Persistent Sexual and Nonsexual Adverse Effects of Finasteride in Younger Men

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ABSTRACT

Introduction. Recent studies have reported persistent sexual and nonsexual adverse effects associated with the 5α-reductase inhibitor finasteride.
Aims. The first aim was to review the clinical studies of persistent sexual and nonsexual adverse effects associated with finasteride in younger men who took the medication for treatment of male pattern hair loss. The second aim was to place these findings into context with what is known from basic and clinical studies about the hormones and neurosteroids affected by finasteride.
Methods. Relevant published literature on the topic was reviewed. Clinical symptomatology in humans was correlated with findings from rodent models to investigate possible underlying mechanisms.
Main Outcome Measures. Persistent sexual and nonsexual adverse effects were summarized.
Results. Two clinical studies have described persistent side effects associated with finasteride use in otherwise healthy younger men. The sexual side effects are typically present in multiple domains that include erectile dysfunction, low libido, and decreased orgasms. Erectile dysfunction may be related to low levels of dihydrotestosterone, which has been shown to be an important androgen in both human and animal studies. Nonsexual side effects include depression and decreased alcohol consumption that are linked to the neurosteroid allopregnanolone in both human and animal studies. Three men with persistent side effects associated with finasteride were found to have lower plasma and cerebrospinal fluid levels of several neurosteroids.
Conclusions. Persistent adverse effects of finasteride in younger men include erectile dysfunction, low libido, lack of orgasms, depression, and decreased alcohol consumption. One study has found lower levels of several neurosteroids in this population. Out of the various persistent side effects, erectile dysfunction and decreased alcohol consumption have been the most studied in animal models. Further research is needed on who is susceptible to the persistent adverse side effects of finasteride and on the underlying mechanisms of the medication. **Irwig MS. Persistent sexual and non-sexual adverse effects of finasteride in younger men. Sex Med Rev 2014;2:24–35.**

Key Words. Depression; Erectile Dysfunction; Finasteride; Neurosteroids; Propecia; Side Effects

Introduction

The 5α-reductase inhibitor finasteride was approved for treatment of benign prostatic hyperplasia (BPH) in 1992 and for male pattern hair loss in 1997. It was well established through multiple randomized, controlled trials (RCTs) that the medication was associated with adverse sexual side effects such as low libido, erectile dysfunction, and ejaculatory disorders. The studies generally concluded that the incidence of sexual side effects was small and that these effects went away over time with or without continuation of finasteride.

Nonetheless, close analysis of the RCTs of finasteride reveals unanswered questions regarding the duration of sexual side effects and subjects who withdrew from the studies because of adverse sexual effects. In a 6-year RCT in which only the first year was double-blinded, rates of withdrawal for a sexual adverse event were 0.2% for placebo, 0.7% for finasteride 1 mg, and 1.3% for finasteride 5 mg in the double-blind phase [1]. Information is lacking on whether the sexual adverse events ever resolved in these men. Similarly, the PROscar Safety Plus Efficacy Canadian Two year (PROSPECT) Study was an RCT of finasteride 5 mg for BPH that did

not address the issue of resolution of adverse sexual disorders [2]. This study stated "regardless of the treatment group, the symptoms of sexual dysfunction tended to be of long duration." A third example comes from the Proscar Long-term Efficacy and Safety Study that was a 4-year RCT in 3,040 men with BPH [3]. Withdrawal from this study, specifically for an adverse sexual event, occurred in 4% of the finasteride group and 2% of the placebo group. Sexual adverse events resolved in 50% of the finasteride group and in 41% of the placebo group. The authors attribute these findings to "the natural history of sexual dysfunction in this patient population and a substantial placebo effect." Whether the adverse effects ever resolved has not been published.

The RCTs for BPH have been included in this section because they have been much larger and longer than the few RCTs for male pattern hair loss that may be underpowered to detect less common adverse events. One RCT for male pattern hair loss involved a different 5α-reductase inhibitor, dutasteride, in which there was a case of a young man with a persistent sexual side effect [4]. However, the etiology was not clear: "in 1 subject decreased libido continued after therapy had been stopped and was presumed by the subject to be unrelated to the trial or drug therapy."

In the case of Propecia® (Merck, Sharp & Dohme Corp., Whitehouse Station, NJ, USA), the warning bells began to ring when post-marketing reports of persistent sexual side effects were reported by two regulatory agencies in Europe. In 2008, the Swedish Medical Products Agency patient information leaflet listed "persistent difficulty having an erection after discontinuation of treatment." In 2009, the Medicines and Healthcare Products Regulatory Agency of the United Kingdom similarly reported "difficulty having erection after stopping treatment" [5]. In 2011, two independent research groups published the first reports of persistent sexual side effects associated with finasteride in younger men [6,7]. The novelty in these reports was the concerning finding that adverse effects of a medication can persist for several years after its discontinuation. While uncommon, irreversible side effects have been described with other medications, most notably the phenothiazines used for the treatment of schizophrenia [8]. The specific neurotoxic effects of this class of medication were tardive dyskinesias that primarily consist of facial grimacing and movements of the mouth, tongue, and jaw.

This review focuses on the population of younger men who have taken finasteride 1 mg (or a similar dose) for male pattern hair loss. Studying the sexual side effects of the medication in a younger population is less prone to methodological problems than using an older population in which aging and comorbidities are confounding factors in sexual dysfunction. Nonetheless, there is no reason to believe that the effects observed in younger men would not also be observed in older men. In fact, one such study of finasteride 1 mg showed that middle and older age men also report sexual side effects [9].

First Studies

In 2011, Traish and colleagues published a report about an otherwise healthy 24-year-old man who began finasteride 1 mg for treatment of male pattern hair loss in 1999 [6]. Within 2–5 days on the medication, he developed testicular pain, low libido, inability to achieve an erection, decreased concentration, and depressed mood. Despite these symptoms, he continued the medication for approximately 1 month in the belief that the symptoms would be temporary. Several years later, he subsequently sought treatment at sexual medicine clinics in both the United States and Denmark, and continued to have persistent sexual side effects 11 years after having stopped finasteride. The remainder of this article is a review of the side effects of 5α reductase inhibitors on libido, erectile function, ejaculatory function, gynecomastia, and depression.

The second study was a case series of 71 otherwise-healthy younger men aged 21–46 who developed persistent sexual side effects temporally associated with the use of finasteride [7]. None of these men had any baseline sexual dysfunction nor did they suffer from any medical or psychiatric conditions prior to using finasteride. This study was conducted principally via telephone and Skype interviews as subjects lived across the United States and around the world. Sexual function was assessed using the Arizona Sexual Experience Scale, a validated instrument in which subjects assessed their sexual function in five domains using a 6-point Likert scale that ranged from hyperfunction (1) to hypofunction (6) [10]. Sexual dysfunction correlated to a total score of ≥19, if any one item was ≥5, or if any three items were ≥4. This instrument was selected based on its high reliability coefficients for internal consistency and test-retest forms, accuracy, and brevity [11]. The mean total scores