Post-Finasteride Syndrome: Medically Unexplained

Abstract

Post-Finasteride Syndrome (PFS) is a controversial illness associated with a host of distressing symptoms—most notably sexual dysfunctions—reported to persist long beyond the intake of finasteride itself. It appears the PFS population consists exclusively of younger patients with alopecia, even though millions take a higher (if pharmacologically similar) dosage of finasteride for benign prostatic hyperplasia. This dichotomy is not what one would expect to observe if finasteride caused PFS. No medical explanation of this one-sided syndrome exists. The surge of cases of PFS following a publicity spike in 2011 and 2012 suggests that PFS owes much nonbiological factors. The present analysis offers an analogy between PFS and another mystery illness: Breast Implant Illness, which entered the headlines in the 1990's.

PFS and Its Uncertainties

If a patient has an adverse reaction to a drug, the doctor may advise trying another, on the reasonable assumption that discontinuing a drug puts a stop to its effects. However, over recent years an unknown number of men who took a drug for hair loss have reported life-altering side effects that persist for months, even years after the drug was discontinued. The drug is finasteride.

Our knowledge of Post-Finasteride Syndrome (PFS) comes largely from self-reported cases, low on the scale of evidence[1] but still a potential source of information about reactions that may previously have escaped notice. By report, then, PFS begins but

by no means ends with sexual dysfunction persisting well beyond the last dose of the drug in question. It includes a host of debilitating symptoms ranging from muscle pains to disordered sleep and vision changes, which in toto produce a transformation of life itself for the worse. A number of PFS symptoms, including fatigue and cognitive problems as well as loss of libido, overlap canonical symptoms of depression. Given the lack of controlled studies of PFS, the nonspecific character of a number of symptoms, the multitude and miscellany of symptoms themselves, and the possibility of confounders, it comes as no surprise that the nature of PFS is in dispute.

One factor in particular strongly suggests that PFS is not an ailment caused by finasteride: its occurrence in younger patients with androgenic alopecia to the exclusion of older patients who take a higher, if pharmacologically similar, dosage of the same drug for benign prostatic hyperplasia (BPH). While the literature concerned with PFS routinely claims that the syndrome occurs in both alopecia and BPH patients, that is not what it shows. I know of no example in the literature of BPH patients treated with finasteride who exhibit full-blown PFS. In effect, the PFS literature is an alopecia literature.

To be sure, there are clinical trials in which BPH patients report sexual dysfunction following the cessation of finasteride treatment. In the Proscar Long-term Safety and Efficacy Study (PLESS), men with BPH aged 45 to 78 took finasteride 5 mg or placebo for four years. Among the 4% in the finasteride arm and 2% in the placebo arm who dropped out of the study due to sexual side effects, the problem resolved in about half of each group, "consistent with the natural history of sexual dysfunction in this patient population and a substantial placebo effect."[2] That is, sexual dysfunction which continued after

cessation of finasteride or placebo for BPH might well be due to the patient's age or the noxious power of suggestion or both. But if a patient's symptoms are indistinguishable from the natural course of age, then by definition he has not incurred a syndrome which is markedly out of the ordinary, like PFS. A PLESS patient who experiences lingering sexual dysfunction is not the same as a patient overwhelmed by a flood of disabling symptoms.

Regulators in the US, the UK and Europe have taken broadly similar positions toward finasteride, which is used by millions of patients both in a 1-mg dosage for alopecia and 5-mg dosage for enlarged prostate. (The trade names are Propecia and Proscar respectively, though the patent on finasteride expired in 2006.) On both sides of the Atlantic, reports of adverse events have followed Propecia in particular, and regulators have taken note of them. The process began in 2011 with the addition of depression and "erectile dysfunction that continued after discontinuation of treatment" to the Propecia label. By contrast, the 2011 Proscar label cites PLESS without mentioning post-treatment sexual dysfunction, which implies that FDA reviewers found the evidence of persistent dysfunction too entangled with the effects of age to be meaningful.[3]

That a regulator notifies the public of adverse events reported to it does not necessarily mean the risk of these events has been established. On the contrary, even while listing adverse events in finasteride labels the FDA has maintained a position of agnosticism regarding the evidence supporting them. In the documentation attached to the change of the Propecia label in 2011, the FDA noted, for example, that in 51 of 59 reports of persistent erectile dysfunction, information about potential confounders was missing.[4] Recently the agency went so far as to place the risk of "suicidal behavior" on the

Propecia label despite notifying the petitioners that the evidence did not warrant a finding that Propecia causes suicide.[5] Much of the debate surrounding PFS follows from the regulatory practice of advising of risks for which evidence remains highly uncertain.

The PFS Dichotomy

The anti-androgenic effects of finasteride are not in question. The synthesis of the drug was inspired by the discovery of a cluster of pseudo-hermaphrodites with a hereditary deficiency of 5-α reductase, the enzyme responsible for the conversion of testosterone into the more potent androgen, dihydrotestosterone (DHT).[6] The subjects neither lose their hair nor suffer from enlarged prostate. The physiological pathways by which finasteride may influence mood are not a matter of controversy, either. Animal studies point to a link to depression.[7] Moreover, in a small study, patients given finasteride for alopecia showed altered levels of neuroactive steroids in cerebrospinal fluid and plasma after treatment ceased, although the duration of these readings remains unclear.[8] Why the authors chose only alopecia patients for their study of PFS is unclear as well.

Also unknown is the means by which finasteride purportedly acts for years beyond the last dose. After all, the alopecia patient who discontinues finasteride will see the resumption of hair loss, just as the patient who stops taking the drug for BPH will see growth of the prostate—over time in both cases. For the purposes for which it is taken, finasteride does not continue to act indefinitely.

Even assuming the plausibility of severe long-term effects, it remains difficult to accept that finasteride, and finasteride alone, is responsible for PFS. If the syndrome is caused by finasteride, then why is it found among alopecia patients but not the population taking finasteride for enlarged prostate? It is true that persistent sexual dysfunction in a BPH patient who took finasteride might or might not be due to the drug (the PLESS lesson), which would complicate the identification of the cardinal symptom of PFS. In the 2013 Proscar label, the FDA noted that sexual side effects "were reported rarely by men taking PROSCAR for the treatment of BPH" and that when they do appear, they are confounded by age and other medications.[9] Possibly Proscar patients report sexual dysfunction so infrequently because they assume it to be a matter of age. Nevertheless, full PFS, encompassing not only sexual dysfunction but an entire complex of physical and neuropsychiatric ills, would seem to be too extreme to go unnoticed in or by patients of any age.

The linkage of PFS to alopecia is written into the medical literature, a process initiated by two studies published the same year as the original changes to the Propecia label (that is, 2011). In the first, a previously healthy subject 24 years of age taking Propecia suffered persistent, life-changing side effects, including both loss of libido and depression.[10] The second study concerns 71 alopecia patients with persistent sexual dysfunction and identifies a cluster of depressive symptoms associated with it. Here, then, is PFS in the making. The report lists among its own limitations a post-hoc approach, selection bias, and recall bias; admits that subjects were recruited from one of the authors'

practices and a Propecia help forum; and notes that "no serum hormone levels were measured."[11]

At the dawn of PFS, then, a picture was emerging of the syndrome as an illness of alopecia patients, even though more patients at the time were taking finasteride for BPH.[12] The special relationship of PFS with alopecia came to be taken for granted in the medical literature and beyond. When the *Economist*'s *1843 magazine* ran a lengthy profile of a victim of PFS, it chose an alopecia patient in his 20's.[13]

Characteristic of the PFS dichotomy is a 2025 bulletin by the European Medicines Agency (EMA) concerning the risk of suicidal thoughts for users of Propecia.

> Following an EU-wide review of available data on finasteride and dutasteride medicines, EMA's safety committee . . . has confirmed suicidal ideation (suicidal thoughts) as a side effect of finasteride 1 and 5 mg tablets. The frequency of the side effect is unknown, meaning that it is not possible to estimate it from available data.
>
> Most cases of suicidal ideation were reported in people using 1 mg finasteride tablets, which are used to treat androgenetic alopecia (hair loss due to male hormones). . . .
>
> Finasteride tablets can cause depressed mood, depression or suicidal thoughts. If you are taking finasteride 1 mg tablets for hair loss and you experience any mood

changes, stop taking finasteride and contact your doctor for further medical advice as soon as possible.[14]

The EMA recognises that both 1-mg and 5-mg dosages of finasteride are in use, notes a risk of suicidal thoughts at both dosages, but finally warns only the users of Propecia—that is, younger patients. The EMA does not explain why low-dose finasteride seems specially risky.

Like the EMA bulletin, the PFS literature as a whole acknowledges both dosages of finasteride but concerns itself in the end with only one, for reasons not given.

Questions Unasked and Unanswered

Proscar, the 5-mg form of finasteride used to treat BPH, was approved by the FDA in 1992. Having learned of hair growth in men using Proscar,[15] and undoubtedly knowing that subjects born with a 5-α reductase deficiency do not lose their hair in the first place, Merck soon brought out a 1-mg dosage of finasteride for alopecia. Propecia was approved by the FDA in 1997. From 1997 to 2011, the FDA received sporadic reports of adverse events, including depression and persistent sexual dysfunction, associated with Propecia. It was the posting of these risks on the Propecia label in 2011, despite evidentiary deficiencies noted in detail by FDA reviewers, that provided the impetus for the PFS movement.

To point out the anomaly of risks one-sidedly associated with low-dose finasteride is not to imply that users of the higher dosage would be expected to show greater risk. In its

review of the finasteride dossier in connection with the revision of the Propecia label in 2011, the FDA found that prostate volume, serum PSA and serum DHT respond almost identically to the two dosages. In short, 1 mg and 5 mg appear virtually equivalent. The problem, then, is the divergent responses of two populations to dosages of finasteride with little to distinguish them pharmacologically. If finasteride causes PFS, why is the syndrome confined to a demographic subset of finasteride users?

Although 1-mg and 5-mg dosages of finasteride come to approximately the same thing, only Propecia has become a topic of public alarm. The Post-Finasteride Syndrome Foundation maintains a "Litigation Library" for Propecia but not Proscar. The reporting of side effects appears similarly skewed. As noted recently by the UK's Medicines and Healthcare Products Regulatory Agency, "In general, the lower dose of finasteride 1 mg is associated with a higher risk of all side effects, compared to the 5 mg dose."[16] A review of the FDA's database of adverse-event reports on finasteride revealed the same pattern, with a higher frequency of such events associated with the 1-mg dosage across 18 of 19 categories.[17] Considering the similar potency of the two dosages, it is hard to see how the drug itself can be responsible for such a lopsided reporting pattern.

A difference in the life-experience of younger and older patients taking finasteride stands out. For the younger group, the occurrence of sexual dysfunction (if any) probably comes as a bolt from the blue; nothing in their history prepares them for it. The older group, however, may already be reckoning with changes in sexual function. In the Prostate Cancer Prevention Trial (PCPT), which enrolled men aged 55 and over, fully 61% and 59% of the placebo group reported erectile dysfunction and decreased libido, respectively—

figures only marginally lower than those in the group treated with finasteride 5 mg.[18] The PLESS report, for its part, notes "the high background prevalence of sexual dysfunction in men with BPH." Whereas the least appearance of sexual dysfunction might well raise alarm in an alopecia patient taking an anti-androgenic drug, a BPH patient might or might not attribute lower libido to the drug at all. If PFS begins not with sexual dysfunction per se but dysfunction that shocks and unnerves the patient, and if sexual problems grow with age, then older patients are likely to be poor candidates for PFS. No reports of PFS appear to have emerged over the seven-year course of the PCPT, even though participants were "asked to call the study site any time they had concerns or symptoms they thought might be related to the study."[19]

Few studies attempt to account for the alopecia/BPH dichotomy. An exception argues in passing that the non-detection of PFS-like symptoms in the BPH population is owing to older patients' reluctance to discuss these problems and doctors' failures to inquire about them.[20] However, this explanation comes very close to assuming the point at issue, namely, the existence of PFS-like symptoms in the BPH cohort.

Sibling Illnesses

A few years ago an editorial on PFS advised, "We should not dismiss the plausibility that certain characteristics of finasteride may precipitate or potentiate psychological morbidities unique to the younger population that has alopecia."[21] Like the suggestion that BPH patients suffer from PFS in silence, a makeshift psychological disorder leaves us no

closer than before to understanding PFS. Regardless of conjectural solutions of the PFS riddle, the fact is that at present no medical explanation of PFS or its skewed distribution exists, and therefore PFS is best classified as a functional illness.[22]

Like other functional somatic syndromes, PFS presents a complex of disabling symptoms whose cause has not been found, even though patients are convinced they know exactly what it is. A number of illnesses of this kind which gained prominence in the 1990's appeared on a small scale, only to "'spread' to other persons with similar risk profiles after widespread publicity and alarm."[23] The same happened with PFS. The event that triggered the PFS movement was not a spontaneous outbreak of cases but the publicity following the addition of adverse events (including depression and persistent sexual dysfunction) to the Propecia label in 2011 and 2012, albeit with explicit disclaimers of causality.

If we have no physiological evidence of greater risks posed by Propecia than Proscar, there is good historical evidence of a cascade effect that brought PFS to public notice. Following the changes to the Propecia label, reports of adverse events shot up. The Post-Finasteride Foundation was established in 2012, Google searches of "post-finasteride syndrome" began their steady rise around the same time,[24] and soon the claim that finasteride, or at least Propecia, has long-lasting, potentially overwhelming effects acquired a life of its own. Even as reports to the FDA about the 1-mg form of finasteride quadrupled from 2011 to 2014, those about the 5-mg form remained unchanged.[25]

According to the FDA analysis accompanying the 2011 label changes, from 1997 to 2011, Merck received a total of 283 reports of depression from users of Propecia, of which

38 were serious. Since 2011, over 1000 *lawsuits* against Merck have been filed on behalf of clients claiming to have suffered depression as well as sexual dysfunction of long duration as a result of Propecia. The numbers alone tell of an explosive increase in adverse events attributed, with or without basis, to low-dose finasteride. The same period witnessed the growth of online communities of Propecia users who found validation of their self-diagnosis in that of others. Together with a flood of litigation and highly repetitive press reports, the support network gives the impression that the harms of Propecia increased as more and more cautionary information about the drug went into circulation.

In many respects, the alarm surrounding Propecia resembles the reaction against silicone breast implants that erupted in the United States in the early 1990's, leading the FDA to suspend the use of the product for breast augmentation in 1992. (The ban was lifted in 2006.) In the case of both Breast Implant Illness (BII) and PFS**,** patients who sought treatment for a cosmetic problem report an anthology of symptoms including, but by no means limited to, many related to depression. "The variety of possible symptoms in PFS conflicts with the idea of a disease-centered model,"[26] and the very same is true of BII. Both are functional illnesses.

As with PFS, we cannot make sense of BII without taking account of the febrile publicity that set it in motion and sustained it thereafter. Panic over silicone implants owed much to an episode of a popular American newsmagazine on December 10, 1990, in which a number of women claimed to suffer from autoimmune diseases caused by the implants. Women who testified in this manner against silicone implants set a precedent for men who would later testify similarly against finasteride on the authority of their history. In each

instance reports by patients led to an action by the FDA which inspired other reports which, by their numbers alone, seemed like a validation of the original claims.

A feature of functional syndromes in general is symptom amplification: an increase of distress as symptoms come to be interpreted as alarming signals.[27] Sexual symptoms that appear in a young Propecia patient lend themselves to amplification precisely because they shock and alarm. In BII it appears the patient's conviction that implants cause disease heightens distresses that would ordinarily not excite alarm.[28] In PFS as in BII, moreover, suggestive publicity provides virtual instructions for the anxious interpretation of symptoms. Warnings about finasteride in particular have been shown to influence response to the drug.[29] In the case of both syndromes, affected patients have joined the campaign to warn others, found some support from the medical profession, had lawyers ratify their claims of injury, and pursued redress in the courts. Both BII and PFS strain probability and electrify the issue of belief.

As noted, the inciting event in the case of PFS was the revision of the Propecia label in response to adverse events reported by patients. Merck itself requested the action. By acknowledging reports of depression and sexual dysfunction, Merck could show concern for users of Propecia even as it fortified its legal position. An example of how *not* to show concern for the users of a medical product was set by Dow Corning two decades before in the furore over silicone implants, of which it was the primary manufacturer. Indeed, it was Dow Corning's indifferent handling of the controversy that led the FDA to take action.[30] In requesting a change to the Propecia label, Merck may have sought to pre-empt the sort of public-relations crisis that overtook Dow Corning. If Merck was in fact determined not to

appear like Dow Corning and not to suffer the same fate (bankruptcy), then the controversy that followed the changes to the Propecia label carried an allusion to the prior cause célèbre.

The analogy goes further. Just as men taking low-dose finasteride have reported side effects after discontinuing the drug, some women appear to suffer from BII after removal of the implant. Upon reviewing reports of women with self-diagnosed BII between 2008 and 2024, the FDA found that of 785 that gave information on the woman's status following removal, "98 noted either no improvement or worsening of symptoms."[31]

In accordance with the PFS dichotomy, reports suggest an increased risk of suicidality among alopecia patients but not their BPH counterparts.[32] By the time the EMA confirmed the association of finasteride 1mg with suicidal thoughts, the FDA had already added the risk of "suicidal behavior" itself to the Propecia label. However, risk of suicide—an adverse outcome which is irreversible indeed—does not remove PFS from the category of medically unexplained illnesses. Cosmetic breast implants too have been linked to suicide,[33] and BII has not been shown to be a disease.

Conclusion

If PFS were caused by finasteride, we would not expect to observe it in younger patients to the exclusion of the older population taking a comparable dosage of the same drug. Like BII, PFS is a functional illness.

The regulatory practice of advising the public of risks that may or may not be well-founded fuels much publicity about finasteride, and publicity itself has served as a vector of recent functional syndromes, including both BII and PFS. Like the lore surrounding BII in the 1990's, the claim that finasteride causes all manner of side effects for many patients—at least many alopecia patients—has been represented as a matter of science. However, medical science has no explanation of the stark demographics of PFS, and neither does the PFS literature.

The effects of inflammatory publicity, the amplification of symptoms, the influence of confounding factors: this storm probably accounts for the disturbance known as PFS.

The question remains: assuming PFS is a functional disorder, why does it occur in alopecia patients but not the BPH population? The most economical theory would be that older patients are less liable to be shocked by sexual symptoms which are consistent with aging. In a manner of speaking, age itself is persistent sexual dysfunction. For a younger patient, by contrast, the sexual side effects of finasteride are highly incongruous, and therefore can stir an anxiety that heightens symptoms and colours their interpretation.

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