COMMENT

Comment on "The post-finasteride syndrome: possible etiological mechanisms and symptoms"

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Leliefeld et al.'s recent IJIR 2023 article, "The post-finasteride syndrome: possible etiological mechanisms and symptoms," as well as recent posts to sex therapy society list serves discuss a "post-finasteride syndrome," regarding both the active use and potential consequences of discontinuing finasteride use for male pattern baldness [1]. There has been much confusion the last number of years regarding this issue. Subsequently, it seems appropriate to offer IJIR readers some additional background information, as my own experience with this syndrome is somewhat unique. I have treated several men presenting with this syndrome successfully using the Sexual Tipping Point® model [2]. More importantly as a consultant to the law firm that represented Merck & Co, Inc. (Propecia's™ USA manufacturer), in decade long lawsuits regarding 5α-reductase inhibitors (5αri), I was able to review individual plaintiff's medical records as well as summary data from over a thousand cases.

Merck introduced Propecia™ in 1997, as the first 5-alpha reductase inhibitor (5αri) to be approved for an androgenetic alopecia indication, which was followed by dutasteride's approval for that indication in 2001 [3]. Merck had investigated reports of several finasteride treated benign prostate hypertrophy (BPH) patients obtaining surprising new hair growth. Subsequently, Merck marketed a 1 mg dose of finasteride (Proscar™ relabeled as Propecia™) to dermatologists, who regrettably (in my opinion) did not receive adequate education regarding a proper informed consent process, given the drug's well known side-effect profile. Consequently, many of those dermatologists provided less than adequate informed consent regarding sexual side effects. Of course, this was a very different class of drugs from what dermatologists were typically used to prescribing. The dermatology patients (unlike BPH patients) were usually much younger men, concerned about their appearance (hair loss as viewed by themselves and others), and thus understandably were deeply concerned by side effects that included diminished sexual capacity. Some were sufficiently disconcerted that they almost immediately discontinued taking the drug. The vast majority of those who discontinued the drug recovered sexual function and merely adjusted to progressive balding like previous generations of men. However, a few had a profoundly different and negative experience.

Initially, the "post-finasteride syndrome (PFS)," as it became known, surprised, and confused many physicians. Despite the known potential side effects, relatively few complaints and/or discontinuations were occurring in the benign BPH population using Proscar™, versus those using Propecia™ for male pattern hair loss (androgenetic alopecia). That was despite the finasteride dosing for BPH is initially prescribed at 5 mg, and often titrated up to 10 mg, while Propecia™ is prescribed at a much lower dosage of 1 mg. What might account for the difference in reported side effects, especially given the much lower dosing indication? Three reasons are currently accepted as the presumed explanation: (1). Men with BPH are typically much older and usually *more distressed* by sleep disturbance (urinary frequency and urgency) caused by BPH than the drug's potential sexual side effects. (2). It appears there may have been more frequent and better-informed consent provided by Proscar™ prescribing urologists (the sexual side effects being well known to them), compared to dermatologists who were the first to begin prescribing Propecia™. (3). Phosphodiesterase Type 5 Inhibitors (PDE5i) (e.g. Viagra®) that often help assist with diminished erectile side effect (not so much the ejaculatory disorders) were more likely to be proffered by prescribing urologists if the patient requested it, or if the patient later complained about a sexual issue. However, some patients and some physicians as well as their attorney's, were convinced the PFS was a direct physiological long-term consequence of having taken Propecia™.

The first Propecia™ lawsuits were filed against Merck in the USA in February 2011. Nonetheless, the number of men using various formats of finasteride continued to increase dramatically with the rise of online pharmaceutical distribution networks/companies (especially during and post-Covid). While the number of men who reported a PFS increased globally, the prevalence of this syndrome is small in comparison with the number of men who both use the drug regularly and what typically happens when its use is discontinued. For the men who have discontinued for reasons of side-effect, a very real "Post-Finasteride Syndrome" may indeed occur for a smaller minority of those men who discontinued the drug.

The syndrome was initially identified mainly by complaints of sexual side effects, (erectile dysfunction, decreased libido, and diminished ejaculatory force, volume, etc.). Later, neurologic, physiologic, hormonal, and psychiatric (cognitive "fog," depression, anxiety, etc.) symptoms were being reported. *While the precipitating cause was likely the finasteride, the factors maintaining the "Post-Finasteride Syndrome" have not been empirically established definitively*. To date finasteride has never been shown to conclusively cause permanent damage physically that in and of itself, would account for the continuation symptoms. Some

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studies showing evidence that 5αri not only inhibits the conversion of testosterone to 5α-dihydrotestosterone (DHT) in the prostate and the scalp, but also in other tissues, have been offered as a purported explanation to account for the PFS [1]. A pilot study showed differences on "gray scale" urological diagnostics, but others have disputed that conclusion, in terms of the methodology used, including the lack of any pre-post diagnostics, raising the correlation versus causation question. Many of the studies supporting finasteride as the primary etiological cause of the syndrome received Post-Finasteride Syndrome Foundation financial and/or promotional support and/or received media rather than academic endorsement. In other words, while presumably precipitated by the finasteride treatment, the observed differences between the "syndrome experiencers" and those without it, may reflect variation in predisposing and maintaining factors, rather than being a direct physiological consequence of Propecia™. Per the Sexual Tipping Point® model a variety of "continuous" (not binary) factors interact to produce manifest symptoms, and regrettably to date such predisposing factors are not fully understood nor can they typically be proactively pre-diagnosed [2]. Providing a good, informed consent process remains the best prophylactic option for a prescribing physician.

Many of the lawsuits were dismissed for lack of evidence and the multi-district litigation was eventually settled with no acknowledgment of wrongdoing as is often the case in such matters. However, that does not mean the drug is harmless as the potential side-effects are clearly noted on both the Proscar™ and the Propecia™ label. The multi-district litigation issue was related to the lack of initial warning regarding the potential of a discontinuation syndrome. A benefit of the litigation was the FDA required changes in the Propecia™ "label" and patient information insert so that patients would be better warned not only about side effects while taking the drug, but also the potential for a post-treatment discontinuation syndrome [3]. In 2017 the Post-Finasteride Syndrome Foundation, petitioned the FDA to require Merck & Co to either stop selling the drug or require far stronger warnings, citing several scientific studies [4]. In 2022, the FDA said the group's petition "does not provide reasonable evidence" of a causal link between Propecia™ and persistent sexual problems, depression, or suicide. However, based on patient reports, the FDA said it is "requiring the addition of suicidal ideation and behavior" to the adverse reactions listed on the Propecia™ label [3]."

The suffering and distress these patients experience is very real, but it is often exacerbated by the suffering individual's psychosocial issues and by social media interactions with groups that have formed around the issue. While constructive support is provided by some groups, provocative and pejorative narratives abound regarding symptoms, etiology, helplessness, hopelessness, and tragically even suicide reports attributed to this condition, that only exacerbate the distress so many of these men experience. Men suffering from a PFS do need support that their experience is "real" and not just "in their head" as too many have initially suggested too often. Sex therapists can help in a variety of ways, as with any multi-determined symptoms and presentation, by clarifying what is the nature of the chief complaint(s) and what is the desired outcome of treatment. All avenues pursued will require some compromise on the part of the patient. If sexual function is to be restored (especially without the use of (PDE5i) (e.g. Viagra®) type medications) then typically finasteride must be discontinued … and the alopecia process is likely to proceed accordingly. Obviously, other treatments can be substituted for Propecia™ by medical personnel, e.g. minoxidil. If continued use of finasteride is desired, then (like any other patient suffering from diminished sexual function) adjustment to that reality is required, with the caveat, that teaching McCarthy's "good enough" sexual model can assist with improving intimate encounters, etc. [5]. Importantly, focusing on the patient's cognitions during various times before, during and after sexual acts is critical and mindful self-awareness of thought must be encouraged. Learning to maintain erotic thought can help trump the consequences of negative anxiety producing thoughts, again per the STP model [2]. While publications and lectures at medical meetings have communicated these types of sex coaching suggestions to prescribing physicians, sex therapists will typically be able to execute such treatment more effectively than non-sexologist physicians.

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AUTHOR CONTRIBUTIONS

All contributions were made by MP.

COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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