Persistent Sexual Dysfunction and Depression in Finasteride Users for Male Pattern Hair Loss

A Serious Concern or Red Herring?

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ABSTRACT

The use of finasteride for the treatment of male pattern hair loss has recently been the focus of media and internet attention for potential irreversible sexual dysfunction and severe depression. The purpose of this study was to perform a critical review of the recent studies reporting prolonged sexual dysfunction and depression with the use of finasteride for the treatment of male pattern hair loss. A literature search was performed using PubMed to review the literature pertaining to any potential adverse effects with the use of finasteride and its treatment of male pattern hair loss. The authors conclude that the reports of potential irreversible sexual dysfunction and severe depression do raise concerns about the safety of finasteride; however, these studies are wrought with significant bias. Therefore, larger, randomized, double blind, controlled trials are warranted to further ascertain the true potential risks or confirm long-term safety profile of finasteride use.
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The use of finasteride for the treatment of male pattern hair loss (MPHL) has received internet and media scrutiny over potential long-term sexual side effects. The goal of this article is to critically review the literature regarding both the safety as well as the potential adverse effects of finasteride for its use in MPHL.

Finasteride has been United States Food and Drug Administration (FDA) approved since 1992 for the treatment of benign prostatic hyperplasia[1] and since 1997 for the treatment of men with MPHL or androgenetic alopecia (AGA).[1] Since that time, according to a PubMed search, there have been more than 2,230 articles published on the medication. Of these articles, 250 were considered randomized, controlled trials.

FINASTERIDE USE AND SEXUAL DYSFUNCTION (TABLE 1)

One of the first published large, multicenter, randomized, controlled, double-blind studies on finasteride was performed in 1992 for its use in benign prostatic hyperplasia (BPH) with the "Finasteride Study Group". They evaluated 895 men with prostatic hyperplasia using the 1mg, 5mg, or placebo dosing over 12 months.[2] There were no reports of irreversible or prolonged sexual side effects. After 24 months, the only adverse effects reported were decreased libido and ejaculation disorders in approximately one percent of patients.[3] A summary of the Phase 3 controlled studies in the Finasteride Study Group with a total of 1,645 patients found that finasteride once again was well tolerated with a good safety profile.[4] A three-year safety trial found that finasteride at the 5mg dose had an excellent safety profile and was a low-risk medication.[5] Again, there were no reports of prolonged or irreversible sexual side effects or depression. Overall, the Finasteride Study Group confirmed that finasteride is well tolerated, and that aside from the slightly increased likelihood of reversible sexual side effects compared to placebo, the overall frequency of adverse effects was minimal.

Since these initial studies, there have been numerous reports stating similar findings. The PROSPECT study was a two-year, double-blind, multicenter, randomized, controlled trial of finasteride 5mg daily for men with BPH. There was no significant difference in the overall frequency of adverse events; however there was a statistically significant increase

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TABLE 1. Summary of randomized, controlled trials investigating the use of finasteride to treat androgenetic alopecia

STUDY (YEAR)	METHODS	STUDY DURATION	NO. OF PARTICIPANTS	ADVERSE EVENTS IN FINASTERIDE GROUP	ADVERSE EVENTS IN PLACEBO GROUP
Finasteride Study Group for BPH[2]	Finasteride 1mg vs. Finasteride 5mg vs. placebo	1 and 2 years	895 total 298 in Finasteride 1mg group	1mg group: • 3 withdrew due to sexual side effects • 2.0% with decreased libido • 1.4% with "ejaculatory disorder" • 1.7% with impotence 5mg group: • 3 withdrew due to sexual side effects	1 withdrew due to sexual side effects
PROSPECT study for BPH[6]	Finasteride 5mg vs. placebo	2 years	246 in finasteride group	• 10.0% with decreased libido • 7.7% experiencing ejaculation dysfunction • 15.8% with impotence	
Finasteride for BPH[7]	Finasteride 5mg vs. placebo	4 years	1000 in finasteride group	Only statistically significant in first year. • 6.4% with decreased libido • 0.8% with ejaculation disorder • 8.1% with impotence	
Finasteride for MPHL[8,9]	Finasteride 1mg vs. placebo	1 year with extension to 5 years	1553 men x 1 year 1215 men in extension 779 in finasteride group at year 1 547 in finasteride group at year 2 379 in finasteride group at year 4	• 4.4% with sexual dysfunction • 1.9% decreased libido at year 1, 1.3% at year 2, 0.5% at year 4 • 1.4% with ejaculation disorder at year 1, 0.9% at year 2, and 0.3% at year 4 • 1.4% with erectile dysfunction at year 1, 0.7% at year 2, 0.3% at year 4 • 1.4% discontinued due to AEs	• 2.2% with sexual dysfunction (p=0.030) • 1.0% discontinued due to AEs
Finasteride study for MPHL[10]	Finasteride 1mg vs. placebo		424 in finasteride group	• 8.7% with sexual dysfunction*	• 5.1% with sexual dysfunction*
Finasteride study for MPHL[11]	Finasteride 1mg vs. placebo	1 year followed by 1 year open extension	326 total	• 0.3% with impotence	• 0.3% with ejaculation disorder
Finasteride study for MPHL[12]	Finasteride 1mg vs. placebo	4 years	212 total	• 1.9% with sexual dysfunction	• 0.9% with sexual side effects

*not statistically significant

specifically in sexual side effects in the finasteride group compared to placebo. Another long-term study of finasteride 5mg daily in patients with BPH showed statistically significant differences in sexual side effects in the first year of use in the 1,000 participants of the finasteride group who completed the four-year trial compared to placebo.[7]

The first double-blind, randomized, controlled study of finasteride and its use for MPHL in the dermatology literature was reported in 1998. Kaufman et al[8] performed a United States and international Phase 3 study evaluating 1,553 men for one year and 1,215 men in the blinded extension over five years. Overall, of the finasteride group participants, the most common adverse events were decreased libido, ejaculation disorder, and erectile dysfunction, which decreased after Years 2 and 4. The sexual adverse effects resolved in all patients after discontinuation of the medication and also resolved in most men who remained on the therapy. Once again, the authors felt the medication was generally well tolerated and safe overall.[9] Other randomized, controlled trials include a 2003 multicenter study of 424 men with MPHL taking 1mg daily of finasteride. Although not reported as significant, the finasteride group reported drug-related sexual dysfunction in 8.7 percent compared to 5.1 percent in the placebo group.[10] Another one-year trial, followed by a one-year open extension of 326 men with MPHL, reported sexual adverse effects in one patient in the placebo arm with an ejaculation disorder and one patient in the finasteride arm with impotence.[11] In a separate 48-week trial of 212 men receiving 1mg finasteride daily or placebo for MPHL, only two in the finasteride group reported sexual side effects, compared to one in the placebo group. These effects were reversible.[12]

The only double-blind, randomized, controlled trial to report persistent sexual side effects was the PLESS trial, which evaluated men with BPH taking finasteride 5mg daily. Only 50 percent of finasteride users that experienced sexual side effects noted resolution after discontinuation; however only 41 percent of the placebo group noted resolution of their sexual side effects.[13]

In 2007, Mondaini et al[14] attempted to explain the reports in the literature of higher percentages of finasteride users experiencing sexual dysfunction, compared to what the authors perceived as a much lower incidence in their everyday clinical practice. In a blinded control trial, they administered 5mg of finasteride daily to 107 patients, with one group counseled on possible sexual side effects and the other not informed of any sexual side effects. They were able to detect a significant placebo effect with 43.6 percent of the informed group reporting sexual side effects compared to 14.3 percent in the group not informed.[14]

In the authors' opinion, the most informative trial specifically analyzing the effect of finasteride and sexual functioning was the Prostate Cancer Prevention Trial. This was a randomized, double-blind, placebo-controlled study that was able to evaluate sexual dysfunction and any possible confounding variables in 17,313 participants over seven years. They utilized a sexual activity scale, ranging from 0 to 100 with higher numbers demonstrating greater sexual dysfunction. The scale evaluated the ability to have an erection, the degree of sexual satisfaction, any change in sexual performance, and frequency of sexual activities. They noted a statistically significant increase on the sexual activity scale of 3.21 in the finasteride group at six months, which decreased to 2.11 at seven years. This was felt to be a small difference on a scale of 100 with very little impact and less pertinent clinically than other causes of sexual dysfunction and individual variation. They detected other covariates in their study population that demonstrated a similar effect as finasteride on sexual dysfunction, including declining physical function, diabetes, hypertension, smoking, and increased body mass index. Age, as an individual covariate, demonstrated a greater effect on sexual dysfunction than finasteride, with an increase of 1.26 points per year on the sexual activity scale. Interestingly, the mental health score did not significantly affect sexual dysfunction over time. None of the 17,313 participants reported persistent sexual dysfunction. The authors concluded that the effect of finasteride on sexual functioning was minimal and that it should not interfere with prescribing practices.[15]

FINASTERIDE USE AND DEPRESSION

There is very little in the literature reporting mood disturbances in finasteride users. Altomare et al[16] reported a retrospective case series of 19 patients who developed mood disturbance after starting finasteride for MPHL, which resolved after discontinuation.[16] In a prospective study, 128 finasteride users for MPHL were given questionnaires regarding symptoms of depression before treatment and two months later. There was a significant increase in depressive symptoms after two months; however, the overall effect was minimal. In addition, the symptoms resolved after discontinuation of the medication. Interestingly, there was no significant difference in depression scores in the participants with loss of libido compared to those unaffected.[17]

PERSISTENT ADVERSE EVENTS

From the above studies, in the last 20 years of its use, finasteride has been considered a well-tolerated, generally safe medication, with the majority of patients not experiencing any adverse events. However, over the last five years, governmental agencies in Sweden, the United Kingdom, and the United States have changed product information to include possible persistent sexual side effects as well as depression. Several articles have been published in recent years, receiving a great deal of media and internet attention, describing these persistent sexual side effects as well as depression.

Traish et al[18] described a healthy, 24-year-old man with new-onset erectile dysfunction, loss of libido, and depression after one month of finasteride for MPHL that still persisted 11 years later. In addition, Irwig et al has published two articles in the *Journal of Sexual Medicine* describing persistent sexual side effects and one article in the *Journal of Clinical Psychiatry* reporting persistent depression with finasteride use. The initial article, published in 2011,

specifically investigated 71 men with MPHL who self-reported persistent sexual side effects for more than three months after discontinuation of finasteride.[19] The authors recruited patients from www.propeciahelp.com, a website for finasteride users with persistent side effects, the author's clinical practice, and physician referrals. They conducted the study via telephone or Skype interview, retrospectively inquiring about symptoms before and after finasteride use. They utilized the Arizona Sexual Experience Scale (ASEX) to objectively evaluate sexual dysfunction, with ≥19 indicating sexual dysfunction. A decrease in frequency of sex from 25.8 times per month to 8.8 times per month at the time of the interview, as well as an increase in the ASEX scale from 7.4 to 21.6 was reported. Some of the participants (an unreported number) stated that the sexual dysfunction started immediately after discontinuing the medication. The mean duration of sexual dysfunction was more than three years. The follow-up article, published in 2012, prospectively followed 54 participants from the 2011 study to evaluate for persistence or resolution of the previously reported sexual dysfunction.[20] Follow-up emails were sent to the participants from 9 to 16 months after the initial study. At this re-assessment, 89 percent of subjects continued to have sexual dysfunction.

The final article evaluated 61 participants for depression from the 2011 study with self-reported prolonged sexual dysfunction from finasteride use and compared these individuals to a control group of men with MPHL from a college campus.[21] They used the Beck Depression Inventory II (BDI-II) scale, with 14 indicating mild depression, 20 indicating moderate, and 29 and over indicating severe depression. Seventy-five percent of the former finasteride users reported depressive symptoms, compared to 10 percent of the controls ($p<0.0001$) with 64 percent of the finasteride arm illustrating moderate-to-severe symptoms compared to none of the controls. Thirty-nine percent reported suicidal thoughts compared to three percent of controls ($p<0.0001$). The mean scores from the BDI-II scores were 23.67 in the finasteride groups compared to 5.93 in the control groups.

Although the three aforementioned studies from Irwig et al raise serious concerns in a select population of otherwise young, healthy finasteride users, it is important to critically analyze the data reported in these studies to best counsel patients about the possible risks of taking finasteride for MPHL. From these studies alone, we cannot conclude that finasteride is definitively linked to persistent sexual dysfunction and depression.

A major concern is the level of selection bias among the participants. Many of the individuals were recruited from an Internet website for individuals with persistent sexual side effects after using finasteride. It is probable that these individuals are more seriously affected by sexuality or have more severe sexual dysfunction and, thus, are more likely to participate in and seek out the study. In addition, these findings may not pertain to individuals with less severe sexual dysfunction. Moreover, as referenced above, in the 2007 study by Mondaini et al,[14] a significant placebo effect was detected when patients were informed in advance about possible sexual dysfunction. Because a number of these patients were self-selected from the Internet, it would be difficult to determine if these individuals are experiencing a placebo effect because of possible counseling provided to these patients prior to initiating finasteride.

In addition, there is potential for a significant recall bias. Thirty-three percent of the patients from the initial study had been experiencing sexual side effects for more than three years. Presumably, it may be difficult to recall accurate responses to the ASEX scale about sexual functioning from years prior. Likewise, the control group used in the depression study, was not statistically similar to the study group. They were more ethnically diverse and younger. These individuals may be less likely to report depressive symptoms. In addition, to truly assess any possible effect of finasteride, the control group should have been young men with sexual dysfunction. It may have also been informative to compare the presence of depressive symptoms of former finasteride users with sexual dysfunction to former finasteride users without sexual dysfunction. As, in one of the articles mentioned above, the authors could not find a significant difference in the incidence of depression between finasteride users with decreased libido and those who were unaffected.[17] Without the proper control group, it is difficult to evaluate the role of sexual dysfunction on depression and vice versa, as they are clearly interlinked.

Moreover, these were retrospective studies with no placebo control. Given the retrospective nature of these studies, we cannot ascertain the true incidence of persistent sexual dysfunction and depression in finasteride users. This would be the most important information to be able to provide our patients.

CONCLUSION

In summary, the findings by Irwig et al are quite disconcerting; however, even if the findings in these three articles by Irwig et al are accurate, this clearly only effects a small proportion of finasteride users. As stated above in the Prostate Cancer Prevention Trial, none of the more than 17,000 participants experienced persistent sexual dysfunction or depression. In addition, the authors were able to demonstrate that finasteride only had a minimal effect on sexual dysfunction. They advised that these sexual adverse effects should not affect prescribing practices.

Once again, given the data from the hundreds of randomized, controlled trials, finasteride should still be considered a safe and well-tolerated medication. It is essential that further research is performed, in the form of randomized control trials, to further evaluate if there are any unique characteristics in these individuals suffering from prolonged sexual dysfunction and severe depression after using finasteride. These future double-blind, placebo-controlled trials are necessary to conclude if these findings by Irwig et al are "a red herring" or a potentially rare but serious side effect about which we should counsel our patients.

REFERENCES

1. FDA Approved Drug Products http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=FINASTERIDE. Accessed September 7, 2012.
2. Gormley GJ, Stoner E, Bruskewitz RC, et al. The effect of finasteride in men with benign prostatic hyperplasia. The Finasteride Study Group. *N Engl J Med*. 1992;327:1185–1191.
3. Stoner E. Maintenance of clinical efficacy with finasteride therapy for 24 months in patients with benign prostatic hyperplasia. The Finasteride Study Group. *Arch Intern Med*. 1994;154:83–88.
4. Grino P, Stoner E. Finasteride for the treatment and control of benign prostatic hyperplasia: summary of phase III controlled studies. The Finasteride Study Group. *Eur Urol*. 1994;25(Suppl 1):24–28.
5. Stoner E. Three-year safety and efficacy data on the use of finasteride in the treatment of benign prostatic hyperplasia. *Urology*. 1994;43:284–292; discussion 292–284.
6. Nickel JC, Fradet Y, Boake RC, et al. Efficacy and safety of finasteride therapy for benign prostatic hyperplasia: results of a 2-year randomized controlled trial (the PROSPECT study). PROscar Safety Plus Efficacy Canadian Two year Study. *CMAJ*. 1996;155:1251–1259.
7. McConnell JD, Bruskewitz R, Walsh P, et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy and Safety Study Group. *N Engl J Med*. 1998;338:557–563.
8. Kaufman KD, Olsen EA, Whiting D, et al. Finasteride in the treatment of men with androgenetic alopecia. Finasteride Male Pattern Hair Loss Study Group. *J Am Acad Dermatol*. 1998;39(4 Pt 1):578–589.
9. Finasteride Male Pattern Hair Loss Study G. Long-term (5-year) multinational experience with finasteride 1mg in the treatment of men with androgenetic alopecia. *Eur J Dermatol*. 2002;12:38–49.
10. Whiting DA, Olsen EA, Savin R, et al. Efficacy and tolerability of finasteride 1mg in men aged 41 to 60 years with male pattern hair loss. *Eur J Dermatol*. 2003;13:150–160.
11. Leyden J, Dunlap F, Miller B, et al. Finasteride in the treatment of men with frontal male pattern hair loss. *J Am Acad Dermatol*. 1999;40(6 Pt 1):930–937.
12. Van Neste D, Fuh V, Sanchez-Pedreno P, et al. Finasteride increases anagen hair in men with androgenetic alopecia. *Br J Dermatol*. 2000;143:804–810.
13. Wessells H, Roy J, Bannow J, et al. Incidence and severity of sexual adverse experiences in finasteride and placebo-treated men with benign prostatic hyperplasia. *Urology*. 2003;61:579–584.
14. Mondaini N, Gontero P, Giubilei G, et al. Finasteride 5mg and sexual side effects: how many of these are related to a nocebo phenomenon? *J Sex Med*. 2007;4:1708–1712.
15. Moinpour CM, Darke AK, Donaldson GW, et al. Longitudinal analysis of sexual function reported by men in the Prostate Cancer Prevention Trial. *J Natl Cancer Inst*. 2007;99:1025–1035.
16. Altomare G, Capella GL. Depression circumstantially related to the administration of finasteride for androgenetic alopecia. *J Dermatol*. 2002;29:665–669.
17. Rahimi-Ardabili B, Pourandarjani R, Habibollahi P, et al. Finasteride induced depression: a prospective study. *BMC Clin Pharmacol*. 2006;6:7.
18. Traish AM, Hassani J, Guay AT, et al. Adverse side effects of 5alpha-reductase inhibitors therapy: persistent diminished libido and erectile dysfunction and depression in a subset of patients. *J Sex Med*. 2011;8:872–884.
19. Irwig MS, Kolukula S. Persistent sexual side effects of finasteride for male pattern hair loss. *J Sex Med*. 2011;8:1747–1753.
20. Irwig MS. Persistent sexual side effects of finasteride: could they be permanent? *J Sex Med*. 2012.
21. Irwig MS. Depressive symptoms and suicidal thoughts among former users of finasteride with persistent sexual side effects. *J Clin Psychiatry*. 2012;73(9):1220–1223