ORIGINAL RESEARCH—ENDOCRINOLOGY

Adverse Side Effects of 5α-Reductase Inhibitors Therapy: Persistent Diminished Libido and Erectile Dysfunction and Depression in a Subset of Patients

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ABSTRACT

Introduction. 5α-reductase inhibitors (5α-RIs), finasteride and dutasteride, have been approved for treatment of lower urinary tract symptoms, due to benign prostatic hyperplasia, with marked clinical efficacy. Finasteride is also approved for treatment of hair loss (androgenetic alopecia). Although the adverse side effects of these agents are thought to be minimal, the magnitude of adverse effects on sexual function, gynecomastia, depression, and quality of life remains ill-defined.
Aim. The goal of this review is to discuss 5α-RIs therapy, the potential persistent side effects, and the possible mechanisms responsible for these undesirable effects.
Methods. We examined data reported in various clinical studies from the available literature concerning the side effects of finasteride and dutasteride.
Main Outcome Measures. Data reported in the literature were reviewed and discussed.
Results. Prolonged adverse effects on sexual function such as erectile dysfunction and diminished libido are reported by a subset of men, raising the possibility of a causal relationship.
Conclusions. We suggest discussion with patients on the potential sexual side effects of 5α-RIs before commencing therapy. Alternative therapies may be considered in the discussion, especially when treating androgenetic alopecia.
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Key Words. Finasteride; Dutasteride; Alopecia; Benign Prostatic Hyperplasia; Sexual Dysfunction Depression; Gynecomastia

Case Study

In 1999, a 24-year-old male was diagnosed with androgenetic alopecia (AGA). He had normal stature (height, 182 cm; weight, 80 kg), had no history of any medical illness, and was not taking any medications. He reported having a normal sex drive and normal erectile capacity. He started treatment with finasteride (Propecia™), 1 mg daily, and within 2–5 days experienced soreness of the testicles, total lack of sex drive, and complete inability to achieve an erection. He had difficulty concentrating and felt depressed. Expecting these initial side effects to be temporary, he continued treatment. Except for some improvement of the soreness in the testicles, he felt numbness and there was no improvement in his sex drive or erectile function. After a little more than 1 month, he discontinued treatment and the side effects diminished to some degree, but sexual function never returned to normal. In the following months and years, the symptoms persisted with loss of libido and erectile dysfunction (ED). In 2003, the patient consulted a specialty clinic for sexual medicine in Boston, MA, USA, and went through extensive examinations. At this point, treatment with Viagra had been tried with only marginal success. Because of hopelessness and depression, two types of antidepressants (citalopram and bupropion) had been prescribed, which helped by "taking away the deepest lows," but with no improvement in either libido or erectile capacity. In addition, there were undesirable side effects to these drugs and treatment was discontinued after several months. In Boston, the patient had a psychological evaluation and underwent duplex Doppler ultrasonography.

Suffering from persistent symptoms of ED, loss of libido, and depression, the patient consulted a clinic in Copenhagen, Denmark, which specializes in testosterone treatment. The total testosterone (T) varied between 22.6 and 14.2 nmol/L (651 and 409 ng/dL) in the baseline state. The fluctuations were felt to be quite wide. No 5 α-dihydrotestosterone (5 α-DHT) measurements were available. The following baseline tests were all found to be normal: sex hormone binding globulin, luteinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone, T3, T4, prolactin, estradiol, dehydroepiandrosterone sulfate (DHEA-S), and androstenedione. He is currently under no treatment, but 11 years later, he still suffers from ED and loss of libido.

Introduction

5α-reductase inhibitors (5α-RIs), finasteride and dutasteride (Figure 1), were developed to treat patients with symptoms of benign prostatic hyperplasia (BPH) and decrease the frequency and risk of BPH-related surgeries [1,2]. Finasteride was also approved for treatment of AGA, a male pattern hair loss which affects approximately 50% of the male population [3]. Long-term studies showed that finasteride and dutasteride reduced prostate size within 3 months to 2 years [1,2,4,5]. Recent studies suggested that 5α-RIs reduce the incidence of prostate cancer (PCa) [6], but this conclusion remains to be substantiated [7]. In this clinical trial [6], it was stated that "there was an unexpected imbalance in a composite event termed 'cardiac failure', which included conditions such as congestive heart failure, cardiac failure, acute cardiac failure, ventricular failure, cardiopulmonary failure, and congestive cardiomyopathy. Although there was no significant difference between the two groups in the overall incidence of cardiovascular events or deaths from cardiovascular events, there was a higher incidence of the composite event of cardiac failure in the dutasteride group than in the placebo group." Moreover, physiological levels of 5 α-DHT attenuated development of atherosclerosis in the animal model through the suppression of intimal foam cell formation of macrophage partly via the suppression of lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) expression, suggesting the role of 5 α-DHT in atheroprotection of vascular health [8].

The potential widespread use of 5α-RIs for treatment of BPH, PCa and AGA may produce undesirable adverse side effects on overall health and in particular, vascular health [6] and sexual function in a subgroup of susceptible patients. Furthermore, treatment of AGA, a benign condition with 5α-RIs may produce persistent side effects in a number of young patients. To date, the adverse side effects of 5α-RIs on sexual function, gynecomastia, and the impact on the overall health have received minimal attention. However, in some patients, these side effects are persistent with regard to sexual function and with an emotional toll including decreased quality of life. The goal of this review is to discuss 5α-RIs therapy, the potential persistent side effects, and the possible mechanisms responsible for these undesirable effects.

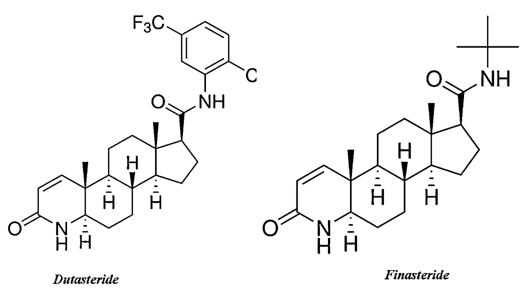

Figure 1 5α-reductase inhibitors.

Biochemistry and Pharmacology of 5α-Reductases (5α-R) and their Inhibitors

Two isozymes, namely, 5α-R type 1 (5α-R1) and 5α-R type 2 (5α-R2) have been well characterized [9]. They are potential targets for drug therapy. 5α-R enzymes reduce the double bond at the 4,5 position in C19 and C21 steroids. 5α-R enzymes

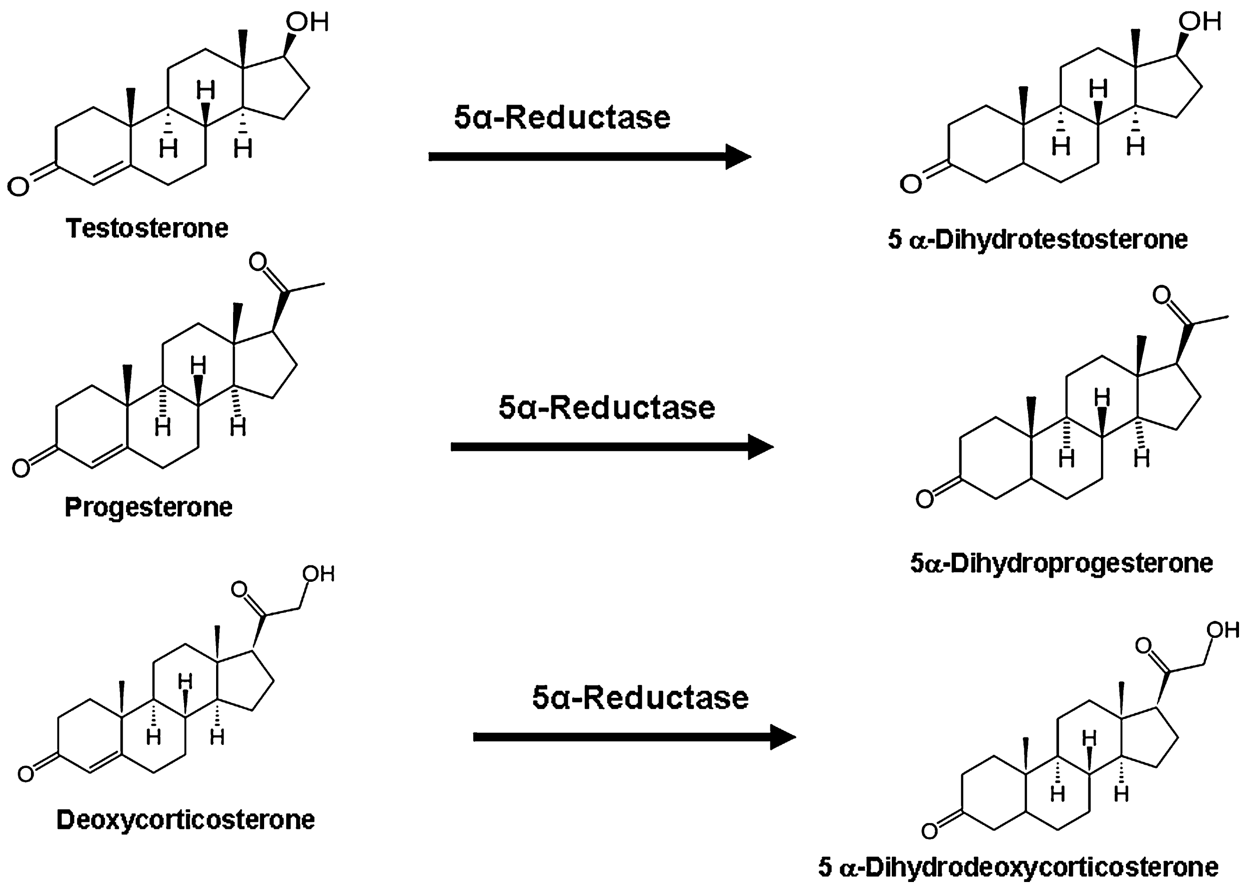

Figure 2 Substrates and products of 5α-reductase reactions.

transfer a hydride from nicotinamide adenine dinucleotide phosphate (NADPH) to the 5α position of a steroid precursor to create its 5α reduced product [10]. 5α-Rs metabolize T, progesterone, and deoxycorticosterone to 5α-DHT, 5α-dihydroprogesterone (5α-DHP), and 5α-dihydrodeoxycorticosterone (5α-DHDOC), respectively. These reactions are depicted in Figure 2.

In the brain, the products of 5α-Rs are transformed by another group of specific enzymes known as 3α-hydroxysteroid dehydrogenases (3α-HSD), which reduce 5α-DHT to 3α, 5α-androstane 17β-diol (3α-diol) and 5α-DHP to 3α, 5α-tetrahydroprogesterone (allopregnanolone). Similarly, 5α-DHDOC is further reduced to 3α, 5α-tetrahydrodeoxycorticosterone (THDOC). These derivatives are thought to function as neurosteroids in the central nervous system (Figure 3), with important physiological functions including modulation of gamma-aminobutyric acid type A ($GABA_A$) receptor, sigma receptor function, nicotinic acetylcholine receptor, voltage-gated calcium channels, and synaptic and brain plasticity. These physiological functions may impact mood, rhythm, stress, sleep, memory, anxiety, and sexual function [11]. 3α-HSD utilizes NADPH as a cofactor, and this reaction is reversible [10–12]. In transformation of these 3α, 5α reduced steroids; the 5α-R reaction is the rate-limiting step [12,13].

The two most investigated inhibitors of 5α-R are finasteride and dutasteride (Figure 1) [10]. Dutasteride is a selective inhibitor of 5α-R1 and 5α-R2 in most tissues examined [9]. Dutasteride approaches maximum inhibition at 1 mg/kg/day, with a peak blood concentration of 140 ng/mL [10], and it reduces serum 5α-DHT by approximately 90% [9,14]. Finasteride is maximally effective at 70 mg/kg/day, with a peak blood level of 7,840 ng/mL in humans [10], and it reduces serum 5α-DHT by approximately 70% [14,15]. Finasteride is considered mainly an inhibitor of 5α-R2 and is approximately 50 times weaker in inhibiting 5α-R1 than 5α-R2 [9]. Finasteride is thought to cross the blood–brain barrier and inhibits 5α-Rs in the central nervous system [16].

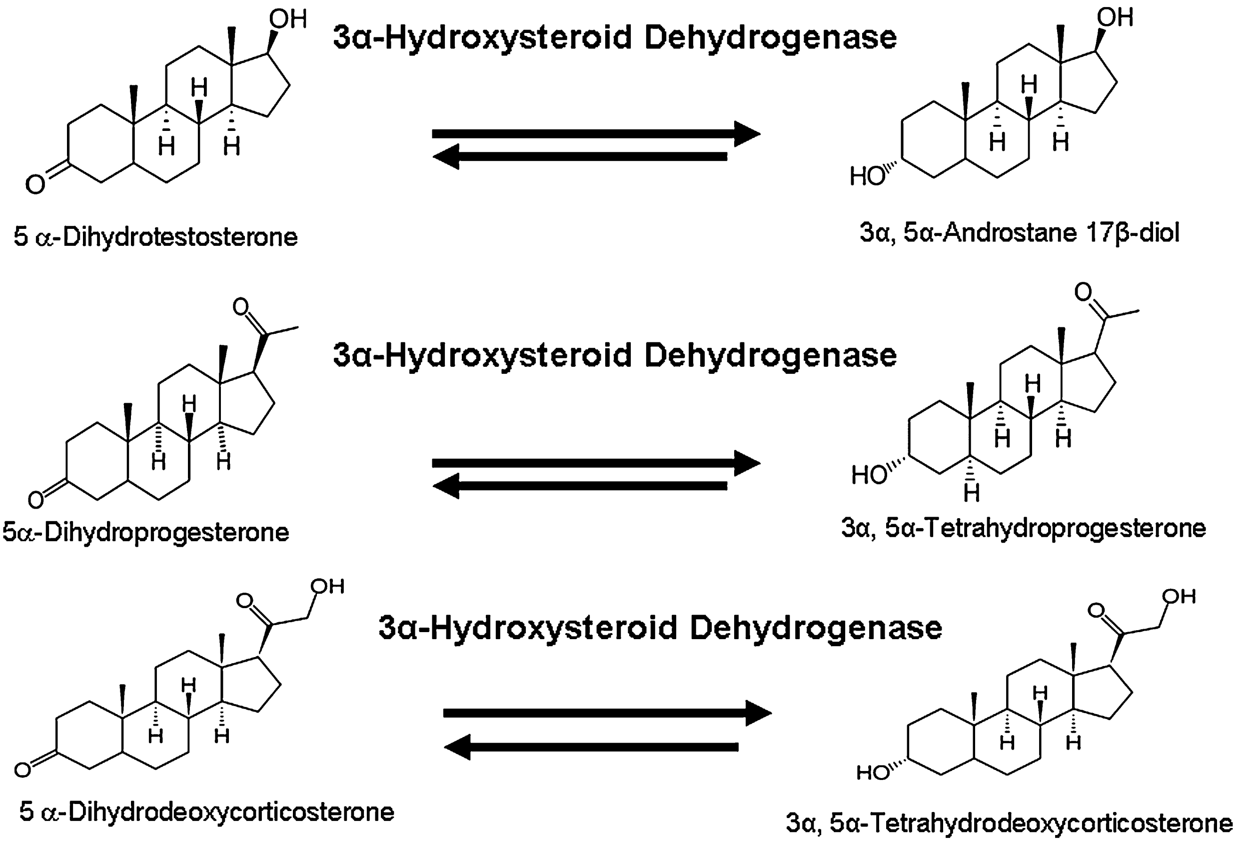

Figure 3 Substrates and products of 3α-hydroxysteroid dehydrogenase reaction.

Finasteride was thought to be a competitive inhibitor of both 5α-Rs isozymes, with an inhibitor dissociation constant (K_i) varying from 3 to 26 nM [17–19]. Recently, finasteride was shown to catalyze T to 5α-DHT via a mechanism-based inhibitor of 5α-R2, with formation of enolate intermediates. The enzyme/NADP-dihydrofinasteride complex is stable, with a half-life of approximately 1 month, and the reaction produces dihydrofinasteride [20]. Finasteride also inhibits 5β-reductase [21]. 5β and 5α-reductases are involved in hepatic steroid metabolism, and thus finasteride might affect liver function [21]. Inhibition of 5β-reductase may impair CYP3A4 activity [21], which is the enzyme responsible for finasteride metabolism [22]. Dutasteride also involves a two-step mechanism and is a time-dependent inhibitor of 5α-R2 [23,24].

Adverse Effects of 5α-R inhibitor Therapy

A host of adverse effects had been observed in the clinical settings as a result of 5α-RIs therapy; however, some of these adverse events are considered either insignificant or temporary, and may not exhibit long-term effects in patients' overall health. Other adverse events including sexual dysfunction appear to either become severe or persistent. In the study by Wessells et al. [25], only 50% of patients experienced resolution of their sexual adverse events after discontinuation. Furthermore, Erdemir et al. [26] stated that "While sexual dysfunction induced by Finasteride and dutasteride diminishes over time, resolving completely with discontinuation of therapy and discontinuation due to sexual adverse events occurs in up to 4% of patients." Additional evidence is found in clinical studies and in the Merck database, which strongly suggest that in some patients, the sexual adverse effects are persistent. In 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 that "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." In the proceeding section, we will discuss the impact of these drugs on sexual function, gynecomastia, and depression.

Effects on Libido

As shown in Tables 1 and 2, most of the studies reported that inhibition of 5α-R contributes to reduction or loss of libido. Finasteride and dutasteride produced decrease in sex drive at week 26 and 52 of drug treatment [42]. Drug-related reduction in libido occurred in 4.2% and 1.8% of patients in the dutasteride and placebo groups, respectively [43]. In a 2-year follow up of patients in the CombAT trial [41,44], approximately 2.8% of the dutasteride group had decreased libido and 1.3% of the group experienced complete loss of libido. Other studies have reported that 4% of the drug-related adverse effects was related to diminished libido [45]. The American Urological Association (AUA) clinical practice guideline [46] reported that 5% and 3% of patients on finasteride and placebo, respectively, experienced reduced libido. In addition, treatment in phase III studies (ARIA3001, ARIA3002, and ARIB3003) showed a negative effect on libido. Data from these trials reported 4–5% decreased libido in the dutasteride arm. Some patients have reported persistent loss of libido after discontinuation of the drug. Although these numbers may appear low or insignificant, their impact on the overall quality of life is not easily measured.

Effects on Erectile Function

ED is consistently observed in double-blind, randomized, placebo-controlled trials, as shown in Tables 2 and 3. Approximately 6–8% of patients reported ED in several trials [33,41,44,45,48,49]. In an observational cohort of 14,772 taking finasteride [50], ED was the most common adverse event, leading to withdrawal (143 patients). The AUA clinical practice guideline reported erectile problems in 8% and 4% of patients taking finasteride and placebo, respectively [46]. ED was the least preferred with side effect, followed by decreased libido [51]. Phase III studies in ARIA3001, ARIA3002, and ARIB3003 also showed an adverse effect of dutasteride on erectile function, reporting ED rates in the drug group to be 6% to 8%, respectively.

ED subsequent to use of 5α-RIs therapy may be explained by the role of androgens in erectile physiology. Several studies have demonstrated that androgens are integral to maintaining the structural integrity of the penile dorsal and cavernosal nerves, the smooth muscle and connective tissue of the corpus cavernosum, and the signaling pathway in the penis [52–55]. Thus, androgen deficiency induced by inhibition of 5α-R may contribute to ED [56]. Animals and human studies have suggested that 5α-DHT plays an important role in erectile physiology [57]. In castrated and adrenalectomized rats, treatment with 5α-DHT for 7 days restored erectile function to levels similar to that of control animals [58]. Other studies demonstrated that 5α-DHT treatment in castrated rats improved the erectile response to electrical field stimulation [59,60]. Castration in male rats eliminates non-contact erections and this response was restored by 5α-DHT implantation [61,62]. Non-contact erections in animals are thought to be similar to human psychogenic erections [63]. Rat studies showed a 50% reduction in erectile response was noted after castration which was reversed by T [64]. However, treatment with T and finasteride together did not restore erectile response in castrated rats. Administration of 5α-DHT, however, restored nitric oxide synthase expression, and activity and erectile response to electric field stimulation [64,65]. Treatment of castrated rats with T or 5α-DHT restored the number of erectile responses and reflex erections. However, only 5α-DHT restored erectile responses and reflex erections, when animals were treated with daily injections of the 5α-R inhibitor MK-434 (1 mg/kg), together with T or 5α-DHT [65]. These observations suggest that 5α-DHT plays a physiological role in erectile function in the animal model, and that 5α-RIs may produce adverse effect on the erectile response.

A double-blind randomized clinical trial with 120 men (aged 50–70) given 5α-DHT gel transdermally daily showed improvement in the modified International Index of Erectile Function (IIEF) questionnaire suggesting that 5α-DHT treatment maintained erection at 3 and 6 months [66]. Furthermore, nocturnal penile tumescence improved in the 5α-DHT group during the first 3 months of treatment [66].

Effects on Ejaculatory function

Table 1 shows that ejaculatory function is adversely affected in 5α-RIs trials. Finasteride and dutasteride treatment resulted in a decrease in ejaculatory function at week 26 and 52, as determined by the sexual function inventory [42]. The CombAT study [41] observed 0.6% retrograde ejaculations, 0.5% ejaculation failure, and 0.3%

Table 1 Double-blind, randomized, placebo-controlled trials demonstrating sexual dysfunction in men taking 5α-RIs (open trial data not included)

Source	Condition	N (Drug groups)	N (Placebo)	Ages	Dosage (daily)	Duration	Libido (D/P)	ED (D/P)	Ejaculatory function disorder or abnormal ejaculate volume (D/P)
Kaufman et al. [27]	Alopecia	779	774	18–41	1 mg fin	1 year + 1 year open	1.9%/1.3%	1.4%/0.9%	1%/0.4% (volume)
Leyden et al. [28]	Alopecia	133	123	18–40	1 mg fin	1 year + 1 year open	1.5%/1.6%	0.75%/0%	0/0.8%
Whiting et al. [29]	Alopecia	286	138	41–60	1 mg fin	2 years	4.9%/4.4%	3.8%/0.7%	2.8%/0.7%
Byrnes et al. [30]	BPH	1,759	583	≥45	5 mg fin	12 months	2.9%/1.0%	5.6%/2.2%	2.1%/0.5%
Clark et al. [31]	BPH	60	59	≥50	0.5 mg dut	24 weeks	4%/2%	11%/3%	N/A
Clark et al. [31]	BPH	55	59	≥50	5 mg fin	24 weeks	13%/2%	11%/3%	N/A
Debruyne et al. [5]	BPH	2,166	2,158	≥50	0.5 mg dut	2 years	0.6%/0.3%	1.7%/1.2%	0.5%/0.1%
Gormley et al. [15]	BPH	297	300	40–83	5 mg fin	12 months	4.7%/1.3%	3.4%/1.7%	4.4%/1.7%
Hudson et al. [32]	BPH	259	N/A	64 (avg)	5 mg fin	1 year + 4 years open	7.7%/3.3%	6.7%/4.0%	4.7%/1.7%
Kirby et al. [33]	BPH	264	269	50–80	5 mg fin	1 year	3.4%/1.9%	4.9%/3.3%	2.3%/1.5% (volume)
Lepor et al. [34]	BPH	310	305	45–80	5 mg fin	1 year	5%/1%	9.4%/4.6%	2%/1%
Lowe et al. [35]	BPH	547	558	64 (avg)	5 mg fin	1 year + 5 years open	3.8%/2.3%	4.8%/1.8%	3.1%/1.1%
Marberger [36]	BPH	1,577	1,591	50–75	5 mg fin	2 years	4.0%/2.8%	6.6%/4.7%	2.1%/0.6%
McConnell et al. [1]	BPH	1,523	1,516	64 (avg)	5 mg fin	4 years	2.6%/2.6%	5.1%/5.1%	0.2%/0.1%
McConnell et al. [37]	BPH	168	737	≥50	5 mg fin	4.5 years	2.4%/1.4%	4.5%/3.3%	1.8%/0.8%
Nickel et al. [120]	BPH	310	303	45–80	5 mg fin	2 years	10%/6.3%	15.8%/6.3%	7.7%/1.7%
Roehrborn et al. [121]	BPH	1,128	1,123	≥50	0.5 mg dut	2 years	0.5%/0.4%	1.3%/1.3%	0.3%/0.1%
Tenover et al. [38]	BPH	1,736	579	≥45	5 mg fin	12 months	5.4%/3.3%	8.1%/3.8%	4.0%/0.9%
Amory et al. [39]	none	34	32	18–55	5 mg fin	1 year + 6 month follow up	18%/3%	3%/6%	6%/0%
Amory et al. [42]	none	33	32	18–55	0.5 mg dut	1 year + 6-month follow up	6%/3%	6%/6%	3%/0%

ED = erectile dysfunction; fin = finasteride; dut = dutasteride; BPH = benign prostatic hyperplasia.

Table 2 Three double-blind, randomized, placebo-controlled trials demonstrating sexual dysfunction in men taking 5α-reductase inhibitors (open trial data not included)

Source	Condition	N (Drug groups)	N (Placebo)	Ages	Dosage (daily)	Duration	Libido (D/P)	ED (D/P)	Ejaculatory function disorder or abnormal ejaculate volume (D/P)	Gynecomastia (D/P)
Andriole et al. [6]	PCa	4,105	4,126	50–75	0.5 mg dut	4 years	3.3%/1.6%	9%/5.7%	1.4%/0.2% (volume)	1.9%/1.0%
Thompson et al. [40]	PCa	9,423	9,457	≥55	5 mg fin	7 years	65.4%/59.6%	67.4%/61.5%	67.4%/61.5% (volume)	4.5%/2.8%
Roehrborn et al. [41]	BPH	1,623	1,611	≥50	0.5 mg dut, 0.4 mg tamsulosin (placebo)	2 years	2.8%/1.7%	6.0%/3.8%	0.5%/0.8%	1.8%/0.8% (breast enlargement)

PCa = prostate cancer; fin = finasteride; dut = dutasteride; BPH = benign prostatic hyperplasia.

Table 3 Sexual adverse effects (SAE) of 5α-reductase inhibitors as assessed by male sexual function-4 (MSF-4) questionnaire in two groups of patients who were either not informed or informed about the drug potential sexual side effects

Study patients	(%) SAE at 6 months	(%) SAE at 1 year	(%) ED at 6 months	(%) ED at 1 year	(%) Diminished libido at 6 months	(%) Diminished libido at 1 year	(%) Ejaculation disorder at 6 months	(%) Ejaculation disorder at 1 year
All patients (N = 107)	24.3%	29.90	15.8%	20.5%	11.2%	15.8%	8.4%	11.2%
Group 1 (N = 52)	11.5%	15.3	5.7%	9.6	3.8%	7.7	5.7%	5.7
Group 2 (N = 55)	36.3%	43.6	25.4%	30.9	18.1%	23.6	10.9%	16.3

Adopted from Mondaini et al., 2007 [47].
ED = erectile dysfunction. Group 1 Blinded, Group 2 not blinded.

semen volume decrease in patients. The AUA clinical practice guideline's review of 5α-RI trials suggested that 4% and 1% of patients taking finasteride and placebo had sexual ejaculation dysfunction [46], respectively, suggesting that the results pertaining to ejaculatory function are mixed and additional data are needed to ascertain the drug impact on ejaculation.

Effects on Breast Tissue

As shown in Table 2, gynecomastia is among the adverse side effects of 5αRIs experienced by patients placed on this therapy [1,5,6,27,40,41]. Gynecomastia had been observed in 214 men receiving finasteride therapy according to reports to the U.S. Food and Drug Administration from 1992 to 1995 [67]. In the Prostate Cancer Prevention Trial (PCPT), approximately 426 of 9,423 subjects (4.5%) in the Finasteride arm had gyncomastia compared with 261 of 9,457 subjects (2.8%) in the placebo arm [40]. In men taking finasteride alone or with doxazosin, 4 out of 1,554 developed beast cancer, a rate approximately 200 times that of the general population [27]. Inhibition of 5α-DHT synthesis by 5α-RIs may shift metabolism of T toward estradiol (E_2) and alter the estrogen to androgen ratio, thus increasing the risk of gynecomastia and male breast cancer.

Serum E_2 levels in patients treated with 1 mg finasteride were significantly higher in the finasteride group compared the placebo treated group. The small rise in serum E_2 levels with finasteride use is not unexpected as finasteride produces a small increase in serum T which is the primary substrate for the production of estradiol in men (Medicines and Health care products Regulatory Agency [MHRA] [122] PUBLIC ASSESSMENT REPORT. The risk of male breast cancer with Finasteride, December 2009). Treatment with T for up to 3 years in healthy older men with low serum T levels significantly increased both total E_2 and T levels in subjects treated with T-only and T + 5 mg finasteride compared with those treated with placebo [68]. Thomas et al. [69] hypothesized that the risk of breast cancer is a function of the number of susceptible cells in breast tissue. Normally, men have low risk of breast cancer as they have little breast epithelium compared with women; however, men with increased E_2 levels or reduced T levels may be at greater risk of breast cancer, and such hormonal perturbations due to finasteride treatment would be expected to enhance growth of the mammary epithelium.

Effects on Depression

An association between androgen deficiency and depression has been proposed, however, the exact mechanisms remain to be investigated. Low androgen levels are associated with symptoms of irritability and dysphoria [70–72], increased risk of depressive symptoms and depression [73–76]. In a large study of elderly men, depressive symptoms were associated with low free T [75]. Men treated for PCa with androgen deprivation therapy suffer from mood disturbances, anxiety, fatigue, lack of drive, and listlessness [77]. Recent studies have shown that administration of T improved depressive symptoms in hypogonadal men [78].

Neurosteroids and neuroactive steroids play an important role in memory enhancement, sedative, hypnotic, anesthetic, anxiolytic, antistress, sleep modulating, anticonvulsant, and antidepressant properties [11,79–83]. Neurosteroids and neuroactive steroids are also involved in neuroprotection and neurogenesis [11,84–86]. Neuroactive steroids are produced in the central nervous system by transforming substrates from adrenal or gonadal steroids to active neurosteroids [11,12,87,88]. Biosynthesis of neurosteroids and neuroactive steroids requires 5α-R function. Indeed, it has been shown that finasteride diminishes neurosteroid biosynthesis [79,89]. $GABA_A$ receptor activity is modulated by neurosteroids produced from the activity of 5α-R and 3α-HSD enzymes. Several studies showed that allopregnanolone and THDOC modulate $GABA_A$ receptors function [11,90–94]. Allopregnenolone has been shown to have anti-anxiety effects [95,96], as well as antidepressant effects [97–100]. A role for neurosteroids in modulating factors that attenuate depression has been proposed [11,101]. Because depression can contribute to ED [87,102], a number of patients treated with 5α-RIs showed a higher incidence of depression compared with untreated patients [103,104]. Although a direct link between depression and 5α-RIs therapy has not been demonstrated, it is plausible that in some individuals, 5α-RIs therapy may reduce neurosteroid biosynthesis significantly and predispose them to onset or progression of depression.

Dopamine agonists and dopaminergic agents have been used to treat sexual dysfunction [102,105] and dopamine synthesis is modulated by neurosteroids [106–109]. 5α-RIs reduce dopamine levels by inhibiting neurosteroid biosynthesis [110,111] and this may have serious implication on several functions including depression.

Dysregulation of neurosteroid metabolism is associated with depression and imbalance in neurosteroid levels are implicated in the pathophysiology of depression [99,112]. Changes in levels of allopregnanolone are associated with depressive disorders [113] and treatment of depression improves neurosteroid concentrations [101]. In clinical studies, it was shown that finasteride induced depressive symptoms in patients, who are more susceptible to depression [103,104].

Several studies suggested a link between inhibition of 5α-R to symptoms of depression and this may be related to decreased production of reduced metabolites of progesterone and deoxycorticosterone (DOC) in the brain [99,103,104,114–116]. Studies in animal models showed that finasteride induces behavioral changes. Finasteride-induced depression has been reported in humans. In one study [104], 128 men with AGA were treated with finasteride. Finasteride treatment increased both Beck Depression Index (BDI) ($P < 0.001$) and Hospital Anxiety and Depression Scale (HADS) depression scores significantly ($P = 0.005$). These findings suggest that finasteride may induce depressive symptoms. In another study [103], 19 patients developed mood disturbance during treatment with finasteride for AGA. Depression developed after 9–19 weeks of treatment with finasteride, and was resolved after stopping use of finasteride.

In animal model studies [114], finasteride treatment led to a significant decrease in brain 5α-DHT levels and induced a reversible reduction in the number of newborn cells and young neurons in the hippocampus. When finasteride injection was stopped, neurogenesis returned to normal 35 days after the last injection. These observations suggest that inhibition of 5α-R activity by finasteride influences neuronal plasticity on a structural level. These changes may contribute to the pathophysiology of depressive episodes observed in humans taking finasteride. Finasteride administration to the amygdala attenuates anti-anxiety behavior in naturally receptive and ovariectomized hormone-primed animals and formation and subsequent actions of 3α, 5α-THP in the amygdala may be important for anti-anxiety and antidepressive effects [116].

Finasteride treatment produced significant decrease in all 5α-reduced steroid metabolites and increased 5β-reduced metabolites of T and progesterone as well as in an increase of 7α-hydoxyderivatives. These neurosteroids are known to modulate $GABA_A$ and N-methyl D-Aspartate (NMAD) receptors in the brain [115]. The authors suggested that in the course of finasteride treatment, decreased concentration of circulating neuroactive steroids with known inhibitory activity on GABA-ergic excitation in the brain is probably an important factor contributing to development of the symptoms of depression observed in some isolated cases of finasteride administration [115]. Neurosteroids modulates the action of GABA at GABA(A) receptors, and may possess anticonvulsant, antidepressant, and anxiolytic effects in addition to altering aspects of sexual- and alcohol-related behaviors. Thus, inhibition of 5α-R in the animal model suggest that endogenous neuroactive steroid levels may be inversely related to symptoms of premenstrual and postpartum dysphoric disorder, catamenial epilepsy, depression, and alcohol withdrawal [99].

One additional concern regarding use of 5α-RIs in older men is the importance of neurosteroids in recovery from brain injury due to stroke. It has been suggested that 5α-RIs therapy may influence the severity of brain injury subsequent to stroke [117]. This argument is supported by the observations that allopregnanolone reduces cortical infarct volume after transient middle cerebral artery occlusion [118], and finasteride treatment inhibits hippocampal neurogenesis in male animals [114]. These observations reinforce the fact that 5α-R activity may play an important role in neuroprotection in the brain.

Discussion

5α-RIs therapy improves urinary symptoms and reduces prostate size in older men and is therefore considered an appropriate treatment for BPH. Use of 5α-RIs therapy has recently been promoted for prevention of PCa; however, it remains controversial and is associated with serious and significant adverse effects including sexual, behavioral, and cardiovascular damage. Randomized clinical trials have demonstrated increased incidences of decreased libido, ED, ejaculatory dysfunction and gynecomastia [6,40,41,119]. ED, ejaculatory disorders, and decreased libido were more frequently observed in finasteride- than placebo-treated men (15% vs. 7%, respectively). The PREDICT trial showed that the incidence of ED and reduced libido were similar between the finasteride and doxazosin groups. In the PCPT, in which 18,882 men were enrolled for 7 years of finasteride therapy versus placebo, approximately 28.9% of men discontinued therapy in the placebo group compared with 36.8% in the finasteride group ($P < 0.001$). Reduced ejaculate volume, ED, loss of libido, and gynecomastia were more common in the finasteride group ($P < 0.001$). Physicians should inform men who are considering a 5α-RIs therapy about the incidence of sexual adverse effects. Such adverse effects as lowered libido associated with a 5α-RIs therapy have been reported consistently. These adverse effects may not be significant in the realm of the overall study, but for the individual patients, this is a serious loss of quality of life and should be given serious considerations prior to commencing therapies with these drugs. The patient has to be made aware of the pros and cons and participate actively in the decision to commence this form of therapy.

The concept that 5α-Rs not only converts T to 5α-DHT but also converts progesterone to 5α-DHP (a precursor of the neurosteroid allopregnanolone) and deoxycorticosterone to 5α-DHDOC (a precursor for neuroactive steroid THDOC) suggest that 5α-RI therapy may adversely impact brain function. This would include mood, depression, and overall well being. 5α-RIs have been shown to induce depression in susceptible patients and may impact brain recovery from injuries.

5α-RIs therapy, while improving urinary symptoms in patients with BPH and may prevent hair loss, produce significant adverse effects in some individuals including loss of libido, ED, ejaculatory dysfunction, and potential depression. They are serious enough to preclude them from pursuing such therapy. The effects of these agents on vascular health should also be noted in light of recent findings that patients treated with 5α-RIs therapy had significant adverse cardiovascular events. These observations suggest that extreme caution should be exercised prior to prescribing 5α-RIs therapy to patients for hair growth or for BPH symptoms. Honest and open discussion with patients to educate them on these serious issues must be pursued prior to commencing therapy because, in some patients, these adverse effects are persistent and may be prolonged and patients do not recover well after discontinuation from drug use. These issues must be addressed in detail with the patients. Additional clinical and preclinical studies are warranted to determine the reason for why some of these adverse effects persist in some individuals. This would be of extreme importance for determining which individuals would be at risk for taking such drugs.

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