ORIGINAL RESEARCH—MEN'S SEXUAL HEALTH

Persistent Sexual Side Effects of Finasteride for Male Pattern Hair Loss

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DOI: 10.1111/j.1743-6109.2011.02255.x

ABSTRACT

Introduction. Finasteride has been associated with reversible adverse sexual side effects in multiple randomized, controlled trials for the treatment of male pattern hair loss (MPHL). The Medicines and Healthcare Products Regulatory Agency of the United Kingdom and the Swedish Medical Products Agency have both updated their patient information leaflets to include a statement that "persistence of erectile dysfunction after discontinuation of treatment with Propecia has been reported in post-marketing use."

Aim. We sought to characterize the types and duration of persistent sexual side effects in otherwise healthy men who took finasteride for MPHL.

Methods. We conducted standardized interviews with 71 otherwise healthy men aged 21–46 years who reported the new onset of sexual side effects associated with the temporal use of finasteride, in which the symptoms persisted for at least 3 months despite the discontinuation of finasteride.

Main Outcome Measures. The types and duration of sexual dysfunction and the changes in perceived sexual frequency and sexual dysfunction score between pre- and post-finasteride use.

Results. Subjects reported new-onset persistent sexual dysfunction associated with the use of finasteride: 94% developed low libido, 92% developed erectile dysfunction, 92% developed decreased arousal, and 69% developed problems with orgasm. The mean number of sexual episodes per month dropped and the total sexual dysfunction score increased for before and after finasteride use according to the Arizona Sexual Experience Scale ($P < 0.0001$ for both). The mean duration of finasteride use was 28 months and the mean duration of persistent sexual side effects was 40 months from the time of finasteride cessation to the interview date. Study limitations include a post hoc approach, selection bias, recall bias for before finasteride data, and no serum hormone levels.

Conclusion. Physicians treating MPHL should discuss the potential risk of persistent sexual side effects associated with finasteride. **Irwig MS and Kolukula S. Persistent sexual side effects of finasteride for male pattern hair loss. J Sex Med 2011;8:1747–1753.**

Key Words. Erectile Dysfunction; Finasteride; Libido; 5 Alpha Reductase Inhibitor; Propecia; Sexual Side Effects

Introduction

Finasteride is a 5α reductase inhibitor that decreases the conversion of testosterone to the more potent androgen dihydrotestosterone (DHT) in many tissues throughout the body. Two 5α reductase inhibitors have clinical applications for the treatment of male pattern hair loss (MPHL) and for benign prostatic hypertrophy, the more commonly prescribed condition for these medications. In multiple randomized trials with placebo controls, finasteride has been associated with an increased rate of sexual dysfunction. In the trials for MPHL, the sexual side effects were reported to resolve with time or with discontinuation of finasteride.

For MPHL, sexual dysfunction data are available from two pharmaceutical-funded trials. In two 1-year studies of 1,553 men, as compared to the placebo group, the finasteride 1 mg/day users

experienced more sexual adverse events (4.2 vs. 2.2%, $P < 0.05$) which included decreased libido (1.9 vs. 1.3%), decreased ejaculate volume (1.0 vs. 0.4%), and erectile dysfunction (1.4 vs. 0.9%) [1]. A small percentage of finasteride (1.4%) and placebo (1.0%) subjects withdrew from the studies due to the sexual adverse events. The rate of sexual adverse events was very similar in phase III clinical studies conducted by Merck in which 1,879 men were randomized to 1 mg/day of finasteride or placebo for 1 year [2]. As compared to the placebo group, the finasteride users reported more sexual adverse events (3.8 vs. 2.1%, $P = 0.04$) which included decreased libido (1.8 vs. 1.3%), ejaculation disorders (1.2 vs. 0.7%), and erectile dysfunction (1.3 vs. 0.7%). Finally, in a trial of 416 men for 24 weeks, subjects on finasteride 5 mg or different doses of dutasteride (0.05 to 2.5 mg) experienced more dysfunction with libido and ejaculation as compared to the placebo group [3]. There was no difference in erectile dysfunction.

The randomized, controlled trials involving subjects with benign prostate hypertrophy have been larger and longer than those for MPHL. In a 1-year study involving 2,342 men, finasteride users were more likely than those taking placebo to develop decreased libido (3.1 vs. 1.2%), impotence (6.8 vs. 3.2%), and ejaculation disorders (2.3 vs. 0.5%) [4]. Similar adverse event rates were reported in a 1-year study of 1,657 men randomized to either finasteride 1 mg or 5 mg or placebo [5]. This study also reported rates of orgasm dysfunction which were higher in the men who used finasteride 1 mg (0.4%) and 5 mg (0.5%) as compared to the controls (0.2%). In the 2-year PROSPECT Study of 613 men, those in the finasteride 5 mg arm had more ejaculation disorders (7.7 vs. 1.7%) and impotence (15.8 vs. 6.3%) than those on placebo [6]. Finally, in a 4-year study of 3,040 men, sexual adverse events were increased in the finasteride group, as compared to the placebo group, but only during the first year of the study (15 vs. 7%) [7]. In men who discontinued the study due to a sexual adverse event, 41–50% experienced resolution of the event after discontinuing the finasteride or placebo.

The Medicines and Healthcare Products Regulatory Agency of the United Kingdom and the Swedish Medical Products Agency have both updated their patient information leaflets to include a statement that "persistence of erectile dysfunction after discontinuation of treatment with Propecia has been reported in post-marketing use." These agencies also report that the frequencies of this possible side effect, and those of testicular pain and infertility, are unknown. To the best of our knowledge, there are no studies that characterize the men who have developed persistent sexual dysfunction associated with finasteride for MPHL.

Aims

We sought to characterize the types and duration of persistent sexual side effects in otherwise healthy men who took finasteride for MPHL. The changes in sexual frequency and sexual dysfunction score between pre- and post-finasteride use were compared.

Methods

Design

Telephone or spoken Skype standardized interviews were conducted with individual subjects who were asked demographic questions about their age, ethnicity, country of residence, and sexual orientation. Information about finasteride included the dose, name of medication used, type of prescriber, and duration of use. The length of persistent sexual side effects was calculated by using the interval between the time of the interview and when finasteride was stopped as most subjects experienced a gradual decline in their sexual function such that it would be nearly impossible for them to recall a precise date when their sexual function began to change. This duration of persistent sexual side effects is an underestimate of the true duration, as subjects continue to suffer from the effects after the dates of the interviews. Subjects were asked to quantify how many all-inclusive sexual experiences, including masturbation, they had per month before and after using finasteride. Subjects were asked to list any prescription medications used before, during, or after finasteride use. Subjects were also asked about medical management of their sexual dysfunction.

Participants

Subjects were recruited from one of the author's clinical practice, from word of mouth, and from Propeciahelp.com, an internet forum about unresolved finasteride side effects with over 1,400 members. A description of the study and a consent form were posted on the Web site Propeciahelp.com. Forum subjects who were interested in participating emailed the study and returned a signed copy of the study consent form. The institutional review board of George Washington University

approved the study. Individual standardized interviews were conducted with 92 subjects by a board-certified endocrinologist via the telephone or Skype.

Inclusion criteria were men over age 18 years who developed new sexual side effects on finasteride which persisted for at least 3 months after discontinuation of the medication. The indication for finasteride was MPHL and all subjects began and finished finasteride use prior to age 40. Exclusion criteria were baseline sexual dysfunction, baseline psychiatric or medical conditions, and baseline use of nontopical prescription medications other than a short course of antibiotics. Subjects with a history of psychiatric disorders or previous use of psychiatric medications were also excluded. Out of the 92 interviews conducted, 17 subjects were excluded for one of the exclusion criteria. Four additional subjects were excluded based on their current scores on the Arizona Sexual Experience Scale (ASEX) which did not meet the threshold for sexual dysfunction.

Main Outcome Measures

In terms of selecting a validated instrument in which to assess sexual dysfunction, we chose the ASEX which was designed to measure five core elements of sexual function: libido, arousal, erectile function, ability to reach orgasm, and orgasm satisfaction [8]. Each domain was measured bimodally, with a 6-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 scale to identify sexual dysfunction were 82% and 90%, respectively [8]. The male control group used in validating ASEX consisted of 16 men with a mean age of 38 years. 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. Another male historical control group used to validate ASEX were 25 Turkish men (mean age 36) with mean scores of 1.52 for sex drive, 1.84 for arousal, 1.92 for erection, 2.52 for orgasm, and 1.24 for orgasm satisfaction [9]. 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 [10]. The scale could be administered regardless of a subject's sexual orientation or the availability of a sexual partner. Using the ASEX, subjects were asked to rate their current sexual function and to retrospectively rate their baseline function prior to starting finasteride.

Statistical Analysis

Statistical analysis was performed with SAS (Cary, NC, USA). Wilcoxon signed-rank tests were performed for the total ASEX scores and sexual frequencies given the non-normal distribution of these variables. Wilcoxon signed-rank tests (two-tailed) were also performed for the comparisons between before and after finasteride use for individual ASEX items.

Results

The demographic characteristics, sexual function of the subjects, and finasteride information are shown in Table 1. The mean age of subjects was

Table 1 Subject characteristics, sexual function, and finasteride information

	N = 71 (%)		
Demographic characteristics			
Mean age, years (range 21–46)	31.3		
Ethnicity			
White	59 (83)		
Asian	7 (10)		
Latino	2 (3)		
Other	3 (4)		
Location			
United States	36 (51)		
International	35 (49)		
Sexual orientation			
Straight	68 (96)		
Gay	3 (4)		
	Before	After	*P* value
Sexual function before and after finasteride use			
Sexual frequency per month (SD)	25.8 (18.0)	8.8 (7.1)	<0.0001
ASEX questionnaire total score (SD)	7.4 (2.3)	21.6 (3.4)	<0.0001
Finasteride information			
Mean age began, years	25.8		
Length of use			
<1 month	7 (10)		
1–3 months	11 (15)		
3–6 months	7 (10)		
6–12 months	9 (13)		
1–5 years	24 (34)		
Over 5 years	13 (18)		
Duration of persistent sexual side effects from finasteride cessation to interview date			
3–6 months	5 (7)		
7–11 months	4 (6)		
1–2 years	30 (42)		
3–5 years	18 (25)		
6 or more years	14 (20)		

31.3 years (range 21–46) and the mean age for beginning finasteride was 25.8 years (range 17–38). In terms of education level, five subjects had high school or less, nine attended some college, 38 completed a Bachelor's degree and 19 had a Master's degree or higher. Sexual frequency declined from 25.8 ± 18.0 to 8.8 ± 7.1 episodes per month before and after finasteride, respectively ($P < 0.0001$). The high level of sexual frequency reflects that many young men reported masturbating at least once a day. Sexual dysfunction scores calculated from the ASEX questionnaire increased from 7.4 ± 2.3 before finasteride to 21.6 ± 3.4 after finasteride at the time of the interview ($P < 0.0001$). The prevalence of sexual dysfunction by item was 94% for low libido, 92% for erectile dysfunction, 92% for decreased arousal, and 69% for problems with orgasm. Most sexual dysfunction began while subjects were on finasteride, but some reported the onset shortly after discontinuing the medication.

The mean length of finasteride use was up to 28 months, as some subjects did not take the medication consistently. Forty-three subjects used finasteride 1 mg tablets, 21 subjects broke finasteride 5 mg into four pieces, and seven subjects used lower or different doses at various times. Finasteride was prescribed by a dermatologist/hair specialist for 36 subjects, by a generalist/primary care physician for 27 subjects, and by a different provider or obtained via the Internet for eight subjects.

The change in sexual dysfunction scores before and after finasteride for individual ASEX items is shown in Figure 1, along with scores from a historical control group [9]. The mean sexual dysfunction scores before finasteride ranged from 1.35 to 1.55 and were similar to those from a historical control group. The mean sexual dysfunction scores after finasteride were dramatically increased in all five ASEX items, ranging from 3.89 to 4.82. Differences in individual ASEX items before and after finasteride were statistically significant (P value of <0.0001).

For management of their sexual dysfunction, subjects sought care with a general physician (60), endocrinologist (57), urologist (47), and mental health professional (34). For medical therapy of the sexual dysfunction, subjects reported trying a phosphodiesterase type 5 inhibitor (55), testosterone (20), human chorionic gonadotropin (9), and clomiphene (9).

Although the main focus of this study was sexual dysfunction, subjects did volunteer other side effects that they believed were associated with finasteride use including fatigue (27), cognitive difficulties (26), depression (20), anxiety (20), and decreased semen volume (9).

Discussion

This study characterizes the types and duration of persistent sexual side effects that began in 71 healthy men taking finasteride for the treatment of MPHL. At the time of the standardized interviews, the mean duration of the persistent sexual side effects was 40 months, with 20% of subjects reporting durations of over 6 years. Most men developed sexual dysfunction in multiple domains with 94% experiencing low libido, 92% experiencing erectile dysfunction, 92% experiencing decreased arousal, and 69% experiencing problems with orgasm.

While this study serves an important purpose to document a risk of persistent sexual adverse events with finasteride for MPHL, the true incidence of these events is unknown as this is a post hoc approach. According to the randomized controlled trials by GlaxoSmithKline and Merck, the actual number of subjects experiencing adverse sexual

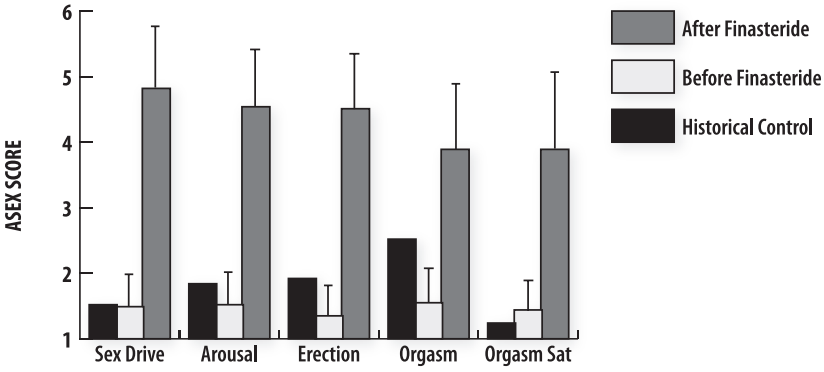

Figure 1 The mean ASEX sexual dysfunction scores (with standard deviation bars) fell between 1 (extremely strong/easily/satisfying) and 6 (absent/never). Differences in ASEX variables before and after finasteride were tested using the Wilcoxon Signed-Rank Test (two-tailed) which revealed a P value of <0.0001 for all five variables. The historical control group was 25 healthy males with a mean age of 36. Orgasm sat = orgasm satisfaction.

events, in either the treatment or placebo groups, was <8% and <3%, respectively [1,3]. Assuming that the vast majority of these events resolved, the incidence of persistent sexual events in finasteride users would probably be less than 1%. Nonetheless, it is the persistence of these sexual side effects that is the most concerning finding. The looming question for all the subjects is whether their sexual function will ever recover. Many of the study participants have developed anxiety and depression as a consequence of their sexual dysfunction and all reported a significantly decreased quality of life, especially with dating and intimacy.

What are the potential biological mechanisms underlying the sexual dysfunction associated with finasteride? Traish and colleagues have recently published a review on this topic [11]. Libido and orgasm are perceived in the brain, where receptors for androgens and progesterones are widely distributed, particularly in the hypothalamus and amygdala. These sex hormone receptors are present not only in neurons, but also in glial cells (astrocytes and oligodendrocytes) which play an important role in neuron development. 5α reductase activity is also found in neurons, oligodendrocytes, and astrocytes [12]. Neuronal and glial cell development may be influenced by steroids metabolized by 5α reductase [13]. Finasteride does cross the blood–brain barrier and can inhibit the production of DHT throughout the central nervous system (CNS) [14]. It is biologically plausible that a lack of DHT or another 5α-reduced hormone is responsible for a decrease in libido and/or orgasm. Our understanding of this area is unfortunately limited due to the complexity of 5α reductase in the brain and very few studies in humans. Studying the effects of a particular hormone is difficult as one hormone (i.e., progesterone) can affect the transcriptional activity of other steroid receptors.

Celotti and colleagues conducted an extensive review of 5α reductase in the brain [15]. This area is challenging to study because steroid hormones are produced in different tissues and they are converted into many metabolites. The brain not only utilizes testosterone and DHT produced by peripheral glands, but the brain can also synthesize neurosteroids which then act via intracrine effects or paracrine effects on neighboring cells. 5α reductase also exists in at least two isoforms that vary in terms of their affinity for hormones, optimal pH, and sensitivity to inhibitors [16]. In the CNS type 1 is the primary isoform which is present in areas rich in white matter, including the midbrain, pons, spinal cord, corpus callosum, anterior commissure, and optic chiasm. 5α reductase is also found in the peripheral nervous system [12].

Although the conversion of testosterone to DHT may play a key role in normal sexual function, another possible player could be progesterone and its metabolites. It turns out that 5α reductase not only converts testosterone to dihydrotestosterone, but it also irreversibly reduces glucocorticoids and progestins: deoxycorticosterone to 5α-dihydrodeoxycorticosterone and progesterone to 5α-dihydroprogesterone. In fact, both human and rat 5α reductases showed a greater preference for progesterone as a substrate over testosterone and androstenedione [16]. Progesterone is synthesized locally in the brain either de novo or from circulating precursors and has been shown to promote CNS myelination [17]. Progesterone and its metabolites (i.e., tetrahydroprogesterone) can modulate several neurotransmitter receptors such as $GABA_A$, sigma-1, and nicotinic acetylcholine [17]. To further complicate the picture, 5α-reduced metabolites may be further converted to different metabolites via 3α hydroxysteroid dehydrogenase.

Regarding 5α reductase and erectile dysfunction, Canguven and Burnett reviewed the literature [18]. While not all studies were in agreement, several showed an important link between DHT inhibition and erections. In a study of castrated rats, those on testosterone replacement had more erections and a greater erectile response to electrical stimulation than the rats receiving testosterone plus a 5α reductase inhibitor [19]. In a study of elderly men with low testosterone levels, treatment with DHT improved parameters of nocturnal penile tumescence [20]. Likewise, in a randomized, placebo-controlled trial of older men with andropause symptoms and serum total testosterones <15 nmol/L, men in the DHT group had an improved ability to maintain erections as compared to men taking placebo [21].

Our study has several limitations. Most importantly, the retrospective nature of this study does not allow us to estimate what percentage of prospective finasteride users would develop persistent sexual side effects. A second limitation is selection bias in which those subjects experiencing more severe side effects, or those for whom sexuality is a more significant aspect of their life, would be more likely to participate in a study looking at sexual parameters. Another limitation is recall bias, in which subjects may not have remembered certain details such as the exact month when they started

finasteride. Furthermore, no serum hormone levels were measured. Although this study does not prove that finasteride caused persistent sexual side effects, the validity of our findings is supported by the known sexual side effects of finasteride in randomized, controlled trials, the temporal association of the onset of sexual dysfunction with the use of finasteride in otherwise healthy men, and the biological plausibility of the role of androgens and progestins in areas of the brain and peripheral nervous system associated with libido, orgasm, and erectile function.

Further research is needed with finasteride to determine the true incidence of persistent sexual side effects, which subjects are susceptible to these effects, and the mechanisms by which altered levels of steroid hormones play a role in the dysfunction.

Until these questions are resolved, it is prudent for patients contemplating the use of a 5α reductase inhibitor to be made aware of and consider the possibility of persistent sexual side effects.

Conclusions

A subset of otherwise healthy men taking finasteride for MPHL developed persistent sexual side effects in temporal association with the medication. Most men developed sexual dysfunction in multiple domains with 94% experiencing low libido, 92% experiencing erectile dysfunction, 92% experiencing decreased arousal, and 69% experiencing problems with orgasm. The mean duration of the persistent sexual side effects was at least 40 months, with 20% of subjects reporting durations of over 6 years. The mean number of sexual episodes per month dropped from 25.8 before finasteride to 8.8 after finasteride ($P < 0.0001$). The total sexual dysfunction score increased from 7.4 to 21.6 for before and after finasteride use ($P < 0.0001$). Physicians treating MPHL should discuss the potential risk of persistent sexual side effects associated with finasteride.

Acknowledgments

The authors thank the study subjects for their willingness to participate in a study dealing with sensitive topics. We also thank Ameeka Pannu for her assistance with subject enrollment and data coding, Sam Simmens, PhD, for statistical analysis, and Thomas Kohout for graphic design.

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Conflict of Interests: None.

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