Depressive Symptoms and Suicidal Thoughts Among Former Users of Finasteride With Persistent Sexual Side Effects

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ABSTRACT

Objective: Finasteride, a commonly prescribed medication for male pattern hair loss, has recently been associated with persistent sexual side effects. In addition, depression has recently been added to the product labeling of Propecia (finasteride 1 mg). Finasteride reduces the levels of several neuroactive steroids linked to sexual function and depression. This study assesses depressive symptoms and suicidal thoughts in former users of finasteride who developed persistent sexual side effects despite the discontinuation of finasteride.

Method: In 2010–2011, former users of finasteride (n = 61) with persistent sexual side effects for ≥ 3 months were administered standardized interviews that gathered demographic information, medical and psychiatric histories, and information on medication use, sexual function, and alcohol consumption. All former users were otherwise healthy men with no baseline sexual dysfunction, chronic medical conditions, current or past psychiatric conditions, or use of oral prescription medications before or during finasteride use. A control group of men (n = 29), recruited from the community, had male pattern hair loss but had never used finasteride and denied any history of psychiatric conditions or use of psychiatric medications. The primary outcomes were the prevalence of depressive symptoms and the prevalence of suicidal thoughts as determined by the Beck Depression Inventory II (BDI-II); all subjects self-administered this questionnaire at the time of the interview or up to 10 months later.

Results: Rates of depressive symptoms (BDI-II score ≥ 14) were significantly higher in the former finasteride users (75%; 46/61) as compared to the controls (10%; 3/29) ($P < .0001$). Moderate or severe depressive symptoms (BDI-II score ≥ 20) were present in 64% (39/61) of the finasteride group and 0% of the controls. Suicidal thoughts were present in 44% (27/61) of the former finasteride users and in 3% (1/29) of the controls ($P < .0001$).

Conclusions: Clinicians and potential users of finasteride should be aware of the potential risk of depressive symptoms and suicidal thoughts. The preliminary findings of this study warrant further research with controlled studies.

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Pharmacovigilance is the science relating to identifying, monitoring, and effectively reducing adverse drug reactions. When a drug comes to market, it is often studied in only a thousand patients or less, as in the case of finasteride.[1,2] Less common adverse effects of a medication may be uncovered only in the postmarketing phase after many thousands of patients have been exposed to the medication.[3] For this reason, the reporting of adverse drug reactions to drug safety surveillance programs is the only way to uncover potentially harmful undescribed effects of a medication. Unfortunately, the major limitation to this process is underreporting due to a variety of causes such as ignorance, diffidence, and lack of time or interest.[4]

Finasteride is a commonly prescribed 5α-reductase inhibitor used for the treatment of male pattern hair loss. It works by lowering the amount of dihydrotestosterone in the skin and hair follicles. In multiple double-blind randomized controlled trials for the treatment of male pattern hair loss, finasteride has been associated with a small but significant amount of sexual dysfunction including low libido and erectile dysfunction.[1,2,5] In these trials, the sexual side effects were reported to resolve with time or with discontinuation of finasteride. Two recent studies, one clinical[6] and the other a case and review article,[7] have documented that a subset of men who take finasteride experience persistent sexual side effects despite discontinuation of the medication.

In April 2012, the US Food and Drug Administration announced changes to the professional labels for Propecia (finasteride 1 mg) to expand the list of persistent sexual adverse events reported.[8] A recent study[9] in rats found that a 5α-reductase inhibitor caused persistent alterations in relaxant and contractile responses of penile tissue. The incidence of persistent sexual side effects associated with finasteride is unknown. Although it is rare for a medication to cause persistent neurologic adverse effects, a classic example is the phenothiazines, which can cause tardive dyskinesias.[10]

Two human studies with limitations have linked finasteride to depression in the treatment of male pattern hair loss. First, a retrospective case series[11] of 23 patients found that 19 developed moderate to severe depression during finasteride treatment. The depression resolved within 3 weeks of stopping the finasteride in all cases. Two subjects who agreed to be rechallenged with finasteride both had a recurrence of depression within 2 weeks. The second study[12] was a noncontrolled prospective study of 128 men who developed significantly higher group mean depression scores on the Beck Depression Inventory 2 months after finasteride therapy as compared to baseline. In December 2010, the product labeling for Propecia in the United States was updated to include the side effect of depression.[13]

The present study was designed to explore the relationship between depressive symptoms and suicidal thoughts in former users of finasteride who experienced persistent sexual side effects despite having stopped taking the medication for at least 3 months.

Clinical Points

- A subset of young men who take finasteride develop persistent sexual side effects accompanied by severe depressive symptoms and suicidal thoughts.
- Prescribers and potential users of finasteride should be aware of the potential CNS side effects of this medication.

METHOD

Participants

The former finasteride users experienced sexual side effects that began while they were taking finasteride and that persisted for at least 3 months despite cessation of the medication. The indication for the medication was male pattern hair loss, and the men started and completed finasteride use before 40 years of age. Men were excluded from the study if they reported baseline sexual dysfunction, chronic medical conditions, current or past psychiatric conditions, a history of taking psychiatric medications, or baseline use of nontopical prescription medications other than a short course of antibiotics.

The former finasteride users were recruited from April 2010 until December 2011 from a previous study[6] (n = 42) and from an ongoing endocrine study (n = 19) relating to persistent sexual side effects of finasteride. The participation rates were 59% for subjects from our first study and 100% for the ongoing study. Most subjects were initially recruited from Propeciahelp.com, an Internet forum dedicated to unresolved side effects of finasteride. Other subjects were recruited from the author's clinical practice and from physician referrals.

The control group consisted of men with male pattern hair loss who had never used finasteride and who did not have any current or past psychiatric conditions or use of psychiatric medications. This control group was chosen as there is evidence that hair loss and other dermatology diagnoses are associated with various psychological/psychiatric conditions, such as body image dissatisfaction, depression, and anxiety.[14,15] A control group of men with both male pattern hair loss and sexual dysfunction was not chosen as the former finasteride users did not have any sexual dysfunction at baseline. In addition, sexual dysfunction in multiple domains is very uncommon in young men with no medical or psychiatric conditions. The control group was recruited from November to December 2011 through flyers posted at a university campus. Interested subjects were personally screened by the author to verify eligibility requirements and the presence of male pattern hair loss. Eligible subjects who completed the questionnaires were compensated $20 for their time.

All former finasteride users provided written consent, and control subjects provided oral consent and did not record their names, in accordance with the protocol approved by the institutional review board of George Washington University.

Design

Telephone or spoken Skype standardized interviews were conducted with the former finasteride users as previously described.[6] Subjects were asked about demographic information, medical and psychiatric histories, medication use, sexual function, and weekly alcohol consumption. At the time of the interview, subjects retrospectively estimated their sexual function prior to starting finasteride. At the time of the interview or up to 10 months after the interview, subjects self-administered the Beck Depression Inventory II (BDI-II), a widely used validated instrument that measures the severity of depression in adults.[16] This questionnaire consists of 21 groups of statements in which each item is rated on a 4-point scale ranging from 0 to 3 in severity. Respondents choose the statement that best describes their feelings over the prior 2 weeks. In patients diagnosed with major depression (diagnosed by psychiatrists and psychologists using *DSM-III-R* or *DSM-IV*), the cutpoints were 14 for mild, 20 for moderate, and 29 for severe.[16] The reference populations in the BDI-II were 120 college students in a psychology class and 500 outpatients in a psychiatric clinic.[16]

The primary outcomes of the study were the prevalence of depressive symptoms and the prevalence of suicidal thoughts as determined by the BDI-II.

Statistical Analysis

All analyses were performed using SAS Version 9.2 (SAS Institute, Cary, North Carolina) using $\alpha = .05$ to declare a result as statistically significant. Two-tailed *t* tests were used to test differences between the finasteride and control groups for mean age and BDI-II items. To detect a difference in total score on the BDI-II between the finasteride and control groups, 25 subjects for the control group were needed assuming 90% power and $\alpha = .05$ (2-sided).

RESULTS

The demographic characteristics and finasteride information are presented in Table 1. As compared to the control group, the former finasteride users were older and less ethnically diverse ($P < .0001$ and $P = .0028$, respectively). For finasteride users, the mean age for beginning finasteride was 25.8 years, and the mean length of finasteride use was 27 months.

According to the total scores from the BDI-II, most former finasteride users exhibited some degree of depressive symptoms: 11% (n = 7) had mild symptoms, 28% (n = 17) had moderate symptoms, and 36% (n = 22) had severe symptoms. In the control group, 10% (n = 3) had mild depressive symptoms with no cases of moderate or severe symptoms. Rates of depressive symptoms (BDI-II score ≥ 14) were significantly higher in the former finasteride users (75%; 46/61) as compared to the controls (10%; 3/29) ($P < .0001$).

For the finasteride users, 39% (n = 24) reported suicidal thoughts (option 1), and an additional 5% (n = 3) chose the statement "I would like to kill myself" (option 2). The rate of suicidal thoughts in former finasteride users was significantly

Table 1. Subject Characteristics and Finasteride Information

	Finasteride Group (n = 61)	Control Group (n = 29)
Demographic characteristics		
Age, mean ± SD, y	31.0 ± 5.7	26.2 ± 4.1
Ethnicity, %		
White	87	55
Asian	8	34
Other	5	10
Sexual orientation, %		
Straight	92	93
Gay	8	0
Bisexual	0	7
Finasteride information		
Age when use began, mean ± SD, y	25.8 ± 5.0	
Length of use, %		
< 1 mo	7	
1–3 mo	16	
4–6 mo	13	
7–11 mo	15	
1–5 y	33	
> 5 y	16	
Duration of persistent sexual side effects after finasteride cessation, %		
3–6 mo	10	
7–11 mo	7	
1–2 y	41	
3–5 y	26	
≥ 6 y	16	

($P < .0001$) higher than in the control group, among whom 3% (n = 1) reported suicidal thoughts (option 1).

Mean (± SD) scores from the 21-item BDI-II were 23.67 (± 12.56) in the former finasteride users and 5.93 (± 4.48) in the control group ($P < .0001$).

DISCUSSION

In a group of 61 otherwise healthy former users of finasteride who developed persistent sexual side effects, depressive symptoms were present and categorized as mild in 11% of users, moderate in 28% of users, and severe in 36% of users. Suicidal thoughts were present in 39% of former finasteride users, and an additional 5% chose the statement "I would like to kill myself." The corresponding rates of depressive symptoms and suicidal thoughts were significantly lower in a control group of young men with male pattern hair loss who had not used finasteride and who did not have any current or past psychiatric conditions or use of psychiatric medications.

The interaction between sexual dysfunction and depression is complex, as one may lead to the other. Remarkably, there are hardly any published studies on depression secondary to sexual dysfunction in young men. The sparse literature is generally limited to older populations. In a group of 120 consecutive men (mean age = 55 years) who presented to a human sexuality clinic for management of erectile function, 13% were found to have major depressive disorder by a psychiatrist using *DSM-IV* criteria, a rate much lower than that seen in this study.[17] A second study[18] found depressive symptoms in 54% of older men with erectile dysfunction (mean age = 55 years) and in 21% of older men with benign prostatic hyperplasia but no erectile dysfunction (mean age = 61 years). It is therefore reasonable to hypothesize that finasteride is associated with depression independently of the sexual dysfunction, especially in the context of 2 human studies of finasteride and depression in younger populations.[11,12] To provide another reference point for comparison, the mean total score from the BDI-II was higher in former finasteride users with persistent sexual side effects as compared to a population of 120 college students used to validate the BDI-II in which the mean score was 12.56.[16] In contrast to the present study's control group, some of these students had depression.

A plausible biological mechanism to explain the association between finasteride and depression lies with neuroactive steroids, neuromodulators that are synthesized in the central nervous system itself and that are also transported to the brain from the gonads and adrenal glands. Some neuroactive steroids alter neuronal excitability by binding to inhibitory γ-aminobutyric acid type A ($GABA_A$) and excitatory receptors.[19,20] GABA is the major inhibitory neurotransmitter for neurons in the adult brain. It turns out that finasteride crosses the blood-brain barrier and blocks the enzyme 5α-reductase, which reduces the concentrations of multiple neuroactive steroids derived not only from testosterone, but also from progesterone and deoxycorticosterone. In men treated for benign prostatic hypertrophy, finasteride significantly lowered plasma levels of neuroactive steroids (α-reduced metabolites of testosterone and progesterone).[21] In particular, one of the metabolites of 5α-dihydroprogesterone, 3α,5α-tetrahydroprogesterone, otherwise known as allopregnanolone, appears to play an important role in depression as it binds to the GABA receptor.[19]

Reduced concentrations of neuroactive steroids are associated with depression in several human studies. Depressed adults have lower concentrations of allopregnanolone in their cerebrospinal fluid as compared to nondepressed subjects.[22] Similarly, serum levels of allopregnanolone were lower in men with a first episode of unipolar major depressive disorder as compared to a control group.[23] Even women who had been in remission from depression for several years had lower serum levels of 4 progesterone-derived GABAergic neuroactive steroids as compared to controls.[24]

Interventional studies in rodents provide further support for the links among finasteride, neuroactive steroids, and depression. Administering finasteride into the amygdalae of rats attenuated antianxiety and antidepressive behavior.[25] Systemic and intrahippocampal finasteride had the same effect on anxiolytic and depressive behaviors as assessed through the forced swim test, open field test, and elevated plus maze test.[26,27] Likewise, rats that received finasteride had lower levels of plasma and hippocampal allopregnanolone and increased depression as measured with the forced swim test.[28]

Limitations to this pharmacovigilance study include its selection bias, retrospective nature, and recall bias. Although subjects from an Internet forum are certainly a biased sample in many regards, the Internet did make it possible to study a group of men in whom it otherwise would not have been

possible, given the likely small, albeit unknown, incidence of persistent sexual side effects of finasteride. The study population was also limited to those suffering from persistent sexual side effects of finasteride. It is therefore unknown whether depressive symptoms and suicidal thoughts are present in general users of finasteride who do not report persistent sexual side effects. The rates of depressive symptoms and suicidal thoughts were low in the control group, which was expected given that psychiatric conditions and psychiatric medication use were exclusion criteria for this group. For a pharmacovigilance study, there unfortunately is no ideal control group, as there would be different limitations depending on the group chosen. It would be very interesting to know the prevalence of depressive symptoms and suicidal thoughts in young men with sexual dysfunction. Unfortunately, there is no published literature on this population. This study employed standardized interviews and validated questionnaire instruments, but no serum or cerebrospinal fluid samples were obtained for measurement of neuroactive steroids. Although obtaining biological samples from subjects who reside across the world would be logistically challenging, such a study would certainly be very valuable. Finally, although the BDI-II is a depression screen, it is not a diagnostic instrument, and it does not substitute for an evaluation by a psychiatrist.

In conclusion, men who report persistent sexual side effects after discontinuing finasteride for at least 3 months have a high prevalence of depressive symptoms and suicidal thoughts. Persistence of sexual side effects after discontinuation of finasteride may therefore indicate the need for depression screening in this population. While sexual dysfunction may lead to depression, another independent and plausible hypothesis is that finasteride lowers the concentrations of neuroactive steroids linked to depression, which has been demonstrated in both human and rodent studies. Although the effects of finasteride in the human brain are poorly understood, clinicians, as well as potential finasteride users, should be aware of the serious potential risks of this medication, especially as it is being used cosmetically to alter a normal age-related process. This is the first study to document suicidal thoughts in (former) users of finasteride. The preliminary findings of this study warrant further research with controlled studies.

Drug names: finasteride (Propecia, Proscar, and others).
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