Neuropsychiatric Reactions to Finasteride: Nocebo or True Effect?

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To the Editor:

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

Table: 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		

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).

Disproportionate safety signals for finasteride concur with reports by others,[1] but some suggest this may represent simulated reporting of a nocebo effect.[2,3] An impact of media coverage, through cognitive availability bias, is usually transient,[4-6] 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 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 (see Figure 1 below).

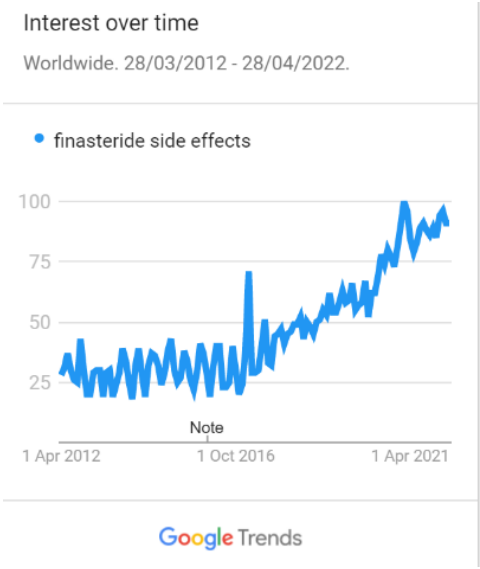

Figure 1. Trends of Google searches for 'finasteride side effects' over last decade worldwide (Google analytics, accessed 4/25/2022)

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).

Users 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 – as seen in Figure 2.

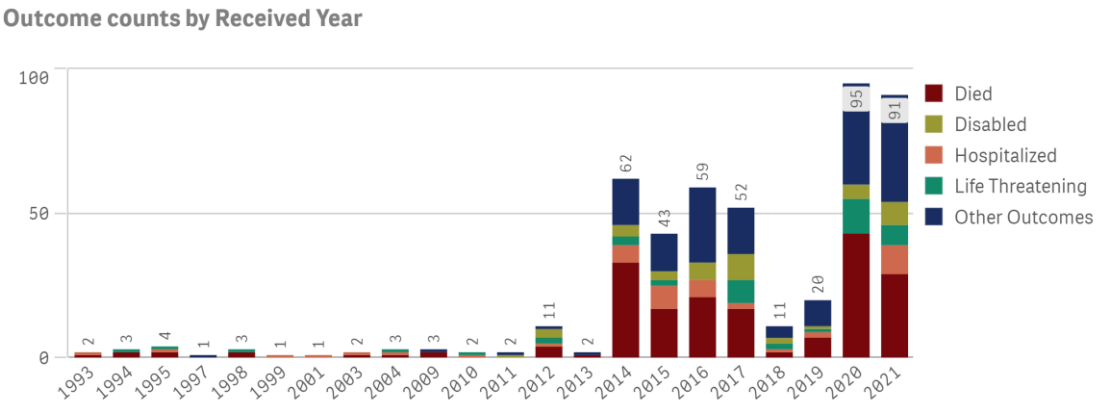

Figure 2. Reported suicide attempts, suicidal behavior, suspected suicide and completed suicide for finasteride (FAERS, accessed 4/26/2022)

Since the nocebo effect has not been associated with suicide,[7] 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.[8-12] Mitigation of finasteride-related suicidality by concomitant administration of testosterone[13] 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.[14]

Awareness of drug safety issues can be slowly arising, as side effects are under-reported by physicians[15] and by pharmaceutical companies.[16] Earlier and more direct reporting by patients for safety monitoring, as increasingly done in pharmacovigilance,[17,18] may accelerate the detection of drug safety signals - in a paradigm shift already widely implemented in healthcare practice.[19]

A recent update on the management of hair loss[20] 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,[2,21] confirming previous reports of serious psychological adverse effects, including anxiety, insomnia, fatigue, depressed mood and completed suicide.[22] Laboratory research shows that finasteride reduces levels of neurosteroids modulating mood[22] and induces in rats long term effects on depressive-like behavior, hippocampal neurogenesis and inflammation.[10]

Serious adverse effects from finasteride appear to be real and not related to simulated reporting of a nocebo effect. 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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References

1. Pompili M, Magistri C, Maddalena S, et al. Risk of Depression Associated With Finasteride Treatment. *Journal of Clinical Psychopharmacology.* 2021;41:304-309.
2. Nguyen D-D, Marchese M, Cone EB, et al. Investigation of suicidality and psychological adverse events in patients treated with finasteride. *JAMA dermatology.* 2021;157:35-42.
3. Nguyen D-D, Herzog P, Cone EB, et al. Disproportional signal of sexual dysfunction reports associated with finasteride use in young men with androgenetic alopecia: A pharmacovigilance analysis of VigiBase. *Journal of the American Academy of Dermatology.* 2022:S0190-9622 (0122) 00527-00528.
4. Brezis M, Halpern-Reichert D, Schwaber MJ. Mass Media–Induced Availability Bias in the Clinical Suspicion of West Nile Fever. *Annals of internal medicine.* 2004;140:234-235.
5. Taylor D, Stewart S, Connolly A. Antidepressant withdrawal symptoms—telephone calls to a national medication helpline. *Journal of affective disorders.* 2006;95:129-133.
6. MacKrill K, Gamble GD, Bean DJ, et al. Evidence of a media-induced nocebo response following a nationwide antidepressant drug switch. *Clinical Psychology in Europe.* 2019;1:1-12.
7. Colloca L, Barsky AJ. Placebo and Nocebo Effects. *New England Journal of Medicine.* 2020;382:554-561.
8. Melcangi RC, Santi D, Spezzano R, et al. Neuroactive steroid levels and psychiatric and andrological features in post-finasteride patients. *The Journal of steroid biochemistry and molecular biology.* 2017;171:229-235.
9. Li L, Kang YX, Ji XM, et al. Finasteride inhibited brain dopaminergic system and open-field behaviors in adolescent male rats. *CNS neuroscience & therapeutics.* 2018;24:115-125.
10. Diviccaro S, Giatti S, Borgo F, et al. Treatment of male rats with finasteride, an inhibitor of 5alpha-reductase enzyme, induces long-lasting effects on depressive-like behavior, hippocampal neurogenesis, neuroinflammation and gut microbiota composition. *Psychoneuroendocrinology.* 2019;99:206-215.
11. Godar SC, Cadeddu R, Floris G, et al. The Steroidogenesis Inhibitor Finasteride Reduces the Response to Both Stressful and Rewarding Stimuli. *Biomolecules.* 2019;9:749.

12. Sasibhushana R, Rao BS, Srikumar BN. Repeated finasteride administration induces depression-like behavior in adult male rats. *Behavioural brain research.* 2019;365:185-189.
13. Campbell K, Velazquez O, Sullivan J, et al. Finasteride-Associated Suicide and Depression in Men Treated for Hypogonadism and Impotence. *The Journal of Sexual Medicine.* 2022;19:S4-S5.
14. Gunay A, Pinna G. The novel rapid-acting neurosteroid-based antidepressant generation. *Current Opinion in Endocrine and Metabolic Research.* 2022:100340.
15. Basch E. The missing voice of patients in drug-safety reporting. *New England Journal of Medicine.* 2010;362:865-869.
16. Golder S, Loke YK, Wright K, et al. Reporting of adverse events in published and unpublished studies of health care interventions: a systematic review. *PLoS medicine.* 2016;13:e1002127.
17. Bahri P, Pariente A. Systematising Pharmacovigilance Engagement of Patients, Healthcare Professionals and Regulators: A Practical Decision Guide Derived from the International Risk Governance Framework for Engagement Events and Discourse. *Drug Safety.* 2021;44:1193-1208.
18. Inácio P, Cavaco A, Airaksinen M. The value of patient reporting to the pharmacovigilance system: a systematic review. *British Journal of Clinical Pharmacology.* 2017;83:227-246.
19. Nelson EC, Eftimovska E, Lind C, et al. Patient reported outcome measures in practice. *BMJ : British Medical Journal.* 2015;350:g7818.
20. Mirmirani P, Fu J. Diagnosis and Treatment of Nonscarring Hair Loss in Primary Care in 2021. *JAMA.* 2021;325:878-879.
21. Welk B, McArthur E, Ordon M, et al. Association of suicidality and depression with 5α-reductase inhibitors. *JAMA internal medicine.* 2017;177:683-691.
22. Irwig MS. Finasteride and suicide: a postmarketing case series. *Dermatology.* 2020;236:540-545.