REVIEW ARTICLE

Post-finasteride syndrome - a true clinical entity?

Simone Cilio[1], Georgios Tsampoukas[2]✉, Afonso Morgado[3], Pedro Ramos[4] and Suks Minhas[5]

This review critically examines Post-Finasteride Syndrome (PFS), a condition eventually reported by men who have used finasteride for androgenetic alopecia or benign prostatic enlargement and experienced persistent adverse effects after discontinuation. We explore the clinical manifestations, including sexual dysfunction, neuropsychiatric symptoms, and physical changes, that collectively challenge both diagnosis and management. This review evaluates the evidence for PFS, discusses potential mechanisms including neurobiological alterations, genetic predispositions, and addresses the controversies surrounding its existence and recognition by the medical community. Emphasis is placed on the role of patient education and the need for thorough risk assessment before prescribing finasteride. Although contrasting data from literature, men treated with finasteride could develop a plethora of non-neglectable physical and psychological symptoms identifying PFS. A multidisciplinary approach to research, policy-making, and patient advocacy is essential to better understand, diagnose, and manage PFS, underlining the necessity for greater awareness and scientific inquiry into this contentious and impactful syndrome.

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INTRODUCTION

Finasteride is a synthetic and specific competitive inhibitor of the enzyme 5 alpha-reductase, which functions intracellularly to convert testosterone into dihydrotestosterone (DHT) [1]. Historically, due to its potential in addressing DHT-mediated disorders, the medication was investigated for its effectiveness against various conditions, including acne, facial hirsutism, frontal alopecia, and could lower the risk or delay the onset of prostate cancer [2–5]. In contemporary times, finasteride is recognized as a viable option for the management of male androgenetic alopecia (MAA), for men at high risk of complications arising from benign prostate enlargement (BPE), and much less commonly in daily practice to reduce risk of prostate cancer [6–8]. Despite clinical effectiveness of finasteride, it is important to acknowledge that its use is associated with a range of known adverse effects (AEs): sexual dysfunction, infertility, mood disorders, gynecomastia, albeit with varying prevalence rates and a degree of uncertainty regarding their clinical significance [9]. In a subset of individuals treated with the inhibitor, the phenomenon of persistence of side effects for many years even after discontinuation of treatment has emerged, leading some authors to express concern that finasteride's impact on quality of life may be permanent [10]. Furthermore, a previous case series by Caruso et al. found that after discontinuation of finasteride patients exhibited a range of neuropsychiatric symptoms, including muscular stiffness, cramps, tremors, and chronic fatigue, despite the absence of clinical or pathological evidence of any obvious disorder before the drug assumption. Taking into account the low numerosity of patients assessed (only seven), the authors reported that the severity and frequency of anxious/depressive symptoms varied among the patients from loss of libido and sexual desire (86%), to anxiety (57%), suicidal thoughts (14%) and panic attacks (14%), collectively forming a complex and persistent neuropsychiatric pattern induced by induce a persistent alteration of neuroactive steroid levels even after discontinuation of the drug [11]. On the other hand, patient counseling and access to drug information sheets may influence the perception and reporting of side effects, even if the actual pharmacological action is not responsible for them (the so-called "nocebo effect") [12]. Nevertheless, the persistence of AEs, even after discontinuation of finasteride, has given rise to the entity known as "post-finasteride syndrome (PFS)".

This syndrome encompasses a range of neuropsychiatric symptoms and long-lasting sexual side effects, raising concerns about the potentially permanent impact of this drug on an individual's quality of life [13]. The AEs exhibit significant variability in their onset, which may be immediate onset upon discontinuation, develop gradually while on the medication, or appear intermittently even when not taking finasteride [14]. Although the syndrome is mostly reported in men treated for MAA in their twenties – thirties [15, 16], the occurrence of PFS may not be limited to a specific age group. The lack of clear definitions, self-reporting bias, stigma, fear and the scarcity of epidemiological studies make the incidence and prevalence of the syndrome difficult to be estimated. On the other hand, a meta-analysis from 2020, based on 34 previous studies, found that 5-ARI use significantly increases the risk of PFS-like adverse effects by 1.87 times compared to placebo (95% CI: 1.64–2.14), although the syndrome was reported also in the placebo arms [17]. However, some observations gather intriguing interest about whether specific groups of individuals may be more susceptible to the

[1]U.O.C. Clinica Urologica, A.O.U. San Giovanni di Dio e Ruggi d'Aragona "Scuola Medica Salernitana", Salerno, Italy. [2]Department of Urology, Homerton University Hospital NHS Trust, Homerton, UK. [3]Department of Urology, ULS São João, Porto, Portugal. [4]School of Medicine, University of Minho, Braga, Portugal; Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal; Department of Urology, Centro Hosspitalar São João, Porto, Portugal. [5]Department of Men's Health and Andrology, Imperial College Health Care, London, UK. ✉email: tsampoukasg@gmail.com

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Table 1. Constellation of symptoms in post-finasteride syndrome.

Type	Symptoms
Central	Convulsions, cerebral thromboembolic events, depression, anxiety, psychotic disorders, personality changes, attention deficit, insomnia
Estrogenic	Gynaecomastia, breast mass
Antiandrogenic	Erectile dysfunction, ejaculatory dysfunction, decreased libido, infertility, reduction in number of sexual activities
Atypical	Orthostatic hypotension, dizziness, penile curvature, Peyronie's disease, hepatic function disorder, obstructive sleep apnea, cardiac adverse events, muscular weakness

syndrome due to clinical or genetic predisposition, without overlooking the possibility of bias against the side effects of the drug [18]. Amid rising concerns about finasteride's potential negative impact on sexual health, a study by Asanad et al. evaluated global online interest in these issues from January 2004 through to December 2020. Triggered by a 2011 FDA alert highlighting sexual side effects of finasteride, the study examined Google search patterns for terms related to finasteride, its side effects, and PFS in the US, UK, and Australia. Findings revealed a marked increase in searches for these terms, underscoring a surge in public concern [19]. Therefore, in modern times of widespread online information, the discussion on the topic is vital as healthcare awareness needs to be raised and scientific research on the subject to be promoted facilitating patient advocacy and emphasizing ethical medication use. Our review aims to examine the existing body of scientific literature and evaluate the evidence related to PFS, highlight controversies and areas of further research on this topic.

MAIN MECHANISM OF FINASTERIDE AND CLINICAL APPLICATIONS

5-alpha reductase is a key enzyme in male hormonal regulation and facilitates the conversion of testosterone into DHT, a more potent androgen. This enzymatic process is vital for the normal development and maintenance of the male reproductive system, extending its influence to various human tissues, both within and beyond the prostate [20]. Finasteride is a commercially available 5-alpha reductase inhibitor (5-ARI) which inhibits type 2 isoenzyme of 5-alpha reductase, selectively and irreversibly [21]. The agent appears not to affect the total serum testosterone levels, although some studies report increase of testosterone levels in men taking finasteride and other suggesting a decrease of serum levels of this hormone [22, 23]. In men struggling with prostate enlargement, the prolonged administration of finasteride can reduce prostate size and enhance urinary flow, while also mitigating the risk of acute retention or risk for surgical intervention [24]. In MAA, the persistent presence of DHT initiates a process of hair follicle miniaturization over time which leads to the conversion of terminal hairs into vellus hairs — finer, shorter, and less pigmented [25]. The strategic use of finasteride (or its counterpart, dutasteride) and the reduction in DHT levels have demonstrated clinical outcomes, manifesting as a tangible improvement in scalp hair growth [26, 27]. Additionally, DHT has been recognized as a etiological factor in many dermatological conditions leading physicians to adopt finasteride as therapeutic compound in conditions such as acne, frontal fibrosing alopecia, hirsutism and hidradenitis suppurativa [28, 29]. Historically, the experimental use of finasteride, both alone and in combination with other agents for the treatment of advanced prostate cancer, has now been overshadowed by the adoption of novel antiandrogens [30, 31]. Finally, while chemoprevention with finasteride at ages coinciding with higher prostate cancer incidence has shown possible cost-effectiveness, early data indicating it increases the risk of detecting more aggressive cancer should be carefully considered [32, 33]. As one of the most known effects of finasteride is to decrease the size of the prostate gland by about 25%, the likelihood of biopsying an area of prostate cancer is higher. However, these studies are based on trials on men at risk for prostate cancer, and the true effect of finasteride on prostate cancer detection is yet to be clarified [34].

COMMON SIDE EVENTS RELATED TO FINASTERIDE

Finasteride, widely prescribed for the management of alopecia and BPH has been implicated in a broad spectrum of side effects. These adverse effects range in severity and presentation. Adverse effects reported include orthostatic hypotension, dizziness, erectile dysfunction, ejaculatory dysfunction, decreased libido, penile curvature/Peyronie's disease, hepatic dysfunction and unilateral mammary hypertrophy-although these are rare [35–37]. Finasteride has also been associated with obstructive sleep apnea and insomnia, prompting some authors to suggest a sleeping quality evaluation for individuals experiencing multiple symptoms possibly associated with finasteride [38]. As an increasing number of symptoms are self-reported, there have been efforts to systematically classify these symptoms into four distinct categories: antiandrogenic effects, which include erectile dysfunction, dysfunction of testicular and accessory glands, diminished libido, and altered hormonal function, may be present in 32% of cases; estrogenic effects, such as gynecomastia and breast mass, occur in 19%; central effects, including convulsions, cerebral thromboembolic events, depression, anxiety, confusion, psychotic disorders, personality changes, insomnia, and attention deficit, are observed in 30%; and nonspecific effects, which cover cardiac adverse events including arrhythmias and myocardial infarction, muscular weakness, paresthesias, and neoplasia of unspecified origin, are noted in 5% of the cases (Table 1). Symptoms spanning all categories are reported in 14% of cases, which may support the notion of a syndromic manifestation of finasteride's side effects [39].

FROM COMMON SIDE EFFECTS TO THE COMPLEXITIES OF A SYNDROME

Biological basis

One of the key features associated with syndrome-like presentations is the persistence of symptoms even after discontinuation of the medication, suggesting a long-lasting impact of finasteride on the body functions. In a rat model, the long-term use of dutasteride (and by extension, finasteride, which operates through a similar mechanism), the critical finding that distinguishes the impact of medication duration on erectile dysfunction is that while erectile function could recover after a 4-week treatment period followed by a 2-week rest, this was not the case for longer durations of use (8 weeks of treatment). This inability to recover erectile function after prolonged exposure is further supported by biological changes observed in the corpus cavernosum, including increased levels of fibrosis-related factors and an imbalance in the smooth muscle to collagen ratio, indicating structural alterations that are not reversed after a period of drug withdrawal [40]. In a mice model, finasteride treatment led to a significant decrease in brain 5-alpha-DHT levels and induced a reversible reduction in the number of newborn cells and young neurons in the hippocampus. Remarkably, 35 days after the last injection, neurogenesis had

returned to normal [41]. Despite evidence concerning reversibility, differences in human and animal studies must be appreciated.

Post-discontinuation symptoms in human populations

Despite potential selection and recall biases, Irwig and Kolukula studied persistent sexual side effects after finasteride use, lasting at least three months post-discontinuation, in 71 young and otherwise healthy men. The study found 94% experienced low sexual desire, 92% had erectile dysfunction, 92% noted decreased arousal, and 69% faced orgasmic dysfunction. The average duration of finasteride use was 28 months, with sexual side effects persisting for an average of 40 months after stopping the drug [42]. In another study Irwig reported that, at the time of the interviews, the duration of persistent adverse effects in 54 patients was 3–6 months for 7% of subjects, 7–11 months for 9% of subjects, 1–2 years for 44% of subjects, 3–5 years for 19% of subjects, and 6 or more years for 20% of subjects. Furthermore, 96% continued to experience these effects at reassessment 9–16 months (mean 14 months) [43]. Moreover, a pooled analysis demonstrated an increased risk of depressive symptoms, suicidal ideation or behavior and risk of persistent sexual dysfunction [44]. As a result, in August 2022 the US Food and Drug Administration (FDA) warned the medical community about the psychological effects of finasteride and now major depression, dementia symptoms, suicidal ideation and behavior are regarded as possible adverse effects [45]. Lastly, an analysis by Kiguradze et al. highlights that the persistence of post-finasteride erectile dysfunction is higher in men with longer exposure to the drug, especially in younger men [46]. It is demonstrated though that these rare AEs, that can possibly contribute to PFS, may be the result of post marketing experience and the reactions have been reported "voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure" [47]. The constellation of symptoms reported by patients with possible PFS is presented at Table 1.

AIMING TO DEFINE PFS

The complexity of defining PFS becomes apparent in light of contemporary methodological inclination in modern medicine towards a disease-centered model which often relies on laboratory tests, imaging studies, and other diagnostic tools to pinpoint the cause of symptoms [48]. The variety of possible symptoms in PFS conflicts with the idea of a disease-centered model, as the diverse manifestations extend beyond a singular pathological entity. Moreover, the multimorbidity pattern of PFS can also be linked to social conditions and individual lifestyles, making it difficult to fit into a rigid, disease-oriented framework [49]. According to "Post-finasteride Syndrome Foundation", the entity is described as "persistent sexual, neurological, physical, and mental adverse reactions in patients who have taken finasteride, a 5-ARI type 2 enzyme inhibitor used to treat hair loss (under the brand name Propecia or generics) and/or enlarged prostate (Proscar or generics)" [50]. While the definition covers the constellation of various symptoms, downsides include subjectivity in reporting, bias originating from an advocacy source, and the exclusion of alternative explanations. Thus, there is a need for a more objective and inclusive approach, considering that as of now, no medical societies have proposed a definition for PFS. A list of pertinent studies on the subject is presented along with their limitations in Table 2.

PREVALENCE

Currently, the absence of studies assessing the epidemiology of PFS, coupled with formidable challenges in its estimation, leaves its exact prevalence unknown. The diversity in dosages and treatment durations of finasteride among individuals, along with the absence of biomarkers for PFS, complicates prevalence determination by relying on subjective reports. Another significant bias impeding the estimation of exact prevalence of PFS is the absence of a control group in relevant studies and the voluntary participation of the participants [16]. Moreover, in contemporary times, young men frequently seek information on urogenital conditions, sexual health and dysfunction from internet communities and social media rather than consulting healthcare professionals. This reliance on peer advice introduces a potential source of bias, leading to incomplete data and the underrepresentation of cases [51, 52]. Low compliance rate by the clinicians may also be responsible for incomplete data of suspected side effects [53]. Moreover, the symptoms in PFS vary in intensity and quality which adds heterogeneity in manifestation and undermines the standardization of complications. In a large cohort of men aged 66 years or older, the use of finasteride did not show an increased risk of suicide, but it revealed a heightened risk of self-harm and depression compared to unexposed men, indicating notable heterogeneity in adverse events [54]. Additionally, although PFS symptoms often manifest with variable timing after the cessation of the drug, individuals may struggle to accurately recall and report the onset, duration, and severity of symptoms. This recall bias can lead to an underestimation or overestimation of prevalence and represents a common bias in epidemiology and clinical outcomes [55, 56]. Last but not least, the lack of clarity in defining the syndrome contributes to variability in reported cases and hinders the establishment of a cohesive understanding of PFS prevalence. Efforts to reach a consensus on diagnostic criteria are essential to enhance the accuracy and reliability of prevalence estimates for PFS.

POTENTIAL MECHANISMS OF PFS

Experimental studies have also provided insights concerning the association of finasteride with mental health through observations at the neurobiological level. Finasteride seems to have a significant impact on neuroactive steroid levels, steroid receptors, and gamma-aminobutyric acid receptor subunits, indicating a potential impact on neurotransmission in adult male mice [57]. In their study Römer et al. administered finasteride over a moderate duration in murine models and observed a notable reduction in the levels of 5-alpha-DHT in the brain and a decrease in the count of newly generated cells and young neurons in the hippocampus were noticed. The hippocampus is associated with cognition and therefore, the findings may represent a linkage of finasteride usage and the manifestation of depression. The effect was reversible several days after the last medication dose [41]. Melcangi et al reported the effect of finasteride on neuroendocrine alteration as the dominant mechanism in 8 of 16 men with possible PFS patients who were diagnosed with major depressive disorder, while all reported ED, varying from mild-moderate to severe. Significant reductions were seen in pregnenolone, progesterone, dihydroprogesterone, dihydrotestosterone, and 17 beta-estradiol, alongside increases in dehydroepiandrosterone, testosterone, and 5-alpha-androstane-3alpha,17beta-diol in cerebrospinal fluid. Although similar disruptions were present in plasma, they did not mirror the CSF changes precisely. These alterations extend beyond the expected impact of finasteride on 5-alpha-reduced steroid metabolites, indicating a broader influence of the drug on neuroactive steroid levels in patients with PFS, suggesting a multifaceted mechanism behind the syndrome [58]. The same authors explored the occurrence of epigenetic modifications in patients with PFS to elucidate the underlying mechanisms of symptom onset and persistence. The authors described a tissue-specific methylation pattern of the SRD5A2 promoter (a regulator of the expression of the gene encoding 5-ARI type 2) in the cerebrospinal fluid of PFS patients, not observed in blood samples nor associated with the SRD5A1

Table 2. Pertinent studies reporting post-finasteride syndrome.

Study (year)	Aim of the study	Population	Main results	Conclusions	Possible biases
Irwig and Kolukula (2011) [42]	To characterize the types and duration of persistent sexual side effects in otherwise healthy men who took finasteride for alopecia	71 male patients, mean age 31.3 years, who developed new sexual side effects on finasteride which persisted for at least 3 months after discontinuation of the medication, were interviewed through Skype or telephone	94% reported low libido, 92% erectile dysfunction, 92% decreased arousal, mean number of sexual episodes per month dropped from 25.8 before finasteride to 8.8 after finasteride ($p < 0.0001$) Effects persisting for 40 months and for 20% of the participants for over 6 years	The study suggests persistent sexual side effects can occur with finasteride use and physicians prescribing the medications should discuss the risk of these long-term side effects	Selection bias and reliance on self-reporting, post-hoc approach, possible recalling bias
Irwig (2012) [43]	To monitor men experiencing ongoing sexual dysfunction after finasteride use to determine if their sexual health issues are resolved.	54 male patients, mean age of 31 years, who developed new sexual side effects on finasteride which persisted for at least 3 months after discontinuation of the medication, were interviewed through Skype or telephone	Persistent sexual side effects continued in 96% of participants at 14 months after original interview (Irwig and Kolukula, 2011) During the interviews, 7% of the participants reported persistent sexual side effects lasting between 3 to 6 months, 9% experienced these effects for 7 to 11 months, 44% had symptoms persisting for 1 to 2 years, 19% for 3 to 5 years, and 20% faced these issues for 6 years or more.	Prescribers and users should be informed about the long-term risks associated with a drug for cosmetic use. A thorough evaluation of men's mental health is advised in men struggling with symptoms in the long term.	Selection bias, reliance on self-reporting, post-hoc approach, possible recalling bias
Melcangi et al. (2013) [58]	To evaluate the levels of neuroactive steroids in both plasma and CSF in male patients with likely PFS syndrome comparing to age-matched, healthy controls	3 male patients 43, 44, 32 years of age, who were treated with finasteride for androgenic alopecia and experienced enduring sexual side effects, anxiety and depression following the cessation of the drug	The CSF levels of testosterone and DHT varied significantly between the patients and controls, as did the levels of 17β-estradiol, suggesting a systemic impact of finasteride on steroid metabolism	Results provided a molecular basis for mental impairment noticed in men having treated with finasteride despite discontinuation of the medication	Small sample size
Cecchin et al. (2014) [80]	To investigate whether there is a variance in the distribution of the number of CAG (rs4045402) and GGN (rs3138869) repeats among patients with possible PFS after treatment for alopecia	69 males, mean age of 35 years The duration of treatment averaged 815 days, with a range spanning from 17 to 5280 day	84% of men reported sexual dysfunction after treatment, while dysfunction was reported at 0% before treatment 24.1% had anxiety, 74.1% irritability, 32.5% depression. polymorphisms in the androgen receptor gene were more frequently found in individuals with androgenetic alopecia who experienced persistent side effects after using finasteride	The presence of polymorphisms shows a significant link between the use of finasteride and the continuation of psychological symptoms even after discontinuing the medication	Retrospective design Lack of control group (men receiving finasteride but not experiencing post-finasteride syndrome)
Ganzer et al (2015) [14]	To experience the extent of post-finasteride syndrome in physical, psychological and cognitive domains in men with a recent history of taking finasteride for alopecia	131 males, mean age of 24 years More than 50% had taken finasteride more than 12 months and had stopped finasteride for than 12 months	84% reported that they had no symptoms while taking the medication Over 50% of men reported a constellation of symptoms (physical, sexual libido, disorders of penis and testes,	Before starting finasteride treatment for hair loss, healthcare providers should inform patients about the possibility of experiencing side effects that could last for an indeterminate amount of time	Selection bias and reliance on self-reporting, Recall bias (participants had attended clinics before conduction of survey) Lack of control group

Table 2. continued

Study (year)	Aim of the study	Population	Main results	Conclusions	Possible biases
			cognition, psychological disorders including suicidal ideation)		No other correlations (rare events, laboratory examinations)
Chiriaco (2016) [16]	To explore the clinical symptoms of men with possible PFS	79 men, mean age of 33.4 years, treated with finasteride for 27.3+/−33.21 months for alopecia an experienced sexual and non-sexual AEs over 6 months after medication discontinuation	In 89.9% of participants symptoms occurred during treatment The most frequent sexual symptoms were loss of penis sensitivity in 87.3%; reduced ejaculatory force, decreased penile temperature, penile flaccidity were observed in more than 50% - erectile dysfunction was noted in ~ 50% of the participants Concerning mental health issues, anhedonia was present in 75.9%, concentrations issues in 72%, anxiety in 25.3%, loss of muscle tone/mass in 51%, weight gain, rigidity in muscle movements in less than 51%	Clinicians dealing with possible PFS can be assisted by the frequency and type of symptoms as reported in the study Arizona Sexual Experience Scale (ASEX) can be used to assess men before and after treatment with finasteride	Lack of baseline information Self-reported symptoms and voluntary participation Lak of objective tests concerning specific symptoms (e.g., penile sensitivity, temperature and flaccidity)
Cauci (2017) [60]	To investigate whether (CAG)n-rs4045402 and (GGN)n-rs3138869 polymorphisms in the androgen receptor gene are involve in men with possible PFS	66 men, median age of 32 years treated with finasteride for alopecia for median time of 360 days and developed persistent adverse effects lasting for at least 6 months after drug discontinuation	57.6% of participants reported symptoms to be worsening after discontinuation Specific polymorphisms [(CAG)n and (GGN)n] were involved in two specific symptoms of scrotal discomfort and increased skin dryness	Genetic implications are involved in men with possible PFS Future research is necessary to clarify the pathophysiologic pathways	Limited sample Reduced clinical applicability Lack of objectivity of symptoms reported Retrospective design
Ganzer (2018) [18]	To investigate if pre-existing psychiatric diagnosis may influence anxiety and depression among men treated with finasteride	Follow-up study (Ganzer et al. [14]) of 97 men treated with finasteride and seeking treatment for both physical and psychological symptoms after having stopped the medication	55% confirmed pre-existing psychiatric diagnosis prior to treatment with finasteride and 28.8% of diagnosis in a first-degree relative	Axis I disorders (anxiety, dissociation, eating and mood, psychotic disorders and substance users et al) may increase the risk of experiencing persistent emotional symptoms possibly triggered by finasteride	Lak of comparison group Self-report design increases the selection bias
Walf (2018) [39]	To categorize the nature of physical and psychological effects of finasteride	244 cases were reviewed from discussions at propeciahelp.com and AEs regarding the previous use of finasteride were recorded	Antiandrogenic AEs were reported in 32%, estrogenic in 19%, central in 30%, non-specific in 5% and 14% reported AEs in all categories	The stratification of AEs associated with PFS could illuminate the underlying mechanisms Patient-reported outcomes offers insights into the effects of finasteride as perceived by those affected	Selection and recall biases Subjective reporting (not assessment by clinician) Lack of specificity and potential risk of cofounders
Borgo (2020) [79]	To examine the gut microbiota in men with finasteride comparing to a healthy cohort	23 men, 25–51 years of age reporting persistent AEs after the administration of finasteride for mean of 1176 days and had discontinued the medication for at	Flying into a rage or anxiety were reported sometimes/often before treatment (69.6% and 65.2%, respectively) Sexual dysfunction, psychological and cognition	Investigating the gut microbiota may offer a diagnostic marker and possible therapeutic area in men with PFS	Small sample size

Table 2. continued

Study (year)	Aim of the study	Population	Main results	Conclusions	Possible biases
		least 3 months compared to 10 healthy men	complaints, muscular problems, and physical alterations were reported in more than 50% of the PFS patients at the moment of sample collection Richness and diversity of gut microbiota was significantly reduced in men with possible PFS compared to controls		
Chiriaco (2016) [16]	To explore the clinical symptoms of men with possible PFS	79 men, mean age of 33.4 years, treated with finasteride for 27.3+/−33.21 months for alopecia an experienced sexual and non-sexual AEs over 6 months after medication discontinuation	In 89.9% of participants symptoms occurred during treatment The most frequent sexual symptoms were loss of penis sensitivity in 87.3%; reduced ejaculatory force, decreased penile temperature, penile flaccidity were observed in more than 50% - erectile dysfunction was noted in ~ 50% of the participants Concerning mental health issues, anhedonia was present in 75.9%, concentrations issues in 72%, anxiety in 25.3%, loss of muscle tone/mass in 51%, weight gain, rigidity in muscle movements in less than 51%	Clinicians dealing with possible PFS can be assisted by the frequency and type of symptoms as reported in the study Arizona Sexual Experience Scale (ASEX) can be used to assess men before and after treatment with finasteride	Lack of baseline information Self-reported symptoms and voluntary participation Lak of objective tests concerning specific symptoms (e.g., penile sensitivity, temperature and flaccidity)

promoter. This epigenetic modification could significantly influence neuroactive steroid levels and contribute to the behavioral and neurological disturbances reported in PFS [59]. Genetic polymorphisms have also been described to be correlated with specific symptoms like scrotal discomfort or sense of dry skin [60].Together, these studies reveal that the repercussions of finasteride extend into intricate neurobiological and epigenetic territories, underlining the necessity for further research to fully comprehend and address the multifaceted nature of PFS and its profound implications on mental and neurological health.

Lastly, one of the emerging mechanisms possibly explaining the onset of symptoms after finasteride discontinuation is the novel state of androgen deficiency [61]. This model depicts that the inhibition of the 5-ARI by finasteride leads to lower levels of 5-DHT, the primary mediator of effects of testosterone's effect on several tissues with important physiological effects. This inhibition results in a novel state of androgen deficiency with normal serum levels of testosterone at clinical analysis, but with hindered peripheriral effects [62].

NOCEBO EFFECT AND CONTROVERSIES

It is important to note that symptoms attributed to finasteride may also be present in men treated with placebo, thus raising concerns regarding the actual occurrence of finasteride-induced adverse events [63]. As a result, this observation underscores the difficulty in distinguishing between symptoms caused directly by finasteride and the anticipation of possible harm rather than the actual effects of the medication. Understanding the psychosomatic effects of medications as illustrated by the nocebo and placebo effect is crucial for a better insight into PFS. The placebo effect refers to the improvement in health conditions or the alleviation of symptoms following treatments that are not known to have any direct physical impact; conversely, the nocebo phenomenon is defined as "patients" reported manifestation or worsening of related symptoms induced by sham or active therapies " [64]. To demonstrate the impact of nocebo effects in men prescribed finasteride, Mondaini et al. conducted a study examining how counseling on sexual side effects could lead to higher rates of sexual dysfunction compared to men that received no counseling. The study involved 107 men diagnosed with prostatic enlargement who were taking finasteride daily. The participants were randomly assigned to group 1 (not informed about sexual side effects) or group 2 (informed about sexual side effects). After one year of therapy, the authors reported a significantly higher incidence of sexual disturbances among men in group 2. They affirmed that this outcome was consistent with the definition of the nocebo effect [12]. It must be cautiously considered that the nocebo effect seems to be prevalent in patients with mental health disorders, such as paranoid and passive-aggressive (negativistic) disorders, with particular emphasis on histrionic personality disorder, which appears to have a higher prevalence in men with androgenetic alopecia [65, 66]. However, the scientific society holds mixed views on PFS, recognizing concerns about mental health, especially for men at risk, while also highlighting the widely agreed-upon benefits of finasteride in easing emotional distress linked to male androgenetic alopecia [67].

POPULATIONS AT RISK

While finasteride is acknowledged for its potential side effects, it is important to recognize that not all of these effects should be deemed syndromicl. The challenge lies in pinpointing those patients who are genuinely at risk of a broad toxicity or report a variety of side effects, necessitating an individualized approach to patient care and management [68]. It should be noted that the AEs of finasteride are dose-independent and may occur in all men, but more likely in young men as shown by the analysis of the FEARS dataset by Harrell et al. [69]. The study by Maffei et al. observed a higher prevalence of personality disorders, including paranoid personality disorder with traits of suspicion and social withdrawal, narcissistic personality disorder characterized by a grandiose sense of self-importance, and features resembling various disorders marked by impulsivity and emotional dependence, among individuals with male pattern hair loss compared to the general population [65]. It is possible that patients with personality disorders may present unique challenges in the treatment of their hair loss, and their responses to interventions, including the use of medications like finasteride and may be more prone to the heightened sensitivity to negative information, cognitive biases, emotional regulation issues and interpersonal sensitivities and enhancement of the nocebo effect [70]. Moreover, a small-size study based on data from three men reported alterations in five genes related to neurobiological circuitry and neurosteroids transmission in men with the profile of PFS, thus strengthening the idea of biological predisposition [15]. These alterations may assist in future individualized management or to be utilized as screening for men who may be at risk. Clinicians should also be cautious about certain risk factors of personality disorders when considering finasteride, particularly in young men, especially those with a history of mental health issues, substance abuse (especially alcohol), antisocial and suicidal behavior [71, 72]. In assessing the risk of suicidal behaviors associated with the use of finasteride compared to dutasteride in men aged 50 years or older, a nationwide cohort study in France found no increased risk of suicide or self-harm with finasteride. However, among individuals with a history of mood disorders, the study found that finasteride was associated with an increased risk of any suicidal outcome with a Hazard Ratio (HR) of 1.64 (95% Confidence Interval [CI] 1.00–2.68), suicide death (HR = 2.71 [95% CI 1.07–6.91]), self-harm by violent means (HR = 3.11 [95% CI 1.01–9.61]), and self-harm resulting in admission to an intensive care unit (HR = 3.97 [95% CI 1.26–12.5]) [73]. We suggest a risk assessment and relevant clinical guidance in Table 3.

DISCUSSION

If treatment with finasteride is necessary, clinicians should be vigilant with men who may be at risk of developing PFS and discuss with them that the drug may exacerbate pre-existing mental health issues, interact with substance abuse at the level of neurosteroids which can possibly impair judgment, increasing risk-taking behaviors and finally trigger suicidal thoughts and actions. When appropriate, clinicians should encourage a comprehensive psychiatric evaluation or a multidisciplinary approach and discuss alternative treatments before prescribing finasteride. Patient education is also pivotal in that regard to raise awareness, optimize decisions and avoid stigmatization.

In this setting, although the nocebo effect could contribute to the complexity of PFS, addressing conflicting perspectives is crucial. Further research is needed to establish clearer diagnostic criteria and explore the psychological nuances of PFS for a more comprehensive understanding. As PFS remains a debate, these insights highlight the urgent need for well-designed clinical trials to accurately determine finasteride's risks. They also draw attention to the psychological aspects of drug side effects, indicating that PFS symptoms may be influenced by psychological factors, not just finasteride's biochemical effects. This adds complexity to diagnosing and managing PFS, stressing the need for a holistic approach that addresses both physical and psychological patient experiences.

Difficulties in defining a clear symptomatologic pattern identifying the syndrome lead to challenges in finding a proper therapeutic approach. Indeed, current literature is scant in possible management strategies and no specific recommendations to treat this syndrome are available [74]. Only clinical

Table 3. Risk assessment and clinical suggestions for patients potentially affected by post-finasteride syndrome.

Who may be at risk?	Suggestions for clinicians
Patients with personality disorders (e.g., paranoid, narcissistic, traits of suspicion, social withdrawal, grandiose sense of self-importance, impulsivity, emotional dependence)	- Be aware of the heightened sensitivity to negative information and cognitive biases and the potential enhancement of the nocebo effect - Screen for personality disorders when considering finasteride, especially in younger men
Individuals with a history of mental health issues	- Discuss the possibility that finasteride may exacerbate pre-existing mental health conditions - Encourage a comprehensive psychiatric evaluation and/or a multidisciplinary approach before prescribing
Patients with a history of substance abuse (especially alcohol), antisocial, and suicidal behavior	- Be vigilant for the risk of neurosteroids interaction which can impair judgment and increase risk-taking behaviors - Discuss the potential for finasteride to trigger suicidal thoughts and actions.
Men with alterations in genes related to neurobiological circuitry and neurosteroid transmission (biological predisposition to PFS)	- Consider utilizing genetic and neurobiological alterations as screening tools for identifying patients at risk - Explore individualized management strategies
Individuals with a history of mood disorders using finasteride	- Be aware of the increased risk of suicidal outcomes, including suicide death, self-harm by violent means, and self-harm resulting in admission to an intensive care unit - Discuss alternative treatments and the importance of psychiatric evaluation

Table 4. Future directions.

Aspect	Future directions
Research	- Focus on identifying causative factors of PFS to redefine it from a symptomatic syndrome to a disease with a clear etiological basis - Well-designed clinical trials to accurately determine prevalence - Explore genetic predispositions and biomarkers for early identification and personalized management strategies
Policymakers	- Implement regulations to ensure thorough reporting and tracking of adverse drug reactions, including those related to finasteride - Encourage funding and support for PFS research to understand its pathophysiology and treatment options better - Develop guidelines for consultation, safe prescribing practices and patient monitoring when using finasteride
Patients advocates	- Creation of educational materials and programs to inform patients about their treatment options, including risks associated with finasteride - Advocate for the rights of PFS patients in healthcare settings and research agendas
Social awareness	- Leverage media and social platforms to share information about the potential risks associated with finasteride use and status of research on PFS - Foster open discussions among patients, clinicians, and researchers to reduce stigma surrounding PFS - Support the establishment of community support groups and forums where PFS patients can exchange experiences and strategies for coping.

collaboration between different medical specialists, such as urologists, endocrinologists, psychiatrists and neurologists, could disclose potential multidisciplinary management of the disease.

Future directions for PFS research should concentrate on elucidating specific causative factors, aiming to redefine PFS from a broadly symptomatic syndrome to a disease with a clear etiological basis, potentially leading to targeted treatment modalities [75]. This endeavor is not only scientifically crucial but also addresses significant bioethical concerns raised by the current syndrome-based diagnosis. Moreover, patient experiences and symptoms must be treated with utmost respect and dignity, especially when causation remains uncertain [76]. Advancing PFS research requires an approach that balances rigorous scientific investigation with compassionate patient care, ensuring that both the scientific and ethical aspects of this condition are adequately addressed. In this regard, patient advocacy groups including consultants and allied clinicians, can also play a significant role in raising awareness about the entity, providing support to those possibly affected, and contributing to the understanding of patient experiences and needs [77, 78]. Their involvement ensures that research directions are aligned with patient concerns, whereas ethical considerations, particularly in respect for patient experiences, are prioritized. Furthermore, research on biomarkers can offer a novel avenue for diagnosing PFS. A study has shown that patients with possible PFS exhibit significant alterations in gut microbiota, evidenced by decreased α-diversity, indicating reduced richness and diversity, and distinct β-diversity patterns compared to healthy controls [79]. Future research could focus on validating these microbiota alterations as diagnostic markers. A list of suggestions for future directions is presented in Table 4.

Our review is not without limitations. First of all, published data are not consistent regarding the onset of the PFS in terms of timing from the drug start or discontinuation, and symptoms manifestation and burden. Second, scientific literature refers to long-term AEs mainly related to finasteride. Possible long-term side effects related to the use of the other and most potent 5-ARI, dutasteride, have not been widely disclosed, with only a few authors reporting concerns on long-term non-reversible effects [69].

CONCLUSION

In conclusion, PFS represents a complex and multifaceted entity, challenging clinicians and researchers alike in its diagnosis, management, and understanding. This complexity necessitates a

multidisciplinary approach, integrating insights from urology, psychiatry, and pharmacology to effectively address the diverse manifestations of PFS. It is crucial to acknowledge that the responsibility for managing and identifying PFS extends beyond urologists, involving a range of healthcare professionals. The recognition of potential risk factors, such as personality disorders and genetic predispositions, emphasizes the need for personalized patient assessments before initiating finasteride treatment. Moving forward, this demands a heightened focus on patient education, careful monitoring for adverse effects, and exploration of alternative therapeutic options which could help avoid prescription of finasteride. The goal is to optimize treatment outcomes while minimizing the risk of PFS, thereby improving patient care for conditions treated with finasteride.

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AUTHOR CONTRIBUTIONS

Simone Cilio: Writing and editing. Georgios Tsampoukas: Writing, editing, and overall project management. Afonso Morgado: Writing. Pedro Ramos: Writing. Suks Minhas: Designing the study, writing, editing, and provided final approval.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Georgios Tsampoukas.