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Review

Finasteride as a model for personalized medicine

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Abstract

The side effects of Finasteride are currently a subject of controversy. Some studies report minor or acceptable adverse effects, which decrease after a variable period of time so that they do not necessitate terminating Finasteride administration. However, several clinical and neuro-endocrine studies show that some adverse effects persist indefinitely in the form of post-Finasteride syndrome, even after the drug cessation.

This paper presents a possible explanation for these inconsistent findings. First, the study design of either informing or not informing patients prior therapy about possible adverse effects can influence the incidence and magnitude of reported adverse effects. Second, structural and information dichotomies of the brain generate four distinct neuronal networks, which are activated through specific cerebral neuromodulators and that are able to support four distinct minds within an individual body.

As a conclusion, the "mind psychophysiology" and the corresponding mental impairments differ across individuals, such that not only the prediction of adverse effects should be addressed from a more individualized medical perspective, but also the therapeutic strategies could be tailored to the four distinct mental profiles described. It is a personalized approach that would be applicable to several interrelated domains of neuroscience, like psychology, psychiatry and sexuality. Finally, this perspective may represent a starting point for a more individualized understanding of mental events, perhaps even a step forward in the understanding of the mind-body problem.

Keywords: Finasteride, adverse reactions, personalized medicine, psychology, psychiatry, sexuality, post-Finasteride syndrome

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Introduction

Finasteride (a 5-α reductase inhibitor) is currently an extensively-used medication for two distinct conditions strongly related to androgens: male androgenic alopecia and benign prostatic hyperplasia. Therapeutic results are maintained only as long as the drug is administered, most patients losing the medical and/ or aesthetic benefits from therapy once the drug is terminated. Moreover, during the therapeutic phase, some patients report variable adverse effects which either diminish during or after therapy in some patients (1), or persist indefinitely in others in the form of post-finasteride syndrome (2).

The most frequent manifestations of post-finasteride syndrome are represented by sexual disorders and mental/ psychological impairments. Interestingly, cognition and sexuality show several interrelations which become apparent not only during normal functioning but also during disease states. Both cognition and sexuality, for example, depend on the same set of environmental stimuli and centrally are presumably supported by a common/ mental operator, namely the attentional focus. The existing psychophysiologic/ neuroendocrine interrelations between cognition and sexuality are bidirectional — cognition affecting sexual response and vice versa— and to a large extent are responsible for the persistence of Finasteride adverse effects after treatment cessation (3).

Even though some data suggest that Finasteride side effects (occurring during the drug administration) should be differentiated from post-finasteride syndrome (registered after treatment cessation) (4), they are relatively similar and both are characterized by mental impairment (anhedonia, depression, lack of mental concentration, suicidal ideations, etc.) and sexual disorders (decreased libido, impotence/ erectile dysfunction, ejaculation disorders, etc.). Other adverse effects include gynecomastia, secondary infertility, chronic fatigue, increased fat deposition, etc (3-5).

Based on previous reports, finasteride appears to decrease sexual function predominantly in right handed men, while tamoxifen—an estrogen modulator—induces adverse reactions especially in left-handed men (6, 7). These different effects appear to result from a lateralized neurosteroid activation process in the brain. As a consequence, finasteride adverse effects could be predicted based on this structural dichotomy of the brain, using such lateralized functions as hand preference and sexual orientation as pretreatment delineating elements (8, 9). Beyond this structural dichotomy, the human brain also presents a functional/ informational dichotomy, with sexual hormones acting primarily upon concrete mental functioning, and sexual pheromones modulating abstract mental functioning (10). Thus, patients having a strong pheromonal activation of sexuality would present a low or minimal risk for developing adverse reactions to Finasteride administration.

As a preliminary conclusion, the incidence and magnitude of Finasteride side effects depend to a great extent on the structural and informational dichotomies of the brain (11), which delineate within the brain four distinct minds (12, 13). The structural dichotomy was partly addressed by our recent report indicating that biological parameters such as hand preference and sexual orientation are linked to brain lateralization (8, 9). The informational dichotomy will be investigated in the near future using specific psychological tests/ tools that enable differentiation between abstract and concrete mental functioning.

This paper presents the most relevant findings regarding the distribution of Finasteride side effects among patients, and argues for the necessity to adopt an individualized approach to the administration of Finasteride in male androgenic alopecia and benign prostatic hyperplasia.

Discussion

Concerns related to Finasteride side effects

Five years ago, a study performed on thirty-three men (with right-handed participants having lower overall IIEF scores than left-handed participants) found that left-

handed men showed better post-treatment scores than right-handed men on IIEF-assessed sexual functioning following Finasteride administration. Interaction effects were found on five subscales—erectile function (EF), intercourse satisfaction (IS), orgasmic function (OF), sexual desire (SD), and overall satisfaction (OS)—such that left-handed men showed increased post-treatment scores whereas right-handed men showed decreased post-treatment scores (6). Two years later, a pilot study revealed that administration of Tamoxifen for male breast cancer induced sexual side effects especially in left handed participants. Thus, a main effect for tamoxifen was found on all five subscales, with tamoxifen decreasing sexual functioning in both groups of men. Interaction effects were found on three IIEF subscales (OF, SD, and OS), such that left-handed men showed greater decreased sexual function under tamoxifen than right-handed men (7).

Studies related to finasteride have shown that the frequency and magnitude of adverse effects are higher when patients are informed about possible adverse effects and lower or absent (even ignored) when not informed (14). As a consequence, the reported adverse effects depend on multiple subjective and objective factors, including study design, the structural dichotomy of the brain (lateralization), and the informational dichotomy of the brain. Not surprisingly, recent reports have advanced the idea that hand preference and sexual orientation (both strongly related to brain lateralization) might be used as possible predictors for finasteride adverse effects in male androgenic alopecia (8, 9). Other data suggest that beyond just predictability, hand preference and sexual orientation might also be used for therapeutic guidance on Finasteride administration, taking into account both structural and informational dichotomies of the brain (11).

Increasing concern for the predictability and management of Finasteride side effects is justified by the severity of some of its adverse events (2). Thus, recent data indicate that androgenic alopecia and benign prostatic hyperplasia can lead to depressive symptoms and suicidal thoughts among former finasteride users who develop persistent sexual side effects (15-18). These side effects are yet under evaluation, a relatively difficult process due to the fact that the pathophysiology of mental and sexual functions (often affected in tandem) are not fully documented. Moreover, the post-finasteride syndrome is only recently recognized as a distinct clinical entity, requiring further study with respect to the psycho-neuroendocrine processes involved (3, 4).

In support of this, a very recent study has shown that some patients treated with finasteride for male pattern hair loss develop post-finasteride syndrome, in the form of persistent sexual side effects, anxiety, depression, and cognitive impairments. These persistent effects are associated with changes in steroid levels in cerebrospinal fluid, represented by decreased levels of pregnenolone, progesterone, dihydroprogesterone, dihydrotestosterone, 17beta-estradiol, and increased levels of dehydroepiandrosterone, testosterone and 5alpha-androstane-3alpha,17beta-diol (19). These neuro-endocrine abnormalities are complicated by the finding that many former users of finasteride experience decreased alcohol tolerance due to cerebral interference of Finasteride with $GABA_A$ receptors (20).

Even though some finasteride side effects appear severe, suggested resolution varies from an extreme therapeutic approach (involving replacement of Finasteride with the more active compound Dutasteride) (21), to an exclusive pharmaco-vigilance perspective imposing prudence and drug substitution (18). Other authors consider that finasteride should be retained as a valid therapeutic approach for androgenic alopecia, due to two important reasons (22). First, dihydrotestosterone has important physiological roles within the body (23) such that partial suppression of this hormone (specific for Finasteride) is preferred over complete suppression (the case of Dutasteride). In addition, replacement of Finasteride with Dutasteride might exacerbate adverse effects. Yet, the therapeutic action of Finasteride could be enhanced using a synergistic compound, such as minoxidil for androgenic alopecia (24). Second, even if Finasteride side effects are more frequent or severe than

initially assumed, these adverse effects could be anticipated through a screening of patients on *a priori* criteria (8, 9). To understand these criteria, namely why some men respond with severe adverse effects and others do not, it is necessary to understand the structural and informational dichotomies of the brain.

Informational dichotomy of the brain

The classical input system for information coursing to the brain is related to the dorsal system of attention, with environmental stimuli/data being transmitted to the thalamus, the somatic cortex, and, further, the autonomic nervous system (ANS). The ANS supports autonomic processing of data/information as well as elaboration of specific responses, which are externalized in the form of motor/ verbal events through the pyramidal motor system. From a psychological perspective, this circuit of information supports the concrete mind. In parallel with, yet mutually exclusive of, this concrete mind is the abstract mind, supported by the ventral system of attention, receiving therefore data through the ventral hypothalamic input route (25). From here information is sent first to the autonomic nervous system of the brain and subsequently to the somatic nervous system of the brain (25, 26).

Recent data suggest that sexual hormones activate the concrete mind, while sexual pheromones activate the parallel, mutually exclusive, abstract mind (11, 27). Thus persons depending on sexual pheromones for activation should be unaffected by antihormonal compounds. Due to limited space herein, the psycho-physiological elements delineating abstract and concrete minds are discussed in a forthcoming paper. Various psychological tests/assessments should enable identification of individuals with a concrete psychological profile, specifically those individuals having an increased risk for adverse effects to finasteride.

Structural dichotomy of the brain (lateralization)

The human brain is structurally divided by the median plane into two opposite/ symmetric (left and right) hemibrains. If data reception is ensured by both hemibrains, processing of information occurs usually in only one hemibrain (defined as the dominant hemibrain). Accordingly, the opposite/ non-dominant hemibrain would support only the neurological connection (inputs/ outputs) between dominant hemibrain and peripheral receptors/ effectors (26). This asymmetric functioning of the brain has been demonstrated for multiple cerebral functions (hand preference, language, memory, affection, sexuality, etc.) and is ensured through the intervention of different neuromodulators that direct environmental information towards either the left or the right hemibrain (26). In the absence of this lateralization, the two distinct hemibrains would receive and process distinct responses to the same internal (memory/ imagination) or external data, a competitive situation that would be physiologically and psychologically counterproductive due to the possibility of conflicting outputs (26, 28).

Structural and informational dichotomies of the brain

Based on such lateralized functioning, estrogens would modulate environmental inputs especially toward the right and concrete hemibrain, while androgens would channel the same environmental information/ inputs toward the left and concrete hemibrain (11). For this reason, administration of antiestrogens such as Tamoxifen induces sexual impairment especially in left handed men, while administration of Finasteride or Bicalutamide induces sexual impairment predominantly in right handed men (6, 7, 29).

In a similar lateralized manner, female sexual pheromones would activate (in heterosexual men) especially the right and abstract hemibrain (right hippocampus, right parahippocampal gyrus, etc.). In contrast, male sexual pheromones would activate in homosexual men predominantly the left and abstract hemibrain (the left angular gyrus, left caudate nucleus, etc.). Imaging studies show that heterosexual men and homosexual women (lesbians) present a rightward volumetric cerebral asymmetry (their connections being

more widespread from the right amygdala), while homosexual men and heterosexual women display more widespread connections from the left amygdala (30-34).

The importance of an individualized approach to the administration of Finasteride

According to previous findings, the "mind psychophysiology" and its corresponding mental impairments differ across individuals, not only resulting in differential adverse effects as described, but also suggesting the need for individualized therapeutic strategies in the future. This approach might serve as one starting point for taking a more individualized approach to the understanding of mental events, and furthermore may represent a step forward in unraveling the mind-body problem.

Specific to the current topic, aggregation of subjects (according to specific individual parameters) in groups having either predictably high or low risks for specific adverse effect might represent one step toward this more personalized medical approach. In other words, administration of Finasteride should be acceptable to those having a low risk for developing adverse effects. But those falling into the high risk category for finasteride side effects should avoid taking the drug, especially given that some adverse effects persist after treatment ceases and no specific measures/consensus exists for treatment of post-finasteride syndrome.

Conclusions

Finasteride side effects are generally related to several domains of neuroscience, including psychology, psychiatry, and sexuality. Unfortunately, such disciplines are not yet fully elaborated and integrated, such that the reporting of adverse effects induced by drugs acting on the brain (interfering with cerebral neuromodulators) is not yet standardized.

Previously we presented in detail the structural (left vs. right) and informational (abstract vs. concrete) dichotomies of the brain, dividing the brain into four distinct neuronal networks able to generate four distinct psycho-physiologic profiles (12, 13). These neuronal networks are generally incompatible with one another, being activated through the intervention of distinct (cognitive or sexual) neuromodulators. As a consequence, the "mind psychophysiology," therapeutic approach, and possible adverse effects to drugs interfering with the brain should be addressed in a more individualized manner, taking into account the mind (structural/ informational) diversity described in this paper.

Structural diversity was addressed through individual elements strongly related to the lateralization process of the brain, like hand preference and sexual orientation. Informational diversity should become quantifiable through specific psychological tools useful for patient screening/ allocation to a specific (abstract and concrete) mind profile responsive to either sexual hormones or pheromones.

While abstract ideas are able to exert control over our biological/physical existence, yet unexplained is the manner in which these abstract-immaterial data interfere with the material/physical nature of the brain. Several Finasteride side effects (depression, low libido, etc.) are strongly related to our conscious domain/ attentional focus, so a better understanding of these adverse effects may inevitably lead to a better understanding of the mind psycho-physiology.

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