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Sexual side effects of 5- α -reductase inhibitors finasteride and dutasteride: A comprehensive review

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Abstract

The 5- α -reductase inhibitors finasteride and dutasteride are frequently used in the treatment of androgenetic alopecia and benign prostatic hyperplasia. These drugs are effective at reducing levels of dihydrotestosterone, the primary androgen responsible for the pathogenesis of both these conditions. However, finasteride and dutasteride have also been shown to produce an increase in the incidence of sexual dysfunction, namely, impotence, decreased libido, and ejaculation disorder. The purpose of this study is to review the existing medical literature with regard to the sexual side effects of 5- α -reductase inhibitor therapy. This review is an extensive look at the sexual effects of 5- α -reductase inhibitors and compares outcomes for finasteride versus dutasteride in addition to comparing sexual side effects for each of the different dosages prescribed of finasteride and dutasteride.

Keywords: dutasteride, finasteride, sexual side effects, sexual dysfunction, depression, androgenetic alopecia, benign prostatic hyperplasia, 5- α -reductase inhibitors

Introduction

Finasteride and dutasteride are 5- α -reductase inhibitors which prevent the conversion of testosterone to dihydrotestosterone via the enzyme 5- α -reductase. Finasteride is a type I 5- α -reductase inhibitor (5 α RI) prescribed in 1 mg and 5 mg doses to treat male pattern androgenetic alopecia (AGA) and benign prostatic hyperplasia (BPH), [1-3]. Dutasteride is also a competitive inhibitor of this enzyme, targeting both type I and II 5- α -reductase and is used to treat benign prostatic hyperplasia at 0.5 mg

doses, with increasing off label use for androgenetic alopecia [4-6]. Additionally, these drugs are under study for their use in prevention of prostate cancer [7]. Dihydrotestosterone has been found to be the primary androgen involved in the pathogenesis of androgenetic alopecia by promoting follicular miniaturization [8], as well as, in the pathogenesis of BPH, by preventing the growth of epithelial cells in the prostate [9, 10]. Finasteride reduces dihydrotestosterone (DHT) levels by up to 70% in both the serum and the scalp skin at the 5 mg/d dose [11, 12], with DHT reduction being dose dependent. Dutasteride 0.5 mg/d can reduce DHT serum levels by upwards of 90%, again in a dose dependent manner [13]. Although both of these drugs have been proven effective at reducing male pattern hair loss and BPH through the reduction of DHT levels, there has been debate over the adverse sexual side effects they produce [14, 15]. These side effects include decreased ejaculate volume, reduced libido, ejaculatory dysfunction, and erectile dysfunction [16]. As these 5 α RI are taken by more than 30 million men, even the infrequent incidence of sexual adverse effects could have a profound effect on the sexual satisfaction and quality of life, of a large population [10]. This review will assess the findings regarding the sexual side effects of finasteride and dutasteride in the current literature.

Body of Article

Materials and Methods

A PubMed search (1950 to 2017) identified documented cases of finasteride and dutasteride sexual side effects in the literature. The search terms used were: "finasteride side effects," "finasteride side*," "finasteride sexual," "finasteride sexual side

effects," "finasteride sexual dysfunction," "finasteride depression," "finasteride suicidal ideation," "finasteride side effects alopecia," "finasteride syndrome," "post-finasteride syndrome," "dutasteride side effects," "dutasteride side*," "dutasteride sexual," "dutasteride sexual side effects," "dutasteride sexual dysfunction," "dutasteride depression," "dutasteride suicidal ideation," "dutasteride side effects alopecia." Clinical trials, review articles, case series, and case reports that mentioned finasteride and dutasteride sexual side effects were included. In addition to our PubMed searches, we examined the references of included sources to add any cases which may have been initially omitted.

Using the American College of Physicians outcome study grading system each studies' level of evidence was ranked from high to very low. This system rates quality of studies in accordance with the underlying methodology in four categories:

1. High, including randomized trials or double-upgraded observational studies.
2. Moderate, including downgraded randomized trials or upgraded observational studies.
3. Low, including double-downgraded randomized trials or observational studies.
4. Very low, including triple-downgraded randomized trials or downgraded observational studies or case series/case reports.

Studies can be downgraded in presence of factors that may decrease the quality level of a body of evidence. These include:

1. Limitations in the design and implementation of available studies suggesting high likelihood of bias.
2. Indirectness of evidence (indirect population, intervention, control, outcomes).
3. Unexplained heterogeneity or inconsistency of results (including problems with subgroup analysis).
4. Imprecision of results (wide confidence intervals).

6. High probability of publication bias.

Sexual Adverse Effects

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 and are summarized in Tables 1 and 2.

Finasteride 5mg

The Prostate Cancer Prevention Trial (PCPT) was a randomized, double-blind, placebo-controlled study that provided an opportunity to prospectively study the effects of finasteride (5 mg/d) and other covariates on sexual dysfunction [15]. Sexual dysfunction in 17,313 PCPT participants was assessed during a 7 year period. Questionnaires assessed sexual dysfunction using the Sexual Activity Scale score, with scores ranging from 0 to 100 (higher numbers correlate with greater sexual dysfunction). Confounding variables analyzed included age, physical function and vitality scores, body mass index, smoking status, and the presence of diabetes and hypertension. Assessments began at month 6 and continued during the 7 year trial period. Trial results concluded that finasteride increased sexual dysfunction only slightly and its impact diminished over time [17]. Finasteride users showed a statistically significant increase in the Sexual Activity Scale score relative to placebo of 3.21 points ($P < 0.001$) at the first assessment conducted at the 6 month mark. This increase in scale score persisted throughout the study but decreased to 2.11 points ($P < 0.001$) relative to placebo at study end [15]. Importantly, other covariates in this study population including diabetes, hypertension, smoking, declining physical function, and increased BMI were found to have a similar detrimental effect on sexual dysfunction, with age demonstrating a greater effect on sexual dysfunction than finasteride [18]. Persistent sexual side effects were not reported in any of the 17,313 study participants [18]. Sexual side effects were more commonly reported with finasteride at some time during the study and included decreased ejaculate volume, erectile dysfunction, and loss of libido [19]. However, based on this covariate analysis, the authors concluded finasteride has a minimal effect on sexual

function for most men that decreases with time and that this finding should not affect the decision to prescribe finasteride for patients [15].

In the PROWESS 2-year multicenter, double-blinded, placebo-controlled study, the long term effects of finasteride (5 mg/d) were examined for men aged 50 to 75 with moderate BPH. Of the 3,168 participants, any sexual adverse event, including a change in libido, ejaculation disorder, impotence, or orgasm dysfunction, was reported in 10% of the finasteride group versus 7% in the placebo group [20]. Decreased libido, ejaculation disorder, and impotence were reported in 4, 2.1, and 6.6%, respectively in the finasteride group, compared to 2.8, 0.6, and 4.7% for the control group. Only ejaculation disorder and impotence were found to be statistically significant differences between the groups ($P < 0.05$). The discontinuation rate was the same for both the finasteride and placebo groups (1%). These sexual side effects were considered to be drug related by the investigators. However, they still consider finasteride a well-tolerated and effective long term treatment for BPH [20].

Another study comparing the long-term effects of finasteride (5 mg/d) and placebo in patients with BPH was the Finasteride Long-Term Efficacy and Safety Study Group [21]. In this 4-year double-blind, randomized, placebo-controlled trial, complete data were available for 2,070 subjects. Adverse events related to sexual dysfunction were found to be significantly higher in the finasteride arm compared to the placebo arm (decreased libido 6.4% versus 3.4%; impotence 8.1% v versus 3.7%; decreased ejaculate volume 3.7% versus 0.8%; ejaculation disorder 0.8% versus 0.1%) [21]. However, the decreased libido and impotence differences existed only in year one of the study. In years 2-4 of the study, there was no difference in decreased libido and impotence in the finasteride group and the placebo group (decreased libido 2.6% both groups, impotence 5.1% both groups). In addition, in years 2-4 there was no statistical difference in ejaculation disorder between the groups. However, a small statistically significant difference of greater incidences of decreased ejaculate volume remained in the finasteride group.

In the Fwu analysis of the MTOPS (Medical Therapy of

Prostatic Symptoms) study, the long term effects of finasteride (5 mg/d) and doxazosin (an α -adrenergic receptor blocker used to treat BPH) were compared to placebo over 4 years [22]. The MTOPS study was a multicenter, randomized, double-blind, placebo-controlled clinical trial. Sexual function was assessed with the Brief Male Sexual Function Inventory, an 11 item questionnaire to determine functional aspects and satisfaction with sexuality in the last 30 days [23]. There were 695 in the finasteride group and 672 in the placebo group, both with a mean age of 62 years old. In the finasteride group compared to baseline, after 1 year 16% of men showed worse sexual function, 11% showed worse erectile function, 9% showed worse ejaculatory function, and 15% showed worse overall sexual satisfaction (placebo showed 11%, 8%, 6%, and 14%, respectively). Of these findings, only worsened sexual drive was a statistically significant difference ($P < 0.0167$). After 4 years, 22% had worse sexual drive, 18% had worse erectile function, 18% had worse ejaculatory function, and 21% had worse overall sexual satisfaction (placebo had 16%, 13%, 12%, and 17%, respectively), with both sexual drive and ejaculatory function being significant ($P < 0.0167$) [22]. Fwu et al. suggest that the impact of finasteride on sexual function is undervalued by physicians and that the potential for long term sexual side effects should be discussed with patients prior to prescribing.

In the Scandinavian BPH Study Group's 2-year, multicenter, double-blind comparison between finasteride 5 mg/d and placebo, sexual dysfunction was 19% and 10%, respectively ($P < 0.01$), [24]. The PROSPECT study compared the long-term effects of finasteride (5 mg/d) and placebo in patients with moderate BPH [25]. A total of 472 subjects were followed in this 2-year double-blind, randomized, placebo-controlled, multicenter study. The incidence of adverse events related to sexual dysfunction were found to be significantly higher in the finasteride arm compared to the placebo arm (ejaculation disorder 7.7% versus 1.7% and impotence 15.8% versus 6.3%, $P < 0.01$), [25].

In another study looking at the long term effects of finasteride (5 mg/d), 190 men were followed for a 6 month double-blind, placebo-controlled study of finasteride with an open-label extension of 7

to 8 years. The findings show that that impotence, decreased libido, and ejaculation disorder were the most common drug related adverse events. However, only 0-1.9% (0% during the double-blind phase and years 4-8, and 1.9% in year 1) of subjects discontinued the study in any given year owing to these sexual side effects [26]. During the initial 6 month study phase there were no cases of sexual adverse effects reported among the placebo group (0%) compared to 0.7% impotence and decreased libido for the finasteride group. Following this period into the open label extension, the first year had by far the most reports of side effects (10.9% decreased libido, 5.8% ejaculation disorder, 6.4% impotence), with subsequent years having fewer new incidences (year 2: 2.5% decreased libido, 0.8% ejaculation disorder, 2.5% impotence; year 3: 2% decreased libido, 1% ejaculation disorder, 1% impotence; falling to 0% in all categories by year 8), [26]. Again, the authors concluded finasteride was effective and well tolerated and recommended it for long term treatment of benign prostatic hyperplasia. In the Wilton et al. observational cohort study involving 14,772 subjects taking finasteride 5 mg/d for BPH, impotence, or ejaculatory failure was reported in 2.1% of subjects and decreased libido in 1% of subjects [27].

Finasteride 5mg versus 1mg

The Finasteride Study Group compared the effects of finasteride 5 mg/d versus finasteride 1 mg/d versus placebo in 895 men aged 40 to 83 years old who had a low urinary flow rate (less than 15 ml/sec), an enlarged prostate gland on digital rectal exam, and the diagnosis of BPH. Of the 295 men in the 5mg finasteride group 4.7% experienced decreased libido, 4.4% experienced ejaculatory disorder, 3.4% experienced impotence, and 0.7% experienced orgasm dysfunction. In the 1mg treatment group, of 298 patients, 6% had decreased libido, 4.4% had ejaculatory disorder, 5% had impotence, and 0.3% had orgasm disorder (compared to 1.3%, 1.7%, 1.7%, and 0.3% for placebo group, respectively, n=300), [28]. Decreased libido and ejaculatory volume were found to be statistically significant findings for both the 5mg and 1mg finasteride treatments groups versus the placebo ($P < 0.05$). Impotence was also found to be significantly higher for the 1 mg treatment group compared to placebo ($P < 0.05$), [28]. During the course of this 1 year, double-blind, randomized,

placebo-controlled study 4 men in the 5mg group withdrew due to sexual side effects, 3 in the 1 mg group, and 1 in the placebo group. At the study's close, Gormley et al. suggest that 5mg finasteride is the recommended dose to effectively treat BPH and that any dose of finasteride is associated with an increased likelihood of sexual dysfunction [28].

In a study by Roberts et al. regarding finasteride dosing, specifically for the treatment of androgenetic alopecia, daily doses of finasteride 5mg, 1mg, 0.2mg, and 0.01mg were compared in 18 to 36-year-olds [29]. In the multicenter, randomized, double blinded, placebo-controlled clinical study it was determined that all doses equal to or greater than 0.2mg were efficacious and that 1mg was the ideal dose to treat male pattern hair loss. At the 6 month point, after which a non-placebo controlled voluntary extension was offered, incidences of any sexual adverse effects, decreased libido, and erectile dysfunction were measured for each of the doses and placebo (5mg: 3.6%, 2.7%, 1.8%, respectively; 1mg: 4.3%, 1.7%, 2.6%, respectively; placebo: 3.4%, 3.0%, 0%, respectively), [29]. None of these differences were considered significant. Another androgenetic alopecia finasteride dosing study by Drake et al. compared daily doses of 0.01mg, 0.05mg, 0.2mg, 1mg, and 5mg to placebo [11]. Among the group of 249 men included in the double-blind, placebo-controlled study, only headache and decreased libido were reported by more than 1 patient in any group. Placebo reported 4.5% incidence of decreased libido, compared to 0% for the 1mg finasteride group, and 2.6% for the 5mg group [11].

Finasteride 1mg

The Finasteride Male Pattern Hair Loss Study conducted two replicate, 1-year, double-blind, placebo-controlled, randomized studies in 1,553 men (age 18 to 41) with male pattern hair loss who received oral finasteride 1 mg or placebo [30]. In the first year, a higher proportion of finasteride-treated patients reported adverse events related to sexual function (4.2% versus 2.2% control arm, $P < 0.05$), [30]. Only 11 men (1.4%) in the finasteride group and 8 (1.0%) in the placebo group discontinued the study because of sexual adverse events. The sexual side effects resolved after finasteride therapy was discontinued. After one year, 1,215 men continued

in blinded 1-year extension studies for a second year. In the extension studies, patients were randomly assigned treatment to either finasteride 1 mg or placebo. Finasteride resulted in slightly more sexual side effects compared to placebo, with the incidence of erectile dysfunction, decreased ejaculatory volume and decreased libido being higher in the finasteride group (1.4%, 1.0%, 1.9%, respectively) compared with the control group (0.9%, 0.4%, 1.3%, respectively), [30].

In a 48 week randomized, double-blind study of finasteride treatment of androgenetic alopecia, efficacy of 1mg and 0.2mg finasteride were compared in 414 men. The incidence of decreased libido was 2.9%, 1.5% and 2.2% for finasteride 1mg, 0.2mg, and placebo, respectively [31]. Most of these cases resolved during the course of therapy and there were no discontinuations of the study related to the adverse drug effects [31].

An additional study conducted by Leyden et al. was a one-year, double-blind, placebo-controlled, randomized study in 326 men with male pattern hair loss who received oral finasteride 1 mg/d or placebo followed by a one-year extension study [32]. The only drug-related adverse effects were sexual adverse effects, reported in approximately 2% of men in both treatment groups, with 2 patients in each treatment group reporting decreased libido and 1 patient in the finasteride-treatment group reporting impotence [32]. No patients discontinued the study because of sexual adverse side effects. In the study extension period, there was no increase in any drug-related adverse experiences. The Merck-sponsored Van Neste et al. multicenter 48-week, randomized, double-blind, placebo-controlled study also looked at the effect of 1 mg/d finasteride in 212 men with AGA, aged 18 to 40 years. They reported that 1.9% of the finasteride 1mg treatment group experienced sexual adverse events compared to 0.9% in the placebo group. There were no discontinuations of the study related to adverse effects [33]. Of the two men who reported sexual adverse events one had resolution during therapy and the other had resolution two weeks after therapy ended [33].

Dutasteride 0.5mg

The REDUCE (Reduction by Dutasteride of Prostate

Cancer Events) trial, a 4-year, multicenter, randomized, double-blind, placebo-controlled study involving 6,729 men, compared dutasteride 0.5 mg daily to placebo. There were 3,305 subjects in the dutasteride group and 3,424 in the placebo group. Erectile dysfunction was reported in 9.0% of the subjects in the dutasteride group and in 5.7% of the subjects in the placebo group ($P < 0.001$), [34]. Moreover, 3.3% of the subjects in the dutasteride group experienced a decrease in libido as compared with 1.6% of the subjects in the placebo group ($P < 0.001$), [34]. Upon comparison of dutasteride 0.5mg to placebo, Roehrborn et al. found dutasteride was associated with a significant increase in impotence, decreased libido, and ejaculation disorder compared to placebo (dutasteride: 7.3%, 4.2%, and 2.2%, respectively, placebo: 4%, 2.1%, 0.8%, respectively, $P < 0.001$) during the first year of this 2 year, randomized, double-blind study ($N=4,325$), [35]. During the second year, there were no significant differences between the two groups.

Erectile dysfunction and decreased libido have also been reported in the CombAT trial, a double-blind, randomized, placebo controlled trial evaluating the efficacy of dutasteride in treating BPH [36]. In this trial, 1,623 subjects were treated with dutasteride (0.5mg) for BPH whereas 1,611 subjects were treated with the alpha blocker tamsulosin (placebo). In a 4-year follow-up analysis, Roehrborn et al. reported that 7% of the patients treated with dutasteride reported erectile dysfunction compared to 5% of subjects treated with tamsulosin [37]. Furthermore, 3% of the patients treated with dutasteride reported decreased libido compared to 2% in the tamsulosin group [37]. Eun et al. completed a similar phase III study comparing 0.5 mg/d dutasteride to placebo for the treatment of male pattern hair loss. The 6 month multicenter, double-blind, placebo controlled trial included 148 men aged 18 to 49 years (38). Assessment of sexual function utilized a problem assessment domain to determine perception of lack of sex drive, ability to obtain and maintain erections, and ejaculation. In the 0.5mg dutasteride group, 4.1% experienced sexual dysfunction compared to 2.7% of the placebo group. These findings were not statistically significant [38].

In the Japanese BPH study by Tsukamoto et al., 0.5mg dutasteride ($n=70$) was compared to placebo

(n=66). Performed at 26 centers in Japan, this 1-year, randomized, double-blind, placebo-controlled study found that in men 50 years or older with BPH, erectile dysfunction occurred in 4% of subjects taking dutasteride [6]. There were no cases of erectile dysfunction in the placebo group. The incidence of sexual dysfunction while taking dutasteride 0.5mg was considered infrequent and the drug was recommended for treatment of BPH owing to its effectiveness.

Finasteride versus Dutasteride

A study comparing the safety profile of dutasteride (0.5 mg/d) and finasteride (5 mg/d) for treating BPH was performed by Andriole et al. In the dutasteride group of 813 subjects, impotence occurred in 7%, decreased libido in 5%, and ejaculation disorder in 1%. Impotence was experienced by 8%, decreased libido by 6%, and ejaculation disorder by 1% in the finasteride 5mg group (n=817), [5]. These differences were not considered significant and the safety profile of dutasteride was considered no different than finasteride by the authors based on their parallel group, comparator trial.

The Gubelin Harcha et al, 2014 multicenter, randomized, double-blind, placebo-controlled study also compared dutasteride (0.02, 0.1, or 0.5mg), finasteride (1mg), and placebo in the treatment of androgenetic alopecia for 917 men (20-50 years old). Dutasteride 0.5mg was found to significantly increase hair growth compared to finasteride 1mg and placebo with a similar rate of adverse side effects. Altered libido, impotence, and ejaculation disorders were listed for all groups (dutasteride 0.5mg: 4.9%, 5.4%, and 3.3%, respectively; finasteride 1mg: 6.7%, 6.1%, 3.9%, respectively; placebo: 1.7%, 3.9%, 3.3%, respectively), [39]. There was no significant difference found between finasteride and dutasteride sexual side effects and additionally, a dose dependent response of sexual side effects for any of the treatment doses of dutasteride was absent [39]. Sexual side effects were found to decrease over time.

In the Olsen et al. androgenetic alopecia study comparing multiple doses of dutasteride (0.05mg, 0.1mg, 0.5mg, 2.5mg) versus finasteride 5mg, dutasteride 0.5 mg was shown to be significantly superior at promoting hair growth compared to

finasteride 5mg after 24 weeks ($P = 0.026$), [13]. Dutasteride 2.5mg was also shown to be significantly more effective than dutasteride 0.5mg at increasing hair growth. Rates of decreased libido, ejaculation disorders, and impotence were 13%, 1%, and 0% for dutasteride 2.5mg, respectively; 1%, 1%, and 0% for dutasteride 0.5mg, respectively; 4%, 3%, and 1% for finasteride 5mg, respectively; and 3%, 0%, and 5% for placebo, respectively [13]. Of the 13% of subjects who reported decreased libido in the dutasteride 2.5mg treatment group, 4 resolved during treatment, 1 within 3 weeks of stopping therapy, and 1 within 8 weeks of stopping; 1 patient had decreased libido that persisted after stopping but was considered by the patient to be unrelated to the drug [13]. Based on these findings the authors suggest that while dutasteride 0.5mg is the recommended daily dose for BPH (this drug is not FDA approved for androgenetic alopecia but it is prescribed for such as an off label use), dutasteride 2.5mg is significantly more effective at reducing DHT levels and thus could have a greater therapeutic impact at these levels.

Finally, Kaplan et al. conducted a retrospective analysis of 378 consecutive men treated at a single clinic with 5 α -reductase inhibitor monotherapy for lower urinary tract symptoms related to BPH [40]. Treatment duration was five years. Of those enrolled, 197 subjects were treated with finasteride (5 mg) and 211 with dutasteride (0.5 mg). At 5 years, 57.4% of men in the finasteride group and 42.5% of men in the dutasteride group remained on treatment. Dutasteride resulted in more sexual side effects leading to discontinuation compared to finasteride, with the incidence of erectile dysfunction, ejaculatory dysfunction, and decreased libido being significantly higher in the dutasteride group (5.1%, 2.4%, 2.7%, respectively) compared with the finasteride group (2.1%, 1.8%, 1.4%, respectively) [40]. Of those subjects who remained on treatment for five years, dutasteride resulted in significantly greater erectile dysfunction than finasteride. At year 5, subjects on dutasteride therapy had significantly worsened International Index of Erectile Function scores relative to baseline than did those on finasteride [40]. This suggests that dutasteride may have stronger negative adverse sexual effects compared to finasteride.

Finasteride Persistent Side Effects

Although the potential for adverse sexual side effects has been adequately demonstrated by the previously discussed studies, none to this point have shown that the effects have lasted more than a few weeks after stopping drug therapy. The Proscar Long-Term Efficacy and Safety Study (PLESS) examined just this, the incidence of persistent sexual adverse experiences in 3,040 men between the ages of 45 and 78 years old with BPH. The study was a 4 year, double-blind, randomized, placebo-controlled attempt to ascertain the efficacy and safety profile of finasteride 5mg/d [41]. Researchers found that 15% of subjects in the finasteride group experience sexual side effects in the first year compared to 7% in the placebo group ($P < 0.001$), [42]. In the remaining years of the study there was no difference between groups (7% for both). The sexual side effects cleared during therapy for 12% and 19% of those in the finasteride and placebo groups, respectively. The discontinuation rate related to sexual adverse effects was 4% for finasteride and 2% for placebo; however, only 50% and 41% experience resolution of their sexual symptoms after discontinuing therapy, respectively [42]. The study concluded that only during the first year was finasteride associated with a higher incidence of sexual adverse events and that the likelihood of sexual side effects was not related to pre-existing sexual dysfunction in men. Half of the population that discontinued owing to sexual side effects experienced persistent sexual dysfunction, which is typical of the natural history of sexual dysfunction in the patient population [42, 43]. Irwig and Kolukula also sought to determine the prevalence of persisting sexual side effects following the use of finasteride 1mg/d to treat male pattern hair loss in two uncontrolled studies, graded very low by the ACP outcome system. In one they interviewed 71 men (21-46 years old) who experience sexual side effects following the discontinuation of finasteride for at least 3 months (patients were recruited from Irwig's clinic and the website propeciahlep.com). Subjects used finasteride for an average of 28 months and sexual side effects persisted for an average of 40 months at the time of interview. Of those interviewed, 94% reported low libido, 92% reported erectile dysfunction, 92% reported decreased arousal, and 69% had difficulty with orgasm [44]. In the following study by Irwig, he reassessed the sexual function of 54 of the original participants after 14 months and

found that 89% still had sexual dysfunction [45]. This raises the possibility of permanent effects related to finasteride in a small portion of patients.

Depression and Sexual Side Effects

These long lasting side effects, albeit infrequent, leads one to ponder the mechanism via which sexual dysfunction persists. Basaria et al. strived to answer this very question in their systematic evaluation of 56 men who had previously used finasteride (1 mg) and were experiencing persistent sexual side effects ($n=25$), men who had previously used finasteride (1 mg) with no persistent sexual side effects ($n=13$), or a control group who had neither used finasteride nor had sexual dysfunction ($n=18$), [46]. It was found that in the persistent side effects group there was not androgen deficiency, androgen insensitivity, nor lasting inhibition of steroid 5 α -reductase. There was, however, depressed mood, negative affect, and neural circuitry in these men that has been associated with major depression, as seen on fMRIs ($P < 0.001$), [45, 46]. Therefore, the authors concluded that treatment for persistent sexual dysfunction in this group should target the depression and sexual symptoms rather than utilize androgen based therapies [46]. This link between depression and sexual dysfunction suggests that 5 α RIs may lead to sexual dysfunction both directly and indirectly through depression and prompted us to delve further into the relationship. All studies on the subject have been summarized in

Table 3.

Neurosteroids and related compounds are hormones that have been shown to be active in the central nervous system. Among the compounds that are active are pregnenolone, allopregnanolone, dihydrodeoxycorticosterone, and dehydroepiandrosterone, among others [47]. These compounds are thought to have neuroprotective effects, namely they are considered antidepressant, anxiolytic, and memory enhancing [47, 48]. Depression has been shown to be related to both androgen deficiency and the dysregulation of these neurosteroids [49, 50]. 5 α RIs are thought to decrease synthesis of these neurosteroids and may lead to psychological effects in addition to sexual effects via this mechanism [51].

Welk et al. performed a retrospective, cohort study

with 93,197 matched pairs; men aged 66 or older who had taken finasteride (52%) or dutasteride (48%) for BPH were matched to men of a similar profile who were not taking 5 α RIs. The study purpose was to measure incidents of suicide, self-harm, or depression among those taking these drugs compared to controls. It was found that there was not a significant increase in the rate of suicide for those taking 5 α RIs versus control (HR 0.88, 95% CI = 0.53-1.45) [52]. However, there was a significant increase in both the risk for self-harm and depression. Self-harm was found to be increased in the drug group for the first 18 months of therapy (HR 1.88, 95% CI = 1.34-2.64), but after that there was no difference compared to the control group. Depression on the other hand was found to be elevated both in the first 18 months of drug therapy (HR 1.94, 95% CI = 1.73-2.16) and thereafter, but to a lesser extent (HR 1.22, 95% CI = 1.08-1.37), [51, 52]. There was not a marked difference in these results for finasteride compared to dutasteride.

A multicenter, prospective, longitudinal case control clinical trial was performed by Melcangi et al. that measured neuroactive steroids in cerebrospinal fluid (CSF) and plasma, peripheral neuropathy, and depression in 16 men with persistent side effects following finasteride 1mg treatment (they had discontinued use for a median of 5.4 years) compared to 25 healthy controls [53]. It was found that of the treatment group 14 out of 16 (87.5%) had abnormal CSF and plasma neuroactive steroids (the normal levels were ascertained from the 25 control subjects). Additionally, 50% of the persistent finasteride side effects group demonstrated major depression and 25% had peripheral neuropathy of the pudendal nerve. Severe erectile dysfunction was present in 62.5% of the finasteride group and 100% of this group showed some level of ED [53].

In a retrospective case series looking at 19 patients (14 men and 5 women) by Altomare and Capella, moderate to severe depression was looked at during the course of AGA treatment with finasteride 1mg. Within one month of starting finasteride drug therapy all 19 of these patients developed mood disturbances [54]. Interestingly, 13 of these patients developed depressive symptoms despite reporting that the treatment seemed effective at stabilizing hair loss. Of the men in the study, 4 of them reported developing

sexual dysfunction (reduced libido or reduced ejaculate volume) in addition to the depression. These drug induced mood affects resolved within 3 days to 3 months after drug cessation [54].

In Rahimi-Ardabili et al's prospective study of 128 men (average age 25.8) who used finasteride (1 mg/d) for AGA, there was found to be a minimal but significant increase in depression after finasteride treatment as compared to before [55]. Depression was assessed before and after treatment using both the Beck Depression Inventory (BDI) and Hospital Anxiety and Depression Scale (HADS). The Beck Depression Inventory showed an increase in depression of 0.69 points (P <0.001). HADS showed a significant increase in depression of 0.57 points and an increase in anxiety that did not prove to be significant. In addition, transient loss of libido was found in 9.4% of subjects. However, there was not a significant difference in either BDI or HADS in this subset [55].

Another study, by Ali et al., utilized the FAERS adverse drug event database and Multi-item Gamma Poisson Shrinker analysis to determine rates of sexual dysfunction and suicidal ideation post finasteride 1mg use for androgenetic alopecia. There were 4,910 FAERS reports from 1998 to 2013 for men 18 to 45 years old. Of these reports 11.8% of them were for persistent sexual dysfunction and 0.79% were for suicidal ideation [56]. Of those reports of suicidal ideation, 87% also reported sexual dysfunction. On average, these men experienced sexual dysfunction for 5.4 months after stopping finasteride use and suicidal ideation for 2.4 years among those who had both suicidal ideation and sexual dysfunction [56]. Although causality cannot be established based on these findings Ali et al. propose a mechanistic relationship between low dose finasteride use, sexual dysfunction, and suicidal ideation. Finasteride inhibits 5- α -reductase, which serves to decrease DHT levels. This androgen is implicated in both sexual function and central nervous system neurosteroids that modulate both depression and anxiety [56].

Caruso et al. performed a case-control study comparing 7 AGA post finasteride (1-1.25 mg/d) patients versus 12 healthy controls. These post finasteride patients (average age 38 years old) are

characterized as having experienced lasting sexual side effects and depression or anxiety after stopping drug therapy (time since therapy ranged from 171-5000 days), [57]. Among the 7 in the post finasteride treatment group, depression was reported in 86%, loss of libido in 86%, and erectile dysfunction in 71%. Lumbar punctures were performed on all subjects. The CSF and plasma findings, somewhat beyond the scope of this paper, showed decreased levels of T metabolite and PROG levels during therapy as well as persistently altered neurosteroid levels (PREG, PROG, DHP, THP T, DHT, among others) associated with symptoms of depression and sexual difficulties [57].

Irwig also examined rates of depression among men with persistent sexual side effects following finasteride (1 mg/d) AGA treatment. It was found that among the 61 men recruited from propeciahelp.com and his personal practice suffering from persistent sexual dysfunction that rates of depression were significantly higher for these men compared to the control group of 29 men recruited from the local community (the control group suffered from AGA but had never taken finasteride), [58]. Rates of depression, as assessed by the Beck Depressive Inventory II, were 75% versus 10% for treatment and control groups, respectively ($P < 0.0001$). Suicidal ideation was also reported in 44% of the finasteride group compared to 3% of controls ($P < 0.0001$), [58].

An internet survey was utilized by Ganzer et al. to characterize the symptoms experienced by men with persistent side effects following finasteride 1mg treatment of AGA (recruitment was via Propeciahelp.com). The goal was to assess the prevalence and characteristics of cognitive, psychological, and physical effects among 131 patients with a mean age of 24 years [59]. Among the symptoms reported were: decreased sex drive (93%), complete loss of sex drive (63%), intermittent erectile dysfunction (83%), complete impotence (40%), diminished semen volume and force (82%), depressed affect (73%), and suicidal ideation (63%), [59]. A subsequent study by Ganzer and Jacobs, meant to expand upon the previous one, assessed the association between preexisting conditions or family history of psychological disorders and the vulnerability for developing persistent finasteride side effects [60]. It was found that 55% of subjects

who were experiencing these long term adverse drug effects had a psychiatric diagnosis prior to starting therapy and 28.8% had a first degree relative with such a diagnosis. The authors thus concluded that preexisting psychological disorders or a family history of such could indicate a vulnerability, which finasteride therapy serves to exacerbate and this has led to persistent effects among this population [60]. The authors advise taking a thorough mental health history on both the individual and family members prior to initiating therapy [60].

Meta-Analysis

In addition to the aforementioned studies, the meta-analysis by Liu et al. pooled 17,494 subjects from 17 randomized control trials to determine the relative risk of sexual dysfunction, erectile dysfunction, and decreased libido in those taking 5 α RIs for benign prostatic hyperplasia and androgenetic alopecia [10]. Of the studies included, 9 evaluated the efficacy of 5 α RIs for BPH whereas 8 assessed their efficacy for AGA. For men with BPH the relative risk of sexual dysfunction was 2.56 (95% CI = 1.48-4.42). The relative risk of sexual dysfunction for AGA was 1.21 (95% CI = 0.85-1.72). Erectile dysfunction relative risk for BPH was 1.55 (95% CI = 1.14-2.12) and for AGA it was 0.66 (95% CI = 0.20-2.25). Finally, the relative risk for decreased libido was 1.69 (95% CI = 1.03-2.79) in those with BPH, compared to 1.16 (95% CI = 0.50-2.72) for AGA [10]. Based on the Liu et al. analysis, it was concluded that there is a significantly increased incidence of adverse sexual effects in men who take 5- α -reductase inhibitors (finasteride and dutasteride) for the treatment of BPH compared to placebo. However, there is not a significant increase in sexual adverse effects in men who take these drugs for the treatment of male pattern hair loss. Something that should be taken into consideration with this distinction is that BPH is common among men over the age of 50 and BPH is typically treated with higher doses of 5 α RIs than AGA. This may suggest that the association between BPH treatment and sexual dysfunction could be at least partially related to drug dosage and older age [10]. Erectile dysfunction was found to be the most common sexual side effect among those taking various doses of finasteride or dutasteride [10, 60].

Interestingly, it was found in subgroup analyses that

for the treatment of BPH dutasteride (RR = 4.09, 95% CI = 1.03-16.31) has a significantly higher relative risk of sexual adverse effects compared to finasteride (RR = 1.54, 95% CI = 1.02-2.32), [10]. The same was not true for the treatment of AGA. For those treated for male pattern hair loss, the relative risk for each treatment was compared. The RRs of sexual side effects were 1.12 (95% CI = 0.63-1.99) for finasteride 5 mg/d, 0.87 (CI = 0.54-1.39) for finasteride 1 mg/d, 0.43 (95% CI = 0.22-0.87) for dutasteride 0.5 mg/d, and 1.40 (95% CI = 0.72-2.71) for 0.1 mg/d. However, none of these findings had a P value of less than 0.3, indicating a lack of significance [10]. Finally, in the treatment of BPH, it was found that there is an increased risk of sexual adverse effects for men taking finasteride 5 mg/d or dutasteride 0.5 mg/d for longer than a year compared to treatment durations for less than a year [10].

Conclusion

Although the 5 α RIs finasteride and dutasteride have been established to be efficacious for the treatment of benign prostatic hyperplasia and androgenetic alopecia by substantially reducing the levels of dihydrotestosterone [2, 3], it has also been documented that they may increase the incidence of sexual dysfunction [10]. Decreased libido, ejaculation disorder, and impotence are among the most commonly reported drug related adverse effects [19]. Erectile dysfunction, or impotence, has been cited as the most common side effect in multiple studies for both finasteride 5 mg/d and dutasteride 0.5mg/d, followed by decreased libido [5, 15, 22, 25, 27, 45]. In the largest meta-analysis to date on 5 α RIs, there was found to be a significantly increased risk of sexual dysfunction (156% increase) for men being treated with finasteride or dutasteride for BPH, whereas there was not a significant association for those treated for AGA [10]. Dutasteride 0.5 mg/d has also been shown to have a greater incidence of adverse sexual effects than finasteride 5 mg/d in the treatment of BPH [10]. Unfortunately, there is no consensus regarding the relation between 5 α RIs dosage and the likelihood of sexual dysfunction and further study is needed in this area [10, 38, 55]. It is based on these findings that we recommend practitioners both consider and discuss the possible sexual side effects and risk of depression with their patients prior to selecting a drug therapy.

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Table 1 Side Effects of 5-Alpha-Reductase Inhibitors Finasteride and Dutasteride

Sexual Side Effects							
Source	Dosage (daily)	N	(%) Side Effect	Placebo (%) Side Effect	Persistent Effects	Level of Evidence	ACP Outcome Study Grading
Moinpour et al. The Prostate Cancer Prevention Trial [15]	Finasteride (5mg)	17,313	Sexual Activity Scale score 3.21 points higher in Finasteride arm at month 6 and 2.11 points higher in Finasteride arm at year 7	Scored lower on Sexual Activity Scale, indicating better sexual function	No	Double-blind, randomized, placebo-controlled study; Sexual Activity Scale (0-100) assessed sexual dysfunction	High
Marberger et al. PROWESS Study [20]	Finasteride (5mg)	3,168	Sexual adverse effects (10%) Decreased libido (4%) Ejaculation disorder (2.1%) Impotence (6.6%)	Sexual adverse effects (7%) Decreased libido (2.8%) Ejaculation disorder (0.6%) Impotence (4.7%)	No	Double-blind, 2-year randomized, placebo-controlled, multicenter study	High
McConnell et al. Finasteride Long-Term Efficacy and Safety Study Group [21]	Finasteride (5mg)	2,070	Decreased libido (6.4%) Impotence (8.1%) Decreased ejaculate volume (3.7%) Ejaculation disorder (0.8%)	Decreased libido (3.4%) Impotence (3.7%) Decreased ejaculate volume (0.8%) Ejaculation disorder (0.1%)	No	Double-blind, 4-year, randomized, placebo-controlled trial	High
Fwu et al. [22]	Finasteride (5mg)	1,367	Baseline vs. 1 year follow-up: Worse sexual drive (16%) Worse erectile function (11%) Worse ejaculatory function (9%) Worse overall sexual satisfaction (15%) Baseline vs. 4 year follow-up: Worse sexual drive (22%) Worse erectile function (18%) Worse ejaculatory function (18%) Worse overall sexual satisfaction (21%)	Baseline vs. 1 year follow-up: Worse sexual drive (11%) Worse erectile function (8%) Worse ejaculatory function (6%) Worse overall sexual satisfaction (14%) Baseline vs. 4 year follow-up: Worse sexual drive (16%) Worse erectile function (13%) Worse ejaculatory function (12%) Worse overall sexual satisfaction (17%)	No	Multicenter, randomized, double-blind, placebo-controlled, clinical trial	High
Andersen et al. Scandinavian BPH Study Group [24]	Finasteride (5mg)	707	Sexual dysfunction (19%)	Sexual dysfunction (10%)	No	Multicenter, 2-year, double-blind, placebo-controlled study	High

Table 1 Side Effects of 5-Alpha-Reductase Inhibitors Finasteride and Dutasteride								
Sexual Side Effects								
Nickel et al. PROSPECT [25]	Study	Finasteride (5mg)	472	Ejaculation disorder (7.7%) Impotence (15.8%)	Ejaculation disorder (1.7%) Impotence (6.3%)	No	Double-blind, 2-year, randomized, placebo-controlled multicenter study	High
Vaughan et al. [26]		Finasteride (5mg)	190	During 6 month study: Impotence (0.7%) Decreased libido (0.7%) Ejaculation disorder (0%) During voluntary extension 1 st year: Impotence (6.4%) Decreased libido (10.9%) Ejaculation disorder (5.8%)	During 6 month study: Impotence (0%) Decreased libido (0%) Ejaculation disorder (0%)	No	Double-blinded, placebo-controlled study	Moderate
Wilton et al. [27]		Finasteride (5mg)	14,772	Impotence (2.1%) Ejaculatory failure (2.1%) Decreased libido (1%)	N/A – No control group	No	Observational cohort study	Low
Gormley et al. The Finasteride Study Group [28]		Finasteride (5mg, 1mg)	893	5mg: Decreased libido (4.7%) Ejaculatory disorder (4.4%) Impotence (3.4%) Orgasm dysfunction (0.7%) 1mg: Decreased libido (6%) Ejaculation disorder (4.4%) Impotence (5%) Orgasm dysfunction (0.3%)	Decreased libido (1.3%) Ejaculation disorder (1.7%) Impotence (1.7%) Orgasm dysfunction (0.3%)	No	Multicenter, 1-year, double blind, randomized, placebo-control study	High
Roberts et al. [29]		Finasteride (5mg, 1mg, 0.2mg, 0.01mg)	548	5mg: Sexual adverse effects (3.6%) Decreased libido (2.7%) Erectile dysfunction (1.8) 1mg: Sexual adverse effects (4.3%) Decreased libido (1.7%) Erectile dysfunction (2.6%)	Sexual adverse effects (3.4%) Decreased libido (3%) Erectile dysfunction (0%)	No	Multicenter, 1-year, randomized, double-blind, placebo-controlled study	High

Table 1 Side Effects of 5-Alpha-Reductase Inhibitors Finasteride and Dutasteride Sexual Side Effects

Drake et al. [11]	Finasteride (5mg, 1mg, 0.2mg, 0.05mg, 0.01mg)	249	5mg: Decreased libido (2.6%) 1mg: Decreased libido (0%)	Decreased libido (4.5%)	No	Multicenter, double-blind, randomized, placebo-controlled study	Moderate
Kaufman et al. The Finasteride Male Pattern Hair Loss Study [30]	Finasteride (1mg)	1,553	Sexual function adverse events (4.2%) Erectile dysfunction (1.4%) Decreased ejaculatory vol (1.0%) Decreased libido (1.9%)	Sexual function adverse events (2.2%) Erectile dysfunction (0.9%) Decreased ejaculatory vol (0.4%) Decreased libido (1.3%)	No	Two replicate, 1-year, double-blind, randomized, placebo-controlled studies	High
Kawashima et al. [31]	Finasteride (1mg vs. 0.2mg)	414	1mg: Decreased libido (2.9%) 0.2mg: Decreased libido (1.5%)	Decreased libido (2.2%)	No	Double-blind, randomized, 48-week study	High
Leyden et al. [32]	Finasteride (1mg)	326	Sexual adverse effects (2%)	Sexual adverse effects (2%)	No	Double-blind, 1-year, placebo-controlled, randomized multicenter study	High
Van Neste et al. [33]	Finasteride (1 mg)	212	Sexual adverse effects (1.9%)	Sexual adverse effects (0.9%)	No	Multicenter, double-blind, randomized, placebo-controlled study	Moderate
Wessells et al. PLESS trial [42]	Finasteride (5mg)	3,040	Sexual adverse events (15%)	Sexual adverse events (7%)	Yes	Double-blind, 4-year, placebo-controlled study	High
Irwig et al. [45], [46]	Finasteride (1mg)	71	Low libido (94%) Erectile dysfunction (92%) Decreased arousal (92%) Problems with orgasm (69%)	N/A – No Control Group	Yes	Two uncontrolled studies	Very low
Andriole et al. REDUCE trial [34]	Dutasteride (0.5mg)	6,729	Erectile dysfunction (9%) Decreased libido (3.3%)	Erectile dysfunction (5.7%) Decreased libido (1.6%)	No	Multicenter, double-blind, 4-year, randomized, placebo-controlled study	High
Roehrborn et al. [35]	Dutasteride (0.5mg)	4,325	Impotence (7.3%) Decreased libido (4.2%) Ejaculation disorder (2.2%)	Impotence (4%) Decreased libido (2.1%) Ejaculation disorder (0.8%)	No	Double-blind, 2-year, randomized, placebo-controlled study	High

Table 1 Side Effects of 5-Alpha-Reductase Inhibitors Finasteride and Dutasteride

Sexual Side Effects							
Roehrborn et al. CombAT trial [37]	Dutasteride (0.5mg)	3,234	Erectile dysfunction (7%) Decreased libido (3%)	Erectile dysfunction (5%) Decreased libido (2%)	No	Double-blind, randomized, placebo-controlled trial	High
Eun et al. [38]	Dutasteride (0.5mg)	148	Sexual adverse events (4.1%) Sexual dysfunction (4.1%) Erectile dysfunction (0%) Ejaculation disorder (0%)	Sexual adverse events (4%) Sexual dysfunction (2.7%) Erectile dysfunction (1.3%) Ejaculation disorder (1.3%)	No	Multicenter, double-blind, randomized, placebo-controlled phase III trial	Moderate
Tsakamoto et al. [6]	Dutasteride (0.5mg)	136	Erectile dysfunction (4%) Decreased libido (0%)	Erectile dysfunction (0%) Decreased libido (0%)	No	Randomized, double-blind, placebo-controlled study	Moderate

**Table 2 Side Effects of 5-Alpha-Reductase Inhibitors Finasteride vs. Dutasteride
Sexual Side Effects**

Source	Dosage (daily)	N	(%) Finasteride Side Effect	(%) Dutasteride Side Effect	Placebo (%) Side Effect	Per-sistent Effects	Level of Evidence	ACP Outcome Study Grading
Andriole et al. [5]	Finasteride (5mg) vs. Dutasteride (0.5mg)	3,160	Impotence (8%) Decreased libido (6%) Ejaculation disorders (1%)	Impotence (7%) Decreased libido (5%) Ejaculation disorders (1%)	N/A	No	Multicenter, randomized, double-blind, placebo-controlled study	High
Gubelin Harcha et al. [39]	Finasteride (1mg) vs. Dutasteride (0.02mg, 0.1mg, 0.5mg)	917	Finasteride (1mg): Altered libido (6.7%) Impotence (6.1%) Ejaculation disorders (3.9%)	Dutasteride (0.5mg): Altered libido (4.9%) Impotence (5.4%) Ejaculation disorders (3.3%)	Altered libido (1.7%) Impotence (3.9%) Ejaculation disorders (3.3%)	No	Multicenter, randomized, double-blinded, 29 week study	High
Olsen et al. [13]	Finasteride (5mg) vs. Dutasteride (0.05mg, 0.1mg, 0.5mg, 2.5mg)	416	Finasteride (5mg) Decreased libido (4%) Ejaculation disorders (3%) Impotence (1%)	Dutasteride (2.5mg): Decreased libido (13%) Ejaculation disorders (1%) Impotence (0%) Dutasteride (0.5mg): Decreased libido (1%) Ejaculation disorders (1%) Impotence (0%)	Decreased libido (3%) Ejaculation disorders (0%) Impotence (5%)	No	Multicenter, randomized, placebo-controlled study	High
Kaplan et al. [40]	Finasteride (5mg) vs. Dutasteride (0.5mg)	378	Erectile dysfunction (2.1%) Ejaculatory dysfunction (1.8%) Decreased libido (1.4%)	Erectile dysfunction (5.1%) Ejaculatory dysfunction (2.4%) Decreased libido (2.7%)	N/A	No	Retrospective 5-year study	High

Table 3 Side Effects of 5-Alpha-Reductase Inhibitors

Depressive Side Effects							
Source	N	Dosage (daily)	(%) Side Effect	Placebo (%) Side Effect	Persistent Effects	Level of Evidence	ACP Outcome Study Grading
Welk et al. [55]	Finasteride or Dutasteride	186,394	Suicide (0.04%) Self-harm (0.18%) Depression (1.95%)	Suicide (0.04%) Self-harm (0.14%) Depression (1.37%)	No	Retrospective, matched cohort study	High
Melcangi et al. [57]	Finasteride (1 mg-1.25mg)	41	Abnormal CSF and plasma neuroactive steroids (0.88%) Major depression (50%) Pudendal neuropathy (25%)	Used for normal CSF and plasma neuroactive steroid levels		Multicenter, prospective, longitudinal, case control clinical trial	High
Basaria et al. [47]	Finasteride (1mg)	56	Sexual desire (17 on MSHQ)	Sexual desire (29.5 on MSHQ)		Retrospective, placebo-controlled study	High
Ali et al. [60]	Finasteride (1mg)	4,910	Sexual dysfunction (11.8%) Suicidal ideation (0.79%) Suicidal ideation and sexual dysfunction (0.69%)	N/A – No Control Group	Yes	Retrospective pharmacovigilance disproportionality analysis	Moderate
Caruso et al. [61]	Finasteride (1mg-1.25mg)	19	Different neuroactive steroid profile in CSF and plasma compared to controls	Different neuroactive steroid profile compared to cases	Yes	Case-control study	Moderate
Rahimi-Ardabili et al. [59]	Finasteride (1mg)	128	HADS-Depression score increased 0.57 pts BDI-Depression score increased 0.69 pts Loss of libido (9.4%)	N/A – No Control Group	No	Two self-administered questionnaires	Low
Irwig et al. [62]	Finasteride (1mg)	61	All had sexual dysfunction post finasteride treatment Depression symptoms (75%) Suicidal thoughts (44%)	Depression symptoms (10%) Suicidal thoughts (3%)	Yes	Self-administered questionnaire	Low
Ganzer et al. [63]	Finasteride (1mg)	131	Decreased sex drive (93%) Complete impotence (40%) Intermittent erectile dysfunction (83%) Depressed affect (73%) Suicidal ideations (63%)	N/A – No Control Group	Yes	Self-administered questionnaire	Very low

Table 3 Side Effects of 5-Alpha-Reductase Inhibitors
Depressive Side Effects

Ganzer et al. [64]	Finasteride (1mg)	97	Moderate to severe depression (39%) Extreme depression (5%) Moderate anxiety (16%)	N/A – No Control Group	Yes	Self-administered questionnaire	Very low
Altomare et al. [58]	Finasteride (1mg)	19	Sexual disturbances (21%)	N/A – No Control Group	No	Retrospective case series of 19 subjects that developed moderate to severe depression on finasteride therapy	Very low