



Adverse Effects of 5-Alpha-Reductase Inhibitors: a narrative review

Efeitos Adversos dos Inibidores da 5-Alfa-Redutase: uma revisão narrativa

Efectos adversos de los inhibidores de la 5-Alfa-Reductase: una revisión narrativa

Gregory Lauar e Souza¹, Samuel Filippe Motta Martins Dias¹, Ailton Gomes Faion³, Felipe Magno Alves Pereira¹, Victor Augusto Pereira Romão¹, Luiza Pereira Campos¹, Rafael Santiago Cypreste², Maria Carmen Barbi Martins¹, Lorena Terra Campos¹, Nicole Meireles Sacco¹.

ABSTRACT

Objective: Analyze adverse effects of 5-ARI's regarding sexual health and fertility (erectile dysfunction and decreased libido); neurology and psychiatry (depressive symptoms, self-harm and suicidal ideation); endocrine, metabolic and cardiovascular (increased body fat, LDL and total cholesterol). **Bibliographic review:** This narrative review reports findings from various scientific articles published online, regarding the adverse effects of 5-ARI's, often used to treat male-pattern baldness and benign prostate hyperplasia in adult males. **Final considerations:** Adverse effects were identified on several studies made in different populations. Thus, it is utterly important to raise public awareness of the implications associated with 5-ARI's treatment. Prescription of 5-ARI's therapy should be carefully assessed for each individual due to potential adverse effects that may occur upon its start, and drastically compromise quality of life in adult males.

Keywords: 5-alpha-reductase inhibitors, Finasteride, Adverse effects, Dutasteride.

RESUMO

Objetivo: Analisar os efeitos adversos dos 5-ARIs em relação à saúde sexual e fertilidade (disfunção erétil e diminuição da libido); neurologia e psiquiatria (sintomas depressivos, automutilação e ideação suicida); endócrino, metabólico e cardiovascular (aumento da gordura corporal, LDL e colesterol total). **Revisão bibliográfica:** Esta revisão narrativa relata achados de vários artigos científicos publicados online, sobre os efeitos adversos dos 5-ARI's, frequentemente usados para tratar a calvície masculina e a hiperplasia benigna da próstata em homens adultos. **Considerações finais:** Foram identificados efeitos adversos em diversos estudos realizados em diferentes populações. Assim, é extremamente importante aumentar a conscientização pública sobre as implicações associadas ao tratamento com 5-ARI. A prescrição da terapia com 5-ARI deve ser cuidadosamente avaliada para cada indivíduo devido aos potenciais efeitos adversos que podem ocorrer no seu início e comprometer drasticamente a qualidade de vida em homens adultos.

Palavras-chave: Inibidores da 5 alfa redutase, Finasteride, Efeitos adversos, Dutasterida.

¹ Centro Universitário de Belo Horizonte (UNIBH), Belo Horizonte – MG.

² Faculdade de Saúde e Ecologia Humana (FASEH), Belo Horizonte – MG.

³ Departamento de Urologia, Hospital de Baleia, Belo Horizonte – MG.

RESUMEN

Objetivo: Analizar los efectos adversos de los 5-ARI en la salud sexual y la fertilidad (disfunción eréctil y disminución de la libido); neurología y psiquiatría (síntomas depresivos, autolesiones e ideación suicida); endocrinas, metabólicas y cardiovasculares (aumento de la grasa corporal, LDL y colesterol total). **Revisión bibliográfica:** Esta revisión narrativa informa los hallazgos de varios artículos científicos publicados en línea, con respecto a los efectos adversos de los 5-ARI, a menudo utilizados para tratar la calvicie de patrón masculino y la hiperplasia prostática benigna em hombres adultos. **Consideraciones finales:** Se identificaron efectos adversos en varios estudios realizados en diferentes poblaciones. Por lo tanto, es sumamente importante aumentar la conciencia pública sobre las implicaciones asociadas con el tratamiento de 5-ARI. La prescripción de la terapia con 5-ARI debe evaluarse cuidadosamente para cada individuo debido a los posibles efectos adversos que pueden ocurrir al inicio y comprometer severamente la calidad de vida en hombres adultos.

Palabras-clave: Inhibidores de la 5 alfa reductasa, Finasterida, Efectos adversos, Dutasterida.

INTRODUCTION

Benign prostatic hypertrophy (BHP) and androgenic alopecia (AGA) are androgen-dependent disorders associated with high levels of dihydrotestosterone (DHT) and increased 5 α -reductase activity in prostate and hair follicles. The enzyme 5 α -reductase is responsible for the conversion of testosterone into DHT, which can ultimately result in BHP and AGA (PALLOTTI F, et al., 2020).

Various therapeutic options for these conditions have been introduced, among which 5-alpha-reductase inhibitors (5-ARI's) represent one of the most effective. The 5-ARI's decrease the dihydrotestosterone concentration in the serum and scalp by 60–70% through inhibition of 5 α -reductase (LEE S, et al., 2018). Both BPH and AGA respond favorably to this class of drugs. In summary, by inhibiting the activity of 5 α -reductase, the 5-ARI's can retard the progression of AGA and prostate growth (WALF AA, et al., 2018).

There are two 5-ARI's used in the treatment of AGA and BPH: finasteride and dutasteride. Both are synthetic 5-ARI's which bind to 5-alpha-reductase (5-AR) active sites with high affinity, promoting long-lasting effects of the drug regardless of the intake dose, ultimately causing epigenetic changes in DNA methylation of the androgen receptor gene. There are two types of 5-AR receptors: the type one is most abundant in the liver and skin, whereas type 2 is more dominant in the prostate. Finasteride has proven to selectively inhibit the type 2 5-AR, whilst dutasteride inhibits both types (LI Y, et al., 2022).

Even though 5-ARI's presented favorable results in the treatment of BHP and AGA, this class of drugs is not exempt from undesirable effects. Moreover, these drugs may act as endocrine disruptors, eliciting undesirable adverse effects (TRAISH AM, et al., 2020). It is even hypothesized that patients receiving 5-ARI's might be vulnerable to COVID-19 infection with poorer prognosis, but it hasn't been proven yet (ADAMOWICZ J, et al., 2020).

Not long ago, the scientific community began acknowledging the adverse effects of 5-ARI's. In 2011, reports emerged of healthy adult males under 40 years old who developed persistent sexual adverse effects lasting at least 3 months post discontinuation of finasteride treatment for AGA. In the same year, additionally 2.1 million men were prescribed 5-ARI's for BPH, and half-million American men for AGA. Depression was added to the product labeling of finasteride in the USA. All of these subjects denied baseline sexual symptoms, medical or psychiatric diagnosis prior to treatment. A follow up study in the subsequent next year documented a high prevalence of moderate/severe depression (64%) and suicidal thoughts (44%) (IRWIG MS 2020).

Neuropsychiatric adverse effects of 5-ARI's have significantly increased among 5-ARI's users in the last few years, with symptoms including depression, anxiety, mood disturbance, self-harm and cognitive complaints. Despite of the current evidence on the association between neuropsychiatric adverse events and 5-ARI's users, the underlying mechanisms associated with the brain dysfunction in PFS are still elusive (SAENGMEARNUPARP T, et al., 2021; IRWIG MS, 2020; SAID MA, et al., 2018; COSKUNER ER, et al., 2018).

Adverse effects of Finasteride in androgenic alopecia are also inconsistent. Studies have shown concerning side effects of Finasteride, even describing a Post-Finasteride Syndrome (PFS) represented by persistence of adverse reactions after the completion of treatment (MOTOFEI IG, et al., 2019). PFS occurs in men undergoing hair loss or BPH treatment with finasteride, in both 1mg or 5mg dosages and regardless of age (TRAISH AM, et al., 2020). Currently, post Finasteride syndrome it is not yet recognized by the medical community, eventhough individuals suffering from PFS present similar symptoms (TRÜEB RM, et al., 2019).

In this narrative review, we summarize occasional findings from the literature, including data reported in case studies, observational studies, non-randomized and randomized clinical trials as well as systematic reviews and meta-analyses.

BIBLIOGRAPHIC REVIEW

Male Sexual Health and Fertility Adverse Effects

One study by Traish AM, et al. (2015) suggested that in men with BPH, long-term finasteride therapy ultimately resulted in worsening of erectile dysfunction (ED), and reduced total serum testosterone concentrations. Erectile dysfunction (ED) was investigated using the International Index of Erectile Function (IIEF-EF), a questionnaire used to measure various aspects of erectile performance. Finasteride treatment in men with BPH resulted in a significant gradual decrease in erectile function, as assessed by the IIEF-EF score. The decrease persisted for over 45 months of follow-up. IIEF-EF score was reduced by more than 6–8 points, which is deemed as clinically meaningful. This retrospective observational registry study showed that 5-ARI's therapy adversely affected erectile function in BPH patients treated with finasteride. Using a similar methodology, Giatti S, et al. (2018) investigated assessed 25 adult males with the IIEF-EF, and reported persistent sexual dysfunction after suspension of treatment.

Likewise, a meta-analysis of 46,733 cases demonstrated increased risk of ED with finasteride. Another multicenter, randomized study comprising 2,783 patients evidenced an increased risk of ED upon finasteride use. Men treated with finasteride or finasteride together with doxazosin experienced worsening of several sexual function domains compared to those on placebo (TRAISH AM, et al., 2020 and TRAISH AM, et al., 2015).

According to Zakhem GA, et al. (2019), a retrospective review of 11,909 patients identified 167 individuals with persistent ED post treatment. Lee S, et al. (2018) calculated a 1.99-fold risk of ED (95% CI 1.10–3.60) in patients who underwent treatment with finasteride (1mg/day). The strongest predictors for the development of the ED were: a) prostate disease; b) duration of therapy, c) age and; d) nonsteroidal anti-inflammatory drug use (NSAID). A daily dose of 1.25 mg of NSAID together with finasteride conferred a 4.8 times higher risk of developing sexual dysfunction (ZAKHEM GA, et al., 2019).

According to the PROWESS study, the long-term effects of finasteride (5 mg/d) were examined in men diagnosed with BPH, ranging from 50 to 75 years of age ($n = 3,168$). Sexual adverse effects (e.g. change in libido, ejaculation disorder, impotence, or orgasm dysfunction) was reported in 10% of the finasteride group versus 7% in control group. Ejaculation disorder and ED were found to be statistically significant differences between the groups ($P < 0.05$). The aforementioned adverse effects were considered to be drug related by the researchers (FERTIG RM, et al., 2017).

As far as libido is concerned, it is worth noting that loss or reduced libido and ED were consistently noted in double-blind, randomized, placebo-controlled trials, as well as observational studies (TRAISH AM, et al., 2020). In the subgroup analysis of 11 studies, finasteride 1 mg/ day presented a 1.66-fold risk of adverse sexual effects (95% CI 1.20–2.30) compared with placebo. The incidence of decreased libido (RR 1.40, 95% CI 0.87–2.27) and difficulty in ejaculation (RR 1.59, 95% CI 0.76–3.29) also tended to be higher than that for placebo, albeit without statistical significance (LEE S, et al., 2018)

These observations were recently confirmed by us in a cohort of sixteen PFS patients: ten of them showed a severe erectile dysfunction, while six patients a mild-moderate one. In addition, we reported for the first time

an objective evidence of neuropathy involving the peripheral neurogenic control of erection. Indeed, abnormal somatosensory evoked potentials of the pudendal nerve were observed in four of these PFS patients (GIATTI S, et al., 2018).

Males with AGA are often at reproductive age, even though the median age at first prescription varies from 68 to 72 in Nordic countries. Finasteride exerts a negative impact on spermatogenesis even when used in small doses of 1mg/day. Spermatogenesis and fertility were usually restored after the treatment cessation, even in the group of patients with severe oligozoospermia or azoospermia (MAKSYM RB, et al, 2019; KJÆRULFF TM, et al., 2019).

Similarly, Pallotti F, et al. (2020) investigated sperm parameters from 55 males aged 18-45 with AGA who underwent systemic therapy with Finasteride (1mg/day), and detected a worsening of all sperm parameters 6 months from treatment initiation, for instance, total sperm number (232.4 ± 160.3 vs. 133.2 ± 82.0 ; $p = 0.01$ vs. T0) and abnormal forms (79.8 ± 6.0 vs. 82.7 ± 5.7 ; $p < 0.05$ vs. T0).

The overall use of 5-ARI's for AGA increased the risk of adverse sexual effects, especially erectile dysfunction and decreased libido, but this increase was not significant for dutasteride 0.5mg/day (LEE S, et al., 2018).

Complete reversibility of sexual dysfunction symptoms was observed in three studies, however, the majority of the studies comprised in the systematic review described patients experiencing irreversible adverse effects (ZAKHEM et al. 2019). Furthermore, the reversibility of 5-ARI's adverse events, for instance loss of libido, erectile dysfunction or ejaculation appeared to be inaccurate and was not supported by evidence-based medicine (TRAISH AM et al. 2015). In regard to infertility and sperm counts, a study of 14 men with infertility issues undergoing treatment with 1 mg of finasteride, for 57 months, revealed a significant improvement in sperm parameters after discontinuing the treatment (SAID MA, et al., 2018).

Curiously, among subjects who reported differences in sexual functioning scores after treatment compared to before treatment, right-handed individuals reported worsening of sexual function, whereas left-handed individuals reported improvements (WALF AA, et al., 2018; MOTOFEI IG, et al., 2019).

Neurologic and Psychiatric Adverse Effect

Since animal studies of finasteride have shown the possibility of behavioral changes, the psychological effect of treatment emerged as an important issue (MAKSYM RB, et al, 2019). Depression was added to the product labeling of finasteride in the USA in 2011. A 2012 study found that suicidality (44%) and depression (64%) were common symptoms among men suffering from persistent sexual adverse effects post finasteride use. The European Medicines Agency (EMA) recommended to include a warning about depression in the product information of finasteride in 2017 (IRWIG MS, 2020; YEON B, et al., 2022).

The enzyme 5-alpha-reductase exerts a key role in the activation of neuroactive steroids. The main neuroactive steroids are pregnenolone (PREG), dehydroepiandrosterone (DHEA), progesterone, testosterone, and 17-beta-estradiol, which exerts control in reproduction and sexual behavior, adjustment of synaptic plasticity, and cytoskeletal protein regulation and in cognition. One case control clinical trial measured neuroactive steroids in cerebrospinal fluid and plasma of individuals undergoing finasteride treatment. Amongst the participants of the group who received the intervention, 87.5% presented abnormal cerebrospinal fluid and plasma neuroactive steroids versus the control group (FERTIG RM, et al., 2017).

Given that neuroactive are correlated with mood symptoms, 5-ARI's may ultimately lead to the development depression (PEREIRA AFJR e COELHO TOA, 2020; TRAISH AM, 2020; DIVICCARO S, et al., 2020). A change in neuroactive levels can promote not only functional, but structural changes in the brain. Finasteride inhibits hippocampal neurogenesis, which has a long-lasting effect on the brain that is characteristic of depression (MAKSYM RB, et al., 2019).

Alterations of the hypothalamic pituitary adrenal axis may cause depression in 5-ARI's users. In animal experiments, the administration of finasteride reduced corticotropin releasing hormone mRNA levels in the periventricular area, and reduced plasma adrenocorticotrophic hormone stimulation after exposure to stress.

Epigenetic modification appears to be another mechanism for depressive symptoms in prior 5-ARI's users. Nonetheless, the key possible mechanism of depression in 5-ARI's users could be related to neuroactive steroids (SAENGMEARNUPARP T, et al., 2021).

A case series by Irwig MS (2020) analyzed medical reports and autopsy reports of 8 victims of suicide received finasteride treatment for male pattern baldness. Erectile dysfunction and insomnia were reported by all victims in previous medical records.

Another cohort study with 93,197 matched pairs (men above 66 of age who had taken finasteride or dutasteride for BPH were matched to men of similar profile who were not taking 5-ARI's), aimed to measure suicide, self-harm or depression incidence among finasteride or dutasteride users. It was found that there was not a significant increase in the suicide rate compared to control (HR 0.88, 95% CI = 0.53-1.45). Nonetheless, there was a noteworthy upsurge in risk of self-injury (HR 1.88, 95% CI = 1.34-2.64), and depression (HR 1.94, 95% CI = 1.73-2.16). There was not a marked difference in these results for finasteride compared to dutasteride (FERTIG RM, et al., 2017; MAKSYM RB, et al, 2019). Diviccaro S, et al. (2020) corroborates with such findings. Intriguingly, the prevalence of the aforementioned symptoms found by the author were superior on the group that received 1mg of finasteride versus 5mg.

A large South Korean study found no detectable difference in the risk of depression between 5-ARI's and alpha blockers treatment of BPH. The risk of depression in the 5-ARI-treated group was lower than in the alpha blocker-treated group. Similarly, in the United Kingdom, a study of 77,732 patients who were prescribed 5-ARI's or alpha blocker were investigated for incidence of depression. As a result of comparing 2,842 patients with depression and 11,333 without depression, it was reported an incidence rate of 7.6 (95% CI [6.9-8.3]) for only 5-ARI's use, alike only alpha-blockers use, that presented a rate of 7.8 (95% CI [7.5-8.1]) (YEON B, et al., 2022).

Nguyen DD, et al. (2020) investigated if finasteride was associated with more spontaneous reports of suicidality, depression or anxiety in 3282 patients treated with finasteride. VigiBase, a global database of individual case safety reports provided by the World Health Organization was used to consult these reports. In stratified analysis, the study found that most of the reports were made by younger patients using finasteride for alopecia, not from older patients undergoing BPH treatment.

Endocrine, Metabolic and Cardiovascular Adverse Effects

By altering steroid metabolism, 5-ARI's may cause insulin resistance, increasing the risk of diabetes, hepatic steatosis, alteration of body fat distribution, metabolic syndrome and cardiovascular diseases, considering that this class of drugs reduce the clearance of glucocorticoids and mineralocorticoids (PEREIRA AFJR e COELHO TO, 2020). Also, one study demonstrated that older men without preexistent cardiovascular disease and diabetes, baseline levels of DHT were associated with lower risk of diabetes and less insulin resistance. Long term dutasteride therapy produced HbA1c and lipid profiles alterations, suggesting induced imbalance in metabolic function (TRAISH A, et al., 2017).

Long-term use of dutasteride is often correlated high LDL and total cholesterol, potentially leading to increased onset of non-alcoholic fatty liver disease and cardiovascular diseases. In addition, dutasteride increased liver aspartate transaminase (AST) and alanine aminotransferase (ALT) activity and Aging Male Symptoms (AMS) score suggesting increased inflammation and reduced quality of life (TRAISH A, et al., 2017). One previous study used AMS score to compare tamsulosin versus finasteride, and found that patients treated with the latter have poor quality of life, which may be attributed to sexual adverse effects of the drug (TRAISH A, et al., 2015).

FINAL CONSIDERATIONS

The studies analyzed suggested an increased risk of adverse sexual effects, especially erectily dysfunction and decreased libido. Since neuroactive steroids such as dihydrotestosterone (DHT) and allopregnanolone are correlated with mood symptoms, 5-ARI's may lead to the development of depressive symptoms. Long-term dutasteride therapy is associated with increased LDL cholesterol and total cholesterol, potentially leading

to increased onset of non-alcoholic fatty liver disease. It also produced an increased progressive rise in fasting blood glucose and HbA1c. Prescription of 5-ARI's therapy should be carefully assessed for each individual due to potential complications that may occur after starting the medications. Banalization of its use, especially amongst young adult males, in order to prevent male pattern alopecia, may cause irreversible, and undesirable, symptoms.

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