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J Mind Med Sci. 2016; 3(2): 99-107. ▸ **Review Article**

The postfinasteride syndrome; an overview

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Abstract

As a 5-α reductase inhibitor, Finasteride has proven effective in ameliorating two conditions documented to be androgen dependent, namely male androgenic alopecia and benign prostatic hyperplasia. Therapeutic results are maintained as long as the drug is administered, with treatment cessation generally leading to the return of symptomatology for each condition. In addition, during the therapeutic phase, several adverse effects have been reported, some of which persist long or indefinitely after treatment cessation, known as "post-finasteride syndrome."

Herein we present and discuss the most common finasteride side effects, along with a psycho-neuroendocrine rationale that could explain the persistence of many adverse effects after treatment cessation. Moreover, we argue that finasteride adverse effects occurring during finasteride administration should be delineated from postfinasteride side effects (encountered after treatment cessation), suggesting the need to be addressed separately within a therapeutic perspective. Until a tailored therapeutic approach of postfinasteride syndrome becomes available, we have noted that hand preference and sexual orientation seem to be useful as possible predicting factors for finasteride side effects and postfinasteride syndrome.

Finally, even though finasteride administration is considered relatively safe, literature data urges prudence. Specifically, recent studies report that some subjects receiving finasteride develop severe depressive episodes including suicidal thoughts, in part due to persistent sexual side effects.

Keywords: finasteride, adverse effects, post-finasteride syndrome, mental disorders, sexual dysfunctions

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Introduction

Finasteride is an extensively used medication for treatment of male pattern hair loss and benign prostatic hyperplasia. It is a type II and type III inhibitor of 5-α reductase, an enzyme that converts testosterone, progesterone and deoxycorticosterone to their corresponding metabolites. Even though therapeutic efficacy has been demonstrated through several studies, the research literature describes multiple adverse effects occurring during therapeutic phase (1, 2). Moreover, for some subjects, these effects have been described as "post-finasteride" syndrome, consisting in signs and symptoms that continue after treatment cessation (at three months or more) and that are related particularly to mental and sexual side effects (depression, anxiety, suicidal thoughts, erectile and orgasmic troubles, etc.) (3). Other adverse effects of postfinasteride syndrome are represented mostly by physical impairments, consisting in gynecomastia, chronic fatigue, increased fat deposition, secondary infertility, etc (4, 5).

Testosterone, progesterone, deoxycortico-sterone (and their corresponding metabolites) act as neurosteroids within the brain, being at least in part responsible for finasteride side effects and postfinasteride syndrome (6). Taking into account that cerebral activation through neurosteroids is generally related to lateralized process of the brain, finasteride adverse effects actually demonstrate a predictability related to hand preference and sexual orientation (7, 8). Regarding the therapeutic approach to postfinasteride syndrome, no specific therapy is yet agreed upon or recommended, current approaches being intended to address the specific signs and symptoms rather than taking the approach of addressing the issue as a broader neuro-endocrine disorder (9).

Discussion

Male androgenic alopecia is a moderately stressful condition that often warrants medical treatment, due to alteration of body image satisfaction. Benign prostatic hyperplasia (BPH/ benign enlargement of the prostate) is a relatively common condition in elderly men, being represented by a variable increase in volume of the prostate through prostatic hyperplasia. Both conditions are closely related to/ favored by action of dihydrotestosterone (DHTT). As a consequence, compounds interfering with DHTT synthesis (finasteride, dutasteride) have been investigated and introduced in clinical practice as therapeutic possibilities for these two conditions (10, 11).

Therapeutic approaches

Finasteride was initially approved for treatment of benign prostatic hyperplasia; five years later it was recognized for the second indication as a therapeutic approach for male androgenic alopecia (12).

Regarding benign prostatic hyperplasia, physicians usually prescribe 5 mg finasteride/day, which has proven effective in ameliorating specific symptoms related to prostate enlargement, such as night time and difficult urination (decreased flow, prolonged initiation etc.). These positive effects can be obtained after six months or more from finasteride administration; however, these

therapeutic results typically cease after finasteride cessation (at variable periods of time) (13).

Regarding androgenic alopecia, finasteride is recommended only in men. It is not approved for use in women due to risks of birth defects in the fetus. At a dose of 1 mg/ day, finasteride provides up to 20-30% improvement in hair loss after about six months of treatment. However, as in the case of benign prostatic hyperplasia, therapeutic benefits are maintained only so long as the drug is administered (14).

Thus, therapeutic recommendations of finasteride imply administration of the drug for a considerable period of time (six months or more, to become effective), for both benign prostatic hyperplasia and androgenic alopecia. During this prolonged period, several neuroendocrine imbalances occur, which form the basis for finasteride and postfinasteride adverse effects.

Pharmacology

Finasteride is a type II and type III inhibitor of 5-α reductase, an enzyme that converts testosterone, progesterone and deoxycorticosterone to their corresponding metabolites, represented by dihydrotestosterone, dihydroprogesterone, and dihydrodeoxycorticosterone respectively. Due to this action, the serum level of DHTT decreases after administration of 1 mg/day finasteride by about 65–70%, and up to 85–90% after 5 mg/ day finasteride administration (15, 16). Finasteride does not completely suppress 5-α reductase and DHTT synthesis, in contrast to dutasteride that, by inhibiting all three isoforms of 5α-reductase enzyme, decreases the DHTT plasmatic level up to 95- 99% (17). In addition to inhibition of type II and III of 5-α reductase isoenzymes, finasteride inhibits type II of the 5β-reductase isoenzyme, which also interferes in androgen metabolism (18). In humans, the 5a reductase isoenzymes are encountered in several tissues including brain, prostate, skin/ hair follicles, liver, seminal vesicles, testicles, and gastrointestinal tract (19).

Centrally, DHTT intervenes in metabolism of testosterone, progesterone and deoxycorticosterone, known as active neurosteroids able to interfere with the activation of the GABAA receptors in the brain (20). Hormonal abnormalities and GABA disruption induced by Finasteride administration are encountered in formerly-treated patients as well. Such men exhibit (at variable periods of time after the therapy) persistent disturbed levels of several active neurosteroids in cerebrospinal fluid and plasma: increased testosterone, 5a-androstane-3a, 17b-diol, pregnenolone, and decreased dihydrotestosterone, progesterone, dihydroprogesterone and allopregnanolone (21).

Adverse effects

The cerebral actions of finasteride (via hormones and GABA transmission) are usually responsible for most finasteride adverse effects, while peripheral effects (reducing androgen activity in the scalp and prostate) are responsible for its therapeutic action. Regarding finasteride side effects, these manifestations are the consequence of indirect actions of the drug within the brain (through hormonal imbalances, GABA, and other possible/ unknown mechanisms) that add to other adverse effects resulting from the direct action of

finasteride on the brain and peripheral organs (nausea, vomiting, allergies, etc.) (22).

Hormonal abnormalities and GABA imbalances induced by Finasteride are encountered in some patients after the therapy as persistent neuroendocrine disorders. As a consequence, finasteride side effects (as clinical expression of neuroendocrine disorders) are also encountered after drug discontinuation, in the form of so-called post-finasteride syndrome. The most frequent manifestations of post-finasteride syndrome are represented by sexual disorders (impotence, erectile dysfunction, decreased libido, ejaculation disorders) and mental/psychological impairments (depression, suicidal ideations, anhedonia, lack of mental concentration, etc.) (23). Other less common adverse effects are represented by: insomnia, premenstrual and postpartum dysphoric disorder, catamenial epilepsy, physical impairments (gynecomastia/ female-like enlargement of the breast, chronic fatigue, muscle twitching and atrophy, decreased body temperature, increased fat deposition/ elevated body mass index), cardiovascular impairments (palpitations, hypotension), dermatologic and oral manifestations (chronically dry, pruritus, rash, urticaria, erythema, purpura, gingival hypertrophy) (24). In addition, finasteride administration may affect tolerance to ethanol, with many former users of finasteride noting decreased tolerance for alcohol and disturbing effects from alcohol consumption (some men cease drinking completely) (25).

Finally, reducing the risk of prostate cancers dependent on androgens (namely low-grade prostate cancers) is due to DHTT decreasing, yet finasteride administration is associated to a greater extent with high-grade prostate cancers (which seem unrelated in its progression to androgens) (26, 27). In addition, finasteride lowers the PSA (prostate-specific antigen), which can be a serious impediment to the early detection of the prostate cancer (28). Although the incidence of male breast cancer has not increased from clinical trials (after 5 mg finasteride, daily), there have been case reports of breast cancer in men taking finasteride. Yet, studies indicate no causative relationship between finasteride administration and male breast cancer (29, 30). Preliminary studies on women show that 5-α reductase inhibitors induce sexual side effects also in women, even if this was reported in a lower extent (31).

The persistence of adverse effects

As noted above, the most frequent manifestations of post-finasteride syndrome are represented by sexual disorders and mental impairments.

Multiple interrelations exist between cognition and sexuality, due to the fact that both functions arise from the same set of environmental stimuli, peripherally sharing common somatic afferents as well as centrally sharing a common/ mental operator for environmental tasks (32, 33). These psychophysiologic/ neuroendocrine interrelations between cognition and sexuality are bidirectional such that, when are disturbed, they often generate a vicious neuro-endocrine reciprocating process (between depression for example, and sexual dysfunctions), with each being

able to maintain or to intensify the other (34). According to several studies, the postfinasteride syndrome is irreversible in some patients (35, 36).

Such looped mechanism could perhaps explain the persistence of finasteride side effects in the form of postfinasteride syndrome. Due to such bidirectional interferences, depression and sexual dysfunctions seem to be frequently associated, not only after finasteride administration but also in a multitude of other distinct situations (34, 37, 38).

The lateralized process of finasteride, in respect to biochemical action and adverse effects

The levels of dihydrotestosterone, dihydro-progesterone and dihydrodeoxycorticosterone decrease substantially in all men receiving Finasteride, effects found in both cerebrospinal fluid and plasma (21). Contrasting with this biochemical action, finasteride adverse effects are encountered only in a subset of men (39), most probably due to lateralization processes of the brain (40).

Based on several clinical studies, finasteride appears to decrease sexual function predominantly in right handed men (7, 8, 39, 40). In contrast, tamoxifen seems to induce adverse reactions (sexual side effects and depression) to a greater extent in left-handed men (41). In addition, imagistic studies with fRMI suggest that male sexual pheromones have an evident impact on homosexual men, activating predominantly the left hemibrain (left angular gyrus, left amygdala, left caudate nucleus, etc.). In contrast, yet in some way paralleling hormone effects, female sexual pheromones have an impact on heterosexual men (opposite orientation), activating in particular the right hemibrain, that is, the opposite hemisphere, including right hippocampus, right amygdala, right parahippocampal gyrus, etc.) (42- 44).

Extrapolating from such findings, it appears that finasteride adverse effects might be correlated with both hand preference and sexual orientation of the men taking the drug. Given that no proven, documented therapeutic approach of postfinasteride syndrome currently exist, it may be worthwhile to use hand preference and sexual orientation as possible predicting conditions for adverse effects so as to identify prior to therapy those subjects having a higher chance of developing such effects, should they receive finasteride (7, 8).

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Conclusions

Finasteride adverse effects (encountered during the drug administration) persist long afterward in some patients, the so-called postfinasteride syndrome (residual side effects). Even so, postfinasteride side effects must be viewed as distinct from finasteride adverse effects, at least due to two important grounds. First, finasteride adverse effects related to the direct presence/ action of the drug (nausea, postural hypotension, urticaria, rash,

etc.) cease after finasteride cessation. Second, many adverse effects that are induced due to indirect action of finasteride (via hormones and GABA receptors) persist after finasteride cessation. This suggests that finasteride merely triggers/ initiates the respective neuroendocrine disorders, which then have the capacity to self-maintain over time, eventually even evolving towards new and more complex neuroendocrine imbalances (not necessarily related to finasteride). For these reasons, we recommend that finasteride adverse effects and postfinasteride syndrome be addressed separately, as they belong to distinct pathophysiological entities and therefore require perhaps distinct therapeutic approaches.

Even though the general perspective is that finasteride administration is relatively safe, the research literature urges prudence. Thus, recent studies report that some subjects treated with finasteride for androgenic alopecia can develop severe depressive symptoms and even suicidal thoughts, in part due to persistent sexual side effects (9, 45). These adverse effects related to Finasteride/ postfinasteride are yet under study, a quite difficult evaluation due to the fact that both mental and sexual functions (usually affected in tandem by Finasteride) are still incompletely described from clinical and psychophysiological perspectives. In addition, the postfinasteride syndrome has been described and recognized only relatively recently, thus requiring further study regarding symptomatology and the best therapeutic approach (46).

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