Adverse Effects and Safety of 5-alpha Reductase Inhibitors (Finasteride, Dutasteride): A Systematic Review

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ABSTRACT

Finasteride and dutasteride, both 5-alpha reductase inhibitors, are considered first-line treatment for androgenetic hair loss in men and used increasingly in women. In each case, patients are expected to take the medications indefinitely despite the lack of research regarding long-term adverse effects. Concerns regarding the adverse effects of these medications has led the United States National Institutes of Health to add a link for post-finasteride syndrome to its Genetic and Rare Disease Information Center. Herein, the authors report the results of a literature search reviewing adverse events of 5-alpha reductase inhibitors as they relate to prostate cancer, psychological effects, sexual health, and use in women. Several large studies found no increase in incidence of prostate cancer, a possible increase of high-grade cancer when detected, and no change in survival rate with 5-alpha reductase inhibitor use. Currently, there is no direct link between 5-alpha reductase inhibitor use and depression; however, several small studies have led to depression being listed as a side effect on the medication packaging. Sexual effects including erectile dysfunction and decreased libido and ejaculate were reported in as many as 3.4 to 15.8 percent of men. To date, there are very few studies evaluating 5-alpha reductase inhibitor use in women. Risks include birth defects in male fetuses if used in pregnancy, decreased libido, headache, gastrointestinal discomfort, and isolated reports of changes in menstruation, acne, and dizziness. Overall, 5-alpha reductase inhibitors were well-tolerated in both men and women, but not without risk, highlighting the importance of patient education prior to treatment. (*J Clin Aesthet Dermatol.* 2016;9(7):56–62.)

Dermatologists as well as primary care physicians widely use finasteride and dutasteride as a first-line treatment for male and female pattern hair loss. Presently there is a lack of research regarding long-term adverse effects of these medications, despite the fact that patients are expected to take them indefinitely to maintain hair growth. Concerns regarding the adverse effects of finasteride and dutasteride has led the United States National Institutes of Health to add a link for post-finasteride syndrome to its Genetic and Rare Disease Information Center website. Of the current literature, the majority of research examining the side effects of these medications are at higher doses intended to treat conditions such as benign prostatic hyperplasia rather than the lower doses commonly used in dermatology for hair loss. Furthermore, 5-alpha reductase inhibitor (5ARI) use in women has been limited due to a lack of research examining adverse reactions in this patient population. Herein, the authors present the results of a literature review examining the side effects of both finasteride and dutasteride.

Androgenetic alopecia (AGA) is a hereditary pattern of hair loss where terminal hairs are converted into miniaturized vellus hairs.[1] This type of hair loss is very common with reports showing up to 80 percent of Caucasian men and 50 percent of women showing evidence of AGA by 70 years of age.[2,3] Men and women, however, typically exhibit different patterns of hair loss. Men tend to have thinning of the hairs in the frontotemporal scalp and scalp vertex, whereas women show thinning of the central scalp.[1] The hair loss seen can lead to a large amount of emotional distress and affect a patient's quality of life in a

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negative way leading them to seek treatment.[4–6] 5-alpha reductase (5AR) inhibitors, such as finasteride and dutasteride, are commonly used to stabilize hair loss and promote regrowth.

The androgen dihydrotestosterone (DHT) is thought to play a large role in inducing AGA and is formed from the conversion of circulating testosterone to DHT by 5AR. Current therapy for AGA is aimed at blocking this conversion at the tissue level. There are three known isoenzymes of 5AR receptors[5] with types I and II playing an important role in the treatment of AGA. Type I 5AR is located predominantly in the skin, including sebaceous glands and hair follicles, whereas type II is the major contributor to the DHT pool[7] and is located in the inner root sheath of hair follicles in the scalp, beard, and chest as well as the genitals and prostate gland.[1,5,8] Of the three isoforms of 5AR, dutasteride inhibits both type I and II, whereas finasteride inhibits only type II. Additionally, dutasteride is three times more potent than finasteride at inhibiting type II and 100 times more potent at inhibiting type I.[9]

METHODS

A search of Medline, Ovid, and Google scholar database and search engines for relevant articles on human subjects, published from 1990 to November 2015 was conducted. The list of references generated was searched by hand to identify additional studies of interest.

RESULTS

Prostate cancer. The antiandrogen effects of drugs such as finasteride and dutasteride are used widely for the treatment of benign prostatic hyperplasia and urinary retention. There is also increased interest in these drugs' potential effect on prostate cancer following studies[4,10,11] showing that some prostate cancer cell lines are androgen dependent for growth and maturation. A seminal study evaluating the long-term effects of finasteride on prostate cancer was the Prostate Cancer Prevention Trial (PCPT).[12] This trial randomized 18,880 patients into placebo versus finasteride groups which were followed for seven years with a 25-percent relative risk reduction in the diagnosis of prostate cancer compared to placebo. Unfortunately, the results of the study were not all positive. In the patient population diagnosed with prostate cancer that was taking finasteride, there was a 27-percent increase in "high grade" Gleason scores of 7 to 10. Recently, Thompson et al published updated survival data after an 18-year follow-up of the original PCPT trial patient population.[13,14] Results of this study showed a reduction in the diagnosis of biopsy-proven prostate cancer in the finasteride group versus placebo (10.5% vs. 14.9%; risk ratio 0.70; confidence interval [CI] = 0.65–0.76), but an increase in the risk of higher grade cancer with a Gleason score of 7 to 10 (3.5% finasteride group vs. 3.0% placebo; RR = 1.17; 95% CI 1.0–1.37). Despite this increase in high-grade cancer, it is important to note that after 18 years of follow-up, there has been no difference in overall survival or the rate of death after diagnosis for patients diagnosed with prostate cancer in either group.

There are other studies looking at 5ARIs that found no statistical differences in prostate cancer Gleason score between those patients who use finasteride and those who do not. Preston et al looked at 5ARIs and the risk of high-grade or lethal prostate cancer in 38,000 men aged 40 to 70 years treated with 5ARIs in the healthcare profession and found no significant increase in high-grade Gleason score.[15] Furthermore, Lacy and Kyprianou, found that the PCPT trial and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial both may have had inherent bias that potentially led to elevated Gleason scores.[16] When computer models attempted to correct for these stated biases there was no significant difference found in high-grade prostate cancer between the finasteride group and control.[16]

Dutasteride's effect on prostate cancer has also previously been evaluated. Andriole et al evaluated 6,729 men randomized into treatment and placebo groups that were followed for four years with a relative risk reduction of 22.5 percent (CI: 15.2–29.8) of prostate cancer in the dutasteride group.[17] Among the men who underwent biopsy, 220 patients in the dutasteride group were found to have Gleason scores of 7 to 10 versus 233 in the placebo group. This was not a clinically significant number; however, during years 3 to 4 of treatment, 12 Gleason score tumors of 8 to 10 were found in the dutasteride group versus 1 in the placebo group ($p<0.003$).

Currently, the reasons behind the increased risk of high-grade cancers in patients taking finasteride and dutasteride have not been fully elucidated. Two possible theories have been proposed to explain the increased risk of high-grade cancer, which center around either direct induction of the cancer or detection bias induced by finasteride. The direct induction theory proposes that finaseride directly promotes more aggressive tumor growth. Kosaka et al[18] looked at DNA replication in human prostate cancer with the use of 5ARIs in three different prostate cancer cell lines: androgen dependent, androgen independent, and castration-resistant prostate cancer cells. Results showed that in androgen-dependent lines, 5ARIs reduced the expression of CDC6 (a marker in pre-replication process) and induced the expression of this protein in the androgen-independent and castration-resistant lines.[18] Another study suggested that long-term anti-androgen therapy may cause prostate cancer cells to differentiate into the neuroendocrine subtype of prostate cancer, which disseminates throughout the body rapidly and has an associated poor prognosis.[19,20] In this study, androgen deprivation therapy included diethylstilbestrol diphosphate, estramustine phosphate, and dexamethasone, but not 5ARIs, such as finasteride or dutasteride.

In the detection bias theory, finasteride is thought to decrease benign hypertrophic prostate stroma with no effect on cancerous cells. Thus there is a higher proportion of prostate affected by cancer leading to higher Gleason scores on biopsy. Lucia et al used samples from the PCPT and analyzed a few of these hypotheses.[21] They concluded

that there was no difference in upgrading of the cancer between the placebo and finasteride groups when evaluated with biopsy and prostatectomy. There were also no significant differences in degenerative hormonal changes in the high-grade biopsies between the treatment group and placebo. Lastly, significant differences in prostate volume were found (25.1 vs. 34.4cm^3; p<0.001), which may lead to increased detection of cancer overall. Furthermore, it has been proposed that most cancers are of mixed grade and finasteride reduced the low-grade proportion, making the diagnosis of high-grade cancer more likely.[21]

In summation, studies examining 5ARI use have shown no increase in incidence of prostate cancer, but have suggested a possible increased risk of high-grade prostate cancer when the disease is detected. Overall, there is no negative impact on the survival rate of patients with prostate cancer with a history of 5ARI use.

Psychiatric effects. The relationship between depression and finasteride use has not been completely defined. In the initial clinical trials of Propecia (finasteride 1mg) and Proscar (finasteride 5mg), depression was seldom reported and it was not listed as an adverse reaction on the medication packaging.[22] With increased medication use, anecdotal evidence of mood changes and small studies reporting depressive symptoms relating to finasteride use have led to depression being added as an adverse reaction to the product labeling of Propecia.

Several small studies report depressive symptoms in patients treated with low-dose 5ARIs. Altomare et al performed a retrospective case series with 17 patients treated with low-dose 5ARIs who experienced moderate-to-severe depression.[23] All the patient's depressive symptoms resolved upon discontinuation of the therapy. Rahimi et al[24] also found that depressive symptoms or anxiety may increase minimally from finasteride administration. In the study, 128 men with androgenetic alopecia who began treatment with 1mg finasteride were evaluated and found to have mild increases in two depression surveys. Both Beck's Depression Inventory (BDI) and Hospital Anxiety and Depression Scale (HADS) depression scores increased minimally, but significantly compared to the placebo groups. The mean ± SD of BDI score was 12.11±7.50 and 12.80±7.64 before and after the treatment, respectively. The HADS score increased from 4.04±2.52 to 4.61±3.19 (p-value 0.005). Interestingly, depression was not self-reported as a side effect by the patients themselves in the study. The only finasteride-associated side effects specifically reported by patients were libido effects, reported by 9.4 percent of patients. A major limitation of this trial was the lack of a control group.

Irwig et al[25] assessed depressive symptoms and suicidal thoughts in former users of finasteride. Otherwise healthy former users of finasteride (n=61) with hair loss and persistent sexual side effects for ≥3 months after discontinuing finasteride were compared against a control group of men with male pattern hair loss, but no sexual dysfunction (n=29). Depressive symptoms were found to be significantly higher in the finasteride group compared to the controls. Moderate or severe depressive symptoms were present in 64 percent of the finasteride group and zero percent of the controls. Suicidal thoughts were present in 44 percent of the former finasteride users and in three percent of the controls (p<0.0001). Confounding this study was the fact the finasteride user group also had sexual dysfunction and the control group did not.

Several mechanisms have been proposed for the depressive symptoms. There has been a demonstrated link between androgen levels (low free testosterone) and depression as depressive symptoms were found in men with prostate cancer treated with androgen deprivation,[26] but the exact mechanism remains unknown.

A second factor influencing mood is the impact on the production of neurosteroids (androstanediol, allopregnanolone, tetrahydrocortisol, tetrahdyrocorticosterone, and tetrahydrodeoxycorticosterone). These neurosteroids modulate seizure susceptibility, anxiety, stress, and depression and require 5AR for synthesis.[27] Finasteride administration decreases CSF and plasma neurosteroid levels and increases the amount of precursor steroids.[28] The decrease of neurosteroid levels also as a consequence decreases dopamine levels, which theoretically could play a role in depressive thoughts and feelings.[29,30] GABAergic receptors are also modulated by 5AR and may possess antidepressant and anxiolytic effects.[31] In 2010, Romer[32,33] published research on the effects of finasteride on mice and found that 5ARI administration decreased neurogenesis of the hippocampal region, which was associated with depression. Additionally the behavior changes in the mice were found to be reversible once treatment was discontinued. Other proposed mechanisms include 5AR acting in the amygdala as well as reduced metabolites of progesterone and deoxycorticosterone in the brain.

As of now, however, no direct link exists between 5ARI and depression, yet it is postulated that in some individuals, the link exists[31] and there is concern for depressive symptoms arising in a small percentage of those treated with 5ARIs. However, further long-term studies would be helpful to better understand finasteride's effects over the course of a lifetime. Further studies on the reversibility of psychiatric mood symptoms are also needed since the data on the matter is not conclusive.

Sexual adverse effects. Sexual adverse effects are the most common category of complications from 5ARI use and have been documented to be anywhere from 0.9 to 38 percent.[4,34] Of these, erectile dysfunction is the most common followed by ejaculatory dysfunction and loss of libido.[34] Several studies have evaluated these parameters and found erectile dysfunction reported in 3.4 to 15.8 percent of patients treated with finasteride 5mg daily versus 1.7 to 6.3 percent treated with placebo, decreased libido in 2.36 to 10.0 percent of patient treated with finasteride versus 1.2 to 6.3 percent of patients treated with placebo, and affected ejaculation in 0.9 to 5.7 percent of patients treated with finasteride versus 0.5 to 1.7 percent treated with placebo.[35–43] When adverse events do occur, some studies indicate that the side effects improve over

time even when patients are continued on finasteride. For example, the Proscar Long Term Efficacy and Safety Study (PLESS) reported an initial adverse event rate of 22 percent, which improved over 2 to 4 years of treatment and eventually returned to rates similar to those reported in the placebo group.[40] Recently, there have been studies that indicated possible persistent sexual dysfunction with finasteride use.[44–45] Irwig et al investigated 71 men from www.propeciahelp.com that self-reported sexual dysfunction three months after discontinuation of finasteride.[44] Additionally, Ali et al reviewed 4,910 reports from young men using finasteride in the United States Food and Drug Administration Adverse Event Reporting System (FAERS) and found 11.8 percent reported sexual dysfunction.[45] On average, the sexual dysfunction occurred 1.8 years after starting finasteride 1mg daily and lasted 5.4 months after stopping the medication.[45] Overall, persistent sexual dysfunction associated with finasteride use is somewhat controversial[46] with conflicting results between studies.

Sexual adverse events in patients treated with dutasteride have been found to be similar to finasteride. Roehrborn et al reported erectile dysfunction in 7.3 percent, decreased libido in 4.2 percent, and ejaculation disturbances in 2.2 percent, which are similar to reported rates for finasteride.[47] Additionally, Andriole et al reported similar rates of sexual adverse events in a direct comparison between finasteride and dutasteride.[17] Like finasteride, the rates of reported adverse events in patients treated with dutasteride in some studies improved over time.[38,48]

A direct link between sexual dysfunction and 5ARIs can be difficult to completely establish. Mondaini et al found that sexual adverse events were higher in patients taking finasteride who had been counseled about potential sexual side effects compared to a group where the counseling was omitted.[34,41] The difference in groups was thought due to a "nocebo" effect where the reported adverse event was not directly related to the pharmacologic action of the drug.[34,41] Additionally, Tosti et al in two different studies found no differences in the International Index of Erectile Function score in patients treated with finasteride versus placebo.[49,50]

The sexual adverse events of low-dose finasteride (1mg daily) have been evaluated as well. Gormley et al compared patients treated with 1mg and 5mg doses of finasteride and placebo in 895 men with benign prostatic hypertrophy.[37] The incidence of reported sexual dysfunction was found to be elevated and equivalent in the two groups taking finasteride. Additionally, Kaufman et al reported sexual effects in 4.4 percent in patients treated with finasteride 1mg daily verses 2.2 percent in the placebo group, which is consistent with values reported using finasteride 5mg daily.[51] Similar rates of adverse events between 1mg and 5mg dosing regimens are not surprising as similar decreases in DHT have been shown for both dosing regimens.[52]

Androgens are known to be important for sexual function in males. This has raised the question about a link between decreased DHT levels and sexual dysfunction. Studies have shown erectile dysfunction/loss of erections with surgical or medical castration for prostate cancer.[53,54] On the other hand, patients with erectile dysfunction who are treated with androgen therapy, in particular DHT, have improvement in erectile function and libido.[54] Thus, androgens have proven to be important in male erection maintenance and libido, however, the exact concentration where function deteriorates needs further research. A study by Marberger et al, attempted to determine this relationship and determined sexual function was more apparent with testosterone levels below 224ng/dL.[55] Furthermore, men with lower baseline testosterone scores experienced more adverse sexual effects than males with normal range testosterone levels suggesting that baseline testosterone levels may be useful when considering treatment with 5ARI in patients with possible low testosterone. If treatment is needed with these agents, then proper counseling should be done before prescribing.

Use in female alopecia. Currently minoxidil is considered the first-line therapy for female pattern alopecia; however, finasteride and dutasteride are becoming more frequently used. The most significant adverse effect of 5ARIs in women who are or may become pregnant is the risk of birth defects in the male fetus. 5ARI exposure to pregnant women has been shown to increase the risk of abnormal male external genital development including hypospadias.[56] Due to this risk, 5ARIs are considered contraindicated in pregnancy with some authors advocating testing to rule out pregnancy before starting 5ARIs and concomitant reliable contraception use in nonpregnant women with childbearing potential.[57]

Early studies evaluating finasteride use in women focused on treating hirsutism. Falsetti et al[58] and Lumachi and Rondione[59] both reported decreased libido in 3 out of 22 women and 2 of 13 women, respectively, taking finasteride 5mg daily for 12 months. Headache was also reported in 2 of 22 women studied by Falsetti et al.[58] Ciotta et al in a randomized, single-blinded study of nine total women, reported decreased libido in two women and headache in four women followed for nine months.[60] Gastrointestinal discomfort was found in two independent prospective trials by Bayram et al[61] and Muderris et al[62] in 4 of 35 women taking finasteride 5mg daily.

To date, there are relatively few studies examining adverse effects of 5ARIs in women with hair loss. In a retrospective study by Kohler et al, 2 out of 12 women receiving finasteride 5mg daily reported decreased libido, dry skin, and slight acne.[63] Oliveira-Soares reported decreased libido in 4 of 40 postmenopausal women taking 5mg of finasteride daily.[64] Breast swelling and tenderness,[57] headache,[65] irregular menstruation,[65] dizziness,[65] and increased body hair[65] have also rarely been reported. Additionally, smaller studies[66,67] have shown finasteride to be well-tolerated with Carmina reporting no adverse effects in 12 hyperandrogenic, premenopausal women in a single-center, open-label controlled trial receiving finasteride 5mg orally daily.[68] Wong et al[69] and Lakryc et al[70] in two independent studies evaluating finasteride 5mg daily for six months found no adverse effects either. There are also several published case reports[71,72] and case series[73] with

similar results showing a lack of side effects.

Currently, there are no long-term studies evaluating finasteride or dutasteride use in women. In a recent study, Price et al followed 137 women aged 41 to 60 years for 12 months in a double-blind, placebo-controlled, randomized study conducted at eight investigational sites within the United States and found no statistical difference in side effects of finasteride 1mg daily versus placebo.[74] In fact, the only adverse event reported in the finasteride group was one case of folliculitis, which resolved with continued treatment.[74] Shum et al presented a case series of four women treated with finasteride 1.25mg daily for up to 2.5 years without reported side effects.[73] The longest trial of finasteride and dutasteride in women found during the literature search was three years by Boersma et al. Unfortunately, side effects were not discussed.[75]

5-alpha reductase inhibitors, such as finasteride and dutasteride, are becoming more commonly prescribed for women with hair loss. The limited number of studies indicate that 5ARIs are well-tolerated initially with no increased risk of malignancy or severe side effects; however, headache, gastrointestinal discomfort, and decreased libido are the most common side effects reported. Future long-term studies would be helpful to fully assess adverse events with chronic use.

CONCLUSION

Overall, 5ARIs are well-tolerated. Several large studies have found no increase in incidence of prostate cancer, but a possible increase of high-grade cancer when detected. No change in survival rate was seen. Currently, there is no direct link between 5ARI use and depression; however, several small studies have led depression to be listed as a side effect on the medication packaging. Sexual adverse effects, such as decreased libido, erectile dysfunction, and decreased ejaculate, have been reported in as many as 3.4 to 15.8 percent of men. Fortunately the effects are usually mild, with large studies suggesting the symptoms improve over time. 5ARI use in women is on the rise; however, to date there are very few studies evaluating their use in this specific population. Risks include birth defects in male fetuses if used in pregnancy, decreased libido, headache, gastrointestinal discomfort, and isolated reports of changes in menstruation, acne, and dizziness.

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