REVIEW ARTICLE

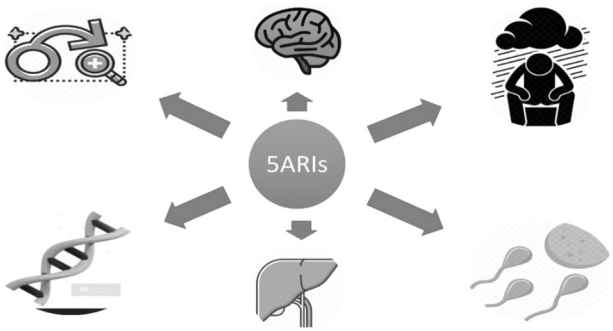
The post-finasteride syndrome: possible etiological mechanisms and symptoms

Herman H. J. Leliefeld[1]✉, Frans M. J. Debruyne[2] and Yakov Reisman[3]

Finasteride and dutasteride, synthetic 5α-reductase inhibitors (5ARIs) are recommended in many guidelines for the treatment of benign prostatic hyperplasia/lower urinary tract symptoms and alopecia despite a variety of side effects like sexual, neurological, psychiatric, endocrinological, metabolic and ophthalmological dysfunctions and the increased incidence of high grade prostate cancer. The sexual side effects are common during the use of the drug but in a small subgroup of patients, they can persist after stopping the drug. This so-called post-finasteride syndrome has serious implications for the quality of life without a clear etiology or therapy. Three types of 5α-reductases are present in many organs in- and outside the brain where they can be blocked by the two 5ARIs. There is increasing evidence that 5ARIs not only inhibit the conversion of testosterone to 5α-dihydrotestosterone (DHT) in the prostate and the scalp but also in many other tissues. The lipophilic 5ARIs can pass the blood-brain barrier and might block many other neurosteroids in the brain with changes in the neurochemistry and impaired neurogenesis. Further research and therapeutic innovations are urgently needed that might cure or relieve these side effects. More awareness is needed for physicians to outweigh these health risks against the benefits of 5ARIs.

IJIR: Your Sexual Medicine Journal; https://doi.org/10.1038/s41443-023-00759-5

Graphical Abstract



INTRODUCTION

Two types of 5α-reductase inhibitors (5ARIs) are currently used in clinical practice: finasteride and dutasteride. Finasteride has been approved by the United States Food and Drug Administration (FDA) in 1992 (5 mg) and 1997 (1 mg) for, respectively, the treatment of symptomatic benign prostatic hyperplasia/lower urinary tract symptoms (BPH/LUTS) and androgenic alopecia (AGA) in men [1, 2]. As about 60% of men older than 60 years will suffer from BPH/LUTS and about 50% of the Caucasian men will have AGA, there is a large clinical implication for the use of these medications [3, 4]. Dutasteride 0.5 mg was approved in 2001 by the FDA for symptomatic BPH/LUTS [1]. Since then, many scientific publications appeared including placebo-controlled randomized clinical trials (PCRCT) showing finasteride and dutasteride to be well tolerated and effective after long term follow-up of 2–4 years of treatment in alleviating urinary tract symptoms, reducing prostate size by 18–28%, improving urinary flow rates, reducing urinary tract infections, the risk of acute urinary retention and the need for surgical intervention for symptomatic BPH/LUTS [5–8]. This leads to improvement of quality of life in men suffering from BPH [9, 10]. Finasteride at 1 mg/day has been shown to lead to a significant reduction in the progression of baldness and to a stimulation of new hair growth [11]. These drugs are currently recommended in urology guidelines [12] with a strong recommendation to use it "*in men who have moderate to severe LUTS (Lower Urinary Tract Symptoms) and an increased risk of disease progression (e.g., prostate volume > 40 ml)*" [12]. Similarly, dermatology societies recommend finasteride for the management of

[1]Andros Clinics The Netherlands, Wilhelminapark 12, 3581 NC Utrecht, The Netherlands. [2]Andros Clinics The Netherlands, Mr. E.N. van Kleffenstraat 5, 6842 CV Arnhem, The Netherlands. [3]Flare-Health, Oosteinderweg 348, 1432 BE Aalsmeer, The Netherlands. ✉email: hleliefe@kpnmail.nl

Received: 9 March 2023 Revised: 22 August 2023 Accepted: 24 August 2023
Published online: 11 September 2023

alopecia [13]. Despite their popularity, there is a clear and recurrent concern regarding their potential side effects like sexual and cognitive dysfunction, which may be persistent [14–16]. More side effects are reported like metabolic changes, depressive like behavior and anhedonia and the increased risk of high grade prostate cancer [17–21]. In this article, the pharmacophysiological mechanism of action of 5ARIs, the wide range of reported side effects, and their possible mechanisms are presented.

MATERIAL AND METHODS

A retrospective review on the Post-Finasteride Syndrome (PFS) was performed between 2000 and 2022. The search for information in PubMed/Medline was performed using the MeSH terms "Finasteride or Dutasteride" and terms "side effects" or "post-finasteride syndrome". Articles have been selected for English or Dutch language. According to the abstracts, one of the authors identified relevant publications for potential PFS pathophysiology and PFS case reports, which were then thoroughly reviewed by all the authors.

MECHANISM OF ACTION OF 5α-REDUCTASE INHIBITORS IN BPH AND AGA

Androgen-effects on the prostate are mediated by 5α-dihydrotestosterone (DHT), the more potent natural androgen [17, 22, 23]. During early fetal development DHT is mainly involved in the virilisation of the external genitalia and development of the prostate [24]. In adult life DHT is important in development and maintenance of male sexual organs and its function [25, 26]. It is converted from testosterone by the enzyme 5α-reductase [27]. The absence of BPH or AGA in men with congenital 5α-reductase deficiency (male pseudohermaphroditism or 'disorder of sexual development 46XY') demonstrates the essential role of DHT and thus of 5α-reductase in the development of BPH and AGA [28, 29]. This enzyme has at least three isoforms [22, 30]:

- 5α-reductase type 1 with mainly expression in the skin and liver, but also in the brain, muscle and prostate.
- 5α-reductase type 2 with mainly expression and activity in the prostate but also in the kidney, brain, muscle, epididymis, hair follicles, liver and seminal vesicles.
- 5α-reductase type 3 with ubiquitously expression and activity in many adult tissues including the brain [22, 31]. Type 3 however is less well understood and therefore not regarded below.

Finasteride is a competitive inhibitor of mainly type 2 5α-reductase [32, 33]. Dutasteride inhibits both type 1 and 2 with greater potency than finasteride [34]. Continuous treatment with 5ARIs reduces the serum DHT concentration by approximately 70% with finasteride [35] and 90% with dutasteride [36]. However, prostate DHT concentration is reduced to a similar level (85–90%) by both 5ARIs [12]. These two drugs induce apoptosis of prostate epithelial cells [5] leading to prostate size reduction of 18–28% and a decrease in PSA levels of 50% after 6 to 12 months of treatment [6]. This mechanism together with the clinical benefits in BPH/LUTS patients formed the basis for the application of the 5ARIs for its treatment [7–9]. DHT is thought to play a significant role in AGA through binding to the androgen receptors (AR) of the hair follicle which leads to miniaturization of hair follicles from terminal hair (coarse, thick hair) to vellus hair (thin, short, barely visible hair) [37]. This also reduces the rate of hair growth [38]. It can be reversed by finasteride 1 mg in young and older men with male pattern hair loss [39, 40]. In the past 10 years a broader view has developed on the *extended* mechanisms of action of 5ARIs, which might explain a wide range of side effects; 5α-reductase type 1 and 2 are firmly established in the human brain [41] and finasteride treatment can block not only the conversion of testosterone to 5α-DHT but lead also to lower levels of other neuroactive steroids like pregnenolone, progesterone, 17β-estradiol and its metabolites in plasma and cerebrospinal fluid (CSF) of patients [30,42–44]. Moreover, it has been shown that finasteride treatment reduces the contents of dopamine and its metabolites in the central nervous system and is able to impair the signaling of dopamine [45, 46]. The possible negative clinical consequences will be discussed below in more detail.

SIDE EFFECTS AND ADVERSE EFFECTS OF 5ARIS

Part I: Sexual side effects, depressive symptoms and suicide

Already in 1981, a 5ARI was found to have a detrimental effect on erectile function in animal models using castrated rats, which was restored with DHT [47]. But it took 30 years to get evidence that inhibition of 5α-reductase by finasteride and dutasteride can potentially affect several different human tissues [22]. In 2011, two independent clinical human studies showed that the use of finasteride and dutasteride could cause several side effects including persistent erectile dysfunction (ED), loss of libido, orgasm problems and depressive symptoms [14, 48]. Moreover, these studies described that these side effects could be *persisting* in young men who used finasteride for AGA during several months and even 3 years after discontinuation of the drug [14, 48]. In this respect it is remarkable that the outcome of the PROSPECT study from 1996 (one year before the official introduction of the drug), which investigated finasteride (5 mg) safety for BPH, is more or less neglected although it demonstrated significant differences between patients and controls in ED (15.8% vs. 6.3%), loss of libido (10% vs. 6.3%), and in ejaculation disorders (7.7% vs. 1.7%) [9]. This negation is partly due to the fact that these adverse side effects were regarded as clinically less important, rare and minimal as was concluded by the authors of the Prostate Cancer Prevention Trial (PCPT) in 17,313 participants over 7 years [49]. In 2012, a study showed depressive symptoms and suicidal thoughts among former users of finasteride with persistent sexual side effects [50]. Shortly before in 2011 the term *Post-Finasteride Syndrome* (PFS) was introduced, first in the media, developed by a community of internet users who were suffering from persistent adverse effects of finasteride [51]. The Post-Finasteride Syndrome Foundation was established in 2012 [52]. The diagnostic criteria according to expert opinion consensus from 2022 are described in Table 1 [53].

This syndrome has no clear etiology and no evidence-based therapy up till now [54]. PFS is poorly understood by medical and scientific associations; the EAU guideline on male BPH/LUTS does not mention the possible persistent nature of the side effects [12]. But already in 2011, the FDA issued two warnings in the labels of 5ARIs-class of drugs: to include new safety information about "*the increased risk of a more serious form of prostate cancer (high-grade prostate cancer)"* and to include the following adverse reactions in the label: "*impotence, decreased libido, decreased volume of ejaculate, depression, breast enlargement, breast tenderness and rash"* [1]. In 2012, the label was adapted and stated that the symptoms of sexual dysfunction could be permanent according post marketing experience [1]. In a meta-analysis from 2015 of 34 clinical trials of finasteride for AGA, it was found that adverse event reporting was of poor quality, systematically biased, not generalizable to routine practice and that most subjects had ≤1 year of finasteride exposure [55]. Therefore, one can assume that those meta-analyses on the side effects of 5ARIs, including the GRADE system from the past 10 years, are less reliable. However, a well-designed study from 2017 on the persistence of erectile dysfunction (PED), 90 days or more after discontinuation of exposure to finasteride or dutasteride in 11,909 men, revealed two important results: 1.4% developed PED with a persistence duration of median 1348 days after stopping the 5ARI and the risk of PED

was higher in men with longer exposure to 5ARIs [15]. In 2016 two large studies were published with contradictory results regarding the risk of ED: a systemic review with meta-analysis of four randomized clinical trials (RCT) found a significant increase of ED and a decrease of libido in 2965 patients treated for BPH/LUTS with a 5ARI comparing with 2947 patients on α-blocker monotherapy [56], while on the other hand one population based study in 71,849 men using 5ARIs for BPH/LUTS or alopecia found no significant increase of ED [57]. This last study, however, has serious bias: in this retrospective cohort study the existence of ED as baseline characteristic and during follow up was only based on data from the electronic medical record database regarding the medical diagnosis and prescription of drugs for ED. No questionnaires were available or recorded. Thereby, in the group of 8977 men that were included and using a 5ARI for BPH/LUTS, the baseline characteristics showed large number of comorbidities associated with ED, which makes it very likely that many of these patients had already a certain grade of ED right at the start of the treatment with a 5ARI [57]. Most current studies on the association of finasteride/dutasteride with ED that were included in a recent review found that finasteride for BPH/LUTS was correlated with an increased risk of ED [58]. See Table 2. This was not the finding related to AGA [58].

Another important source for research regarding side effects of finasteride is Vigibase, the World Health Organization's international database of individual case safety reports. It showed in 7700 reports a disproportional signal of sexual dysfunction with an overall reporting odds ratio (ROR) of 50.3 (95% confidence interval, 49.0–51.6) associated with finasteride use in male users, with more reports than would be expected by chance alone [59]. The ROR in patients with AGA and under the age of 45 years was even higher (respectively 64.9 and 56.4) [59]. The same accounts for the pharmacovigilance study of 3282 users of finasteride using Vigibase in which a disproportional signal was found of suicidality, depression and anxiety associated with finasteride use for alopecia in patients younger than 45 years [60].

A very recent study on genetic determinants on human health was able to identify a genetic association between lower levels of androsterone sulfate and epiandrosterone sulfate and depression [61]. This supports concerns about widespread use of 5ARIs [18, 54, 60], because these antiandrogens cause likewise lower levels by 5α-reduction of these androgenic neurosteroids [30, 42, 44].

Table 1. PFS Diagnostic criteria: adapted from Healy D et al. [53].

Necessary	1. Prior treatment with a 5 alpha-reductase inhibitor. 2. Enduring sexual dysfunction after stopping treatment
Additional	3. Enduring reduction or loss of sexual desire. 4. Enduring erectile dysfunction. 5. Enduring reduction in genital and orgasmic sensation. 6. The problem is present for ≥3 months after stopping treatment.
Exclude	7. No evidence of pre-drug sexual dysfunction that matches the current profile. 8. No current medical conditions that could account for the symptoms. 9. No current medication or substance misuse that could account for the symptoms. 10. No other prior medication that could account for the symptoms.
Additional finasteride effects that can occur independently of any sexual difficulties	- Cognitive impairment - Depression - Suicidality
Features of 5ARIs' side effects but not diagnostic for PFS	- Gynecomastia - Altered seminal quantity and quality

5ARIs 5Alpha-Reductase Inhibitors, *PFS* Post-Finasteride Syndrome.

Table 2. Recent clinical studies of 5ARIs for BPH/LUTS and sexual function (extended and adapted from Shin et al. 2019 [58]).

Study and reference	Study design	Population: 5ARI versus placebo or alfa-blocker	Sexual Function evaluation	Sexual function/ Erectile function	Sexual drive/libido
Fwu [95]	PCRCT	695 finasteride 672 placebo	BMSFI	no significant difference	decreased
Traish [96]	Retrospective	470 finasteride 230 tamsulosin	IIEF	decreased	–
Liu [97]	Meta-analysis PCRCT	14,075; 5ARI versus placebo	Questionnaire BMSFI	decreased	decreased
Favilla [56]	Meta-analysis	2965 5ARI 2947 alfa-blocker	IIEF	decreased	decreased
Corona [16]	Meta-analysis PCRCT	24,463 5ARI 22,270 placebo	Questionnaire	decreased	decreased
Hagberg [57]	Retrospective cohort study from database	8977 5ARI 60,280 alfa-blocker	Database	no significant difference, but biased	no significant difference, but biased
Roehrborn [98]	Multicentre PCRCT	243 Dut/Tam 246 Placebo	MSHQ, but incomplete: 3 questions for ED only and 7 questions for libido left out	No significant difference	Poorly investigated
Kosilov [99]	RCT	106 Dut 99 Dut/Solif 10 112 Dut/Solif 20	6 month IIEF MSHQ-EjD	No impact on EF	No impact on desire. More EjD

BPH Benign Prostatic Hyperplasia, *LUTS* Lower Urinary Tract Symptoms, *ED* Erectile Dysfunction, *EF* Erectile Function, *IIEF* International Index of Erectile Function, *EjD* Ejaculatory Dysfunction, *BMSFI* Brief Male Sexual Function Inventory, *PCRCT* Placebo Controlled Randomized Clinical Trial, *Dut* Dutasteride, *Tam* Tamsulosin, *Solif* Solifenacin.

In 2018 a review of the FDA Adverse Event Reporting System came out concerning 1 mg use in 1581 cases (mean age 35.8 years) and 5 mg in 240 cases (mean age 59.1 years) with a cluster of adverse events grouped in four categorical domains: sexual, physical, psychological (and "other"). See Table 3 including a priority list [62].

These data and the above-mentioned data of Vigibase suggest that side effects are more common in younger patients on 1 mg finasteride for AGA than in older men with 5 mg finasteride for BPH/LUTS. But here the literature is inconclusive [15, 55]. In a large single-group study (15,634 men, age 16–89 years) published in 2017 the authors concluded that the risk for new ED increased in patients with BPH if the age was below 69 years (15.6% versus 3.7%); in AGA the risk for new ED increased from 2.7% to 5.3% after a duration of 5ARI use of more than 106 days, concluding that age and duration of exposure does matter for new ED, even as predictor for PED in this study [15].

Part II: Adverse effects in liver, ocular system and kidney; impaired spermatogenesis

Recent studies on the health risks in humans and in animal models during long-term use of finasteride and dutasteride gave an important overview on the possible role of 5α-DHT in the physiological function of liver, pancreas, ocular system and kidney [17, 18]. All these organs contain the expression of 5α-reductase enzymes that can be blocked by the 5ARIs leading to reduction of the 5α-DHT levels, see Fig. 1.

- In the *human liver* 5α-reductase type 1 and 2 are highly expressed and their deficiencies or pharmacological inhibition may result in metabolic diseases due to reduced 5α-DHT levels [63]. In animal model inhibition of 5α-reductase type 1 and 2 with finasteride induced hyperinsulinemia and hepatic steatosis [64]. In men inhibition of 5α-reductase type 1 and 2 with dutasteride resulted in hepatic insulin resistance and hepatic lipid accumulation [65, 66].
- Finasteride administration significantly downregulated AR in the *lacrimal gland* in the animal model. Finasteride treated female and male rats showed a significant reduction in tear flow of respectively 49% and 40% after 10 days [67]. Besides a diminished tear flow, finasteride treated rats showed a severe inflammation of the lacrimal gland as was shown with histopathological changes [68]. These observations suggest that inhibition of the conversion of testosterone to 5α-DHT potentiates an inflammatory response that increases the infiltration of lymphocytes into the lacrimal gland [67, 68].
- The physiological processes in the *kidney* are mediated by AR, which are located in the cells of most parts of the nephron. In a recent animal study, it was shown that finasteride administration downregulated AR expression in the cortical region of the kidney. This led to histopathological changes such as apoptosis, fibrosis and infiltration of mononuclear cells [69].
- Type 2 5α-reductase predominates in the *reproductive tissues*, genital skin and epididymis [70]. In a double-blinded PCRCT it was shown that the decrease in DHT induced by 5ARIs is associated with mild decreases in semen parameters which appear reversible after discontinuation [71]. Other studies showed that finasteride may aggravate cases of subfertility or infertility and advised to stop finasteride with significant improvement in sperm concentration [72–74].

Table 3. Adverse events due to finasteride 1 mg according to the FDA Adverse Event Reporting System in 1,581 cases with frequency (%) of reporting [62].

Class	Type
Sexual: 81.4%	Erectile dysfunction: 56.2% Diminished libido: 41.9% Reduction in volume and strenght of ejaculation: 25.6% Testicular atrophy:12.8%
Psychological: 63.0%	Depression and anxiety: 47.5% Slow cognition: 39.5% Sleep disturbances: 11.0% Suicidal thoughts: 2.5%
Physical: 28.3%	Skin rash: 83% Fatigue: 10.8% Muscle weakness: 9.3%

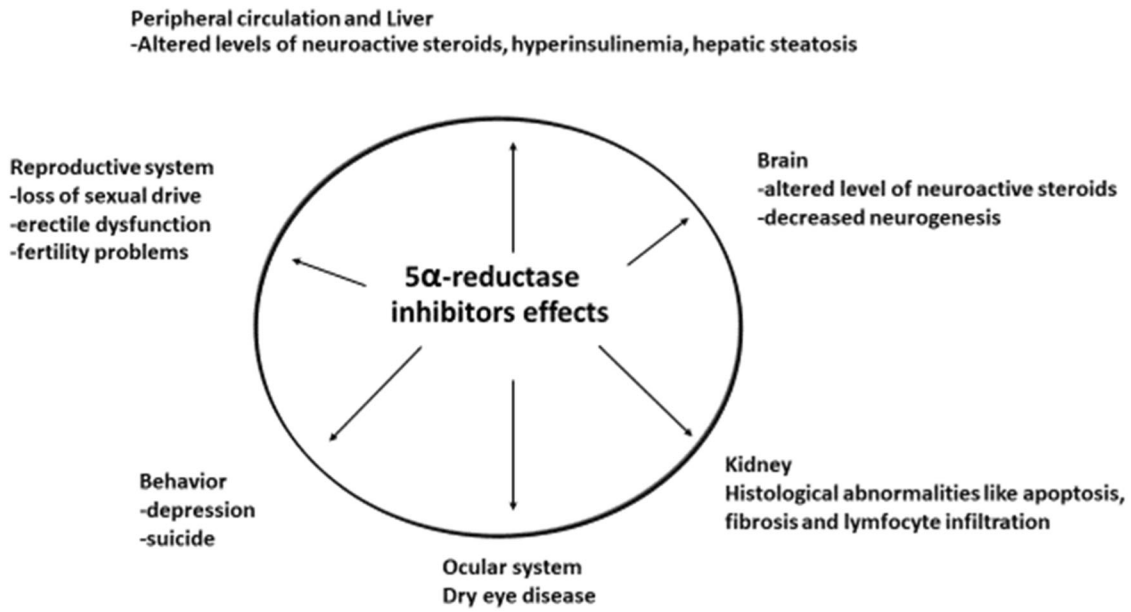


Fig. 1 A graphical overview of possible side effects of treatment with 5ARIs in experimental models [18] (modified and adapted from Diviccaro S [18]).

Part III: Finasteride, dutasteride and prostate cancer

In the double-blind randomized multicentre PCPT finasteride 5 mg was compared with placebo to determine whether it might reduce the risk of prostate cancer [19]. This trial demonstrated a clear reduction of lower grade prostate cancer over a 7-year period in the finasteride group compared with the placebo group, but with an increased risk of high-grade prostate cancer with no proven causal relationship [19]. The REDUCE trial with dutasteride came to the same conclusion [20]. A possible explanation of this unexpected association was delivered in a recent large cohort study in which 80,875 patients with stage I-IV prostate cancer were included with a median follow up of 5.90 years [21]. A total of 8587 patients (10.6%) used 5ARIs with a median treatment duration of 4.85 years before the diagnosis of prostate cancer. As primary outcome it appeared that the prostate cancer specific mortality was significant higher in the group of 5ARI users (HR: 1.39, $p < 0.001$). The secondary endpoints showed in the 5ARI group in comparison to the group of non-users a significant higher median *adjusted* PSA at time of biopsy, a significant higher % of Gleason grade ≥8 and a significant higher % of metastasis (all with $p < 0.001$). The authors concluded that prescribers of 5ARIs need more awareness of the decrease of PSA about 50% after 6 to 12 months of use [6, 21]. They suggest that PSA suppression in 5ARI users was not routinely accounted for during prostate cancer screening [21]. No other pathophysiologic explanation has been found so far.

WHAT ARE THE POSSIBLE ETIOLOGICAL MECHANISMS OF ACTION THAT CAUSE THE SIDE EFFECTS?

Many of the side effects that are presented in the literature are based on epidemiological studies without etiological explanations. Therefore, our knowledge about the causes of the side effects is still lacking and incomplete. But in the recent years the insight in the mechanisms by which 5ARIs can cause side effects is increasing rapidly from animal and human studies. We can distinguish at least three possible etiological mechanisms of action:

a. Changes in neurochemistry and neurogenesis.

Type I and 2 5α-reductase is present in many organs [22, 31, 75] including the brain [41] in which it takes care for adequate levels of 5α-DHT with a potent inhibition by finasteride and dutasteride [34, 76]. These drugs are synthetic lipophilic steroids that can pass the blood-brain barrier [30, 43]. Once in the cerebral fluid and brain, finasteride can block not only the conversion of testosterone to 5α-DHT but also the reduction of progesterone to 5α-dihydroprogesterone and of deoxycorticosterone to 5α-dihydrodeoxycorticosterone, associated with higher levels T, DHEA and 3alfa-diol as was reported in the CSF of PFS patients in comparison with those observed in healthy patients [30, 43, 44]. All these neurosteroids are important physiological modulators of the nervous system by interacting with steroid receptors [18, 30]. So, after passing the blood-brain barrier finasteride might induce a deficit in the neurosteroid metabolism in the central nervous system in humans [42, 43]. Persistent changes in neuroactive steroids have actually been documented in male rat brains after finasteride discontinuation [77]. Not only the levels of neuroactive steroids but also the expression of their receptors are altered by finasteride treatment in certain brain areas of male rats leading to a decrease of the neurogenesis of the hippocampus in the male mice [77, 78], a histopathological process that is also reported in depressed patients [79]. These changes in the neurochemistry and neuropathology of the brain could be the link between depression/suicide and finasteride use as was suggested in animal and human studies [54, 80].

b. A novel state of androgen deficiency

In target cells, both testosterone and 5α-DHT come to expression by binding to the AR. The binding of 5α-DHT is stronger compared to testosterone [17, 22, 23]. This difference in affinity between testosterone and 5α-DHT for the AR and the ubiquitous presence of 5α-reductases in many tissues [22, 31, 81], makes 5α-DHT the most important factor for the androgen action in various target cells. Inhibition of biosynthesis of 5α-DHT in many tissues and organs by 5ARIs results in a novel state of androgen deficiency with normal plasma levels of testosterone but a decreased cellular level of 5α-DHT with an inhibited function in many organs and tissues which will not be visible in routine testosterone measurement in the blood [17]. Several clinical examples due to this novel state of androgen deficiency exist like:

- the well-known reduction of prostate growth by 18–28% in 6 months' time in men after taking 5ARIs [6],
- liver fat accumulation, liver fibrosis [63, 65] and dry eye disease [67] (see above),
- ED in the animal model after 5ARIs due to impairment of corpus cavernosum growth, of trabecular smooth muscular relaxation and of endothelial function, loss of weight of the corpus spongiosum and increased connective tissue deposition in the presence of normal total testosterone levels [82]. 5α-DHT plays a key role in neuronal and endothelial nitric oxide synthases, important mediators of smooth muscle relaxation and therefore erectile function [83, 84].
- impaired spermatogenesis in men lacking 5α-reductase type 2 and impairment of the seminiferous tubules with damage to the blood-testis barrier [85].

c. The nocebo effect in finasteride treated men

In a group of men ($n = 60$) who were informed about the possible sexual side effects before prescribing finasteride, the percentages for ED, decreased libido and ejaculation disorders were significant higher than the percentages in the group without information ($n = 60$) [86]. According to this study the legal obligation of every physician to inform his patient on side effects makes the incidence of side effects worse: the nocebo-effect. The adverse effects of finasteride like depression and suicidal thoughts got public awareness in 2012.This could have led to stimulated reporting and a nocebo effect as well, the so-called Weber effect [60, 87].

DISCUSSION AND CONCLUSIONS

The 5ARIs finasteride and dutasteride are widely used drugs over 20 years for alopecia and BPH/LUTS with a variety of side effects like sexual, neurological, psychiatric, endocrine, metabolic, ophthalmological, testicular dysfunctions and the increased incidence of high-grade prostate cancer [17, 21, 54]. The sexual side effects are common and transient, but in a small subgroup of patients these side effects can persist even years after discontinuation of the drug [48, 88, 89]. This so-called PFS has serious implications for the quality of life and unfortunately till now no effective therapy exists [17, 54].

Physiological mechanisms of PED and genital anesthesia are yet to be understood; is there an endocrinological, psychological or neurological cause (central or peripheral) [90]? The above mentioned etiological mechanisms like the change in neurochemistry and neurogenesis, the novel state of androgen deficiency and the nocebo-effect are steps further but by far insufficient to explain why there are subgroups of patients with side effects during and after use of 5ARIs and to reach in the end a concrete therapy. For a better understanding of the existing relations between hormonal and cerebral symptoms a consistent

cross-consultation is needed between urologists/sexologist/endocrinologist/dermatologists on one end and psychiatrists/neurologists/researchers on the other hand. In general it is sometimes difficult for patients and professionals to recognize the link between symptoms and the 5ARIs because symptoms exist or appear (long time) after discontinuation of the drug. A very interesting and promising development is the identification of genetically influenced metabotypes, so called GIMS [91], that represent the genetic basis of chemical individuality, which gave new biological insights. With the help of these GIMS it was possible to prove a consistent genetic association between greater 5α-reductase activity and the risk of male-pattern hair loss [61].The investigators also observed genetic associations consistent with lower 5α-reductase activity with lower levels of metabolites downstream of 5α-reduction of androgenic steroids. Another study identified a separate genetic association between androsterone sulfate, epiandrosterone sulfate and depression [92]. This chemical individuality might be the way to identify subgroups of patients at risk for side effects due to 5ARIs.

The lack of quality studies is a major problem in assessing the presence and frequency of the side effects. Further research is warranted with PCRCT including validated questionnaires at baseline with detailed history regarding past psychiatric disorders, the use of medications or drugs and relevant comorbidities, and with a follow up for several years. But this is unlikely to happen due to a lack of funding. Until then it is utmost important to identify individuals with a previous history of depression, sexual dysfunction or infertility who may be more susceptible for the various side effects [93]. The possible risks should than be discussed with the patient and weighed out against the benefits of the use of 5ARIs as mentioned in the introduction. Men under the age of 40 who use finasteride for alopecia are at risk for suicide if they develop persistent sexual adverse effects and insomnia [94]. Physicians need more awareness regarding the decrease of PSA due to 5ARIs of 50% after 6 to 12 months use [6] which can mask high-grade prostate cancer [21]. They should restrict the 5ARIs to patients with a prostate volume of >40 ml according the EAU guideline 2023 [12]. Therapeutic innovation is urgently needed that might cure or relieve this wide range of health risks.

LIMITATIONS

Scientific literature on the PFS has the intrinsic limitation, by definition, that symptoms can persist or even appear after cessation of the 5ARIs and therefore have been unnoticed and not documented in the literature.

The earlier mentioned lack of quality studies has hampered our knowledge of the presence, frequency and duration of the side effects.

The incomplete scientific knowledge of the 5α-reductase isoforms is concerning regarding the widespread use of 5ARIs like finasteride and dutasteride.

REFERENCES

1. Access data. https://www.fda.gov/drugs/information-drug-class/5-alpha-reductase-inhibitor-information. Assessed 18 April 2023.
2. Cather JC, Lane D, Heaphy MR, Nelson BR. Finasteride—an update and review. Cutis. 1999;64:167–72. https://pubmed.ncbi.nlm.nih.gov/10500917/.
3. Taylor BC, Wilt TJ, Fink HA, Lambert LC, Marshall LM, Hoffman AR. et al. Prevalence, severity, and health correlates of lower urinary tract symptoms among older men: the MrOS study. Urology. 2006;68:804–9. https://pubmed.ncbi.nlm.nih.gov/17070357/.
4. Severi G, Sinclair R, Hopper JL, English DR, McCredie MRE, Boyle P. et al. Androgenetic alopecia in men aged 40–69 years: prevalence and risk factors. Br J Dermatol. 2003;149:1207–13. https://pubmed.ncbi.nlm.nih.gov/14674898/.
5. Rittmaster RS, Norman RW, Thomas LN, Rowden G. Evidence for atrophy and apoptosis in the prostates of men given finasteride. J Clin Endocrinol Metab. 1996;81:814–9. https://pubmed.ncbi.nlm.nih.gov/8636309/.
6. Naslund MJ, Miner M. A review of the clinical efficacy and safety of 5α-reductase inhibitors for the enlarged prostate. Clin Ther. 2007;29:17–25. https://pubmed.ncbi.nlm.nih.gov/17379044/.
7. McConnell JD, Bruskewitz R, Walsh P, Andriole G, Lieber M, Logan Holtgrewe H. et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. N Engl J Med. 1998;338:557–63. https://pubmed.ncbi.nlm.nih.gov/9475762/.
8. Roehrborn CG, Boyle P, Nickel JC, Hoefner K, Andriole G. Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. Urology. 2002;60:434–41. https://pubmed.ncbi.nlm.nih.gov/12350480/.
9. Nickel JC, Fradet Y, Boake RC, Pommerville PJ, Perreault J-P, Afridi SK, et al. Efficacy and safety of finasteride therapy for benign prostatic hyperplasia: results of a 2-year randomized controlled trial (the PROSPECT study). PROscar Safety Plus Efficacy Canadian Two year Study. Can Med Assoc J. 1996;155:1251–9.
10. Roehrborn CG, Siami P, Barkin J, Damião R, Major-Walker K, Nandy I, et al. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. Eur Urol. 2010;57:123–31.
11. McClellan KJ, Markham A. Finasteride: a review of its use in male pattern hair loss. Drugs. 1999;57:111–26. https://pubmed.ncbi.nlm.nih.gov/9951956/.
12. Cornu JN, Gacci M, Hashim H, Herrmann TRW, Malde S, Netsch C, et al. Non-neurogenic male lower urinary tract symptoms (LUTS), including benign prostatic obstruction (BPO). EAU guidelines. Presented at the EAU Annual Congress Milan. The Netherlands; 2023.
13. Mysore V, Shashikumar BM. Guidelines on the use of finasteride in androgenetic alopecia. Indian J Dermatol Venereol Leprol. 2016;82:128–34. http://www.ncbi.nlm.nih.gov/pubmed/26924401.
14. Irwig MS, Kolukula S. Persistent sexual side effects of finasteride for male pattern hair loss. J Sex Med. 2011;8:1747–53. https://pubmed.ncbi.nlm.nih.gov/21418145/.
15. Kiguradze T, Temps WH, Yarnold PR, Cashy J, Brannigan RE, Nardone B, et al. Persistent erectile dysfunction in men exposed to the 5α-reductase inhibitors, finasteride, or dutasteride. PeerJ. 2017;5:e3020 https://doi.org/10.7717/peerj.3020.
16. Corona G, Tirabassi G, Santi D, Maseroli E, Gacci M, Dicuio M, et al. Sexual dysfunction in subjects treated with inhibitors of 5α-reductase for benign prostatic hyperplasia: a comprehensive review and meta-analysis. Andrology. 2017;5:671–8. https://pubmed.ncbi.nlm.nih.gov/28453908/.
17. Traish AM. Health risks associated with long-term finasteride and dutasteride use: it's time to sound the alarm. World J Mens Health. 2020;38:323. https://pubmed.ncbi.nlm.nih.gov/32202088/.
18. Diviccaro S, Melcangi RC, Giatti S. Post-finasteride syndrome: an emerging clinical problem. Neurobiol Stress. 2019;12:100209. https://pubmed.ncbi.nlm.nih.gov/32435662/.
19. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, et al. The influence of finasteride on the development of prostate cancer. N Engl J Med. 2003;349:215–24.
20. Andriole GL, Bostwick DG, Brawley OW, Gomella LG, Marberger M, Montorsi F. et al. Effect of dutasteride on the risk of prostate cancer. N Engl J Med. 2010;362:1192–202. https://pubmed.ncbi.nlm.nih.gov/20357281/.
21. Sarkar RR, Parsons JK, Bryant AK, Ryan ST, Kader AK, McKay RR, et al. Association of treatment with 5α-reductase inhibitors with time to diagnosis and mortality in prostate cancer. JAMA Intern Med. 2019;179:812–9.
22. Yamana K, Fernand L, Luu-The V, Luu-The V. Human type 3 5α-reductase is expressed in peripheral tissues at higher levels than types 1 and 2 and its activity is potently inhibited by finasteride and dutasteride. Horm Mol Biol Clin Investig. 2010;2:293–9. https://pubmed.ncbi.nlm.nih.gov/25961201/.
23. Wilson EM, French FS. Binding properties of androgen receptors. Evidence for identical receptors in rat testis, epididymis, and prostate. J Biol Chem. 1976;251:5620–9.
24. Siiteri PK, Wilson JD. Testosterone formation and metabolism during male sexual diflferentiation in the human embryo. J Clin Endocrinol Metab. 1974;38:113–25. https://pubmed.ncbi.nlm.nih.gov/4809636/.
25. Baldinotti F, Majore S, Fogli A, Marrocco G, Ghirri P, Vuerich M, et al. Molecular characterization of 6 unrelated Italian patients with 5α-reductase type 2 deficiency. J Androl. 2008;29:20–8.
26. MacLaughlin DT, Donahoe PK. Sex determination and differentiation. N Engl J Med. 2004;350:367–78. https://www.nejm.org/doi/10.1056/NEJMra022784.
27. Andriole G, Bruchovsky N, Chung LWK, Matsumoto AM, Rittmaster R, Roehrborn C. et al. Dihydrotestosterone and the prostate: the scientific rationale for 5α-reductase inhibitors in the treatment of benign prostatic hyperplasia. J Urol. 2004;172:1399–403. https://pubmed.ncbi.nlm.nih.gov/15371854/.
28. Walsh PC, Madden JD, Harrod MJ, Goldstein JL, Macdonald PC, Wilson JD. Familial incomplete male pseudohermaphroditism, type 2: decreased dihydrotestosterone formation in pseudovaginal perineoscrotal hypospadias. N Engl J Med. 1974;291:944–9. https://pubmed.ncbi.nlm.nih.gov/4413434/.

29. Imperato-McGinley J, Guerrero L, Gautier T, Peterson RE. Steroid 5α-reductase deficiency in man: an inherited form of male pseudohermaphroditism. Science. 1974;186:1213–5. https://pubmed.ncbi.nlm.nih.gov/4432067/.
30. Melcangi RC, Santi D, Spezzano R, Grimoldi M, Tabacchi T, Fusco ML, et al. Neuroactive steroid levels and psychiatric and andrological features in post-finasteride patients. J Steroid Biochem Mol Biol. 2017;171:229–35.
31. Godoy A, Kawinski E, Li Y, Oka D, Alexiev B, Azzouni F. et al. 5α-reductase type 3 expression in human benign and malignant tissues: a comparative analysis during prostate cancer progression. Prostate. 2011;71:1033–46. https://onlinelibrary.wiley.com/doi/full/10.1002/pros.21318.
32. Finn DA, Beadles-Bohling AS, Beckley EH, Ford MM, Gililland KR, Gorin-Meyer RE, et al. A new look at the 5α-reductase inhibitor finasteride. CNS Drug Rev. 2006;12:53–76. https://pubmed.ncbi.nlm.nih.gov/16834758/.
33. Traish AM, Melcangi RC, Bortolato M, Garcia-Segura LM, Zitzmann M. Adverse effects of 5α-reductase inhibitors: what do we know, don't know, and need to know? Rev Endocr Metab Disord. 2015;16:177–98. https://pubmed.ncbi.nlm.nih.gov/26296373/.
34. Frye SV, Bramson HN, Hermann DJ, Lee FW, Sinhababu AK, Tian G. Discovery and development of GG745, a potent inhibitor of both isozymes of 5 alpha-reductase. Pharm Biotechnol Pharm Biotechnol. 1998;11:393–422. https://pubmed.ncbi.nlm.nih.gov/9760689/.
35. Roberts JL, Fiedler V, Imperato-McGinley J, Whiting D, Olsen E, Shupack J, et al. Clinical dose ranging studies with finasteride, a type 2 5α-reductase inhibitor, in men with male pattern hair loss. J Am Acad Dermatol. 1999;41:555–63.
36. Rittmaster R, Hahn RG, Ray P, Shannon JB, Wurzel R. Effect of dutasteride on intraprostatic androgen levels in men with benign prostatic hyperplasia or prostate cancer. Urology. 2008;72:808–12. https://pubmed.ncbi.nlm.nih.gov/18718641/.
37. Kligman AM. The comparative histopathology of male pattern baldness and senescent baldness. In: Clinics in Dermatology. Philadelphia: Lippincot. p. 2008;108–13.
38. Hoffmann R van. Recent findings with computerized methods for scalp hair growth measurements. J Investig Dermatol Symp Proc. 2005;10;285–8.
39. Kaufman KD, Olsen EA, Whiting D, Savin R, DeVillez R, Bergfeld W. et al. Finasteride in the treatment of men with androgenetic alopecia. J Am Acad Dermatol. 1998;39:578–89. https://pubmed.ncbi.nlm.nih.gov/9777765/.
40. Brenner S, Matz H. Improvement in androgenetic alopecia in 53-76-year-old men using oral finasteride. Int J Dermatol. 1999;38:928–30. https://pubmed.ncbi.nlm.nih.gov/10632776/.
41. Stoffel-Wagner B. Neurosteroid metabolism in the human brain. Eur J Endocrinol. 2001;145:669–79. https://pubmed.ncbi.nlm.nih.gov/11720889/.
42. Duskova M, Hill M, Hanuš M, Matoušková M, Stárka L. et al. Finasteride treatment and neuroactive steroid formation. Prague Med Rep. 2009;110:222–30. https://pubmed.ncbi.nlm.nih.gov/19655698/.
43. Melcangi RC, Caruso D, Abbiati F, Giatti S, Calabrese D, Piazza F, et al. Neuroactive steroid levels are modified in cerebrospinal fluid and plasma of post-finasteride patients showing persistent sexual side effects and anxious/depressive symptomatology. J Sex Med. 2013;10:2598–603.
44. Caruso D, Abbiati F, Giatti S, Romano S, Fusco L, Cavaletti G, et al. Patients treated for male pattern hair with finasteride show, after discontinuation of the drug, altered levels of neuroactive steroids in cerebrospinal fluid and plasma. J Steroid Biochem Mol Biol. 2015;146:74–9. https://pubmed.ncbi.nlm.nih.gov/24717976/.
45. Li L, Kang YX, Ji XM, Li YK, Li SC, Zhang XJ. et al. Finasteride inhibited brain dopaminergic system and open-field behaviors in adolescent male rats. CNS Neurosci Ther. 2018;24:115–25. https://pubmed.ncbi.nlm.nih.gov/29214729/.
46. Roberto Frau R, Mosher LJ, Bini V, Pillolla G, Pes R, Saba P, et al. The neurosteroidogenic enzyme 5α-reductase modulates the role of D1 dopamine receptors in rat sensorimotor gating. Psychoneuroendocrinology. 2016;63:59–67. https://pubmed.ncbi.nlm.nih.gov/26415119/.
47. Bradshaw WG, Baum MJ, Awh CC. Attenuation by a 5α-reductase inhibitor of the activational effect of testosterone propionate on penile erections in castrated male rats. Endocrinology. 1981;109:1047–51. https://pubmed.ncbi.nlm.nih.gov/7285860/.
48. Traish AM, Hassani J, Guay AT, Zitzmann M, Hansen ML. Adverse side effects of 5α-reductase inhibitors therapy: persistent diminished libido and erectile dysfunction and depression in a subset of patients. J Sex Med. 2011;8:872–84. http://www.ncbi.nlm.nih.gov/pubmed/21176115.
49. Moinpour CM, Darke AK, Donaldson GW, Thompson IM, Langley C, Ankerst DP. et al. Longitudinal analysis of sexual function reported by men in the Prostate Cancer Prevention Trial. J Natl Cancer Inst. 2007;99:1025–35. https://pubmed.ncbi.nlm.nih.gov/17596576/.
50. Irwig MS. Depressive symptoms and suicidal thoughts among former users of finasteride with persistent sexual side effects. J Clin Psychiatry. 2012;73:1220–3. https://pubmed.ncbi.nlm.nih.gov/22939118/.
51. Jim Thornton. The Truth about Propecia. https://www.menshealth.com/health/a19531052/hair-raising-effect/ 18, 2011.
52. Post-Finasteride Syndrome Foundation. https://www.pfsfoundation.org/about-post-finasteride-syndrome-foundation/. Accessed 16 Jan 2023.
53. Healy D, Bahrick A, Bak M, Barbato A, Calabrò RS, Chubak BM, et al. Diagnostic criteria for enduring sexual dysfunction after treatment with antidepressants, finasteride and isotretinoin the Creative Commons Attribution-NonCommercial License (CC BY-NC 4.0). 66 D. Healy et al. / Diagnostic criteria for enduring sexual dysfunction after treatment. Int J Risk Saf Med. 2022;33:65–76.
54. Pereira AFJR, Coelho TODA. Post-finasteride syndrome. Bras Dermatol. 2020;95:271–7.
55. Belknap SM, Aslam I, Kiguradze T, Temps WH, Yarnold PR, Cashy J. et al. Adverse event reporting in clinical trials of finasteride for androgenic alopecia meta-analysis. JAMA Dermatol. 2015;151:600–6. https://pubmed.ncbi.nlm.nih.gov/25830296/.
56. Favilla V, Russo GI, Privitera S, Castelli T, Giardina R, Calogero AE, et al. Impact of combination therapy 5-alpha reductase inhibitors (5-ARI) plus alpha-blockers (AB) on erectile dysfunction and decrease of libido in patients with LUTS/BPH: a systematic review with meta-analysis. Aging Male. 2016;19:175–81. https://pubmed.ncbi.nlm.nih.gov/27310433/.
57. Hagberg KW, Divan HA, Persson R, Nickel JC, Jick SS. Risk of erectile dysfunction associated with use of 5-α reductase inhibitors for benign prostatic hyperplasia or alopecia: population based studies using the Clinical Practice Research Datalink. BMJ. 2016;354:i4823. https://pubmed.ncbi.nlm.nih.gov/27659058/.
58. Shin YS, Karna KK, Choi BR, Park JK. Finasteride and erectile dysfunction in patients with benign prostatic hyperplasia or male androgenic alopecia. World J Mens Health. 2019;37:157–65.
59. Nguyen DD, Herzog P, Cone EB, Labban M, Zorn KC, Chughtai B, et al. Disproportional signal of sexual dysfunction reports associated with finasteride use in young men with androgenetic alopecia: a pharmacovigilance analysis of VigiBase. J Am Acad Dermatol. 2023;88:179–81. https://pubmed.ncbi.nlm.nih.gov/35351540/.
60. Nguyen DD, Marchese M, Cone EB, Paciotti M, Basaria S, Bhojani N. et al. Investigation of suicidality and psychological adverse events in patients treated with finasteride. JAMA Dermatol. 2021;157:35–42. https://jamanetwork.com/journals/jamadermatology/fullarticle/2772818.
61. Surendran P, Stewart ID, Yeung VPWA, Pietzner M, Raffler J, Wörheide MA, et al. Rare and common genetic determinants of metabolic individuality and their effects on human health. Nat Med. 2022;28:2321–32. https://doi.org/10.1038/s41591-022-02046-0.
62. Baas WR, Butcher MJ, Lwin A, Holland B, Herberts M, Clemons J. et al. A review of the FAERS data on 5-alpha reductase inhibitors: implications for postfinasteride syndrome. Urology. 2018;120:143–9. https://pubmed.ncbi.nlm.nih.gov/29960004/.
63. Dowman JK, Hopkins LJ, Reynolds GM, Armstrong MJ, Nasiri M, Nikolaou N. et al. Loss of 5α-Reductase Type 1 accelerates the development of hepatic steatosis but protects against hepatocellular carcinoma in male mice. Endocrinology. 2013;154:4536–47. https://pubmed.ncbi.nlm.nih.gov/24080367/.
64. Livingstone DEW, Barat P, Di Rollo EM, Rees GA, Weldin BA, Rog-Zielinska EA. et al. 5α-Reductase type 1 deficiency or inhibition predisposes to insulin resistance, hepatic steatosis, and liver fibrosis in rodents. Diabetes. 2015;64:447–58. https://pubmed.ncbi.nlm.nih.gov/25239636/.
65. Hazlehurst JM, Oprescu AI, Nikolaou N, Di Guida R, Grinbergs AEK, Davies NP. et al. Dual-5α-reductase inhibition promotes hepatic lipid accumulation in man. J Clin Endocrinol Metab. 2016;101:103–13. https://pubmed.ncbi.nlm.nih.gov/26574953/.
66. Upreti R, Hughes KA, Livingstone DEW, Gray CD, Minns FC, Macfarlane DP, et al. 5α-reductase type 1 modulates insulin sensitivity in men. J Clin Endocrinol Metab. 2014;99. https://pubmed.ncbi.nlm.nih.gov/24823464/.
67. Li K, Zhang C, Yang Z, Wang Y, Si H. Evaluation of a novel dry eye model induced by oral administration of finasteride. Mol Med Rep. 2017;16:8763–70. https://pubmed.ncbi.nlm.nih.gov/29039509/.
68. Zhang C, Li K, Yang Z, Wang Y, Si H. The effect of the aqueous extract of Bidens pilosa L. on androgen deficiency dry eye in rats. Cell Physiol Biochem. 2016;39:266–77. https://pubmed.ncbi.nlm.nih.gov/27337217/.
69. Baig MS, Kolasa-Wołosiuk A, Pilutin A, Safranow K, Baranowska-Bosiacka I, Kabat-Koperska J, et al. Finasteride-induced inhibition of 5α-reductase type 2 could lead to kidney damage—animal, experimental study. Int J Environ Res Public Health. 2019;16. https://pubmed.ncbi.nlm.nih.gov/31100850/.
70. Mahony MC, Swanlund DJ, Billeter M, Roberts KP, Pryor JL. Regional distribution of 5α-reductase type 1 and type 2 mRNA along the human epididymis. Fertil Steril. 1998;69:1116–21.
71. Amory JK, Wang C, Swerdloff RS, Anawalt BD, Matsumoto AM, Bremner WJ. et al. The effect of 5alpha-reductase inhibition with dutasteride and finasteride on semen parameters and serum hormones in healthy men. J Clin Endocrinol Metab. 2007;92:1659–65. https://pubmed.ncbi.nlm.nih.gov/17299062/.
72. Chiba K, Yamaguchi K, Li F, Ando M, Fujisawa M. Finasteride-associated male infertility. Fertil Steril. 2011;95:1786.e9–1786.e11. http://www.fertstert.org/article/S0015028210029250/fulltext.

73. Irwig MS. Androgen levels and semen parameters among former users of finasteride with persistent sexual adverse effects. JAMA Dermatol Am Med Assoc. 2014;150:1361–3. https://pubmed.ncbi.nlm.nih.gov/25229565/.
74. Samplaski MK, Lo K, Grober E, Jarvi K. Finasteride use in the male infertility population: effects on semen and hormone parameters. Fertil Steril. 2013;100:1542–6.
75. Traish AM. 5α-reductases in human physiology: an unfolding story. Endocr Pract Am Assoc Clin Endocrinol. 2012;18:965–75. https://pubmed.ncbi.nlm.nih.gov/23246684/.
76. Bull HG. Mechanism-based inhibition of human steroid 5 alfa-reductase by finasteride: enzyme-catalyzed formation of NADP-dihydrofinasteride, a potent bisubstrate analog inhibitor. J Am Chem Soc. 1996;118:2359–65.
77. Giatti S, Foglio B, Romano S, Pesaresi M, Panzica G, Garcia-Segura LM. et al. Effects of subchronic finasteride treatment and withdrawal on neuroactive steroid levels and their receptors in the male rat brain. Neuroendocrinology. 2016;103:746–57. https://pubmed.ncbi.nlm.nih.gov/26646518/.
78. Römer B, Pfeiffer N, Lewicka S, Ben-Abdallah N, Vogt MA, Deuschle M. et al. Finasteride treatment inhibits adult hippocampal neurogenesis in male mice. Pharmacopsychiatry. 2010;43:174–8. https://pubmed.ncbi.nlm.nih.gov/20486040/.
79. Hercher C, Turecki G, Mechawar N. Through the looking glass: examining neuroanatomical evidence for cellular alterations in major depression. J Psychiatr Res. 2009;43:947–61. https://pubmed.ncbi.nlm.nih.gov/19233384/.
80. Diviccaro S, Giatti S, Borgo F, Barcella M, Borghi E, Trejo JL, et al. Treatment of male rats with finasteride, an inhibitor of 5alpha-reductase enzyme, induces long-lasting effects on depressive-like behavior, hippocampal neurogenesis, neuroinflammation and gut microbiota composition. Psychoneuroendocrinology. 2019;99:206–15. https://pubmed.ncbi.nlm.nih.gov/30265917/.
81. Azzouni F, Godoy A, Li Y, Mohler J. The 5 alpha-reductase isozyme family: a review of basic biology and their role in human diseases. Adv Urol. 2012;2012. http://blast.ncbi.nlm.nih.gov/Blast.cgi.
82. Da Silva MHA, Costa WS, Sampaio FJB, De Souza DB. The corpus cavernosum after treatment with dutasteride or finasteride: a histomorphometric study in a benign prostatic hyperplasia rodent model. Asian J Androl. 2018;20:505–10. https://pubmed.ncbi.nlm.nih.gov/29893293/.
83. Lugg JA, Rajfer J, González-Cadavid NF. Dihydrotestosterone is the active androgen in the maintenance of nitric oxide-mediated penile erection in the rat. Endocrinology. 1995;136:1495–501. https://pubmed.ncbi.nlm.nih.gov/7534702/.
84. Zhang MG, Wang XJ, Shen ZJ, Gao PJ. Long-term oral administration of 5α-reductase inhibitor attenuates erectile function by inhibiting autophagy and promoting apoptosis of smooth muscle cells in corpus cavernosum of aged rats. Urology. 2013;82:743.e9–.e15. https://pubmed.ncbi.nlm.nih.gov/23876578/.
85. Kang HJ, Imperato-Mcginley J, Zhu YS, Rosenwaks Z. The effect of 5α-reductase-2 deficiency on human fertility. Fertil Steril. 2014;101:310–6. https://pubmed.ncbi.nlm.nih.gov/24412121/.
86. Mondaini N, Gontero P, Giubilei G, Lombardi G, Cai T, Gavazzi A, et al. Finasteride 5 mg and sexual side effects: How many of these are related to a Nocebo phenomenon? J Sex Med. 2007;4:1708–12.
87. Hoffman KB, Dimbil M, Erdman CB, Tatonetti NP, Overstreet BM. The Weber effect and the United States Food and Drug Administration's Adverse Event Reporting System (FAERS): analysis of sixty-two drugs. Drug Saf. 2014;37:283–94.
88. Irwig MS. Safety concerns regarding 5α reductase inhibitors for the treatment of androgenetic alopecia. Curr Opin Endocrinol Diabetes Obes. 2015;22:248–53. https://pubmed.ncbi.nlm.nih.gov/25871957/.
89. Maksym RB, Kajdy A, Rabijewski M. Post-finasteride syndrome–does it really exist?. Aging Male. 2019;22:250–9. https://pubmed.ncbi.nlm.nih.gov/30651009/.
90. Healy D, Le Noury J, Mangin D. Enduring sexual dysfunction after treatment with antidepressants, 5α-reductase inhibitors and isotretinoin: 300 cases. Int J Risk Saf Med. 2018;29:125–34.
91. Kastenmüller G, Raffler J, Gieger C, Suhre K. Genetics of human metabolism: an update. Hum Mol Genet. 2015. https://academic.oup.com/hmg/article/24/R1/R93/671706.
92. Howard DM, Adams MJ, Clarke T-K, Hafferty JD, Gibson J, Shirali M, et al. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. http://www.nature.com/authors/editorial_policies/license.html#terms.
93. Ganzer CA, Jacobs AR. Emotional consequences of Finasteride: fool's gold. Am J Mens Health. 2018;12:90–5. https://pubmed.ncbi.nlm.nih.gov/26868914/.
94. Irwig MS. Finasteride and suicide: a postmarketing case series. Dermatology. 2020;236:540–5. https://pubmed.ncbi.nlm.nih.gov/31935720/.
95. Fwu CW, Eggers PW, Kirkali Z, McVary KT, Burrows PK, Kusek JW. Change in sexual function in men with lower urinary tract symptoms/benign prostatic hyperplasia associated with long-term treatment with doxazosin, finasteride and combined therapy. J Urol. 2014;191:1828–34. https://pubmed.ncbi.nlm.nih.gov/24342143/.
96. Traish AM, Haider KS, Doros G, Haider A. Finasteride, not tamsulosin, increases severity of erectile dysfunction and decreases testosterone levels in men with benign prostatic hyperplasia. Horm Mol Biol Clin Investig. 2015;23:85–96. https://pubmed.ncbi.nlm.nih.gov/26053014/.
97. Liu L, Zhao S, Li F, Li E, Kang R, Luo L, et al. Effect of 5α-reductase inhibitors on sexual function: a meta-analysis and systematic review of randomized controlled trials. J Sex Med. 2016;13:1297–310. https://pubmed.ncbi.nlm.nih.gov/27475241/.
98. Roehrborn CG, Manyak MJ, Palacios-Moreno JM, Wilson TH, Roos EPM, Santos JC. et al. A prospective randomised placebo-controlled study of the impact of dutasteride/tamsulosin combination therapy on sexual function domains in sexually active men with lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH). BJU Int. 2018;121:647–58. https://pubmed.ncbi.nlm.nih.gov/29044968/.
99. Kosilov K, Kuzina I, Kuznetsov V, Gainullina Y, Kosilova L, Karashchuk E, et al. The risk of sexual dysfunction and effectiveness of treatment of benign prostatic hyperplasia with severe lower urinary tract dysfunction with combination of dutasteride and solifenacin. J Sex Med. https://doi.org/10.1016/j.jsxm.2018.09.011.

AUTHOR CONTRIBUTIONS

HL corresponding author, confirms that the two other contributing authors (2 and 3) played an important role in the final result of the manuscript, with revisions and approval of the final version. They agreed to be accountable for all aspects of the work.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Herman H. J. Leliefeld.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.