

REGULAR ARTICLE

Controversies in the treatment of androgenetic alopecia: The history of finasteride

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Male androgenetic alopecia (AGA) affects up to 60% of men by the age of 50. Currently, there are only two approved drugs for the treatment of male AGA: topical minoxidil and oral finasteride. Topical minoxidil is readily available over the counter and has a well-established safety record. However, following 24 weeks of treatment, less than 40% of men respond to the drug. Additionally, due to the topical route of administration, compliance with minoxidil remains low. In contrast, oral finasteride, a 5- α reductase inhibitor, demonstrated efficacy in arresting hair loss in more than 80% of patients following 12 months of treatment. However, controversy surrounding potential adverse sexual side effects has negatively affected public perception of the drug and may significantly reduce the number of patients that can benefit from the drug.

KEYWORDS

androgenetic alopecia, finasteride, sexual dysfunction

1 | HISTORY

In 1992 the U.S. FDA approved Proscar (finasteride 5 mg daily) for the treatment of benign prostatic hyperplasia (BPH). A 4-year placebo-controlled study of 3,040 men suffering from BPH (the Proscar Long Term Efficacy and Safety Study [PLESS]) was conducted (US FDA, 2011). About 1,524 subjects were administered Proscar and 1,516 subjects were administered a placebo. During the first year, decreased libido was reported in 6.4% of subjects in the Proscar group versus 3.4% observed in the placebo group. Erectile dysfunction was reported in 8.1% of subjects in the Proscar group versus 3.7% in the placebo group. However, in the second year of the study there was no significant difference in the rate of sexual adverse events between the Proscar and placebo groups. Decreased libido was reported in 2.6% of subjects in the Proscar group versus 2.6% in the placebo group ($p = 1.00$). Erectile dysfunction was reported in 5.1% if subjects in the Proscar group versus 5.1% in the placebo group ($p = 1.00$) (US FDA, 2011).

As early as 1942, James Hamilton observed that low testosterone due to castration prevented the development of AGA in males (Hamilton, 1942). Additional evidence for hormonal involvement in the development of AGA came from a group suffering from congenital

5- α reductase deficiency. In this group, males failed to develop AGA (Imperato-McGinley, Guerrero, Gautier, & Peterson, 1974). Subsequently, scientists at Merck, Inc. developed a lower dosage oral finasteride for the treatment of AGA. In 1997, the U.S. FDA approved Propecia (finasteride 1 mg daily) for the treatment of AGA.

In three 12 months clinical studies, 945 subjects were administered Propecia and 934 subjects were administered a placebo. During the first year, decreased libido was reported in 1.8% of subjects in the Propecia group versus 1.3% in the placebo group. Erectile dysfunction was reported in 1.3% of subjects in the Propecia group versus 0.7% in the placebo group. In the fifth year of treatment the rate of adverse events decreased to less than 0.3% in all groups (US FDA, 2011). Additionally, men that discontinued therapy had no further sexual adverse events. A recent study by Gupta et al. examined finasteride adverse events from 2004–2015 using the Food and Drug Administration Adverse Event Reporting System (FAERS) database. Similarly, they concluded that occurrence sexual adverse events from finasteride are rare (Gupta, Carviel, MacLeod, & Shear, 2017).

In 2011 the U.S. FDA conducted a post marketing evaluation of reported cases of persistent sexual dysfunction after finasteride discontinuation. About 2,527 cases of Propecia related adverse events were identified from December 19, 1997 to April 14, 2011. Of the

TABLE 1 Number of search results for different finasteride search terms on google.com

Search term	Number of search results
"Finasteride sex"	2,370,000
"Finasteride impotence"	863,000
"Finasteride lawsuit"	513,000

2,527 cases, the U.S. FDA identified 59 reported cases of sexual dysfunction that lasted three or more months after finasteride discontinuation. In 20 of these cases (34%) sexual dysfunction persisted for 1–2 years and in 7 of the cases (12%) sexual dysfunction persisted for three or more years (US FDA, 2011). It was noted that in some of the cases subjects had low testosterone values. Subsequently, the FDA has required Merck to revise the Propecia label to disclose the post marketing sexual adverse events. Shortly after Merck revised its label, thousands (or perhaps hundreds of thousands) of websites claim that Propecia and finasteride cause erectile dysfunction and loss of libido. In addition, dozens of lawsuits and support group websites were formed. As of the writing of this chapter, a Google search (www.google.com) yielded the following number of results (Table 1).

2 | CLINICAL PRACTICE

2.1 | Aging in males

Lower testosterone is associated with erectile dysfunction, decreased libido, and depression (Wu, 2010). It is widely recognized that males experience a gradual decline in testosterone concentration starting as early as their third decade (Dimopoulou et al., 2016); however, erectile dysfunction can afflict men of all ages. In a study of 27,839 men from eight countries, Rosen et al. (2004) observed a prevalence of erectile dysfunction of 11% in men between the ages of 30 and 39, and 8% in men between the ages of 20 and 29. Different methodologies are often used to diagnose erectile dysfunction (Nguyen, Gabrielson, & Hellstrom, 2017) and these varied methodologies can produce different prevalence rates. Nevertheless, it is evident that the rate of sexual adverse events in patients treated with finasteride is consistent with the prevalence of erectile dysfunction in the general population. Additionally, the age of onset for hormonal changes that manifest as sexual dysfunction often coincide with the age of onset for the development of AGA. As such, subjects experiencing AGA may be more likely to experience sexual dysfunction; hence, it may be difficult to attribute the development of sexual dysfunction to finasteride use alone.

2.2 | Other drugs

It is important to note that several widely used drugs elicit sexual dysfunction. Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are well known for their sexual side effects. In his review, Rothschild (2000) concluded that antidepressants may cause sexual adverse events in up to 40% of patients. Higgins, Nash, and Lynch (2010) literature review concludes that incidence of sexual adverse events among SSRIs users is greater

than 50%. In contrast, the long-term rate of sexual adverse events among patients using finasteride is less than 1%.

2.3 | RECOMENDATIONS

All drugs carry a risk of adverse events. As clinicians, when prescribing drugs, we strike a balance between the risk of developing adverse events and the benefit of the treatment. While some drugs such as finasteride are effective in the treatment of the underlying disease, the controversy surrounding the risk of adverse events clouds patient's willingness to use the drug. This is a dilemma frequently faced by pediatricians when attempting to immunize children. Pediatricians attempt to overcome the resistance to immunization by educating parents with evidence from controlled studies.

While physicians should avoid controversial topics, finasteride is unfortunately the only U.S. FDA approved drug with significant efficacy in arresting the progress of AGA. The other common alternative, minoxidil, has relatively low efficacy; less than 40% of patients regrow hair following 16 weeks of daily application of 5% minoxidil (Olsen et al., 2007). Prior to prescribing finasteride, physicians should adequately educate patients and thoroughly assess their current sexual and psychological well-being. To that end we have developed the following short workup questionnaire:

- Do you experience any symptoms of sexual or erectile dysfunction?
- Do you experience nocturnal erection three or more times per week?
- How often do you have sex?
- Are you using any anti-depressants?
- Do you suffer from hypertension?
- Do you suffer from diabetes?
- Do you have a history of depression?

Together these questions help assess the risk a patient has or is likely to develop sexual dysfunction. Patients that are not suffering from sexual dysfunction or are less likely to develop sexual dysfunction, are good candidates for finasteride. In patients that are candidates for finasteride, it would be appropriate to explain the evidence from the controlled studies presented on the finasteride FDA label. It is ultimately up to the patient to decide if the relatively low risk of sexual dysfunction outweighs the benefit of finasteride in the treatment of AGA, but the evidence speaks for itself.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Andy G, John M, Mirna S, et al. Controversies in the treatment of androgenetic alopecia: The history of finasteride. *Dermatologic Therapy*. 2018;e12647. <https://doi.org/10.1111/dth.12647>