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Investigation of the Plausibility of 5-Alpha-Reductase Inhibitor Syndrome

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Key Words

Dutasteride · Finasteride · Side effects · Psychiatric adverse effects · Physical adverse effects · Permanent sexual dysfunction · Psyche

Abstract

Postfinasteride syndrome (PFS) is a term recently coined to characterize a constellation of reported undesirable side effects described in postmarketing reports and small uncontrolled studies that developed during or after stopping finasteride treatment, and persisted after drug discontinuation. Symptoms included decreased libido, erectile dysfunction, sexual anhedonia, decreased sperm count, gynecomastia, skin changes, cognitive impairment, fatigue, anxiety, depression, and suicidal ideation. The aim of this study is to review the existing medical literature for evidence-based research of permanent sexual dysfunction and mood changes during treatment with 5-alpha-reductase inhibitors including finasteride and dutasteride.

Postfinasteride Syndrome

Postfinasteride syndrome (PFS) is a term recently coined to characterize a constellation of reported undesirable side effects described in postmarketing reports and small uncontrolled studies that developed during or after stopping finasteride treatment, and persisted after drug discontinuation. Symptoms included decreased libido, erectile dysfunction, sexual anhedonia, decreased sperm count, gynecomastia, skin changes, cognitive impairment, fatigue, anxiety, depression, and suicidal ideation.

The Postfinasteride Syndrome Foundation, which was created to raise awareness about PFS, recently sent an email to dermatologists practicing in the United States to inform them about the syndrome and its inclusion into the National Institute of Health's Genetic and Rare Diseases Information Center (GARD) even though inclusion in the GARD is not an official recognition of PFS by the NIH as explained in the website disclaimer. The NIH is currently founding a study on the epidemiology of adverse events of 5-alpha-reductase inhibitors (5αRIs) specifically focused on persistent side effects.

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According to information from the website, the Postfinasteride Syndrome Foundation is also funding research projects seeking to elucidate the nature of the condition including hormonal, genetic, and epigenetic causes. The foundation's website lists a number of physicians that collaborate with them including urologists, endocrinologists, psychiatrists and psychologists, but no dermatologists. The aim of this study is to review the existing medical literature for evidence-based research of permanent sexual dysfunction and mood changes during treatment with 5αRIs including finasteride and dutasteride.

Materials and Methods

A MEDLINE search (PubMed 1950–2016) was performed to identify the cases described in the literature. The following MEDLINE search terms were used: 'finasteride side effects', 'finasteride side*', 'finasteride sexual', 'finasteride side effects alopecia', 'finasteride gynecomastia', 'finasteride male breast cancer', 'finasteride cognitive effects', 'finasteride anxiety', 'finasteride depression', 'finasteride suicidal ideation', 'finasteride syndrome', 'post-finasteride syndrome', 'dutasteride side effects', 'dutasteride side*', 'dutasteride sexual', 'dutasteride side effects alopecia', 'dutasteride gynecomastia', 'dutasteride male breast cancer', 'dutasteride cognitive effects', 'dutasteride anxiety', 'dutasteride depression', and 'dutasteride suicidal ideation'. We included case reports, case series, review articles, and clinical trials which specifically mentioned side effects of finasteride and dutasteride use. After the initial search was performed, we reviewed the bibliographies of all manuscripts to discover any cases not uncovered in our initial MEDLINE search. We also reviewed the information obtained online including the content on the Post-Finasteride Syndrome Foundation website (www.pfsfoundation.org).

Level of evidence of the studies was graded from high to very low according with the American College of Physicians outcome study grading system. This system rates quality of studies in accordance with the underlying methodology in four categories:

1 High, including randomized trials or double-upgraded observational studies.
2 Moderate, including downgraded randomized trials or upgraded observational studies.
3 Low, including double-downgraded randomized trials or observational studies.
4 Very low, including triple-downgraded randomized trials or downgraded observational studies or case series/case reports.

Studies can be downgraded in presence of factors that may decrease the quality level of a body of evidence. These include:

1 Limitations in the design and implementation of available studies suggesting high likelihood of bias.
2 Indirectness of evidence (indirect population, intervention, control, outcomes).
3 Unexplained heterogeneity or inconsistency of results (including problems with subgroup analysis).
4 Imprecision of results (wide confidence intervals).
5 High probability of publication bias.

Results

Sexual Adverse Effects

Sexual side effects in men who have been taking finasteride (1 and 5 mg) and dutasteride (0.5 mg) are well documented and include decreased libido, erectile dysfunction, and ejaculatory dysfunction [1–11] (table 1).

Persistent Sexual Side Effects

Persistent sexual side effects were discussed in 1 high-quality randomized trial and 2 low-quality uncontrolled studies (table 1). The Proscar Long-Term Efficacy and Safety Study (PLESS), a 4-year, double-blind, placebo-controlled study of 3,040 men with BPH evaluated the efficacy of finasteride (5 mg/day) as well as the incidence of sexual adverse events [4]. Subjects completed a questionnaire at screening pertaining to their history of sexual dysfunction. At screening, 46% of patients in each treatment group reported some history of sexual dysfunction, with a higher rate expected given the older age of the study population (aged 45–78 years). During year 1 of the study, 15% of total finasteride subjects (n = 1,524) and 7% of total placebo subjects (n = 1,516) experienced sexual adverse events, including decreased libido, erectile dysfunction, and decreased ejaculate volume [4]. During years 2–4, the incidence of new sexual adverse events (decreased libido, erectile dysfunction, or ejaculation disorders) was the same in each group (7% in each group) [4, 8]. The drug-related sexual adverse event profile for subjects who took finasteride was similar for subjects with or without a history of sexual dysfunction at baseline. A total of 4% of finasteride and 2% of placebo subjects discontinued the study due to sexual adverse events. A surprising finding in this study was that in these subjects who withdrew from the study due to sexual adverse events, 50% of finasteride users experienced continual sexual side effects after discontinuing finasteride, while 59% of placebo subjects noted continual sexual side effects. Thus, in this study persistent sexual side effects were reported more in placebo subjects than in patients treated with finasteride.

Persistent sexual side effects following finasteride use were also reported in 2 uncontrolled studies. Irwig and Kolukula [12] interviewed 71 men with male pattern hair loss (MPHL) (aged 21–46 years) who reported new-onset sexual side effects that persisted for more than 3 months after discontinuation of finasteride. The mean duration of finasteride use was 28 months and the mean duration of persistent sexual side effects was 40 months at the standardized interview date. Patients were recruit-

Table 1. Side effects of the 5αRIs finasteride and dutasteride

Source	Dosage	n	Side effect	Placebo side effect	Persistent effects	Level of evidence	ACP outcome study grading
Sexual side effects							
Nickel et al. [10], PROSPECT Study	Finasteride (5 mg/day)	472	Ejaculation disorder (7.7%), impotence (15.8%)	Ejaculation disorder (1.7%), impotence (6.3%)	No	Double-blind, 2-year, randomized, placebo-controlled multicenter study	High
McConnell et al. [11], Finasteride Long-Term Efficacy and Safety Study Group	Finasteride (5 mg/day)	2,070	Decreased libido (6.4%), impotence (8.1%), decreased ejaculate volume (3.7%), ejaculation disorder (0.8%)	Decreased libido (3.4%), impotence (3.7%), fecreased ejaculate volume (0.8%), ejaculation disorder (0.1%)	No	Double-blind, 4-year, randomized, placebo-controlled trial	High
Moinpour et al. [9], The Prostate Cancer Prevention Trial	Finasteride (5 mg/day)	17,313	Sexual Activity Scale score 3.21 points higher in the finasteride arm at month 6 and 2.11 points higher in the finasteride arm at year 7	Scored lower on Sexual Activity Scale, indicating better sexual function	No	Double-blind, randomized, placebo-controlled study; Sexual Activity Scale (0–100) assessed sexual dysfunction	High
The Finasteride Male Pattern Hair Loss Study	Finasteride (1 mg/day)	1,553	Adverse events related to sexual function (4.2%), erectile dysfunction (1.4%), decreased ejaculatory volume (1.0%), decreased libido (1.9%)	Adverse events related to sexual function (2.2%), erectile dysfunction (0.9%), fecreased ejaculatory volume (0.4%), decreased libido (1.3%)	No	Two replicate, 1-year, double-blind, randomized, placebo-controlled studies	High
	Finasteride (1 mg/day)	326	Sexual adverse effects (2%)	Sexual adverse effects (2%)	No	Double-blind, 1-year, placebo-controlled, randomized study	High
Roehrborn et al. [38], CombAT trial	Dutasteride (0.5 mg)	3,234	Erectile dysfunction (7%), decreased libido (3%)	Erectile dysfunction (5%), decreased libido (2%)	No	Double-blind, randomized, placebo-controlled trial	High
Andriole et al. [37], REDUCE trial	Dutasteride (0.5 mg/day)	6,729	Erectile dysfunction (9%), decreased libido (3.3%)	Erectile dysfunction (5.7%), decreased libido (1.6%)	No	Multicenter, double-blind, 4-year, randomized, placebo-controlled study	High
	Dutasteride (0.5 mg)	148	Adverse events (6.9%), sexual dysfunction (4.1%)	Adverse events (9.3%), sexual dysfunction (2.7%)	No	Double-blind, randomized, placebo-controlled phase III trial	High
Kaplan et al. [40]	Finasteride (5 mg) vs. dutasteride (0.5 mg/day)	378	Dutasteride: erectile dysfunction (5.1%), ejaculatory dysfunction (2.4%), decreased libido (2.7%)	Finasteride: erectile dysfunction (2.1%), ejaculatory dysfunction (1.8%), decreased libido (1.4%)	No	Retrospective 5-year study comparing dutasteride to finasteride	High
Wessells et al. [4], PLESS trial	Finasteride (5 mg/day)	3,040	Sexual adverse events (15%)	Sexual adverse events (7%)	Yes	Double-blind, 4-year, placebo-controlled study	High
Mondaini et al. [15]	Finasteride (5 mg/day)	107	Informed of sexual side effects: erectile dysfunction (30.9%), decreased libido (23.6%), ejaculation disorders (16.3%)	Not informed: erectile dysfunction (9.6%), decreased libido (7.7%), ejaculation disorders (5.7%)	No	Blinded control in which cases were informed of possible sexual side effects before finasteride therapy and controls were not informed of sexual side effects	High
Irwig and Kolukula [12]	Finasteride (1 mg/day)	71	Low libido (94%), Erectile dysfunction (92%), decreased arousal (92%), problems with orgasm (69%)	n.a. – no control group	Yes	Two uncontrolled studies	Low
Psychiatric side effects							
Ali et al. [27]	Finasteride (1 mg/day)	4,910	39 reports of suicidal ideation in a total of 4,910 total adverse reports of finasteride (39/4,910) (0.79%)	n.a. – no control group	n.a.	Retrospective pharmacovigilance disproportionality analysis	Moderate
Caruso et al. [26]	Finasteride (1–1.25 mg/day)	19	Different neuroactive steroid profile in CSF and plasma compared to controls	Different neuroactive steroid profile compared to cases	Yes	Case-control study	Moderate
Rahimi-Ardabili et al. [28]	Finasteride (1 mg/day)	128	HADS-D score increased by 0.57 points, BDI depression score increased by 0.69 points	n.a. – no control group	No	Two self-administered questionnaires	Low
Irwing et al. [29]	Finasteride (1 mg/day)	61	Depression symptoms (75%), moderate/severe depressive symptoms (64%), suicidal thoughts (44%)	Depression symptoms (10%), moderate/severe depressive symptoms (0%), suicidal thoughts (3%)	Yes	Self-administered questionnaire	Low

Table 2 (continued)

Source	Dosage	n	Side effect	Placebo side effect	Persistent effects	Level of evidence	ACP outcome study grading
Ganzer et al. [30]	Finasteride (1 mg/day)	131	Elevated anxiety (74%), depressed affect (73%), sleep disturbances (58%), suicidal ideations/negative thoughts (63%)	n.a. – no control group	Yes	Self-administered questionnaire	Low
Ganzer and Jacobs [32]	Finasteride (1 mg/day)	97	Moderate to severe depression (39%), extreme depression (5%), moderate anxiety (16%)	n.a. – no control group	Yes	Self-administered questionnaire	Low
Altomare and Capella [31]	Finasteride (1 mg/day)	19	Impairment of sociofamilial relations (89%), eating behavior changes (anorexia) (47%), sleep behavior changes: insomnia (73%) or hypersomnia (11%), concomitant anxiety (32%)	n.a. – no control group	No	Retrospective case series of 19 subjects that developed moderate to severe depression on finasteride therapy	Very low
Physical side effects							
Thompson et al. [35], Prostate Cancer Prevention Trial	Finasteride (5 mg/day)	9,457	Gynecomastia (4.5%)	Gynecomastia (2.8%)	Yes	Double-blind, 7-year, randomized, placebo-controlled study	High
McConnell et al. [41], Medical Therapy of Prostatic Symptoms	Finasteride (1 mg/day)	2,291	Finasteride either alone or with doxazosin: 1,554 total subjects; male breast cancer in (n = 4/1,554) (0.26%)	737 total placebo subjects; no male breast cancer	Yes	Double-blind, placebo-controlled trial	High
McConnell et al. [11], PLESS	Finasteride (5 mg/day)	3,040	No male breast cancer (n = 0)	Male breast cancer (n = 2)	Yes	Double-blind, 4-year, randomized, placebo-controlled study	High
Kaplan et al. [40]	Dutasteride (0.5 mg/day)	378	Dutasteride: self-reported breast tenderness and breast enlargement (3.5%)	Finasteride : self-reported breast tenderness and breast enlargement (1.2%)	Yes	Retrospective 5-year study comparing dutasteride to finasteride	Moderate
Chiriacò et al. [45]	Finasteride (0.5 mg/day; 5.1%) (1.0 mg/day; 22.8%) (1.25 mg/day; 72.1%)	79	Loss of penis sensitivity (87.3%), decreased penile temperature (78.5%), penile flaccidity/wrinkling (68.4%), loss of scrotum sensitivity (62.0%), reduction in penile dimension (65.8%), loss of body muscle tone and mass (51.9%)	n.a. – no control group	Yes	Observational-retrospective study	Low

ed from the authors' clinical practice and the website www.propeciahelp.com. The Arizona Sexual Experience Scale (ASEX) was used during subject interviews to assess sexual dysfunction and was designed to measure 5 core elements of sexual function: libido, sexual arousal, erectile function, ability to reach orgasm, and satisfaction of orgasm [12, 13]. Scores range from 5 to 30, with sexual dysfunction present if the total ASEX score is ≥19. ASEX scores increased from 7.4 ± 2.3 before finasteride use to 21.6 ± 3.4 after finasteride use at the time of interview [12]. The prevalence of sexual dysfunction was 94% for low libido, 92% for erectile dysfunction, 92% for decreased arousal, and 69% for problems with orgasm [12]. The majority of patients experienced sexual adverse events while on finasteride, but some subjects reported onset after discontinuing therapy. In a subsequent study by Irwig [14], 54 subjects from the prior study with persistent sexual side effects associated with finasteride were reassessed after a mean of 14 months following the last interview. A total of 89% of these subjects had ASEX scores of sexual dysfunction, raising the possibility of permanent effects connected with finasteride in a small subset of patients.

Possible Placebo Effect

A significant placebo effect has been detected in patients who were informed of potential sexual side effects before taking finasteride [15]. In a blinded control study,

107 subjects with a clinical diagnosis of BPH were randomized to receive finasteride (5 mg/day) for 1 year with 1 group receiving counseling (n = 55) on the drug sexual side effects and the other group not receiving such counseling (n = 52). The phrase used to inform counseled patients was this drug 'may cause erectile dysfunction, decreased libido, problems of ejaculation but these are uncommon'. Those patients informed of the potential sexual side effects of the drug reported a significant higher proportion of sexual side effects (43.6%) as compared to those who were not informed (15.3%). The incidence of erectile dysfunction, decreased libido, and ejaculation disorders was 9.6, 7.7, and 5.7% for patients not informed, and 30.9, 23.6, and 16.3% for informed patients [15].

Psychiatric Adverse Effects

The physiological basis of mood disorders caused by 5αRIs has been associated with the dysregulation of neurosteroids and androgen deficiency [16, 17]. Neurosteroids, along with their derivatives, are steroids active in the brain and include allopregnanolone, dihydrodeoxycorticosterone, dehydroepiandrosterone, and pregnenolone [18]. It has been postulated that neurosteroids have anxiolytic, antidepressant, and memory enhancement properties and play a role in neuroprotection [19, 20]. As 5αRIs inhibit the enzyme 5-alpha-reductase required to synthesize these neurosteroids, the resulting decrease in the neurosteroid biosynthesis could contribute to psychiatric adverse events. Reduction in allopregnanolone is associated with depressive symptoms and unipolar major depression in men [16, 17, 21]. Although finasteride and dutasteride were shown to inhibit allopregnanolone in animal models, there is no information in humans [22, 23]. Other possible mechanisms involve reduction in levels of DHT. A study by Barrett-Connor et al. [24] showed that BDI survey scores for measuring depression were inversely associated with bioavailable DHT levels and genetic predisposition. Two polymorphisms (CAG) rs4045402 and (GGN) rs3138869 in the gene encoding for the androgen receptor have been hypothesized to play a role in finasteride sensitivity [25].

Psychiatric side effects have not been documented in high-quality randomized trials. Psychiatric side effects were reported in 2 moderate-quality studies [26, 27], 4 low-quality studies [27–30], and 1 very low-quality study [31]. These included depression, anxiety, and suicidal ideation.

Depression and Anxiety

Altomare and Capella [31] reported a series of 19 patients that developed a moderate to severe depressive syndrome when treated with finasteride (1 mg/day) for androgenetic alopecia (AGA). All these patients fit the diagnosis of 'substance-induced mood disorder' as defined by the DSM-IV-TR criteria [31]. In this retrospective case series, 14 of the patients were male and 5 were female with a mean age of 28 years, all of whom had a negative history of psychiatric disorders prior to starting treatment with finasteride. Depression in these subjects developed at approximately 9–19 weeks, with an average time of onset of 14 weeks after commencing treatment with finasteride. Depression developed despite the fact that the majority of the patients were satisfied with the impact that finasteride had in stabilizing hair loss. The reported adverse symptoms that are consistent with depression included impairment of sociofamilial relations, eating behavior changes (anorexia), and sleep behavior changes including insomnia or hypersomnia. In addition to depression, 6 of the patients developed concomitant anxiety while taking finasteride. Such depression resolved completely after discontinuing finasteride therapy, with resolution of depressive symptoms ranging from 3 days to 3 weeks. Two patients who were rechallenged with finasteride after discontinuing therapy due to depressive symptoms quickly relapsed within 2 weeks and experienced a recurrence of the depressive symptoms.

A prospective study conducted by Rahimi-Ardabili et al. [28] investigated whether mood disorders developed in 128 male patients who were treated for androgenetic alopecia with finasteride (1 mg/day). This study had no controls. The average age was 25.8 years for the study subjects. Patients who had a history of diagnosed mood disorder were excluded from the study. In addition, patients who used any medications prior to 10 days of study commencement were excluded, as were patients who had a positive history of medication use, with the exception of acetaminophen, antacids, or cold medicine. Information on depressed mood and anxiety was elicited using two self-administered questionnaires: the Beck Depression Inventory (BDI) and Hospital Anxiety and Depression Scale (HADS). Subjects completed the BDI and HADS questionnaires at study onset and then again 2 months following daily finasteride treatment.

The BDI is a survey of 21 questions, with each question having a range of 0 to 3 points for a maximum score of 63. Higher total scores indicate more severe depressive symptoms. A score from 0–9 suggests a normal score with absence of depression, while a score of 10–15 indicates a minimal depressive state, with 16–31 (mild depression), 32–47 (moderate depression), and >47 (severe depression). The mean BDI score of the study subjects was 12.11

at study onset with a standard deviation of ±7.50. After 2 months of finasteride therapy, the mean BDI score was 12.80 with a standard deviation of ±7.64. The increase in BDI score was minimal, yet statistically significant ($p < 0.001$). While the BDI survey measures depression, the HADS survey measures both depression (HADS-D) and anxiety (HADS-A). The HADS consists of 7 questions, with a point range of 0 to 3 per question. There are 7 questions corresponding to depression and 7 questions that measure anxiety. The depression and anxiety scores are divided into 4 score categories: normal (0–7), mild (8–10), moderate (11–15), and severe (16–21). The mean ± standard deviation of the HADS-D score before treatment was 4.04 ± 2.51 and 4.61 ± 3.19 after treatment. This slight increase in the HADS-D was found to be statistically significant ($p = 0.005$). However, there was no significant change in the anxiety scores before and after finasteride treatment. The mean HADS-A score increased slightly from 6.24 to 6.60, but this was deemed not to be statistically significant. The results of this study showed that there was a statistically significant increase in the BDI and HADS survey scores that measure depression in subjects taking daily finasteride treatment, although such increase was minimal. Notably, transient libido loss occurred in 9.4% of subjects, yet no significant difference in BDI and HADS scores was found between the group that reported libido loss and the group that did not experience such side effects.

Suicidal Ideation

Ali et al. [27] performed a retrospective pharmacovigilance disproportionality analysis to detect disproportional reporting of suicidal ideation events in finasteride users compared to suicidal ideation events reported in users of other drugs. For this statistical study, the authors searched the United States Food and Drug Administration Adverse Event Reporting System (FAERS) database for finasteride-related adverse event reports for men aged 18–45 years that were submitted to the FAERS between 1998 and 2013. A total of 4,910 finasteride-related adverse reports were found for this time period, of which 39 reports (0.79%) were filed for suicidal ideation. A disproportional reporting of suicidal ideation was found with finasteride use compared to other drugs within the FAERS database (empirical Bayes geometric mean 1.72) [27]. The majority of patients who reported suicidal ideation also reported persistent sexual dysfunction, with 34 of the 39 patients with suicidal ideation reporting persistent sexual dysfunction. The authors speculated that possible sexual dysfunction experienced by finasteride users could have contributed to the suicidal ideation. Of note, the authors found 577 reports of sexual dysfunction connected to finasteride use and concluded that finasteride was associated with significantly more than expected reporting of sexual dysfunction in young men compared with reporting of these events with all other drugs within FAERS (empirical Bayes geometric mean 28.0) [27].

Persistent psychiatric effects were reported in 2 studies including a low-quality [29] and a moderate-quality study [26]. Both of these studies selected participants through the Internet or patient groups, and 1 study received financial support from the PFS Foundation.

Persistent Depression and Suicidal Ideation

A study conducted by Irwing [29] investigated the prevalence of depressive symptoms and suicidal thoughts in 61 former users of finasteride 1 mg who developed chronic sexual side effects after discontinuing finasteride therapy. Patients were recruited from www.propeciahelp.com, a website for finasteride users with persistent side effects, the author's clinical practice, and physician referrals. The prevalence of depressive symptoms and suicidal thoughts was determined by the BDI-II, a self-administered questionnaire. Similar to the original BDI survey, the BDI-II contains 21 questions, albeit with differing standardized cutoffs. With the BDI-II scale, a score of 14–19 indicates mild depression, 20–28 indicates moderate depression, and 29 and over indicates severe depression. Survey results from the 61 patients with self-reported prolonged sexual side effects following finasteride use were compared to survey results from a control group recruited from the local community. The control group consisted of 29 men diagnosed with MPHL with no history of finasteride use, sexual dysfunction, or psychiatric disorders.

The mean BDI-II score was 23.7 in the former finasteride user group compared to 5.9 in the control group. Rates of depressive symptoms were significantly higher in the finasteride arm with 75% (46/61) of former finasteride users reporting depression (BDI-II score ≥14) compared to 10% (3/29) of controls ($p < 0.0001$) [29]. Moderate or severe depressive symptoms, as determined by a BDI-II score ≥20, were present in 64% (39/61) of the finasteride group. None of the controls exhibited moderate or severe depressive symptoms according to the BDI-II. In addition, suicidal thoughts were present in 44% of former finasteride users and in 3% of controls ($p < 0.0001$).

A subsequent study by Ganzer et al. [30] sought to characterize the symptoms following finasteride therapy for MPHL that persisted once treatment was abated. Spe-

cifically, the study aim was to investigate the extent to which generally healthy men with a recent history of taking finasteride for MPHL experienced persistent psychological, physical, and cognitive adverse effects (≥3 months) after discontinuing finasteride. An online questionnaire was constructed that targeted each of these domains. Patients for the study were recruited from a link to the questionnaire posted to the website www.propeciahelp.com and the author's clinical practice. In total, 131 patients were recruited with a mean age of 24 years. Patients who had a positive history of sexual dysfunction or psychological conditions prior to starting finasteride therapy were excluded. Of note, most patients were asymptomatic during treatment and experienced symptoms after stopping finasteride therapy.

The results from this study showed a high prevalence of negative psychological effects in former finasteride users with 74% (96/131) of study subjects reporting elevated anxiety, 73% (95/131) reporting depressed affect, and 58% (75/131) reporting sleep disturbances [30]. Furthermore, 73% (95/131) of subjects experienced anhedonia and 55% (72/131) experienced emotional sensitivity once they discontinued finasteride therapy [30]. In addition, 63% (82/131) of subjects experienced suicidal ideations and negative thoughts that persisted once treatment was halted [30]. Adverse cognitive effects in former finasteride users were also reported in this study. Such cognitive effects include memory problems (71/131), attention difficulties (93/131), slowed thought processes (93/131), and mental cloudiness or brain fog (95/131) [30].

Persistent Anxiety and Depression

The most recent study by Ganzer and Jacobs [32] investigated the psychological health of 97 users of finasteride. The authors explored whether having a preexisting personal or family history of a psychiatric diagnosis and certain personality traits influenced anxiety and depression among finasteride users. Subjects in the study had taken finasteride for AGA for at least 3 months and stopped taking finasteride after experiencing negative side effects including anxiety and depression. Once again, patients were recruited from a link to the questionnaire posted to the website www.propeciahelp.com and the author's clinical practice. Subjects completed the BDI, the Beck Anxiety Inventory (BAI), and the Ten-Item Personality Inventory (TIPI). The TIPI assesses the personality domains: openness, conscientiousness, extraversion, agreeableness, and neuroticism.

According to the BDI results, 38 subjects scored within the moderate to severe depression range and 5 subjects scored within the extreme depression range. In addition, based on the BAI results, 16 subjects reported moderate anxiety and 17 scored a potential cause for concern [32]. A noteworthy finding in this study is that the authors postulated that subjects would score high on the neuroticism personality domain according to the TIPI, but found that this was not the case as subjects were extroverted, agreeable, emotionally stable, and open to experiences. A total of 55% (n = 53) of subjects had an established psychiatric diagnosis prior to initiating finasteride therapy, while 28.8% (n = 27) had a first-degree relative with a mental health disorder [32]. The authors concluded that pre-existing mental health disorders among finasteride users may put this subset of users at an increased risk of developing emotional disorders caused by finasteride therapy.

The aforementioned studies suffer from a number of flaws, such as selection bias and recall bias. Selection bias is particularly a factor in studies where patients were recruited from the website www.propeciahelp.com and sought treatment of reported symptoms after taking finasteride. These patients may have experienced more severe symptoms and have been more likely to seek out the study. Control groups are lacking in all but 1 of the studies related to mood disorders. Additionally, it is unclear whether symptoms such as depression were caused by the drug itself or if side effects experienced by the patient, such as sexual dysfunction, contributed to the depression. Due to the inadequacy of these studies, no definitive conclusions can be reached at this time. However, these study findings suggest that finasteride may induce psychological adverse effects in susceptible patients such as depressive symptoms and anxiety.

Physical Adverse Effects

Gynecomastia and Male Breast Carcinoma

Gynecomastia has been noted with finasteride (1 and 5 mg) and dutasteride (0.5 mg), while male breast cancer has been noted with finasteride (5 mg). Finasteride and dutasteride are potent inhibitors of type 2 5-alpha-reductase, inhibiting the conversion of testosterone to dihydrotestosterone (DHT) causing a decrease in formation of DHT. Inhibiting DHT synthesis may alter the estrogen to androgen ratio by shifting metabolism of testosterone to estradiol, thus increasing the risk of gynecomastia and male breast cancer [7, 30, 33]. Relative estrogen excess is associated with an increased risk of breast cancer in men [34].

Gynecomastia, an enlargement of breast tissue, is a reported side effect in males prescribed finasteride therapy. Results from the Prostate Cancer Prevention Trial (PCPT), a randomized, double-blind, placebo-controlled study showed that gynecomastia is among the more com-

mon side effects of finasteride therapy along with sexual dysfunction [35]. Men age 55 years and older were randomly assigned to treatment with finasteride (5 mg/day) or placebo for 7 years. At trial conclusion, gynecomastia was observed in 4.5% (426/9,423) of finasteride subjects and 2.8% (261/9,457) of placebo subjects [7, 35]. In the survey conducted by Ganzer et al. [30] that involved subjects who complained of persistent side effects following finasteride use, approximately 69% (90/131) of survey respondents reported gynecomastia.

Gynecomastia has also been experienced by subjects prescribed dutasteride therapy (0.5 mg) for BPH [36–39]. Study results obtained by Kaplan et al. [40] comparing safety and efficacy of BPH patients treated with finasteride or dutasteride suggest that the incidence of gynecomastia is greater in dutasteride users than in finasteride users. In this retrospective 5-year study, the incidence of self-reported breast tenderness and breast enlargement was significantly greater in the dutasteride (3.5%) group compared with the finasteride (1.2%) group ($p < 0.01$) [40].

Reports of male breast carcinoma have appeared in patients who received finasteride. Evidence of the association of finasteride with male breast cancer comes from the Medical Therapy of Prostatic Symptoms (MTOPS) study [41]. The MTOPS, sponsored by the NIH, was a double-blind, placebo-controlled trial (mean follow-up, 4.5 years) involving 3,047 men that compared the effects of placebo, Proscar (finasteride 5 mg/day), doxazosin (8 mg) and combination therapy (finasteride 5 mg and doxazosin 8 mg) for the treatment of BPH. Subjects were randomly assigned to 1 of 4 treatment arms: Proscar (n = 768), Proscar and doxazosin (n = 786), doxazosin (n = 756), and placebo (n = 737). Four cases of breast cancer occurred, with 3 cases reported in the Proscar treatment group and 1 case reported in the Proscar/doxazosin group. Therefore, the rate of male breast cancer in this trial for subjects taking finasteride either alone or with doxazosin was 4 in 1,554, which is high given that the incidence of male breast cancer is 1 in 100,000 man years [33, 42]. This rate is approximately 200 times that observed in the general population [33].

In contrast to the MTOPS study results, results from 2 other large trials do not support the association of finasteride with male breast cancer [3, 11]. In the PLESS, a double-blind, randomized, placebo-controlled trial, 3,040 men with moderate to severe urinary symptoms and enlarged prostate glands were treated with finasteride (5 mg/day) or placebo for 4 years [11]. At study conclusion, no cases of male breast cancer were reported in the finasteride-treated subjects. However, 2 cases of breast cancer were reported in the placebo-treated subjects [42]. Furthermore, the PCPT randomly assigned 18,882 men 55 years of age or older to treatment with finasteride (5 mg/day) or placebo for 7 years [3]. One case of breast cancer was reported in the finasteride arm and 1 case in the placebo arm [42]. Therefore, according to results from the PCPT, an increased incidence of breast cancer in the finasteride group compared to placebo was not observed.

Other Physical Adverse Effects

In addition to gynecomastia and breast cancer, an aggregate of other physical adverse effects have been reported with finasteride use (1 and 5 mg). Three studies have reported fatigue, lethargy, and listlessness in males who took finasteride for BPH or MPHL, although the cause of these symptoms could not be definitively attributable to finasteride [7, 12, 30]. In addition, skin changes have been reported, most commonly dry skin [30]. DHT is known to stimulate sebum production, and as finasteride lowers DHT, it may also cause sebum production to fall and the resultant dry skin [43, 44]. Penile shrinkage and sensory changes, as well as scrotal shrinkage and sensory changes, have also been reported [30]. Less commonly, Peyronie's disease has been reported in finasteride users [30].

Chiriacò et al. [45] employed an observational retrospective study to assess the type of persistent symptoms experienced by patients following finasteride therapy for AGA. Seventy-nine males (aged 18–50 years) were enrolled who used finasteride for AGA and developed persistent side effects for at least 6 months following drug discontinuation. Subjects were enrolled an average of 44 months after finasteride discontinuation. Subjects were recruited from the author's clinical practice (n = 17) and from the website www.propeciahelp.com (n = 62). The study subjects completed a series of questionnaires, including a 100-question ad hoc questionnaire. The most common somatic and sexual adverse symptoms were loss of penis sensitivity (87.3%), decreased penile temperature (78.5%), penile flaccidity/wrinkling (68.4%), loss of scrotum fullness (68.4%), loss of scrotum sensitivity (62.0%), reduction in penile dimension (65.8%), and loss of body muscle tone and mass (51.9%) [45].

Conclusion

A literature review of adverse side effects associated with 5αRIs shows that persistent sexual side effects were only documented in low-quality studies with strong bias

selection as participants were part of an Internet blog. The only high-quality study documenting persistent sexual side effects showed that these were more frequent in the placebo than in the treatment group, implying that the effects were not necessarily related to the treatment. A significant placebo/nocebo effect has been documented among patients informed about possible side effects of finasteride and this may explain the high prevalence of reported sexual dysfunction including persistent dysfunction in subjects participating in Internet groups and blogs. Psychiatric side effects were only documented in moderate- or low-quality studies including studies performed on patients with sexual side effects, which could influence patient's mood. Most of these studies recruited patients through the same Internet patient website.

Is the PFS a reality or not? Up to now, this question has gone unanswered. The addition of PFS to the NIH's GARD database does not officially recognize PFS by the NIH, but rather serves as a resource to find more information regarding reported adverse events. Persistent side effects of finasteride have garnered much media attention. In fact, legal action has been taken with 742 Propecia (finasteride) lawsuits filed against the manufacturer Merck. These cases were consolidated into a multidistrict class action lawsuit in the Eastern District of New York, led by US District Judge John Gleeson. The lawsuit is estimated to go before a United States federal panel in October 2016. The website propeciahelp.com has a link that offers visitors the possibility to join the lawsuit.

Persistent sexual and psychiatric side effects after 5αRIs are not documented by high-quality studies, and prospective studies to establish true incidence and frequency of the problem are really needed. The NIH is currently funding a large epidemiological study, and we hope that the PFS Foundation will start to involve dermatologists in their advisory board in order to generate data from prospective and not retrospective studies. As dermatologist dealing with hair loss patients, we need to keep in mind that finasteride 1 mg is an improved medication and that Propecia (finasteride) labeling includes warnings of possible sexual dysfunction including persistent sexual dysfunction (such as difficulty in achieving an erection after discontinuing the medication), depression, breast tenderness, breast enlargement, and male breast cancer.

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