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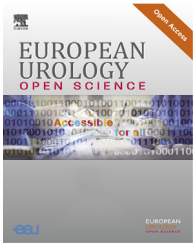

European Association of Urology

Brief Correspondence

US Food and Drug Administration Warning Regarding Finasteride and Suicidal Ideation: What Should Urologists Know?

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Abstract

Finasteride competitively inhibits 5α-reductase (5-AR) isoenzymes, which blocks dihydrotestosterone (DHT) production, thereby reducing DHT. Finasteride is used in the management of benign prostatic hyperplasia (BPH) and androgenic alopecia. Amid patient reports of suicidal ideation (SI), the Post Finasteride Syndrome advocacy group has petitioned for either a stop to selling of the drug or advertisement of stronger warnings. The US Food and Drug Administration recently added SI to the adverse effects listed for finasteride. Here we provide a brief but comprehensive review of the literature on the psychological side effects of 5-AR inhibitors (5-ARIs) to provide an opinion to help in guiding treating urologists. Most of the current evidence, obtained from the literature on dermatology, suggests that 5-ARI users experience a higher rate of depressive symptoms. However, given the lack of comprehensive randomised studies, the causal link between finasteride and SI remains unclear. Urologists prescribing 5-ARIs should be aware of the recent addition of suicide and SI risk to the list of side effects. A mental health screen should be performed and appropriate resources provided to patients commencing treatment. Furthermore, a review should be arranged with the general practitioner to assess new-onset mental health or SI symptoms.

Patient summary: We provide recommendations for urologists who prescribe finasteride for the treatment of benign prostate enlargement. Urologists should be aware of the recent addition of suicidal ideation to the list of side effects for this drug. Finasteride prescription should be continued; however, we recommend a detailed medical history to screen for prior mental health and personality disorders, with discontinuation of the medication in patients with new onset of depression or suicidal symptoms. Close liaison with the patient's general practitioner is vital for management of depressive or suicidal symptoms.

Finasteride is a synthetic 4-azasteroid compound that acts by competitively inhibiting type II and III 5α-reductase (5-AR) isoenzymes. This in turn blocks the conversion of testosterone to dihydrotestosterone (DHT), thereby reducing prostatic and serum DHT by 90% and 70%, respectively [1]. In the prostate, DHT causes cellular hyperplasia, while

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in the skin it acts as an active androgen and is attributed in androgenic alopecia (AGA). Finasteride was first introduced in 1992 to manage the bothersome symptoms of benign prostatic hyperplasia (BPH) [2]. Stabilisation of hair loss in men with BPH was an incidental finding and led to the use of finasteride for AGA in 1997 [2]. Finasteride reduces the risk of incident clinical BPH [3] and may potentially reduce the risk of low-grade prostate cancer [4].

BPH is commonly treated with finasteride 5 mg daily, while AGA is treated with 1 mg daily. To minimise its bothersome adverse effects (AEs), some dermatologists recommend three doses per week [2].

The commonly advertised side effects of finasteride include sexual dysfunction (SD), depression, infertility, breast swelling/tenderness, breast cancer, rash, testicular pain, allergic reaction, and anaphylaxis. Depression was not identified during the first clinical trials but was added to the list in 2011 owing to concerns about potential mood changes. In 2017, the Post Finasteride Syndrome (PFS) advocacy group petitioned for a stop to selling of the drug or advertisement of stronger warnings. The US Food and Drug Administration (FDA) had advised that the PFS petition "does not provide reasonable evidence" of a link to suicide, but in August 2022 added suicidal ideation (SI) and behaviour to the adverse reactions listed for finasteride. According to the FDA statement, the PFS petition "does not provide reasonable evidence" of a causal link between finasteride and persistent SD, depression, or suicide. However, on the basis of reports from patients using the 1-mg dose for AGA, the FDA is "requiring the addition of SI and behaviour" to the listed AEs.

Interestingly, in 2021 the Australian Therapeutic Goods Administration included "depression (feelings of severe sadness and unworthiness) including suicidal thoughts" as an uncommon AE reported with finasteride. More recently, France's National Agency for the Safety of Medicines and Health Products released product information in July 2022 that includes "suicidal thoughts that could lead to suicide". In September 2022, tentative findings from a web-based worldwide trend analysis by the USC Keck School of Medicine highlighted that the AEs of finasteride are "clearly a problem", "warrant intervention", and are "inappropriate to dismiss".

Several pathophysiological mechanisms have been proposed for the neuropsychiatric effects of finasteride. These include reduced production of several neuroactive steroids, a reduced stress response, reductions in allopregnanolone, and lower levels of type I 5-AR in the prefrontal cortex [2].

There are limited reports in the literature on the causative link between finasteride and SI. Nguyen et al [5] performed a pharmacovigilance case/noncase examination of VigiBase, the case safety system of the World Health Organization. They found higher rates of suicidality and psychological AEs among young patients (aged 18–44 yr) taking finasteride. Older patients using the drug for BPH did not have increased signals, indicating a lower level of suicidality.

Moreover, an assessment of the FDA database for the adverse event reporting system revealed disproportionate reporting of suicidal ideation. Among a total of 4910 reports, 39 SI AEs where recorded. The group concluded that persistent SD is a potential risk of finasteride, and this risk may contribute to SI [6].

In a postmarketing case series, the clinical histories and symptoms of six suicide victims who took finasteride for treatment of AGA were assessed. The most common constellation of symptoms in patients who committed suicide was insomnia and persistent SD after medication discontinuation. There were no other baseline medical or psychiatric diagnoses before finasteride initiation. The group concluded that men younger than 40 yr using finasteride for AGA are at risk of suicide if they develop persistent SD and insomnia [7]. This is in keeping with a meta-analysis by Pompili et al [8], who found that the risk of SI was greater with (21.2%) than without (14%) finasteride. By contrast, in a population-based retrospective matched cohort study of 93 197 men aged ≥66 yr, Welk et al [9] found that while the risk of depression was higher among 5-AR inhibitor (5-ARI) users, no increase in the risk of suicide attributed to 5-ARIs was observed.

Most of the current evidence is from the dermatology field and suggests that 5-ARI users experience a higher rate of depressive symptoms. Given the lack of large randomised studies, it is difficult to establish clear causation between finasteride and SI. AGA itself may be associated with low self-esteem, poor body image, and depression. Suicide rates are already high for young men with AGA, who are probably the most emotionally affected as hair loss is critical to their self-image.

For patients with BPH, the benefits of finasteride probably outweigh the risks, and the multiple proposed AEs should not dissuade urologists from prescribing the drug. Patients may be suffering from mental health disorders and reduced quality of life due to bothersome LUTS and SD, further necessitating a screen for mental health disorders.

Urologists prescribing 5-ARIs should be aware of the recent addition of suicide and SI risk to the list of AEs. A mental health screen should be performed and appropriate resources provided to all patients starting on finasteride. A timely review should be arranged with the general practitioner to assess new-onset mental health or SI symptoms. Dose titration adjustments for AGA indications or discontinuation of the medication in these circumstances may be appropriate.

Further research is required to establish causation between finasteride and SI.

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Study concept and design: Lawrentschuk.
Acquisition of data: Al Saffar.
Analysis and interpretation of data: Al Saffar, Xu, O'Brien.
Drafting of the manuscript: Al Saffar, Xu, O'Brien.
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