Neuropsychiatric Reactions to Finasteride: Nocebo or True Effect?

Mayer Brezis, MD MPH*

Professor of Medicine (Emeritus), Brown School of Public Health, Hebrew University, Jerusalem, Israel, Former Director of the Center for Clinical Quality & Safety, Hadassah Medical Center

ABSTRACT

Finasteride, which inhibits conversion of testosterone to dihydrotestosterone, is in wide use for hair loss and prostatic hyperplasia. Reports of adverse reactions increasingly suggest that finasteride may cause depression, anxiety, suicidality and sexual dysfunction, even after discontinuation of the drug. On the other hand, some publications have claimed that this could represent simulated reporting of a nocebo effect. In the present paper, we analyse reports to the FDA of neuropsychiatric events for finasteride in comparison to control medications, and demonstrate remarkably disproportionate safety signals for finasteride. Furthermore, the rise in neuropsychiatric reactions to finasteride over the last decade concurs with a striking increase in suicides reported to the FDA in relationship to this medication. In addition, Google analytics show a growing interest for finasteride in recent years, including concern about side effects. Since suicide has not been associated with a nocebo effect, it seems likely that we are facing real and serious adverse effects on mood from finasteride. Increased reporting could relate to enhanced awareness and not to a nocebo effect. Health care professionals should be aware of these concerns and share them with patients to allow informed decision regarding their care.

Key Words: Finasteride, Adverse effect, Suicide, Anxiety, Mood, Neurosteroids, Neuropsychiatric reaction

Correspondence:

Mayer Brezis, Professor of Medicine (Emeritus), Brown School of Public Health, Hebrew University, Jerusalem, Israel, Former Director of the Center for Clinical Quality & Safety, Hadassah Medical Center,
E-mail: brezis@mail.huji.ac.il

INTRODUCTION

Finasteride, an inhibitor of the 5α-reductase-catalysed conversion of testosterone to dihydrotestosterone, is in wide use for hair loss and prostatic hyperplasia. Increasingly reports of neuropsychiatric adverse reactions suggest that finasteride may cause depression, anxiety, suicidality and sexual dysfunction, which sometimes persist after discontinuation of the drug. On the other hand, some scholars have claimed that this represents simulated reporting of a nocebo effect. In the present paper, we analyse reports to the FDA of neuropsychiatric events for finasteride in comparison to control medications, and demonstrate strikingly disproportionate safety signals for finasteride.

Results

We have analyzed neuropsychiatric events reported to the FDA for finasteride in comparison to other medications and show the results in the Table below.

Table 1: Neuropsychiatric reactions reported to the FDA for finasteride in comparison to similar reactions reported for other medications.

Reaction	Finasteride	Minoxidil	Spironolactone	Inderal	Adjusted Relative Risk for Finasteride	
					vs. (S)	*vs.* (I)
Depression	2040	134	124	153	x21	x14
Anxiety	1643	143	85	51	x25	x33
Insomnia	822	20	163	99	x6	x9
Fatigue	799	118	481	75	x2	x11
Suicidality	550	22	101	41	x7	x14
Suicide	119	12	91	51	x2	x2
Number of prescriptions	8,986,897		11,432,027	9,277,061		
Number of patients	2,314,978		2,985,578	2,421,089		

Note: The numbers in the upper rows are reactions reported to FAERS (accessed in 3/8/2020). The last two rows are data available for year 2019 in the USA at https://clincalc.com/DrugStats/Default.aspx. Both minoxidil and spironolactone are used for alopecia, and Inderal has been linked to depression. The relative risk for adverse reactions to finasteride in comparison to Spironolactone (S) and to Inderal (I) was adjusted for the corresponding relative rate of prescriptions or patients (the relative risk in comparison to minoxidil was not adjusted as prescriptions data were not available).

The right columns in the table show markedly increased risks of depression and anxiety-in the range of 14-33 times higher-for finasteride than for controls. The analysis also shows increased risks of insomnia, fatigue, suicidality and suicide-in the range of 2-14 times higher-for finasteride than for controls. Disproportionate safety signals for finasteride concur with reports by others [1-6]. Some publications have suggested this may represent simulated reporting of a nocebo effect. An impact of media coverage, through cognitive availability bias, is usually transient [7-9], and negative news about finasteride have in fact decreased (from 3.5 items per month in the years 2011-2, to 1.0 per month in recent years-LexisNexis database, accessed 4.25.2022). Alternatively, awareness may be increased by discourse in social

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media, as reflected by an analysis of web searches related to finasteride: Google analytics for trends show growing interest for finasteride in recent years, including concern about side effects (Figure 1). Users of finasteride could either imagine or realize that symptoms such as sexual dysfunction, fatigue and altered mood relate to a cosmetic medication they have been taking. A rise in reporting to the FDA of neuropsychiatric reactions over the last decade concurs with a remarkable increase in suicides related to finasteride (Figure 2).

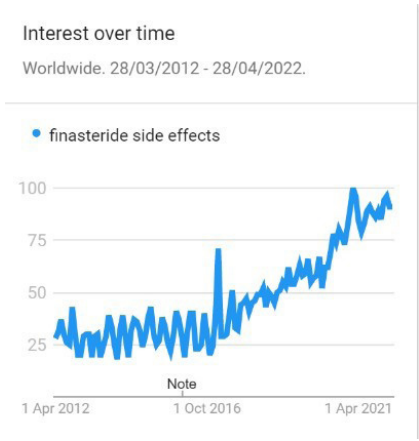

Figure 1: Trends of Google searches for 'finasteride side effects' over last decade worldwide (Google analytics, accessed 4/25/2022). Numbers in the Y-axis represent search rate relative to the highest point: a value of 100 is the peak popularity for the term (a value of 50 means that the term is half as popular).

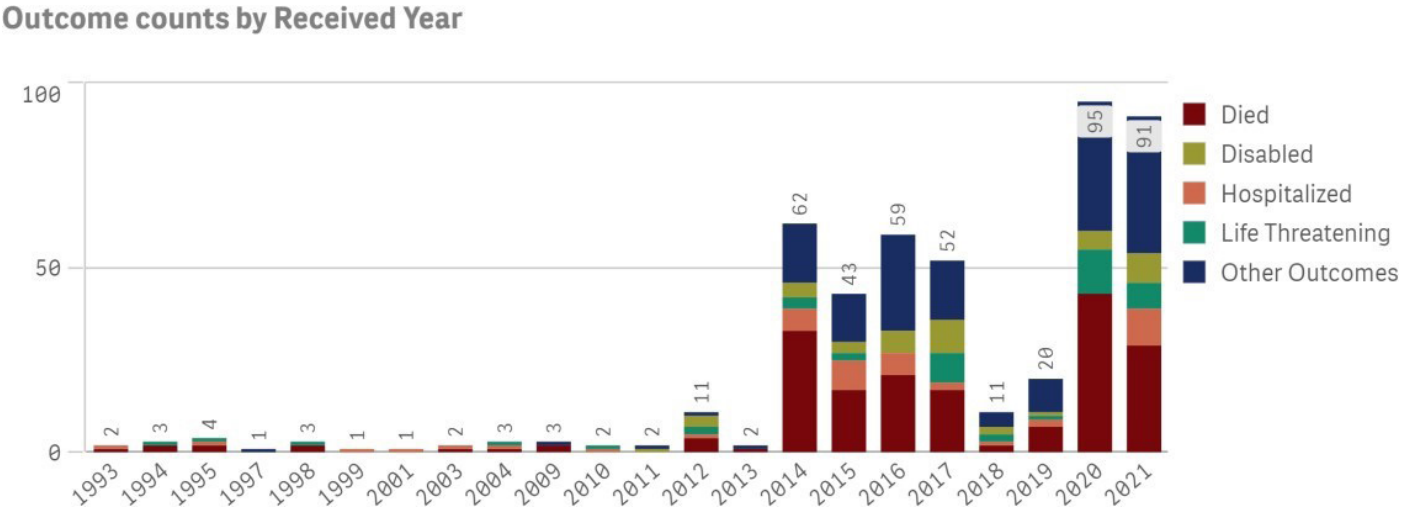

Figure 2: Reported suicide attempts, suicidal behavior, suspected suicide and completed suicide for finasteride (FAERS, accessed 4/26/2022).

DISCUSSION

Reports to the FDA of neuropsychiatric events for finasteride in comparison to control medications demonstrate remarkably disproportionate safety signals for finasteride with a striking increase in suicides. Google analytics show a growing interest for finasteride in recent years with enhanced awareness of its side effects. Since suicide has not been associated with the nocebo effect, [10] more likely is a true effect on mood from finasteride, via inhibition of the 5-alpha reductase enzyme needed in the biosynthesis of neurosteroids-as shown in animals and patients studies [11-15]. Mitigation of finasteride-related suicidality by concomitant administration of testosterone [4] is also consistent with an actual biological effect. A potential key role of brain hormones in the control of mood is evidenced by novel neurosteroid-based antidepressant agents, recently approved by the FDA [16].

Awareness of drug safety issues can be slowly arising, as side effects are under-reported by physicians[17] and by pharmaceutical companines. [18] Earlier and more direct reporting by patients for safety monitoring, as increasingly done in pharmacovigilance, [19,20] may accelerate the detection of drug safety signals-in a paradigm shift already widely implemented in healthcare practice [21]. A recent update on the management of hair loss [22] omitted to mention depression and suicidality-debilitating and potentially fatal risks from finasteride, which may continue after its discontinuation. Two large pharmacovigilance studies have shown a significant risk for depression and suicidality with finasteride, [1,2] confirming previous reports of serious psychological adverse effects, including anxiety, insomnia, fatigue, depressed mood and completed suicide [23]. Laboratory research shows that finasteride reduces levels of neurosteroids modulating mood [23] and induces in rats long term effects on depressive-like behavior, hippocampal neurogenesis and inflammation [13].

The cosmetic effect of finasteride on self-image may improve mood and quality of life. Such improvements for a bulk of people in post marketing surveillance can dilute or even completely mask a drastic deterioration of mood in a significant minority of patients. Competing effects, including both benefit and harm from a medication, might explain conflicting data in the literature and the heterogeneity found in systematic reviews on the risk of depression for finasteride, [24] as for

isotretinoin [25].

When considering finasteride to improve self-image and quality of life, it seems critical to warn individual patients about the potential risk of getting just the opposite outcome with neuropsychiatric reactions associated with a dismal, potentially permanent deterioration in quality of life. Health care professionals should be aware of these concerns, share them with patients and discuss alternative options, to allow a truly informed decision regarding their care.

Conclusion

Reports to the FDA of neuropsychiatric events for finasteride in comparison to control medications show disproportionate safety signals for finasteride with a striking increase in suicides. Increased reporting could relate to enhanced awareness and not to a nocebo effect. In pharmacovigilance surveys, the actual rate of serious adverse effects on mood from finasteride in some patients may be diluted by the beneficial cosmetic outcome in many others. Health care professionals should be aware of these concerns and share them with patients to allow informed decision regarding their care.

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