

Finasteride and sexual side effects

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ABSTRACT

Finasteride, a 5-alpha reductase inhibitor, widely used in the medical management of male pattern hairloss, has been reported to cause sexual side effects. This article critically examines the evidence available and makes recommendations as to how a physician should counsel a patient while prescribing the drug.

Key words: Androgenetic alopecia, finasteride, sexual side effects

INTRODUCTION

Some of the commonly faced questions by a physician while treating a patient of pattern hairloss are about the possible sexual side effects caused by finasteride. Reports in the press, internet sites, and misinformation by practitioners of alternative medicine, all have contributed to this image of the drug, and has lead to apprehension in the minds of patients. Often even dermatologists seem to hesitate to prescribe the drug on a long term basis. This article examines this subject in the light of evidence available.

ROLE OF ANDROGENS IN PATTERN HAIRLOSS AND SEXUAL FUNCTION

Pattern hair loss in males is androgenic in etiology. Antiandrogens such as finasteride are therefore useful in the management of the condition. Androgens, especially testosterone increases the libido. Any drug which interferes with the action of androgens is therefore assumed, by the lay person, to induce impotence. However, the precise role of androgen in penile erection needs to be fully elucidated.^[1,2] Even an individual with low testosterone levels can achieve erection. In addition to androgens, visual, olfactory, tactile, auditory, and imaginative stimuli influence the libido. The penile erection is mainly under the control of parasympathetic nervous system. Ejaculation and detumescence require an intact sympathetic system.^[2,3]

The androgens testosterone and

dihydrotestosterone (DHT) have somewhat different actions. The enzyme, 5 α -reductase converts testosterone to DHT. It exists in two isoenzyme forms. While type I is predominant in liver, type II is predominant in prostate, seminal vesicles, epididymes, hair follicles, and liver.^[2] Within the hair follicle too, the two types have a different distribution. Type I 5AR, is present in the sebaceous gland, while type II 5AR is found on the outer root sheath of the hair follicles and dermal papillae. At all these sites, the testosterone is converted to DHT.^[4] Although the type II 5AR enzyme has a more significant role in pattern hairloss (and therefore mechanism of action of finasteride), the predominant enzyme in scalp skin is type I, largely because of localization to the sebaceous glands, which are large and plenty in scalp. Finasteride is a specific and competitive inhibitor of Type II 5-AR, and has therefore a selective action on hair follicles. Scalp skin DHT levels fall by more than 60% after administration of finasteride, thereby suggesting that a significant amount of DHT found in scalp skin is derived from both local DHT production and circulating DHT. Thus, the effect of finasteride on scalp DHT is likely because of its effect on both local follicular DHT levels as well as serum DHT levels. This explains why relatively small dose of finasteride may be adequate therapeutically.

PHARMACOKINETICS OF FINASTERIDE

The bioavailability of finasteride 1 mg following oral intake ranges from 26-170% with a mean of 65%.^[5] The average peak plasma concentration has been found to be 9.2 ng/ml measured 1-2

Access this article online

Website: www.idoj.in

DOI: 10.4103/2229-5178.93496

Quick Response Code:



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hours after administration. The bioavailability of finasteride is not related to food intake. Finasteride is extensively metabolized in liver by Cytochrome P450 3A4 enzyme subfamily and excreted both in urine and feces. The terminal half-life is approximately 5-6 hours in men between 18-60 years of age and 8 hours in men more than 70 years of age.^[5]

SIDE EFFECTS RELATED TO SEXUAL FUNCTION

A number of studies have looked at the problem of side effects caused by finasteride.^[6-11] These studies which are discussed below reveal that sexual adverse effects occur at the rates of 2.1% to 3.8%, erectile dysfunction (ED) being the commonest followed by ejaculatory dysfunction and loss of libido. These effects occurred early in the therapy and returned to normal on stopping or over a time on continuous use of the drug. The only causal relation between finasteride and sexual adverse effects is decreased ejaculatory volume because of predominant action of DHT on prostate.^[5]

A comprehensive review of a total of 73 papers on medical therapies for BPH was conducted, with a focus on the effects of different pharmacological agents on sexual function.^[6] The review revealed that finasteride is infrequently associated with problems of ejaculation (2.1-7.7%), erection (4.9-15.8%), and libido (3.1-5.4%).

The role of nocebo effect in the causation of ED due to finasteride has been investigated.^[7] Nocebo effect refers to an adverse effect that results from the psychological awareness of the possibility of the side effects, but is not a direct result of the specific pharmacological action of the drug. In this study, the group informed about the sexual adverse effects of finasteride reported increased incidence of ED, when compared to the group without information.^[7] The side effects were completely reversible in 5 days when the medicine was discontinued, confirming that nocebo effect has an influence in causation of side effects and suggesting the role of psychological factors.

Two studies in 1998 and 1999 showed that the incidence of these side effects with finasteride therapy was generally comparable to that observed with the treatment with placebo,^[8,9] and there was no evidence of dose dependency or increased incidence with longer therapy out to 12 months. In addition, the side effects ceased in patients even when they continued to receive finasteride.

A long term study showed that drug-related sexual side effects such as decreased libido, ED, and ejaculatory disorders occurred in <2% of men.^[10] These side-effects disappeared not only in all men who stopped the drug because of the side effects but also in most of those who continued therapy. The

incidence of each side effect mentioned decreased to $\leq 0.3\%$ by the fifth year of treatment with finasteride. The incidence of side effects were comparable to that of placebo both at one year and at 5 years.

A large prospective study in as many as 17,313 patients was conducted to look into the effects of finasteride and other covariates on sexual dysfunction as part of the analysis of The Prostate Cancer Prevention Trial (PCPT).^[11] Sexual dysfunction was assessed in the 17,313 PCPT participants who received finasteride 5 mg during a 7-year period. Finasteride increased sexual dysfunction only slightly even at 5 mg dosage (which is much higher than the 1 mg administered in pattern hair loss) and its impact diminished over time. The authors concluded that the effect of finasteride on sexual functioning is minimal for most men and should not impact the decision to prescribe or take finasteride. A recent review of the available literature too arrived at similar conclusions.^[12]

However, there are more recent studies, which seem to have documented contrary findings.^[13] A very recent study by Irwig MS *et al*,^[13] which has been widely reported in lay press and internet reported findings after conducting standardized interviews with 71 otherwise healthy men aged 21-46 years who reported new onset of sexual side effects associated with the temporal use of finasteride in which the symptoms persisted for at least three months despite stopping the drug. The study revealed that the subjects reported new-onset persistent sexual dysfunction (low libido, ED, and problems with orgasm) associated with the use of finasteride. The mean number of sexual encounters per month dropped and the total sexual dysfunction score increased for both before and after finasteride use ($P < 0.0001$ for both). The mean duration of finasteride use was 28 months and the mean duration of persistent sexual side effects was 40 months from the time of finasteride cessation to the interview date. However, there were many limitations in the study, such as small number of patients, selection bias, recall bias for before finasteride data, and no serum hormone analysis. The study recommended that physicians treating male pattern hair loss (MPHL) should discuss the potential risk levels with patients while prescribing the drug.

An important earlier study by Mella *et al*,^[14] conducted a systematic review of twelve randomized trials evaluated the efficacy and safety of finasteride therapy in 3927 male patients. Moderate-quality evidence was found for an increase in erectile dysfunction (RR, 2.22 [95% CI, 1.03-4.78]) and a possible increase in the risk of any sexual disturbances (RR, 1.39 [95% CI, 0.99-1.95]); However, the risk of discontinuing treatment because of sexual adverse effects was similar to that of placebo (RR, 0.88 [95% CI, 0.51-1.49]) (moderate-quality evidence).

A number of isolated case reports have also been published on the effect of low dose finasteride on DNA changes in sperms,^[15]

on motility, and sperm counts.^[16] These patients were under investigation for oligospermia and infertility when these findings were discovered. Significantly, these parameters improved after stopping the drug.

Another small study^[17] reported three cases of young men, who had used finasteride for five years, investigated for male Infertility. Semen quality was investigated by light microscopy to evaluate sperm concentration and motility, sperm morphology by transmission electron microscope (TEM), presence of Y microdeletions by PCR, and meiotic segregation by fluorescence *in situ* hybridization (FISH). TEM analysis revealed altered sperm morphology consistent with necrosis and FISH data revealed elevated diploidy and sex chromosome disomy frequencies. One year after the men had stopped the use of finasteride without receiving any other treatment, a recovery of spermatogenic process was observed. Motility and morphology improved whereas the meiotic pattern did not change.

Traish^[18] conducted a review of different published studies and concluded that altered sexual functions such as erectile dysfunction and diminished libido are reported by a subset of men receiving finasteride, raising the possibility of a causal relationship. The review suggested discussion with patients on the potential sexual side effects and possible alternate treatments before administration of the drug.

In view of the conflicting and continuing data and importance of the subject, the International Society of Hair Restoration Surgery (ISHRS) established a Task Force on Finasteride Adverse Event Controversies to evaluate published data and make recommendations. The taskforce posted their initial update on the subject as follows:

“To date, there is no evidence-based data substantiating the link between finasteride and persistent sexual side effects in the numerous double blinded, placebo controlled studies using finasteride 1 mg for hairloss. Reports of persistent sexual side effects have come from a variety of sources with some internet sites attracting individuals claiming to have sexual and psychological issues related to finasteride. While continued difficulty having erections after discontinuing finasteride has been reported in post-marketing surveillance the incidence of this problem remains unknown. This rare side effect is included in Merck’s patient product information in the United States, and in Public Assessment Reports of the Medicines and Health Regulatory Agency of the United Kingdom and the Medical Products Agency of Sweden.

The persistence of sexual side effects appears to be a rare event, and it has yet to be determined whether these recent reports represent a true causal relationship, or if they are simply coincidental and related to other factors such as the high

incidence of sexual dysfunction in the general population, and/or the placebo effect. Also, little data is available concerning the medical and psychological work-up of these patients to exclude other potential causative factors.

At the present time, the mechanism of interaction between the brain, 5 alpha-reductase metabolism, and hormones on sexual dysfunction is speculative and poorly understood. Clearly, this is a complicated issue, which overlaps with other disciplines in medicine such as Endocrinology, Urology, and Psychiatry. More research is needed to assess the actual incidence of side effects, to determine if there is a true causal relationship for persistent side effects and if so, to identify who may be at risk. We hope to participate in a multidisciplinary forum to further evaluate this topic.

Millions of patients have benefitted from finasteride with no side effects at all, or minimal and reversible side effects. It is important for the medical community to verify anecdotal reports and if necessary, conduct further studies so that accurate information may be given to our patients to enable them to make informed choices regarding the use of this medication.

The ISHRS Task Force on Finasteride Adverse Event Controversies is in the process of gathering information and forming an interdisciplinary panel to address these issues and to keep our ISHRS members informed regarding post-marketing adverse events.”

(available from <http://www.ishrs.org/articles/finasteride-announcement.htm> 11 apr2011)

Thus, the evidence available about the safety of the drug can be considered as questionable, but cannot certainly be ignored. The matter needs further systematic investigation and documentation. However, there is no doubt that to the lay man the prospect of impotence while taking a drug for hairloss is daunting, however theoretical and small the risk may be. The drug brochures mention the possibility of the side effect and the patient is often unable to distinguish between the effects of 1 mg and 5 mg. Several websites give a rather unfavorable opinion about the side effects, contrary to the evidence presented above. Several blogs also discuss the side effects, and individual and anecdotal experiences are highlighted and often exaggerated. Any patient who reads such reviews is understandably apprehensive, and therefore may stop therapy with in a few weeks of starting or, in other instances, do not start the treatment at all. Losing potency for gaining hair is not an attractive proposition, however remote that possibility is!

In view of this, it is very important to properly counsel patients about the treatment. In particular, the following facts need to be stressed:

1. The drug is probably the best available to treat androgenetic

- alopecia and the only one to address the root of the problem.
- Its effects are proven.
 - Several studies have shown its safety over long duration of administration. The dosage given (1 mg) is small and unlikely to cause side effects. Even in those cases where side effects were reported, the changes were found to be reversible.
 - There are very few effective alternatives to the drug and it is therefore important for the patient not to stop the drug unless he experiences any side effects.
 - The patient should contact the doctor for any advice, should he experience a side effect.
 - Most importantly, the intake of the drug is totally voluntary, as male pattern hair loss is only a cosmetic condition and it is entirely up to the patient to take or not take the drug.
 - The treating physician should provide full information about the drug to enable the patient to make an informed decision.
 - It is better to avoid the drug for any patient who has prior history of oligospermia, infertility, particularly if he is newly married and is trying to raise a family.

In addition, the author also feels that in patients who are apprehensive about the side effects, it is worthwhile considering administration of lower daily doses or staggered pulse doses of the drug, to enhance patient compliance. As discussed earlier, there is sound rationale for such regimens. Plasma half life of finasteride is 6-8 hours and tissue binding is 4-5 days.^[5] Doses of 0.2 mg are adequate to suppress both scalp skin and serum DHT levels. While 0.2 mg caused 55% DHT suppression, 5 mg per day achieved 69% DHT suppression. Efficacy has been demonstrated for all end points for finasteride at doses of 0.2 mg/day or higher, with 1 and 5 mg demonstrating similar efficacy that was superior to lower doses.^[8,9,19] The drug may be therefore initially administered at 0.5 mg daily or one tablet alternate days, to gain confidence of the patient and the 1 mg/day dosage may be restored once patient is comfortable about the drug. The value of such a regimen was shown in a preliminary study.^[20] However, further large, long term studies are needed to establish the value of such regimens.

ACKNOWLEDGEMENT

Dr. Anitha B, Dermatologist, Venkat Charmalaya, for correcting the draft.

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Cite this article as: Mysore V. Finasteride and sexual side effects. *Indian Dermatol Online J* 2012;3:62-5.

Source of Support: Nil, **Conflict of Interest:** None declared.