Persistent Sexual Side Effects of Finasteride: Could They Be Permanent?

Michael S. Irwig, MD

Center for Andrology and Division of Endocrinology, The George Washington University, Washington, DC, USA

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ABSTRACT

Introduction. Finasteride has been associated with sexual side effects that may persist despite discontinuation of the medication. In a clinical series, 20% of subjects with male pattern hair loss reported persistent sexual dysfunction for ≥6 years, suggesting the possibility that the dysfunction may be permanent. These subjects also reported a wide range of symptoms including changes in cognition, ejaculate quality, and genital sensation. Other medications have been associated with irreversible neurological effects, such as phenothiazines with tardive dyskinesias.
Aim. To prospectively study whether the persistent sexual side effects associated with finasteride resolve or endure over time.
Methods. Subjects (N = 54) with persistent sexual side effects associated with finasteride were reassessed after 9–16 months (mean 14 months). All subjects were otherwise healthy young men without any baseline sexual dysfunction, medical conditions, psychiatric conditions, or use of oral prescription medications prior to taking finasteride for male pattern hair loss.
Main Outcome Measure. Scores from the Arizona Sexual Experience Scale (ASEX).
Results. The participation rate was 81%. At reassessment persistent sexual side effects continued to be present in 96% of subjects. According to the ASEX scores, 89% of subjects met the definition of sexual dysfunction. Neither the length of finasteride use nor the duration of the sexual side effects correlated to changes in scores of sexual dysfunction.
Conclusion. In most men who developed persistent sexual side effects (≥3 months) despite the discontinuation of finasteride, the sexual dysfunction continued for many months or years. Although several rat studies have shown detrimental changes to erectile function caused by 5 alpha reductase inhibitors, the persistent nature of these changes is an area of active research. Prescribers of finasteride and men contemplating its use should be made aware of the potential adverse medication effects. **Irwig MS. Persistent sexual side effects of finasteride: Could they be permanent? J Sex Med **;**:**–**.**

Key Words. Finasteride; Sexual Dysfunction; Neurosteroids; Low Libido; Erectile Dysfunction

Introduction

Finasteride is a 5 alpha reductase inhibitor used in the treatment of male pattern hair loss (MPHL) and benign prostatic hypertrophy. Finasteride blocks the conversion of testosterone to the more potent androgen dihydrotestosterone (DHT) in many tissues including the skin, hair follicles, and prostate. Lesser known effects of the 5 α reductase inhibitors are that they also block the conversion of progestogens and glucocorticoids: progesterone to 5α-dihydroprogesterone and deoxycorticosterone to 5α-dihydrodeoxycorticosterone, respectively.

When Propecia was approved for the treatment of MPHL, it was known through several double-blind randomized controlled trials that it may cause a small but significant amount of sexual dysfunction with libido, orgasm, and erectile problems [1–3]. These trials reported that the sexual side effects resolved with time or with discontinuation of finasteride. Since Propecia's release, post-marketing surveillance has found that a subset of

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young men who take finasteride experience persistent sexual side effects despite the discontinuation of the medication [4,5]. Unfortunately, less common adverse effects of a medication are often only uncovered after several thousands of patients have been exposed to the medication [6]. In April of 2011 the product labeling for Propecia in the United States was updated to include the side effect of "difficulty in achieving an erection that continued after stopping the medication."

While the incidence of persistent sexual side effects associated with finasteride is unknown, it is very likely that over 1,000 men worldwide are experiencing the effects. This estimate is based upon the number of registered users (N = 2,170) on the Internet forum Propeciahelp.com which focuses on "persistent sexual, mental and physical side effects which continue despite quitting" finasteride [7]. Although it is difficult to ascertain how many of the registered users on the Propeciahelp.com forum suffer from the medication effects, 1,000 is likely a gross underestimate as many sufferers have not stumbled upon the Web site, do not surf English Web sites due to language barriers, or are skeptical to register sensitive personal information on an online forum.

Irreversible neurological effects of a medication have been reported and studied with tardive dyskinesias, which are caused by the use of phenothiazines for treatment of schizophrenia [8]. In a gerbil model, a 30-day course of finasteride caused persistent changes in the structural and ultrastructural morphology of the prostate [9]. There is a solid and growing body of basic science evidence that finasteride reduces the concentrations of several neuroactive steroids that play a role in neurogenesis and neuronal survival. Male mice treated with finasteride had reversibly lower levels of brain DHT and less neurogenesis as demonstrated by fewer young neurons in the hippocampus [10]. Likewise, finasteride lowers the concentration of 3α5α tetrahydroprogesterone, otherwise known as allopregnanolone (ALLO), a downstream metabolite of dihydroprogesterone that protects neurons from apoptosis via the Bcl-2 and Bcl-xL genes [11].

Aims

This study was designed to prospectively follow men with persistent sexual side effects of finasteride to see whether their sexual dysfunction would resolve, improve, or remain diminished over time.

Methods

Subjects

Participants for this study reported sexual side effects associated with finasteride which persisted for at least 3 months despite cessation of the medication. The indication for the medication was MPHL, and all men started and completed finasteride use before age 40. Men were excluded from the study if they reported any of the following before starting finasteride: baseline sexual dysfunction, chronic medical conditions, psychiatric conditions, a history of taking psychiatric medications or baseline use of non-topical prescription medications other than a short course of antibiotics.

Subjects were recruited from a previous study (N = 54) relating to persistent sexual side effects of finasteride [4]. 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. All subjects provided written consent to this study which was approved by the university's institutional review board.

Design

Telephone or spoken Skype standardized interviews were conducted with all subjects as previously described [4]. Subjects were asked about demographic information, medical and psychiatric histories, medication use, and sexual function before and after finasteride. Follow-up e-mails were sent to participants 9–16 months (mean 14 months) after their initial interview dates to reassess their sexual function. Subjects were asked to readminister the Arizona Sexual Experience Scale (ASEX). The ASEX consists of five questions that measure core elements of sexual function: libido, arousal, erectile function, ability to reach orgasm, and orgasm satisfaction [12]. Each domain was measured bimodally, with a six-point Likert scale ranging from hyperfunction (1) to hypofunction (6). Sexual dysfunction was present if the total score was ≥19 or if any one item was ≥5 or if any three items were ≥4. The sensitivity and specificity of this instrument to identify sexual dysfunction were 82% and 90%, respectively [12]. The validation of ASEX consisted of a control group of 16 men with a mean age of 38 [12]. Their mean scores were 2.25 for sex drive, 2.19 for arousal, 2 for erection, 2.69 for orgasm, and 1.81 for orgasm satisfaction. The ASEX scale was found to have excellent reliability coefficients for internal

consistency and test–retest forms, accuracy in quantification of the major elements of sexual dysfunction, and brevity and ease of administration [13]. The scale could be administered regardless of a subject's sexual orientation or the availability of a sexual partner.

Statistical Analysis

All analyses were performed using SAS Version 9.2 (SAS Institute, Cary, NC, USA) using $\alpha = 0.05$ to declare a result as statistically significant. Paired two-tailed *t*-tests were used to test differences between individual items and the total scores on the ASEX questionnaire at three points in time: before finasteride, after finasteride at the interview, and after finasteride at reassessment.

Results

At the time of the interviews, the mean age of the subjects was 31 years and the mean age for beginning finasteride was 26 years. The majority of the subjects self-identified as white (80%) with the remainder identifying as Asian (13%) or other (7%). The self-identified sexual orientations of the subjects were 94% straight and 6% gay. Most (57%) of the subjects lived outside of the United States. The mean length of finasteride use was 23 months. At the time of the interviews, the duration of persistent sexual side effects was 3–6 months for 7% of subjects, 7–11 months for 9% of subjects, 1–2 years for 44% of subjects, 3–5 years for 19% of subjects, and 6 or more years for 20% of subjects.

Figure 1 shows the mean scores (with bars for 95% confidence intervals) for the five ASEX sexual dysfunction domains for subjects before finasteride, after finasteride at the time of the interview, and at reassessment. The mean total scores (±standard deviation) were 7.2 ± 2.0 before finasteride, 22.2 ± 2.6 after finasteride at the time of the interview, and 20.8 ± 3.6 at reassessment. As compared with "before finasteride," the total score and scores from all five domains were statistically significant at the reassessment with a *P* value < 0.0001. As compared with the "after finasteride at interview" time point, the total score and scores from sex drive, arousal, and erectile function were statistically significant at the reassessment with a *P* value < 0.01. At reassessment persistent sexual side effects continued to be present in 96% of subjects, and 89% of subjects continued to meet the definition of sexual dysfunction according to ASEX.

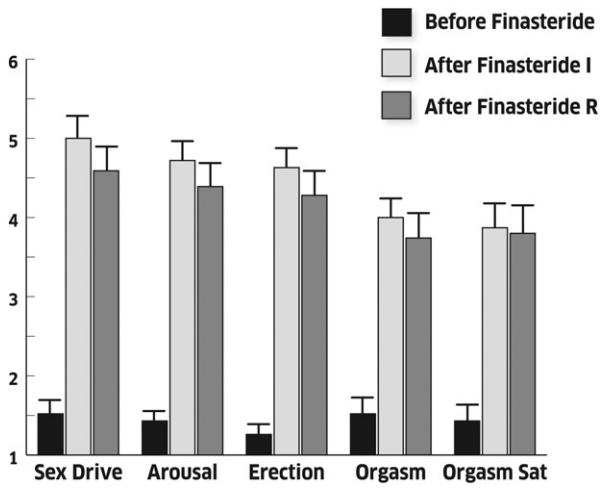

Figure 1 Arizona Sexual Experience Scale (ASEX) sexual dysfunction scores The mean ASEX sexual dysfunction scores (with 95% confidence intervals) fell between 1 (extremely strong/easily/satisfying) and 6 (absent/never). Differences in ASEX variables before finasteride, after finasteride at the interview (I) and after finasteride at reassessment (R) were compared using two-tailed paired *t*-tests. As compared with before finasteride, all five scores at the reassessment were statistically significant with a $P < 0.0001$. Orgasm Sat = orgasm satisfaction.

Two subjects had an improvement in their ASEX reassessment scores that approximated their baseline scores. One subject's scores were 5 before finasteride, 20 after finasteride at the interview and 6 at the reassessment. He reported that intramuscular testosterone has alleviated his symptoms. A second subject's scores were 9 before finasteride, 21 after finasteride at the interview and 13 at the reassessment. He reported no pharmacological therapy. Four other subjects did not meet the definition of sexual dysfunction (total score was ≥19 or if any one item was ≥5 or if any three items were ≥4) at reassessment as their scores were 15, 15, 17, and 17. Nonetheless, these scores were worse than their baseline scores of 7, 5, 11, and 8, respectively.

There were no differences in scores of sexual dysfunction based upon either the length of use of finasteride or the duration of the sexual side effects (results not shown).

In addition to the five sexual domains formally assessed, subjects volunteered additional signs and symptoms temporally associated with the use of finasteride. Men reported a change to semen quality and volume (11%), a change in penis size, curvature or reduced sensation (19%), a decrease in spontaneous erections (9%), a change in testicular size or pain (15%), and a change to mental abilities and/or depressive symptoms (17%).

At the time of the interview, subjects reported having tried pharmacological therapy with the phosphodiesterase 5 inhibitors (74%), testosterone (22%), human chorionic gonadotropin (9%), and clomiphene (7%). However, at the time of the interviews a smaller fraction of men were actually taking phosphodiesterase 5 inhibitors (22%), testosterone (11%), human chorionic gonadotropin (4%), and clomiphene (4%).

Discussion

In a group of 54 otherwise healthy former users of finasteride who developed persistent sexual side effects that lasted for at least 3 months, 96% continued to experience these effects when reassessed 9–16 months (mean 14 months) later, raising the possibility of permanent effects. Eighty-nine percent of subjects continued to meet the definition of sexual dysfunction according to ASEX. Neither the length of finasteride use nor the duration of the sexual side effects had any impact on the change in sexual dysfunction scores at reassessment.

To explain the long-term neurological effects of finasteride, it is possible that reduced concentrations of neuroactive steroids are affecting the plasticity of neuronal architecture in regions of the brain responsible for sexual function. Unfortunately, there are very little human data in this area due to the obvious issues of performing invasive neurosurgical procedures to sample brain tissue in living humans. Nonetheless, there is a body of interesting work from rodent models that may shed light on the mechanisms of finasteride's effects.

Finasteride crosses the blood-brain barrier and blocks the enzyme 5 α reductase type 1 which reduces the concentrations of three neuroactive steroids (DHT, 5α-dihydroprogesterone, and 5α-dihydrodeoxycorticosterone) and their downstream metabolites. Sexual desire is related to brain dopamine systems in the hypothalamus and limbic areas, especially the medial preoptic area, amygdala, and nucleus accumbens [14]. In adult male mice, 5 α reductase type 1 and 3α hydroxysteroid dehydrogenase colocalize in glutamatergic and GABAergic neurons in the cortex, hippocampus, olfactory bulb, amygdala, cerebellum, and thalamus [15].

Neuroactive steroids have been shown to modulate neurogenesis and neuronal survival. Neuroactive steroids protect neurons from apoptosis or programmed cell death [16]. Finasteride may therefore be reducing the number of neurons in particular regions of the brain. An important neurosteroid is ALLO, a metabolite of dihydroprogesterone. ALLO and 3α5α-tetrahydrodeoxycorticosterone are potent ligands of the inhibitory GABA-barbiturate receptor [17]. $GABA_A$ receptors have variable sensitivities to ALLO in the settings of neurosteroid withdrawal, stress, social isolation, and aging [18]. New neurons are dependent upon GABA signaling to form synaptic inputs with the existing circuitry in the mouse hippocampus [19]. A therapeutic injection of ALLO increased neuronal survival from 67 to 124 days and delayed neurological symptoms in mice with Niemann–Pick disease [20]. Furthermore, intracerebroventricular infusion of ALLO in rats increased dopamine levels in the nucleus accumbens, a region linked to sexual activity [21]. Less ALLO, as a consequence of finasteride, could alter GABAergic transmission which can have implications for neuronal progenitors and young neurons.

Curiously, the mechanism of irreversible tardive dyskinesias of phenothiazines may be similar to the mechanism of the persistent side effects of finasteride. In rats treated with haloperidol to induce orofacial dyskinesias, coadministration of progesterone prevented these movements [22]. Pretreatment of the rats with finasteride reversed the protective effect of progesterone, demonstrating an important role of the progesterone pathway and its metabolites such as ALLO [22].

In addition to ALLO, a decrease in androgens in the brain may affect neurogenesis by altering levels of growth factors such as brain-derived neurotrophic factor and vascular endothelial growth factor. Male mice treated with finasteride had lower levels of brain DHT and less neurogenesis in the hippocampus [10]. In castrated male rats, testosterone or DHT replacement can reverse a decrease in cell survival in the hippocampus [23].

Among the various types of sexual problems, erectile dysfunction has been the most studied thus far. In studies using castrated male rats, 5 α reductase inhibitors were found to have a detrimental effect on erectile function which was restored with DHT [24,25]. A recently published elegant series of experiments have further shown that a 30-day course of dutasteride to adult rats had a marked effect on erectile function. In vivo, rats exposed to dutasteride had a decreased ratio of intracavernosal pressure/mean arterial pressure in response to a 5 Hz voltage stimulation of the cavernosal nerve [26]. In vitro, strips of corpus cavernosum smooth muscle from the dutasteride-treated group showed

decreased relaxation to electrical field stimulation and acetylcholine [26]. Immunohistochemistry demonstrated increased collagen deposition and altered expression of neuronal and inducible nitric oxide synthase in the dutasteride group [26]. Another recently published study found that rats treated with finasteride for 4 weeks had a 26% reduction in the weight of their corpora cavernosa as compared with a control group [27]. This finding is consistent with the reports of genital shrinkage reported by some of the human subjects in this study.

In addition to the five sexual domains formally assessed by the ASEX, men reported a broad range of persistent signs and symptoms that point to the systemic effects of finasteride, as 5 α reductase is widely distributed throughout many organ systems. The most volunteered changes related to the urogenital system in terms of semen quality and decreased ejaculate volume, reduction in penis size, penile curvature or reduced sensation, fewer spontaneous erections, decreased testicular size, testicular pain, and prostatitis. Many subjects also noted changes to their mental abilities, sleeping patterns, and/or depressive symptoms. Many subjects reported a "disconnection" between the mental and physical aspects of sexual function.

The treatment and management of men with persistent sexual side effects is a real challenge for the treating clinician as no known pharmacological therapies exist to restore sexual function, other than the modest effects of the phosphodiesterase 5 inhibitors for erectile dysfunction. The one subject who reported dramatic improvement with intramuscular testosterone is the exception to the rule as almost all of the men who used testosterone in this study, as well as those who posted their stories on Propeciahelp.com, have not experienced sustained improvement in sexual function with testosterone. In addition, testosterone therapy does not seem biologically plausible as a treatment as men who take finasteride generally have normal testosterone levels.

The typical story of men with persistent sexual and other side effects is that they unsuccessfully seek help from various providers in multiple medical specialties. It is important for physicians to acknowledge with their patients the current limitations in medical knowledge, particularly as it relates to neuroscience. There is no known blood or imaging test to study or measure neuroactive steroids or their metabolites in different areas of the brain associated with sexual function. One possible avenue for future human research is the measurement of neuroactive steroids in the cerebrospinal fluid via lumbar puncture, a relatively low-risk procedure. Further valuable research could determine who would be susceptible to finasteride through genetic studies of polymorphisms of 5 α reductase and the androgen receptor. Further research with validated instruments is needed to study the nonsexual persistent side effects associated with finasteride. Although a large well-powered randomized control trial lasting several years would be the ideal way to determine the incidence of persistent side effects of finasteride, such a large trial is unlikely to be funded.

An important limitation to this study is selection bias, in that those most affected by finasteride are more likely to participate in a study such as this one. The results here may not apply to men with less severe sexual side effects who do not meet the ASEX definition of sexual dysfunction. Another limitation is recall bias for the retrospective reporting of baseline sexual function prior to starting finasteride. Recall bias is unlikely to be a significant factor as all of these younger men clearly remembered having a normal sexual function prior to starting finasteride. Despite this study's limitations, it is important for the medical community to be aware of this population of men who developed persistent sexual side effects associated with finasteride in the setting of no baseline sexual dysfunction or psychiatric conditions.

Conclusions

Men who developed persistent sexual and other side effects lasting for at least 3 months after discontinuing finasteride continue to have a high prevalence of sexual dysfunction for subsequent months or years. Further human research is needed to compliment the important basic science work showing the key role of neuroactive steroids in neurogenesis and neural survival. It is recommended that prescribers of finasteride, as well as potential users, be aware of the potential serious long-term risks of a medication used for a cosmetic purpose. To help men cope with their persistent symptoms, a careful mental health assessment should be performed.

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Corresponding Author: Michael S. Irwig, MD, Division of Endocrinology, Medical Faculty Associates, 2150 Pennsylvania Ave. NW, Suite 3-416, Washington, DC 20037, USA. Tel: 202-741-2489; Fax: 202-741-2490; E-mail: mirwig@mfa.gwu.edu

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Statement of Authorship

Category 1

(a) Conception and Design
Michael S. Irwig
(b) Acquisition of Data
Michael S. Irwig
(c) Analysis and Interpretation of Data
Michael S. Irwig

Category 2

(a) Drafting the Article
Michael S. Irwig
(b) Revising It for Intellectual Content
Michael S. Irwig

Category 3

(a) Final Approval of the Completed Article
Michael S. Irwig

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