A Comment on the Post-Finasteride Syndrome

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ABSTRACT

The post-Finasteride syndrome (PFS) has been claimed to occur in men who have taken oral finasteride to treat either hair loss or benign prostatic hyperplasia. While the incidence of persistent sexual, mental, and physical side effects despite quitting finasteride is unknown, and the condition is not recognized by the scientific community, individuals who suffer from PFS do present with very distinctive and homogenous symptoms. The concept has emerged from reports of nondermatologists, neuroendocrinological research, case reports, and uncontrolled studies. These have been scrutinized by hair experts who found that persistent sexual side effects were only documented in low-quality studies with a strong bias selection and a significant nocebo effect. Others totally dispute the credibility of the PFS. In any case, the PFS is a problem that has to be dealt with. Low-quality studies neither confirm nor refute the condition as a valid nosologic entity. Therefore, it is as inappropriate to dismiss the condition, as it would be to demonize finasteride for the treatment of male pattern hair loss. Whether the PFS represents a nocebo reaction or a real drug adverse event is irrelevant, while the best way to alleviate the emotional distress related to hair loss is to effectively treat the condition causing the problem. It is not sufficient to only discuss the plausibility of the PFS. There is a need for practical recommendations to include such important issues as patient selection and risk assessment, appropriate patient information, how to react in case of drug-related adverse events, issues of fertility and malignancy, management of the PFS, and alternatives, specifically the use of topical finasteride. It is the aim of this commentary to provide the respective information.

Key words: Neuroendocrinological research, nocebo reaction, plausibility, post-Finasteride syndrome, risk management

Arrogance is a product of narrow vision and ignorance. Jerome Groopman, How Doctors Think

The post-Finasteride syndrome (PFS) has been claimed to occur in men who have taken oral finasteride to treat either hair loss or benign prostatic hyperplasia. Reported symptoms claimed to continue despite quitting finasteride include: loss of libido, erectile dysfunction, reduction in penis size, penile curvature or reduced sensation, gynecomastia, muscle atrophy, cognitive impairment, severely dry skin, and depression. The condition allegedly may have a life-altering impact on sufferers and their families, such as job loss and the break-up of romantic relationships or marriages, while also being linked to suicides.

As yet, the condition is not recognized by the scientific community, although individuals who suffer from the syndrome do present with very distinctive and relatively homogenous symptoms.

While the incidence of persistent sexual, mental, and physical side effects which continue despite quitting...
The Post-Finasteride Syndrome Foundation (www.pfsfoundation.org) is a nonprofit organization dedicated to helping fund research on the characterization, underlying biologic mechanisms, and treatments of the PFS while improving public awareness of the condition.

The concept of the PFS has emerged from reports primarily of nondermatologists, neuroendocrinological research and considerations, case reports, and uncontrolled studies. These have recently been scrutinized by a group of hair experts. Their investigations into the plausibility of the syndrome were based on a comprehensive review of the respective medical literature. The authors found that persistent sexual side effects were only documented in low-quality studies with strong bias selection, while a significant nocebo effect has been documented among patients informed about the possible side effects of finasteride. Since the PFS has received disproportionate attention, especially of the nonmedical community, and legal action has been taken against the manufacturer of Propecia (Merck), reinforcing the common belief in the authenticity of the condition, the authors concluded that prospective studies to establish the true incidence and frequency of the problem are mandatory, and that dermatologists need to be included in further investigations and the advisory board of the Post-Finasteride Syndrome Foundation, as they represent the major primary prescribers of finasteride for treatment of hair loss.

Other key opinion leaders totally dispute the credibility of the PFS, while challenging and publicly ridiculing its authors. The denial of uncertainty, the inclination to substitute certainty for uncertainty, is a remarkable human psychological trait. It is both adaptive and maladaptive, and therefore guides and risks to misguide. Taking uncertainty into account can enhance a physician's therapeutic effectiveness because it demonstrates his honesty, his willingness to be more engaged with his patients and fellow physicians, and his commitment to the reality of the situation rather than resorting to evasion.

In any case, the PFS is obviously a problem that has to be dealt with. Low quality studies neither confirm nor refute the condition as a valid nosologic entity. Therefore, it would be only as inappropriate to dismiss the PFS as nonsensical, as it is to demonize finasteride for the treatment of male pattern hair loss.

Finasteride represented a major breakthrough in the treatment of male pattern hair loss, based on an understanding of the underlying pathophysiology and observations on the respective genetic defect of 5-alpha reductase. Clinical studies have revealed both a high efficacy of treatment and a very favorable safety profile, establishing the drug as first-line treatment of male pattern hair loss. In the most recent study published in 2012, Sato and Takeda reported on efficacy and safety of 1 mg oral finasteride for treatment of male pattern hair loss in the so far largest population study of enrolled 3177 Japanese men. Efficacy was evaluated by global photographic assessment, and safety data were assessed by interviews and laboratory tests. The overall effect on hair growth was seen 87.1%, in whom hair increased greatly in 11.1%, moderately in 36.5%, and slightly in 39.5%. The response rate improved with increasing duration of treatment. Adverse reactions occurred in 0.7% of men. Seven men discontinued treatment based on risk-benefit considerations. No specific safety problems associated with long-term use were observed. The authors concluded that in Japanese men with male pattern hair loss, 1 mg oral finasteride used for long-term treatment maintains progressive hair regrowth without recognized side-effect.

Ultimately, dutasteride has been proposed for enhancement of efficacy in the treatment of male pattern hair loss due to its dual 5-alpha-reductase inhibition, therefore capable of decreasing dihydrotestosterone levels to a greater extent than finasteride. Respective clinical studies demonstrated the superiority of 0.5 mg oral dutasteride versus 1 mg oral finasteride in the treatment of male pattern hair loss, and efficacy in men with male pattern hair loss recalcitrant to finasteride, while being well tolerated.

Nevertheless, the denial of a patient complaint, not to mention that of a group of affected individuals, even if incomprehensible, is dangerous on two accounts: first, it denies the fallibility of all physicians and second, it splits the mind from the body.

Persistent neurological effects from other drugs are well recognized, such as the tardive dyskinesias related to the use of phenothiazines for treatment of chronic schizophrenia. There is a body of scientific evidence from studies in rodents which finasteride may reduce the concentration of several neuroactive steroids important for neurogenesis and neuronal survival. An important
neurosteroid is allopregnanolone (ALLO), a metabolite of dihydropregosterone. ALLO is a potent ligand of the inhibitory GABA-barbiturate receptor. GABAA receptors have variable sensitivities to ALLO in the settings of neurosteroid withdrawal, stress, social isolation, and aging. Less ALLO, as a consequence of finasteride treatment, could alter GABAergic transmission with implications for neuronal progenitors and young neurons. Interestingly, the mechanisms of irreversible tardive dyskinesias from phenothiazines may be similar to the mechanisms underlying the persistent side effects of finasteride: in rats treated with the phenothiazine haloperidol to induce orofacial dyskinesias, co-administration of progesterone prevented this side effect, while pretreatment of the rats with finasteride reversed this protective effect, demonstrating an important role of the progesterone pathway and its metabolites. Since neurosteroids are believed to have anxiolytic, antidepressant, and memory enhancement properties and play a role in neuroprotection, the decrease of neurosteroid biosynthesis through inhibition of the enzyme 5-alpha reductase required to synthesize these neurosteroids, may contribute to the respective psychiatric adverse events.

Accordingly, a study investigating the characteristics of men who report persistent sexual adverse effects after finasteride use for treatment of hair loss, revealed depressed mood, and brain functional magnetic resonance imaging findings consistent with those observed in depression, and no evidence of androgen deficiency, decreased peripheral androgen action, or persistent peripheral inhibition of steroid 5-alpha-reductase enzymes. Although the investigators excluded men who were depressed before initiating finasteride, they admit not knowing whether the depressed mood was causally related to finasteride, the hair loss itself, or a nocebo effect.

For now, how are we to deal with the PFS? In any case, whether it represents a nocebo reaction or a real drug adverse effect is irrelevant, while the best way to alleviate the emotional distress related to hair loss is to effectively treat the condition that is causing the problem.

It is therefore not sufficient to only discuss the plausibility of the PFS, not alone to downplay its significance. Rather, there is a need for practical recommendations to include such important issues as:

- Patient selection and risk
- Appropriate patient information
- How to react in case of drug-related adverse events
- Further issues: of fertility of malignancy
- Management of the PFS
- Alternatives, specifically the use of topical finasteride.

Until date, there are no predictive factors for the risk of development of PFS and no known treatment for the disorder.

Based on their observations that compounds interfering with sexual hormones may decrease sexual activation and response depending on hand preference and sexual orientation, such as tamoxifen for the treatment of breast cancer and bicalutamide for prostate cancer, respectively, Motofei et al. suggested that hand preference and sexual orientation may offer possible predicting factors for finasteride adverse effects in male pattern baldness, with right-handed homosexual men being at an increased risk. The rationale basis for this assumption would be that sexual hormones, sexual orientation, handedness, and cognition might all be interrelated, presumably due to overall lateralized processes of the brain. However, taking an estimated frequency of 87%–92% right-handedness in the general population into consideration, this attribute would seem unfit for risk prognostication. Moreover, inquiring into an individual’s sexual preference for therapeutic decision-making risks the reproach of sexual discrimination. Alternatively, a study on the relationship of the digit (or 2D: 4D) ratio to the frequency of finasteride-related mental and sexual adverse effects has been proposed to serve as a surrogate marker, should this hypothesis seriously hold true. The 2D: 4D ratio represents the ratio of the lengths of the 2nd (index) and 4th (ring) finger measured from the midpoint of the bottom crease (where the finger joins the hand) to the tip of the finger. This 2D: 4D ratio is considered by some to represent a crude measure for prenatal androgen exposure, with lower 2D: 4D ratios pointing to higher prenatal androgen exposure.

More importantly, it would seem appropriate to ascertain a history of depression or sexual dysfunction before starting treatment, since preexisting mental health disorders among finasteride users may put this subset of patients at an increased risk of developing emotional disorders related to finasteride therapy. Furthermore, caution is recommended while prescribing oral finasteride to male-to-female transsexuals, since the depression, anxiety, and suicidal ideation are particularly common in patients with gender dysphoria.

The psychological effects of hair loss may be hard to differentiate clinically from preexisting psychopathology. Furthermore, Maffei et al. found the prevalence of personality disorders in patients with male pattern hair loss to be significantly higher than in the general population, with three distinct personality profiles:
Specifically, patients with personality disorders tend to experience more distress from hair loss than nondisordered patients, since these individuals lack a secure sense of self and effective coping skills, and therefore may be particularly vulnerable to the adverse effects of pattern hair loss. Ultimately, these patients tend to be more difficult to handle with respect to the treatment of their hair loss:³⁰⁻³¹
- Patient compliance issues are a problem in patients with paranoid, avoidant, or passive-aggressive (negativistic) personality disorders
- Nocebo reactions are more frequent in patients with paranoid, passive-aggressive (negativistic), or histrionic personality disorders
- Overvalued ideas are typical for patients with histrionic or narcissistic personality disorders.

Patient understanding and involvement are central to optimal treatment selection and active patient role in treatment. Patient education is more than a simple transfer of information. Understanding, emotion, satisfaction, rapport, and empathy are among the factors involved. This maximizes patient benefit and safety.

Patients frequently become preoccupied with side effects when they are reluctant to undergo treatment, and some physicians also overestimate side effects.¹¹ Moreover, a significant nocebo effect has been revealed in patients who were informed of potential sexual adverse effects before taking finasteride versus patients who were not informed.³⁷⁻³⁸ Of course, it is of up-most importance to inform patients on potential adverse effects, their frequencies, and appropriate management. Yet, the real concern should be the underlying medical condition, which is often displaced in the patient’s mind by fear of the treatment. Patients must adopt a broader perspective, the long view, not a vision narrowed by fear. The physician’s role is to help the patient figure out what he really wants and then to use the power of persuasion to show the patient the way there. At length, the way a physician phrases his recommendations can powerfully sway a patient’s choice and have an influence on the treatment outcome.¹¹

Ultimately, the physician’s choice has to be consistent with the patient’s philosophy of living.¹¹ This particularly pertains to the prescription of oral finasteride for treatment of male pattern hair loss, where a choice must be made for long-term systemic medication with known (sexual side-effects, gynecomastia, depression) and unknown risks (PFS, male infertility, breast cancer) for treatment of an essentially cosmetic condition.

In any case of adverse effects [Table 1],³⁸ oral finasteride treatment should be stopped. Since the plasma half lifetime of dutasteride (3–5 weeks) is significantly longer than that of finasteride (age-dependent, from 5 to 8 h), with respect to possible adverse effects related to therapeutic 5-alpha-reductase inhibition, it is advisable to start patients on oral finasteride, and only if results are unsatisfactory at 6 months and tolerance is good, to switch from finasteride to dutasteride. Finally, in men aged 40 years or more a switch from oral finasteride to topical minoxidil may be considered in anticipation of age-related more frequent sexual function-related problems. Although finasteride has been proven to also be effective in the aging male,¹⁰⁻¹¹ it does so with a lesser degree of efficacy at the cost of a higher frequency of sexual adverse effects,³⁹⁻⁴¹ while clear treatment benefits

### Table 1: Adverse reactions to 1 mg oral finasteride

| Common (frequency between 2/1 and 1/10) |
|----------------------------------------|
| Sexual dysfunction (finasteride 3.8% vs. 2.1% within first 12 months of treatment, 1% of men withdrew finasteride because of sexual dysfunction within first 12 months of treatment, thereafter frequency decreased to 0.6% during following 4 years of treatment) |
| Diminished libido (finasteride 1.8% vs. placebo 1.3%) |
| Erectile dysfunction (finasteride 1.3% vs. placebo 0.7%) |
| Occasional (frequency between 2/10 and <1/100) |
| Abnormal ejaculation |
| Decreased ejaculatory volume |
| Rare (frequency between 2/10 and <1/100) |
| Testicular pain |
| Breast tenderness |
| Gynecomastia (may persist for months to years after cessation of finasteride treatment) |
| Allergic reactions: Rash, itching, hives, swelling of the mouth, face, lips, or tongue (angiedema) |
| Very rare (frequency between <1/10,000) |
| Depression |
| Male breast cancer |
| Unknown (frequency cannot be estimated from existing data) |
| Persistent diminished libido or erectile dysfunction (after cessation of finasteride treatment) |
| Male infertility (usually in association with preexistent subfertility) |
| Decrease in quality of semen (there are reports on normalization or improvement of semen quality following withdrawal of drug) |
| PFS |
| Cause-relationship unresolved |

PFS: Postfinasteride syndrome
of topical minoxidil solution are noted in the older age group that has retained some hair.\(^{[41]}\)

Finally, there have been some concerns beyond the PFS, regarding male infertility and cancer development.

In a double-blind, placebo-controlled multicenter study of 181 men 19–41 years old randomized to receive 1 mg finasteride or placebo for 48 weeks followed by a 60-week off-drug period, no significant effects of 1 mg finasteride on sperm concentration, total sperm per ejaculate, sperm motility or morphology were found in the analysis of sequential semen samples.\(^{[42]}\) Nevertheless, some recent observations have suggested that in subfertile patients, the effects of the drug might be amplified. Therefore, counseling may be particularly critical for men taking finasteride and planning a pregnancy.\(^{[43]}\) When fertility is an issue, one may consider performing a sperm count before and during treatment with oral finasteride. Ultimately, there have been case reports of infertile patients with azoospermia or severe oligospermia who showed significant improvements in sperm concentrations after the discontinuation of finasteride.\(^{[44]}\)

The Prostate Cancer and Prevention Trial (PCPT) was a landmark study that sought to evaluate the morbidity and mortality of prostate cancer with the use of oral finasteride. The investigators randomly assigned 18,882 men 55 years of age or older with a normal digital rectal examination and a prostate-specific antigen (PSA) level of 3.0 ng/ml or lower to treatment with finasteride (5 mg/day) or placebo for 7 years. Prostate biopsy was performed if the annual PSA level, adjusted for the effect of finasteride, exceeded 4.0 ng/ml, or if the digital rectal examination was abnormal. Prostate cancer was detected in 803 of the 4368 men in the finasteride group who had data for the final analysis (18.4%) and 1147 of the 4692 men in the placebo group who had such data (24.4%), for a 24.8% reduction in prevalence over the 7-year period (95% confidence interval, 18.6%–30.6%; \(P < 0.001\)). Tumors of Gleason Grade 7 or more were more common in the finasteride group than in the placebo group. Sexual side effects were more common in finasteride-treated men, whereas urinary symptoms were more common in men receiving placebo.\(^{[45]}\)

To seek to alleviate the concern of the increase in a number of high-grade cancers detected in the original PCPT, the long-term all-cause mortality among PCPT participants was further examined. The results were reassuring with an overall 15-year rate of death of 22% in both the finasteride group and the control group. The investigators were unable to report prostate-cancer-specific mortality.\(^{[46]}\)

As a general rule, in all men 45 and over, PSA levels should be performed before and after starting therapy with oral finasteride, and thereafter on a yearly basis. The level should drop by ca. 50% on initiation of therapy. In case of increase >0.4 ng/ml/year, referral to urologist to check prostate condition is recommended. In fact, for men who choose regular prostate-cancer screening, the use of oral finasteride meaningfully reduces the risk of prostate cancer.

Case reports have suggested that 5-alpha reductase inhibitors for the treatment of benign prostatic hyperplasia may increase the risk of gynecomastia\(^{[47]}\) and male breast cancer,\(^{[48]}\) but epidemiological studies have been limited. The most recent cohort study with nested case-control analyses using the UK Clinical Practice Research Datalink revealed that gynecomastia risk was significantly elevated for users of 5-alpha reductase inhibitors. The risk was higher for dutasteride than for finasteride. 5-alpha reductase inhibitors users did not have an increased risk of breast cancer compared to unexposed men.\(^{[49]}\)

To finish, with regard to management of the PFS, attention must be focused on the treatment of depression and sexual symptoms. Since there is no evidence of androgen deficiency, persistent steroid 5-alpha-reductase inhibition, or androgen insensitivity, symptomatic finasteride users are unlikely to benefit from treatment with testosterone, dihydrotestosterone, or any other androgen.\(^{[29]}\)

Probably, preventive measures are more helpful, specifically: refraining from prescribing oral finasteride to patients with a personal history of depression, sexual dysfunction, or fertility problems, and in any case of adverse effects, immediately stopping oral finasteride treatment. The symptomatic patient gains therapeutic benefit already from venting concerns in a safe environment with a caring physician. The physician should be careful not to be judgmental, ridiculing, or scolding because this may rapidly close down communication and potentially aggravate the situation.

Currently, alternatives with increased patient confidence and safety profiles are being explored, specifically the topical application of 5-alpha reductase inhibitors. Lee et al.\(^{[50]}\) conducted a systematic search for studies regarding topical finasteride treatment efficacy, including case reports, randomized controlled trials, and prospective studies. In all of seven articles identified for the review, there was a significant decrease in the rate of hair loss, increase in total and terminal hair counts, and positive hair growth assessment with topical finasteride. Both scalp and plasma dihydrotestosterone significantly decreased with application.
of topical finasteride. The authors concluded that the preliminary results on the topical use of finasteride were limited, but safe and promising, and advocated continued research into drug-delivery, ideal topical concentration and application frequency, and adverse effects. Finally, Suchonwanit et al.,[20] performed a randomized, double-blind controlled study of the efficacy and safety of a topical solution of 0.25% finasteride enhanced with 3% minoxidil vs. 3% minoxidil solution for treatment of male androgenetic alopecia. They found the combined solution of finasteride and minoxidil to be significantly superior to minoxidil alone in improvements of hair density, hair diameter, and global photographic assessment. About 90% of patients treated with the combined solution experienced moderate to marked improvement, with minimal effect on plasma dihydrotestosterone levels (approximately 5% reduction), and no systemic adverse events.

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Conflicts of interest

There are no conflicts of interest.

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