Editor's note: This English translation was done by a third party. The original report can be accessed here.

Paul-Ehrlich Institut Pharmaceutical Safety Bulletin
Depression and Sexual Dysfunction: Using finasteride to treat androgenetic alopecia
September 2018

The active ingredient finasteride is approved in Germany in a formulation of 1 mg per tablet for the treatment of early stages of androgenetic alopecia in men, and in a formulation of 5 mg per tablet for the treatment of benign prostatic hyperplasia. In post-marketing use, there have been reports of depression and sexual dysfunction, some of which persisted after finasteride was discontinued. The aim of the article is to summarize this topic and to inform doctors and patients about these side effects so that their possible occurrence can be considered in an individual benefit-risk assessment before starting finasteride therapy.

FINASTERIDE FOR THE TREATMENT OF ANDROGENETIC ALOPECIA

Androgenetic alopecia can be divided into different degrees of severity. Its prevalence increases with age and, according to the literature, rises to 30 percent in 30-year-old men and to 50 percent in 50-year-old men. Males of Asian and African origin are affected less frequently than males of European origin. A genetic predisposition is considered to be the main reason for its development. Androgenetic alopecia does not primarily have any significant health disadvantages, but can substantially impair individual well-being.

The active ingredient finasteride is approved in Germany for the treatment of early stages of androgenetic alopecia in men aged 18 to 41 in a formulation of 1 mg per tablet. It is taken once a day. Finasteride in this indication is not usually reimbursed by the statutory health insurance companies, so there are no publicly accessible prescription figures. Finasteride is also approved for the treatment of benign prostatic hyperplasia, but in a formulation of 5 mg per tablet. This article focuses on the 1 mg formulation for use in androgenetic alopecia.

INHIBITING THE CONVERSION OF TESTOSTERONE TO THE POTENT DIHYDROTESTOSTERONE

The fact that finasteride is effective in two different indications can be explained by its pharmacological principle of action, which is used in both indications. In the prostate and in the skin, testosterone becomes the potent one by the enzyme 5α-reductase androgen dihydrotestosterone (DHT). The normal growth of the prostate and its enlargement are dependent on DHT. Analogously, DHT also plays a crucial role in the development of androgenetic alopecia in the hair follicle. Finasteride inhibits DHT due to a structural structure similarity to testosterone competing with the enzyme 5α-reductase (Figure 2: original file).

PREFERENTIAL INHIBITION OF ISOFORMS 2 AND 3 OF 5αα-REDUCTASE

5α-reductase occurs in the human organism in three isomeric forms (types 1, 2 and 3).

– Type 1 is found in the hair follicles and sebaceous glands of the non-genital skin, in the liver and in expressed in some brain regions (e.g. hippocampus).
– Type 2 occurs in relatively high concentrations, especially in the prostate, the genital skin, the seminal glands, epididymis, liver and muscles.
– Type 3 was described in 2008, and is believed to be primarily in the brain, but also present in the liver, prostate and epididymis.

Finasteride preferentially inhibits isoforms 2 and 3 of 5α-reductase. The affinity for these two isoforms is said to be ten to 100 times higher than for isoform 1 of 5α-reductase. Because 5α-

reductase isoforms 1 and 2 are expressed in many tissues, inhibition of these enzymes has the potential to affect organ systems other than the skin and prostate.

REPORTS OF SEXUAL DYSFUNCTION USING FINASTERIDE

Results from clinical and epidemiological studies

Sexual dysfunction was observed in clinical trials investigating the use of 1 mg finasteride in the indication “androgenetic alopecia.” These occurred compared to placebo treatment with a frequency of ≥1/1,000 to <1/100 (uncommon). The clinical spectrum included erectile dysfunction and ejaculation disorder as well as decreased libido. These studies, however, have not reported on the persistence of these dysfunctions.

Yet a meta-analysis concluded that the clinical studies were not suitable for adequately recording sexual dysfunction and its persistence. In two epidemiological studies, no increased incidence of sexual dysfunction could be found in the use of finasteride compared to unexposed men with alopecia.

Prior information about the possible occurrence of sexual dysfunction can also be important for the occurrence or perception of this side effect. In one study, half of the patients receiving finasteride 5 mg were warned about the possibility of sexual dysfunction beforehand, while the other half were not. Evidence of persistent sexual dysfunction from case series and the spontaneous reporting system. In the post-marketing experience of finasteride for the treatment of androgenetic alopecia, there have been spontaneous reports of persistent sexual dysfunction (decreased libido, erectile dysfunction and ejaculation disorders) after discontinuation of the drug.

Similarly, an analysis of the FDA’s side effects database also showed that the use of 1 mg finasteride in the indication androgenetic alopecia could be associated with the risk of persistent sexual dysfunction due to disproportionate reporting rates. Furthermore, case series and smaller studies also indicated that sexual dysfunction could persist after discontinuation of finasteride. The persistence of sexual dysfunction after discontinuation of finasteride therapy ranged from months to years. In individual case reports, they lasted longer than ten years. A study based on electronic medical records calculated an average duration of persistence of 1,534 days. BfArM is aware of a case from Germany in which the reported sexual dysfunctions persisted for more than ten years after stopping the intake of finasteride in the indication “androgenetic alopecia.” A total of 38 case reports on sexual dysfunction when taking finasteride are available in Germany, for which the outcome is given as “not recovered/not resolved.” Twenty-five reports related to the indication androgenetic alopecia and two to the indication “benign prostatic hyperplasia.” No indication was given in eleven reports.

OCCURANCE OF DEPRESSION WITH THE USE OF FINASTERIDE

Post-marketing use of finasteride has also been associated with reports of depression. A retrospective case series reported on patients who experienced mood changes while using finasteride to treat androgenetic alopecia. However, these disappeared after discontinuation of finasteride. In another investigation, an uncontrolled prospective study, a significant increase in depressive symptoms was observed with the use of finasteride for the treatment of androgenetic alopecia. Symptoms did not persist after treatment discontinuation. Furthermore, there was a significantly higher rate of depressive disorders in former users of finasteride, in whom sexual dysfunction persisted. It has been suggested that persistent sexual dysfunction may also increase the risk of suicidal ideation. It has not been conclusively clarified to what extent depressive disorders occur reactively because of experiencing sexual dysfunction, or independently, also as a side effect of treatment with finasteride. On the other hand, it is conceivable that depressive disorders lead to sexual dysfunction. However, there are hardly any published studies on this question. The topic of persistent sexual and depressive disorders was

also taken up in various German media. In this context, the term post-finasteride syndrome was used, for which there is also a website.

PHARMACOLOGICAL PLAUSIBILITY OF THE OCCURRENCE OF DEPRESSION AND SEXUAL FUNCTIONAL DISORDERS USING FINASTERIDE

Finasteride can penetrate the blood-brain barrier and inhibit 5α-reductase there. Isoform 1 in particular occurs in the brain. Finasteride, however, inhibits this to a much lesser extent than the isoform. A certain prerequisite for the concept from the literature presented below is that this inhibition of isoform 1 and the associated hormonal changes in the brain are sufficient. 5α-reductase is of great importance for the synthesis of various neuroactive steroids in the brain. In this respect, it is reasonable to consider that their inhibition can be associated with side effects of different nature. In this context, it has been described that finasteride, by inhibiting 5α-reductase, reduces the concentration of various neuroactive steroids, not only those derived from testosterone, but also those derived from progesterone and deoxycorticosterone. This is also said to affect those neuroactive steroids that trigger increases in libido and sexual arousal.

It has also been suggested that a reduction in concentrations of those steroids that inhibit GABAergic excitation may play a role in the development of depressive disorders with finasteride treatment. One metabolite, allopregnanolone, seems to be of particular importance, which binds to the GABA receptor 18 and is said to develop anxiolytic effects. Thus, lower levels of allopregnanolone in the cerebrospinal fluid are found in depressed individuals than in non-depressed individuals.

Data from animal studies support this concept. In animal studies, finasteride inhibited the metabolism of testosterone and progesterone in the brain and reduced the formation of allopregnanolone. Furthermore, increased rates of depression were found in rats using finasteride. According to information in the literature, even a 1 mg dose leads to almost maximum inhibition of 5α-reductase. Similarly, the 1 mg and 5 mg formulations reduce dihydrotestosterone (DHT) formation to a similar extent. This could explain why the side effect profile is similar at both dosages. The dosage (low vs. high) also yeilds a different risk factor for the development of persistent sexual dysfunction than the duration of treatment with finasteride.

In summary, there is a pharmacological plausibility for the occurrence of the side effects observed during treatment with finasteride. However, it is still unclear how these symptoms can persist after treatment has been discontinued. A recent study compared 25 finasteride users with persistent sexual dysfunction after finasteride discontinuation, 13 finasteride users without sexual dysfunction, and 18 healthy men who had never used finasteride. There were no differences with regard to androgen deficiency, reduced peripheral androgen activity or persistent peripheral 5α-reductase inhibition. However, symptomatic finasteride users showed depressive moods as in depression.

RISK FACTORS FOR DEVELOPING DEPRESSION AND SEXUAL DYSFUNCTION WHILE USING 1 MG FINASTERIDE

The question arises as to whether there are risk factors for developing depression or (persistent) sexual dysfunction, or whether a group of patients can be identified that is particularly susceptible to developing such side effects. Not much data is available in this regard. In a study based on an online survey of men, more than 50 percent of the patients with persistent physical and psychological side effects had a previous psychiatric illness before starting therapy with finasteride. This group of patients could possibly be more susceptible to mental disorders when using finasteride. However, as the authors themselves point out, this study has relevant limitations inherent in the method. But another study concludes that finasteride should be used cautiously in patients at high risk of depression.

CURRENT INFORMATION IN THE PRODUCT INFORMATION

Sexual dysfunction, specifically erectile dysfunction, ejaculation disorder (including decreased ejaculate volume), decreased libido, and depression are listed as side effects in the finasteride product information for use in androgenetic alopecia and benign prostatic hyperplasia. It is noted that sexual dysfunction (decreased libido, erectile dysfunction and ejaculation disorders) may persist after discontinuation of therapy. A warning has recently been included in the product information and package leaflet of all finasteride-containing medicines that patients treated with finasteride should be monitored for psychiatric symptoms. Should a patient develop psychiatric symptoms on finasteride 1 mg, treatment should be discontinued and the patient advised to seek medical advice. Should a patient develop psychiatric symptoms on finasteride 5 mg, the patient should be advised to seek medical advice. Additionally, anxiety will be included as a new side effect in the product information for both dosages. In a current Red Hand letter dated July 5th, 2018, information was provided on the subject and the most recent changes to the product information were pointed out.

CONCLUSION

Spontaneous reports and publications from the literature report on the occurrence of depression and sexual dysfunction that occurred during the use of finasteride and can sometimes persist after finasteride has been discontinued. This applies to both the 1 mg formulation for the treatment of androgenetic alopecia and the 5 mg formulation for the treatment of benign prostatic hyperplasia. In the case of androgenetic alopecia, there are isolated case reports of persistent sexual dysfunction that persisted for more than ten years after discontinuation of therapy. The occurrence of the side effects (sexual dysfunctions including erectile dysfunction, ejaculation disorder and reduced libido as well as depression) is pharmacologically plausible. Physicians and patients should consider the possible side effects of therapy with finasteride, including depression and sexual dysfunction, listed in the product information to assess an individual benefit-risk assessment, especially in the indication “androgenetic alopecia,” before starting therapy with finasteride. Patients should be monitored appropriately during therapy.