Post-finasteride syndrome: a surmountable challenge for clinicians

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Post-finasteride syndrome (PFS) is a constellation of serious adverse side effects manifested in clinical symptoms that develop and persist in patients during and/or after discontinuing finasteride treatment in men with pattern hair loss (androgenetic alopecia) or benign prostatic hyperplasia. These serious adverse side effects include persistent or irreversible sexual, neurological, physical and mental side effects. To date, there are no evidence-based effective treatments for PFS. Although increasing number of men report persistent side effects, the medical community has yet to recognize this syndrome nor are there any specific measures to address this serious and debilitating symptoms. Here we evaluate the scientific and clinical evidence in the contemporary medical literature to address the very fundamental question: Is PFS a real clinical condition caused by finasteride use or are the reported symptoms only incidentally associated with but not caused by finasteride use? One key indisputable clinical evidence noted in all reported studies with finasteride and dutasteride was that use of these drugs is associated with development of sexual dysfunction, which may persist in a subset of men, irrespective of age, drug dose or duration of study. Also, increased depression, anxiety and suicidal ideation in a subset of men treated with these drugs were commonly reported in a number of studies. It is important to note that many clinical studies suffer from incomplete or inadequate assessment of adverse events and often limited or inaccurate data reporting regarding harm. Based on the existing body of evidence in the contemporary clinical literature, the author believes that finasteride and dutasteride induce a constellation of persistent sexual, neurological and physical adverse side effects, in a subset of men. These constellations of symptoms constitute the basis for PFS in individuals predisposed to epigenetic susceptibility. Indeed, delineating the pathophysiological mechanisms underlying PFS will be of paramount importance to the understanding of this syndrome and to development of potential novel therapeutic modalities. (Fertil Steril® 2020;113:21–50. ©2019 by American Society for Reproductive Medicine.)

Key Words: Sexual dysfunction, erectile dysfunction, loss of libido, depression, suicidal ideation

5α-reductases (5α-Rs) are a family of isozymes expressed in a wide host of organs and tissues including central nervous system (CNS). 5α-Rs play key physiological roles in regulation and development of male sexual differentiation and metabolism (1–7). 5α-Rs catalyze the transformation of multiple gonadal, adrenal and CNS steroid precursors into active functional hormones and neuroactive steroids (8–15).

Finasteride and dutasteride are synthetic 5α-reductase inhibitors (5α-RIs) which bind to 5α-Rs active sites with high affinity. The pharmacokinetics of finasteride and dutasteride are as such that they are nearly irreversible inhibitor of 5α-Rs, with slow rate of dissociation, leading to a long-lasting effect of the drug, regardless of dose administered. The irreversible nature of the inhibition by this class of drugs may lead to epigenetic changes, such as DNA methylation of the androgen receptor gene or the 5α-reductases genes. In addition, this class of drugs may act as endocrine disruptors, contributing to several potential mechanisms by which these drugs elicit serious and undesirable sexual and psychological adverse effects.

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Since 5α-dihydrotestosterone (5α-DHT) plays a key role in erectile physiology (16–22), including activation of nitric oxide synthase (NOS) and increasing blood flow in penile tissue, inhibition of 5α-Rs by finasteride or dutasteride contributes to erectile dysfunction (ED). Studies in the animal models (16–22) demonstrated decreased biosynthesis and circulation of 5α-DHT, reduced expression and activation of endothelial (eNOS) and neural (nNOS) nitric oxide synthases (19–22), thus attenuating penile tissue relaxation and resulting in ED. In addition, absence of or reduced levels of 5α-DHT result in penile trabecular smooth muscle cells death concomitant with increased deposition of connective tissue leading to alterations in penile tissue histoarchitecture and impeding its

compliance, thus, contributing to ED (20–22). The consequence of these pathophysiological changes is fibrosis (scarring) of penile tissue, leading to poor tissue compliance, venous leakage and ultimately ED (20–22).

Several pre-clinical studies emphasized the importance of neuro-steroids in maintaining central nervous system (CNS) function (23–48). Since neuro-steroid biosynthesis is limited by 5α-Rs activities, inhibition of these enzymes in the CNS by finasteride or dutasteride reduces the bioavailability of these critical physiological modulators. Indeed, several studies have assessed the concentrations of neuroactive steroids in cerebrospinal fluid (CSF) of patients who were former finasteride users and exhibited persistent symptoms. These studies demonstrated a significant reduction in 5α-DHT concomitant with increased testosterone and 3α-diol derivatives and decreased progesterone metabolites such as 5α-dihydroprogesterone (DHP) and 5α, 3α, tetrahydroprogesterone (5α, 3α, THP; allopregnenolone) concomitant with increased levels of substrate precursor, such as pregnenolone (46–48). These findings suggest that alteration in neuroactive steroids, may be associated with depression symptoms in patients who were treated with finasteride and/or discontinued finasteride use (46–48). A recent clinical trial reported on the role of neuro-steroids in treatment of depression, suggesting a critical role of neuro-steroids and their interactions with neurotransmitter receptors (49).

Post-finasteride syndrome (PFS) represents a constellation of sexual, physical, and neurological symptoms that develop and persist during treatment and/or after finasteride discontinuation (Fig. 1) (50, 51). Among the reported sexual and physical adverse effects associated with PFS are: loss of libido; ED; ejaculatory disorders; reduction in penis size; penile curvature; reduced sensation; gynecomastia; muscle atrophy; fatigue; and severely dry skin. Reported neurological (psychiatric) adverse events include: depression and anxiety; cognitive impairment; and suicidal ideation (50–75). Furthermore, several case studies have linked finasteride with male infertility (76–79), cataract and intraoperative floppy-iris syndrome (80), pseudoporphyria (81), and T cell–mediated acute localized exanthematous pustulosis (82).

In this review, we summarize the findings from the scientific and clinical literature including data reported in case studies , observational studies, non-randomized and randomized clinical trials as well as systematic reviews and meta-analyses to shed light on this highly controversial and very complex clinical issue which deserves a deeper and more careful assessment in order to provide appropriate clinical care for individuals afflicted PFS.

METHODS

A search of Medline, PubMed, Ovid, and Google scholar database was conducted for relevant articles published from 1989 to August 2019 on clinical use of finasteride and dutasteride and revealed more than 250 published articles. These articles were reviewed, and data were extracted from case studies, observational studies, non-randomized and randomized clinical trials as well as systematic reviews and meta-analyses.

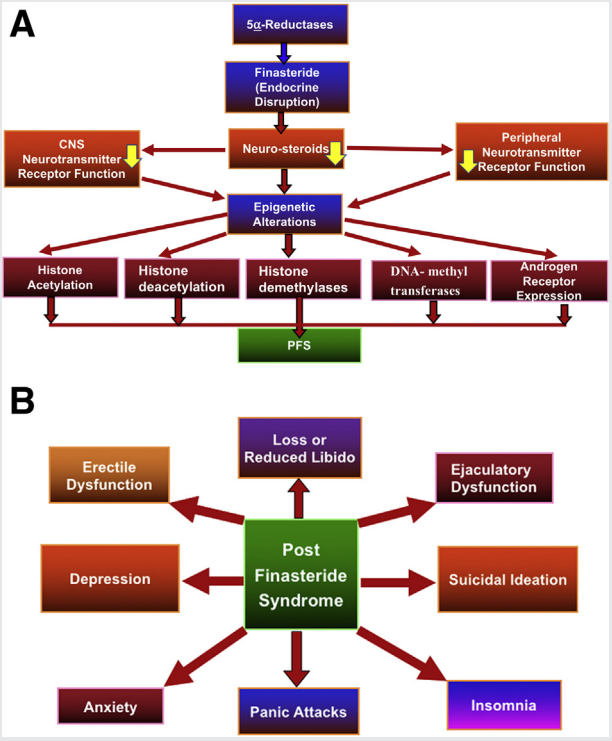
RESULTS

Clinical Studies Reporting Sexual Adverse side effects

A body of evidence exists supporting the presence of a constellation of sexual, physical, and psychological symptoms that develop during and/or after finasteride exposure and persist after drug discontinuation (83–86). It is important to note that the sexual adverse side effects of finasteride have been reported in almost all clinical studies, albeit with varying degrees of severity (12, 13, 14, 87–118). Table 1 summarizes findings of studies with finasteride or dutasteride in the treatment of men with BPH or for prevention of prostate cancer (87, 88, 90, 95, 97–99, 106, 112, 115, 119–126). One of the most prominent observations on the safety of these drugs is the increased incidence and persistence of sexual dysfunction (decreased or loss of libido, ED and orgasmic dysfunction), irrespective of duration of study, drug or dose used. Table 2 summarizes the findings in young men with male pattern hair loss (AGA) who were treated with finasteride or dutasteride. The most notable serious adverse effects in these studies were loss or reduced libido, ED, orgasmic dysfunction, increased anxiety, depression and suicidal ideation (46–48, 52, 53, 56, 67, 69, 71, 74, 84, 89, 127–160). Out of the studies listed in Table 2, more than half of these studies were randomized controlled clinical trials. However, adequate safety evaluations or reporting was not provided in many of these studies. Only few studies reported on the methods for assessments or the scales or questionnaires used to evaluate the sexual and neurological adverse side effects. In most cases the reporting of harm in these studies was considered, at best, inadequate. It is possible that because in many clinical trials reporting on sexual adverse effects in response to finasteride or dutasteride were made by an interview, thus introducing a real bias given many men are hesitant to answer question regarding their sexual activity, especially if the interviewer is a female. While some studies have disclosed conflicts of interest, roughly half of all studies are funded by the drug manufacturer and in many cases the data management, evaluation and reporting also carried out by the manufacture. Such studies may suffer from serious biases, inaccurate data reporting and lack of standardized methods of adverse events assessment. Findings from these studies were used by clinicians to argue against the existence of persistent sexual adverse side effects and in turn dismissed any claims that PFS is a real syndrome.

Table 3 summarizes the findings from systematic reviews and meta-analyses and pharmacovigilance studies and general reviews (60, 83, 85, 86, 102, 161–176). While some of these studies attempted to dismiss the mere existence of persistent sexual and psychiatric adverse events, the overwhelming conclusions of majority of these studies acknowledged the evidence for the persistent sexual and neurological adverse side effects and

FIGURE 1



(**A**) A hypothetical model of finasteride acting as an endocrine disrupter. Finasteride via inhibiting key neuro-steroid biosynthesis promotes epigenetic changes in gene expression leading to silencing or attenuating physiological responses. Inhibition of 5α-reductases activities by the high affinity, slow dissociating inhibitor (finasteride) results in depleting the substrate precursors for the 3α-hydroxy-steroid dehydrogenases and therefore blocking biosynthesis of neuro-steroids. This inhibition results in attenuating the function of neurotransmitter receptors and promotes changes in the expression of a host of gene products, thus eliciting epigenetic changes manifested in histone acetylation, methylation, and DNA methylation and upregulation of androgen receptor (AR) gene expression. These changes together with depleted neuro-steroid pool manifest itself in the development of PFS in susceptible individuals. (**B**) The epigenetic changes induced by finasteride elicited endocrine disruption, illustrated in a, produce pathophysiological changes that are manifested as constellations of symptoms of PFS. (Adapted, with permission from the publisher, from Traish AM. The post-finasteride syndrome: clinical manifestation of drug-induced epigenetics due to endocrine disruption. Current Sexual Health Reports 2018;10(3):88–103.)

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highlighted the need for better understanding of this syndrome in order to offer treatment for afflicted individuals. Furthermore, some of these studies pointed to the potential bias in many of the reported clinical trials and highlight the need to educate clinicians to consider these adverse effects more seriously. It is important to note that in some studies, safety assessments were not carried out appropriately or were not reported.

It is worth noting that loss or reduced libido and ED were consistently noted in double-blind, randomized, placebo-controlled trials, as well as observational studies (Tables 1–3). For example, the findings of Corona et al. (170, 177), in a meta-analysis of 46,733 cases demonstrated increases the risk of ED with finasteride. In the study by Liu et al. (173) a meta-analysis of 17 clinical trials with 17,494 subject's safety evaluation was reported only in 10 trials with 6,779 patients. The authors stated, "The pooled relative risks for sexual dysfunction were 2.56 (95% confidence interval [CI] 1.48–4.42) in men with BPH and 1.21 (95% CI 0.85–1.72) in men with AGA; those for erectile dysfunction were 1.55 (95% CI 1.14–2.12) in men with BPH and 0.66 (95% CI0.20–2.25) in men with AGA; and those for decreased libido were 1.69 (95% CI 1.03–2.79) in men with BPH and 1.16 (95% CI 0.50–2.72) in men with AGA." Interestingly, the authors concluded that there were no connections between finasteride use and ED. Similarly, Hagberg et al. (174), in a cohort 12,346 medical records also concluded that there was no relationship between finasteride use and ED. This contrasts with the study by Corona et al. (170, 177). More importantly, Fwu et al. (115), reported on a data from a multicenter, randomized study comprising 2,783 patients in which risk of ED was increased with finasteride use.

It is important to note several studies have reported that finasteride-induced adverse effects may not resolve with drug discontinuation and may become persistent or irreversible in a subset of patients (67–75, 83, 84, 128, 129). This may be attributed to susceptibility of such subjects to epigenetic predisposition (50). In men who exhibit symptoms of PFS approximately 40.5% of patients had difficulties with erection, and 3.8% had no erections at all. Other difficulties include achieving orgasm and loss of penis sensitivity, decreased ejaculatory force, anhedonia; lack of mental concentration, and loss of muscle tone or mass (67–75, 83, 84, 128, 129). In a study by Wessells et al. (88), a 4-year, randomized, double-blind, placebo-controlled trial assessing the efficacy and safety of finasteride 5 mg in 3,040 men, aged 45 to 78 years, with symptomatic BPH, enlarged prostates, and no evidence of prostate cancer, the authors reported that during year 1 of the study, 15% of finasteride-treated patients and 7% of placebo-treated patients had sexual adverse events that were considered drug related by the investigator ($P < .001$), The authors reported that sexual adverse events resolved, while continuing therapy, in 12% of finasteride patients and 19% of placebo patients. Only 4% of finasteride and 2% of placebo patients discontinued the study because of sexual adverse events. In men who discontinued finasteride treatment, only 50% of patients experienced resolution of their sexual adverse events after drug discontinuation. Although few studies claimed complete reversibility of sexual dysfunction in all patients after discontinuation of finasteride treatment (88, 89, 145), other studies describe patients experiencing irreversible and persistent adverse side effects (46–48, 50, 52, 53, 55, 56, 58–62, 67–72, 74, 75, 83, 84, 127–129). These findings were supported by data from a retrospective study by Kiguradze et al. (84), in which they examined records of 11,909 patients in which 167 patients were identified with

TABLE 1

Studies in Men with BPH treated with finasteride or dutasteride

Author, year (reference)	Nature of the study	Authors' interpretations	Safety evaluations methods
Nickel JC et al., 1996 (95)	Double-blind, parallel-group, placebo-controlled, multicenter, prospective randomized study. A total of 613 men were entered into the study; 472 completed the 2 years of treatment.	The incidence of adverse events related to sexual dysfunction were significantly higher in the finasteride group than in the placebo group (ejaculation disorder 7.7% vs. 1.7% and impotence 15.8% vs. 6.3%; $P < .01$ for both parameters).	Investigators assessed patient well-being, incidence of adverse events and treatment compliance during an open-ended interview at each visit.
McConnell et al., 1998 (98)	Double-blind, randomized, placebo-controlled trial of 3,040 men with moderate- to-severe urinary symptoms and enlarged prostate glands who were treated daily with 5 mg of finasteride or placebo for four years. Complete data on outcomes were available for 2,760 men.	The only drug-related adverse effects that occurred in 1% or more of the men for which the rates differed significantly between the groups were symptoms of sexual dysfunction, breast enlargement or tenderness, and rashes.	Investigators assessed patient well-being, incidence of adverse events and treatment compliance during an open-ended interview at each visit.
Moinpour et al., 2007 (122)	Longitudinal analysis of sexual function reported by men in the Prostate Cancer Prevention Trial. Sexual dysfunction was assessed in 17,313 PCPT participants during a 7-year period.	Finasteride increased sexual dysfunction only slightly and its impact diminished over time. The effect of finasteride on sexual functioning is minimal for most men and should not impact the decision to prescribe or take finasteride.	A battery of questionnaires was used to assess sexual dysfunction
Hudson et al., 1999 (99)	A Phase III North American BPH clinical trial originally enrolled 895 men, 297 of whom were randomized to receive finasteride 5 mg.	Finasteride was well tolerated, with no significant increase in the prevalence of sexual adverse events over time.	Safety was assessed throughout the study by physical examination and laboratory tests and by monitoring all clinical and laboratory adverse events at least every 6 months
Thompson et al 2003 (87)	Randomized clinical trial, 18,882 men 55 years age or older randomly assigned to treatment with finasteride (5 mg per day) or placebo for seven years.	Reduced volume of ejaculate, erectile dysfunction, loss of libido, and gynecomastia was more common in the finasteride group than in the placebo group ($P < .001$ for all comparisons).	Adverse events and side effects were reported by the men during directed interviews over the course of their treatment.
Andriole et al 2010 (119)	Randomized clinical trial, of 6,729 men who underwent a biopsy or prostate surgery 3,305 men were treated with dutasteride and 3,424 men in the placebo group	A drug-related decrease and or loss of libido was reported by the men in the dutasteride group, as compared with the men in the placebo group ($P < .001$ and $P = .03$, respectively). A drug related decrease in or loss of erectile function was reported in men in the dutasteride group as compared to the placebo group ($P < .001$).	Adverse events were reported by the investigators of the study. No details on how such events were fully assessed.
Wessells et al., 2003 (88)	A 4-year, randomized, double-blind, placebo-controlled trial assessing the efficacy and safety of finasteride 5 mg in 3,040 men, aged 45 to 78 years.	15% of finasteride-treated patients and 7% of placebo-treated patients had sexual AEs that were considered drug related by the investigator ($P < .001$) during year 1 of the study. In men who discontinued with a sexual AE, 50% and 41% experienced resolution of their sexual AE after discontinuing finasteride or placebo therapy, respectively.	During the treatment period, spontaneously self-reported sexual adverse events were recorded. Physicians were asked to classify the intensity of sexual AEs as mild, moderate or severe.
Debruyne et al., 2004 (106)	A total of 4,325 patients were randomized to dutasteride or placebo in the double-blind portion of the Phase III studies. Patients were eligible for a 2-year open-label extension, where all patients received dutasteride 0.5 mg daily (dutasteride/dutasteride (D/D) group and placebo/dutasteride (P/D group)).	The most common drug-related adverse events were sexual events (impotence, decreased libido, and ejaculation disorders) and gynecomastia. The onset of most new drug-related sexual AEs occurred within the first 6 months of therapy.	Safety was assessed through AE reporting, clinical laboratory assessments, and yearly physical examinations, which included focused gynecomastia evaluations.

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TABLE 1

Continued.

Author, year (reference)	Nature of the study	Authors' interpretations	Safety evaluations methods
Brenner &Matz 1999 (123)	Twenty-eight men with AGA, aged 53–76 years (mean, 65 years), were selected to, participate in this trial from a double blind, placebo controlled, multicenter study of subjects with moderate symptoms of BPH.	No adverse event reporting.	No assessments of adverse events were made.
Gormley et al., 1992 (122)	Double-blinded study of 1 and 5 mg of finasteride vs placebo in 895 men with BPH.	The proportion of men reporting decreased libido and decrease ejaculate volume was significantly higher ($P < .05$) in both finasteride treated groups than in the placebo group. The proportion of men reporting impotence with 1 mg finasteride were higher than in the placebo group ($P < .05$). Two men died. One died of cardiac arrest and one committed suicide.	Investigators assessed patient well-being, incidence of adverse events and treatment compliance during an open-ended interview at each visit.
Marberger et al., 1998 (97)	A double-blinded placebo controlled multicenter trial assessing long term effects of finasteride on men with BPH. Of the 3,270 men enrolled, 3,168 contributed data to the safety analysis, and 2,902 to the efficacy evaluation.	Only decreased libido, ejaculation disorders, and impotence were considered by the investigators to be drug related. A total of 273 patients reported a sexual adverse event (change in libido, ejaculation disorder, impotence, or orgasm dysfunction) during the treatment period, 165 (10%) in the finasteride group and 108 (7%) in the placebo group ($P \leq .001$).	Investigators assessed patient well-being, incidence of adverse events and treatment compliance during an open-ended interview at each visit.
Roehrborn et al., 2002 (90)	A total of 4,325 men (2,951 completed) with clinical BPH were enrolled into three identical clinical trials and randomized to 0.5 mg dutasteride daily or placebo. After a 1-month, single-blind, placebo lead-in, patients were followed up for 24 months in a double-blind trial with multiple interval assessments.	Drug-related AEs were seen in 14% and 19% of placebo-treated and dutasteride-treated patients, respectively, with sexually related AEs the most common in both groups. Impotence, reduced libido, ejaculation disorders, and gynecomastia occurred more frequently in dutasteride-treated patients. .	Investigators assessed patient well-being, incidence of adverse events and treatment compliance during an open-ended interview at each visit.
Vaughan et al., 2002 (113)	A total of 190 men with BPH entered one of two Phase II double-blind 3 to 6-month studies and 156 patients continued to take finasteride in an open label study and more than 70 patients completed 7 to 8 years of treatment.	The most common drug-related adverse events were impotence, ejaculation disorder, and decreased libido. The incidence of new occurrences of drug-related sexual adverse events was highest during the first year of the open extension and decreased to much lower levels throughout the extension.	No information was provided on how assessment of adverse events was made.
Andriole et al., 2003 (120)	The safety and tolerability data from four large, randomized, double-blind clinical trials (n =5,655) with the novel, dual 5α-reductase inhibitor, dutasteride.	Sexual adverse events were the most commonly reported class of drug-related adverse event.	Safety was assessed at each visit by asking the patient about any adverse events that had been experienced.
Tsukamoto et al., 2009 (126)	This was a randomized, double-blind, placebo-controlled, parallel-group study of 378 subjects with clinical BPH were randomized to receive placebo or dutasteride once daily for 52 weeks.	The percentages of subjects with drug-related adverse events were 5% and 6% in the placebo and dutasteride groups, respectively. The most common drug-related adverse events ($\geq$1% in any treatment group) included erectile dysfunction, stomach discomfort, libido decreased, and dizziness.	Investigators assessed patient well-being, incidence of adverse events and treatment compliance during an open-ended interview at each visit.

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TABLE 1

Continued.

Author, year (reference)	Nature of the study	Authors' interpretations	Safety evaluations methods
Fwu et al., 2014 (115)	The Medical Therapy of Prostatic Symptoms study was a multicenter, randomized, double-blind, placebo controlled clinical trial with a primary outcome of time to benign prostatic hyperplasia progression.	Men assigned to finasteride and combined therapy experienced overall statistically significant but slight worsening of ejaculatory function compared with men on placebo. Men assigned to combined therapy also experienced significant worsening in erectile function and sexual problem assessment.	Change in sexual function was a secondary outcome. We analyzed the records of 2,783 men enrolled in the study who completed the inventory at baseline and at least once during follow-up.
Kaplan et a., 2012 (112)	A retrospective analysis of 378 consecutive men treated with 5α-reductase inhibitor monotherapy (197 on finasteride and 211 on dutasteride) in a single clinic was performed.	The incidence of erectile dysfunction, ejaculatory dysfunction and decreased libido resulting in discontinuation from therapy was significantly ($P < .01$) higher in the dutasteride (5.1%, 2.4%, and 2.7% respectively) compared with the finasteride group (2.1%, 1.8%, 1.4% and respectively).	Safety assessments included International Index of Erectile Function and adverse events. Patients were evaluated at 3 months, 1 year and yearly thereafter.

Note: AE= adverse event; AGA = androgenetic alopecia; BPH = benign prostatic hyperplasia; PCPT = Prostate Cancer Prevention Trial.

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persistent ED (1.4% of the cohort versus 31.5% of patients with treatment related ED).

Clinical Studies Reporting Depression, Anxiety and Suicidal Ideation

In a series of 23 subjects (17 males, 5 females; mean age 28.16 years ± 7.68 standard deviation) who were treated with finasteride, 1 mg/day orally, for AGA, Altomare et al. (149) reported that 19 patients (14 males, 5 females) developed a mood disturbance (moderate to severe depression) during treatment (149). In this cohort, depression significantly impaired social relations, sleep and eating behavior, and increased anxiety. Irwig and colleagues reported that rates of sexual and depressive symptoms were significantly higher in former finasteride users as compared to controls (67–73). Several studies (69, 73, 74, 127, 149) reported that depressive symptoms were significantly more prevalent in finasteride users than in non-users and the incidence of moderate to severe depressive symptoms were higher in the finasteride treated patients than in non-users. Suicidal thoughts were declared in 44% of the former finasteride users and only in 3% of the controls (62, 69, 73, 74, 75). An analysis of the FDA database (FEARS) revealed persistent suicidal ideation in 7.9% of males (127).

Pathophysiological Mechanisms Contributing to Erectile Dysfunction

Several potential mechanisms account for the persistent sexual problems encountered after use of finasteride or dutasteride, including inhibition of steroidogenesis, alternations in neural network structure and function and altered blood vessels, smooth muscle cell atrophy and fibrosis of erectile tissue. It is important to note that 5α-DHT plays a key role in erectile physiology (16–22, 178–180). Thus, inhibition of T conversion to 5α-DHT by finasteride or dutasteride may interfere with erectile physiology in men treated with finasteride or dutasteride. Pinsky et al. (21) and Öztekin et al. (22) demonstrated that treatment of mature intact animals with the 5α-R inhibitor, dutasteride, resulted in a significant reduction in the expression of neuronal nitric oxide synthase (nNOS) (Fig. 2) and loss of trabecular smooth muscle and a significant increase in connective tissue deposition (Fig. 2) resulting in poor tissue compliance and ED. This pathology resulted in blunting of the in vivo erectile response, even after drug discontinuation (22) (Fig. 3). Zhang et al. (20) examined the effects of long-term finasteride treatment of erectile function in mature male animals for 16 weeks with a daily oral dose of 4.5 mg/kg and confirmed the findings of Pinsky et al. (21) and Oztekin et al. (22) in that finasteride significantly attenuated penile erectile response in vivo to electric field stimulation (EFS) of the cavernous nerve with concomitant loss of trabecular smooth muscle content and increased connective tissue deposition. More profoundly the expression of endothelial nitric oxide synthase (eNOS) was significantly attenuated by finasteride treatment, contributing to ED.

TABLE 2

Studies in men with AGA treated with finasteride or dutasteride.

Author, year (reference)	Nature of the study as described by authors	Study authors assessment of adverse events	Safety assessments as described by the study investigators
Ganzer and Jacobs, 2016 (52)	This is a retrospective observational study using self-administered questionnaire in which participants in this online survey completed the BDI, the BAI, and Ten-Item Personality Inventory.	An important finding in this study was that almost 57% (n = 97) of men reported a psychiatric diagnosis and 28% (n = 27) had a first-degree relative with a mental health disorder, of this group 17 only had a family history. Nearly 50% of the men surveyed reported clinically significant depression as evidenced by BDI score and 34% experienced anxiety on the BAI.	Psychological sequelae were assessed using two self-report scales, the BDI and the BAI. The BAI, selected to evaluate anxiety, is a 21-item self-report questionnaire that distinguishes anxious diagnostic groups (e.g., panic disorder) from non-anxious diagnostic groups (e.g., major depressive disorder).
Melcangi et al., 2017 (48)	A multicentric, prospective, longitudinal, case-control clinical trial. PFS patients were recruited through the Italian network finasteride side effects. Only subjects who had discontinued finasteride at least 3 months earlier, did not use drugs known to potentially interfere with neuroactive steroid levels and did not report depression or sexual dysfunction before finasteride use were included.	Objective evidence in PFS patients of peripheral neuropathy of the pudendal nerve which is critical for normal neurogenic control of erection. Pelvic nerve somatosensory evoked potential abnormalities were found in 25% of PFS patients, despite normal neurological examination and no prior history of neurological disease. PFS patients show altered levels of important physiological regulators of brain function, such as neuroactive steroids.	A questionnaire was used to evaluate the absence of PFS signs and symptoms before the finasteride treatment, as well as the presence of this accompanying signs and symptoms during and after the drug treatment. Patients were assessed for the presence of any neurological impairment through careful personal and family history assessment and physical examination performed by a certified neurologist.
Kiguradze et al., 2017 (84)	A single-group study design and CTA to model PED lasting greater than 90 days after stopping finasteride or dutasteride. The data source was the electronic medical record data repository for Northwestern Medicine.	Among men with finasteride or dutasteride exposure, 167 of 11,909 (1.4%) developed PED. Of 530 men with new ED, 167 (31.5%) had new PED. Men without prostate disease who combined nonsteroidal anti-inflammatory drug use with >208.5 days of 5α-RI exposure had 4.8-fold higher risk of PED than men with shorter exposure (NNH 59.8, all $P < .002$). Young men with >205 days of finasteride exposure had 4.9-fold higher risk of PED (NNH 108.2, $P < .004$) than men with shorter exposure.	Main outcome measure was diagnosis of PED beginning after first 5a-RI exposure, continuing for at least 90 days after stopping 5α-RI, and with contemporaneous treatment with a phosphodiesterase-5 inhibitor (PDE5I). Other outcome measures were ED and low libido. PED was determined by manual review of medical narratives for all subjects with ED. Risk of an adverse effect was expressed as NNH.
Basaria, et al., 2016 (56)	A clinical study utilizing biochemical and imaging techniques to assess sexual function, mood, affect, cognition, hormone levels, body-composition, fMRI response to sexually and affectively-balanced stimuli were assessed in finasteride users, who reported persistent sexual symptoms after discontinuing finasteride	Symptomatic finasteride-users had impaired sexual function, higher depression scores, a more negative affectivity balance, and more cognitive complaints than men in groups 2 and 3 but had normal objectively-assessed cognitive function. These men also exhibited depressed mood; and moderate to severe depression. Symptomatic finasteride-users revealed depressed mood and fMRI findings consistent with those observed in depression.	Sexual function was assessed using the IIEF and the Male Sexual Health Questionnaire for more precise assessment of sexual desire and ejaculatory function than is provided by IIEF. Sexual activity was ascertained using sexual encounter profile diaries for a period of 7 days. Mood/depression was assessed using Patient Health Questionnaire-9 depression scale, BDI, and Hamilton Depression Scale 17, and affect using the Positive and Negative Affect Scale.
Chiriaco et al., 2016 (128)	An observational retrospective evaluation of 79 young men with long-term adverse effects after use of finasteride against androgenetic alopecia. The type and frequency of symptoms in men having long-term sexual and non-sexual side effects after finasteride treatment (a condition recently called PFS against AGA were assessed.	The most frequent non-sexual symptoms were reduced feeling of life pleasure or emotions (anhedonia) (75.9%); lack of mental concentration (72.2%), and loss of muscle tone/mass (51.9%). By ASEX questionnaire, 40.5% of participants declared getting and keeping erection very difficult, and 3.8% never achieved; reaching orgasm was declared very difficult by 16.5%, and never achieved by 2.5%. By the ad hoc questionnaire, the most frequent sexual symptoms referred were loss of penis sensitivity (87.3%), decreased ejaculatory force (82.3%), and low penile temperature (78.5%).	Symptoms were investigated by an ad hoc 100 questions' questionnaire, and by validated ASEX and Aging Male Symptom Scale questionnaires.

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TABLE 2

Continued.

Author, year (reference)	Nature of the study as described by authors	Study authors assessment of adverse events	Safety assessments as described by the study investigators
Guo et al., 2016 (129)	A retrospective cohort study using the Intercontinental Medical Statistics U.S. health claims database. From an original cohort of 6,110,723 patients, 1,390 men were identified who had stopped using finasteride 1mg and 20,000 randomly selected age- and calendar time-matched users of omeprazole.	The median time to first PSD event after discontinuation of finasteride 1mg prescription was 339 days. The rate of PSD for finasteride users and omeprazole users was 37.9 and 15 per 1,000-person-years, respectively.	In the primary analysis, we followed the cohorts to the first incidence of one of the following sexual dysfunction codes: erectile dysfunction, inhibited sex excitement, psychosexual dysfunction, premature ejaculation, hypoactive sexual desire disorder, decreased libido, or unspecified psychosexual disorder.
Choi et al., 2016 (130)	Open label, multi-center, non-interventional observational study. 712 subjects with AGA (18 to 41 years of age) with no experience of dutasteride were enrolled.	Most frequent AEs were libido decreased, dyspepsia, impotence and fatigue. Other interested AEs were sexual function abnormality, gynecomastia, and ejaculation disorder. Dutasteride 0.5 mg is well-tolerated in AGA patients in a clinical practice environment.	Physicians were guided to record any treatment-emergent adverse events during the follow up. At the last treatment visit, the effectiveness was additionally evaluated as ''improved,'' ''no change,'' ''worsened,'' and ''not assessed.'' The overall effectiveness assessment will depend on the physician's medical judgement
Caruso et al., 2015 (47)	A case control study of 19 post-finasteride syndrome patients to assess changes in neuroactive steroid levels.	Overall all the subjects had a complex and constant neuropsychiatric pattern. The present observations show that altered levels of neuroactive steroids, associated with depression symptoms, are present in AGA patients even after discontinuation of the finasteride treatment.	Symptoms reported by the patients were collected using standardized questionnaire. In order to limit selection and recall bias, it was filled in by the patients only once before they were made aware of the possibility to undergo neuroactive steroid assessment.
Ali et al., 2015 (127)	Using the United States FAERS Database to retrieve adverse drug events that were voluntarily submitted to the FAERS between 1998 and 2013. The database was restricted to reports of male patients between 18 and 45 years of age to investigate the risk in young men and to minimize exposure misclassification.	In total, of 4,910 reports, 577 exhibited persistent SD and 39 SI adverse event reports (11.8% and 7.9%, respectively) were identified for young men using low-dose finasteride; 34 (87.2%) of the 39 men with SI also experienced SD. Most of these events were serious (e.g., contributed to the patient's death, hospitalization, or disability). Low-dose finasteride was associated with more than expected reporting of SD in young men compared with reporting of these events with all other drugs within the database.	A real-world adverse event reporting database to detect SD and SI signals in men aged 18–45 years who were treated with low-dose finasteride for treatment of men with AGA.
Ganzer et al., 2015 (53)	A web-based survey was constructed after conducting an extensive literature search of MEDLINE (restricted to the years 1995-2013) using the key words finasteride, sexual dysfunction, 5-α reductase, male pattern hair loss, Propecia, and side effects. A total of 149 surveys were retrieved with 18 excluded because they were less than 70% complete.	Persistent sexual side effects were prevalent. A large majority of respondents reported an overall decrease in sexual drive, intermittent erectile dysfunction, or a loss of spontaneous morning erections—or all three—and many reported physical and sensory changes to the penis and scrotum included penile and scrotal shrinkage and diminished semen volume and force.	Questions were asked about symptom onset after starting and stopping therapy. Symptom onset was characterized as beginning immediately after initiating finasteride, 3 to 6 months or 6 to 12 months into the therapy, or never while taking finasteride.

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TABLE 2

Continued.

Author, year (reference)	Nature of the study as described by authors	Study authors assessment of adverse events	Safety assessments as described by the study investigators
Di Loreto , et al., 2014 (131)	A retrospective case-control study of healthy, AGA positive, with no history of finasteride or any other drug capable of impairing androgens action use and no use of hormonal treatments ever were enrolled.	In all subjects, adverse side effects persisted for over 6 months after finasteride discontinuation and were still affecting the patients at the time of the visit day for study enrolment. All of the 8 finasteride treated patients had loss of penis sensitivity and loss of pleasurable response to touch, 7 out of 8 cases had loss of scrotum and/or testicles sensitivity, hardened tissue and/or rubbery texture, flaccidity, wrinkledness and retraction into the scrotum, and erectile dysfunction. All cases except 2 reported reduced penis dimension and declared pain in penis and/or scroto or testis.	Two different structured questionnaires were administered to the former finasteride users (cases) to evaluate the development and severity of persistent side effects. Additionally, formers finasteride users filled the ASEX questionnaire.
Harcha, et al., 2014 (132)	A randomized, active- and placebo-controlled study of the efficacy and safety of different doses of dutasteride versus placebo and finasteride in the treatment of male subjects with AGA. Men aged 20 to 50 years (n = 917) with AGA were randomized to receive dutasteride (0.02, 0.1, or 0.5 mg/d), finasteride (1 mg/d), or placebo for 24 weeks.	The incidence of adverse events of special interest related to sexual functioning and breast disorders was greater in the treatment groups and lower with placebo, with the composite adverse events ''altered libido'' being the main cause for the difference between placebo and active treatments.	AEs, vital signs, clinical laboratory tests, breast examinations, and prostates specific antigen levels were monitored during the study.
Irwig 2014 (71)	Healthy young men (n = 24) who developed persistent sexual adverse effects associated with finasteride use ($\leq$1.00-1.25 mg/d) for AGA were administered standardized interviews that included the use of a validated instrument to assess sexual function.	Low serum androgen levels at the time of the study cannot explain the persistent sexual adverse effects because mean levels were like those in other studies.	Participants were administered standardized interviews that included the use of a validated instrument to assess sexual function.
Motofei et al., 2013 (133)	In total, 33 sexually healthy Romanian men participated in this study. Patients prospectively provided information regarding their sexual functioning (over 4 weeks), as measured by the IIEF prior to and after commencing treatment with 1 mg finasteride for male pattern baldness.	In the current study, because patients were advised about possible inhibitory or stimulatory effects on sexual function, a higher level was reported, but the direction of these effects appeared to be related to the patients' handedness.	For 4 weeks prior to treatment, patients prospectively noted their sexual functioning, which was then assessed using the IIEF. At the end of this 6-week period of treatment, sexual functioning was then again assessed using the IIEF, using the prior 4 weeks as the reference period.
Irwig 2012 (69)	Standardized interviews of 61 former finasteride users with persistent sexual dysfunction used to gather demographic, information, medical and psychiatric histories and information on medication use, sexual dysfunction, chronic medical conditions, current or past psychiatric conditions or use of oral prescription medication before or during finasteride use.	Rates of depressive symptoms were significantly higher in the former finasteride users (75%) compared with 10% in the control group. Also, suicidal thoughts were present in almost half of all former finasteride users and only 3% in the control group.	AE assessment was based on structured interviews.

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TABLE 2

Continued.

Author, year (reference)	Nature of the study as described by authors	Study authors assessment of adverse events	Safety assessments as described by the study investigators
Olsen et al., 2012 (134)	A multicenter, double-blind randomized study of patients with vertex hair loss to finasteride (1 mg/d) or placebo. Men (N = 1553) were randomized to daily finasteride (1 mg) or placebo in a 1:1 ratio for 1 year. Men who completed the original 1-year studies were enrolled in 1-year, double-blind, placebo-controlled extension studies.	A higher incidence of drug-related sexual adverse experiences including decreased libido, ejaculation disorder, primarily decreased ejaculate volume, and erectile dysfunction were reported in the finasteride group than in the placebo group, irrespective of age. In addition, there were higher rates of discontinuation in the younger men (18-41 years), as a result of drug-related sexual adverse experiences in men treated with finasteride compared with placebo	Investigators evaluated potential risk of persistent sexual side effects associated with finasteride. Safety assessments included clinical and laboratory evaluations and reports of adverse experiences.
Sato et al., 2012 (135)	The efficacy and safety of finasteride (1 mg) was evaluated in Japanese men with AGA in a long-term study. The study enrolled 3,177 men.	No specific safety problems associated with long-term use were observed. Many patients did not receive follow-up examination. Adverse reactions occurred in 0.7% of the entire study population (23 of 3,177) during the entire period of the study. Decreased libido (n = 8), hepatic functional disorder (n = 3) and unilateral mammary hypertrophy (n = 2).	Safety data were assessed by interviews and laboratory tests in all men enrolled in the study.
Rossi et al., 2011 (136)	One hundred eighteen men, aged between 20 and 61 years, in good physical and mental health, with mild to moderate AGA were enrolled.	Five patients of 118 abandoned the study during the years because of adverse reactions. Side effects were observed in 5.9% (7) patients. Libido and ejaculated semen reduction plus erection problems were reported only by one patient, which interrupted the treatment just at the beginning of the treatment. The most frequent side effect was the libido reduction (5.1%) of the ejaculated semen amount, leading to therapy discontinuation in 67% of cases (13–15). Gynecomastia and depression were not reported at all.	Patients were evaluated for loss of libido or ejaculated semen reduction, erection problems.
Yamazaki et al., 2011(137)	A case control study of twenty-seven male AGA patients aged 19-76 years (average, 33.8) answered the Visual Analog Scale, Dermatology Life Quality Index, WHO/QOL-26 and State-Trait Anxiety Inventory questionnaires before and after the administration of finasteride (1mg/day) for 6 months.	No assessment of adverse events.	No assessment of adverse events.
Irwig and Kolukula, 2011 (67)	A retrospective study utilizing interviews with 71 healthy men aged 21–46 years who reported new onset of sexual side effects associated with the temporal use of finasteride, in which the symptoms persisted for at least 3 months after discontinuation of finasteride.	Approximately 94% of all subjects developed low libido, 92% developed erectile dysfunction, 92% developed decreased arousal, and 69% developed problems with orgasm. The mean duration of finasteride use was 28 months and the mean duration of persistent sexual side effects was 40 months from the time of finasteride cessation to the interview date.	Investigators evaluated potential risk of persistent sexual side effects associated with finasteride.
Camacho et al., 2008 (138)	A 12-month study of 270 men was conducted to determine the hormonal influences of finasteride 1 mg daily on hair growth in men aged 14–58 years with AGA were treated with finasteride 1 mg daily.	No assessment of adverse events was provided.	No reported method of assessment.

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TABLE 2

Continued.

Author, year (reference)	Nature of the study as described by authors	Study authors assessment of adverse events	Safety assessments as described by the study investigators
Kaufman et al., 2008 (139)	Data from two Phase III trials in which 1,553 men with AGA with mean age of 33 years who received finasteride 1 mg/day or placebo for up to 5 years.	No assessment of adverse events was provided.	No reported method of assessment.
D'Amico et al., 2007 (140)	A randomized controlled trial of 355 men aged 40–60 years with male-pattern hair loss who were stratified by age decade (40–49 years and 50–60 years) and randomized in a ratio of four to one to 1 mg/day finasteride or placebo.	Adverse events were not fully assessed. The authors state that 30 men discontinued treatment 12 because of clinical adverse Events. In the placebo 7 discontinued treatment 2 because of clinical adverse events.	No reported method of assessment.
Olsen et al., 2006 (141)	Four hundred sixteen men, 21 to 45 years old, were randomized to receive dutasteride 0.05, 0.1, 0.5, or 2.5 mg, finasteride 5 mg, or placebo daily for 24 weeks. In total, 11 subjects withdrew because of adverse events.	There were no significant differences in total adverse events, serious adverse events, or withdrawals due to adverse events among any of the treatment groups, including placebo. Some subjects had more than one adverse event. Decreased libido was noted in 2 subjects in the placebo group, 2 subjects in each of the 0.05-mg and 0.1-mg dutasteride groups, 1 subject in the 0.5-mg dutasteride group, 9 subjects in the 2.5 mg dutasteride group, and 3 subjects in the finasteride group.	Safety assessments included were based on the investigator's evaluations.
Ryu et al., 2006 (142)	Twenty-one healthy men between the ages of 23 and 52 years (mean 31-36) with moderate male-pattern hair loss were enrolled. Patients were then given finasteride 1 mg once daily. The patients with male pattern bolding, aged 23-52 years, were treated with finasteride 1 mg daily for 5 months.	No reported adverse effects	No assessment of adverse events was made.
Price et al., 2006 (143)	Sixty-six men with mild to moderate AGA who were between 22 and 40 years of age and in good physical and mental health were enrolled in this study. Men were randomized to receive finasteride (1 mg/d) or placebo for 192 weeks.	Finasteride was generally well tolerated. No patients were discontinued from the study because of an adverse event. No other drug-related clinical or laboratory adverse events were reported during either the second or the third study extensions.	Percentage of patients with a given clinical or laboratory adverse event was estimated.
Rahimi-Ardabili et al., 2006 (74)	A prospective observational study of 128 men with AGA, who were prescribed finasteride (1 mg/day) were enrolled in this study. Information on depressed mood and anxiety was obtained by BDI, and HADS. Participants completed BDI and HADS questionnaires before beginning the treatment and two months after.	Finasteride treatment increased both BDI ($P < .001$) and HADS depression scores significantly ($P = .005$). HADS anxiety scores were increased, but the difference was not significant ($P = .061$).	Information on depressed mood was acquired using translated and validated Persian versions of BDI and HADS
Leavitt et al., 2005 (144)	In this randomized, double-blind, placebo-controlled Study, 79 men with AGA (20–45 years of age) were assigned to treatment with finasteride 1 mg (n = 40) or placebo (n = 39) once daily from 4 weeks before until 48 weeks after hair transplant.	The authors stated that finasteride treatment was generally well tolerated, however, no detailed information on the assessment of adverse events or the accuracy of reporting of such events.	Vital signs were recorded at screening and on the day of hair transplant. Adverse events were documented at each clinic visit during treatment with study medication.

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TABLE 2

Continued.

Author, year (reference)	Nature of the study as described by authors	Study authors assessment of adverse events	Safety assessments as described by the study investigators
Arca et al., 2004 (145)	An open, randomized, comparative study of oral finasteride and 5% topical minoxidil in male androgenetic alopecia in which 40 (61.53%) patients were randomly assigned to receive 1 mg/day oral finasteride for 12 months, and 25 (38.47%) patients applied 5% topical minoxidil solution twice daily for 12 months.	Encountered side effects were all mild, and there was no need to stop the treatment. In the group given oral finasteride, side effects were noted in 7 patients: 6 patients suffered from loss of libido, and 1 patient had an increase in other body hairs; irritation of the scalp was seen in 1 patient in the group administered 5% minoxidil. These adverse events disappeared as soon as the treatment was stopped. Adverse events were not considered important either, and these side effects disappeared as soon as the treatment was stopped.	Safety assessments included were based on the investigator's evaluations.
Tostie et al., 2004 (146)	A total of 186 patients with androgenetic alopecia were evaluated before and 4 to 6 months after the initiation of finasteride therapy (1 mg).	Our results support the clinical impression that sexual side effects are much less common than reported in clinical trials. The sexual function of all patients remained stable during treatment with 1mg of finasteride.	Patients (N =186) with androgenetic alopecia were asked to complete the IIEF-5 regarding the domain of erectile function before (at baseline) and 4 to 6 months after beginning finasteride treatment. The test was self-administered.
Kawashima, et al., 2004 (147)	In this double- blind randomized study, 414 Japanese men with male pattern hair loss received finasteride 1 mg (n = 139), finasteride 0.2 mg (n = 137), or placebo (n = 38) once daily for 48 weeks.	Finasteride treatment was generally well tolerated.	Safety assessments included were based on the investigator's evaluations.
Whiting et al., 2003 (148)	A 24-month double-blind, randomized, placebo-controlled, parallel-group, multicenter study of 424 men was conducted to determine the efficacy and tolerability of finasteride 1 mg on hair growth/loss in men aged 41 to 60 years with mild-to-moderate, predominantly vertex male pattern hair loss.	Treatment with finasteride 1 mg was generally well tolerated.	Safety analyses included assessment of clinical and laboratory adverse experiences, including sexual adverse experiences.
Altomare, Capella, 2002 (149)	A retrospective case series in which 23 patients were treated and followed up for AGA. Nineteen of them developed a mood disturbance. Mean age 28.16 years ± 7.68 standard deviation	19 patients (14 males, 5 females) developed a mood disturbance (moderate to severe depression) during treatment with finasteride, 1 mg/day orally, for AGA.	Safety assessments included were based on the investigator's evaluations.
Kaufman et al., 2002 (150)	Two 1-year, Phase III trials, 1,553 men with male pattern hair loss were randomized to receive finasteride 1 mg/day or placebo, and 1,215 men continued in up to four 1-year, placebo-controlled extension studies.	Finasteride was generally well tolerated, and no new safety concerns were identified during long-term use.	Safety assessments included were based on the investigator's evaluations.
Lin et al., 2002 (151)	An open-label study assessed the efficacy and safety of finasteride for the treatment of Taiwanese men with AGA. Thirty-four men (aged 18-40 years) with AGA were enrolled.	Adverse effects, including abnormal liver function (5/34), were minimal, and the causal relationship with finasteride could not be established.	Safety assessments included were based on the investigator's evaluations.

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TABLE 2

Continued.

Author, year (reference)	Nature of the study as described by authors	Study authors assessment of adverse events	Safety assessments as described by the study investigators
Khandpur et al., 2002 (152)	One hundred male patients with AGA were enrolled in an open, randomized, parallel-group study, designed to evaluate and compare the efficacy of oral finasteride (1 mg per day), topical 2% minoxidil solution and topical 2% ketoconazole shampoo alone and in combination.	No significant adverse events occurred during the follow-up period of one year. One patient (1.32%) complained of loss of libido after 3 months of finasteride administration but continued to take the drug without any further decrease in sexual function.	Any medical event occurring during the course of the study was recorded with special emphasis on the vital signs, i.e., pulse rate, blood pressure, weight, ECG changes, local reactions on the scalp secondary to topical applications, or sexual dysfunction including loss of libido, ejaculation disorder or impotence.
Price et al., 2002 (153)	Sixty-six men with AGA received finasteride, 1 mg/d, or placebo in a 48-week study, and 49 men continued in a 48-week extension. One hundred and seventy-seven patients completed the 48-week study.	Treatment with finasteride was generally well tolerated, and no subject discontinued the study because of an adverse effect of treatment. One subject receiving finasteride reported decreased libido during the initial 48-week study but did not withdraw from the trial.	No data or discussion of the adverse events or how they were assessed. Conflict of interest may have introduced a large bias in this study.
Tostie et al., 2001 (154)	236 subjects, aged 18–47 years, who were followed as outpatients for hair disorders during finasteride 1 mg treatment for androgenetic alopecia.	The sexual and erectile function of subjects taking finasteride does not significantly differ from that of age-matched controls. This is consistent with the experience of many dermatologists who do not see sexual or erectile dysfunction in patients taking Propecia.	The IIEF, a brief, reliable questionnaire, was self-administered to 236 patients taking Propecia and 236 age-matched males
Van Neste et al., 2000 (155)	Two hundred and twelve men, age 18-40 years, with androgenetic alopecia were randomized to receive finasteride 1 mg daily or placebo for 48 weeks.	In this study, drug-related sexual adverse events occurred in two patients in the finasteride group and in one patient in the placebo group. Of the two finasteride patients, one reported resolution of the adverse event while on therapy, whereas the other reported resolution of the adverse event 2 weeks after completion of therapy. Treatment with finasteride was generally well tolerated.	Safety measurements included clinical and laboratory evaluations, and adverse event reports.
Overstreet et al., 1999 (156)	In this double-blind, placebo controlled multicenter study 181 men 19 to 41 years old were randomized to receive 1 mg. finasteride or placebo for 48 weeks followed by a 60-week off-drug period. Of the 181 men 79 were included in a subset for the collection and analysis of sequential semen samples.	During the treatment period 4 (4.4%) finasteride and 3 (3.3%) placebo treated subjects spontaneously reported sexual adverse experiences considered by the investigator to be related to the study drug. These reports included ejaculation disorders, erectile dysfunction or changes in libido. The sexual adverse experiences were mild, and in 3 of the 4 men on finasteride they resolved with continued treatment.	Adverse events assessments were based on investigator clinical evaluation
Drake et al., 1999 (157)	Men with AGA (N = 249) underwent scalp biopsies before and after receiving 0.01, 0.05, 0.2, 1, or 5 mg daily of finasteride or placebo for 42 days.	Of the 249 patients who entered the study, only 2 drug-related adverse experiences were reported in more than 1 patient in any treatment group: headache (placebo 3%, 1 mg 2.7%, none on 5, 0.2, 0.05, or 0.01 mg) and decreased libido (placebo 4.5%, 0.01 mg 2.7%, 0.05 mg 2.9%, 0.2 mg 8.3%, 1 mg 0%, and 5 mg 2.6%).	Adverse events assessments were based on investigator clinical evaluation.

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TABLE 2

Continued.

Author, year (reference)	Nature of the study as described by authors	Study authors assessment of adverse events	Safety assessments as described by the study investigators
Roberts et al., 1999 (158)	One clinical study conducted in 13 centers in the United States, randomized 227 men into a 12-month, double-blind, placebo-controlled study to evaluate the effects of finasteride 5 mg/day on male pattern hair loss. The second clinical trial (dose range study), conducted in 23 centers in the United States, randomized 466 men into a 6-month, double-blind, placebo-controlled study to evaluate the effects of low doses (1, 0.2, and 0.01 mg/day) of finasteride.	The incidence of these side effects with finasteride therapy was generally comparable to that observed with treatment with placebo, and there was no evidence of dose dependency or increased incidence with longer therapy out to 12 months. In addition, these side effects ceased in some patients while they continued to receive finasteride. No significant safety issues were identified in the trials.	Safety was assessed by clinical and laboratory measurements and by analysis of adverse experiences. A physical examination was performed at baseline and at months 6 and 12. All adverse events that were considered by the investigator to be possibly, probably, or drug-related and that occurred in at least 1% of patients in any treatment group during the placebo-controlled portion of the pilot and dose range studies were reported.
Leyden et al., 1999 (159)	This was a multicenter, double-blind, placebo-controlled study conducted at 15 investigational sites in the United States. Of 326 patients with mean age of 33 years, 166 received finasteride 1 mg dose for 52 weeks.	Over the course of the study, finasteride was generally well tolerated. The only drug-related adverse experiences were sexual adverse effects and were reported in approximately 2% of men in both treatment groups.	Adverse events were assessed by the Investigators clinical judgments.
Kaufman et al., 1998 (89)	In two 1-year trials, 1,553 men (18 to 41 years of age) with male pattern hair loss received oral finasteride 1 mg/d or placebo, and 1,215 men continued in blinded extension studies for a second year.	Adverse effects occurred in a higher proportion in the finasteride-treated arm than placebo treated patients (sexual function 4.2% vs 2.2%, $P < .05$). Eleven men (1.4%) in the finasteride group and 8 (1.0%) in the placebo group discontinued the study because of sexual adverse events, which resolved after discontinuation, however no data was provided to document this resolution of adverse events.	Safety measurements included clinical and laboratory evaluations, adverse event reports, and patient body hair assessment via a self-administered questionnaire.
Dallob et al., 1994 (160)	In a double-blind study, 17 male patients undergoing hair transplantation with mean age of 30-55 years were treated with oral finasteride (n = 8, 5 mg/day) or placebo for 28 days.	Inadequate adverse event reporting and unknown quality of blindness coupled with conflict of interest.	No adverse effects assessments were reported.

Note: 5α-RI = 5α-reductase inhibitors; AE = adverse event AGA = androgenetic alopecia; ASEX = Arizona Sexual Experience Scale; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CTA = classification tree analysis; ED = erectile dysfunction; FAERS = FDA Adverse Event Reporting System; fMRI = functional magnetic resonance imaging; HADS = Hospital Anxiety and Depression Scale; IIEF = International Index of Erectile Function; NNH = number needed to harm; PED = persistent erectile dysfunction; PDE5I = phosphodiesterase-5 inhibitor; PFS = post-finasteride syndrome; PSD = persistent sexual dysfunction; SD = sexual dysfunction; SI = suicidal ideation.

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TABLE 3

Comprehensive reviews, systematic reviews, and metanalyses in subjects treated with finasteride or dutasteride.

Author, year (reference)	Systematic reviews and/or meta-analyses studies	Study authors' summary and interpretations	Study authors' conclusions
Zakhem et al., 2019 (162)	A systematic review was conducted of all articles in the PubMed database published from the time of inception to May 2018 to identify studies evaluating the use of systemic dermatologic medications in men with evidence of sexual adverse effects. Sexual dysfunction was measured using any existing validated instrument and self-reported adverse events.	Among men taking 1 mg finasteride for androgenic alopecia, the evidence for sexual adverse effects is less conclusive. Five studies t did not support the increased rates of sexual dysfunction in men taking 1 mg finasteride for AGA. However, 10 studies demonstrated sexual adverse effects, including ED and decreased libido, in patients taking 1 mg finasteride and we find the evidence describing increased rates of sexual dysfunction is more compelling.	The information in this review may serve as a reference of adverse effects when deciding on a therapeutic agent and a guide to help identify patients to screen for sexual dysfunction.
Zhou et al., 2019 (163)	The efficacy and safety of Dutasteride compared with finasteride in treating men with androgenetic alopecia: a systematic review and meta-analysis. Randomized controlled trials of dutasteride and finasteride for treating AGA were searched using MEDLINE, EMBASE, and the Cochrane Controlled Trials Register.	With regard to the assessment of safety, altered libido ($P=.54$), erectile dysfunction ($P=.07$), and ejaculation disorders ($P=.58$), dutasteride did not show a significant difference compared with finasteride. According to the current analysis of the safety of the two drugs, the application of two drugs should be carefully considered for young middle-aged men, especially for patients who are sexually active.	Dutasteride seems to provide a better efficacy compared with finasteride in treating AGA. The two drugs appear to show similar rates of adverse reactions, especially in sexual dysfunction.
Lee et al., 2019 (164)	A systematic review and meta-analysis were performed following the principles of the PRISMA.	The authors reported that 9 of 11 studies on finasteride 1 mg/day, and all of 5 studies on dutasteride 0.5 mg/day, provided individual incidence of erectile dysfunction, decreased libido, and difficulty in ejaculation. One hundred thirty two of 2,257 subjects treated with 5α-RIs (5.85%) (vs. placebo: 80 of 2,122 [3.77%]) had at least one adverse sexual effect. For each regimen,100 of 1,882 subjects treated with finasteride 1 mg/day (5.31%) (vs. placebo: 57 of 1,869 [3.05%]) had adverse sexual effects, whereas 32 of 375 subjects treated with dutasteride 0.5 mg/day (8.27%) (vs. placebo: 23 of 369 [6.23%]) had adverse sexual effects.	Use of 5α-RIs carried a 1.57-fold risk of sexual dysfunction (95% confidence interval (95% CI 1.19–2.08). The relative risk was 1.66 (95% CI 1.20– 2.30) for finasteride and 1.37 (95% CI 0.81–2.32) for dutasteride. Both drugs were associated with an increased risk, although the increase was not statistically significant for dutasteride.
Shin et al., 2019 (165)	The authors reviewed most recent studies of finasteride treatment for BPH and male AGA and the incidence of ED.	Evidence from clinical studies suggested that finasteride was associated with increased adverse effects on ED in men with BPH. The authors, however believe that such association was not statistically significant in men with AGA.	Although there is not enough evidence to prove the relationship between finasteride and ED, most studies in this review found that finasteride for BPH was correlated with ED. However, most studies included in this review revealed that finasteride for MAA was not correlated with ED. On the other hand, some studies reported side effects of finasteride associated with sexual dysfunction, including ED, male infertility, ejaculation problem, and loss of libido, even in MAA patients.

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TABLE 3

Continued.

Author, year (reference)	Systematic reviews and/or meta-analyses studies	Study authors' summary and interpretations	Study authors' conclusions
Healy et al., 2018 (60)	Data from RxISK.org, a global adverse event reporting website, have been used to establish the clinical features, demographic details and clinical trajectories of syndromes of persistent sexual difficulties following three superficially different treatment modalities.	The symptom profile and frequency for finasteride were reported. ED 216 (88.2%); loss of libido 193 (78.8%); Pleasureless or weak orgasm 80 (32.7%); difficulties achieving orgasm 61 (24.9%); emotional blunting 46 (18.8%); loss of nocturnal erections 36 (14.7%); reduced seminal volume 33 (13.5%); penile or testicular pain 20 (8.2%); reduce penile size 20 (8.2%);	These data point to a legacy syndrome or syndromes comprising a range of disturbances to sexual function.
Lee et al., 2018 (166)	A Systematic Review of Topical Finasteride in the Treatment of Androgenetic Alopecia in Men and Women. Clinically relevant case reports, RCTs, and prospective studies were included.	No assessment of adverse events was reported.	Preliminary results on the use of topical finasteride are limited but safe and promising.
Bass et al., 2018 (167)	FAERS dataset for 5 alpha reductase inhibitors from April 2011 to October 2014 was obtained. Each FAERS report had 16 categories for completion, but not every report was fully completed. Statistical analysis compared variables of interest between the two doses of finasteride (1mg vs 5 mg).	Finasteride use was reported with many sexual AEs including diminished libido, erectile dysfunction, and ejaculatory complaints. Other common AEs included dermatologic, metabolic, and psychological and/or neurologic complaints. There were more AE reports with the 1mg dose than the 5mg dose. Data suggests that finasteride exposure is reported with a diverse collection of symptoms, particularly in younger men on 1 mg dosage compared to older men on 5mg.	FAERS data suggests that finasteride exposure is reported with a diverse collection of symptoms, particularly in younger men on 1 mg dosage compared to older men on 5 mg. Many of these complaints fall well out of the realm of previously established adverse events from long-term controlled studies.
Sorbellini et al., 2018 (168)	A tablet-based survey was conducted from February 2017 to January 2018 in Italy to investigating use of 1 mg/day finasteride in the treatment of AGA. Approximately 1,153 Italian dermatologists were surveyed about prescription frequency, therapy duration, treatment practices, and side effects eventually reported	Data on sexual side effects from our survey are in line with previous scientific evidence, especially regarding loss of libido, erectile dysfunction, and problems with ejaculation, but also in the psychological sphere and regarding physical impairments such as myalgia and loss of muscle tone.	Italian dermatologists are rather confident regarding use of finasteride, as reflected in its prescription. Even if side effects, especially in the sexual sphere, are reported, due to a lack of alternative treatments with the same efficacy, this does not significantly impact on dermatologists' decisions to prescribe finasteride, with a tendency to prolong therapy in the long term, unless symptoms became incompatible with patient quality of life.
Adil et al., 2017 (169)	A systematic review of randomized controlled trials was conducted. PubMed, EMBASE, and Cochrane were searched up to December 2016, with no lower limit on the year. We included only randomized controlled trials of good or fair quality based on the U.S. Preventive Services Task Force quality assessment process.	No assessments of adverse events were reported.	No assessments of adverse events were reported.
Corona et al., 2017 (170)	This meta-analysis was performed in line with the PRISMA reporting guideline. An extensive Medline, EMBASE and Cochrane search was performed. The search, which accrued data from January 1, 1969 up to May 1st, 2016, was restricted to placebo-controlled RCTs and humans.	Use of finasteride or dutasteride in men with BPH is associated with an increased risk of ED and HSD, when compared with placebo. No difference between finasteride and dutasteride was observed.	In conclusion, present data show that the use of 5α-RI significantly increases the risk of erectile dysfunction and hypoactive sexual desire in subjects with benign prostatic hyperplasia. Patients should be adequately informed before 5α-RIs are prescribed.

Traish. Post-finasteride syndrome: a new challenge. Fertil Steril 2019.

TABLE 3

Continued.

Author, year (reference)	Systematic reviews and/or meta-analyses studies	Study authors' summary and interpretations	Study authors' conclusions
Fertig et al., 2017 (85, 86)	A PubMed search identified documented cases of finasteride and dutasteride sexual side effects in the literature. Clinical trials, review articles, case series, and case reports that mentioned finasteride and dutasteride sexual side effects were included.	Sexual side effects in men who have taken finasteride (1mg, 5mg) and dutasteride (0.5mg) are well documented and include decreased libido, erectile dysfunction, and ejaculatory dysfunction. Randomized clinical trials have demonstrated increased incidences of these sexual side effects	Persistent sexual and psychiatric side effects after 5α-RIs are not documented by high-quality studies, and prospective studies to establish true incidence and frequency of the problem are really needed.
Hirshburg et al., 2017 (171)	A systematic review: a search of Medline, Ovid, and Google scholar database and search engines for relevant articles on human subjects, published from 1990 to November 2015 was conducted. The list of references generated was searched by hand to identify additional studies of interest.	Finasteride and dutasteride are well-tolerated. Currently, there is no direct link between finasteride and dutasteride use and depression; however, several small studies have led depression to be listed as a side effect on the medication packaging. Sexual adverse effects, such as decreased libido, erectile dysfunction, and decreased ejaculate, have been reported in as many as 3.4 to 15.8 percent of men.	Currently, there is no direct link between 5α-RI inhibitor use and depression; however, several small studies have led to depression being listed as a side effect on the medication packaging. Sexual effects including erectile dysfunction and decreased libido and ejaculate were reported in as many as 3.4 to 15.8 percent of men.
Jun et al., 2017 (172)	A systematic review and meta-analysis of RCT, quasi-randomized trials, and systematic reviews comparing finasteride with dutasteride, either as monotherapy or in combination with a-blockers, for treatment of men with BPH were included.	No assessment of adverse events was reported.	No assessment of adverse events was reported.
Liu et al., 2016 (173)	A systematic review and meta-analyses	The pooled relative risks for sexual dysfunction were 2.56 (95% CI 1.48-4.42) in men with BPH and 1.21 (95% CI 0.85- 1.72) in men with AGA; those for erectile dysfunction were 1.55 (95% CI 1.14- 2.12) in men with BPH and 0.66 (95% CI 0.20- 2.25) in men with AGA; and those for decreased libido were 1.69 (95% CI 1.03- 2.79) in men with BPH and 1.16 (95% CI 0.50-2.72) in men with AGA.	Evidence from the randomized controlled trials suggested that 5α-RIs were associated with increased adverse effects on sexual function in men with BPH compared with placebo. However, the association was not statistically significant in men with AGA.
Belknap et al., 2015 (83)	AE reporting in clinical trials of finasteride for androgenic alopecia: a meta-analysis.	Of 34 clinical trials, none had adequate safety reporting, 19 were partially adequate, 12 were inadequate, and 3 reported no adverse events. Funnel plots were asymmetric with a bias toward lower odds ratio for sexual adverse effects, suggesting systematic under detection. No reports assessed adequacy of blinding, 18 (53%) disclosed conflicts of interest, and 19 (56%) received funding from the manufacturer. Duration of drug safety evaluation was 1 year or less for 26 of 34 trials (76%). Of 5704 men in the clinical data repository who were treated for AGA with finasteride, 1.25mg/d or less, for AGA, only 31% met inclusion criteria for the pivotal trials referenced in the manufacturer's full prescribing information and 33%took finasteride for more than 1 year.	Available toxicity information from clinical trials of finasteride in men with AGA is very limited, is of poor quality, and seems to be systematically biased. In a cohort of men prescribed finasteride for routine treatment of AGA, most would have been excluded from the pivotal studies that supported US Food and Drug Administration approval for AGA. Published reports of clinical trials provide insufficient information to establish the safety profile for finasteride in the treatment of AGA.

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TABLE 3

Continued.

Author, year (reference)	Systematic reviews and/or meta-analyses studies	Study authors' summary and interpretations	Study authors' conclusions
Mella JM et al., 2010 (161)	A systematic review and meta-analysis.	Finasteride therapy increased the risk of erectile dysfunction: RR, 2.22 (95% CI 1.03- 4.78). Finasteride therapy did not decrease libido: RR, 1.08 (95% CI 0.67-1.76); We considered the quality of evidence as moderate because of imprecision.	Moderate-quality evidence suggests that daily use of oral finasteride increases hair count and improves patient and investigator assessment of hair appearance, while increasing the risk of sexual dysfunction.
Hagberg et al., 2016 (174)	A population-based study using the Clinical Practice Research Datalink. Cohort studies with nested case-control analyses	The authors suggested that 5-α reductase inhibitors do not increase the risk of clinically meaningful incident erectile dysfunction and sexual dysfunction in men who are free of sexual dysfunction prior to treatment.	5-α reductase inhibitors do not seem to significantly increase the risk of incident erectile dysfunction, regardless of indication for use. Risk of erectile dysfunction increased with longer duration of benign prostatic hyperplasia.
Gacci et al., 2014 (175)	Impact of medical treatments for male lower urinary tract symptoms due to benign prostatic hyperplasia on ejaculatory function: a systematic review and meta-analysis	EjD was significantly more common with 5α-RI s as compared with placebo (OR 2.73; $P < .0001$). Both finasteride (OR 2.70; $P < .0001$) and dutasteride (OR 2.81; $P = .0002$) were associated with significantly higher risk of EjD than placebo. EjD was significantly more common with combination therapy as compared with ABs alone (OR 3.75; $P < .0001$), or with 5α-RIs alone (OR 2.76; $P = .02$).	ABs and 5α-RI were both associated with significantly higher risk of EjD than placebo. More the AB is effective over time, greater is the incidence of EjD. Finasteride has the same risk of Dutasteride to cause EjD. Combination therapy with ABs and 5α-RIs resulted in a 3-fold increased risk of EjD as compared with ABs or 5α-RIs alone. These data can be relevant both for drug selection and patients counseling
Edwards and Moore, 2002 (102)	Finasteride in the treatment of clinical benign prostatic hyperplasia: a systematic review of randomized trials.	The most commonly reported adverse effects were impotence, decreased libido and ejaculation disorder. Definitions of these adverse effects were generally not provided in the trials. Since cumulative adverse effect information was not available after year one in some studies, analyses were conducted for different time points up to one year for most adverse effects. Significantly more men reported any sexual dysfunction, decreased libido, impotence, or ejaculation disorder with finasteride than with placebo at 12 months of treatment.	No specific conclusion about adverse side effects.
Park and Choi, 2014 (176)	Efficacy and safety of dutasteride for the treatment of symptomatic BPH: a systematic review and meta-analysis.	Pooled data indicated adverse events and drug-related adverse events were more significantly common in patients treated with dutasteride compared with placebo (RR 1.04, 95 % CI 1.00–1.07 and RR 1.35, 95 % CI 1.19–1.54, respectively). They also more frequently reported sexual adverse events, including erectile dysfunction, decreased libido, and gynecomastia (RR 1.83, 95 % CI 1.42–2.36, RR 2.00, 95 % CI 1.42–2.83, and RR 3.11, 95 % CI 1.79–5.40, respectively).	Dutasteride can be used to improve urinary symptoms (IPSS and Qmax) and reduce TPV but with awareness of its potential adverse events.

Note: 5α-RI = 5α-reductase inhibitors; AB = alpha adrenergic receptor blocker; AE = adverse event; AGA = androgenetic alopecia; BPH = benign prostatic hyperplasia; CI = confidence interval; ED = erectile dysfunction; EjD = ejaculatory disfunction; FAERS = FDA Adverse Event Reporting System; HSD = hypoactive sexual desire; MAA = male androgenetic alopecia; OR = odds ratio; PRISMA = preferred reporting items for systematic reviews and meta-analyses; RCT = randomized controlled trial; RR = relative risk; TPV = total prostate volume.

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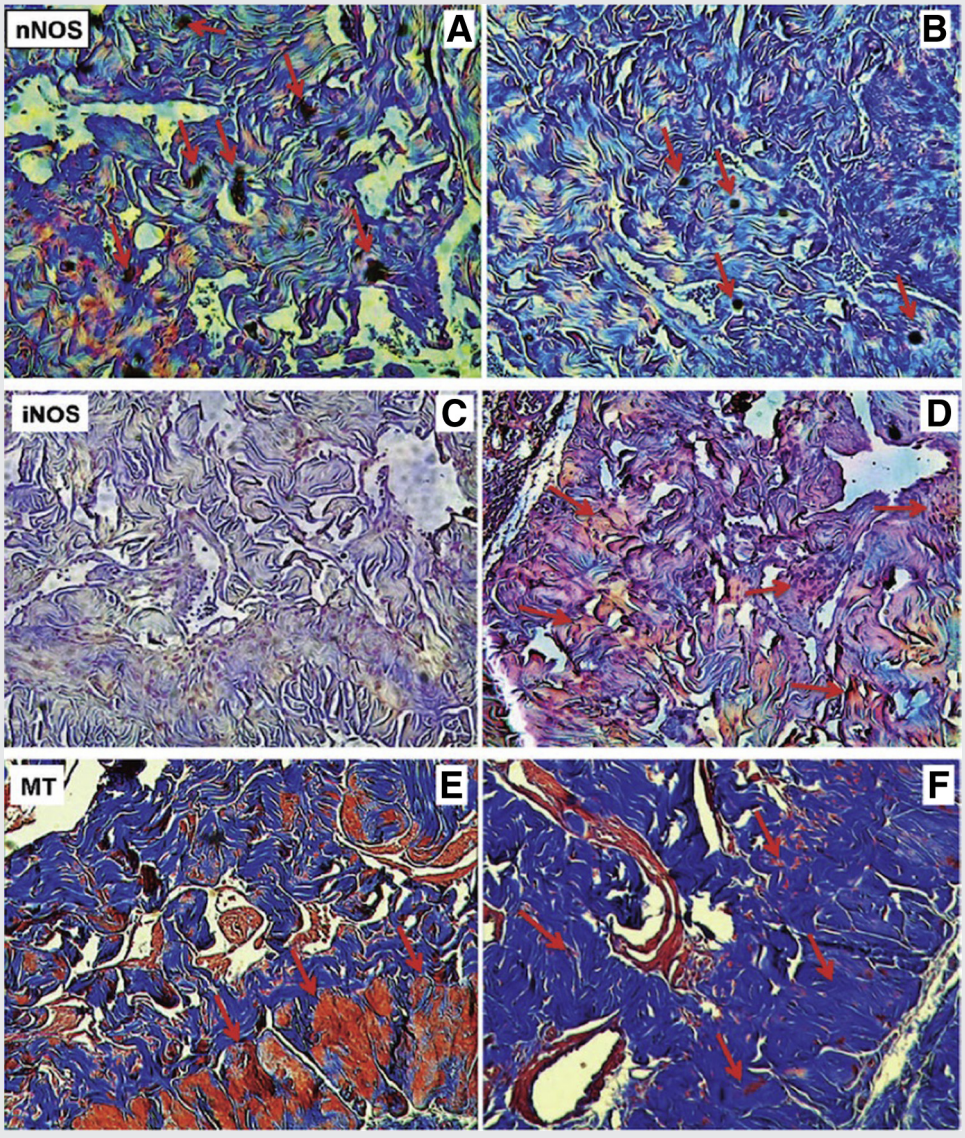
FIGURE 2



Effects of chronic treatment of animals with Dutasteride on the expression of eNOS, iNOS and trabecular smooth muscle content in the adult male rat. Immunohistochemical localization of nNOS and iNOS in rat penis (40× magnification). (**A**, **B**) nNOS staining (dark brown) with decreased localization to the nerves of the corpus cavernosal smooth muscle from control (**A**) to treatment (**B**) groups. (**C**, **D**) iNOS staining (dark brown) enhanced in the corpus cavernosal smooth muscle from the treatment group. The negative control section processed without antibodies did not stain (data not shown). (**E**, **F**) Masson's trichrome (MT) staining results. MT staining is presented as ratio of smooth muscle: collagen in a percentage (mean ± standard deviation), which is markedly different between control (**E**) and treatment (**F**) groups. Quantitative analysis of collagen, and smooth muscle content in cavernosal tissue was performed with an image analyzer. nNOS = neuronal nitric oxide synthase; iNOS = inducible nitric oxide synthase. (Adapted, with permission from the publisher, from Pinsky MR, Gur S, Tracey AJ, Harbin A, Hellstrom WJG. The effects of chronic 5-alpha-reductase inhibitor (dutasteride) treatment on rat erectile function. J Sex Med 2011;8:3066–3074.)

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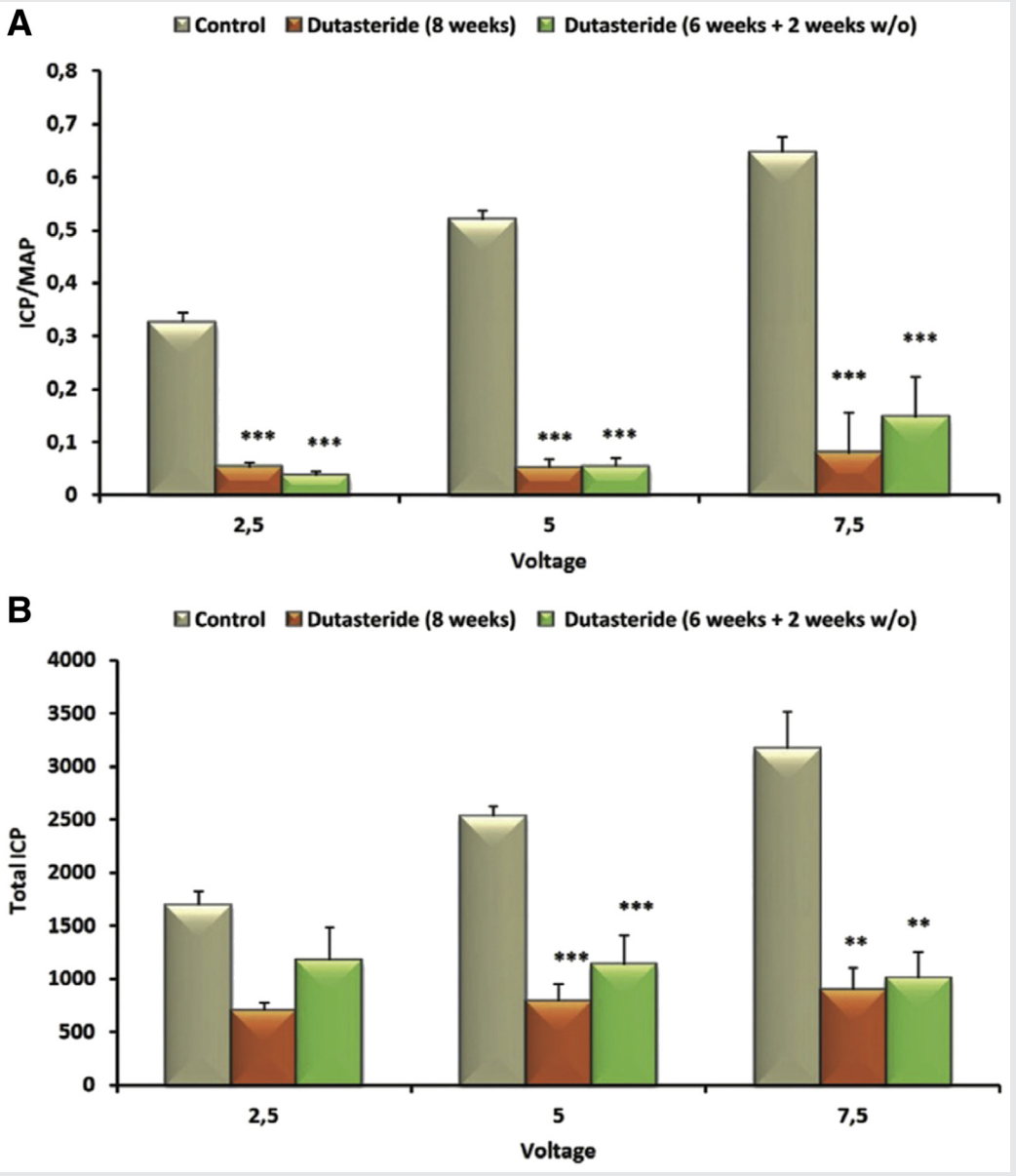
Potential Pathophysiological Mechanisms Contributing to Anxiety, Depression or Suicidal Ideation

Finasteride treatment inhibits biosynthesis of neuro-steroids, which are deemed critical regulators of central (CNS) (23–48), as well as peripheral nervous system functions, since they modulate neurotransmitter receptors function, such as gamma amino butyric acid receptors (GABA-R) (Fig. 4) (36). Thus, neuroendocrine disruption by finasteride of biosynthesis of critical signaling molecules, such as neuro-steroids, alters sexual activity, mood, and cognition. In addition, finasteride alters gene expression, including upregulation of androgen receptors (AR), increased histone acetylation, and methylation of a host of receptors and enzymes that may impair dopaminergic signaling and other

FIGURE 3



(**A**) Intracavernosal pressure (ICP)/mean arterial pressure (MAP) and (**B**) total ICP at 2.5, 5, and 7.5 voltage levels in control, 8-week Dutasteride and 6-week Dutasteride plus 2-week washout groups. Data are mean ± standard error of the mean (N = 8–10). $^{**}P < .01$ and $^{***}P < .001$ versus control group (ANOVA, Bonferroni post hoc). (Adapted, with permission from the publisher, from Oztekin CV, Gur S, Abdulkadir NA, et al. Incomplete recovery of erectile function in rat after discontinuation of dual 5-alpha reductase inhibitor therapy. J Sex Med 2012;9:1773-81.)

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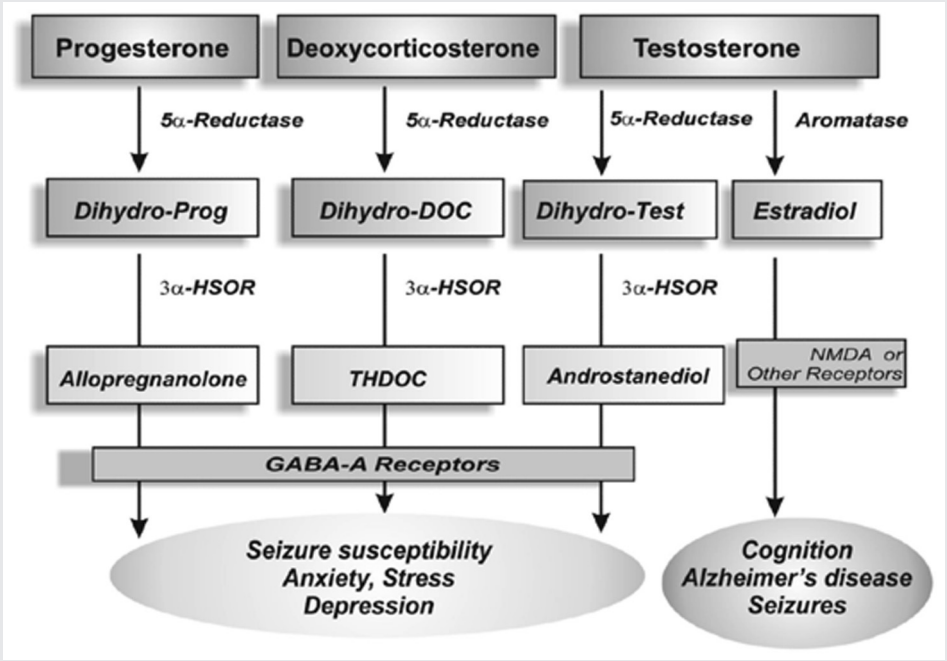
neurotransmitter receptors thus causing persistent or permanent adverse effects, manifested in anxiety, depression, and suicidal ideation (50). Schüle et al. (181) reported that neuroactive steroids such as allopregnanolone alter neuronal excitability via interactions with specific neurotransmitter receptors. It was suggested that allopregnanolone is a potent positive allosteric modulator of the GABA-A receptor complex and inhibition of its biosynthesis may be associated with major depression, anxiety disorders, and impulsive aggression. Recently Gunduz-Bruce et al. (49) reported on a clinical trial for the treatment of depression by synthetic neurosteroids that interact specifically with GABA receptors, demonstrating the importance of these physiological modulators in regulating depressive symptoms. Thus, inhibition the biosynthesis of allopregnanolone may contribute to anxiety and depression in patients with PFS. Studies by Basaria et al. (56) utilizing functional MRI confirmed abnormalities in brain regions implicated in depression and sexual arousal, such as nucleus accumbens and prefrontal cortex. Melcangi et al. (48) confirmed reduced neuro-steroid levels and nerve

FIGURE 4



Biosynthetic pathways of neuro-steroids in the human brain and their impact on brain function. 5α-Reductase converts progesterone, testosterone and deoxycorticosterone into 5α-dihydro reduced steroids, which are then reduced further to 3α-hydroxylated neuro-steroids by 3α-HSOR. Testosterone is converted into 17β-estradiol by the aromatase enzyme. These and related enzymes involved in neuro-steroid biosynthesis and metabolism are present in the human brain. (Adapted, with permission from the publisher, from Reddy SD. Neuro-steroids: Endogenous role in the human brian and therapeutic potentials. Prog Brain Res 2010;186: 113–137.)

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neuropathy in a cohort of PFS patients of which 10 showed a severe ED, while six patients showed a mild-moderate ED. Furthermore, Melcangi et al. (48) reported an objective evidence of neuropathy involving the peripheral neurogenic control of erection. Indeed, abnormal somatosensory evoked potentials of the pudendal nerve were observed in four of these PFS patients. The authors observed that eight of the PFS patients showed a DSM-IV major depressive disorder similar to those reported by Basaria et al. (56).

The Case Against PFS

A large number of reports suggested that finasteride use in treatment of BPH (Table 1) as well as of AGA (Table 2) is deemed tolerable and safe, with little or no observed adverse effects (46–48, 52, 53, 56, 67, 69, 71, 74, 84, 87–89, 95, 97–99, 106, 112, 115, 119–160).

This contrasts with data derived from metanalyses or pharmacovigilance studies in which sexual and neurological adverse events were deemed present (83, 102, 163–165, 167, 168, 173, 177). A Longitudinal analysis of sexual function reported by men in the Prostate Cancer Prevention Trial (122) argued that the low incidences of sexual adverse side effects, which resolve with continuous treatment, does not represent serious adverse events and do not support the claim of PFS existence. Furthermore, Mella et al. (161) advanced arguments that only minimal decrease in erectile function were recorded with finasteride therapy when compared with the placebo arm and only a small proportion (2%–7 %) of patients experience ED, and for this reason calling such symptoms PFS is unwarranted. Fertig et al. (85, 86) reviewed the adverse effects of finasteride and concluded that "persistent sexual and psychiatric side effects after 5α-reductase inhibitors (5α-RIs) are not documented by high-quality studies" and therefore, PFS has no place in clinical medicine.

Many clinical trials on finasteride lacked spontaneous reporting, as well as quantitative and validated scales to adequately assess reduction in sexual function. For example, until recently, many of the previous trials did not utilize the international index of erectile function (IIEF) questionnaire, which is shown to be the standard for assessment of sexual dysfunction. Thus, we believe that such studies may suffer from significant methodological and interpretational flaws and inaccurate data reporting. As discussed in this report and the study by Belknap et al. (83), one of the concerns is that the data on the side effects may have not been acquired via scientific methods and heavily relied on self-report and the concern that many of the data appear to be inaccurately reported. Furthermore, other confounding factors such as studies of short duration, loss of patients to follow-up and lack of reporting on persistent side effects makes the suggestions made in these reports questionable.

To highlight the considerable controversies surrounding this syndrome, Butcher et al. (182) in a presentation at the AUA, Post-Finasteride Syndrome: Real or Imagined?, offered summaries of their analyses of data from the US FDA Adverse Events Reporting System (FAERS) and concluded, "whether or not PFS is real or imagined is not discernable within this context and database." The authors conclusion casted serious doubts on the existence of PFS, albeit, no concrete evidence was provided. More recently, Rezende et al. (65) and Trueb et al. (66) published an article, Post-Finasteride Syndrome: An Induced Delusional Disorder with the Potential of a Mass Psychogenic Illness? The authors labeled patients with PFS as psychotic and delusional, as stated in their discussion, "In our opinion, PFS demonstrates some analogies to such controversial "mystery syndromes" as amalgam illness, multiple chemical sensitivity, Morgellons disease, and Koro for the following reasons: patients complain of symptoms that cannot be adequately explained biologically, and the frequency of consultations for the conditions parallels the respective media coverage, which points to a high degree of suggestibility. Finally, the tenacity with which the patients hold on to their belief system, despite any rational argumentation against it, is indicative of at least a delusional aspect to their disorder."

The Case for PFS

A large number of studies presented compelling evidence describing increased rates of sexual dysfunction in men with BPH and AGA treated with finasteride (Tables 1–3) (46–50, 52, 53, 55, 56, 58, 59, 60–62, 67–72, 74, 75, 83, 84, 89, 127–129, 139, 145, 150, 183–186). For example, the recent study by Basaria et al. (56) reported men who discontinued finasteride treatment continue to experience sexual adverse effects. These men had lower international index of erectile function (IIEF) scores, fewer vaginal penetrations, lower sexual desire and worse ejaculatory function and fewer satisfactory sexual encounters. Mood and depression were evaluated. Based on granular and limited functional magnetic resonance imaging analyses, abnormalities in the brain regions of symptomatic former finasteride users were like those identified in patients with psychogenic erectile dysfunction. Since these patients were not assessed by fMRI prior to finasteride treatment, it is difficult to assess with certainty that such abnormalities are attributed to finasteride exposure. Nevertheless, the study confirms that a subset of men who were treated with finasteride and discontinue treatment remain afflicted with sexual dysfunction due to persistence of the effects. Rahimi-Ardabili et al. (74) reported on 128 men with AGA, who were prescribed finasteride (1 mg/day). Information on depressed mood and anxiety was obtained by Beck Depression Inventory (BDI), and Hospital Anxiety and Depression Scale (HADS). Participants completed BDI and HADS questionnaires before beginning the treatment and two months after it. At baseline, mean (± standard deviation) BDI and HADS depression scores were 12.11(± 7.50) and 4.04 (± 2.51), respectively. Finasteride treatment increased both BDI (P <.001) and HADS depression scores significantly (P =.005). The authors suggested finasteride may induce depressive symptoms. Melcangi et al. (48) reported that PFS patients exhibited altered level of important physiological regulators of brain function, such as neuroactive steroids. This may explain, in part, the psychiatric features observed in PFS patients. Such biochemical alterations may disrupt dopaminergic signaling in the nucleus accumbens and contribute to the observed adverse side effects. In an observational-retrospective study, Chiriaco et al. (128) reported that in 79 males (>18 and <50 years old) who used finasteride for AGA developed persistent side effects for at least 6 months after drug discontinuation. Patients were enrolled 180–5057 days after drug discontinuation. In all subjects, adverse side effects persisted for over 6 months after finasteride discontinuation and were still affecting the patients at the time of the study enrolment. In 89.9% of participants' onset of symptoms occurred during finasteride use, and the trend of symptoms worsened in 62% based on the ad hoc questionnaire, the most frequent sexual symptom was loss of penis sensitivity (87.3%); among mental disorders was reduced feeling of life pleasure or emotions (anhedonia) (75.9%); and among somatic symptoms was loss of muscle tone/mass (51.9%).

Kiguradze et al. (84) queried an archive for an electronic medical record (EMR) database at a large, urban academic medical center (Northwestern University, Chicago) to identify healthy men who developed sexual dysfunction (SD) after taking finasteride. The authors searched EMR database approximately 2.9 million individual records for the interval January 2001 to September 2013. The researchers identified a cohort of healthy men < 42 years-old (N = 4,274) with an exposure to finasteride ≤ 1.25 mg/day and without exposure to other 5α-reductase inhibitors except finasteride. Most importantly, these men had no sexual dysfunction prior to finasteride exposure and no prior phosphodiesterase-type 5 inhibitor (PDE5i) use. The authors used ICD-9 codes to identify erectile dysfunction and low libido with confirmation by manual review of the EMR. They further identified new onset sexual dysfunction as new erectile dysfunction, low libido, or use of PDE-5i to treat ED. Most importantly, the authors defined persistent sexual dysfunction or low libido lasting more than 90 days after discontinuation of finasteride. The authors reported that 47 patients experiencing persistent SD with median duration of SD following termination of finasteride was 1,398 days and persistence > 365 days occurred in 36 of the 270 individuals (13.3%). The maximum observed persistence was 3,356 days.

Ali et al. (127) noted that in 4910 reports, 577 exhibited persistent sexual dysfunction (SD) and 39 suicidal ideation (SI). In 34 (87.2%) of the 39 men with SI also experienced SD. Most of these events were serious (e.g., contributed to the patient's death, hospitalization, or disability). The authors concluded that persistent sexual dysfunction is a potential risk of finasteride for AGA therapy in young men, and this risk contributes to suicidal ideation. In 131 men on finasteride therapy Ganzer et al. (52, 53) reported on sexual dysfunction, including changes in libido, loss of morning erections, erectile dysfunction, and anhedonia in sex. Decreased sex drive was noted in 121 men (93%); complete loss of sex drive in 82

men (63%); intermittent erectile dysfunction in 108 men (83%); complete impotence in 52 men (40%); loss of morning and spontaneous erections in 116 men (89%); failure to achieve orgasm on most occasions in 52 men (40%); and sexual anhedonia, loss of pleasurable orgasm in 91 men (70%). Choi et al. (130) reported that 110 patients with AGA who were treated with dutasteride, seven patients experienced ED. Only three patients reported their ED was resolved. Three other patients reported that their ED were not resolved, and one remains with unknown results.

Similarly, Tsunemi et al. (187) reported that patients with AGA who were treated with dutasteride sexual dysfunction adverse events (SDAE) were the most common side effects. At one year, three patients reported events that were possibly suicidal-related. The authors concluded that all reported sexual dysfunction adverse events of special interest were drug-related except one case of impotence. Sexual dysfunction adverse events reported in six patients were resolved during 52-week treatment period. The remaining 13 patients with sexual dysfunction adverse events that persisted at the end of the treatment period (one year) were all resolved within the 6-month follow-up period after treatment cessation (187). Guo et al. (129) identified 1390 men who were finasteride users and compared them to 20,000 omperazole users. Since omperazole does not induce sexual dysfunction it was used for comparison. The authors found that the median time to first persistent sexual dysfunction after discontinuation was 339 days. The rate of persistent sexual dysfunction for 1 mg finasteride users and omperazole users were 37.9 and 15 per 1000-person years, respectively. The rates and Hazard ratios of persistent sexual dysfunction of users in the primary analysis of persistent sexual dysfunction defined as the first sexual dysfunction code were 2.19 (crude) and 1.62 (adjusted) for finasteride compared to 1 in the Omeprazole. In the secondary analysis of persistent sexual dysfunction defined as the first use of phosphodiesterase type 5 inhibitor the crude and adjusted hazard ratios were 2.41 and 2.73, respectively, suggesting an increased risk of persistent sexual dysfunction with finasteride.

DISCUSSION

Until recently, the adverse effects of finasteride and dutasteride therapy on sexual function were not recognized or well-understood. However, a body of emerging evidence suggests that the assessment of sexual side effects of finasteride in many clinical studies were not accurately captured or reported (83). In addition, considerable bias and inaccuracies in reporting adverse effects of finasteride or dutasteride in most clinical trials of men AGA (83). An editorial following the report by Belknap (83) highlighted the need to re-think the safety of these drugs (188).

It is not surprising that almost all studies published to date do report increased sexual adverse effects. However, even when such sexual adverse events were reported, many argued that the numbers of subjects afflicted are small and propagated the falsehood that the adverse effects do resolve with continued treatment. This is unfortunately a willful blindness and a deceptive method to continue to prescribe these drugs to unsuspecting young men. The number of subjects experiencing adverse events is neither small nor irrelevant, given the persistent nature of adverse events in susceptible individuals. For those individuals afflicted, this constitutes a life sentence of sexual dysfunction, depression and/or anxiety. To put this in perspective, approximately 30 million young men, worldwide, would be prescribed finasteride or dutasteride to treat male pattern hair loss. Even if the incidence of persistent sexual adverse events is 3% to 5%, which may be viewed as a small number, approximately 900,000 to 1.5 million men would suffer persistent sexual and psychiatric adverse events. By no means this would be considered a small number and should not be dismissed or ignored. By no means this can be considered a small number and should not be dismissed or ignored.

The key argument raised by many clinicians remains: What is the level of evidence supporting the persistent nature of the sexual adverse effects and psychological symptoms caused by finasteride? Considerable evidence exists in the contemporary literature regarding the physiological role of 5α-reductases in the peripheral tissues and CNS and the pathophysiological implication of inhibiting this family of enzymes and blunting biosynthesis of neurosteroids, which are critical biological mediators in the CNS, and contribute to altered mood, cognition, and libido (23–50). Also, significant pre-clinical evidence exists demonstrating that inhibition of 5α-RIs contributes to erectile dysfunction (16–22) and may also contribute to neurological symptoms (Fig. 4 (36). Data from several studies as well as from the manufacturer own reporting that some adverse events do not resolve and may persist. A number of studies discussed in this review demonstrated that not all adverse events resolve with drug discontinuation and in some cases they persist or become irreversible (8,12, 13, 52–54, 83, 84, 88, 67, 68, 115, 127, 129, 130, 170, 186–189). For these reasons, we find the argument that sexual adverse events resolve with continued treatment is outright inaccurate and, at best, deceptive.

The increased reporting of and documentation of persistent side effects in the clinical literature resulted in warnings by the Medicine Health Care Products Regulatory Agency (MHRA) public assessment report on the risk of finasteride published in December of 2009 in Section 4.8 Undesirable Effects, it was stated, “In addition, the following have been reported in post-marketing use: persistence of ED after discontinuation of treatment with PROPECIA.” Clearly, the sexual adverse events do not necessarily resolve completely in all patients, who discontinue use of finasteride, again supporting the premise that in some patients these sexual side effects remain “persistent.” Furthermore, in December 2008, the Swedish Medical Products agency concluded its safety investigation of Propecia. The Agency’s updated safety information now lists as a possible side-effect difficulty in obtaining an erection that persists even after discontinuing Propecia. In addition, in 2011, the USA FDA mandated that labeling of finasteride includes information about potential risks of depression as well as sexual dysfunction and problems and high-grade prostate cancer. In 2017, the European

Medical Agency recommended adding depression and suicidal ideation to the finasteride label.

One other argument consistently made in the literature is that the low-quality evidence available do not support a causal link between finasteride and persistent symptoms. Examining the contemporary clinical literature, it appears that almost all studies published to date (Tables 1–3) demonstrated increased onset of sexual dysfunction and psychiatric dysfunction, irrespective of the assessment method, age or drug dose. How could such evidence be totally ignored and dismissed as low-quality evidence? Given that considerable level of bias is introduced in many of these studies since large number of these clinical trials were funded and administered by the drug manufacturers, it is paramount that clinicians do their due diligence and not fall for the slogan, "these drugs are well tolerated and safe."

It is imperative that we consider how safety reporting of adverse events due to finasteride and dutasteride have been inadequate in most clinical trials (83, 84). Indeed, this inaccurate reporting of harm makes the evidence regarding the adverse events to be limited and may appear of poor-quality. Given the level of bias due to conflict of interest, it is not surprising that the level of harm is tampered down significantly. Well-trained and experienced clinicians may see the coexistence of adverse events as distinct syndrome with its own pathogenesis rather than a simple random or haphazard co-occurrence. Despite the lack of final proofs, the presence of severe and persistent side effects induced by these drugs raises serious concerns for the clinicians. Simply, a low estimated prevalence of PFS should not be used as an excuse for non-vigilance, given that these drugs are prescribed for millions of relatively young healthy men.

Although the concerns regarding finasteride adverse effects led the NIH to add PFS to its Genetic and Rare Disease Information Center, PFS has yet to be recognized by the medical community, even though several patients do present with very severe, peculiar and classical symptoms. It is distressing that many clinicians and key opinion leaders from various clinical disciplines continue to dispute and dismiss any notion that PFS is real (64–66, 82, 85, 87–89, 93, 119, 120, 132, 134, 135, 139,141, 143, 144, 150, 153, 160, 162, 167, 171, 173, 174, 181, 185, 190–200). Most disturbing, however, is clinicians labeling of patients with PFS as unstable, psychotic or delusional (65, 66).

Rejecting new ideas in science and medicine is very common in the scientific and clinical literature. It would be reasonable to expect that even with limited available evidence, it would be unacceptable to outright dismiss PFS and deny afflicted patients a basic medical evaluation and appropriate treatment, if available. Several examples illustrate the development of syndromes elicited as a result of drug treatments. The development of tardive dyskinesias due to use of phenothiazines in the treatment of patients with chronic schizophrenia is well understood and recognized (201–211). Similarly, other recognized drug-induced syndromes include: long QT syndrome (LQTS) (202–206), Brugada syndrome (208), hematologic Syndromes (209) and Fanconi's syndrome (210). Contrary to PFS, persistent side effects arising from treatment with other drugs are well-recognized and accepted (201–211) while those persistent adverse side effects arising from finasteride treatment are fiercely denied.

If drug-induced syndromes, other than finasteride, are well recognized by the medical community, it raises a fundamental question why the resistance by the clinical profession to recognizing PFS? Recently, Maksym et al. (63) reviewed the literature on PFS and stated that despite the lack of final proof for PFS, the presence of severe and persistent side effects caused by the treatment of AGA raises great concern for the clinician. A low estimated prevalence of PFS should not be an excuse for non-vigilance since the drug is used by millions of relatively young and healthy individuals. Since imaging data from former finasteride users derived by fMRI (56) and assessment of neuro-steroids levels in CSF by HPLC-Mass spectrometry analysis (46–48) point to a disruption of neurotransmitters and chemical messengers by finasteride, it is difficult to continue to argue that such drugs are "safe and tolerable and without adverse side effects." Such dismissal of this syndrome may be considered a willful blindness on the part of the clinical community, at large.

The argument often made is why only some individual are affected but not all those who are treated with these drugs? The susceptibility of individuals to adverse reactions may lie in their epigenetic phenotype (50). Interestingly, with so many drug-induced syndromes recognized by the clinical community (201–211), it is surprising that PFS appears to be difficult to recognize or acknowledge. This raises several fundamental questions for why such fierce resistance?

We are fully cognizant that risk of bias arises from various sources, including randomized clinical trials (83, 188, 212, 213), given that many of such trials on finasteride or dutasteride were supported and administered by the manufacturers with potential conflict of interest. Most often, ascertainment of harms in clinical trials is rarely disclosed in any publicly available documents. For that reason, it is, at best, to be vigilant about the results of such trials which may have under-reported the adverse effects of finasteride and dutasteride. As reported by Belknap et al. (83) a lack of information about harm is usually the case in published trials and meaningful analyses cannot be made and the evidence may appear questionable, at best. Adverse events produced by drugs in randomized clinical trials are not systematically evaluated with the quality, scientific rigor, and objectivity available for assessment of drug benefits. As pointed out recently by Golder et al. (212) and Kaptchuck et al. (213) not all data reported in clinical trials are unequivocal and accurate and therefore we need to take a deeper look at the data reporting and have better assessment of the data presented in order to arrive to a real evidence-based approach to determining the extent, scale and scope of the adverse sexual side effects. These shortcomings should not come in the way of understanding this complex syndrome known as PFS.

The failure of the clinical and scientific communities to develop better understanding of the pathophysiological mechanisms underlying the various symptoms of this syndrome should not be a reason to label PFS patients as psychotic or delusional (65, 66). Furthermore, considerable evidence exists from pre-clinical studies on the role of

5α-RIs in sexual function (16–22) and effects on the CNS, which may explain adverse events on mood, anxiety and depression (23–43). Finally, new studies have demonstrated that these drugs may increase the incidences of type 2 diabetes (214) and Kidney diseases (215). For these reasons, we should be more vigilant about the harm produced by these drugs. Thus, to dismiss outright such obvious clinical symptoms in patients with PFS represents a new level of arrogance adopted by some in the clinical community due to scientific and clinical ignorance.

It is time to acknowledge and recognize that patients who are suffering from PFS are not psychotic or delusional, as some in the clinical community wish to label them (65, 66). It is time for action, and this necessitates development of more effective approaches to understanding the pathophysiological mechanism of PFS and development of novel therapeutic options. The medical community has an obligation not to turn a blind eye on this rare yet debilitating condition in young men. Patients with this condition should not be stereotyped or stigmatized by untrained and unprepared clinicians, due to lack of awareness and knowledge pertaining to this new and rare syndrome. Greater awareness and education are needed among the medical and scientific communities in order to develop better approaches for managing men with PFS. It is paramount that steps are taken to develop better understanding of the underlying mechanisms contributing to the onset and progression of PFS and to promote educational and training programs to increase awareness and improve management of this condition.

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