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Finasteride side effects and post-Finasteride syndrome in male androgenic alopecia

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Abstract

Finasteride is in present a relatively frequent prescribed drug for male androgenic alopecia. The adverse effects reported by some patients seem to be notable, consisting of various (physical, mental/ neurological, sexual, etc.) manifestations which are encountered both during Finasteride administration and after treatment cessation (in the form of `post-Finasteride syndrome`).

The pharmacological action and the corresponding adverse effects related to Finasteride administration were investigated and published in literature through several and successive studies. In respect to psychiatric disorders, the most notable concern is related to depressive symptoms and suicidal thoughts among former users of finasteride with persistent adverse effects. Regarding genito-urinary symptoms, these are usually represented by gynecomastia, decreased interest in sexual intercourse/ low level of sexual desire and erectile dysfunction.

Finally, we viewed Finasteride side effects and post-Finasteride syndrome as distinct physio-pathologic entities, thus requiring possible distinct therapeutic approaches. Additional studies will be necessary, in order to further investigate the cerebral neuromodulation of the two relational (cognitive

and sexual) functions, both of which may be interfered by administration of hormones or by the corresponding compounds such as Finasteride.

Introduction

Male androgenic alopecia (known also as male androgenetic alopecia, male-pattern hair loss, or male pattern baldness) is the most frequent cause of hair loss, affecting up to 50% of men and 40% of women by the age of 50 (1). Usually, women lose hair in diffuse patterns over the top of the scalp, while men present a hairline/ balding delineation at the temples and vertex. Even so, multiple and relatively common (genetic, environmental, etc.) factors are involved, in both men and women (2). The most common treatment methods are represented by finasteride and minoxidil administration, with some studies also suggesting tretinoin, ketoconazole and spironolactone (3, 4).

Finasteride is a competitive inhibitor for 5 alpha-reductase enzyme, being currently used as a pharmacological therapeutic approach of male androgenic alopecia and benign prostatic hyperplasia. Administration of Finasteride is able to induce behavioral changes to animals, while in humans depressive symptoms were relatively frequently reported. For this reason, it was recommended for Finasteride to be carefully administered to patients presenting a history or a high risk to developing depression (5).

With respect to antiandrogenic treatment, in previously published studies it was investigated the sexual side effects of Finasteride and Tamoxifen, specifically as related to handedness of the participants (6, 7). The results showed that sexual hormones could exert a cerebral neuromodulation of the dorsal/ thalamic route, which is according to lateralization process of the brain (8). Moreover, these results and other partial published data delineated within the brain the ventral/ hypothalamic input (afferent) route, as a common neural network underlying both abstract cognition and sexuality (perhaps under pheromonal modulation) (9). It is in part a continuation of a previous published paper, which argues for somatic peripheral afferents that serve processes underlying cognition and sexual response (10).

A new study regarding Finasteride side effects and post-Finasteride syndrome in a sample of men with male androgenic alopecia was currently performed (8, 11). Taking advantage of data already published through a series of separate investigations, the intent of this paper is to consolidate these findings into a unitary perspective for understanding Finasteride action and the distribution of psychiatric and sexual side effects within the sample of men with androgenic alopecia. This perspective includes attention to both neuroendocrinological and neuropsychological systems that impinge upon both cognitive and sexual processing of information. Further empirical studies will be necessary to clarify the proposed perspective regarding cerebral neuromodulation of sexual function via hormones and pheromones, as a possible premise for understanding the existing cerebral interferences between cognition and sexuality.

Discussion

Finasteride is a competitive 5 alpha-reductase inhibitor for type II and III isoenzymes, preventing thus conversion of testosterone to dihydrotestosterone. As a consequence, the serum level of dihydrotestosterone decreases after Finasteride administration with about 65–70%. The partial inhibition of dihydrotestosterone synthesis is due to the fact that Finasteride doesn't inhibit the type I of 5 alpha-reductase isoenzyme (1, 2).

Decreasing the level of dihydrotestosterone, Finasteride contributes to reduction of $GABA_A$ activity (dihydrotestosterone helps activation of $GABA_A$ receptors), which has been involved in depression, anxiety and sexual dysfunctions. Yet, Finasteride decreases androgen activity in the scalp and prostate (8, 11).

1. Finasteride side effects

In a preliminary study regarding Finasteride side effects, the right-handed men reported on the most IIEF subscales either no effect or lower sexual functioning, while the left-handed men presented

either no effect or improved sexual function. These results differed substantially from previously published studies examining finasteride sexual side effects, a result that may have been due to the more precise way in which it was defined the "relevant sexual activity." Thus, the patients were alerted to the possibility of either positive or negative sexual effects, assessing separately the effects in right-handed vs left-handed patients. Handedness, as a possible proxy for cognitive style and lateralization process of the brain, appears to be a fairly reliable predictor when considering the sexual side effects of specific antiandrogenic compounds (6).

In that study, it was taken into account only the subject's hand preference, which is strongly related to anatomical dichotomy/ lateralization process of the brain. For this reason the samples were grouped based on right and left handedness, and the results interpreted accordingly—as mentioned above, right-handed men presented either no effect or lower sexual function while left-handed men reported either no effect or improved sexual function. However, the informational dichotomy related to hypothalamic route was not incorporated into this interpretation, because the potential role for this factor was unclear/ unknown to us at that time (6).

Subsequent investigations were then designed to investigate not only the anatomical but also the informational/ hypothalamic dichotomy of sexuality (examining relationships among sexual hormones, pheromones, cognitive and sexual laterality of information processing). This study was undertaken in part to identify factors that might be responsible for men showing no effect vs those showing either enhanced or diminished sexual function. Accordingly, it was found that the right-handed men demonstrated either no effect (group B, sensitive to female pheromones) or lower sexual function (group C, sensitive to androgens/ antiandrogens such as Finasteride), while the left-handed men noted either no effect (group A, sensitive to male pheromones) or improved sexual function (group D, which would be sensitive to estrogens/ antiestrogens such as Tamoxifen) (7, 8, 11). From this study, it was concluded that there is also an informational/ hypothalamic dichotomy that affects sexual response (in addition to

anatomical dichotomy), presumably with sexual pheromones acting on the hypothalamic input route but sexual hormones acting on the thalamic input route (7, 8).

2. Post-Finasteride syndrome

Multiple clinical studies show that Finasteride administration induces in some patients various (physical, mental/ neurological, sexual, etc.) adverse effects, which may be either reversible or persistent after treatment cessation. When persistent (even at three months after medication cessation), the respective side effects are named `post-Finasteride syndrome` (12). We consider that the `post-Finasteride syndrome` should be differentiated from side effects occurring to Finasteride (during the drug administration), even if symptoms are relatively similar and successive during treatment vs posttreatment. On one hand, patients treated for male pattern hair loss with finasteride show, after discontinuation of the drug, a persistent altered level of some neuroactive steroids in cerebrospinal fluid and plasma (13). On the other hand, in preliminary studies Finasteride side effects (occurring during Finasteride administration) occurred especially to right handed men, while the post-Finasteride syndrome (occurring after Finasteride administration) were encountered not only in androgenic-sensitive (right handed) men but also in estrogenic-sensitive (left handed) men (11).

In order to understand this new approach, we can resort to a suggestive example. Thus, selective serotonin reuptake inhibitors (SSRIs) increase serotonin available at serotonergic synapses. In contrast, tianeptine is a drug that decreases serotonin at serotonergic synapses. Yet although the pharmacologic actions of the two drugs are opposite, both drugs have the capacity to decrease clinically depressive symptoms (14). Along similar lines, finasteride side effects (occurring during finasteride administration) and post-finasteride syndrome (occurring after finasteride administration) may share common clinical manifestations, yet this does not require that these two conditions act similarly with respect to pharmacologic/ physio-pathologic mechanisms.

Finally, it was found that the post-finasteride symptoms were relatively similar after various doses, administered for two distinct medical conditions (male pattern hair loss and benign prostatic hyperplasia) (15). In subjects with benign prostatic hyperplasia, the post-finasteride syndrome seems to lesser in magnitude, due perhaps to the fact that such patients have greater tolerance to treatment (a better adaptation/ a disease with a greater impact on the health), or due to an increased mean age (with possible implications on lifestyle). Such factors could be assessed and controlled in future studies.

Conclusions

Male androgenic alopecia is a moderately stressful condition for which patients often resort to a medical assistance, due to the fact that it seriously diminishes body image satisfaction. Early stages of the hair loss can be slowed or reversed through medication; finasteride being one of the drugs that are used for this condition, with a proved efficacy.

Even if at first glance it might seem that the finasteride use is pretty safe, in fact it is not so. Recent studies show the fact that androgenic alopecia may actually underlie to depressive symptoms and suicidal thoughts among former users of finasteride with persistent sexual side effects (16). These side effects of finasteride are still under evaluation, a relatively difficult process due to the fact that physiologies of mental and sexual functions (often affected by finasteride) are only now being clarified. On the other hand the post-finasteride syndrome is only a recently recognized entity, which needs to be further studied with respect to symptomatology and therapeutic approach.

The current paper, we believe, offers a better understanding of Finasteride action as well as prediction of sexual side effects; furthermore, our current line of investigation aimed at specifying factors related to the distribution of sexual side-effects related to Finasteride administration could help develop models regarding the neural processing of sexual information as well as the representation of sexual information in the mind that ties to both sexual desire and arousal. Such ideas remain under exploration.

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