

## AROMATASE INHIBITORS IN MEN – OFF-LABEL USE, MISUSE, ABUSE AND DOPING

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### Abstract

Aromatase (oestrogen synthase, CYP19A1, EC 1.14.14.1) is a monooxygenase from the cytochrome P450 family involved in the conversion of androgens to oestrogens. It is the final step in steroidogenesis of oestrogens, catalysing androgen aromatisation (with the formation of oestradiol from testosterone, and of oestrone from androstenedione, respectively). Tissue localization is ubiquitous, being found mainly in gonads, brain, adipose tissue, bone. Congenital aromatase deficiency is a very rare genetic disease characterized by androgen impregnation, pseudo-hermaphroditism and osteopenia in women, and high stature in both sexes, due to delayed ossification of growth cartilage. Aromatase inhibitors (anastrozole, letrozole, exemestane) are indicated according to data included in the marketing authorization, in the treatment of oestrogen-dependent cancers in women (breast cancer with positive oestrogen receptors in postmenopausal women, including relapsing forms after prior therapy with antioestrogens). Aromatase inhibitors have no official recommendation in male pathology. However, these substances are used off-label in selected cases of male infertility (in case of inadequate testosterone/ oestradiol ratio, and in patients with hypogonadotropic hypogonadism, including that caused by anabolic steroid abuse). Also, aromatase inhibitors are detoured from medical use in athletes, as indirect doping, as corrective treatment of paradoxical feminisation (gynecomastia), following administration of androgens and as "therapy" after doping cycle to restore endogenous testicular secretory activity.

### Rezumat

Aromataza (estrogen sintaza, CYP19A1, EC 1.14.14.1) este o monooxigenază din familia citocromului P<sub>450</sub> implicată în conversia androgenilor în estrogeni. Este ultima etapă în steroidogeneza estrogenilor, catalizând aromatizarea androgenilor (cu formarea de estradiol din testosteronă, respectiv, a estronei din androstendionă). Localizarea tisulară este ubicuitară, fiind găsită preponderent în gonade, creier, țesut adipos, os. Deficitul congenital de aromatază este o boală genetică foarte rară, caracterizată prin impregnare androgenică, pseudohermafroditism și osteopenie la femei și statură înaltă, la ambele sexe, datorită osificării tardive a cartilajelor de creștere. Inhibitorii de aromatază (anastrozol, letrozol, exemestan) sunt indicați conform datelor incluse în RCP în tratamentul unor forme de cancer estrogeno-dependente la femei (neoplasm mamar, cu receptori estrogenici pozitivi la femei post-menopauză, inclusiv formele recidivante după terapia anterioară cu antiestrogeni). Nici un inhibitor de aromatază nu are vreo indicație oficială în patologia masculină. Cu toate acestea, aceste substanțe sunt utilizate *off label* în cazuri selecționate de infertilitate masculină (în caz de raport inadecvat testosteron/estradiol și la bolnavi cu hipogonadism hipogonadotrop, inclusiv cel datorat abuzului de steroizi anabolizanți). De asemenea, inhibitorii de aromatază sunt deturnați de la uzul medical în cazul sportivilor ca dopante indirecte, ca tratament corectiv al feminizării paradoxale (ginecomastie) consecutiv administrării de androgeni și ca „terapie” post ciclul de dopaj pentru refacerea activității secretorii endogene testiculare.

**Keywords:** aromatase inhibitors, male, off label use, abuse, doping

### Introduction

Using androgen as a substrate, aromatase is a key enzyme involved in oestrogen biosynthesis. Both the excess and deficiency of aromatase may be innate and lead to rare genetic diseases. Aromatase excess, leads to a high stature (in both sexes), and

to pseudo-hermaphroditism (only in the case of women) [11, 17].

Aromatase inhibitors are officially recommended only in female pathology, in the treatment of oestrogen-dependent breast cancer; they are used in the tumours expressing oestrogen receptors, in the case of recurrence following anti-oestrogen therapy

with tamoxifen or when adverse reactions caused by the agonist effect of tamoxifen in the uterus appear after long-term treatment with tamoxifen (endometrial proliferation in women after menopause).

In men, aromatase inhibitors used in therapy are all off-label, based on pharmacological arguments and confirmed by small scale prospective clinical trials. High exposure of the male population to aromatase inhibitors (not included in the official reports) can be found in professional athletes, as doping (both indirect doping by oestrogen blockade and as corrective medication for side effects caused by administration of exogenous androgens and anabolic steroids - AAS). Abuse of aromatase inhibitors is amplified in amateur athletes who do not participate in official competitions and their use is also common in young men preoccupied with their own image (*body image perception*). As such, aromatase inhibitors are perceived as substances with "aesthetic" properties in combination with androgens in a social environment that glorifies the muscled, tanned, shaved man [19, 30].

#### Off-label use of aromatase inhibitors in males

Aromatase inhibitors are used in a number of male pathologies in which the effectiveness was proven by clinical studies, without their inclusion in the marketing authorization. A few data is known, however, about long-term risks, especially in the young male population, in terms of reproductive toxicology and bone damage. Main off-label uses of aromatase inhibitors are male pathologies caused by oestrogen excess (gynecomastia), decreased height in adolescents with late puberty or, on the contrary, rapid progressive puberty, and male infertility induced by inadequate testosterone/oestradiol ratio (abuse of androgens, severe obesity, metabolic syndrome).

##### *Male pathologies caused by oestrogen excess*

*Rare genetic diseases causing estrogenic/androgenic excess.* Genetic oestrogen excess (*aromatase excess syndrome, McCune-Allbright and Peutz-Jeghers syndrome* [8, 36]) may benefit from treatment with aromatase inhibitors, as well as other pathologies such as androgen excess - testotoxicosis (the treatment includes an antiandrogen that prevents early virilisation and an aromatase inhibitor to prevent the rapid ossification of growth cartilage) [24, 37].

*Gynecomastia.* As glandular breast tissue growth is dependent on oestrogen, any oestradiol excess can cause gynecomastia. This can be transient, physiological (pubertal gynecomastia caused by testosterone/oestradiol imbalances) or may be drug-induced - by generating oestrogens from androgen aromatization substrates (AAS- androgens and anabolic steroids), by androgen blockade - anti-androgens, spironolactone, digitalis, cimetidine, azole

antifungal agents and other drugs with anti-androgenic effect [9].

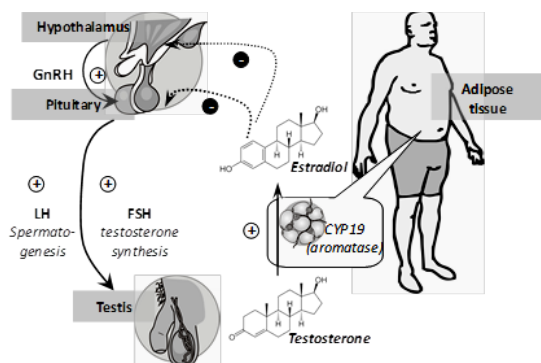
Pubertal gynecomastia does not usually require treatment, as it is transient and reversible. Any persistent gynecomastia requires treatment, the first choice being selective oestrogen receptor modulators with antiestrogenic effect on the breast (tamoxifen) and aromatase inhibitors [9, 20, 27]. The treatment with aromatase inhibitors is effective for the prevention or in early forms of gynecomastia (as adjuvant in antiandrogenic therapy of prostate cancer, however, their effectiveness is limited or absent) [2], but not in the cases where the glandular breast tissue is already well represented, when surgery is the only radical and effective choice.

*Adolescent idiopathic short stature.* The most frequent off-label use of aromatase inhibitors is in boys of short stature with or without delay in pubertal development [8, 36]. The blockade of oestrogen synthesis favours the onset of puberty in boys with delayed puberty (by increasing the available androgens) and favours a final height closer to the genetic potential - longitudinal bone growth (as it is prevented by oestrogens bone epiphyseal fusion). Besides the highlighted adverse effects - pharmacotoxicological tropism in bone (morphological abnormalities of the spine), hematologic (increased haematocrit) and alterations in lipid profile (decrease in HDL cholesterol) [13, 29], the safety of aromatase inhibitors in long-term use (including possible reproductive toxicity) is yet to be established by randomized controlled trials.

*Infertility caused by obesity.* The male adult obesity (especially severe, morbid forms), in addition to the known risks (cardiovascular risk, increased incidence of type 2 diabetes and metabolic syndrome), also involves reproductive toxicity - erectile dysfunction and infertility by hypogonadotropic hypogonadism [3, 14]. Erectile dysfunction in obese men may be considered a warning sign as it may precede the onset of metabolic syndrome and type 2 diabetes [5, 31, 35].

The excess of body fat changes the testosterone/oestradiol ratio (T/E2) in favour of oestradiol. The aromatase is highly active in the adipose tissue resulting in large amounts of oestrogen. Normally, the serum level of oestradiol in eugonadal men is about 1/200 of the average serum testosterone [7, 32]. Since the negative pituitary feedback loop in males is partially caused by oestrogen, a large amount of aromatized testosterone to oestradiol in adipose tissue markedly decreases the secretion of pituitary gonadotrophins reducing intra-testicular testosterone concentration (ITT) necessary for effective spermatogenesis (*obesity-related hypogonadotropic hypotestosteronemia*). The consequences of the oestrogen excess are, on the one hand, *oligospermia*, and on the other hand, enabling subsequent

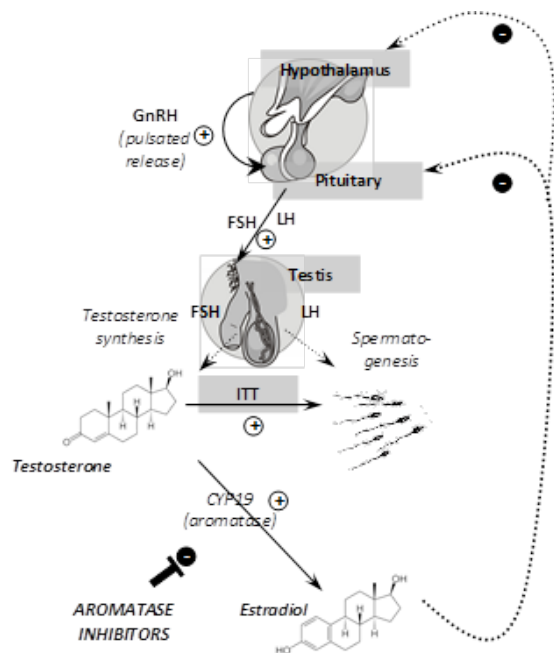
deposit of lipids in the adipose tissue, which by aromatization further modifies the testosterone/oestradiol ratio (vicious circle) – see Figure 1.



**Figure 1.**

Impaired feed-back control of androgen synthesis due to estrogen excess in the adipose tissue

Oligospermia induced by relative hyperestrogenism in obese males can be treated with Selective Oestrogen Receptor Modulators that block pituitary oestrogen receptors (clomiphene, in continuous treatment) or by administration of aromatase inhibitors that disrupt the vicious circle that modifies the testosterone/oestrogen ratio [5, 21, 22, 25]. Treatment effectiveness is due to increased pituitary gonadotropin release (only effective in infertility with decreased T/E2 ratio and in selected cases of hypogonadotropic hypogonadism with intact hypothalamic-pituitary-testicular axis) - see Figure 2.



**Figure 2.**

Stimulation of spermatogenesis and testosterone secretion by inhibitors of aromatase  
ITT – intratesticular testosterone

### Aromatase inhibitors in males. Misuse and abuse

The diversion of aromatase inhibitors from medical use is based on their pharmacological properties – indirect doping by oestrogen blockade (increased secretion of endogenous testosterone by preventing oestrogen negative feed-back on the hypothalamic-pituitary axis) and correcting medication for anabolic androgenic steroid abuse by preventing adverse reactions caused by aromatization of androgens. Due to these properties, aromatase inhibitors are considered doping agents and are included on the WADA Prohibited List (World Anti-Doping Agency) [38].

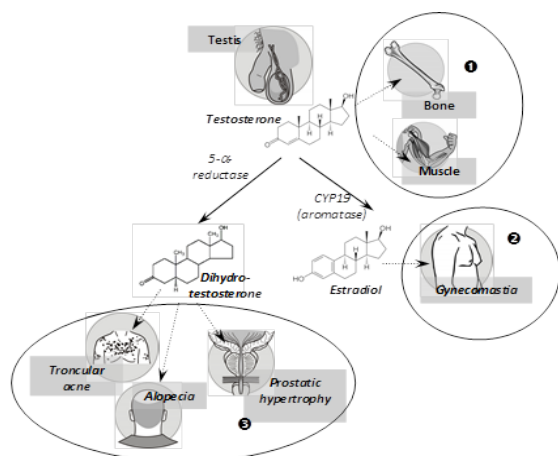
Their use goes beyond professional sports and is widely employed by amateur athletes, especially young people, to generate a "masculine appearance" for aesthetic purpose (muscular hypertrophy, preventing estrogenic disturbing effects of androgens such as gynecomastia). Androgens and anabolic steroids are able to generate pathological behaviour changes – aggression ("roid rage") in susceptible people, narcissistic changes of their image perception ("body appearance enhancing drugs") that may cause an obsessive – compulsive behaviour in muscle mass gain ("muscle dysmorphia", "bigorexia") [1, 4, 10, 16, 30].

*Aromatase inhibitors as indirect doping.* The increase in the endogenous secretion of testosterone (up to 50%) can be achieved by blocking the negative feedback by using antioestrogens or the aromatase inhibitors [7]. The use of these drugs markedly increases the release of pituitary LH (approx. 3 times higher than normal), the pulsatile secretion is similar to the physiological one. The use of aromatase inhibitors has ergogenic effects supporting the effort and muscular hypertrophy in men only; in women, effects on testosterone level are negligible, that is why they are prohibited only in male athletes [38]. Unlike females, the use of aromatase inhibitors in men does not totally suppress oestrogen secretion (reduction of circulating oestrogen is approx. 70% and can reach 80% in the case of co-administration of androgens). The explanation of incomplete enzyme inhibition is the increased aromatase sensitivity in adipose, brain and other tissues, compared to testicular aromatase, which is resistant to inhibition [7]. Since the increased secretion of endogenous testosterone is not satisfactory for most people who pursue a rapid gain in muscle mass, aromatase inhibitors are most commonly used during or after a cycle of doping with high, non-pharmacological doses of androgens or anabolic steroids.

*Aromatase inhibitors as correcting medication for androgen abuse (PCT – "post cycle therapy")*

AAS (androgen anabolic steroids) are the most frequently used doping substances included on the WADA Prohibited List (S2 - Anabolic agents) [1,

26, 38], in doses that increase plasma testosterone levels by at least an order of magnitude. They are administered in cycles of 6 - 8 weeks progressively increasing and subsequently decreasing the dose administered in order to allow the recovery of the hypothalamic-pituitary-testicular axis (“pyramiding”). They can also be administered in concomitantly with compounds with different latency and half-life, based on an alleged pharmacodynamic synergy (“stacking”). Numerous bodybuilding Internet sites and forums (“bodybuilding subculture”) provide “counselling” on the administered doses and correcting medication for the adverse reactions, which often include aromatase inhibitors. AAS produce virilizing effects (mediated primarily by analogues of dihydrotestosterone, obtained under the action of 5- $\alpha$ -reductase), anabolic effects (especially in muscle and bone) and, paradoxically, feminizing effects by aromatizing the used compounds to oestrogen - Figure 3.



**Figure 3.**

Anabolic (1), feminizing (2), and virilizing (3) effects produced by androgens

High doses of androgens produce proven adverse effects - reproductive toxicity (oligospermia, testicular hypotrophy - reversible depending on the dosage and duration of treatment, which reflects the cumulative total dose), heart (cardiomegaly, hypertrophic cardiomyopathy, dyslipidaemia caused by the reduction of HDL cholesterol), hematologic (increase in haematocrit and haemoglobin, polycythaemia), skin (acne, often severe, androgenic alopecia), and effects caused by oestrogen excess (gynecomastia) [1, 23]. Furthermore, there are also cases of liver peliosis, benign and malignant liver tumours [23]. Androgens in eugonadal men have contraceptive effect by decreasing FSH and LH secretion (the effect is also observed in men with androgen deficiency undergoing testosterone replacement therapy by reducing the intratesticular testosterone concentration due to the LH suppression

and FSH decrease necessary to stimulate Sertoli cells) [6].

Aromatase inhibitors are used during the doping cycle (during a cycle of 6 - 8 weeks starting from week 3 - 4) to avoid gynecomastia (in slang language “pecs with puffy nipples”, “man boobs”); most commonly, aromatase inhibitors are administered at the end of the doping cycle (PCT – “post cycle therapy”) to force spermatogenesis and secretion of endogenous testosterone. Without the PCT, fertility and normal testosterone secretion returns within weeks-months after the break, but there are recorded/ documented cases of permanent hypogonadism [12, 23]. Additionally, many doped subjects do not agree with a discontinuation of androgenic treatment to facilitate the return of normal functioning of the hypothalamus-pituitary axis, and as such, they develop forms of addiction and withdrawal syndrome at the end of the treatment (depression, loss of libido, impotence). Therefore, the post-doping cycle treatment includes selective oestrogen receptor modulators (clomiphene), aromatase inhibitors or administration of gonadotropin [1, 28, 34].

The self-medication with aromatase inhibitors is based on pharmacological fundamentals, similar to off-label hypogonadotropic hypogonadism therapy (ASIH - anabolic steroid induced hypogonadism). Without medical supervision, post-cycle therapy can, in its turn, generate adverse effects (loss of libido - oestrogens are necessary for normal sexual stimulation; reduced HDL cholesterol, which is additive to that caused by the androgens previously used; bone demineralization).

## Conclusions

The off-label use of aromatase inhibitors in men has proven clinical applications, but long-term risks are yet unknown. The experimental animal studies show that oestrogens have a direct effect on the seminiferous tubules and letrozole administration in rats induces, in time, degeneration phenomena similar to aging [18]. The association with androgens may also be dangerous, as they can emphasize the loss of renal mass in patients with reduced renal function (studies on rats) [15]. Taking into account the long-time carcinogenic potential of androgens in the liver, a combination with aromatase inhibitors could produce additional side effects, since the increased ratio testosterone/oestrogen in cirrhotic patients is positively correlated with the development of hepatocellular carcinoma [33].

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