**A proposed etiopathology of persistent dysfunctions emerging
from use and discontinuation of 5-alpha reductase inhibitors:
sequelae of drug-mediated microvasculopathy**

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Summary

A proposed explanation of lasting dysfunctions after discontinuing use of finasteride or dutasteride

Men who previously took finasteride and dutasteride have reported sexual dysfunction, anxiety, cognitive problems and other dysfunctions which have continued long after stopping the drug. This paper proposes an explanation for how these dysfunctions may develop. Studies have linked finasteride and dutasteride treatment to changes in penile tissue including reduced size, muscle loss and increased connective tissue, as well as changes to vascular structure and neural signaling pathways supporting erectile function. In some men, perhaps especially younger men, finasteride or dutasteride may stress small blood vessels in penile tissue, reducing the supply of oxygen. The tissue attempts to restore blood flow, but the process may turn pathological, setting off a vicious cycle of vascular deterioration, tissue damage and inflammation. This local progression might develop into a broader inflammatory condition, posing a risk of injury to other structures and systems regulating psychological well-being, thought, sleep, vision and hearing. In this hypothesis, all dysfunctions would arise from tissue injuries in supporting structures and organs. Similar to stroke outcomes, these dysfunctions are variable in nature, severity and course over time. (See also Figures from p. 33 & Disclaimer on p. 24.)

Abstract

Persistent dysfunctions emerging from use and discontinuation of 5-alpha reductase inhibitors (5ARIs) may be explained as the aftermath of a pathological response to microvasculopathy. Focusing on sexual dysfunction, the most common class of symptoms: 5ARIs' inhibition of angiogenesis leads to stress on penile microvasculature, depriving the tissue of blood supply and oxygen. These hypoxic conditions lead to tissue injury and atrophy, triggering a pathological recovery that further alters penile tissue, including smooth muscle loss, fibrosis, damage to vascular architecture and impairment of neural pathways supporting arousal and erectile function. This damaging cascade may result in severe and lasting sexual dysfunction. Neuropsychiatric, cognitive, sensory and sleep dysfunctions emerging from 5ARI treatment may similarly be explained as pathological responses to microvasculopathy in supporting structures, particularly those in the limbic system. Systemic spread is proposed to arise from a vicious cycle of tissue injury, oxidative stress and proinflammatory activity which spreads via the vascular network, leading to systemic endothelial dysfunction. The latter may in turn set off a damaging cascade in other organs and tissues. Risks of developing lasting dysfunctions may arise from 5ARI-mediated disruptions of vascular tone, angiogenesis and neoangiogenesis. Pharmacovigilance data, animal studies and human studies provide converging evidence for the proposed etiopathology. It is, moreover, consistent with variable presentation and severity of symptoms; irreversibility; typically normal results of clinical lab tests; and resistance to treatment.

Introduction

In the last decade, there has emerged a cottage industry of physicians and researchers advancing psychosocial explanations of persistent dysfunctions after discontinuation of 5-alpha reductase inhibitors (PD-5ARI).¹⁻⁸ A conference abstract hints at paranormal phenomena with the title: “Post-Finasteride Syndrome: Real or Imagined?”⁹ Three papers from leading lights in urology—strikingly similar in their design, findings and conclusions—have sown doubts about the validity of adverse event (AE) reports.¹⁻³ Doctors and researchers have ventured the following explanations for reports of PD-5ARI: nocebo effect, psychogenic erectile dysfunction, distress and psychopathology associated with hair loss, advocacy group efforts, media coverage, social media use, mass psychogenic illness,⁴ false reports by dissatisfied patients and litigation interests.⁵ One author disclosed he was retained by Merck for its Propecia litigation defense,² while others had prior involvement with the drug maker related to finasteride.^{3,8}

My own body and functioning changed drastically after taking and discontinuing finasteride. For nearly a decade, my libido has been at zero. My sexual anatomy and physiology are damaged and incapacitated. The situation has not improved since stabilizing after an initial acute phase. From this perspective, the response from luminaries of urology and dermatology looks like a guild closing ranks to protect its interests.¹⁰ Considerable resources have gone to deflecting drug safety signals by blaming patients in clinical jargon. The medical establishment received notice of this iatrogenic disease from heretics within their own ranks more than a decade ago,^{11,12} yet doctors remain largely in denial.

Integrating research, AE data, and indeed my own experience, I will propose an etiopathology for PD-5ARI—one which is classically biomedical and recognizable as a variant of known disorders.

Overview of the hypothesis

The hypothesis emerged from consideration of evidence linking use of 5-alpha reductase inhibitors (5ARIs) to alterations of penile anatomy and physiology in animals and humans. Among younger men taking finasteride for androgenetic alopecia, sexual AEs were the largest cluster among those reported to FDA from 2018 to 2020 (Table 1;

Appendix: Methodological note on the use of AE data). AEs range from the broad terms *Erectile Dysfunction* and *Sexual Dysfunction* to specific abnormalities of the male reproductive system (Tables 2A & 2B). AEs affecting the penis include *Genital Hypoaesthesia* (numbness), *Penile Size Reduced*, *Genital Atrophy*, *Penile Curvature* and *Peyronie's Disease*. A recent pharmacovigilance analysis found a disproportionate signal in reports of penile curvature and Peyronie's disease for finasteride compared to 9 other drugs.¹³ Penile alterations are not associated with depression, anxiety or Internet use.^{14,15} This class of AEs therefore offers a potential foothold to differentiate PD-5ARI from depression and other reductionist interpretations.

It is proposed that PD-5ARI is the aftermath of unsuccessful recoveries from microvasculopathy in structures and systems supporting sexual function, emotion and behavior, cognition, sleep, vision, hearing and orientation (Figure 1A). 5ARIs have been found to inhibit angiogenesis—an effect which may be beneficial for the treatment of prostate conditions in older men.¹⁶ At the same time, angiogenesis inhibition in normal tissue might stress microvasculature, potentially leading to microvasculopathy and hypoxia. Under hypoxic conditions, tissue damage and cell death may occur¹⁷ while neoangiogenesis engages to restore microvascular function. Paradoxically, the recovery process may become pathological—not only failing to restore vascular function but resulting in secondary damage and, in some cases, loss of function (Figure 1B). Ischemia-reperfusion injury describes such a pathological response, leading to alterations including atrophy, collagen growth, fibrosis and disruption of neural signaling pathways.^{18,19} These outcomes are similar to penile alterations associated with 5ARI treatment and discontinuation cited above. In PD-5ARI, this same progression may also damage tissue in the limbic system and adjacent brain structures, the eye and inner ear. Such damage could lead to temporary or permanent dysfunctions of behavior, affect, cognition, vision, hearing, balance and other functions.

This explanation has analogues in stroke, ischemic kidney diseases and retinopathies which share a similar progression. It is consistent with the very properties of PD-5ARI that have provoked puzzlement and doubt in some observers: variable symptom presentation and course; dysfunctions in multiple systems; resistance to treatment; and typically normal lab results.

The case for this etiopathology will be developed as follows: 1) 5ARI treatment is associated with penile abnormalities; 2) the course of PD-5ARI has a multiphase character consisting of an acute period, adaptation and stabilization; 3) 5ARIs are angiogenesis inhibitors and are associated with a risk of microvascular events; 4) penile tissue alterations in PD-5ARI are consistent with outcomes of microvasculopathy or ischemia-reperfusion injury; therefore, 5) PD-5ARI is hypothesized to emerge from a vicious cycle of vascular deterioration, cell death and inflammation resulting in tissue damage and dysfunction in one or more systems. The remainder of the paper will provisionally explore risk factors and mechanisms, implications for diagnosis and treatment, and future research directions.

5ARI treatment has been associated with penile abnormalities

Several lines of evidence support an association of 5ARI treatment with penile alterations. Animal research has found 5ARI treatment is associated with: reduced size and weight of the penis^{20,21}; reduced erectile response; apoptosis²²; decreased smooth muscle density and increased collagen density in corpus cavernosum^{20,22,23}; fibrosis^{24–26}; reduced size of sinusoidal spaces in corpus cavernosum^{20,25}; reduced expression of endothelial nitric oxide synthase (eNOS)^{23,27}; reduced expression of erectile neurotransmitter calcitonin gene-related peptide (CGRP)²⁸; and, in a dutasteride study, reduced expression of androgen receptor.²⁶ A review commented that an animal study's findings "indicate that 5ARIs have a significant pathogenic impact on the penile histo-architecture and attenuate the NOS signaling pathway."²⁹ Da Silva et al. attributed morphological changes to depletion of dihydrotestosterone (DHT) in penile tissues and observed: "The possibility of recovering normal penile morphology after discontinuing [finasteride or dutasteride] and whether either of the drugs is associated with a faster or more complete return to a normal penile morphology remains unknown."²⁰ Two studies investigated whether erectile parameters in dutasteride-treated rats recovered after a washout period. Öztekin et al. found that after 6 weeks of dutasteride treatment followed by a 2-week washout period, certain erectile parameters—including intracavernosal pressure and contractile response in cavernosal smooth muscle—did not recover.³⁰ Sung et al. found that persistence of erectile dysfunction depended on duration of treatment: rats receiving 4 weeks of dutasteride

treatment recovered erectile function after the washout period, but 8 weeks of treatment led to irreversible erectile dysfunction. Penile tissue changes were also noted in treatment groups. The ratio of smooth muscle to collagen in cavernosal tissue remained low after the washout period, while expression of fibrosis-related factors such as TGF- β 1 and TGF- β 2 remained elevated.²⁴ Selected images of penile alterations emerging from 5ARI treatment have been reproduced in Figures 2–4.^{20,22,25}

Human research on penile abnormalities associated with 5ARI treatment is sparse, but bears consistency with the animal research. A study which performed penile ultrasound imaging on men with PD-5ARI found penile vascular abnormalities in 68% of participants.³¹ The abnormalities were arterial insufficiency, venous leak and peak systolic velocity in a “gray zone” below normal range. A previously-cited pharmacovigilance analysis found a disproportionate signal for reports of penile curvature or Peyronie’s disease associated with finasteride.¹³ A pilot study reported abnormal somatosensory evoked potentials of the pudendal nerve in 4 of 16 post-finasteride patients. Three of the 4 patients had no reproducible response to the stimulus.³²

Two cases of penile alterations associated with finasteride treatment were reported in Argentina.³³ After discontinuing finasteride, Case 1 began to experience “a ‘flaccid but rigid’ penile state, less penile length and girth, scrotal shrinking, more visible superficial penile veins, mild flaccid penile pain, mild distal penile curvature to the right, severe post ejaculatory asthenia and less muscle tone and strength.” Penile ultrasound imaging showed a plaque in right corpus cavernosum suggesting possible fibrosis, while the penile MRI result was normal. Case 2 had a history of Ewing Sarcoma and testicular cancer followed by unilateral orchiectomy, but had been disease-free for 5 years with no sexual dysfunction prior to the reported changes. After a single dose of finasteride, he reported “severe erectile dysfunction...lack of any morning erections, less penile length and girth...penile hyposensitivity, more visible superficial penile veins, moderate penile, testicular and perineal pain...hypospermia and a ‘more watery’ semen, less intense orgasms, asthenia and articular and muscular pain...”

AEs reported to the Food & Drug Administration (FDA) Federal Adverse Events Reporting System (FAERS) are consistent with the animal and human research (Tables 2A & 2B). Filtering criteria were applied to minimize confounding factors (Table 2A caption).

The proportion of genitourinary AEs of finasteride in men 18–40 was 10.2x greater than that of a comparable group of men who used minoxidil, another hair loss treatment taken by a similar population. In the subset of AEs affecting the penis and erectile function, the proportion of AEs was 11.2x greater for finasteride compared to minoxidil. These included: *Penile Size Reduced*, *Peyronie's Disease*, *Male Genital Atrophy* and *Penile Curvature*, as well as the broader terms *Erectile Dysfunction* and *Sexual Dysfunction*. Although researchers have advanced psychogenic explanations of these last two AEs,^{1–8} in fact these terms are non-specific as to origin. For exploratory purposes these AEs have been included with penile AEs. Tables 2A and 2B summarize genitourinary AEs of finasteride by subsystem. Figure 5 provides a visual overview of genitourinary AEs of finasteride.

PD-5ARI has a multiphase course

The course of PD-5ARI has received scant attention in research literature. By the time a man with PD-5ARI sees a clinician, files an AE report or enrolls in a research study, a sequence of events has unfolded. Figure 6 shows a canonical disease course integrating my experience with that of others (systematic evidence is not available; see sources of firsthand reports in Supplement). The four major phases are: injury, pathological recovery, adaptation and stabilization. The figure shows a correspondence with the phases of ischemia-reperfusion injury.

To return to the original, practical question: what could explain that a young man with a healthy, functioning penis begins taking a 5ARI, experiences AEs and, within a few weeks or months after discontinuation, emerges with a collagenous, fibrotic, non-functioning penis? The next section lays the foundation by reviewing the basics of angiogenesis as well as angiogenic effects and risks of 5ARI use.

Background on angiogenesis

Under normal conditions, microvascular tissue is sustained by oxygen, a process in which vascular endothelial growth factor (VEGF) has an important role.³⁴ Oxygen levels in tissue fluctuate over time. When oxygen runs low, hypoxia-inducing factor 1 α (HIF-1 α) is expressed, inducing neoangiogenesis.^{35,36} VEGF is then upregulated, leading to increased

vascularization and restoring oxygen supply.^{36,37} Ongoing adjustments to expression of angiogenic factors thus allow tissue to remain healthy under fluctuating levels of oxygen.^{37,38}

Under hypoxic conditions, such as after ischemia, neoangiogenesis may go awry. The recovery process may paradoxically trigger further injuries, resulting in potentially permanent loss of function. This has been described as pathological angiogenesis or ischemia-reperfusion injury.^{36,39} Early in the process, apoptosis occurs. Anti-inflammatory processes may trigger the production of collagen, culminating in fibrosis which can interfere with normal organ function.⁴⁰ In kidney disease this has been described as an acute kidney injury-to-chronic kidney disease transition.⁴¹

Angiogenic effects and risks associated with 5ARI use

5ARIs inhibit angiogenesis

Benign prostatic hyperplasia and prostate cancer have been associated with increased microvascular density and increased expression of VEGF in prostate tissue.^{42–44} 5ARI treatment has been shown to suppress VEGF and HIF-1 α in the prostate.^{16,45,46} In an animal model, finasteride treatment also reduced VEGF expression in kidney tissue.⁴⁷

As a drug class, VEGF inhibitors have been associated with thrombotic microangiopathy^{48–51} and arterial thromboembolic events.⁵² Touyz et al. described how VEGF inhibition can lead to an imbalance in vasodilatory and vasoconstricting factors, producing “vascular toxicities.”⁵² Kuenen et al. linked thromboembolic events under VEGF inhibition to VEGF’s role in maintenance and repair of endothelial cells.⁵³

Association of microvascular events with 5ARI use

Several lines of evidence indicate microvascular risks of 5ARI treatment. In an epidemiological study, 5ARI use was associated with an elevated risk of venous thromboembolism, with a higher risk for long-term users.⁵⁴ A systematic review of cardiovascular risks of dutasteride in an older population found no increased risk of stroke⁵⁵; however, it included trials with active controls, one of which was finasteride, and a placebo-controlled trial likely to underestimate risk (relatively short duration; 39% of participants on 2% or 10% of the standard dose). Excluding these trials, recalculated RR of

stroke for dutasteride was higher than placebo at 1.36 (1.004, 1.845; $P = 0.048$) (details in Supplement).

A cohort study by Shores et al. explored predictors of stroke risk in 1,032 men of mean age 76.5. The analysis found a nonlinear relationship where DHT levels below or above 50–75 ng/dL were significantly associated with stroke risk.⁵⁶ This suggests indirectly that 5ARIs' effect of lowering DHT could be a contributor to stroke risk.

The above studies focus on older men, but several case reports concern younger men. Two cases of serious vascular events associated with finasteride treatment were reported in Japan: a 35-year-old male who had been taking finasteride for 6 months was diagnosed with sinus thrombosis and brain hemorrhage; and a 41-year-old male taking finasteride and minoxidil was diagnosed with cerebral infarction. The paper noted other vascular AEs of finasteride recorded by the Japanese regulatory authority: 14 cases of thrombosis, 4 cases of stroke (including the 2 mentioned here), 6 cases of myocardial infarction and 4 cases of other thrombotic diseases.⁵⁷ In Korea, a case of cerebral venous thrombosis (CVT) and retinal hemorrhage was reported in a 25-year-old male taking dutasteride, with the drug seen as a potential cause of CVT.⁵⁸ Another case report from Korea described finasteride-induced CVT in a 41-year-old man.⁵⁹

Selected vascular AEs of finasteride and minoxidil in men 18–40 are summarized in Table 3. The proportion of vascular occlusive AEs (involving thrombosis, embolism, occlusion, ischemia or infarction) is 5.8x greater for finasteride compared to minoxidil (6.5x greater if the ambiguous term *Cerebral Disorder* is included).

We have reviewed an association of angiogenesis inhibitors with microvascular risks, as well as specific evidence linking 5ARI treatment to microvascular events including stroke. We will next review examples of ischemia-reperfusion injury as analogues of the course and outcomes of PD-5ARI.

Examples of ischemia-reperfusion injuries

Much of the clinical research on ischemia-reperfusion injury relates to kidney disease, stroke and surgery. Related basic research has delved into its progression at cellular and molecular levels with reference to angiogenesis, neoangiogenesis,

inflammation, neural signaling and epigenetic changes. This brief review includes research spanning these several levels of explanation.

Ischemia-reperfusion injury in kidney diseases

An ischemic event in the kidney may cause inflammation and microvasculopathy. The microvasculopathy may in turn result in permanent deterioration of the capillary network and increase the risk of chronic kidney disease.⁶⁰ Following ischemia, microvascular rarefaction and hypoxia can lead to fibrosis, scar formation, and a “vicious progression” towards eventual kidney failure.^{40,61,62} This damaging cascade has been attributed to “inappropriate activation” of HIF which may increase the expression of fibrogenic genes;⁶¹ and to dysregulation of angiogenic factors as a consequence of hypoxia.⁶³ A review on the transition from acute kidney injury to chronic kidney disease (AKI-CKD transition) describes how, in recovering from injury, a subpopulation of tubules stops growing and becomes atrophic. These tubules interfere with normal tissue recovery, leading to profibrotic signaling and capillary disintegration and rarefaction.⁴¹ Another study in nephrology examined the effect of different lengths of induced ischemia on markers for injury, inflammation and fibrosis.⁶⁴ They noted a “point of no return” time of 35 minutes, beyond which markers for inflammation, injury and partially for fibrosis remained elevated through 5 weeks after the ischemic event. Persistent cell death and atrophy were observed in the groups with ischemia of 35 minutes or greater, but not the shorter-duration ischemia groups.

The comparison with kidney disease is not merely theoretical. As mentioned earlier, 5ARI treatment has been shown to suppress VEGF in kidneys.⁴⁷ Animal research has shown that 5ARI treatment can result in morphological and functional damage to kidneys.⁶⁵ Baig et al. found Type I and Type III collagen were increased, respectively, in the interstitial cortical region and glomerulus of finasteride-treated rats, with the latter leading to glomerulosclerosis. The overall percentage of collagen in sampled kidney tissue of finasteride-treated rats was more than double that of controls. Baig et al. also found: reduced expression of androgen receptor in the cortical region; reduced expression of intercellular junctional proteins; increased ratio of apoptotic to proliferative nuclei; and proliferation of IL-6 and lymphocyte markers in kidney tissue.⁶⁶ This study’s observations

of tubulointerstitial fibrosis and tubular atrophy recall findings of fibrosis and atrophy of penile tissue linked to finasteride treatment discussed earlier.

Ischemia-reperfusion injury in stroke

The progression of ischemic stroke parallels that of hypoxic kidney injury. Nour et al. described a paradoxical process in which a post-ischemic recovery process may lead to further damage. Following ischemia, activation of the immune system and complement system may cause cell death, setting off a proinflammatory cascade. Another contributor to injury is the production of reactive oxygen species (ROS) via inducible nitric oxide synthase (iNOS), leading to necrosis and apoptosis. These injuries result in “a change in the nature of the vascular system as a whole.” Dysfunction in cellular metabolism induces inflammation of endothelial cells and increased vascular permeability. Importantly, Nour et al. point out: “this injury lasts beyond the period of ischemia.” Ischemia-reperfusion injury alters DNA and protein expression in the blood-brain barrier (BBB), leading to oxidative cell damage. Increased vascular permeability of BBB may lead to edema, interfering with reperfusion. The degree of permeability of BBB has been correlated with severity of clinical outcomes of stroke. Reperfusion injury may, moreover, affect autoregulation of cerebral blood flow.³⁹

Ischemia-reperfusion injury as a model for PD-5ARI progression

Emergence of sexual dysfunction

The background has been established to trace how penile alterations could emerge and progress from 5ARI treatment and discontinuation. The sequence would begin with stress on microvascular tissue in the penis, creating hypoxic conditions. As in acute kidney injury and stroke, hypoxia may induce capillary rarefaction,^{67,68} apoptosis and necrosis, triggering neoangiogenesis. 5ARI use may disrupt angiogenesis in several ways. First, 5ARI use reduces expression of VEGF, HIF-1 α and eNOS, all of which are involved in physiological angiogenesis. Second, discontinuation of 5ARI use might lead to a rebound of these factors—potentially explaining reports of worsening conditions after drug discontinuation.⁶⁹ Finally, a low DHT environment has been associated with proinflammatory activation.⁷⁰ Similar to the “vicious progression” in kidney disease, a

pathological recovery in penile tissue could produce secondary effects such as tissue atrophy, fibrosis, damage to neural signaling pathways, and consequently erectile dysfunction (Figure 6 & Figure 1B).

Progression of the autoimmune disease systemic sclerosis (SSc) provides a reference point. In SSc, microangiopathy may produce hypoxic conditions in multiple organs and systems. Attempted neoangiogenesis fails because of an imbalance of pro- and anti-angiogenic factors.⁷¹ A pathological tissue recovery process ensues, resulting in loss of microvasculature, an impaired vascular repair mechanism and fibrosis.^{72–74} 80 to 90% of men with SSc have erectile dysfunction. In these men, blood flow in penile arteries is inhibited due to corporal fibrosis and myointimal proliferation.⁷⁵

Emergence of other areas of dysfunction

It is proposed that the neuropsychiatric, cognitive, sleep and sensory dysfunctions of PD-5ARI may be a consequence of 5ARI-related injuries in supporting structures and organs. Oral 5ARIs are systemic, so it is plausible that microvascular effects observed in prostate or kidneys might affect other tissues, organs and functions. The mechanism for systemic progression (elaborated in more detail in the following section) is proposed as a local vicious cycle culminating in proinflammatory activity which spreads via the vascular network, resulting in systemic endothelial dysfunction (Figure 1B).

Table 4 indicates anatomical structures supporting functions which are impaired in PD-5ARI. Neuropsychiatric, cognitive and sleep dysfunctions show a correspondence with functions of the limbic system—for example, the medial preoptic area is a crucial site mediating male sexual behavior.⁷⁶ Regarding cognitive dysfunction, Diviccaro et al. have shown alterations to hippocampal neurogenesis 30 days after withdrawal from finasteride in an animal model.⁷⁷

Regarding ocular adverse effects, systemic finasteride is associated with decreased vision and tear film abnormalities. It has a probable association with intraoperative floppy iris syndrome and conditional association with retinal vascular accidents.^{78,79} A recent retrospective study of 116 patients found an association of finasteride and meibomian gland dysfunction, as well as conjunctival and corneal abnormalities.⁸⁰ In another study, ophthalmologists reviewed histories of 28 patients of their clinic known to have taken

finasteride. While acknowledging selection bias, Nguyen et al. reported evidence of visual dysfunction in 25 patients (89%), 7 of whom had optic nerve and retinal damage as measured by visual evoked potentials and electroretinogram.⁸¹ A co-author of this research published a letter of concern suggesting ocular adverse effects of finasteride are under-recognized.⁸²

A cohort study on dental effects of finasteride found gingivo-periodontal lesions in 21% of 84 patients.⁸³ In the present author's experience and in reports of others, rapid and irreversible gum recession may occur during the erratic recovery phase after discontinuation of 5ARI use.

Parallels with stroke

A comparison of stroke and PD-5ARI shows a striking parallelism (Table 5). In both conditions, there is considerable variability of course and outcomes. Varying outcomes of stroke are unsurprising because we have a mature understanding of the condition.⁸⁴ A stroke rehabilitation clinic advises: "Every stroke recovery prognosis is different because every stroke is different."⁸⁵ As for the variability of PD-5ARI, Figure 7 represents a wide range of possible courses and outcomes across four areas of dysfunction. As in stroke, this variability becomes more plausible as a consequence of variable localization, severity, progression and outcomes of drug-mediated tissue injuries.

Figure 8 contrasts a *symptom view* with a *system view* of the disease. In the former view, symptoms are considered piecemeal. This limited frame of reference has led to a stalemate over whether there is any disease entity to speak of at all.^{3,7} Conversely, in the system view, symptoms may be understood as the aftermath of a complex cascade following tissue injuries—one in which variability is multiplied at each stage (Figure 1B). In this account, variability need not prompt suspicions of malingering or factitious disorder; it is, rather, a natural consequence of the disease process.

Risk factors and potential mechanisms

Risk factors for developing PD-5ARI are unknown. Anecdotally, the disorder seems more common in younger men, with some men reporting severe, complex reactions after as little as 1 dose.³³ This section will review candidate mechanisms and risk factors:

1) mediation of angiogenesis by androgen levels and age; 2) effects of 5ARIs on angiogenic factors; and 3) the progression from a local vicious cycle to a systemic condition.

Androgen mediation of angiogenesis

Androgens and androgen receptors (AR) have a critical role in maintaining and repairing vascular function in health and disease.⁸⁶⁻⁸⁸ Using dermal fibroblasts from young and old men, Lecce et al. found DHT treatment resulted in an increase in VEGF expression in tissue of young men, but not that of old men. This difference was found to depend upon the sensitivity of androgen receptor in tissues.⁸⁹ Ye et al. examined the effect of DHT treatment on endothelial progenitor cells (EPCs). DHT enhanced the angiogenic action of EPCs and differentially upregulated angiogenic genes in EPCs.⁹⁰ DHT has been shown to reduce the inflammatory response in vascular endothelial cells. Low androgen levels are associated with apoptosis of cavernosal endothelial cells.⁸⁸ These findings suggest a low DHT environment could disrupt the angiogenic balance and fail to contain inflammation in vascular tissue.

AR, which mediates beneficial effects of DHT on vascular tone, has been found over- or underexpressed across several studies involving 5ARI treatment. Baig et al. found decreased expression of AR in kidneys of finasteride-treated rats,⁶⁶ while Enatsu et al. found reduced AR expression in the prostate and penis of rats treated with dutasteride compared to controls.²⁶ Conversely, a human study found higher expression of AR in prepuce of post-finasteride patients.⁹¹

Androgen mediation of post-ischemic neoangiogenesis

Androgens, AR and age also mediate the response to ischemic events. Lam et al. investigated the effects of DHT treatment on a mouse model of hindlimb ischemia. In wild-type, castrated mice (inducing an androgen deficiency), DHT treatment enhanced blood flow recovery after ischemia and increased HIF-1 α levels in ischemic tissues. In knockout mice with inactivated AR, DHT treatment did not lead to blood flow recovery and the increase in HIF-1 α was attenuated.⁹² A subsequent study identified age-related differences in vasculogenesis after ischemia, including that HIF-1 α was increased in young

but not old mice.⁹³ Shafighi et al. found that in male human umbilical vein endothelial cells, DHT increased HIF-1 α . In a second experiment, mice with an induced androgen deficiency (via orchiectomy) were given a skin flap operation. Compared to controls, this group had lower VEGF, lower perfusion and lower survival of tissue compared to controls. The authors concluded that androgen-mediated HIF-1 α expression results in increased expression of VEGF and perfusion.⁹⁴

A model of cerebral ischemia in castrated mice found that mice treated with 0.5 mg DHT had smaller infarct volumes compared to untreated controls. A higher dose of 1.5 mg DHT led to a worse outcome than controls. All DHT effects were blocked by an androgen receptor antagonist, suggesting that DHT mediation of angiogenesis requires the AR pathway.⁹⁵

Aging has been associated with impairment of angiogenesis.⁹⁶ In elderly patients, outcomes from ischemia and infarction tend to be worse because of age-related impairments to angiogenesis. The HIF-1 α response to ischemia is mediated by age, with older mice showing reduced HIF-1 α expression under hypoxic conditions.³⁸ Bosch-Marce et al. compared ischemia in mice with a partial HIF-1 α deficiency (HET) to wild type (WT). After ischemia in 2-month old mice, expression of HIF-1 α was lower in HET compared to WT, but this difference was not observed in 20-month old mice, where HIF-1 α expression was relatively low in both groups.⁹⁷

The evidence reviewed suggests angiogenesis is generally more responsive, and potentially more sensitive to androgen mediation, at younger ages. HIF-1 α expression is mediated by DHT. 5ARIs inhibit DHT levels, and their effect of angiogenesis inhibition is considered therapeutic for prostate conditions, typically in older men.^{45,46} There is a plausible basis to hypothesize that 5ARI treatment may differentially disrupt angiogenesis in young men because of greater androgen sensitivity. This disruption could create the conditions for microvasculopathy in the first place, and also impair the post-ischemic response. Moreover, an increase in DHT after discontinuation could cause a rebound in angiogenic factors, potentially further disrupting recovery.

Effects of 5ARIs on angiogenic factors

This section provides background on VEGF, then reviews additional evidence linking 5ARI use to altered levels of angiogenic factors. VEGF increases microvascular permeability, and has been implicated in microvascular events leading to organ dysfunction. VEGF activation can cause a loss of integrity of endothelial cell junctions⁹⁸ and lead to the formation of fenestrations⁹⁸ whereby a segment of a single artery divides into at least two channels.⁹⁹ Fenestrations may contribute to loss of glomerular function in kidneys.⁹⁸ In diabetes, systemic endothelial dysfunction induces hypoxia and upregulation of VEGF in the retina. VEGF upregulation in turn contributes to vessel proliferation, leakage and neovascularization, disrupting vision.⁹⁸ Circumstantially, these outcomes recall penile vascular abnormalities observed in post-5ARI patients such as arterial insufficiency, venous leak and marginal peak systolic velocity. As noted previously, 5ARI treatment is associated with reduced expression of VEGF in the prostate and kidneys.^{45,47} Discontinuation of 5ARI use could therefore prompt a rebound of VEGF levels, disrupting neoangiogenesis already underway.

Animal studies have demonstrated effects of 5ARI treatment on expression of NOS isoforms in rat corpus cavernosum. eNOS expression was reduced in corpus cavernosum of finasteride-treated rats.²² Two recent animal studies found differing effects of dutasteride on expression of NOS isoforms in rat corpus cavernosum.^{22,24} A review described the critical role of nitric oxide (NO) production and sensitivity in maintaining vascular homeostasis, and suggested that impairment of NO signaling has a “central link” to endothelial dysfunction. The resulting imbalance in vascular homeostasis has a proinflammatory effect on blood vessel walls, and is linked to dysfunctions in multiple organs.¹⁰⁰ A study of cultured endothelial cells (ECs) confirmed these observations. Inhibiting eNOS in ECs reduced NO and induced endothelial dysfunction. ECs expressed signals for growth of connective tissue, microvascular rarefaction and fibrosis.¹⁰¹ In light of the foregoing findings and background, inappropriate expression of NOS isoforms—during 5ARI use or after discontinuation—could underlie pathological neoangiogenesis following hypoxia.

A low DHT environment or off-target effects of 5ARIs could affect other angiogenic factors. Giatti et al. identified an off-target effect of finasteride on

phenylethanolamine *N*-methyltransferase (PNMT), a limiting enzyme for the production of epinephrine (EPI) from norepinephrine.¹⁰² Catecholamines including EPI have been found to have a mediating role in angiogenesis.^{103–105} A study of bovine aortic endothelial cells (BAECs) found that hypoxia induced BAECs to produce PNMT. Separately, inhibition of a different catecholamine-producing enzyme impaired revascularization after ischemia, suggesting a role of catecholamines in angiogenesis. Sorriento et al. proposed that catecholamine release is an autoregulatory mechanism of ECs to initiate angiogenesis following hypoxia.¹⁰⁶

In summary, demonstrated effects of 5ARIs on VEGF, NOS isoforms or PNMT could disrupt vascular homeostasis in several ways: by altering physiological angiogenesis, impairing vascular repair mechanisms, and inducing a compensatory rebound of angiogenic factors after 5ARI discontinuation.

Systemic progression of PD-5ARI

We have explored two complementary mechanisms for the pathogenesis of PD-5ARI: androgen sensitivity of angiogenesis, and altered expression of angiogenic factors. A conundrum remains: how does PD-5ARI progress in a systemic manner? As illustrated in Figure 1B, damage in one organ or system might result in proinflammatory activity spreading to other organs and tissues. As an example, the “vicious progression” of CKD includes a proinflammatory component⁶² which may have impacts beyond the kidney. CKD has been associated with elevated risk of stroke^{107,108} and cerebrovascular disease.^{109,110} Marini et al. proposed that several factors, including chronic inflammation and endothelial dysfunction, additively increase the risk of renal dysfunction leading to cerebral small vessel disease. They described CKD patients as having a “systemic proinflammatory status.”¹⁰⁹

Rapid gum recession has been anecdotally associated with PD-5ARI, although the only known study of dental effects of finasteride, with 84 participants, did not identify this symptom.⁸³ In a recent review on systemic aspects of periodontal disease, Celik & Kantarci note that hypoxia may trigger a cascade of pathological angiogenesis and inflammatory processes, contributing to the progression of periodontal disease.¹¹¹ Their conclusion notes: “The relationship between periodontal diseases and systemic

inflammatory diseases includes uncontrolled inflammation. The interaction of distant tissues and organs via the vascular network and common inflammatory mediators, which may trigger the systemic inflammation in the circulation, make this link even more probable.”¹¹¹

To summarize, recent research supports a link from kidney dysfunction to an elevated risk of cerebrovascular events, owing in part to proinflammatory activity and potentially systemic endothelial dysfunction. Likewise, periodontal disease is implicated in systemic inflammatory disease. The link is proposed to result from a cascade of hypoxia, endothelial dysfunction and inflammation.

Figure 1B represents a hypothesis for the systemic spread of a 5ARI-mediated pathological process. There are two nested vicious cycles: one at the local tissue level, involving vascular rarefaction, oxidative stress and inflammation; and the other at the systemic level, where proinflammatory mediators spread via the vascular network, inducing a systemic endothelial dysfunction. This may induce microvascular stress in other organs and tissues, setting off the same vicious cycle. Diviccaro et al. reported evidence of a proinflammatory effect of finasteride, both during treatment and after withdrawal. mRNA levels of tumor necrosis factor alpha (TNF- α) were significantly increased at the end of the finasteride treatment period compared to controls.⁷⁷ Glial fibrillary acidic protein (GFAP) immunoreactive astrocytes, considered a biomarker for neuroinflammation and brain injury,¹¹² were elevated in the dentate gyrus of hippocampus of rats 1 month after withdrawal from finasteride, compared to controls.⁷⁷ In a study of the effects of finasteride on kidney tissue of rats, Baig et al. found “huge concentrations” of T cells and B cells around atrophic, pathologically changed tubules of the treatment group. IL-6 was also expressed in pathologically changed structures, as well as in renal corpuscles and epithelial cells of the nephron.⁶⁶ These findings lend preliminary support to a hypothesis that injury, inflammation and immune activation in one organ could progress to a systemic endothelial dysfunction, putting other organs and tissues at risk of similar damage. Given the observation that PD-5ARI stabilizes after several months to one year, systemic endothelial dysfunction may eventually remit—though the injuries it induced may be irreversible.

Neuroendocrine, microbiotic and epigenetic changes associated with 5ARI exposure

Human and animal studies have identified differences in neuroactive steroid levels, gut microbiota composition and gene expression persisting after discontinuation of finasteride.^{32,77,91,113,114} In an animal model, Giatti et al. identified neuroendocrine abnormalities 30 days after discontinuation of finasteride treatment: upregulation of androgen receptor in cerebral cortex; increased dihydroprogesterone in cerebellum; and downregulation of two GABA-A receptor subunits in cerebral cortex.¹¹³ The mechanism for the emergence of these alterations is not clear. A phenomenon called “hypoxic memory” refers to epigenetic changes subsequent to hypoxia and ischemia.¹¹⁵ Research has identified epigenetic changes as both cause and consequence of cerebral ischemia and stroke.^{116,117} Therefore it is conceivable that ischemia could lead to altered expression of neurosteroidogenic enzymes and neuroactive steroids.

A recent study found widespread epigenetic changes in penile tissue biopsies of post-5ARI patients with long-term symptoms.⁹¹ Here too, hypoxic memory and epigenetic consequences of ischemia could explain the emergence of such changes.

The ischemia-reperfusion hypothesis is not incompatible with changes in gut microbiota composition found in finasteride-treated animals.¹⁹ A review has identified “two-way communication” between the gut and brain in ischemic stroke.¹¹⁸

In summary, 5ARI-mediated changes in the neuroendocrine system, microbiome and epigenome could conceivably be downstream consequences of microvasculopathy or ischemia-reperfusion injury (Figure 9).

Tentative implications for diagnosis and treatment

Following are exploratory remarks related to an unproven hypothesis; they are not intended to be a substitute for medical advice, diagnosis or treatment.

Tentative implications for diagnosis

A focus on *symptoms* and a proposed *syndrome* persisting after discontinuation of 5ARIs has provoked consternation and skepticism.⁷ In the present formulation of PD-5ARI, symptoms are manifestations of organ or system dysfunctions, which in turn arose from tissue injuries and their sequelae. Rather than taking a snapshot of symptoms at the

time of a consultation, clinicians might explore the “movie” of how dysfunctions emerged over time (Figure 8). The patient could be prompted for histories of sexual function, neuropsychiatric well-being, cognition, sleep, and other areas. These developments should be integrated with the timeline of beginning and discontinuing 5ARIs (including interruptions and changes in product and dosage). Figures 6 and 7 and Table 4 provide examples of how these several dimensions may be represented and integrated.

There is an opportunity to seek diagnostic signs of putative injuries underlying dysfunctions of PD-5ARI. Tissue alterations such as increased collagen, fibrosis and neuropathy may primarily occur at the cellular level, presenting a challenge given the limitations of imaging techniques. Duplex ultrasonography and magnetic resonance imaging (MRI) have been used to assess penile vascular function and tissue composition.^{119–121} Diagnostic techniques for cognate diseases such as stroke and microvasculopathies might be explored (Table 4, column 3).

Tentative implications for treatment

Treatments for the proposed model of PD-5ARI might explore those used for cognate diseases and conditions such as Peyronie’s disease, penile fibrosis, penile injury, stroke,¹²² kidney disease^{60,62,63} and retinopathies (Table 4, column 3). In men with non-surgical erectile dysfunction, hyperbaric oxygen therapy was found to induce angiogenesis and improve erectile function.¹²³ Penile revascularization is one of several treatments available for vasculogenic ED.¹²⁴ Therapies for Peyronie’s disease and penile fibrosis might be adapted.¹²⁵ Stem cell therapy for penile fibrosis has been explored.¹²⁶ Penile tissue engineering has been explored in animal models.¹²⁷

Research directions

Figure 1B suggests two potential lines of research: one investigating the inner loop describing local progression, and another investigating the outer loop describing the systemic spread of inflammation and endothelial dysfunction. Regarding the inner loop, is there a differential risk of 5ARI-mediated microvasculopathy based on age, genetics, epigenetics and drug exposure patterns? Techniques used by Lecce et al.⁸⁹ might be adapted to observe the effects of 5ARI administration and discontinuation on dermal

fibroblasts of younger and older men, including levels of HIF-1 α , VEGF and eNOS, as well as inflammatory markers TNF- α , IL-6 and TGF- β . A hypoxia-on-a-chip model has been used to observe the effects of hypoxia on tissue in a controlled environment.¹²⁸

A cohort study identified duration of finasteride use as the strongest predictor of young men developing persistent erectile dysfunction after discontinuation.¹²⁹ Future research could explore whether prolonged or irregular use of 5ARIs might progressively degrade and disrupt vascular homeostasis, leading to the pathological inner loop in Figure 1B.

Investigation of the outer loop representing systemic progression seems more challenging. Researchers could draw on approaches used to study systemic inflammation and endothelial dysfunction.^{130,131}

Conclusion

It has been proposed that PD-5ARI emerges from two nested vicious cycles. Locally within tissue or an organ, drug-mediated disturbance of vascular homeostasis may induce a vicious cycle of microvascular rarefaction, tissue injury, oxidative stress and inflammation. This progression may lead to alterations such as apoptosis, fibrosis, atrophy, structural changes, damage to neural signaling pathways and, consequently, organ dysfunction. Inflammatory mediators may also spread via the vascular network, leading to an episode of endothelial dysfunction. These systemic conditions may in turn trigger a similar vicious cycle in other organs and tissues such as the limbic system, eyes, inner ear, kidneys and gums. Finally, discontinuation of 5ARI use after tissue injury might cause a rebound in angiogenic factors such as VEGF, further disrupting neoangiogenesis.

The hypothesis accounts for some of the very properties of PD-5ARI that have led some to question its validity: dysfunctions in multiple systems; treatment-resistance; lack of abnormalities in lab tests; and high variability in symptoms, severity and course. In this reconceptualization, dysfunctions are merely a downstream consequence of prior injuries. This hypothesis may be reconciled with previous findings of epigenetic, neuroendocrine and microbiotic changes associated with prior use of 5ARIs.

Appendix: Methodological note on the use of adverse event data

AE data has numerous limitations and caveats including underreporting,^{132,133} overreporting under certain conditions, differing sources, lack of follow-up and co-occurring conditions and drugs. In this paper, AE data has been filtered fairly strictly to minimize confounding factors, and is considered in the context of published research. It should not be taken as conclusive or comprehensive on its own, nor does it reveal prevalence. With these cautions and measures in place, AE data can reasonably be used as a means of exploring and developing a hypothesis.

To derive clusters of adverse events of finasteride among younger men, the top 30 AEs from 2018–2020 were analyzed (Table 1). This relatively short period reflects a recent understanding of potential impacts of 5ARIs, with lower variation in AE terms used. This period likely excludes litigation-related reports since the vast majority of plaintiffs in Propecia litigation accepted a settlement agreement in 2018.¹³⁴ In targeted explorations of genitourinary and vascular AEs, a different data set was used, spanning the years 2000–2020. This longer period provides greater power in detecting less-common events. While a signal analysis has not been performed, AE counts are compared with those of minoxidil since it has a similar indication and is used by a similar population as finasteride.

Supplementary materials

A Supplement and adverse event data files are available at osf.io/mn7rj

Competing interests

The author declares no competing interests. The author has contributed funds towards research on adverse effects of finasteride by Drs. Roberto Melcangi, Silvia Giatti and colleagues at the University of Milan. Their work has been cited in this manuscript. They had no role in the preparation of this manuscript.

Permissions

The main flow of Figure 1B has been adapted from Figure 1 in Textor & Lerman⁶² with permission of the corresponding author. Images in Figure 2 from Zhang et al.²² are used under license from Elsevier. Images in Figure 3 from Da Silva et al.²⁰ are used under CC BY-NC-SA 4.0 license. Images in Figure 4 from Shen et al.²⁵ are used with permission of *Asian Journal of Andrology*. The illustration in Figure 5 is used under license from Adobe Stock.

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Disclaimer

This manuscript describes an unproven hypothesis which does not reflect medical consensus. Its purpose is to stimulate discussion and further research on lasting dysfunctions after use of 5ARIs. The information provided is not intended to be a substitute for medical advice, diagnosis or treatment.

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Abbreviations in figure and table captions

5ARI	5-alpha reductase inhibitor
AE	adverse event
DHT	dihydrotestosterone
FAERS	Federal Adverse Event Reporting System of the U.S. Food and Drug Administration
HIF-1α	hypoxia-inducible factor 1 α
IL-6	interleukin 6
PD-5ARI	lasting dysfunctions after use of 5- α reductase inhibitors
PDE5	phosphodiesterase type 5
TBI	traumatic brain injury
TGF-β	transforming growth factor- β
TIA	transient ischemic attack
TNF-α	tumor necrosis factor- α
VEGF	vascular endothelial growth factor
VAE	vascular adverse event

Fig. 1. Overview of proposed etiopathology of PD-5ARI. (A) Major stages of disease progression. (1) Tissue injury may induce more severe AEs, resulting in discontinuation of 5ARI. (B) Progression of acute injury. A vicious cycle progresses from microvascular rarefaction to (2) oxidative stress injury and inflammation. (3) Inflammatory mediators may spread via the vascular network and lead to endothelial dysfunction, elevating risk of inflammation and injury in other organs. (4) Discontinuation of 5ARI use may cause a rebound in angiogenic factors, potentially contributing to endothelial dysfunction. Fig. 1B main flow has been adapted from Fig. 1 of Textor & Lerman (*Semin Nephrol* 2019;39:589–598)⁶² with permission of the corresponding author.

Fig. 2. Penile tissue changes in finasteride-treated rats vs. controls. (Top left) Histologic stain of tissue from corpus cavernosum. Purple = smooth muscle; blue = connective tissue. (A) Sample from control group; (B) Sample from finasteride-treated group. Smooth muscle density in finasteride-treated group was reduced by $44.2\% \pm 7.2\%$ ($P < .001$) vs. controls. Authors wrote: “Substantial reductions in the smooth muscle content...and increases in connective tissue...in the corpus cavernosum were associated with 5ARI treatment.” **(Bottom left)** Stain for endothelial nitric oxide synthase (eNOS) (brown) in corpus cavernosum. (C) Sample from control group; (D) Sample from finasteride-treated group. eNOS expression was reduced by 58.5% in finasteride-treated animals vs. controls. **(Top right)** Proportion of apoptotic cells in corpus cavernosum. (A) Control group; (B) Finasteride-treated group. The finasteride-treated group had “a much greater apoptotic index” compared to the control group. **(Bottom right)** Labeling assay of apoptosis in cavernosal tissue. (A) Control group; (B) Finasteride-treated group. Arrows indicate apoptotic cells with brown-stained nuclei.

Source: Figs. 2 & 4 from Zhang et al (*Urology* 2013;82:743.e9-15).²² Reproduced with permission of the publisher.

Fig. 3. Penile tissue changes in 5ARI-treated rats. (Top row) Penile cross-section at magnification x20. (b) Dutasteride and (c) Finasteride groups have reduced cross-sectional penile area when compared to (a) Control group. **(Middle row)** Smooth muscle in corpus cavernosum at x400. Smooth muscle was reduced in (b) Dutasteride group compared to (a) Control group. (c) Finasteride group had no difference from controls in smooth muscle density or area (mean area was 55% lower in finasteride group without statistical significance). **(Bottom row)** In corpus cavernosum at x600, beige areas indicate elastic fibers. (b) Dutasteride and (c) Finasteride groups show increased amounts of elastic fibers compared to (a) controls.

Source: Figs. 1–3 from Da Silva MHA et al (*Asian J Androl* 2018;20:505-510).²⁰ Reproduced with permission of the publisher.

Fig. 4. Ultrastructure of corpus cavernosum in finasteride-treated rats vs. controls. (Left) Control rats. (Right) Finasteride-treated rats. Top images x300; bottom images x900. Shen et al. noted that in the corpus cavernosum of control rats, “the smooth muscle fibers in the trabeculae were rich and contained a few elastic and collagenous fibers. Structure of the sinusoids was perfect and clear.” In finasteride-treated rats, “the corpus cavernosum... contained a considerable amount of thick and irregularly-arranged collagenous fibers, but the degree of fibrosis was not so marked as in [the castrated group – not shown] and the types of fibrosis were different between these two groups. The sinusoids were partially depressed, but the structure of the sinusoids was still retained [in finasteride-treated rats].”

Source: Figs. 4 & 6 from Shen ZJ et al (*Asian J Androl* 2003;5:33-36).²⁵ Reproduced with permission of the publisher.

Fig. 5. Overview of adverse events of finasteride affecting male genitourinary system in men 18–40. Filters (below) were applied to limit confounding factors. Captions show the most common AEs; see a complete list in Table 2B. Penile tissue changes (right, in italics) are imputed based on research discussed in text, with selected examples reproduced in Figures 2–4.

Source: FDA FAERS. Criteria: Received by FDA: 2000–2020; Sex: Male; Age: 18–40 years; Suspected Product: Finasteride only; Concomitant Products: None.

Fig. 6. Correspondence of PD-5ARI with phases of ischemia-reperfusion injury. In men who have developed PD-5ARI, a multiphase course is anecdotally common. Composition and severity of symptoms may change considerably over time (see also Figure 7). **(Above timeline)** The phased course of ischemia-reperfusion injury show a suggestive correspondence with phases anecdotally associated with PD-5ARI.

Fig. 7. Hypothetical cases illustrating variability of PD-5ARI. Columns A–E represent hypothetical cases. Rows refer to four areas of dysfunction: sexual, neuropsychiatric, cognitive and fatigue/weakness. Small charts represent severity of dysfunction over time: Y axis: 1, low severity; 3, high severity (more debilitating). X-axis: d, day; m, month; y, year. **(A)** Significant sexual and neuropsychiatric dysfunction in the first weeks and months. Over time, these dysfunctions moderate while cognitive dysfunction and energy deficits resolve. **(B)** More severe cognitive and neuropsychiatric dysfunction with relatively mild, but lasting, sexual dysfunction. **(C)** A severe case involving all four areas of dysfunction, which remain moderate to severe over the long term. **(D)** A mild case: relatively low-severity sexual dysfunction persists while other areas remit. **(E)** A “near-miss” case. Sexual, neuropsychiatric and cognitive symptoms arise after 5ARI discontinuation; however all dysfunctions resolve within weeks to months.

Fig. 8. Symptom view vs. system view of PD-5ARI. In the **symptom view**, doctors consult with patients, may find no diagnostic signs (e.g., lab tests normal) and conclude the condition is psychogenic. In the **system view**, symptoms would be interpreted as downstream consequences of prior injuries leading to organ dysfunction. This suggests a different clinical approach: seeking to identify and characterize tissue alterations and injuries rather than attempting to treat symptoms piecemeal.

^a Hypothalamus, particularly medial preoptic area; hippocampus; thalamus; basal ganglia (see also Table 4).

Fig. 9. Hypothetical downstream impact of hypoxic injury on epigenetics, neurosteroidogenesis and microbiome. Previous research has identified epigenetic and microbiome changes as consequences of ischemic injuries. Altered levels of neuroactive steroids could result from altered expression of enzymes due to tissue injury and inflammation.

Table 1. 30 most frequently reported adverse events of finasteride by category

Category	AE terms	AE count	% of all AEs
Sexual anatomy & function	Erectile Dysfunction; Sexual Dysfunction; Organic Sexual Dysfunction; Loss Of Libido; Libido Decreased; Testicular Pain; Genital Hypoaesthesia ^a ; Penile Size Reduced; Penis Disorder; Ejaculation Disorder	565	21.3%
Neuropsychiatric	Depression; Depressed Mood; Anxiety; Suicidal Ideation; Feeling Abnormal; Panic Attack; Anhedonia	416	15.7%
Energy & musculoskeletal	Fatigue; Asthenia; Muscle Atrophy; Arthralgia	144	5.4%
Memory, cognition & attention	Amnesia; Cognitive Disorder; Disturbance In Attention	96	3.6%
Sensory & vestibular	Tinnitus; Dizziness; Vision Blurred	76	2.9%
Sleep	Insomnia	71	2.7%
General	Post 5-Alpha-Reductase Inhibitor Syndrome	20	0.8%
Endocrine	Gynaecomastia	18	0.7%
Subtotal		1,406	52.9%
All AEs of finasteride		2,657	100.0%

Top 30 AEs reported to FDA FAERS for younger men taking finasteride for hair loss from 2018–2020, with filters (below) applied to reduce confounding factors. Filters yielded 376 cases (13.7%) out of a total of 2,736 cases. AEs were disaggregated from cases and categorized (column 1). See Appendix for further background on the use of AE data.

Source: FDA Federal Adverse Events Reporting System Public Dashboard. Selection criteria: Received by FDA: 2018–2020; Sex: Male; Age: 18–40; Suspected product: Finasteride only; Reason for use: Androgenetic Alopecia and other hair loss conditions only, excluding Hair Transplant; Concomitant Products: None.

^a Penile numbness.

Table 2A. Genitourinary adverse events of finasteride and minoxidil by subsystem

Subsystem affected	Finasteride		Minoxidil	
	AE count	% of total	AE count	% of total
Penis; erectile & sexual function	1,399	14.6%	39	1.3%
Testicles	243	2.5%	11	0.4%
Semen and sperm	219	2.3%	8	0.3%
Urinary function, anus & pelvis	59	0.6%	1	–
Prostate	51	0.5%	–	–
Global / ambiguous	28	0.3%	3	0.1%
Subtotal	1,999	20.8%	62	2.0%
Total drug AEs	9,593	100%	3,031	100%

Filters (below) have been applied to minimize confounding factors. A pharmacovigilance signal analysis has not been performed; however, a comparison with minoxidil AEs may suggest drug-specific effects because both are used by a similar population as treatment for hair loss. Genitourinary AEs were 10.2x more common for finasteride (20.8%) than for minoxidil (2.1%).

Source: FDA FAERS. Selection criteria: Received by FDA: 2000–2020; Sex: Male; Age: 18–40; Suspected Product: Finasteride only or Minoxidil only; Concomitant Products: None.

Table 2B. Genitourinary adverse events of finasteride

Subsystem & AE terms	Count
Erectile & sexual function	888
Erectile Dysfunction; Organic Erectile Dysfunction	686
Sexual Dysfunction; Male Sexual Dysfunction	202
Penile anatomy	223
Penile Size Reduced; Penis Disorder; Peyronie's Disease; Male Genital Atrophy; Genital Disorder; Penile Curvature; Genital Atrophy; Male Genital Examination Abnormal	223
Penile sensation	154
Genital Hypoaesthesia ^a	84
Penile Pain; Genital Pain; Genital Paraesthesia; Genital Burning Sensation; Genital Discomfort; Painful Erection	70
Ejaculatory function	134
Ejaculation Disorder; Ejaculation Failure	121
Premature Ejaculation	13
Testicles	243
Testicular Pain	145
Testicular Atrophy	50
Testicular Disorder; Testicular Failure; Seminoma; Other testicular AEs ^b	48
Sperm & semen	219
Semen Volume Decreased	70
<i>Sperm concentration</i> : Sperm Concentration Decreased; Azoospermia; Oligospermia; Sperm Concentration Zero; Hypospermia; Sperm Concentration Abnormal	43
<i>Semen consistency</i> : Semen Viscosity Decreased; Semen Viscosity Increased; Semen Viscosity Abnormal; Semen Liquefaction Abnormal; Semen Liquefaction	34
Semen / Sperm Analysis Abnormal	27
Semen Discolouration; Haematospermia	19
<i>Sperm morphology</i> : Spermatozoa Abnormal; Spermatozoa Morphology Abnormal; Teratospermia; Spermatogenesis Abnormal	16
<i>Sperm motility</i> : Asthenospermia; Spermatozoa Progressive Motility Abnormal / Decreased	10
Urinary function, anus & pelvis	59
Urine Flow Decreased; Urinary Retention; Urinary Incontinence; Bladder Pain; Bladder Disorder; Perineal Pain; Anorectal Discomfort; Pelvic Pain; Other AEs ^c	59
Prostate	51
Prostatitis; Prostatic Pain; Prostatic Disorder; Other prostatic AEs ^d	51
Global / ambiguous	28
Male Reproductive Tract Disorder; Urogenital Disorder; Genital Tract Inflammation	28
Total genitourinary AEs	1,999

This table lists specific adverse events of finasteride which are summarized in Table 2A.

^a Penile numbness.

^b Testicular Mass; Testicular Torsion; Testicular Yolk Sac Tumour.

^c *Urinary*: Gallbladder Disorder; Calculus Urinary; Bladder Discomfort; Bladder Dysfunction; Bladder Dysplasia; Bladder Neck Obstruction; Loss Of Bladder Sensation; Urine Output Decreased. *Anus*: Rectal Haemorrhage; Anal Haemorrhage; Anal Fissure; Anal Spasm; Rectal Spasm; Anorectal Disorder; Haematochezia. *Pelvis*: Pelvic Floor Dysfunction.

^d Benign Prostatic Hyperplasia; Prostatomegaly; Prostate Tenderness; Carcinoid Tumour Of The Prostate

Table 3. Vascular adverse events of finasteride and minoxidil

Subcategory	Finasteride		Minoxidil	
	Count	% VAEs	Count	% VAEs
Circulation & blood pressure	54	59%	27	73%
Occlusive events	29 ^a	32%	2	5%
Hemorrhage	9	9%	8 ^b	22%
Subtotal	92		37	
Total drug AEs	9,593		3,031	
% of total drug AEs	1.0%		1.2%	

Occlusive AEs are those involving thrombosis, embolism, occlusion, ischemia or infarction. Within this set of vascular AEs, the proportion of occlusive events was 5.8x greater for finasteride compared to minoxidil. If the ambiguous term Cerebral Disorder is included (5 occurrences for finasteride only), the proportion of occlusive events was 6.5x greater for finasteride compared to minoxidil. See Supplement for a complete list of vascular AEs.

Source: FDA FAERS. Selection criteria: Received by FDA: 2000–2020; Sex: Male; Age: 18–40; Suspected Product: Finasteride only; Concomitant Products: None.

^a Cerebrovascular Accident (4); Cerebral Venous Sinus Thrombosis (4); Retinal Vein Thrombosis (3); Venous Thrombosis (2); Superior Sagittal Sinus Thrombosis (2); Pulmonary Embolism (2); Deep Vein Thrombosis (2). One each of: Arterial Thrombosis; Basilar Artery Thrombosis; Brain Stem Ischaemia; Cerebellar Infarction; Cerebral Infarction; Cerebral Thrombosis; Cerebral Venous Thrombosis; Peripheral Arterial Occlusive Disease; Peripheral Embolism; Transient Ischaemic Attack. Excludes an ambiguous term, Cerebral Disorder (5).

^b 4 AEs were Application Site Haemorrhage. 2 cases specified a topical product while the other 2 did not specify a product name.

Table 4. Anatomical structures and systems implicated in PD-5ARI

Dysfunction / symptom	Supporting structures & systems	Disease analogues / references
Sexual dysfunction	Penis & genitourinary system; medial preoptic area and arousal circuits in brain	Penile fibrosis; Peyronie's disease; penile injury; acute kidney injury to chronic kidney disease transition
Neuropsychiatric dysfunction	Hypothalamus including medial preoptic area; thalamus; ventral striatum	Stroke; TIA; TBI
Cognitive dysfunction	Striatum, thalamus & hippocampus	Stroke; TIA; TBI
Musculoskeletal dysfunction & fatigue ^a	Bioenergetics & microvascular endothelium	Vasculitis; mitochondrial dysfunction
Vestibular & auditory dysfunction ^b	Thalamus; vestibulothalamic & auditory circuits	Vestibulopathy; vestibular neuritis; Ménière's Disease
Eye conditions	Eye including optic nerve	Ischemic retinopathies
Sleep dysfunction	Sleep circuits in brain including ventral tegmental area	Stroke; TIA; TBI
Gum recession	Gum tissue	Inflammatory processes leading to periodontitis; systemic inflammation
Systemic	Vascular homeostasis; angiogenesis and neoangiogenesis; inflammatory response	Systemic inflammation; endothelial dysfunction; microvasculopathy; systemic sclerosis; ischemia

Column 2 lists candidate structures and systems where injury might lead to dysfunctions in column 1. Disease analogues and references (column 3) are not proposed as equivalents, and may only overlap with dysfunctions of PD-5ARI in certain respects.

^a E.g., joint pain, muscle weakness and muscle atrophy.

^b E.g., tinnitus and orthostatic hypotension.

Table 5. Comparison of stroke and PD-5ARI

	Ischemic stroke	PD-5ARI (hypothesized)
Etiology	Ischemia-reperfusion injury in brain	Microvasculopathy or ischemia-reperfusion injuries affecting multiple systems
Course	Critical vascular event → Acute period → Tissue recovery process → Stabilization Evolves over days, months & years	Parallel to stroke
Signs & symptoms	Variable symptom presentation & severity Limb paresthesia Neuropathy Brain tissue alterations Depression, anxiety & apathy Sleep disturbance	Variable symptom presentation & severity Genital hypoesthesia & paresthesia Loss of skin sensitivity Cerebrovascular events; penile tissue alterations Depression, anxiety & anhedonia Sleep disturbance
Diagnostic tests	CT scan; MRI; cerebral angiography Neuropsychological tests	Penile ultrasound imaging; MRI; pudendal nerve evoked potentials Sexual function questionnaires
Treatment	Neurorehabilitation Psychiatry; psychotherapy	PDE5 inhibitors; other sexual medicine therapies Psychiatry; psychotherapy
Prognosis	Variable outcomes	Variable outcomes. Anecdotally, recovery of sexual function seems uncommon while moderation or resolution of neuropsychiatric & cognitive dysfunctions seems more common.
Impact on life	Reduced motor and/or cognitive capacity Occupational & social challenges May require major life changes	Impaired sexual function affecting relationships, sex and dating Occupational & social challenges May require major life changes
Alternative diagnoses & misdiagnoses	TIA Stroke mimic Confusional state; dementia Depression	Depression or other psychiatric diagnosis, sometimes attributed to hair loss Psychogenic erectile dysfunction Somatic symptom disorder; factitious disorder; mass psychogenic illness