorders; moderate estrogen suppression can boost testosterone levels, improve spermatogenesis, and reduce gynecomastia progression. Across both sexes, individualized dosing guided by pharmacogenomic profiling and careful monitoring of bone, metabolic, and hepatic parameters is critical to maximizing efficacy while minimizing adverse effects. These sex-specific considerations underscore the need for personalized strategies when applying AI therapy in diverse clinical contexts (table 6).

Table 6: Clinical Applications and Comparative Effects of AIs in Men and Women

Aspect	Females	Males	Ref
Primary indication	ER ⁺ breast cancer	Hypogonadism, infertility, gynecomastia	[145]
Dose considerations	Standard daily dosing	Lower/intermittent dosing often sufficient	[146]
Duration	5–10 years	6–24 months typically; adjusted per response	[147]
Monitoring	BMD, lipids, cardiovascular, neurocognitive	BMD, estradiol, testosterone, sperm parameters	[148]
Adverse effect management	Bisphosphonates, lipid therapy, SSRIs, physical therapy	Vitamin D, low-dose therapy, lifestyle, periodic lab monitoring	[149]

The aims of therapy vary by sex. Men want to restore hormonal balance without resorting to overt suppression of estradiol, whereas women primarily need tumour management, embracing systemic estrogen deprivation [150].

5. Innovations and Future Perspectives in AI Therapy

Aromatase inhibitor research continues to evolve, with several promising avenues aimed at optimizing efficacy while minimizing adverse effects across sexes. Sex-specific dosing strategies, including low-dose or intermittent regimens, are being explored to balance systemic estrogen suppression with therapeutic outcomes. Pharmacogenomic profiling, particularly of CYP19A1 and CYP3A4 variants, may allow personalized treatment

by predicting individual metabolism and drug responsiveness [151]. Combination therapies are also under investigation, such as pairing AIs with clomiphene or human chorionic gonadotropin in men to enhance fertility, or with selective estrogen receptor degraders (SERDs) or CDK4/6 inhibitors in women to improve breast cancer outcomes. Skeletal protection remains a key focus, with agents like denosumab, bisphosphonates, or targeted drug delivery approaches being employed to mitigate bone loss [152]. Emerging digital health tools enable real-time monitoring of hormone levels, bone density, and cardiovascular markers, paving the way for fully individualized AI therapy and improved long-term management [153]. A Comparative Overview of Aromatase Inhibitor Effects Across Men and Women is depicted in table 7.

Table 7: Comparative Overview of Aromatase Inhibitor Effects Across Men and Women

System	Female Response	Male Response	Comparative Note	Ref
Endocrine	Estradiol ↓95–98%, minimal T change	Estradiol ↓40–60%, T ↑25–50%	Women experience deprivation; men gain hormonal restoration	[154]
Skeletal	Significant BMD loss	Mild-moderate BMD loss	Risk higher in women	[155]
Cardiovascular	Slight ↑ risk, dyslipidemia	Minimal risk, mild dyslipidemia	Women more vulnerable	[156]
Reproductive	Fertility suppressed in premenopause	Fertility improved	Opposite effect	[157]
Cognitive/Mood	Mild deficits, fatigue, depression	Mild, reversible changes	More pronounced in women	[158]
Musculoskeletal	Arthralgia common, reduced mobility	Arthralgia rare, muscle gain	Sex-specific cytokine and hormonal mediation	[159]
Sexual Health	Dyspareunia, low libido	Improved libido, possible acne	Hormonal context differs	[160]
Immunologic	Increased proinflammatory cytokines	Minor changes	Women more susceptible	[160]
Metabolic	Insulin resistance, dyslipidaemia	Mild insulin resistance	Degree correlates with estradiol suppression	[161]

6. Optimizing Aromatase Inhibitor Treatment in Males and Females

6.1. Clinical Considerations for AI Use in Men and Women

AIs in women are primarily indicated for postmenopausal estrogen receptor–positive breast cancer and should be used premenopausally only in combination with ovarian suppression. Standard daily dosages typically include 1 mg of anastrozole, 2.5 mg of letrozole, or 25 mg of exemestane, depending on disease stage, administered for five to ten years. Baseline and annual dual-energy X-ray absorptiometry (DEXA) scans are recommended to monitor bone mineral density, alongside periodic assessment of lipid profiles and cardiovascular risk. Regular evaluations of musculoskeletal health, including joint symptoms and pain, are advised. Psychological and neurocognitive assessments should also be incorporated to monitor fatigue, mood, and cognitive changes. For premenopausal women, fertility counselling is essential prior to initiating therapy, with discussion of potential ovarian suppression and fertility preservation strategies [162, 163].

In men, AIs are primarily used for hypogonadism, idiopathic or obesity-related infertility, and gynecomastia. Low-dose (0.5–1 mg anastrozole every other day) or intermittent regimens are generally sufficient to optimize the testosterone-to-estradiol ratio and restore serum testosterone levels. Estradiol and testosterone concentrations should guide dose adjustments. Monitoring should include regular assessment of serum testosterone, FSH, LH, and estradiol, as well as DEXA scans for therapies extending beyond one year. Periodic evaluation of lipid profiles, metabolic markers, and blood pressure is recommended to identify potential cardiometabolic effects. For men receiving treatment for infertility, semen parameters should be closely monitored and therapy adjusted as necessary to optimize spermatogenesis. In men, AIs are primarily used for hypogonadism, idiopathic or obesity-related infertility, and gynecomastia. Low-dose (0.5–1 mg anastrozole every other day) or intermittent regimens are generally sufficient to optimize the testosterone-to-estradiol ratio and restore serum testosterone levels. Estradiol and testosterone concentrations should guide dose adjustments. Monitoring should include regular assessment of serum testosterone, FSH, LH, and estradiol, as well as DEXA scans for therapies extending beyond one year. Periodic evaluation of lipid profiles, metabolic markers, and blood pressure is recommended to identify potential cardiometabolic effects. For men receiving treatment for infertility, semen parameters should be closely monitored and therapy adjusted as necessary to optimize spermatogenesis [164–167].

6.2. Maintaining Bone Integrity in Aromatase Inhibitor Therapy

Bisphosphonates, such as alendronate or zoledronic acid, and the RANKL inhibitor denosumab are recommended for women with osteopenia or osteoporosis, either at baseline or during aromatase inhibitor therapy, to prevent further bone loss. Adequate calcium and vitamin D supplementation is also advised, aiming for daily calcium intake of 1,000–1,200 mg and maintaining serum vitamin D levels at or above 30 ng/mL [168].

Lifestyle interventions, including weight-bearing and resistance exercises, further support bone mass preservation and reduce fracture risk. In men, regular bone density assessment is recommended during long-term AI therapy, with preventive supplementation considered for those at high risk of skeletal complications [169].

6.3. Management of Cardiovascular and Metabolic Risk in AI Treatment

Management of cardiovascular and metabolic risks is an important aspect of long-term aromatase inhibitor therapy. Lipid profiles, including HDL, LDL, triglycerides, and total cholesterol, should be assessed at baseline and periodically thereafter. Statin therapy may be considered for patients—particularly women—who develop dyslipidaemia during prolonged AI treatment [170]. Blood pressure should be regularly monitored in both sexes, with lifestyle interventions such as diet modification, regular exercise, and weight management recommended to maintain cardiovascular health. Long-term AI users should also be assessed for insulin resistance or impaired glucose tolerance, and appropriate dietary and physical activity strategies should be implemented to reduce metabolic risk [171]. Sex-specific considerations indicate that women are generally at higher cardiometabolic risk, particularly when estradiol levels are maintained near the lower end of the physiological range, whereas men typically experience a lower risk profile under comparable AI therapy [172].

6.4. Approaches to Musculoskeletal Care During Aromatase Inhibitor Therapy

Management of aromatase inhibitor-associated musculoskeletal symptoms involves a combination of pharmacologic and nonpharmacologic strategies. Nonsteroidal anti-inflammatory drugs (NSAIDs) can be used to alleviate arthralgia and myalgia. Regular exercise and physical therapy are recommended to reduce joint stiffness and improve mobility. Adjunctive agents, such as duloxetine or omega-3 fatty acids, may provide additional benefit in mitigating AI-related musculoskeletal discomfort, particularly in women [54]. Patient education is essential, ensuring that individuals are aware of the potential for musculoskeletal pain and are supported with strategies to maintain adherence to therapy [173].

6.5. Psychological and Cognitive Interventions for Patients on AIs

Management of cognitive and psychological effects during aromatase inhibitor therapy should include regular monitoring of mood and cognitive function, particularly over long-term treatment. Supportive interventions such as cognitive training exercises and mental health counselling can help mitigate these effects. Pharmacologic therapy, including selective serotonin reuptake inhibitors (SSRIs), may be considered for clinically significant depression or anxiety [174]. Sex-specific observations indicate that women often experience more pronounced mood and cognitive disturbances due to abrupt estrogen depletion, whereas men typically encounter milder and more transient effects [175].

6.6. Reproductive and Sexual Health Recommendations

In premenopausal women, aromatase inhibitor therapy necessitates concurrent ovarian suppression, which can significantly impact fertility and the ability to conceive. Counselling regarding potential reproductive effects and fertility preservation strategies is essential prior to initiating treatment. In postmenopausal women, monitoring should focus on hypoestrogenic genital changes, including vaginal atrophy, dyspareunia, and sexual dysfunction. Therapeutic interventions, such as selective estrogen receptor modulators (e.g., ospemifene) or topical lubricants, may alleviate symptoms and improve sexual comfort [176]. In men, AI therapy is often used to optimize the testosterone-to-estradiol ratio, particularly for hypogonadism or infertility. Fertility monitoring should include regular assessment of semen parameters, with dose adjustments made as necessary to maximize spermatogenesis. Sexual function should also be evaluated, including libido and erectile performance, which typically improve with the AI-induced increase in testosterone levels [123].

6.7 Pharmacogenomic Guidance and Personalized Medicine

Personalized aromatase inhibitor therapy can be optimized through several emerging strategies. Genotyping for CYP19A1 and CYP3A4 variants may help predict individual differences in drug metabolism, efficacy, and susceptibility to adverse events [177]. Therapy can then be tailored based on patient-specific factors, including age, sex, genetic profile, comorbidities, and baseline hormone levels, to achieve optimal estrogen suppression while minimizing toxicity. Additionally, digital health tools, such as wearable devices or mobile applications, can facilitate real-time monitoring of hormone levels, bone density, and cardiovascular parameters, enabling timely interventions and more precise, individualized care [178].

6.8. Strategies for Adverse Event Mitigation

Comprehensive management of aromatase inhibitor-related adverse effects involve targeted strategies across multiple organ systems. For bone and skeletal health, interventions include regular weight-bearing and resistance exercise, adequate calcium and vitamin D intake, and pharmacologic support with bisphosphonates. Musculoskeletal symptoms, such as arthralgia and myalgia, can be managed with NSAIDs, duloxetine, and structured physical therapy. Cardiovascular and metabolic health requires monitoring and control of blood pressure, lifestyle modifications, and, when indicated, statin therapy [179]. Neurocognitive and psychological support may include SSRIs, cognitive training exercises, and counselling, while sexual health can be optimized through the use of topical lubricants, patient counselling, and hormonal management strategies [180].

6.9. Long-Term Clinical Surveillance During Aromatase Inhibitor Treatment

Monitoring strategies for aromatase inhibitor therapy should be tailored to sex-specific risks and physiological responses. In women, cardiovascular assessment, lipid profiling, and dual-energy X-ray absorptiometry (DEXA) scans are recommended every six to twelve months, with annual evaluations of joint symptoms, mood, and

cognitive function [181]. In men, hormone levels—including FSH, LH, estradiol, and testosterone—should be measured every three to six months, while annual assessments should include DEXA scans as well as lipid and metabolic panels to track bone and cardiometabolic health [182].

CONCLUSIONS AND FUTURE DIRECTIONS

Aromatase inhibitors (AIs) have transformed endocrine therapy by providing a powerful mechanism for suppressing estrogen biosynthesis, yet their physiological impact is profoundly shaped by sex-specific hormonal physiology. In females, especially in postmenopausal breast cancer, AIs deliver substantial oncologic benefit but impose a notable burden of bone loss, cardiovascular and metabolic complications, and neurocognitive sequelae due to sustained estrogen deprivation. In males, AIs can serve as adjunctive agents in selected forms of hypogonadism and infertility by enhancing gonadotropin-driven testosterone production, although long-term safety remains of concern. Understanding these sex-dependent effects is essential for optimizing therapeutic outcomes; routine monitoring of bone density, lipid profiles, and neurocognitive status, combined with individualized dosing and supportive interventions, can help mitigate adverse effects.

Future research should prioritize selective aromatase modulation, sex-specific pharmacogenomic strategies (including CYP19A1 and CYP3A4 profiling), and combination regimens with targeted agents such as mTOR inhibitors, CDK4/6 inhibitors, or SERDs to enhance tumor selectivity and overcome resistance. Low-dose or intermittent AI protocols in men may preserve fertility and avoid excessive estradiol suppression, while advanced delivery systems (e.g., liposomal or nanoparticle formulations) could improve tissue specificity and limit systemic exposure. Longitudinal studies on skeletal, metabolic, and neurocognitive outcomes in both sexes, together with integrated digital health tools for continuous hormone, bone, and cardiovascular monitoring, will be critical. Ultimately, the goal is to refine AIs into patient-centered, precision-guided therapies that balance efficacy with long-term health preservation.

Ethical statement

This review article is based exclusively on previously published literature. No original research involving human participants or animals was conducted by the authors, and therefore ethical approval and informed consent were not applicable. The authors have followed ethical guidelines for literature citation and publication integrity.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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