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MALE SEXUAL DYSFUNCTION AND DISORDERS (AW PASTUSZAK AND NK GUPTA, SECTION EDITORS)

Post-finasteride Syndrome: A Review of Current Literature

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Abstract

Purpose of Review A constellation of persistent adverse effects—collectively termed post-finasteride syndrome (PFS)—after 5α-reductase inhibitor treatment for benign prostatic hyperplasia (BPH) and androgenic alopecia (AGA) has recently been described. The severity of these sexual, physical, neurological, and psychiatric side effects raises important concerns regarding the treatment of these conditions, especially given the prevalence of indications for these medications. Here we review the literature exploring the symptoms, proposed mechanisms, and potential disease modulating factors for PFS.

Recent Findings While the persistent sexual side effects associated with PFS are well documented, research on the physical, neurological, and psychiatric adverse effects is much less ubiquitous. Though the mechanisms leading to PFS have been proposed, a clear treatment plan for these patients has not been established. In the treatment of BPH and AGA with 5α-reductase inhibitors, the risks of PFS should be considered.

Summary The occurrence of persistent adverse sexual, physical, neurological, and psychiatric side effects after 5α-reductase inhibitor is well supported by the existing data. While additional studies are needed to better evaluate the role of 5α-reductase inhibitors in the manifestation of the symptoms of PFS, the risks of PFS should be critically evaluated when treating patients with BPH or AGA.

Keywords Finasteride · Post-finasteride syndrome · Benign prostatic hyperplasia · Androgenic alopecia

Introduction

Post-finasteride syndrome (PFS) is defined as a syndrome with symptoms that can include erectile dysfunction (ED), decreased libido, fatigue, penile and scrotal atrophy and numbness, gynecomastia, muscle atrophy, anxiety, blunted affect, and emotional sensitivity in patients who have taken 5α-reductase inhibitors such as finasteride or dutasteride [1]. These symptoms can have a significant impact on quality of life, yet the syndrome has only recently been described. Though finasteride has been prescribed for more than 20 years to treat androgenic alopecia (AGA) and benign prostatic hypertrophy (BPH), these persistent sexual adverse reactions were not listed on the drug's label until 2012 [2]. Dutasteride is only FDA approved to treat BPH, though off-label use to treat AGA has also been observed [3].

Finasteride and dutasteride block the conversion of testosterone to 5α-dihydrotestosterone (5α-DHT) by competitively inhibiting 5α-reductase. Specifically, finasteride preferentially inhibits the Type 2 isozyme with minimal Type 1 affinity [4]. Dutasteride inhibits both the Type 1 and Type 2 isozymes, displaying a 98% reduction in serum 5α-DHT levels compared to the 70% reduction observed with finasteride [5]. The Type 1 and Type 2 isozymes are localized to the adult male prostate, epididymis, seminal vesicles, testis, and brain while Type 3 is expressed widely in adult tissues [6]. 5α-DHT—a more potent androgen than testosterone—plays a crucial role in the normal development and function of the male reproductive system, particularly of the prostate. In addition, 5α-DHT contributes to male pattern baldness, facial hair growth, and acne [7]. By reducing the levels of 5α-DHT in the prostate, finasteride and dutasteride are used to reduce prostate size in the treatment of BPH and in the

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prevention of prostate cancer [4]. Similarly, the significant drop in scalp and serum 5α-DHT levels with finasteride treatment contributes to the slowing of hair loss in AGA [8].

Due to the broad constellation of symptoms and the paucity of data, the incidence of PFS in patients is unclear. Given that BPH affects 50% of men by ages 51–60 and AGA affects 50% of Caucasian men by age 40, a large proportion of the population has, or will develop, an indication for treatment with finasteride or dutasteride [9, 10]. While many patients describe the sexual symptoms after months or years of taking finasteride, some men have reported symptoms even after a few doses [11••]. These symptoms have been described in patients taking the finasteride 5 mg, finasteride 1 mg, and dutasteride 0.5 mg though much of the literature centers on these symptoms only after finasteride use [6]. Though PFS encapsulates physical, neurological, psychiatric, and sexual symptoms, much of the research appears to be focused on the sexual adverse effects. Given the chronicity and spectrum of both regarding BPH and AGA, the symptoms described in PFS raise important medical questions about the treatment of these patients.

Material and Methods

A literature review using the PubMed database was performed using the following independent search terms: post finasteride syndrome, finasteride adverse effects, benign prostatic hyperplasia, and androgenic alopecia. Given the recent definition of PFS, we conducted the review on English language studies and past review articles published in the last 10 years to evaluate the current research and treatments for PFS.

Post-finasteride Syndrome Symptoms

Sexual Dysfunction

Changes in sexual function are a cardinal feature of PFS. A 2016 meta-analysis including 17 trials of men taking finasteride or dutasteride ($n = 17{,}494$) found that men treated for AGA with 5ARIs were at slightly higher risk of developing sexual dysfunction (RR 1.21 (95% CI = 0.85–1.72)), erectile dysfunction (RR 0.66 (95% CI = 0.20–2.25)), and decreased libido (RR 1.16 ((95% CI = 0.50–2.72)) when compared to untreated men. Similarly, men treated for BPH were at slightly higher risk of developing sexual dysfunction (RR 2.56 (95% CI = 1.48–4.42)), erectile dysfunction (RR 1.55 (95% CI = 1.14–2.12)), and decreased libido (RR 1.69 (95% CI = 1.03–2.79)) [12•]. A study including men reporting sexual effects 9–16 months after their treatment with finasteride for AGA ($n = 54$) found that 89% of men met the definition of sexual dysfunction according to the Arizona Sexual Experience Scale (ASEX). These scores had no correlation with the duration of finasteride use [13]. Similarly, in a web-based survey of men experiencing adverse symptoms for more than 3 months after discontinuing finasteride treatment for AGA ($n = 131$), Ganzer et al. (2015) found that a significant proportion reported decreased sex drive (93%), intermittent erectile dysfunction (83%), sexual anhedonia (70%), complete loss of sex drive (63%), and complete impotence (40%) [14]. Many of these men, however, presented for treatment for, or posted online regarding PFS related symptoms, potentially introducing bias. A 2012 study found that self-reported sexual function—measured by the International Index of Erectile Function (IIEF) scores—dropped significantly more in patients treated for BPH with dutasteride compared with finasteride ($p < 0.01$) [15]. A meta-analysis of 14 publications commenting on symptoms related to PFS found headache (2.2%) and decreased libido (1.9%) as the two most common reported adverse effects reported by women treated with finasteride for AGA ($n = 270$) [16•]. The rate of sexual dysfunction in PFS women reported by the analysis is significantly less than what the existing literature reports in men, suggesting that future studies may help better outline the presentation of PFS in women.

Interestingly, a 2007 study randomized men with BPH ($n = 107$) to receive blinded treatment of finasteride 5 mg with or without informing them about the sexual side effects. After 1 year of treatment, the group counseled on the sexual side effects reported significantly higher rates of one or more sexual side effects than the uninformed group ($p = 0.03$). Specifically, the patients who are aware of the sexual side effects had higher reported rates of erectile dysfunction and decreased libido ($p = 0.02$, $p = 0.04$), suggesting a clinically significant placebo effect [17]. Future additional randomized trials may be needed to further investigate this effect.

The persistent sexual effects of 5α-reductase inhibitors have been supported by numerous studies investigating men treated for BPH and AGA with finasteride in combination with another pharmaceutical agent. Traish et al. (2015) conducted a retrospective review comparing BPH patients treated with finasteride 5 mg ($n = 470$, mean age = 57.8 ± 4.8 years) or tamsulosin 0.4 mg ($n = 230$, mean age = 62.6 ± 4.7 years). The men treated with finasteride had an increased rate of erectile dysfunction (a 6–8 point reduction in IIEF scores) than the men treated with tamsulosin [18]. In contrast, Stojanovic et al. found the highest rates of diminished orgasmic and ejaculatory dysfunction in patients treated for BPH with tamsulosin alone compared to tamsulosin + finasteride or finasteride alone ($n = 156$, $p < 0.01$) [19]. In men treated for AGA with

a combination therapy of topical minoxidil (Rogaine®) and oral finasteride ($n = 100$), Perez et al. found no significant difference in the rate of reported sexual side effects compared to patients receiving only minoxidil [20]. Men using 5ARIs and alpha-blockers should be counseled regarding the increased risk of ejaculatory dysfunction while on these medications.

These sexual adverse effects may be correlated to physiologic and neural changes in patients treated with finasteride. A 2017 study found abnormal pelvic somatosensory evoked potentials of the pudendal nerve in 25% of PFS men ($n = 16$) [21•]. Basaria et al. investigated the sexual symptoms after finasteride use for AGA and found aberrant fMRI responses to erotic and neutral images in symptomatic finasteride users ($n = 25$) compared to asymptomatic finasteride users ($n = 13$) and healthy men ($n = 18$). In the symptomatic finasteride users, a decrease in sexual function (measured by IIEF scores) correlated with increasing activity in the neural circuits implicated in sexual arousal (including the hypothalamus, right posterior cingulate cortex, and bilateral thalamus) and decreasing activity in the brain areas associated with cognitive and motivational function (namely the right mid and posterior cingulate and left insula) after viewing an erotic image ($p < 0.01$). Further, the symptomatic finasteride users had significantly lower IIEF median composite scores (30.0, 67.0, and 68.5 for the symptomatic, asymptomatic, and healthy groups, respectively) and reported lower scores in all domains including sexual desire, orgasmic function, and intercourse satisfaction. The IIEF scores were independent of the duration ($p = 0.725$) or time elapsed since discontinuation of treatment ($p = 0.194$) [11••].

Physical Changes

The available evidence supports that many symptomatic men commonly report gynecomastia after discontinuing finasteride treatment. Ganzer et al. (2015) found that 70% of the participants surveyed regarding their PFS symptoms reported enlarged breast tissue [14]. Further, 19% of online forum posts from men experiencing PFS analyzed by Walf et al. reported estrogenic side effects, mainly gynecomastia [22]. This enlargement appears to be driven by the metabolism of testosterone into estradiol leading to a shift in the ratio of estrogens to androgens [23]. The risk of self-reported breast tenderness and/or enlargement is higher in men treated for BPH with dutasteride compared to finasteride ($p < 0.01$) [15].

In addition to gynecomastia, many men report changes in muscle mass, strength, and fat deposition after treatment with finasteride. Ganzer et al. (2015) surveyed men with persistent symptoms after discontinuing finasteride use for AGA and found that a significant proportion experience symptoms of muscle weakness (56%), increased fat deposition (54%), and muscle twitching (47%) [14]. However, Basaria et al. found no difference in whole-body, truncal, or appendicular lean and fat mass or visceral adipose tissue mass ($p > 0.1$) or leg press strength ($p = 0.31$) among symptomatic finasteride users, asymptomatic finasteride users, and untreated men. The study found a significant yet small difference in self-reported physical function in the symptomatic group compared to the men in the other two groups ($p = 0.002$) [11••]. Additionally, a 20-year retrospective analysis of men treated with finasteride for BPH found no relationship between hip fracture and finasteride exposure when stratified by total finasteride exposure ($p = 0.12$) [24]. The contrast between the self-reported musculoskeletal symptoms and physical findings in PFS patients has not been adequately explored by the existing literature and may require additional investigation.

Several studies have also documented changes to the penis and testis after the discontinuation of finasteride. Ganzer et al. (2015) found that the men surveyed experienced diminished ejaculatory volume and force (82%), penile atrophy and sensory changes (79%), and Peyronie's disease (20%) [14]. Though the subjects of Ganzer et al. (2015) had a mean age of 24 years, a 2016 study surveyed PFS men ($n = 79$) with a mean age of 33.4 years who reported similar symptoms such as decreased penile sensation (87.3%) and decreased ejaculatory force (82.3%) [25]. Also, a 2016 study analyzing online discussion forum posts ($n = 244$) noted that 32% of men reported "demasculinizing" side effects including impaired erectile function, penile atrophy, genital numbness, and abnormal semen viscosity or volume after treatment cessation. Walf et al. poses that these effects are largely due to androgen deprivation (mainly 5α-DHT) of the genitals [22]. Immunohistochemical analysis of nerve integrity and androgen receptor density in the prepuce of patients with PFS found an increased density of nuclear androgen receptors in stromal cells and epithelial cells compared to controls ($p = 0.023$, $p = 0.043$). In contrast, both groups had similar nerve density and androgen receptor positive vessel smooth muscle. These findings suggest that local androgen receptor levels may drive some of the adverse effects of PFS [26]. Using ultrasonography to estimate testicular volume, Melcangi et al. found no significant change in testicular or epididymal head volume between PFS males ($n = 16$) and healthy controls [21•].

Neurological and Psychiatric Changes

Basaria et al. found significantly higher scores in the PHQ-9 and Hamilton Depression Inventory in symptomatic finasteride users, indicating higher levels of depressive mood compared to asymptomatic finasteride users and untreated men ($p < 0.001$). Additionally, the symptomatic men scored significantly higher on the Eyesenck Personality Questionnaire neuroticism scale ($p < 0.001$) and lower on the extroversion scale ($p = 0.003$). However, while the symptomatic group had

higher subjective memory complaints adjusting for years of education ($p = 0.02$), the three groups did not differ in the Wechsler Memory Scale measuring cognitive function ($p = 0.08$), the Card Rotation test measuring memory retention ($p = 0.98$), or the Delayed recall test measuring memory recall ($p = 0.10$) [11••]. Additionally, 74% of men analyzed by Ganzer et al. (2015) reported increased anxiety and 73% noted depressed affect and anhedonia. Many of these men also reported mental cloudiness (75%), slowed thought process (74%), and attentional difficulties (74%) [14]. In contrast, only 30% of men studied by Walf et al. reported central effects such as depression or anxiety [22]. Several studies described the presence of mild to severe depression according to the DSM-5 criteria, Beck's Depression Inventory, or Beck's Anxiety Inventory in participants [21•, 27, 28•].

These central changes are thought to be mediated by reduced levels of neuroactive steroids [29]. Melcangi et al. found that men treated with finasteride had decreased CSF levels of pregnenolone, progesterone, 5α-DHP, 5α-DHT, and 17 beta-estradiol and elevated CSF levels of testosterone, 17 beta-estradiol, and DHEA compared to healthy controls ($p < 0.05$). These patients also had altered plasma levels of these neuroactive steroids, though the plasma changes did not perfectly mirror the changes in the CSF ($p < 0.05$) [21•]. However, the serum and free levels of testosterone and 5α-DHT did not differ among the groups ($p > 0.1$) [11••]. Traish et al. (2011) suggest that finasteride may adversely impact brain function by inhibiting the conversion of progesterone to 5α-DHP, leading to the symptoms of depression, depressed mood, and lower overall well-being [23]. These findings are summarized in Table 1.

Disease Modulating Factors

Though limited, the existing research suggests that certain factors may protect or predispose individuals taking finasteride in developing the symptoms of PFS. A 2016 study correlating questionnaire responses (ASEX, Aging Male Symptom Scale (AMS) and an ad hoc 100-item survey) to androgen receptor polymorphisms found that long and/or short (CAG)n and (GGN)n repeats had varying frequencies based on the sexual symptoms experienced by PFS males ($n = 66$). Specifically, subjects with long GGN repeat length had no scrotal discomfort compared to 34.1% of subjects with medium length repeats experiencing the symptom ($p = 0.012$) and subjects with short GGN repeat length had less reported muscle tone loss than subjects with medium length repeats ($p = 0.05$). These data suggest that permutations of the androgen receptor may modulate the progression and presentation of PFS [30].

In a survey of men seeking treatment for the physical and psychological symptoms of PFS ($n = 87$), Ganzer et

Table 1 Neurohormonal findings

Author [ref.]	Sample size	Sample site	Total testosterone	Hormone levels compared to control											
				DHT	DHEA	3α-diol	Progesterone	Estradiol	Pregnenolone	Isopregnenolone	THP	SHBG	FSH	LH	DHP
Basaria [11••]	25	Plasma	ND	ND	ND	ND	ND	ND	–	–	–	ND	ND	ND	–
Melcangi [21•]	14	Plasma	Increased	ND	Increased	ND	ND	ND	Increased	ND	Decreased	–	–	–	Decreased
		CSF	Increased	Decreased	Increased	Increased	Decreased	Decreased	Decreased	ND	ND	–	–	–	Decreased

DHT 5α-dihydrotestosterone; *DHEA* dehydroepiandrosterone; *3α-diol* 5α-androstane-3α, 17 β-diol-glucuronide; *THP* tetrahydroprogesterone; *SHBG* sex-hormone binding globulin; *FSH* follicle-stimulating hormone; *LH* luteinizing hormone; *DHP* dihydroprogesterone; – not measured; *ND* no significant difference compared to control. $p < 0.05$ for all significant values

al. (2018) found that 55% of participants confirmed an established Axis I or II psychiatric diagnosis prior to finasteride treatment and 28.8% had a positive history of a psychiatric diagnosis in a first-degree relative. These findings support that pre-treatment factors have an impact on the development of PFS [28•]. However, these data may lack generalizability given that the survey was only offered to PFS patients and individuals on a PFS forum.

Motofei et al. (2018) hypothesize that the adverse effects of finasteride may vary based on handedness based on the lateralized distribution of sexual pheromones. Additionally, the study proposes that sexual orientation may alter the manifestation of PFS given the differences in neural areas involved in sexual activation in heterosexual and homosexual individuals [31].

Conclusions

The persistent symptoms reported by men after treatment of BPH or AGA with 5α-reductase inhibitors have been increasingly studied over the past decade. However, many of the studies investigated PFS using surveys of patients seeking treatment for PFS or from PFS-specific online forums, exposing the results to potential selection and recall bias. Further, there is a paucity of randomized clinical trials to more definitively outline the relationship between 5α-reductase inhibitors and persistent adverse effects. Additionally, much of the research centers on the adverse effects after finasteride use leaving the occurrence of PFS after dutasteride use inadequately explored. Treatment options for the symptoms of PFS have also yet to be clearly outlined or investigated. However, the existing evidence supports an association between 5α-reductase inhibitor use in AGA and BPH and persistent adverse sexual, physical, and central effects. Given our growing understanding of the constellation of symptoms described by PFS, we can better evaluate the risks and benefits of using these agents for patients with BPH and AGA while continuing to explore methods to ameliorate the adverse effects.

Compliance with Ethical Standards

Conflict of Interest Jeffrey K Than and Katherine Rodriguez declare no conflicts of interest; Mohit Khera reports research support from the Post-Finasteride Foundation and Boston Scientific, and consulting fees from Boston Scientific, Abbvie, Endo, and Coloplast, outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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