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Citizen Petition

September 18, 2017

On behalf of the Post-Finasteride Syndrome Foundation, a 501(c)(3) not-for-profit, patient advocacy and research organization (more than 150,000 patients, family members, health care professionals and other interested parties have visited the PFS Foundation's website), the undersigned submit this petition under Sections 352 and 355(e) of the Federal Food, Drug, and Cosmetic Act and under Food and Drug Administration (FDA) regulations at 21 C.F.R. §§ 10.30, 201.56, 201.57, 201.80, and 208.1 to request the Commissioner of Food and Drugs to immediately require (1) withdrawal of marketing approval for Propecia (and generic formulations of finasteride, 1 mg, for androgenic alopecia) because the risk of serious injury from the drug outweighs its limited benefits. Alternatively, we request the Commissioner to immediately require (2) amendment of false or misleading safety information, and addition of boxed warnings, warnings, precautions, and contraindications to the product label for Propecia (and generic formulations of finasteride, 1 mg, for androgenic alopecia).

A. ACTION REQUESTED

1. Require the immediate removal of Propecia (and generic formulations of finasteride, 1 mg, for androgenic alopecia) from the market.

    a. Whether or not marketing approval for Propecia is withdrawn, add **WARNINGS**, **PRECAUTIONS**, **HIGHLIGHTS OF PRESCRIBING INFORMATION**, a **BOXED WARNING** and a **CONTRAINDICATION** to the Proscar product label (and generic formulations of finasteride, 5 mg) that the 5-mg finasteride tablet should not be split into quarters for the treatment of androgenic alopecia.

2. Alternatively, require the immediate revision of the Propecia product label (and generic formulations of finasteride, 1 mg, for androgenic alopecia) to warn of serious and severe risks, and to amend false and misleading information, as follows:

    a. Add **WARNINGS**, **PRECAUTIONS**, **HIGHLIGHTS OF PRESCRIBING INFORMATION** and a **BOXED WARNING** for persistent and permanent erectile dysfunction that develops with Propecia use, results in the substantial or complete inability to engage in sexual relations, and continues indefinitely for years after discontinuation of Propecia.

    b. Add **WARNINGS**, **PRECAUTIONS**, **HIGHLIGHTS OF PRESCRIBING INFORMATION** and a **BOXED WARNING** for major depressive disorder and

suicidal ideation that develops with Propecia use, results in substantial or complete disruption of the ability to conduct normal life functions, continues indefinitely for years after discontinuation of Propecia, and may culminate in self-harm or completed suicide.

c. Add a **CONTRAINDICATION** that Propecia should not be used in any individual with sexual dysfunction, and a **BOXED WARNING** that Propecia should be immediately discontinued in any individual who develops sexual dysfunction while taking Propecia.

d. Add a **CONTRAINDICATION** that Propecia should not be used in any individual with depression, and a **BOXED WARNING** that Propecia should be immediately discontinued in any individual who develops depression while taking Propecia.

e. Add **WARNINGS**, **PRECAUTIONS**, and **HIGHLIGHTS OF PRESCRIBING INFORMATION** of the potential adverse effects of Propecia on spermatogenesis and male fertility.

f. Add a **CONTRAINDICATION** that Propecia should not be used in any individual with male infertility, and a **BOXED WARNING** that Propecia should be immediately discontinued in any individual who develops male infertility while taking Propecia.

g. Send Merck a notification letter of the need for a Risk Evaluation and Mitigation Strategy Plan to include the following:

i. Require Merck to send a Dear Health Care Provider Letter to dermatologists, hair restoration surgeons, internists, family practitioners, psychiatrists, psychologists, urologists and endocrinologists that informs the health care providers that Propecia has serious adverse reactions associated with its use, and poses a significant public health concern.

ii. Require Merck to develop a Medication Guide and Communication Plan to make the patients aware that Propecia has serious risks (relative to benefits) that could affect the patients' decision to use, or continue to use, the product.

h. Delete or amend the language in the **ADVERSE REACTIONS, Clinical Trials Experience** section (6.1) of the product label that states, "Resolution [of sexual adverse reactions] occurs in men who discontinued therapy with PROPECIA due to these side effects and in most who continued therapy." We suggest the following amended language: "Resolution [of sexual adverse reactions] does not occur in all men who discontinue therapy with PROPECIA due to these side effects and who continue therapy." [emphasis supplied]

i. Delete the language in the **ADVERSE REACTIONS, Clinical Trials Experience** section (6.1) of the product label that states, "There is no evidence of

increased sexual adverse experiences with increased duration of treatment with PROSCAR 5 mg."

j. Add a paragraph(s) in the **ADVERSE REACTIONS, Clinical Trials Experience** section (6.1) of the product label describing the sexual adverse event data from the Phase 4 clinical trial with Propecia in men 41 to 60 years old and other clinical trials with finasteride, 1 mg and 5 mg, for benign prostatic hyperplasia.

k. Add a paragraph(s) in the **ADVERSE REACTIONS, Clinical Trials Experience** section (6.1) of the product label describing the significant increase in penis disorders, testicular pain, breast enlargement and breast tenderness in men taking finasteride in the Prostate Long-term Efficacy and Safety Study.

l. Delete the language in the **ADVERSE REACTIONS, Postmarketing Experience** section (6.2) of the product label that states, "Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

m. Amend the language in the **ADVERSE REACTIONS, Postmarketing Experience** section (6.2) of the product label that states, "The following adverse reactions have been identified during post approval use of PROPECIA. … Reproductive System: … male infertility and/or poor seminal quality (normalization or improvement of seminal quality has been reported after discontinuation of finasteride)." We suggest the following language in the product label to more accurately reflect the information in the scientific literature: "Reproductive System: … male infertility, spermatogenic failure and/or poor seminal quality that continued after discontinuation of treatment."

n. Add a warning for anxiety, cognitive function and fatigue in the **ADVERSE REACTIONS, Postmarketing Experience** section (6.2) of the product label.

o. The **CLINICAL PHARMACOLOGY, Mechanism of Action** section (12.1) of the product label is misleading. The product label does not disclose critically important information about the mechanism of action of Propecia. Additional information needs to be disclosed about all the steroid hormones metabolized by 5α-reductase, type 1 and type 2, and the 5α-reductase, type 1 and type 2, metabolic pathways that synthesize neurosteroids.

We suggest the addition of the following language to the Propecia product label: "The deficiency of 5α-reductase activity induced by finasteride is not specific for androgen metabolism, but is a general deficiency in steroid metabolism affecting C_{19} and C_{21} steroids, including testosterone, progesterone, glucocorticoids and aldosterone. Inhibition of Type I and II 5α-reductase isozymes reduces formation of biologically active metabolites and neuroactive steroids, including

dihydrotestosterone, dihydroprogesterone, allopregnanolone, dihydrodeoxycorticosterone and tetrahydrodeoxycorticosterone."

p. Amend the language in the **CLINICAL PHARMACOLOGY, Mechanism of Action** section (12.1) of the product label that states, "The Type II 5α-reductase isozyme is primarily found in prostate, seminal vesicles, epididymides, and hair follicles as well as liver." This statement is misleading because it does not disclose important target tissues where 5α-reductase, type 2 is present.

   We suggest the following language: "In humans, the Type II 5α-reductase isozyme is primarily found in prostate, the spermatogonia, seminiferous tubules and Sertoli cells of the testes, genital skin and organs, seminal vesicles, epididymides, the cerebral cortex, hypothalamus and pituitary gland of the brain, and hair follicles as well as liver. In mammals, the Type II 5α-reductase isozyme additionally localizes in the penis and spinal cord, as well as the nucleus accumbens, amygdala, hippocampus, cerebellum and locus coerulus of the brain."

q. Amend the language in the **CLINICAL PHARMACOLOGY, Mechanism of Action** section (12.1) of the product label that states, "Finasteride is a competitive and specific inhibitor of Type II 5α-reductase, an intracellular enzyme that converts the androgen testosterone into DHT" by changing the word 'specific' to 'selective.'

r. Amend the language in the **CLINICAL PHARMACOLOGY, Pharmacodynamics** section (12.2) of the product label that states, "Finasteride has no affinity for the androgen receptor and has no androgenic, antiandrogenic, estrogenic, antiestrogenic, or progestational effects." We suggest the following language: "Finasteride has no affinity for the androgen receptor and has no androgenic, antiestrogenic or progestational effects."

s. Amend the two sentences in the **CLINICAL PHARMACOLOGY, Pharmacodynamics** section (12.2) of the product label that state, "In studies with finasteride, no clinically meaningful changes in luteinizing hormone (LH), follicle-stimulating hormone (FSH) or prolactin were detected. In healthy volunteers, treatment with finasteride did not alter the response of LH and FSH to gonadotropin-releasing hormone indicating that the hypothalamic-pituitary-testicular axis was not affected." These sentences are misleading.

   We suggest the following amended language: "In studies with finasteride, changes in follicle-stimulating hormone (FSH) or prolactin were not detected. Studies with finasteride 1 mg in men with benign prostatic hyperplasia have reported significant increases in luteinizing hormone (LH), while studies with finasteride 1 mg in men with androgenic alopecia did not detect significant changes in LH."

t. The **CLINICAL STUDIES, Studies in Men, Other Results in Vertex Baldness Studies** section (14.1) of the product label states, "At Month 12, statistically significant differences in favor of placebo were found in 3 of 4 domains (sexual interest, erections, and perception of sexual problems)." This section is misleading. We suggest the following product label revisions:

i. This section needs to be moved from Section 14.1 to the **ADVERSE REACTIONS, Clinical Trials Experience** section (6.1) of the product label where the information will be more accessible to prescribing physicians.
ii. The heading needs to be changed from '**Other Results in Vertex Baldness Studies**' to '**Sexual Function Questionnaire**' for the same reason.
iii. This section needs to disclose the results of the sexual function questionnaire for the domain of 'morning erections' which is important information for clinicians who are treating finasteride-associated sexual dysfunction.
iv. The language 'in favor of' is vague and needs to be changed for improved clarity.
v. We suggest the following amended language: "At Month 12, statistically significant decreases in the finasteride group were found in 4 of 5 domains (sexual interest, morning erections, erections, and perception of sexual problems)."

B. STATEMENT OF GROUNDS

1. Post-Finasteride Syndrome - Clinical Considerations

The post-finasteride syndrome (PFS) is a heterogeneous disorder with variability in the type of symptoms experienced by different individuals with PFS. PFS is a life-changing syndrome characterized by sexual dysfunction and psychoneurocognitive symptoms that first develop during Propecia use and continue indefinitely for years after the drug has been discontinued. There are no known effective treatments and the syndrome is indiscriminate in that it develops in men without any prior medical or psychiatric history, pre-existing sexual dysfunction, or any other apparent risk factors. We estimate that tens of thousands of men worldwide who have taken Propecia or finasteride, 1 mg or 1.25 mg, for the treatment of androgenic alopecia (AGA) have developed PFS.

The term PFS has been suggested in numerous peer-reviewed medical journal articles, but there is no consensus case definition for PFS. However, the defining characteristic of PFS is persistent sexual dysfunction that first develops during finasteride use and continues indefinitely after discontinuation of finasteride treatment. Clinicians and sex therapists who treat PFS patients often remark that the presentation, quality and nature of the persistent sexual dysfunction in PFS is completely unlike any other sexual dysfunction that they have previously treated, especially as compared to other young men with more typical sexual dysfunctions.

The most common symptoms of PFS are erectile dysfunction (ED), loss of libido, depression, suicidal ideation, anxiety, panic attacks, insomnia and cognitive dysfunction.

However, the range of sexual symptomatology attributed to Propecia by PFS patients also includes the complete absence of any sexual attraction, Peyronie's disease, penile numbness/pain, testicular numbness/pain, atrophy of the penis, change in consistency of the scrotum, hard and rubbery feel to the penis, painful orgasm, premature ejaculation with decreased ejaculatory force within seconds of sexual stimulation, orgasm dysfunction, and ejaculatory disorders.

The psychological symptoms and cognitive dysfunction of PFS can be more debilitating than the sexual symptoms. Depression, anxiety and insomnia are often resistant to typical therapeutic interventions. Many PFS patients feel physically fatigued. Social isolation is common. Cognitive dysfunction and insomnia can make it difficult to function at the most basic level. Many PFS patients are unable to be gainfully employed.

For young, single men who are sometimes teenagers and often in their 20's, their sexual dysfunction leaves them unable to date and precludes them from ever finding a spouse, or having a family. When married men develop PFS, it inevitably puts a tremendous strain on their relationship with their wives, often with divorce as the eventual outcome.

Unfortunately, too many men have suffered so much that they either seriously contemplate, attempt or commit suicide. The PFS Foundation has provided intensive emotional support to dozens of PFS patients who were seriously contemplating suicide, a dozen PFS patients who attempted suicide, and more than a dozen PFS patients (or their families) who committed suicide.

2. Introduction

Testosterone (T), the principal androgen circulating in male plasma, was believed to be the only active male hormone and dihydrotestosterone (DHT) was believed to be an inactive metabolite of T until 1968, when it became clear that DHT was a true hormone and the mediator of many actions previously attributed to T. Bruchovsky and Wilson determined that DHT is more potent than T, and preferentially binds to the androgen receptor (AR).[1] They also characterized the intranuclear binding of DHT and provided the first definitive evidence that the AR is a protein.

In 1974, Imperato-McGinley et al. identified 13 families with 24 male pseudohermaphrodites in the Dominican Republic and determined that 5α-reductase (5αR) deficiency was the genetic cause of pseudohermaphroditism in this cohort,[2] a discovery that eventually led to the clinical development of finasteride. Imperato-McGinley et al. explained, "The affected males (46XY) are born with marked ambiguity of the external genitalia" and are frequently raised as girls. "At birth, they have bilateral testes presenting as inguinal or labial masses, a labial-like scrotum, a urogenital sinus with a blind vaginal pouch, and a clitoral-like phallus. … At puberty, their voice

[1] Bruchovsky N and Wilson JD, *Intranuclear Binding of Testosterone and 5α-Androstan-17β-ol-3-one by Rat Prostate*, J Biol Chem (1968), Vol. 243(22), pp. 5953-5960.
[2] Imperato-McGinley J et al, *Steroid 5α-Reductase Deficiency in Man: An Inherited Form of Male Pseudohermaphrotidism*, Science (1974) Vol. 186, pp. 1213-1215.

deepens and they develop a typical male phenotype. … The phallus enlarges to become a functional penis. … The testes descend from the inguinal canal and there is an ejaculate." Psychosexual orientation (postpubertal) is male and they have a libido directed toward the opposite sex.

Biochemical data demonstrated that these pseudohermaphrodites have 5αR deficiency with a markedly elevated ratio of plasma T to DHT. The defect in 5α-reduction is a general deficiency affecting 5β/5α metabolism of both C_{19} androgens and C_{21} steroids.[3] The fraction of DHT formed by 5α-reductase, type 2 (5αR2) in normal males is 83%. In genetic 5αR2 deficiency, DHT production is approximately 30% of normal, slightly higher than the 17% estimated to be produced by 5α-reductase, type 1 (5αR1).[4] Genetic 5αR2 deficiency is a heterogeneous disorder with approximately 60 different types of 5αR2 mutations discovered to date.[5] DHT levels and 5αR2 activity in genetic 5αR2 deficiency depend on the type of 5αR2 mutation. Mutated 5αR2 genes in genetic 5αR2 deficiency often result in 5αR2 enzyme that is partially functional and able to convert some T to DHT.

The biochemical features of genetic 5αR2 deficiency include: (i) normal to elevated levels of plasma T, (ii) decreased levels of plasma DHT, (iii) an increased T to DHT ratio, (iv) decreased conversion of T to DHT *in vivo*, (v) decreased production of urinary 5α-reduced androgen metabolites, (vi) decreased plasma and urinary 3α-androstanediol (3α-diol), a major metabolite of DHT, (vii) a global defect in steroid 5α-reduction with decreased urinary 5α-reduced metabolites of both C_{21} and C_{19} steroids, (viii) increased plasma levels of LH, and (ix) elevated plasma FSH levels in some patients.[6]

The observations by Hamilton in 1942 that prepubertal castration prevents AGA[7] and by Imperato-McGinley in 1974 that pseudohermaphrodites with genetic 5αR deficiency have decreased body hair, a scant to absent beard, no temporal hair line recession, no acne and a small prostate[8,9] eventually led to the development by Merck of finasteride for benign prostatic hyperplasia (BPH) and AGA. As Elizabeth Stoner, head of Merck's finasteride clinical research program, explained, "The clinical features which define the genetic syndrome of 5αR2 deficiency have provided a model for predicting the biological effects of chronic inhibition of this enzyme in the adult male."[10] Glenn Gormley, head of Merck's finasteride clinical development program for BPH, stated,

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[3] Stoner E, *The Clinical Development of a 5α-Reductase Inhibitor, Finasteride*, J Steroid Biochem Molec Biol (1990), Vol. 37(3), pp. 375-378.
[4] Gisleskog P et al, *A model for the turnover of dihydrotestosterone in the presence of the irreversible 5α-reductase inhibitors GI198745 and finasteride*, Clin Pharmacol Therapeutics (1998), Vol. 64, pp. 636-647.
[5] Kang H et al, *The effect of 5α-reductase-2 deficiency on human fertility*, Fertil Steril (2014), Vol. 101(2), pp. 310-316.
[6] Imperato-McGinley J and Zhu Y, *Androgens and male physiology the syndrome of 5α-reductase-2 deficiency*, Molec Cell Endocrin (2002), Vol. 198, pp. 51-59.
[7] Hamilton J, *Male Hormone Stimulation is Prerequisite and an Incitant in Common Baldness*, Amer J Anat (1942), Vol. 71(3), pp. 451-480.
[8] Imperato-McGinley (1974) *op. cit.*, pp. 1213-1215.
[9] Imperato-McGinley (2002) *op. cit.*, pp. 51-59.
[10] Stoner (1990) *op. cit.*, pp. 375-378.

"Inhibition of 5αR by finasteride occurs without affecting DHT binding to the AR, and thus, mimics hereditary 5αR2 deficiency."[11]

3. Basic Physiology

a. Androgen Action.

The natural ligand for the AR is DHT which is converted by 5αR from the less active T in an irreversible reaction.[12] DHT binds to the AR with up to 10-fold greater affinity than T and dissociates more slowly from the AR forming a stable complex more resistant to degradation.[13] Human AR cDNA was first cloned and sequenced in 1988.[14] Unbound AR is mainly located in the cytoplasm where it binds to T or DHT. Upon binding to T or DHT, the AR goes through a series of conformational changes and the transformed AR-androgen complex translocates to the nucleus.[15] In the nucleus, the AR binds to androgen response elements located in the chromatin of androgen-regulated genes, recruits coregulator proteins, and directs transcription of androgen dependent genes.[16]

The relative potency of T and DHT was first characterized in 1990 by Grino et al.[17] The human AR of a man with genetic 5αR2 deficiency was studied in genital skin fibroblasts. The affinity binding of DHT to the AR was 2-fold greater than T. The dissociation rate of DHT from the AR was one-fifth of the dissociation rate of T from the AR. AR binding of T was equally thermostable as AR binding of DHT at a 10-fold higher concentration of T than DHT. The net effect of the difference in dissociation rates between T and DHT is to favor the binding of DHT to the AR under equilibrium conditions.

The relative potency of T and DHT was further characterized in 1992 by Deslypere et al.[18] who introduced a plasmid encoding AR cDNA and a reporter gene linked to a promoter that contains an androgen response element (MMTV-CAT) into Chinese hamster ovary cells. Deslypere et al. reported "DHT was approximately 10 times as potent (half maximal of 0.018 nM) as T (half maximal of 0.2 nM)."[19] Deslypere et al.

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[11] Gormley GJ et al, *Effects of Finasteride (MK-906), a 5α-Reductase Inhibitor, on Circulating Androgens in Male Volunteers*, J Clin Endocrinol Metab (1990), Vol. 70, pp. 1136-1141.
[12] Azzouni F et al, *The 5 Alpha Reductase Isozyme Family: A Review of Basic Biology and Their Role in Human Diseases*, Advances Urology (2011), Vol. 2012, pp. 1-18.
[13] Schmidt L and Tindall D, *Androgen Receptor: Past, Present and Future*, Curr Drug Targ (2013), Vol. 14, pp. 401-407.
[14] Chang C et al, *Structural analysis of complementary DNA and amino acid sequences of human and rat androgen receptors*, Proc Natl Acad Sci (1988), Vol. 85, pp. 7211-7215.
[15] Gao W et al, *Chemistry and Structural Biology of Androgen Receptor*, Chem Rev (2005), Vol. 105(9), pp. 3352-3370.
[16] Schmidt *op. cit.*, pp. 401-407.
[17] Grino P et al, *Testosterone at High Concentrations Interacts with the Human Androgen Receptor Similarly to Dihydrotestosterone*, Endocrinology (1990), Vol. 126, pp. 1165-1172.
[18] Deslypere JP et al, *Testosterone and 5α-dihydrotestosterone interact differently with the androgen receptor to enhance transcription of the MMTV-CAT reporter gene*, Molec Cell Endocrinol (1992), Vol. 88, pp. 15-22.
[19] Ibid.

concluded, "In androgen target tissue such as penis and prostate … DHT formation appears to be essential for virilization."[20]

T is primarily synthesized in the Leydig cells of the testes, but is also synthesized in the adrenal cortex and liver. T synthesis is regulated by luteinizing hormone (LH) which is released from the pituitary gland. LH release is controlled by LH releasing hormone (LH-RH, also known as gonadotropin releasing hormone (GnRH)) from the hypothalamus with negative feedback regulation by T and DHT at both the pituitary and hypothalamic levels.[21]

The main metabolites of DHT, 3α-diol and androsterone, are conjugated primarily in the liver to form 3α-diol glucuronide (Adiol-G) and androsterone glucuronide (Andros-G), respectively.[22,23] Serum concentrations of Adiol-G and Andros-G are the most reliable parameters of the total androgen pool in men.[24]

b. Animal Studies demonstrating DHT as the Active Androgen in Penile Erection.

DHT is necessary for normal erectile function in rats.

Bradshaw W et al, *Attenuation by a 5α-Reductase Inhibitor of the Activational Effect of Testosterone Propionate on Penile Erections in Castrated Male Rats* (1981).[25]

Bradshaw et al. published the first article demonstrating that DHT is the androgen that activates penile erection in mammals. After castration, rats were treated with (i) vehicle, (ii) T, (iii) T + 5αR inhibitor (5αRI), or (iv) T + 5αRI + DHT. Castrated rats have impaired erectile function. T treatment of castrated rats restored erection, but not when treated with T + 5αRI. DHT facilitates penile erections in the rat by acting in motoneurons in the lumbar spinal cord.

Bradshaw et al. concluded, "The present findings suggest that the activational effect of T on penile erections displayed by rats … is mediated by the 5α-reduced metabolite(s) of T. These metabolites include 3α- and 3β-androstanediol in addition to DHT."

[20] Ibid.
[21] Gao *op. cit.*, pp. 3352-3370.
[22] Rittmaster R et al, *Androstanediol Glucuronide Production in Human Liver, Prostate, and Skin: Evidence for the Importance of the Liver in 5α-Reduced Androgen Metabolism*, J Clin Endocrinol Metab (1993), Vol. 76, pp. 977-982.
[23] Labrie F et al, *Marked Decline in Serum Concentrations of Adrenal C19 Sex Steroid Precursors and Conjugated Androgen Metabolites During Aging*, J Clin Endocrinol Metab (1997), Vol. 82, pp. 2396-2402.
[24] Ibid.
[25] Bradshaw W et al, *Attenuation by a 5α-Reductase Inhibitor of the Activational Effect of Testosterone Propionate on Penile Erections in Castrated Male Rats*, Endocrinology (1981), Vol. 109, pp. 1047-1051.

Burnett A et al, *Nitric Oxide: A Physiologic Mediator of Penile Erection* (1992).[26]

Nitric oxide (NO) is a major neuronal messenger. Immunohistochemistry (IHC) studies localize nitric oxide synthase (NOS), the synthetic enzyme for NO, to neurons in the brain and autonomic nerves where NO functions as a neurotransmitter. Burnett et al. localized NOS by IHC to rat penile tissue (pelvic plexus, cavernosal nerve, neuronal plexuses of the cavernosal arteries and neurons of the corpora cavernosa). A NOS inhibitor abolished electrophysiologically induced penile erections in rats.

Burnett et al. concluded, "The selective localization of NOS in penile neurons that subserve erection, as well as the ability of NOS inhibitors to block physiologic erection selectively, potently, and completely, imply NO is the major if not sole neuronal mediator of erection."

Lugg JA et al, *Dihydrotestosterone is the active androgen in the maintenance of nitric oxide-mediated penile erection in the rat* (1995).[27]

Lugg et al. castrated rats which induced the loss of penile reflexes, reduced erectile response to electrical stimulation of the cavernosal nerve, and reduced NOS activity. The effects of castration were reversed by T replacement, but not when finasteride was present. DHT replacement reversed the effects of castration on the erectile response, even when finasteride was present.

Lugg et al. concluded, "These results show that DHT is the active androgen in the prevention of erectile failure seen in castrated rats."

Park KH et al, *Effects of androgens on the expression of nitric oxide synthase mRNAs in rat corpus cavernosum* (1999).[28]

Park et al. evaluated the erectile response to electrical stimulation, the NOS activity in the corpus cavernosum, and the neuronal NOS (nNOS) mRNA expression in castrated rats supplemented with (i) T, (ii) T + finasteride, and (iii) DHT. T and DHT both restored the decrease in NOS activity, nNOS mRNA expression and erectile response in castrated rats to normal levels, but DHT was more potent, and nNOS mRNA expression was less influenced by T than DHT. T did not restore the decrease in NOS activity, nNOS mRNA and erectile response when given with finasteride and these parameters remained at castrate levels.

Park et al. concluded, "Androgens enhance nNOS gene expression in the penile corpus cavernosum of rats, suggesting that they play an important role in maintaining NOS activity. Of the two androgens, DHT was more potent."

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[26] Burnett A et al, *Nitric Oxide: A Physiologic Mediator of Penile Erection*, Science (1992), Vol. 257, pp. 401-403.
[27] Lugg JA et al, *Dihydrotestosterone is the active androgen in the maintenance of nitric oxide-mediated penile erection in the rat*, Endocrinology (1995), Vol. 136, pp. 1495-1501.
[28] Park KH et al, *Effects of androgens on the expression of nitric oxide synthase mRNAs in rat corpus cavernosum*, British Journal of Urology International (1999), Vol. 83, pp. 327-333.

c. Activity of 5α-Reductase.

The **CLINICAL PHARMACOLOGY, Mechanism of Action** section (12.1) of the product label is misleading as it does not disclose critically important information about the mechanism of action of Propecia. Additional information about all the steroid hormones metabolized by 5αR1 and 5αR2, and the 5αR1 and 5αR2 metabolic pathways that synthesize neurosteroids, needs to be disclosed. The neurosteroids formed by the 5αR1 and 5αR2 metabolic pathways are necessary for normal behavioral regulation and sexual function.

In 1990, human 5αR cDNA was first cloned and sequenced.[29] The deficiency of 5αR activity induced by finasteride is not specific for androgen metabolism, but is a general deficiency in steroid metabolism affecting C_{19} and C_{21} steroids (steroids with 19 or 21 carbon molecules).[30]

C_{19} steroids that interact with 5αR include androstanes (T, epitestosterone and androstenedione). C_{21} steroids that interact with 5αR include pregnanes (progesterone), glucocorticoids (cortisol, corticosterone and DOC) and mineralocorticoids (aldosterone).[31]

The Propecia product label discloses the effects of finasteride on the metabolism of T into DHT by 5αR2, but does not disclose the effects of finasteride on at least 8 other steroid substrates that are 5α-reduced by 5αR. The 5αR1 and 5αR2 enzymes catalyze the 5α-reduction of all C_{19} and C_{21} steroids, including T, progesterone, androstenedione, epitestosterone, cortisol, cortisone, corticosterone, deoxycorticosterone (DOC) and aldosterone, into biologically active metabolites.[32,33,34,35,36]

Reactions of T, progesterone and DOC with 5αR1 and 5αR2 result in the synthesis of the neuroactive steroids, DHT, dihydroprogesterone (DHP) and dihydrodeoxycorticosterone (DHDOC), respectively. Reactions of glucocorticoids and aldosterone with 5αR1 and 5αR2 result in the synthesis of dihydrocorticosterone, dihydrocortisol and dihydroxyaldosterone. In the nervous system, DHT and DHP are converted by

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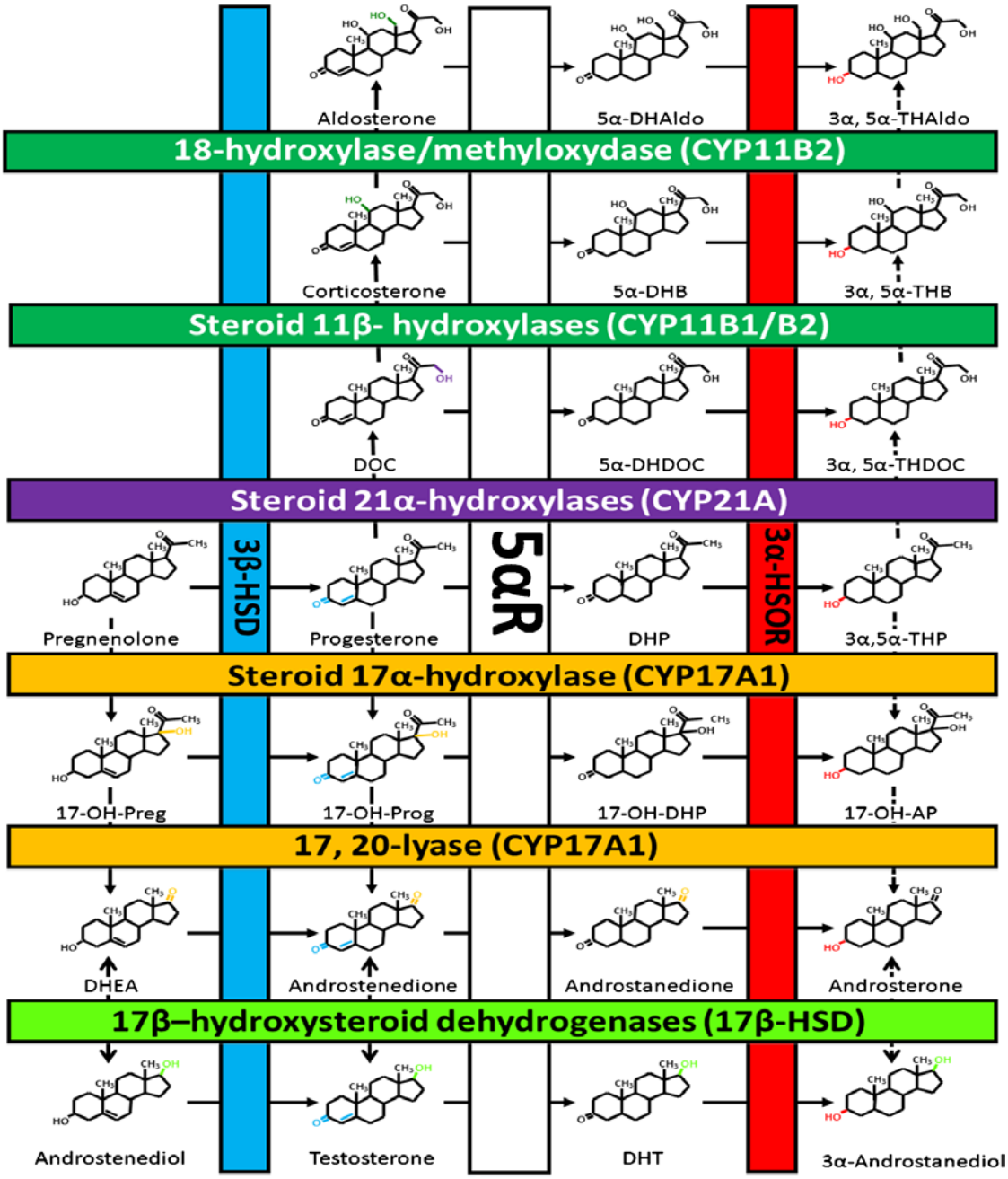
[29] Andersson S and Russell D, *Structural and biochemical properties of cloned and expressed human and rat steroid 5α-reductases*, Proc Natl Acad Sci USA (1990), Vol. 87, pp. 3640-3644.
[30] Stoner (1990) *op. cit.*, pp. 375-378.
[31] Ibid.
[32] Fisher L et al, *Clinical, Endocrinological, and Enzymatic Characterization of Two Patients with 5α-R Deficiency: Evidence that a Single Enzyme is Responsible for the 5α-Reduction of Cortisol and Testosterone*, J Clin Endocrinol and Metab (1978), Vol. 47(3), pp. 653-664.
[33] Imperato-McGinley J et al, *C_{19} and C_{21} 5β/5α Metabolite Ratios in Subjects Treated with the 5α-Reductase Inhibitor Finasteride: Comparison of Male Pseudohermaphrodites with Inherited 5α-Reductase Deficiency*, J Clin Endocrinol Metab (1990), Vol. 70, pp. 777-782.
[34] Belelli D et al, *Neurosteroids: Endogenous Regulators of the $GABA_A$ Receptor*. Nat Rev Neurosci (2005), Vol. 6, pp. 565-575.
[35] Traish AM et al, *Adverse effects of 5α-reductase inhibitors: What do we know, don't know, and need to know?*, Rev Endocr Metab Dis (2015), Vol. 16(3), pp. 177-198.
[36] Azzouni *op. cit.*, pp. 1-18.

3α-hydroxysteroid oxidoreductase into the neuroactive steroids, 3α-diol and tetrahydroprogesterone (THP or allopregnanolone), respectively, and by 3β-hydroxysteroid oxidoreductase into 3β-diol and isopregnanolone.[37,38]

The following schematic[39] illustrates most of the metabolic pathways in which 5αR1 and 5αR2 play a major role:



[37] Melcangi RC et al, *Neuroactive steroid levels and psychiatric and andrological features in post-finasteride patients*, J Ster Biochem Molec Biol (2017), Vol. 171, pp. 229-235.
[38] Traish (2015) Rev Endocr Metab Dis *op. cit.*, pp. 177-198.
[39] Ibid.

Elizabeth Stoner, head of Merck's finasteride clinical research program, asserted to the Advisory Committee reviewing the Propecia New Drug Application (NDA), "Finasteride's mechanism of action is targeted specifically at inhibiting Type II 5-alpha-Reductase *without other adventitious effects*."[40] [emphasis supplied]

This statement seems incongruous with statements in her report of a clinical trial that provided objective evidence of the effects of finasteride on steroid hormone action and metabolism.[41] This study demonstrated that finasteride treatment results in a defect in the 5α-reduction of C_{19} and C_{21} steroids with affinity for multiple steroid substrates. Stoner concluded, "Finasteride has a broad steroid spectrum inhibiting C_{19} and C_{21} 5α-steroid metabolism and affecting hepatic and peripheral 5α-metabolism."[42]

d. Tissue Localization of 5α-Reductase.

The **CLINICAL PHARMACOLOGY, Mechanism of Action** section (12.1) of the product label states, "The Type II 5α-reductase isozyme is primarily found in prostate, seminal vesicles, epididymides, and hair follicles as well as liver." This statement is misleading because it does not disclose important target tissues where 5αR2 is present.

Additional target tissues that need to be added to the Propecia product label include: (i) genital skin and organs in humans,[43,44] (ii) the spermatogonia, seminiferous tubules and Sertoli cells of the testes in humans,[45,46] (iii) the cerebral cortex, hypothalamus and pituitary gland of the brain in humans,[47,48,49,50] (iv) the penis[51,52,53] and spinal cord[54] in

[40] Dermatologic and Ophthalmic Drugs Advisory Committee Meeting No. 48 (November 13, 1997), transcript pp. 1-206, pg. 95.
[41] Imperato-McGinley (1990) *op. cit.*, pp. 777-782.
[42] Ibid.
[43] Hellwinkel OJ et al, *Influence of androgens and age on androgen receptor and 5α-reductase II transcription,* Eur J Endocrinol (2000), Vol. 143, pp. 217-225.
[44] Eicheler W et al, *Immunocytochemical localization of 5 alpha-reductase 2 with polyclonal antibodies in androgen target and non-target human tissues*, J Histochem Cytochem (1994), Vol. 42(5), pp. 667-675.
[45] Steger K et al, *Reversion of the differentiated phenotype and maturation block in Sertoli cells in pathological human testis*, Human Reproduction (1999), Vol. 14(1), pp. 136-143.
[46] Hadziselimovic F and Dessouky N, *Differences in Testicular Development Between 5α-Reductase 2 Deficiency and Isolated Bilateral Cryptorchidism*, J Urol (2008), Vol. 180, pp. 1116-1120.
[47] Aumuller G et al, *Immunocytochemical Evidence for Differential Subcellular Localization of 5α-Reductase Isoenzymes in Human Tissues*, Acta Anatom (1994), Vol. 156, pp. 241-252.
[48] Thigpen AE et al, *Tissue Distribution and Ontogeny of Steroid 5α-Reductase Activity*, J Clin Invest (1993), Vol. 92, pp. 903-910.
[49] Eicheler *op. cit.*, pp. 667-675.
[50] McPhaul M, *Defects of Androgen Action*, Princip Mol Med (2006), pp. 466-472.
[51] Shen Z et al, *Effect of androgen deprivation on penile ultrastructure*, Asian J Andrology (2003), Vol. 5, pp. 33-36.
[52] Zhang M et al, *Effects of Oral Finasteride on Erectile Function in a Rat Model*, J Sex Med (2012), Vol. 9, pp. 1328-1336.
[53] Zhang M et al, *Long-term Oral Administration of 5α-reductase Inhibitor Attenuates Erectile Function by Inhibiting Autophagy and Promoting Apoptosis of Smooth Muscle Cells in Corpus Cavernosum of Aged Rats*, Urology (2013), Vol. 82(3), pp. 743.e9-743.e15.
[54] Schirar A et al, *Androgens Modulate Nitric Oxide Synthase Messenger Ribonucleic Acid Expression in Neurons of the Major Pelvic Ganglion in the Rat*, Endocrinology (1997), Vol. 138, pp. 3093-3102.

rats, and (v) the nucleus accumbens, amygdala, hippocampus, cerebellum and locus coeruleus of the brain in rats.[55]

Thigpen et al, *Tissue Distribution and Ontogeny of Steroid 5α-Reductase Activity* (1993).[56]

5αR2 expression in human males was detected by immunoblotting with polyclonal antibodies in epididymis, liver, pituitary, prostate, seminal vesicle, testis and medulla oblongata.

Eicheler W et al, *Immunocytochemical localization of 5 alpha-reductase 2 with polyclonal antibodies in androgen target and non-target human tissues* (1994).[57]

The tissue distribution and cellular localization of 5αR2 in human males was found (with decreasing intensity) in inner epithelial sheath of hair follicles, pyramidal cells of the cerebral cortex, hepatocytes and bile duct cells, prostate epithelial cells, seminal vesicle epithelial cells, endothelial cells of small vessels, fat cells, fibrocytes of genital and extragenital organs, and smooth muscle cells of the prostate and seminal vesicles.

Aumuller G et al, *Immunocytochemical Evidence for Differential Subcellular Localization of 5α-Reductase Isoenzymes in Human Tissues* (1996).[58]

5αR2 immunoreactivity in human males localized to testis (spermatogonia), epididymis, seminal vesicle, prostate, kidney (proximal tubule and collecting ducts), adrenal, pituitary, liver, pancreas, skin, hair follicle (inner root sheath) and cerebral cortex (small neurons and pyramidal cells). 5αR1 is thought to be involved catabolic pathways (the inactivation of T), while 5αR2 is thought to be responsible for the intracellular activation of T in androgen target tissues.

Celotti F et al, *Steroid Metabolism in the Mammalian Brain: 5α-Reduction and Aromatization* (1997).[59]

Local synthesis of neuroactive steroids within the brain occurs in glial cells, mainly in the oligodendrocyte, which constitute the myelinating cells of the CNS. In general, the affinity of 5αR1 for the various substrates is in the micromolar range, while the affinity of 5αR2 is in the nanomolar range. Progesterone is the preferred substrate of 5αR followed by T and, at a considerable distance, by corticosterone. 5αR1 is present in the cerebellum (predominant), pons, hypothalamus and medulla oblongata of the brain.

[55] Castelli MP et al, *Regional distribution of 5α-reductase type 2 in the adult rat brain: An immunohistochemical analysis*, Psychoneuroendocrinol (2013), Vol. 38, pp. 281-293.
[56] Thigpen *op. cit.*, pp. 903-910.
[57] Eicheler *op. cit.*, pp. 667-675.
[58] Aumuller *op. cit.*, pp. 241-252.
[59] Celotti F et al, *Steroid Metabolism in the Mammalian Brain: 5α-Reduction and Aromatization*, Brain Res Bull (1997), Vol. 44(4), pp. 365-375.

5αR2 is present in the cerebellum, medulla oblongata (predominant) and pyramidal cells of the cerebral cortex of the brain.

Kaufman K, *Testimony at Dermatologic and Ophthalmic Drugs Advisory Committee Meeting No. 48* (November 13, 1997).[60]

Keith Kaufman, head of the Propecia clinical development program, made a representation to the Advisory Committee members reviewing the Propecia NDA that was inconsistent with the mainstream scientific literature when he stated, "DHT does not appear to have any essential physiological role in the adult male, but is involved in the production of beard and body hair, enlargement of the prostate with age and development of male pattern baldness."

McPhaul M, *Defects of Androgen Action* (2006).[61]

Although T is the most abundant circulating androgen, DHT is the predominant hormone found complexed to the AR in the nuclei of targeted cells. Human 5αR2 is localized to the pons, cerebral cortex and hypothalamus of the brain.

Castelli MP et al, *Regional distribution of 5α-reductase type 2 in the adult rat brain: An immunohistochemical analysis* (2013).[62]

5αR2 is distributed in most adult rat brain regions and is particularly expressed in the olfactory lobe, neocortex, hippocampus, amygdala, thalamus, locus coeruleus, basal ganglia (globus pallidus and nucleus accumbens) and cerebellum. Moderate 5αR2 levels are distributed in the hypothalamus (paraventricular and arcuate nuclei) and midbrain. The localization of 5αR2 largely overlaps with the localization of the key enzymes for the synthesis and metabolism of androgens in the brain.

5αR2 in adult rat brain is distributed in neurons in critical regions for behavioral regulation. The localization of 5αR2 in the major output neurons of key corticolimbic structures, such as prefrontal cortex, amygdala, striatum and hippocampus, and the basal ganglia, is consistent with a role for 5αR2 in the modulation of emotion, stress, motivation and cognitive functions.

e. Tissue Localization of the Androgen Receptor.

The AR localizes to many tissues in men. DHT (bound to the AR) is the predominant androgen that localizes to the perinuclear area of cells in androgen responsive tissues. Therefore, AR localization in target tissues defines those tissues that are expected to be adversely affected by finasteride treatment. Important examples of these tissues include

[60] Advisory Committee Meeting No. 48 *op. cit.*, pg. 21.
[61] McPhaul *op. cit.*, pp. 466-472.
[62] Castelli *op. cit.*, pp. 281-293.

the anterior and posterior pituitary gland,[63] corpora cavernosa of the penis,[64,65,66] foreskin of penis,[67,68] and the spermatogonia, spermatocytes, Sertoli cells, Leydig cells, and fibroblasts of the testes,[69,70,71] etc.

Ruizeveld de Winter JA et al, *Androgen Receptor Expression in Human Tissues: An Immunohistochemical Study* (1991).[72]

Human AR localized by IHC was found in the foreskin (keratinocytes and fibroblasts), prostate, seminal vesicle, vas deferens, epididymis, testis (Sertoli cells, Leydig cells, cells in a ring around spermatogonia, peritubular myoid cells and interstitial cells), smooth muscle tissue of the male reproductive organs, cardiac muscle, sweat and sebaceous glands, and liver (hepatocytes). The authors concluded, "In all tissues examined, the selective nuclear localization of the AR has now been established."

Janssen PJ et al, *Immunohistochemical Detection of the Androgen Receptor with Monoclonal Antibody F39.4 in Routinely Processed, Paraffin-embedded Human Tissues After Microwave Pre-treatment* (1994).[73]

Human AR localized by IHC was confined to the nuclei in all cells; cytoplasm was negative. The AR localized to prostate (epithelium, basal cells, smooth muscle, fibroblast), seminal vesicle, epididymis, testis (spermatogenic cells, Sertoli cells, Leydig cell, fibroblast), foreskin, skin (sweat and sebaceous gland), salivary gland, liver (hepatocyte), and cardiac muscle.

Kimura N et al, *Immunocytochemical localization of androgen receptor with polyclonal antibody in paraffin-embedded human tissues* (1993).[74]

Human AR localized by IHC was restricted to the nuclei in all cells. The AR localized to prostate (epithelium, basal cell, smooth muscle, fibroblast), testis (spermatogonia, spermatocyte, Sertoli cell, Leydig cell, fibroblast), breast, skin (epidermis, sweat and

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[63] Kimura N et al, *Immunocytochemical localization of androgen receptor with polyclonal antibody in paraffin-embedded human tissues*, J Histochem Cytochem (1993), Vol. 41(5), pp. 671-678.
[64] Nonomura K, et al, *Androgen Binding Activity in the Spongy Tissue of Mammalian Penis*, J Urol (1990), Vol. 144, pp. 152-155.
[65] Schultheiss D et al, *Androgen and estrogen receptors in the human corpus cavernosum penis: immunohistochemical and cell culture results*, World J Urol (2003), Vol. 21, pp. 320-324.
[66] Lewis RW and Mills TM, *Effect of Androgens on Penile Tissue*, Endocrine (2004), Vol. 23(2-3), pp. 101-105.
[67] Ruizeveld de Winter JA et al, *Androgen Receptor Expression in Human Tissues: An Immunohistochemical Study*, J Histochem Cytochem (1991), Vol. 39(7), pp. 927-936.
[68] Janssen PJ et al, *Immunohistochemical Detection of the Androgen Receptor with Monoclonal Antibody F39.4 in Routinely Processed, Paraffin-embedded Human Tissues After Microwave Pre-treatment*, J Histochem Cytochem (1994), Vol. 42(8), pp. 1169-1175.
[69] Ibid.
[70] Kimura *op. cit.*, pp. 671-678.
[71] Ruizeveld de Winter *op. cit.*, pp. 927-936.
[72] Ibid.
[73] Janssen *op. cit.*, pp. 1169-1175.
[74] Kimura *op. cit.*, pp. 671-678.

sebaceous gland, hair follicle), smooth muscle (artery, GI tract), skeletal and cardiac muscle, anterior and posterior pituitary (LH, FSH and GH cells), thyroid, adrenal cortex, kidney, urinary bladder and liver (hepatocytes).

f. **Mechanism of Action of Finasteride.**

The **CLINICAL PHARMACOLOGY, Mechanism of Action** section (12.1) of the product label states, "Finasteride is a competitive and specific inhibitor of Type II 5α-reductase, an intracellular enzyme that converts the androgen testosterone into DHT." This is a misleading statement. Finasteride is a selective, not a specific, inhibitor of Type II 5α-reductase.

Tian G et al, *17β-(N-tert-Butylcarbamoyl)-4-aza-5α-androstan-1-en-3-one is an Active Site-Directed Slow Time-Dependent Inhibitor of Human Steroid 5α-Reductase 1* (1994).[75]

In 1994, Tian et al. determined that finasteride is a potent inhibitor of the human 5αR1 enzyme with formation of an enzyme-inhibitor complex. *In vitro*, 5αR1 is completely inactivated by finasteride, suggesting either an irreversible reaction or a half-life for the enzyme-inhibitor complex of greater than 10 days. The inability to recover 5αR1 activity after incubation with finasteride suggests a covalent binding step. Tian et al. concluded that finasteride is a potent inhibitor of both 5αR1 and 5αR2.

Azzouni et al. described the findings of Tian et al, "Finasteride is a potent (mean inhibitory concentration [IC_{50}] 69 nM) competitive inhibitor of 5αR2 but inhibits less effectively 5αR1 (IC_{50} 360 nM)."[76] Based on these IC_{50}s, finasteride is a 5.2-fold more potent inhibitor of 5αR2 than 5αR1.

The Propecia product label states that finasteride inhibits 5αR with a 100-fold selectivity for 5αR2 (IC_{50} = 4.2 nM) over 5αR1 (IC_{50} = 500 nM).[77]

Bull H et al, *Mechanism-Based Inhibition of Human Steroid 5α-Reductase by Finasteride: Enzyme-Catalyzed Formation of NADP-Dihydrofinasteride, a Potent Bisubstrate Analog Inhibitor* (1996).[78]

Bull et al. determined that finasteride is a potent inhibitor of the human 5αR2 enzyme in which "essentially every catalytic event is lethal." The membrane-bound, enzyme-inhibitor complex has a half-life of 1 month. Finasteride continues to inhibit 5αR even when the patient misses a dose. Additional finasteride is only required to inhibit the

[75] Tian G et al, *17β-(N-tert-Butylcarbamoyl)-4-aza-5α-androstan-1-en-3-one is an Active Site-Directed Slow Time-Dependent Inhibitor of Human Steroid 5α-Reductase 1*, Biochemistry (1994), Vol. 33(8), pp. 2291-2296.
[76] Azzouni *op. cit.*, pp. 1-18.
[77] *Propecia® Full Prescribing Information* (2014). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020788s024lbl.pdf.
[78] Bull H et al, *Mechanism-Based Inhibition of Human Steroid 5α-Reductase by Finasteride: Enzyme-Catalyzed Formation of NADP-Dihydrofinasteride, a Potent Bisubstrate Analog Inhibitor*, J Amer Chem Soc (1996), Vol. 118, pp. 2359-2365.

newly synthesized 5αR. Finasteride is also an inhibitor of human 5αR1 in which "more than half the catalytic events of finasteride remain lethal."

Bull H and Harris G, *Irreversible Inhibition of Human 5α-Reductase* (1999).[79]

Bull and Harris explained in this Merck patent that "the efficacy of finasteride far exceeded expectations" in clinical trials as about two weeks were required for DHT levels to return to baseline after withdrawal of finasteride. "The potency of finasteride had been mistakenly underestimated." The inventors concluded that finasteride binds to 5αR1 and 5αR2 without covalently modifying the enzymes "to form an essentially irreversible enzyme-inhibitor complex" that displays the "characteristics of a suicide inhibitor. … 'Suicide inhibitors' are not favored as pharmaceutical agents because the covalently-modified enzyme may be recognized by the immune system of the treated organism as foreign matter and trigger an undesirable immunological response."

Scolnik E, *Testimony during Dermatologic and Ophthalmic Drugs Advisory Committee Meeting No. 48* (November 13, 1997).[80]

Edward Scolnik, President of Merck Research Labs, provided testimony before the Advisory Committee reviewing the Propecia NDA that is inconsistent with Merck's preclinical data and data from the scientific literature when he stated, "The inhibitor finasteride inhibits somewhat selectively the Type II in rat, but also, with the doses, inhibits both enzymes. In man, it *only inhibits the Type II enzyme*, and it would, *even if you went up to 80 or 100 milligrams* of the drug in man." [emphasis supplied]

Pharmacodynamic analysis of finasteride by Suzuki et al. demonstrated that 5αR1 inhibition is dose-dependent from 0.2 to 100 mg finasteride.[81] Finasteride potently and irreversibly inhibits the 5αR1 enzyme.[82,83]

Merck's preclinical data found that finasteride has 100-fold selectivity for 5αR2 over 5αR1.[84] According to Merck's data, finasteride 100 mg should inhibit the 5αR1 enzyme to approximately the same degree as finasteride 1 mg inhibits the 5αR2 enzyme.

According to the data of Tian et al, finasteride 1 mg should inhibit the 5αR1 enzyme to approximately the same degree as finasteride 0.2 mg inhibits the 5αR2 enzyme.

[79] Bull H and Harris G (Assignee: Merck & Co., Inc.), *Irreversible Inhibition of Human 5α-Reductase*, U.S. Patent No. 5,962,442 (October 5, 1999).
[80] Advisory Committee Meeting No. 48 *op. cit.*, pg. 191.
[81] Suzuki R et al, *Saturable Binding of Finasteride to Steroid 5α-reductase as Determinant of Nonlinear Pharmacokinetics*, Drug Metab Pharmacokinetics (2010), Vol. 25(2), pp. 208-213.
[82] Bull (1999) *op. cit*.
[83] Tian *op. cit.*, pp. 2291-2296.
[84] *Propecia® Full Prescribing Information* (2014) *op. cit.*

Yamana K et al, *Human type 3 5α-reductase is expressed in peripheral tissues at higher levels than types 1 and 2 and its activity is potently inhibited by finasteride and dutasteride* (2010).[85]

The mRNA expression levels of 5αR2 and 5αR, type 3 (5αR3) are similarly sensitive to finasteride. Finasteride inhibits 5αR2 (IC_{50} = 14.3 μM) and 5αR3 (IC_{50} = 17.4 μM) with similar potency. Finasteride inhibits 5αR2 (IC_{50} = 14.3 μM) with a 7.5-fold greater potency than 5αR1 (IC_{50} =106.9 μM).

Tissue distribution analysis shows that 5αR3 mRNA expression levels are higher than those of 5αR1 and 5αR2 in 20 analyzed tissues. 5αR3 could be the main enzyme responsible for 5αR activity previously believed to be associated with 5αR1 in many tissues and cell lines. Except for BPH and muscle, 5αR3 is more highly expressed than 5αR1 and 5αR2 in all tissues, including the normal prostate, mammary gland, brain, skin and adipose tissue.

g. Role of Androgens in Erectile Function.

Mantzoros et al, *Contribution of dihydrotestosterone to male sexual behavior* (1995).[86]

Mantzoros et al. studied the importance of endogenous sex steroids in modulating the frequency of orgasms in 92 healthy army recruits age 18 to 22 years. Serum DHT concentration was the only independent hormonal predictor of the frequency of orgasms. Mantzoros et al. concluded their "results strongly support the hypothesis that DHT is the active hormone for male sexual function as reflected in the frequency of orgasms."

Treatment of Micropenis with Transdermal DHT

Choi and Lignieres treated 22 patients age 2 to 15 years with microphallus with transdermal DHT gel to the external genitalia for 8 weeks.[87] All patients demonstrated growth of the penis with a mean increase of 153% in the first 4 weeks of treatment and 118% in the second 4 weeks. Of note, positive responses were observed in 4 patients who had previously failed T therapy for microphallus.

Charmandari et al. treated children age 1.9 to 8.3 years with micropenis with application of percutaneous 2.5% DHT gel and achieved an increase in phallic growth ranging from 0.5 to 2.0 cm after 3 to 4 months.[88]

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[85] Yamana K et al, *Human type 3 5α-reductase is expressed in peripheral tissues at higher levels than types 1 and 2 and its activity is potently inhibited by finasteride and dutasteride*, Horm Mol Biol Clin Invest (2010), Vol. 2(3), pp. 293-299.
[86] Mantzoros C et al, *Contribution of dihydrotestosterone to male sexual behavior*, Brit Med J (1995), Vol. 310(6990), pp. 1289-1291.
[87] Choi S and de Lignieres B, *Transdermal Dihydrotestosterone Therapy and its Effect on Patients with Microphallus*, J Urol (1993), Vol. 150, pp. 657-660.
[88] Charmandari E et al, *Kinetics and Effect of Percutaneous Administration of Dihydrotestosterone in Children*, Horm Res (2001), Vol. 56, pp. 177-181.

Traish AM and Kim N, *The Physiological Role of Androgens in Penile Erection: Regulation of Corpus Cavernosum Structure and Function* (2005).[89]

In the penis, T is converted to DHT, the active androgen, which regulates rat penile erectile function by modulation of NOS via the AR. DHT is more potent than T in maintaining penile nNOS and endothelial NOS (eNOS) activity. Veno-occlusion is modulated by the smooth muscle tone of the arteries and cavernosal tissue, and a balance between the amount of trabecular smooth muscle and connective tissue matrix of the corpus cavernosum. In men with ED, venous leakage is attributed to penile smooth muscle atrophy.

In the mammalian animal model, androgen deprivation produces penile tissue atrophy with alterations in dorsal nerve and endothelial morphology, reduction in trabecular smooth muscle content, increased collagen deposition, accumulation of sub-tunical fat cells (adipocytes), changes in fibro-elastic properties, and diminished expression of eNOS, nNOS and phosphodiesterase type 5 (PDE_5), resulting in venous leakage and ED.

Traish AM, *Androgens Play a Pivotal Role in Maintaining Penile Tissue Architecture and Erection: A Review* (2009).[90]

Androgens play a critical role in erectile physiology by (i) maintaining the structure and function of the peripheral penile nerve network, (ii) maintaining the structural integrity of the corpora cavernosa, the tunica albuginea, and endothelium of the cavernous spaces, and (iii) regulating the differentiation of stem cells into trabecular smooth muscle.

During erection, the penis accumulates blood under pressure. This process (veno-occlusive function) depends on (1) sexual stimulation activating the release of NO by the parasympathetic nerves, (2) dilation of cavernosal arteries resulting in flow and pressure to the corpora cavernosa, (3) relaxation of the trabecular smooth muscle allowing penile expansion, and (4) compliance of the tunica albuginea and the connective tissue matrix which compresses the subtunical venules and reduces blood outflow. Veno-occlusive dysfunction is an important cause of organic ED and is the hemodynamic abnormality that causes lack of response to ED pharmacotherapy.

[89] Traish AM and Kim N, *The Physiological Role of Androgens in Penile Erection: Regulation of Corpus Cavernosum Structure and Function*, J Sex Med (2005), Vol. 2, pp. 759-770.
[90] Traish AM, *Androgens Play a Pivotal Role in Maintaining Penile Tissue Architecture and Erection: A Review*, J Androl (2009), Vol. 30(4), pp. 363-369.

h. Animal Studies of the Role of Androgens in Sexual Function.

Rittmaster R et al, *Evidence for Atrophy and Apoptosis in the Ventral Prostate of Rats Given the 5α-Reductase Inhibitor Finasteride* (1995).[91]

Rittmaster et al. evaluated apoptosis (programmed cell death) of rat ventral prostate in castrated and finasteride-treated rats. Finasteride and castration decreased prostate weight 65% and 93%, respectively. Castration reduces both intraprostatic T and DHT, whereas finasteride causes a marked rise in intraprostatic T concentration. The increased concentration of T attenuates the degree of androgen deprivation, prostate involution and apoptosis induced by finasteride. Apoptosis is the primary mechanism of cell death resulting from finasteride treatment.

Schirar A et al, *Androgens Modulate Nitric Oxide Synthase Messenger Ribonucleic Acid Expression in Neurons of the Major Pelvic Ganglion in the Rat* (1997).[92]

Schirar et al. examined in castrated male rats by IHC the expression and androgen regulation of nNOS in neurons of the major pelvic ganglion (MPG) which innervate the penis, produce NO and play a major role in penile erection. Androgens act through neurons in the MPG in the rat to control sexual functions. DHT is likely more potent than T in preventing the decrease in nNOS mRNA levels in the MPG elicited by castration. Schirar et al. concluded, "It is well established that in the central nervous system (CNS) and in seminal vesicle, the active compound is not T on its own, but, rather its 5α-reduced metabolite, DHT."

Shen Z et al, *Effect of androgen deprivation on penile ultrastructure* (2003).[93]

Shen et al. studied ultrastructural changes of the penile corpus cavernosum and tunica albuginea by electron microscopy in rats treated with finasteride. The tunica albuginea of the penis plays a major role in erection. With finasteride treatment, the tunica albuginea was about 15% thinner. The trabecular smooth muscle of corpus cavernosum was greatly diminished and was replaced by irregularly arranged collagenous fibers.

Corradi L et al, *Increased Androgen Receptor and Remodeling in the Prostate Stroma After the Inhibition of 5-Alpha Reductase and Aromatase in Gerbil Ventral Prostate* (2009).[94]

Corradi et al. evaluated AR staining and tissue architecture of the prostate in gerbils chronically treated with finasteride. Marked stromal remodeling with increased

[91] Rittmaster R et al, *Evidence for Atrophy and Apoptosis in the Ventral Prostate of Rats Given the 5α-Reductase Inhibitor Finasteride*, Endocrinology (1995), Vol. 136(2), pp. 741-748.
[92] Schirar *op. cit.*, pp. 3093-3102.
[93] Shen *op. cit.*, pp. 33-36.
[94] Corradi L et al, *Increased Androgen Receptor and Remodeling in the Prostate Stroma After the Inhibition of 5-Alpha Reductase and Aromatase in Gerbil Ventral Prostate*, Microsc Res and Technique (2009), Vol. 72, pp. 939-950.

deposition of extracellular matrix proteins and AR overexpression were observed in the prostate glands of the gerbils. Twenty-one days after the end of treatment, AR expression was still elevated. The authors explained, "[AR] immunohistochemical patterns were more accentuated in the final post-treatment phase." The long-term absence of 5αR action imposed persistent physiological dysfunction that was not restored after the conclusion of treatment.

Corradi et al. concluded, "The findings of the present study reinforce the hypothesis that long-term inhibition of 5αR … significantly and persistently alters the hormonal intraprostatic microenvironment in gerbil ventral prostate, results that were not expected after cessation of Finasteride. … Taken together, the remodeled stromal compartment, with its accumulation of collagen and reticular fibers, its greater quantities of phenotypically altered fibroblast and smooth muscle cells as well as its persistent AR overexpression may be important signs of an altered intraprostatic microenvironment, as a consequence of enzymatic inhibition."

Corradi L et al, *Long-term inhibition of 5-alpha reductase and aromatase changes the cellular and extracellular compartments in gerbil ventral prostate at different postnatal ages* (2009).[95]

Corradi et al. evaluated prostate morphology and structure in gerbils chronically treated with finasteride and an aromatase inhibitor up to 21 days after discontinuation of treatment. At all times during the post-treatment period, morphology of the prostate, including tissue architecture, ultrastructure and extracellular matrix arrangement, was affected in a persistent manner. When finasteride was discontinued, the prostatic tissues responded in a different manner to the new hormonal situation established by the long-term absence of 5αR activity and interference with androgen action.

Oztekin C et al, *Incomplete Recovery of Erectile Function in Rat after Discontinuation of Dual 5-Alpha Reductase Inhibitor Therapy* (2012).[96]

Oztekin et al. evaluated male rats after chronic dutasteride (a dual 5αR1 and 5αR2 inhibitor) therapy and after 2-week washout to evaluate persistent effects. *In vivo* erectile response to cavernous nerve electrical stimulation and α1-adrenergic (phenylephrine) stimulation, and relaxation of smooth muscle in response to cholinergic (acetylcholine) stimulation, were significantly reduced after the washout period. Long-term 5αRI administration in rats increased the risk of ED via alterations in relaxant and contractile responses of penile tissue.

The authors concluded, "Some of these changes in corpus cavernosum smooth muscle function are persistent and may be irreversible."

[95] Corradi L et al, *Long-term inhibition of 5-alpha reductase and aromatase changes the cellular and extracellular compartments in gerbil ventral prostate at different postnatal ages*, Intl J Exp Path (2009), Vol. 90, pp. 79-94.
[96] Oztekin C et al, *Incomplete Recovery of Erectile Function in Rat after Discontinuation of Dual 5-Alpha Reductase Inhibitor Therapy*, J Sex Med (2012), Vol. 9(7), pp. 1773-1781.

Zhang M et al, *Effects of Oral Finasteride on Erectile Function in a Rat Model* (2012).[97]

Zhang et al. first demonstrated that a 58% reduction of serum DHT levels significantly reduces the weight of the corpus cavernosum and prostate in rats. Zhang et al. examined erectile function with electrical stimulation of the cavernous nerve, serum T and DHT levels, intraprostatic DHT, and weight and histopathology of the penile corpus cavernosum and prostate in rats chronically treated with finasteride. The tissue weights of the corpus cavernosum and prostate were reduced by 26% and 92%, respectively, with finasteride treatment. Finasteride treatment significantly elevated mean arterial blood pressure.

Zhang M et al, *Long-term Oral Administration of 5α-reductase Inhibitor Attenuates Erectile Function by Inhibiting Autophagy and Promoting Apoptosis of Smooth Muscle Cells in Corpus Cavernosum of Aged Rats* (2013).[98]

Zhang et al. first demonstrated decreased autophagy (cellular waste processing and disposal) and increased apoptosis (programmed cell death) in the corpus cavernosum of aged male rats treated with long-term finasteride. Autophagy is the system by which cytoplasmic materials and damaged organelles are digested and disposed in the lysosome.

Plasma DHT was lowered 52.1% and the weight of the corpus cavernosum was decreased 22.4% with finasteride ($p < 0.001$). The *in vivo* erectile response to electrical stimulation of the cavernous nerve, smooth muscle content (-45%) and autophagy (-81%) of the corpus cavernosum, and eNOS RNA expression (-58%) and protein expression (-68%) of the cavernosal endothelium were all decreased significantly in the finasteride group ($p < 0.001$). Collagen deposition and the rate of apoptosis (+62%) of cavernosal smooth muscle cells (CSMCs) were significantly increased in the finasteride group ($p < 0.001$). Mitochondria of the CSMCs showed marked ultrastructural injury.

Zhang et al. demonstrated that prolonged administration of finasteride in aged rats reduces the erectile response to electrical stimulation of the cavernous nerve due to structural changes (decreased smooth muscle and enhanced collagen deposition), cellular changes (increased apoptosis, decreased autophagy and aggravated mitochondrion injury), and reduced expression of eNOS in the corpus cavernosum. DHT maintains the development and differentiation of CSMCs by regulating autophagy and apoptosis. This study provides direct evidence that DHT positively regulates the maintenance of smooth muscle and negatively regulates fibroplasia in the corpus cavernosum.

[97] Zhang (2012) *op. cit.,* 1328-1336.
[98] Zhang (2013) *op. cit.,* pp. 743.e9-743.e15.

i. Neurologic Pathways in Sexual Function.

Steers WD, *Neural pathways and central sites involved in penile erection: neuroanatomy and clinical implications* (2000).[99]

Steers reviewed the neurological pathways involved in erectile function. The penis receives innervation from the spinal cord via sacral parasympathetic (pelvic nerve), thoracolumbar sympathetic (hypogastric nerve and lumbar sympathetic chain), and somatic (pudendal nerve) nerves.

The parasympathetic nervous system provides the major excitatory input to the penis (vasodilation and erection). The cavernous nerves contain parasympathetic (vasodilation) and sympathetic (vasoconstriction) fibers that project to penile smooth muscle. Excitatory neurons in the sacral spinal cord contain acetylcholine and NO. The sympathetic nervous system modulates detumescence of the penis. The penis receives sensory branches of the pudendal nerve as the dorsal nerve of the penis (DNP) which initiates and maintains reflexogenic erections. Reflexive erections are mediated by a sacral spinal reflex with sensory input through the DNP and motor pathways consisting of sacral parasympathetic nerves conveyed by the pelvic and cavernous nerves.

The sacral spinal cord receives descending inputs from the brain (hypothalamus and brainstem) with spinal pathways that originate in the nucleus paragigantocellularis (nPGi) and locus coeruleus. The nPGi inhibits erectile function through descending axons that contain serotonin. Onuf's nucleus in the sacral spinal cord is responsible for contraction of the bulbospongiosus and ischiocavernosus muscles which are activated during ejaculation and erection.

Pathways involving the hypothalamus and limbic system (e.g. nucleus accumbens and amygdala) of the brain play a key role in erection. The medial preoptic area (MPOA) of the hypothalamus modulates erections and coordinates autonomic events associated with sexual responses (e.g. changes in heart rate and cutaneous flushing). The MPOA is not critical for erectile function. Direct projections from the paraventricular nucleus (PVN) of the hypothalamus to the lumbosacral autonomic centers are involved in erectile function.

j. 5α-Reductase Metabolic Pathways and Neurosteroids.

The **CLINICAL PHARMACOLOGY, Mechanism of Action** section (12.1) of the Propecia product label is misleading because it does not disclose critically important information about the mechanism of action of Propecia. Additional information about all the steroid hormones metabolized by 5αR1 and 5αR2, and the 5αR1 and 5αR2 metabolic pathways that synthesize neurosteroids, needs to be disclosed in the product label.

[99] Steers WD, *Neural pathways and central sites involved in penile erection: neuroanatomy and clinical implications*, Neurosci Biobehav Rev (2000), Vol. 24, pp. 507-516.

The Propecia product label only discloses the effects of finasteride on the metabolism of T into DHT by 5αR2, but does not disclose the effects of finasteride on at least 8 other steroid substrates that are 5α-reduced by 5αR.

The neurosteroids formed by the 5αR1 and 5αR2 metabolic pathways are necessary for normal behavioral regulation and sexual function. Allopregnanolone and DHP in the brain have anxiolytic, analgesic, sedative, anticonvulsant, hypnotic and anesthetic properties.[100] Reduced neurosteroid levels in the plasma and cerebrospinal fluid (CSF) of PFS patients are likely critical factors in the pathophysiologic mechanism involved in the ED, loss of libido, orgasm dysfunction, depression, suicidality, anxiety, panic attacks, cognitive dysfunction, insomnia and lack of motivation experienced by PFS patients.

Fisher L et al, *Clinical, Endocrinological, and Enzymatic Characterization of Two Patients with 5α-R Deficiency: Evidence that a Single Enzyme is Responsible for the 5α-Reduction of Cortisol and Testosterone* (1978).[101]

The first evidence that 5αR metabolizes multiple steroid hormones was published by Fisher et al. The authors explained, "Peterson et. al. have recently observed, however, that in one family with 5αR deficiency, the excretion of 5α-reduced glucocorticoids and 5α-reduced androgens was equally deficient (Peterson, R.E., and J. Imperato-McGinley, personal communication)." Fisher et al. measured the level of 5αR activity on multiple steroid hormones, including T, epitestosterone, progesterone, corticosterone, DOC, cortisol and cortisone, in 2 siblings with genetic 5αR deficiency as compared to normal controls.

Fisher et al. concluded, "A single enzyme is responsible in the normal person for the 5α-reduction of T and cortisol (and probably other Δ^4-3-ketosteroids as well)."

Majewska M et al, *Steroid Hormone Metabolites are Barbituate-Like Modulators of the GABA Receptor* (1986).[102]

Majewska et al. published the first evidence quantifying the potency of the sedative and anesthetic effects of the neurosteroids tetrahydrodeoxycorticosterone (THDOC) and allopregnanolone in rat brain. Anesthetic and hypnotic drugs, including benzodiazepines, barbiturates and alphaxalone (an anesthetic drug that is a synthetic neuroactive steroid analogue), directly interact with $GABA_A$ receptors in the brain causing inhibitory neurotransmission via the same pathways as the neurotransmitter GABA. Allopregnanolone and THDOC interact with the $GABA_A$ receptor and function as barbiturate-like modulators of GABA-mediated neurotransmission. Allopregnanolone and THDOC are 700 to 1000 times more potent than the anesthetic barbiturate

[100] Belelli *op. cit.*, pp. 565-575.
[101] Fisher *op. cit.*, pp. 653-664.
[102] Majewska M et al, *Steroid Hormone Metabolites are Barbituate-Like Modulators of the GABA Receptor*, Science (1986), Vol. 232, pp. 1004-1007.

pentobarbital at binding the $GABA_A$ receptor. Both allopregnanolone and THDOC dramatically increase $GABA_A$-activated neurotransmission.

Majewska et al. concluded, "These data may explain the ability of certain steroid hormones to rapidly alter neuronal excitability and may provide a mechanism for the anesthetic and hypnotic actions of naturally occurring and synthetic anesthetic steroids."

Imperato-McGinley J et al, *C_{19} and C_{21} 5β/5α Metabolite Ratios in Subjects Treated with the 5α-Reductase Inhibitor Finasteride: Comparison of Male Pseudohermaphrodites with Inherited 5α-Reductase Deficiency* (1990).[103]

Imperato-McGinley et al. (and Stoner) published the first article describing the global defects of C_{19} and C_{21} 5α-reduction caused by finasteride and the affinity that 5αR has for multiple steroid substrates. In a phase 1 clinical trial, urinary 5β/5α-reduced metabolite ratios of T, cortisol, 11β-hydroxyandrostenedione and corticosterone were measured in men receiving 0.2 to 80 mg finasteride. All 5β/5α-reduced metabolite ratios in finasteride-treated subjects were elevated compared to pretreatment and placebo values. Subjects treated with 0.2 to 0.5 mg finasteride had a statistically significant, 31-fold increase in the 5β/5α-reduced ratio of cortisol compared to pretreatment values.

Imperato-McGinley et al. concluded, "Finasteride has a broad steroid spectrum inhibiting C_{19} and C_{21} 5α-steroid metabolism and affects hepatic and peripheral 5α-metabolism. … The steroid profile [with finasteride] is strikingly similar to that of male pseudohermaphrodites with inherited 5αR deficiency." However, compared to 46 men with genetic 5αR2 deficiency, the defect in 5α-reduction is greater with 40 to 80 mg finasteride treatment.

Imperato-McGinley was an important Merck consultant who was a clinical investigator in several Merck clinical trials.

Vermeulen A et al, *Hormonal Effects of an Orally Active 4-Azasteroid Inhibitor of 5α-Reductase in Humans* (1989).[104]

In another phase 1 clinical trial, Vermeulen et al. (and Stoner) measured levels of plasma DHT, 3α-diol, and Adiol-G, as well as urinary androsterone and allotetrahydrocortisol in 54 healthy men (age 18 to 45 years) after single doses of 0.04 to 40 mg finasteride. After a single dose of 1.5 or 0.5 mg finasteride, urinary allotetrahydrocortisol and androsterone excretion decreased by 50%, a further indication that finasteride treatment results in inhibition of 5α-reduction of multiple steroid substrates. The effects of the 1.5 and 0.5 mg doses on 3α-diol and Adiol-G levels were comparable to the 5 to 40 mg doses.

[103] Imperato-McGinley (1990) *op. cit.*, pp. 777-782.
[104] Vermeulen A et al, *Hormonal Effects of an Orally Active 4-Azasteroid Inhibitor of 5α-Reductase in Humans*, Prostate (1989), Vol. 14, pp. 45-53.

Purdy R et al, *Stress-induced elevations of y-aminobutyric acid type A receptor-active steroids in the rat brain* (1991).[105]

Purdy et al. published the first evidence of the biosynthesis of allopregnanolone in the brain and increased CNS neurosteroid levels under stress-induced conditions. Allopregnanolone and THDOC bind with high affinity to the $GABA_A$ receptor. Rapid 4- to 20-fold increases of allopregnanolone and THDOC were detected in the brain (cerebral cortex and hypothalamus) of male rats one hour after acute swim stress. Plasma allopregnanolone levels increased 8-fold after swim stress.

Bitran D et al, *Anxiolytic Effect of Progesterone is Mediated by the Neurosteroid Allopregnanolone at Brain GABA-A Receptors* (1995).[106]

Bitran et al. evaluated the effect of progesterone on two behavioral anxiety tests (plus-maze and defensive burying paradigm) and $GABA_A$ receptor sensitivity in cortical synaptoneurosomes of rats pre-treated with 4-MA, a 5αRI provided by Merck. Progesterone increased serum allopregnanolone levels 3-fold v. controls ($p < 0.001$). 4-MA pre-treatment decreased allopregnanolone levels in controls ($p < 0.05$) and blocked the increase in allopregnanolone levels after progesterone treatment.

In the plus-maze, progesterone increased time spent in the open arms ($p < 0.0005$), an anxiolytic effect that was blocked by pre-treatment with 4-MA. In the defensive burying paradigm, the duration of burying behavior was significantly decreased by progesterone ($p < 0.02$), an anxiolytic effect that was blocked by pre-treatment with 4-MA. GABA-stimulated activity in cortical synaptoneurosomes was potentiated by progesterone ($p < 0.05$ and $p < 0.001$ by 2 different analytical measures), and these effects were blocked by pre-treatment with 4-MA.

Bitran et al. concluded, "Together, these studies provide evidence that the anxiolytic effect of progesterone is not associated with an intracellular steroid receptor that initiates genomic-mediated responses. The evidence is consistent with a nongenomic mechanism whereby progesterone is metabolized [by 5αR] to allopregnanolone, a neuroactive steroid that potentiates $GABA_A$ receptor-mediated responses."

Lancel M et al, *Allopregnanolone Affects Sleep in a Benzodiazepine-Like Fashion* (1997).[107]

Lancel et al. demonstrated that allopregnanolone administration significantly influences sleep in rats. Allopregnanolone reduced the latency to non-REM sleep, indicating rapid hypnotic action, and significantly increased the time spent in pre-REM sleep. The sleep

[105] Purdy R et al, *Stress-induced elevations of y-aminobutyric acid type A receptor-active steroids in the rat brain*, Proc Natl Acad Sci (1991), Vol. 88, pp. 4553-4557.
[106] Bitran D et al, *Anxiolytic Effect of Progesterone is Mediated by the Neurosteroid Allopregnanolone at Brain GABA-A Receptors*, J Neuroendocrinol (1995), Vol. 7, pp. 171-177.
[107] Lancel M et al, *Allopregnanolone Affects Sleep in a Benzodiazepine-Like Fashion*, J Pharmacol Exp Ther (1997), Vol. 282, pp. 1213-1218.

effects of allopregnanolone on EEG activity during non-REM and REM sleep are very similar to the effects of benzodiazepines and larger doses of progesterone on sleep, suggesting the effects of allopregnanolone on sleep are mediated by $GABA_A$ receptors.

It is not surprising that insomnia is a common issue for PFS patients.

Belelli D et al, *Neurosteroids: Endogenous Regulators of the $GABA_A$ Receptor* (2005).[108]

$GABA_A$ receptors mediate most 'fast' synaptic inhibition in the mammalian brain. Pregnane steroids (e.g. DHP and allopregnanolone) are synthesized in the brain, allosterically enhance $GABA_A$ receptor function in a nongenomic manner, and have anxiolytic, analgesic, anticonvulsant, sedative, hypnotic and anesthetic properties.

Steroid hormones synthesized in the periphery can cross the blood-brain barrier and function at the genomic level to produce slow (minutes to hours), but persistent, changes in mood and behavior. Certain steroids produce immediate changes (seconds) in neurons via a non-genomic locus of action. The molecular mechanisms that underlie these rapid effects remained unknown until the early 1980's.

Changes in neurosteroid levels are associated with physiological and pathophysiological conditions, including response to stress, pregnancy, depression, pre-menstrual tension, catamenial epilepsy, neural development and aging. Their levels are altered by psychoactive drugs, e.g. ethanol, benzodiazepines, antidepressants, barbituates, anesthetics, etc. The interaction between pregnane steroids and $GABA_A$ receptors is highly selective, specific to individual brain regions and to specific types of neurons.

The antiseizure properties of progesterone are blocked by finasteride. Progesterone facilitates inhibitory transmission in a finasteride-sensitive manner. Therefore, the anticonvulsant effect of progesterone requires its metabolism to allopregnanolone.

King SR, *Emerging Roles for Neurosteroids in Sexual Behavior and Function* (2008).[109]

King reviewed the important role of neurosteroids in sexual behaviors and behaviors that influence sexual interest. Neurosteroids have immediate effects on selective neuronal pathways that regulate sexual function and are localized in regions of the brain critical for sexual function (amygdala, olfactory bulb and hypothalamus). Allopregnanolone potentiates $GABA_A$ activity in neurons of the MPOA of male rats. The MPOA produces neurosteroids and is essential for sexual interest, erection, copulation, and ejaculation.

[108] Belelli *op. cit.*, pp. 565-575.
[109] King SR, *Emerging Roles for Neurosteroids in Sexual Behavior and Function*, J Androl (2008), Vol. 29(5), pp. 524-533.

Romer B et al, *Finasteride Treatment Inhibits Adult Hippocampal Neurogenesis in Male Mice* (2010).[110]

Allopregnanolone promotes neurogenesis in humans and has regenerative and protective effects. 5αR1 and 5αR2 are expressed in brain regions important for emotional behavior, such as the hippocampus and amygdala. Romer et al. assessed adult neurogenesis in male mice treated subchronically with finasteride or vehicle. Finasteride significantly decreased brain DHT levels and "induced a reversible reduction in the number of newborn cells and young neurons in the hippocampus." Finasteride reduced neuronal plasticity on a structural level.

Giatti S et al, *Effects of Subchronic Finasteride Treatment and Withdrawal on Neuroactive Steroid Levels and their Receptors in the Male Rat Brain* (2016).[111]

Giatti et al. documented prominent organic brain abnormalities in rats treated subchronically with finasteride that were more pronounced after withdrawal than during treatment. The effects of subchronic, low-dose finasteride treatment (20 days) and the consequences of its withdrawal (1 month after last dose) on neuroactive steroids in plasma, CSF, cerebral cortex, cerebellum and hippocampus were evaluated in male rats.

After subchronic finasteride treatment, DHP was significantly upregulated and 5αR gene expression was increased ($p < 0.05$) in the cerebellum. 3α-diol and 3β-diol were significantly decreased and increased, respectively, in the cerebellum and CSF. Gene expression of the β3 subunit of the $GABA_A$ receptor was increased in the cerebellum.

After the withdrawal period (1 month), additional changes were detected. DHP was decreased in the cerebral cortex and upregulated in the cerebellum and hippocampus. 5αR gene expression was significantly decreased in the cerebral cortex ($p < 0.05$) and increased in the cerebellum ($p < 0.05$). Allopregnanolone levels in the cerebral cortex and plasma were decreased. The mRNA levels of the α4 and β3 subunits of the $GABA_A$ receptor in the cerebral cortex were decreased.

In the cerebral cortex, upregulation of AR expression was detected during treatment and after withdrawal of finasteride. Stronger effects on neuroactive steroid levels at the end of the withdrawal period than during finasteride treatment were detected in the cerebral cortex, the cerebellum and hippocampus.

Giatti et al. concluded, these findings indicate that finasteride treatment has long-term effects and "suggests that the steroidogenic system is able to partially adapt and compensate for the chronic inhibition of 5αR activity. However, after this adaptation, the system may be less flexible to compensate for a new alteration and could be further disrupted when 5αR activity is recovered."

[110] Romer B et al, *Finasteride Treatment Inhibits Adult Hippocampal Neurogenesis in Male Mice*, Pharmacopsych (2010), Vol. 43, pp. 174-178.
[111] Giatti S et al, *Effects of Subchronic Finasteride Treatment and Withdrawal on Neuroactive Steroid Levels and their Receptors in the Male Rat Brain*, Neuroendocrinol (2016), Vol. 103, pp. 746-757.

In summary, finasteride treatment caused changes in the levels of neuroactive steroids and their receptors in brain tissue that were even more prominent after a prolonged period of drug withdrawal.

Soggiu T et al, *Exploring the neural mechanism of finasteride: A proteomic analysis in the nucleus accumbens* (2016).[112]

In rat models, finasteride blocks the effects of dopamine receptors in the nucleus accumbens of the dopamine mesolimbic system. These mechanisms may also account for the lowering of mood and libido, given the importance of the dopaminergic signaling in the nucleus accumbens in the regulation of sex drive, reward, and motivation.

The proteomic profile of rat nucleus accumbens was evaluated after acute and sub-chronic finasteride treatment. Two-dimensional electrophoresis coupled to mass spectrometry revealed significant changes in the expression of nine proteins in the nucleus accumbens: collapsin response mediator protein 2 (CRMP2), PSMD1, STX18, KCNC3, CYP255, the π subunit of the $GABA_A$ receptor (GBRP), GABA transaminase (GABT), PRPS1, and CYP2B3 ($p < 0.05$ for all comparisons). Several processes are relevant to the role of finasteride in behavioral regulation and dopamine signaling modulation, such as the synthesis and catabolism of GABA, and the regulation of the activity of $GABA_A$ receptor.

The finasteride-induced increase in CRMP2 expression in the nucleus accumbens may lead to changes in dopamine release from mesolimbic projections. Increases in CRMP2 in response to acute finasteride treatment may reflect the action of neuroactive steroids on multiple targets of this protein. GBRP reduces the sensitivity of the GABA channel to allopregnanolone. Reduction of GBRP expression by subacute finasteride treatment and reduction of GABT by both acute and subacute finasteride treatment may be compensatory mechanisms in response to the suppression of allopregnanolone.

Soggiu et al. concluded, "Finasteride treatment affected the expression of a number of accumbal proteins involved in key functional processes, such as regulation of GABAergic neurotransmission, as well as steroid and pyrimidine metabolism."

4. Antiandrogenic Effects of Finasteride

The **CLINICAL PHARMACOLOGY, Pharmacodynamics** section (12.2) of the Propecia product label states, "Finasteride has no affinity for the androgen receptor and has no androgenic, antiandrogenic, estrogenic, antiestrogenic, or progestational effects."

The representation that finasteride has 'no antiandrogenic effects' is an untrue statement of a material fact.

[112] Soggiu T et al, *Exploring the neural mechanism of finasteride: A proteomic analysis in the nucleus accumbens*, Psychoneuroendocrinology (2016), Vol. 74, pp. 387-396.

21 U.S.C. §355(e) provides that the Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds the application contains any untrue statement of a material fact.

This untrue statement is material because it gives prescribing physicians a false sense of comfort about Propecia's side effect profile. Awareness of Propecia's antiandrogenic effects would likely alter physician prescribing patterns for a cosmetic indication and significantly impact the informed consent that is given to patients.

a. Finasteride as an Antiandrogen.

Merck's approach to the classification of finasteride as an antiandrogen went through an evolution. When finasteride was initially developed for the treatment of BPH, Merck referred to finasteride as a potent antiandrogen. Later, Merck represented that finasteride had no antiandrogenic effects *in vitro*. After the early clinical development of Proscar, Merck eliminated references to finasteride as an antiandrogen and suggested that finasteride *clinically* had no antiandrogenic effects *in vivo* because it did not directly bind to the AR.

The antiandrogenic effects of finasteride are both the primary mechanism of action for its effects in AGA and a primary etiologic factor in the development of the sexual adverse events (AEs) associated with the use of Propecia. The antiandrogenic effects of Propecia are highly undesirable in young men in their sexual and reproductive prime. Any representation that Propecia has antiandrogenic effects would substantially limit its market potential. By actively promoting that Propecia has no antiandrogenic effects, Merck downplayed the potential for sexual AEs with Propecia.

<u>Finasteride Patents</u>

- Merck's 5αR Inhibitors Composition of Matter patent[113] covers a class of compounds that includes finasteride and method claims to treat BPH and other hyperandrogenic conditions with these compounds. The specific chemical structure of finasteride is not covered by the approved claims, but finasteride is in the class of compounds that are covered more generally by the approved claims.

The composition of matter patent states, "The novel compounds of the present invention are, therefore, *potent antiandrogens* by virtue of their ability to specifically inhibit testosterone-5.alpha.-reductase." [emphasis supplied] Male pattern baldness is identified as a hyperandrogenic condition, but the patent stops short of claiming that the covered compounds might be used topically or systemically to treat male pattern baldness.

[113] Rasmusson G et al (Assignee: Merck & Co., Inc.), *4-Aza-17.beta.-substituted-5.alpha.-androstan-3-one-reductase inhibitors*, U.S. Patent # 4,377,584 (March 22, 1983).

- Merck's Finasteride Composition of Matter patent[114] covers the specific chemical structure of finasteride (17.beta.-(N-t-butylcarbamoy1)-4-aza-5.alpha.-androst-1-en-3-one), and claims to treat BPH and other hyperandrogenic conditions with finasteride.

The Finasteride Composition of Matter patent states, "The compounds of the present invention, prepared in accordance with the method described above, are, as already described, *potent antiandrogens* by virtue of their ability to specifically inhibit testosterone-5.alpha.-reductase." [emphasis supplied] Once again, male pattern baldness is identified as a hyperandrogenic condition, but the patent stops short of claiming that the covered compounds might be used topically or systemically to treat male pattern baldness.

- Merck's first Methods of Treating Androgenic Alopecia with Finasteride patent[115] claims:

"1. A method of treating androgenic alopecia which comprises orally administering to a human in need of such treatment a therapeutically effective amount of 17.beta.-(N-tert-butylcarbamoy1)-4-aza-5.alpha.-androst-1-en-3-one [finasteride]."

There is no mention in this method patent of finasteride as a 'potent antiandrogen' as there is in the composition of matter patents for finasteride and the method patents for finasteride to treat BPH.

At this time, Merck still referred to male pattern baldness as *androgenic* alopecia. Later Merck publications referred to male pattern baldness as *androgenetic* alopecia.

- Merck's second Method of Treating Androgenic Alopecia with 5-α Reductase Inhibitors patent[116] which was filed on March 17, 1994 claims:

"1. A method of treating male pattern baldness comprising orally administering to a male person having a balding area 17.beta.-(N-tert-butylcarbamoyl)-4-aza-5.alpha.-androst-1-ene-3-one [finasteride] in a dosage amount from 0.05 to 3.0 mgs/day at least until growth of hair can be detected in the balding area by haircount analysis of the balding area. …
5. A method of arresting and reversing male pattern baldness comprising orally administering to a bald or balding male person having a balding area 17.beta.-(N-tert-butylcarbamoyl)-4-aza-5.alpha.-androst-1-ene-3-one [finasteride] in a dosage amount

[114] Rasmusson G and Reynolds G (Assignee: Merck & Co., Inc.), *17.beta.-N-monosubstituted carbamoy1-4-aza-5.alpha.-androst-1-en-3-ones which are active as testosterone 5.alpha.-reductase inhibitors*, U.S. Patent No. 4,760,071 (July 26, 1988).
[115] Rasmusson G and Reynolds G (Assignee: Merck & Co., Inc.), *Methods of treating androgenic alopecia with finasteride [17.beta.-N-mono-substituted-carbamoy1-4-aza-5-.alpha.-androst-1-en-ones]*, U. S. Patent No. 5,571,817 (November 5, 1996).
[116] Gormley GJ, Kaufman KD, Stoner E and Waldstreicher J (Assignee: Merck & Co., Inc.), *Method of treating androgenic alopecia with 5-.alpha. reductase inhibitors*, U.S. Patent No. 5,547,957 (August 20, 1996).

from 0.05 to 3.0 mgs/day at least until growth of hair can be detected in the balding area by haircount analysis of the balding area.
6. The method of claim 1 wherein the dosage amount is about 1.0 mg/day.
7. The method of claim 5 wherein the dosage amount is about 1.0 mg/day."

There is no mention in this method patent of finasteride as a 'potent antiandrogen' as there is in the composition of matter patents for finasteride and the method patents for finasteride to treat BPH.

With a filing date of March 17, 1994, Merck had already decided on the 1 mg/day dose for Propecia, a perceived milder version of Proscar from a marketing perspective. However, the magnitude of the biological response to 1 mg and 5 mg finasteride is substantially equivalent for all measured parameters.[117] Merck submitted its IND for the clinical development of finasteride for AGA to FDA on June 29, 1994.[118]

Merck's inventors of this patent were Glenn Gormley, Keith Kaufman, Elizabeth Stoner and Joanne Waldstreicher.

At this time, Merck still referred to male pattern baldness as *androgenic* alopecia. Later Merck publications referred to male pattern baldness as *androgenetic* alopecia.

Medical Dictionary Definitions of an Antiandrogen

Medical dictionaries define antiandrogen in a manner that would include finasteride.

The 2006 Stedman's Medical Dictionary defines an 'antiandrogen' as "any substance capable of preventing full expression of the biologic effects of androgenic hormones on responsive tissues, either by producing antagonistic effects on the target tissue, as estrogens do, or by merely inhibiting androgenic effects, such as by competing for binding sites at the cell surface."[119] Finasteride inhibits androgenic effects by competing with T for 5αR binding sites.

The 2013 Free Online Medical Dictionary, Thesaurus and Encyclopedia defines 'antiandrogen drugs' as "a diverse group of medications given to counteract the effects of androgens (male sex hormones) on various body organs and tissues. Some

[117] Shukla C and Tran D, *Dose Response Data for Finasteride*, FDA Clinical Pharmacology & Biopharmaceutics (April 28, 2011), Reference ID: 2939204, pp. 1-13.
[118] Ko HS, *FDA CDER Medical Review of Propecia® NDA 20-788* (1997), pg. 7. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/97/20788_PROPECIA%20TABLETS,%201MG_MEDR_P1.PDF, https://www.accessdata.fda.gov/drugsatfda_docs/nda/97/20788_PROPECIA%20TABLETS,%201MG_MEDR_P2.PDF, https://www.accessdata.fda.gov/drugsatfda_docs/nda/97/20788_PROPECIA%20TABLETS,%201MG_MEDR_P3.PDF, and https://www.accessdata.fda.gov/drugsatfda_docs/nda/97/20788_PROPECIA%20TABLETS,%201MG_MEDR_P4.PDF.
[119] Antiandrogen Definition, Stedman's Medical Dictionary (2006) (accessed online August 24, 2013).

medications in this category work by lowering the body's production of androgens. … Antiandrogen drugs may be given for any of several conditions or disorders, ranging from … androgenetic alopecia [to] … male-to-female (MTF) transsexuals as part of the hormonal treatment that precedes gender reassignment surgery."[120] Finasteride lowers the body's production of the androgen DHT.

An 'antiandrogen' is defined by various other medical dictionaries as follows:

(i) "any substance capable of inhibiting the biological effects of androgens,"[121]
(ii) "a substance that prevents expression of biological effects of androgenic hormones on responsive tissues,"[122]
(iii) "a substance that blocks the actions of androgens, the hormones responsible for male characteristics,"[123]
(iv) "any substance capable of inhibiting the biological effects of androgenic hormones,"[124] and
(v) "any substance capable of preventing full expression of the biological effects of androgenic hormones on responsive tissues."[125]

Evolution of Merck's Denial that Finasteride has Antiandrogenic Effects

Although Merck's composition of matter patents clearly characterized finasteride as a potent antiandrogen in the 1980's, Merck gradually changed this characterization over time from about 1990 until about 1998. Ever since the FDA approval of Propecia to treat AGA, the **CLINICAL PHARMACOLOGY, Pharmacodynamics** section (12.2) of the Propecia product label has always stated, "Finasteride has no affinity for the androgen receptor and has no androgenic, antiandrogenic, estrogenic, antiestrogenic, or progestational effects."[126]

In the 1989 publication of a Merck phase 1 clinical trial for finasteride, Vermeulen et al. (and Stoner) represented that finasteride "has no progestational, androgenic, estrogenic, gonadotrophin inhibitory or antiestrogenic effects."[127] Conspicuously absent is the representation that finasteride has 'no antiandrogenic effects.'

In a 1990 finasteride review article, Stoner stated, "Inhibition occurs without affecting the binding of T or DHT to the androgen receptor. Finasteride *in itself* possesses no

[120] Antiandrogen Drug Definition, Free Online Medical Dictionary, Thesaurus and Encyclopedia (accessed online July 30, 2013).
[121] Antiandrogen Definition, Dorland's Medical Dictionary for Health Consumers (2007) (accessed online July 30, 2013).
[122] Antiandrogen Definition, American Heritage Medical Dictionary (2007) (accessed online July 30, 2013).
[123] Antiandrogen Definition, Gale Encyclopedia of Medicine (2008) (accessed online July 30, 2013).
[124] Antiandrogen Definition, Saunders Comprehensive Veterinary Dictionary, 3rd ed. (2007) (accessed online July 30, 2013).
[125] Antiandrogen Definition, Farlex Partner Medical Dictionary (2012) (accessed online July 30, 2013).
[126] *Propecia® Full Prescribing Information* (2014) *op. cit.*
[127] Vermeulen *op. cit.*, pp. 45-53.

androgenic, antiandrogenic, or other steroid hormone-related properties. "[128] [emphasis supplied] This statement appears to mark a transition in Merck's position about the antiandrogenic properties of finasteride. The phrase 'in itself' is focused on the intrinsic hormonal properties of finasteride and finasteride is devoid of intrinsic hormonal activity. Finasteride does not function as a hormone. Finasteride competes with T for binding sites on the 5αR enzyme and irreversibly binds to 5αR.

In 1993, Sawaya and Hordinsky, who later became Merck consultants participating in the Propecia marketing launch, published a review article about antiandrogens[129] that clearly characterized finasteride as an antiandrogen. Excerpts from this article state the following:

- "Antiandrogens are drugs that interfere with androgen action at target organs."
- "There are various types of antiandrogens, and they vary in their mode of action. Some antiandrogens block enzyme reactions and limit the formation of potent androgens. Other antiandrogens work by specifically blocking the AR, and still other agents have an effect on both the enzyme and the receptor."
- "The structures of antiandrogens vary. Some are competitive inhibitors; i.e., they compete against the true substrate hormone, for example, T, and block the formation of DHT mediated by the 5αR enzyme. Many competitive inhibitors look structurally similar to the native substrate compound, such as T or DHT. The agents may have no hormonal activity."
- "One should be cautious when using antiandrogens because these agents may have many side effects, while usually having less than the desired effect on the specific androgen-related skin condition."
- "Effective antiandrogens either block the metabolism of T by inhibiting 5αR or inhibit DHT binding to the AR. Future development of antiandrogens for treating androgen-related conditions will be based on finding a drug that has site specificity, i.e., an agent that localizes to the hair follicle and/or sebaceous gland and specifically inhibits 5αR, the AR or both in order to be effective. The antiandrogen will also have to be safe, have minimal systemic absorption, be locally metabolized, and have minimal or no effects on other target tissues, sex organs, and gonadotropin levels."

The article reporting the results of Merck's phase 2 clinical trial with finasteride for AGA states, "*In vitro,* finasteride has no androgenic, antiandrogenic, estrogenic, antiestrogenic, or progestational effects. *In vivo,* inhibition of the type 2 enzyme blocks peripheral conversion of T to DHT, resulting in significant reductions in serum, prostate and scalp DHT levels."[130] [emphasis supplied]

During the 1990's, Merck made a decision to change from describing finasteride as a potent antiandrogen to focusing on the lack of intrinsic hormonal properties of

[128] Stoner (1990) *op. cit.*, pp. 375-378.
[129] Sawaya ME and Hordinsky MK, *The Antiandrogens: When and how they should be used*, Dermatology Clinics (1993) Vol. 11(1), pp. 65-72.
[130] Roberts J, *Clinical dose ranging studies with finasteride, type 2 5α-reductase inhibitor, in men with male pattern hair loss*, J Amer Acad Derm (1999), Vol. 41, pp. 555-563.

finasteride *in vitro* to marketing finasteride as a drug that *clinically* has no antiandrogenic effects *in vivo*.

Keith Kaufman, head of Merck's Propecia clinical development program, made a statement to the Advisory Committee members during Dermatologic and Ophthalmic Drugs Advisory Committee Meeting No. 48 which is inconsistent with the representation in Merck's finasteride composition of matter patent that finasteride is a potent anti-androgen[131] and the mainstream scientific literature when he asserted, "Finasteride is not an anti-androgen, and it has no affinity for the androgen receptor. Thus, it does not block the beneficial and necessary physiological roles of testosterone when administered to men."[132] The beneficial and necessary physiological roles of T require its conversion to DHT.

By 1998, Sawaya (who had since become a Merck consultant promoting Propecia in its product launch) had completely changed her position about whether finasteride is an antiandrogen. Sawaya stated, "Propecia® (finasteride; Merck Co, Rahway, NJ) has recently been approved by the Food and Drug Administration (FDA) in the US for men with AGA. Propecia® is a specific 5αR2 enzyme inhibitor and does not bind to the AR; therefore, it is not called an antiandrogen, but an androgen inhibitor."[133]

As of 2011, Merck still actively marketed Propecia to health care professionals on a "Selected Safety Information – Not an antiandrogen" page on its Propecia website[134] that claimed, "*Clinical studies* [emphasis supplied] showed:

- "no androgenic, antiandrogenic, estrogenic, antiestrogenic or progestational effects,"
- "no clinically meaningful effect on LH or FSH," and
- "no effect on the HPT [hypothalamic-pituitary-testicular] axis."

The "Selected Safety Information – Not an antiandrogen" website page also stated, "Clinical studies showed men treated with PROPECIA® (finasteride) had increased mean T and estradiol levels (approximately 15%), but these levels were within normal physiologic range." A 15% increase in T levels is evidence of an effect on the HPT axis and a clinically meaningful effect on LH production.

The phase 3 clinical trials with finasteride for AGA demonstrated a significant decrease in serum DHT levels and a significant increase in the rate of sexual AEs.[135] Both are antiandrogenic effects of Propecia.

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[131] Rasmusson (1988) *op. cit.*
[132] Advisory Committee Meeting No. 48 *op. cit.*, pg. 23.
[133] Sawaya ME, *Novel Agents for the Treatment of Alopecia*, Seminars in Cutaneous Medicine and Surgery (1998), Vol. 17(4), pp. 276-283.
[134] *Propecia® Selected Safety Information* (20753248(2)-12/07-PRP), Previously available from: http://web.archive.org/web/20081005174521/http://www.Propecia®.com. Accessed online October 15, 2011.
[135] Kaufman K et al, *Finasteride in the treatment of men with androgenetic alopecia*, J Amer Acad Derm (1998), Vol. 39, pp. 578-589.

b. Comparison of the Effects of Finasteride to Castration.

As of 2014, the Merck Manual stated, "After 6 months of treatment with 5 mg/day: Circulating dihydrotestosterone levels are reduced to castrate levels."[136]

In a 1990 article reviewing the clinical development of finasteride, Stoner stated, "In clinical studies where finasteride was administered for 6 months, a marked decrease in circulating DHT levels was observed, with 80% suppression of DHT at the 5-mg dose. These circulating levels of DHT are similar to those following castration."[137]

Gormley G et al, *The Effect of Finasteride in Men with Benign Prostatic Hyperplasia* (1992).[138]

In Merck's phase 3 finasteride clinical trial for BPH, 895 men were given 1 mg or 5 mg finasteride, or placebo. Gormley et al. stated, "Serum DHT concentrations decreased to levels present after castration soon after the initiation of finasteride therapy. … Approximately 50 percent of the men who received finasteride had a decrease of 20 percent or more in the size of the prostate, a response similar to that reported in men treated with an analogue of GnRH (24 percent reduction in size) [medical castration] or surgical castration (31 percent reduction in size)."

McConnell J et al, *Finasteride, an inhibitor of 5α-Reductase, Suppresses Prostatic Dihydrotestosterone in Men with Benign Prostatic Hyperplasia* (1992).[139]

In a double-blind, placebo-controlled clinical trial published by McConnell et al, 69 men age 47 to 77 years with BPH were treated with placebo, or 1, 5, 10, 50 or 100 mg/day finasteride, for 7 days prior to surgical resection of their prostate. After 7 days at all doses of finasteride, prostatic DHT declined to ≤ 15% of control levels.

McConnell et al. stated, "The degree of suppression of intraprostatic DHT with finasteride is similar to that seen after therapy with LH-RH agonists [medical castration] in patients with BPH." In one study, the mean prostatic DHT concentrations fell about 90% after 3 months of treatment with a long-acting LH-RH drug. McConnell concluded, "Thus, finasteride achieves a suppression of intraprostatic DHT similar to that seen with medical castration, but without affecting plasma T."

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[136] Merck Manual for Health Care Professionals, *Finasteride*, pp. 1-15. Previously available from: http://www.merckmanuals.com/professional/lexicomp/finasteride/html. Accessed online June 25, 2014.
[137] Stoner (1990) *op. cit.*, pp. 375-378.
[138] Gormley GJ et al, *The Effect of Finasteride in Men with Benign Prostatic Hyperplasia*, N Engl J Med (1992), Vol. 327(7), pp. 1185-1191.
[139] McConnell J et al, *Finasteride, an inhibitor of 5α-Reductase, Suppresses Prostatic Dihydrotestosterone in Men with Benign Prostatic Hyperplasia*, J Clin Endocrinol Metab (1992), Vol. 74, pp. 505-508.

Geller J and Sionit L, *Castration-Like Effects on the Human Prostate of a 5α-Reductase Inhibitor, Finasteride* (1992).[140]

Geller and Sionit estimated the degree of androgen deprivation in humans with finasteride as compared to surgical castration. In untreated BPH, prostate tissue levels of DHT and T average 4.2 and 0.2 ng/g, respectively. In surgically castrated men, prostate tissue levels of DHT and T average 1.14 mg/g and 0.1 ng/g, respectively. In men treated with finasteride, prostate tissue levels of DHT and T average 0.62 ng/g and 1.32 ng/g, respectively. Using the relative binding affinity of T and DHT to the AR as a criterion of biological androgen potency,[141] DHT was conservatively estimated by Geller et al. to be 4-fold more potent than T.

When this DHT equivalent for T (1 T = 0.25 DHT) was added directly to the measured DHT, the prostates of men treated with finasteride had a total DHT equivalent of 0.95 ng/g as compared to a total DHT equivalent of 1.14 ng/g in prostates of surgically castrated patients. Geller and Sionit concluded, "In acute studies, [finasteride] produces changes in the concentration of androgenic hormones in the prostate similar to surgical castration."

Rittmaster R, *Finasteride* (1994).[142]

Rittmaster published a review of finasteride in which he compared the effects of finasteride and castration. In the article, he explained, "Inhibition with 5αR is frequently compared with castration, but there are important differences. Whereas prostatic concentrations of both T and DHT are reduced by castration, 5αRIs increase prostatic T concentrations. Castration reduces only testicular sources of T; 5αRIs block the production of DHT from both adrenal and gonadal precursors. Finasteride reduces prostatic concentrations of DHT more than castration, but the increase in prostatic T blunts the physiologic effects of decreased DHT. In rats, both castration and the inhibition of 5αR cause cell death, but this occurs more slowly and to a lesser extent with enzyme inhibition."

Rittmaster R et al, *Evidence for Atrophy and Apoptosis in the Prostates of Men Given Finasteride* (1996).[143]

Rittmaster et al. evaluated markers of apoptosis (programmed cell death) in prostate tissue collected during prostatectomy from men with BPH taking finasteride or no medication at the time of surgery. These markers indicated an increased rate of apoptosis in men taking finasteride. Rittmaster et al. concluded that finasteride causes prostate involution through a combination of atrophy and cell death.

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[140] Geller J and Sionit L, *Castration-Like Effects on the Human Prostate of a 5α-Reductase Inhibitor, Finasteride*, J Cell Biochem (1992), Supplement 16H, pp. 109-112.
[141] Grino (1990) *op. cit.*, pp. 1165-1172.
[142] Rittmaster R, *Finasteride*, N Engl J Med (1994), Vol. 330(2), pp. 120-125.
[143] Rittmaster R et al, *Evidence for Atrophy and Apoptosis in the Prostates of Men Given Finasteride*, J Clin Endocrinol Metab (1996), Vol. 81(2), pp. 814-819.

Rittmaster explained, "The effect of finasteride on the prostate gland is not the same as that of castration. Whereas castration causes a profound decrease in both prostatic T and DHT concentrations, finasteride increases prostatic T levels. Because finasteride inhibits DHT production from testicular and adrenal precursors, it can lower the prostatic DHT concentration more than castration. Nevertheless, there is evidence in both rats and humans that the finasteride-induced increase in prostatic T levels lessens the degree of androgen deprivation compared to that caused by castration. … The effects of finasteride on epithelial cell and duct size are similar to castration, although the lack of quantification in earlier studies makes it difficult to directly compare the degree of atrophy with finasteride vs. castration."

c. Dose-Response of Finasteride.

While the difference between a 1 mg and 5 mg dose of finasteride may seem like a lot, the biological responses to 1 mg and 5 mg finasteride are substantially equivalent because both doses are on the far-right side of the dose-response curve. The steepest portion of the finasteride dose-response curve is between about 0.05 mg and 0.2 mg finasteride. Above doses of 0.2 mg finasteride, the dose-response curve flattens out and plateaus.

The decrease in DHT levels is an antiandrogenic effect of finasteride. Since the effects of 1 mg and 5 mg finasteride on DHT levels are substantially equivalent, any comparison of the effects of finasteride 5 mg to castration should be just as valid for any comparison of the effects of finasteride 1 mg to castration.

In the phase 3 RCT with finasteride for BPH, patients received 1 mg or 5 mg finasteride. Gormley et al. compared the effects on serum DHT levels of both 1 mg and 5 mg finasteride to serum DHT levels present after castration.[144]

McConnell J et al, *Finasteride, an inhibitor of 5α-Reductase, Suppresses Prostatic Dihydrotestosterone in Men with Benign Prostatic Hyperplasia* (1992).[145]

In a double-blind, placebo-controlled clinical trial sponsored by Merck, 69 men aged 47 to 77 years with BPH were treated with placebo, or 1, 5, 10, 50 or 100 mg/day finasteride for 7 days, prior to surgical resection of their prostate. After 7 days at all doses of finasteride, prostatic DHT declined to < 15% of control levels, and T levels increased reciprocally. In men who received 1 mg finasteride, prostatic DHT decreased by 86%. The prostatic T and DHT levels for all finasteride groups were significantly different from the placebo group, but were not significantly different from each other.

[144] Gormley *op. cit.*, pp. 1185-1191.
[145] McConnell *op. cit.*, pp. 505-508.

Vermeulen A et al, *Hormonal Effects of an Orally Active 4-Azasteroid Inhibitor of 5α-Reductase in Humans* (1989).[146]

Vermeulen et al. (and Stoner) measured plasma DHT, 3α-diol and Adiol-G, as well as urinary androsterone and allotetrahydrocortisol, in 54 healthy men age 18 to 45 years for 7 days after single doses of 0.04 to 40 mg finasteride. Urinary allotetrahydrocortisol dropped to 39% and 45% of basal value after the 5 mg and 0.5 mg doses, respectively. Excretion of androsterone dropped to 30% and 53% of basal value after 5 mg and 0.5 mg doses, respectively.

The effects of the 40, 20, 10, 5 and 1.5 mg doses on 5αR function were not statistically different. The 0.5 mg dose was slightly, but significantly, less effective than the higher doses. The effects of the 1.5 and 0.5 mg doses on 3α-diol and Adiol-G levels were comparable to the 5 to 40 mg doses.

Gormley G et al, *Effects of Finasteride (MK-906), a 5α-Reductase Inhibitor, on Circulating Androgens in Male Volunteers* (1990).[147]

Gormley et al. gave finasteride (0.04, 0.12, 0.2, and 1.0 mg for 14 days) to 30 healthy men age 40 to 77 years. Maximal suppression of DHT occurred rapidly in the 1.0 mg (65% decreased DHT levels on day 1) and 0.2 mg groups. After 8 days of treatment, all doses of finasteride resulted in similar suppression of DHT. DHT levels returned to baseline after 14 days of drug discontinuation, significantly longer than the serum half-life of 5 to 6 hours. The DHT metabolites Adiol-G and Andros-G were significantly reduced at all finasteride doses. The degree of Adiol-G suppression was not significantly different among the four groups, but the degree of Andros-G suppression was less in the 0.04 mg group ($P = 0.09$).

Roberts J et al, *Clinical dose ranging studies with finasteride, type 2 5α-reductase inhibitor, in men with male pattern hair loss* (1999).[148]

Roberts et al. conducted two phase 2 clinical trials in men with AGA (age 18 to 36). In the first clinical trial (FDA pilot study #047), 227 men with AGA received 5 mg finasteride or placebo for 12 months. In the second clinical trial (FDA dose range study #081), 466 men received low doses (1, 0.2, and 0.01 mg/day) of finasteride or placebo for 6 months.

Treatment with finasteride significantly decreased serum DHT levels at all doses at month 6 (decrease of 67.6%, 68.5%, 61.2%, and 10.8% for the 5, 1, 0.2, and 0.01 mg groups, respectively; $p < 0.01$ v. placebo). At month 6, the reductions in serum DHT at doses of finasteride ≥ 0.2 mg/day were associated with a significant increase in serum T (18.3%, 19.4%, and 18.1% for 5, 1, and 0.2 mg finasteride, respectively; $p < 0.01$ v.

[146] Vermeulen *op cit.*, pp. 45-53.
[147] Gormley *op. cit.*, pp. 1136-1141.
[148] Roberts *op cit.*, pp. 555-563.

placebo). At month 12, T increased by 20.3% and 29.9% in the 1 mg and 0.2 mg groups, respectively.

Drake L et al, *The effects of finasteride on scalp skin and serum androgen levels in men with androgenetic alopecia* (1999).[149]

Drake et al. evaluated scalp skin hormones in a 42-day phase 2 clinical trial (FDA Protocol #065) in 249 subjects with AGA (age 18 to 50). Scalp skin DHT levels decreased significantly by 14.9%, 61.6%, 56.5%, 64.1%, and 69.4% with 0.01, 0.05, 0.2, 1, and 5 mg finasteride, respectively. Serum DHT levels decreased significantly by 49.5%, 68.6%, 71.4%, and 72.2% with 0.05, 0.2, 1, and 5 mg finasteride ($p < 0.01$ for all doses), respectively. Finasteride, 0.2 mg/day, maximally decreased scalp skin and serum DHT levels.

Scalp skin T levels increased from baseline by 27.2%, 53.2%, 41.4% and 29.7% with 0.05, 0.2, 1, and 5 mg finasteride, respectively ($p < 0.001$). Serum Adiol-G levels decreased from baseline by 15.2%, 63.3%, 68.1%, 74.8%, and 73.6% with 0.01, 0.05, 0.2, 1, and 5 mg finasteride, respectively ($p < 0.002$).

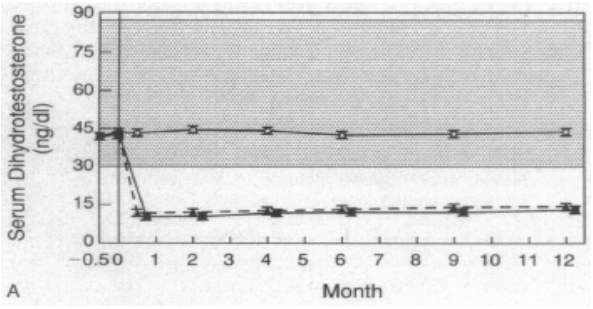
Gormley G et al, *The Effect of Finasteride in Men with Benign Prostatic Hyperplasia* (1992).[150]

In Merck's phase 3 finasteride clinical trial for the treatment of BPH, 895 men with BPH were given 1 mg or 5 mg finasteride, or placebo. Patients in the 1 mg and 5 mg finasteride groups had nearly identical increases in the maximal urinary-flow rate (22% and 23%, respectively, $p < 0.001$), and decreases in prostatic volume (19% and 18%, respectively, $p < 0.001$). At 12 months, the incidences of decreased libido (6.0% v. 4.7%) and impotence (5.0% v. 3.4%) were greater in the 1 mg than the 5 mg finasteride groups, respectively.

Serum DHT concentrations decreased to levels present after castration. The decreases in serum DHT were significantly greater in the men who received 5 mg vs. 1 mg of finasteride ($p \leq 0.01$) at all times from 2 weeks to 12 months, as presented in Figure 1, Panel A below.

Figure 1. Effect of Treatment with Placebo (Circles), 1 mg of Finasteride (Triangles), or 5 mg of Finasteride (Squares) on Mean (±SE) Serum Dihydrotestosterone (Panel A) and Median (±95 Percent Confidence Interval) Serum Prostate-Specific–Antigen (Panel B) Concentrations in Men with Benign Prostatic Hyperplasia.

The stippled area in Panel A indicates the normal range in men. To convert values for dihydrotestosterone to nanomoles per liter, multiply by 0.033. Month 0 represents the base line. Values before month 0 were obtained during the two-week placebo run-in period.



[149] Drake L et al, *The effects of finasteride on scalp skin and serum androgen levels in men with androgenetic alopecia*, J Amer Acad Derm (1999), Vol. 41, pp. 550-554.
[150] Gormley (1992) *op. cit.*, pp. 1185-1191.

Shukla C and Tran D, *Dose Response Data for Finasteride* (2011).[151]

Due to safety concerns with Propecia, FDA's Division of Dermatology and Dental Products requested dose response information from the original Clinical Pharmacology review of Propecia NDA 020788 to assess the potential safety risk of Propecia. From the literature reviewed (i.e. FDA protocol #065 (Scalp Skin and Sebum), Gormley et al.[152] and McConnell et al.[153]), the magnitude of change in serum DHT was similar for the 1 mg and 5 mg finasteride doses.

In one case,[154] the response was statistically significant between 1 mg and 5 mg doses [Figure 1, Panel A above]. However, Shukla and Tran concluded, "It is the opinion of this reviewer that such a decrease, although deemed statistically significant, might not be clinically relevant."

The reviewers concluded, "Based on the limited literature survey, the dose response relationships … indicate there is no significant difference in the effect of finasteride 1 mg versus 5 mg doses on the above listed biomarkers [i.e. scalp skin DHT, scalp skin T, prostate DHT, prostate T, serum Adiol-G, urine androsterone to etiocholanolone ratio, serum PSA, prostate size and prostatic volume]."

Shukla C and Tran D, *Analysis of comparative pharmacodynamic effects of 1 mg and 5 mg dose of finasteride* (2011).[155]

Merck responded to the dose-response review by Shukla and Tran by pointing out the significant differences in serum DHT between the 1 mg and 5 mg finasteride groups.

Study	5 mg		1 mg		Placebo		5 vs 1 mg p-Value
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
North American	286	-65.6** (20.8)	290	-61.7** (21.6)	295	7.2 (34.2)	<0.001
International	210	-50.6** (32.5)	217	-45.2** (37.7)	215	0.3 (33.9)	0.02
** p<0.001 vs placebo							

Table 1: Mean percentage change in serum dihydrotestosterone levels at Month 12

In response, Shukla and Tran concluded, "This study reported a significant difference in the mean % change in the serum DHT levels at month 12 between doses of 1 and 5 mg. However, from Figures 3 and 4 and Table 1, comparing the magnitude of change in the % serum DHT levels following finasteride administration with that observed for placebo, the difference between % serum DHT levels following 1 and 5 mg dose was small."

[151] Shukla (April 28, 2011) *op. cit.*, pp. 1-13.
[152] Gormley (1992) *op. cit.*, pp. 1185-1191.
[153] McConnell (1992) *op. cit.*, pp. 505-508.
[154] Gormley (1992) *op. cit.*, pp. 1185-1191.
[155] Shukla C and Tran D, *Analysis of comparative pharmacodynamic effects of 1 mg and 5 mg dose of finasteride*, FDA Clinical Pharmacology Review (June 1, 2011), Reference ID: 3046462, pp. 1-10.

Suzuki R et al, *Saturable Binding of Finasteride to Steroid 5α-reductase as Determinant of Nonlinear Pharmacokinetics (2010)*.[156]

Suzuki et al. concluded, "Pharmacodynamic model analysis suggested that 5αR1 inhibition is dose-dependent in the dose range from 0.2 to 100 mg finasteride, while 5αR2 inhibition is almost saturated in the same dose range. … The effect on DHT level[s] was estimated to be almost equivalent within the dose range from 0.2 to 5 mg."

d. Sexual Function Questionnaire in Finasteride Clinical Trials.

Sexual function questionnaires were administered in the phase 2 and 3 randomized controlled trials (RCTs) with finasteride for AGA. Any impairment in sexual function is an antiandrogenic effect of finasteride.

The **CLINICAL STUDIES, Studies in Men, Other Results in Vertex Baldness Studies** section (14.1) of the Propecia product label states, "At Month 12, statistically significant differences in favor of placebo were found in 3 of 4 domains (sexual interest, erections, and perception of sexual problems)." This section is misleading.

Roberts J et al, *Clinical dose ranging studies with finasteride, type 2 5α-reductase inhibitor, in men with male pattern hair loss* (1999).[157]

Roberts et al. conducted two phase 2 clinical trials in men with AGA (age 18 to 36). In the first clinical trial (FDA pilot study #047), 227 men with AGA received 5 mg finasteride or placebo for 12 months. In the second clinical trial (FDA dose range study #081), 466 men received low doses (1, 0.2, and 0.01 mg/day) of finasteride or placebo for 6 months.

The sexual function questionnaire in pilot study #047 demonstrated a significant decrease in morning erections from baseline in the 5-mg finasteride group at month 12 ($p < 0.01$).[158] The sexual function questionnaire in dose ranging study #081 demonstrated a significant decrease in sexual drive for the 1 mg and 0.2 mg groups ($p = 0.007$ and 0.019, respectively) and frequency of morning erections for the 1 mg, 0.2 mg and 0.01 mg groups ($p = 0.002$, 0.008 and 0.015, respectively).[159] The results of these sexual function questionnaires have never been reported in the medical literature.

[156] Suzuki *op. cit.*, pp. 208-213.
[157] Roberts *op. cit.*, pp. 555-563.
[158] Ko *op. cit.*, pg. 19.
[159] Ko *op. cit.*, pg. 27.

Kaufman K et al, *Finasteride in the treatment of men with androgenetic alopecia* (1998).[160]

Merck's two 1-year pivotal phase 3 clinical trials with finasteride for AGA (U.S. Study #087 and International Study #089) enrolled 1,553 men 18 to 41 years old who received finasteride 1 mg, or placebo.

The validated sexual function questionnaire in study #087 demonstrated a significant decrease in the finasteride group v. placebo in:

(i) sexual interest at 3, 6 and 9 months ($p = 0.037$, < 0.001 and 0.04),
(ii) erections at 6 and 12 months ($p < 0.001$ and 0.039),
(iii) ejaculation at 6 and 9 months ($p = 0.015$ and 0.05),
(iv) morning erections at 3, 6, 9 and 12 months ($p < 0.001$ at all times), and
(v) perception of sexual problems at 6, 9 and 12 months ($p < 0.001$, 0.039 and 0.006).[161]

The validated sexual function questionnaire in study #089 demonstrated a significant decrease in the finasteride group v. placebo in:

(i) sexual interest at 3, 6, 9 and 12 months ($p < 0.001$, 0.011, < 0.001 and 0.004),
(ii) erections at 3, 9 and 12 months ($p = 0.005$, 0.035 and 0.02),
(iii) ejaculation at 3 months ($p = 0.058$), and
(iv) morning erections at 3, 6, 9 and 12 months ($p = 0.001$, 0.001, 0.006 and 0.017).[162]

The results of the sexual function questionnaire in studies #087 and #089 have never been reported in the medical literature, but are presented in the **CLINICAL STUDIES, Other Results in Vertex Baldness Studies** section (14.1) of the Propecia product label, not the **ADVERSE REACTIONS, Clinical Trials Experience** section (6.1) where data from a pivotal phase 3 RCT demonstrating sexual dysfunction needs to be presented.

The description of the sexual function questionnaire results in the Propecia product label doesn't mention the effect of finasteride on morning erections, uses language that is not consistent with scientific norms ("statistically significant differences *in favor of* placebo"), [emphasis supplied] and as written, it is unclear whether the finasteride or placebo group had worse sexual function. A decrease in morning erections is an important clinical sign of organic ED.

Overstreet J et al, *Chronic treatment with finasteride daily does not affect spermatogenesis or semen production in young men* (1999).[163]

In Merck's long-term reversibility-of-effect study (FDA Protocol # 094), 181 men

[160] Kaufman *op. cit.*, pp. 578-589.
[161] Ko Medical Review *op. cit.*, pp. 40-41.
[162] Ko Medical Review *op. cit.*, pp. 50-51.
[163] Overstreet J et al, *Chronic treatment with finasteride daily does not affect spermatogenesis or semen production in young men*, J Urology (1999), Vol. 162, pp. 1295-1300.

(age 19 to 41) received 1 mg finasteride or placebo for 48 weeks followed by a 60-week, off-drug period. The sexual function questionnaire found a statistically significant decrease in sexual interest at week 36 ($p = 0.023$) and morning erections at week 48 ($p = 0.021$).[164] A decrease in morning erections is an important clinical sign of organic ED.

e. Sexual AEs with Finasteride in Men Older than 41 Years.

The efficacy of Propecia was demonstrated in men with mild to moderate AGA between 18 and 41 years old.[165] However, Propecia is commonly used to treat AGA in men in their 40's and 50's, and even in some men in their 60's or older. The 2001 Propecia Patient Information[166] stated, "If you stop taking PROPECIA, you will likely lose the hair you have gained within 12 months of stopping treatment." So men who started taking Propecia between the ages of 18 and 41 will have to continue taking the drug as they age beyond 41 years old if they want to maintain the benefits of Propecia treatment. Therefore, it is essential that the Propecia product label contain as much disclosure as possible about the risk of sexual dysfunction in men taking Propecia beyond age 41.

There is a considerable amount of data on the risk of sexual dysfunction with Proscar in older men. A full discussion of all this data is beyond the scope of this petition, but some relevant RCTs are discussed below. However, the data is clear that the risk of sexual AEs with Propecia and Proscar in older men is considerably higher than the risk of sexual AEs with Propecia in younger men. In all RCTs that directly compared the effects of 1 mg and 5 mg finasteride,[167] the risk of sexual AEs with 1 mg and 5 mg were comparable. The dose-response curve between 1 mg and 5 mg finasteride is almost flat and the biological responses of these 2 doses are almost equivalent.[168,169]

Gormley G et al, *The Effect of Finasteride in Men with Benign Prostatic Hyperplasia* (1992).[170]

At 12 months in the U.S. phase 3 clinical trials with finasteride in 895 men with BPH, the incidences of decreased libido (6.0% v. 4.7%) and impotence (5.0% v. 3.4%) were greater in the 1 mg than the 5 mg finasteride groups, respectively. The total number of any sexual AEs with 5 mg finasteride at 12 months was 15.5%.

[164] Ko Medical Review *op. cit.*, page 91.
[165] *Propecia® Full Prescribing Information* (2014) *op. cit.*
[166] *Propecia® Full Prescribing Information* (2001). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2001/20788s3lbl.pdf.
[167] Gormley (1992) *op. cit.*, pp. 1185-1191.
[168] Shukla (April 28, 2011) *op. cit.*, pp. 1-13.
[169] Suzuki *op. cit.*, pp. 208-213.
[170] Gormley (1992) *op. cit.*, pp. 1185-1191.

Grino P et al, *Finasteride for the Treatment and Control of Benign Prostatic Hyperplasia: Summary of Phase III Controlled Studies* (1994).[171]

Merck tested finasteride, 1 mg and 5 mg, in phase 3 clinical trials in 1,645 men with BPH over a 1-year period. Finasteride was associated with a greater incidence of sexual dysfunction with 1 mg (12.6%) than 5 mg (10.8%) finasteride.

Nickel et al, *Efficacy and safety of finasteride therapy for benign prostatic hyperplasia: results of a 2-year randomized controlled trial (the PROSPECT Study)* (1996).[172]

The PROSPECT study treated 613 men with BPH with finasteride 5 mg or placebo for 2 years. The incidence of sexual AEs was significantly higher with finasteride than placebo (ejaculation disorder 7.7% v. 1.7% and impotence 15.8% v. 6.3%, respectively; $p \leq 0.01$). These are some of the highest reported rates of sexual dysfunction for RCTs with finasteride for BPH.

Whiting et al, *Efficacy and tolerability of finasteride 1 mg in men aged 41 to 60 years with male pattern hair loss* (2003).[173]

Merck conducted a 2-year U.S. RCT from 1999 to 2002 in 424 men with AGA age 41 to 60 years who received Propecia or placebo. There were 8.7% subjects taking Propecia v. 5.1% taking placebo who experienced a drug-related sexual AE. Ejaculation disorder was reported in 2.8% of finasteride and 0.7% of placebo subjects. ED was reported in 3.8% of finasteride and 0.7% of placebo subjects.

The incidences of sexual AEs were greater with finasteride in older men (age 41 to 60 years) with AGA than in younger men (age 18 to 41 years) with AGA in prior studies. The Propecia product label was never amended to include the results of this RCT. Since the use of Propecia in men older than 41 years is common, this is a material omission. The results from this RCT need to be disclosed in the Propecia product label.

f. Concerns of the FDA Advisory Committee Reviewing the Propecia NDA.

On November 14, 1997, the Chicago Tribune reported that FDA Advisory Committee reviewing the Propecia NDA "did not vote on [Propecia's] safety or effectiveness."[174] A November 19, 1997 Pharma Letter article stated that the Advisory Committee "stopped short of recommending Propecia … with members of the committee raising a number of concerns."[175] A January 1998 Pharma Letter article reported "An FDA advisory panel refused to recommend approval of [Propecia]. Although it was not disputing its efficacy,

[171] Grino P et al, *Finasteride for the Treatment and Control of Benign Prostatic Hyperplasia: Summary of Phase III Controlled Studies*, Eur Urol (1994), Vol. 25 (supplement), pp. 24-28.
[172] Nickel J et al, *Efficacy and safety of finasteride therapy for benign prostatic hyperplasia: results of a 2-year randomized controlled trial (the PROSPECT Study)*, Canadian Med Assn J (1996), Vol. 155(9), pp. 1251-1259.
[173] Whiting D et al, *Efficacy and tolerability of finasteride 1 mg in men aged 41 to 60 years with male pattern hair loss*, Eur J Derm (2003), Vol. 13, pp. 150-160.
[174] Wilson T, *Anti-baldness Drug for Men Clears Major FDA Hurdle*, Chicago Tribune (November 14, 1997).
[175] The Pharma Letter, *FDA C'tee Raises Concerns Over Merck's Propecia*, (November 19, 1997).

the committee members expressed some concerns about the possibility of long-term side effects on sexual function, and possibly even fertility."[176]

With all the compelling new data that has since been published, it is now time for the FDA to act on the concerns expressed by the FDA's Propecia Advisory Committee 20 years ago.

5. Persistent/Permanent Sexual Side Effects with Finasteride after Drug Discontinuation

The **ADVERSE REACTIONS, Clinical Trials Experience** section (6.1) of the product label states, "Resolution [of sexual adverse reactions] occurs in men who discontinued therapy with PROPECIA due to these side effects."

The publications of large-scale, observational epidemiologic studies by Guo et al.[177] and Kiguradze et al,[178] and the deposition testimony of Charlotte Merritt,[179] a Merck regulatory executive, confirm that this is an untrue statement of a material fact.

In addition to large-scale, observational epidemiologic studies, (i) a voluminous medical literature that conclusively establishes biological plausibility, (ii) hundreds of case reports of persistent ED following discontinuation of finasteride in the medical literature and FDA Adverse Event Reporting System (FAERS) database, and (iii) studies documenting objective findings in patients with persistent sexual dysfunction following discontinuation of finasteride firmly support the scientific case for causation by Propecia of sexual dysfunction that persists indefinitely even after the drug has been discontinued for many years.

a. Randomized Controlled Trials.

While the phase 2 and 3 RCTs with finasteride for BPH and AGA recorded spontaneously reported sexual AEs,[180,181,182] they were not specifically designed to evaluate whether sexual AEs persisted many months after discontinuation of treatment.

Only one finasteride for BPH RCT, the Prostate Long-Term Efficacy and Safety Study (PLESS), evaluated the persistence of sexual AEs in some study subjects 6 months after withdrawal of finasteride, but this study had major methodological flaws that prevent

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[176] The Pharma Letter, *Propecia Approved in USA for Male Pattern Baldness*, (January 12, 1998).
[177] Guo M et al, *Persistent Sexual Dysfunction with Finasteride 1 mg Taken for Hair Loss*, Pharmacother (2016), Vol. 36(11), pp. 1180-1184.
[178] Kiguradze T, *Persistent erectile dysfunction in men exposed to the 5α-reductase inhibitors finasteride or dutasteride*, PeerJ (2017), 5:e3020, DOI 10.7717/peerj.3020, pp. 1-31.
[179] Becker TJ et al, *In re: Propecia (Finasteride Products Liab. Litig. MDL 2331) Plaintiffs' Motion to Amend PPO No. 10 and Extend Discovery Deadline to Allow for Requests for Admission* (2016 Jul 20), pp. 1-7, Exhibits A-F. Available from: https://ecf.nyed.uscourts.gov/cgi-bin/ShowIndex.pl (Case # 1:12-md-02331).
[180] Roberts *op. cit.*, pp. 555-563.
[181] Kaufman *op. cit.*, pp. 578-589.
[182] Gormley (1992) *op cit.*, pp. 1185-1191.

any conclusion about an association between finasteride for BPH and persistent sexual dysfunction.

We have obtained the PLESS trial protocol[183] and Clinical Study Report Synopsis[184] from the FDA in response to a Freedom of Information Act request. Joanne Waldstreicher authored the Clinical Study Report Synopsis.

Persistent Sexual Dysfunction in the Phase 2 Clinical Trials with Finasteride for AGA

Two men in the phase 2 finasteride AGA clinical trials developed persistent sexual dysfunction that was not reversible after drug discontinuation.

Roberts et al. conducted two phase 2 clinical trials in men with AGA (age 18 to 36).[185] In the first clinical trial (FDA pilot study #047), 227 men with AGA received 5 mg finasteride or placebo for 12 months. In the second clinical trial (FDA dose range study #081), 466 men received low doses (1, 0.2, and 0.01 mg/day) of finasteride or placebo for 6 months.

The FDA Medical Review of the Propecia NDA disclosed that a 35-year-old man in the phase 2 pilot study #047 reported "moderate" impotence that was not resolved 170 days after discontinuation.[186] This persistent sexual AE is not disclosed in the Propecia product label, nor in the published report of the clinical trial results.

The FDA Medical Review of the Propecia NDA also disclosed that one man in the phase 2 uncontrolled extension of studies #047 and #081 developed delayed ejaculation that did not resolve after discontinuation of finasteride.[187] This persistent sexual AE has never been reported in the medical literature or disclosed in the Propecia product label.

Prostate Long-term Efficacy and Safety Study.[188,189,190]

The PLESS trial, a 4-year study in 3,040 men 50 to 75 years old with symptomatic BPH, is the only finasteride RCT that evaluated persistence of sexual side effects in some study subjects several months after drug discontinuation. There were 1,524 men in the finasteride group and 1,516 men in the placebo group. Unfortunately, this study had major methodological flaws that prevents any conclusion about the safety of finasteride and its association with persistent sexual dysfunction.

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[183] MK-906 Protocol No. 048-04, *Long-Term Effects of Finasteride (MK-906) in Patients with Benign Prostatic Hyperplasia* (November 20, 1991, revised November 26, 1991).
[184] Waldstreicher J and Wang D, *Finasteride (MK-906) Clinical Study Report Synopsis* (July 31, 1997, revised August 19, 1997).
[185] Roberts *op. cit.*, pp. 555-563.
[186] Ko Medical Review *op. cit.*, page 18.
[187] Ko Medical Review *op. cit.*, page 77.
[188] MK-906 Protocol No. 048-04 *op. cit.*, (November 20, 1991).
[189] Waldstreicher *op. cit.* (July 31, 1997).
[190] Wessells H et al, *Incidence and Severity of Sexual Adverse Experiences in Finasteride and Placebo-Treated Men with Benign Prostatic Hyperplasia*, Urology (2003), Vol. 61, pp. 579-584.

Wessells et al. (and Waldstreicher) stated, "Among the patients who discontinued the study (for any reason) and had a sexual AE present at the time of discontinuation, the sexual AEs resolved in 50% of the finasteride-treated patients and 41% of placebo-treated patients after discontinuation from the study."

Over the last 15 years, Wessells et al. has been relied upon by clinicians and researchers as proof that sexual AEs with finasteride are reversible upon drug discontinuation. However, the PLESS study design was so flawed with respect to the evaluation and reporting of persistent sexual AEs that no conclusion about the association of finasteride with sexual AEs that persist after discontinuation of treatment is possible. Wessells et al. does not address the limitations of the PLESS study design. This is a material reporting omission.

Sexual AEs in the PLESS trial were spontaneously self-reported and classified as mild (easily tolerated), moderate (interference with performance of usual sexual activity), or severe (unable to perform usual sexual activity).

Men with a drug-related sexual AE who discontinued finasteride were contacted by study staff about their status by telephone six months after completion of the final study visit. Over the phone, the patients completed a Symptom Questionnaire A, a Quality-of-Life Questionnaire B, and a Sexual Function Questionnaire C.

Some sexual dysfunction variables in the PLESS trial were either not analyzed at all, or not reported in Wessells et al, or the PLESS Clinical Study Report Synopsis. The following bullet points present methodological issues that raise concerns about the validity of the PLESS trial results:

- The FDA guidance document, *Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials*,[191] states, "FDA law and regulations recognize that a complete and accurate risk/benefit profile of an investigational product depends upon the data from every subject's experience in the clinical trial. … The validity of a clinical study would also be compromised by the exclusion of data collected during the study. There is long-standing concern with the removal of data, particularly when removal is non-random, a situation called 'information censoring.'… Complete removal of data, possibly in a non-random or informative way, raises great concerns about the validity of the study."

- Men with a pre-existing history of sexual dysfunction should have been systematically excluded from being classified as having a drug-related sexual AE, but were included in the data analysis of percentage of men with drug-related sexual AEs.

[191] *Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials*, FDA Guidance for Sponsors, Clinical Investigators, and IRBs (October 2008), pp. 1-6. Available from: https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126489.pdf.

At baseline, 45.6% of finasteride patients (695 patients) and 46.2% of placebo patients (700 patients) in the PLESS trial had a background history of sexual dysfunction before randomization. At baseline, a history of decreased libido was reported in 21.4% of finasteride patients and 22.6% of placebo patients, while 12.9% of finasteride patients and 13.9% of placebo patients reported a history of ejaculation disorders, and 33.5% of patients in both groups reported a background history of impotence.

In the finasteride (N=1,524) and placebo (N=1,516) groups, 329 men (22%) and 207 men (14%), respectively, were reported in the Clinical Study Report Synopsis as having a drug-related sexual AE. However, the denominator for these percentages included men with a pre-existing history of sexual dysfunction. Since these men should not have been classified as having a drug-related sexual AE, they should not have been included in the denominator of this calculation. Subtracting the 695 men in the finasteride group and 700 men in the placebo group who had a pre-existing history of sexual dysfunction from the denominator, a percentage calculation that only includes men at risk for new sexual dysfunction determines that 40% of men in the finasteride group (329 ÷ [1,524 - 695]) and 25% of men in the placebo group (207 ÷ [1,516 – 700]) had drug-related sexual AEs.

Such high percentages of new drug-related sexual AEs in at-risk men have never been reported in the medical literature. Such a reporting omission calls into question the validity of the study's results.

To the extent that men with a pre-existing history of sexual dysfunction have been included in the denominator when calculating the percentage of men with drug-related sexual AEs in other Proscar RCTs, the reported rates of drug-related sexual AEs with Proscar in the medical literature have significantly underestimated the percentage of at-risk men who have developed new drug-related sexual AEs.

To the extent that men with a pre-existing history of sexual dysfunction have not been systematically excluded from being classified as having a drug-related sexual AE, this would be problematic and cast serious doubt on the validity of the PLESS trial's safety findings.

- Only a small subset of men with drug-related sexual AEs were included in the persistent sexual AE data analysis. Of the 329 finasteride patients and 207 placebo patients with a drug-related sexual AE in the PLESS study, only 100 (30%) finasteride patients and 79 (38%) placebo patients were evaluated for persistence of sexual AEs after drug discontinuation. This is a design flaw that prevents any conclusion about the persistence of sexual AEs with finasteride.

- Data for persistent sexual AEs in men who withdrew from the study due to a sexual AE were not presented in the Clinical Study Report Synopsis. There were 57 finasteride patients and 32 placebo patients who withdrew from the study due to a sexual AE. This reporting omission may have biased the reported study results.

In addition, there were inconsistencies in how this data was reported. For example, one of the 57 finasteride patients who withdrew due to a sexual AE (AN 2124) experienced a serious sexual AE and had a pre-existing history of arteriogenic impotence. The investigator did not feel that this serious sexual AE was drug related and the patient was reported as "remained on study drug."

- The data in the Clinical Study Report Synopsis was not reported according to severity (mild, moderate or severe) of the sexual AE. This reporting omission may have biased the reported study results.

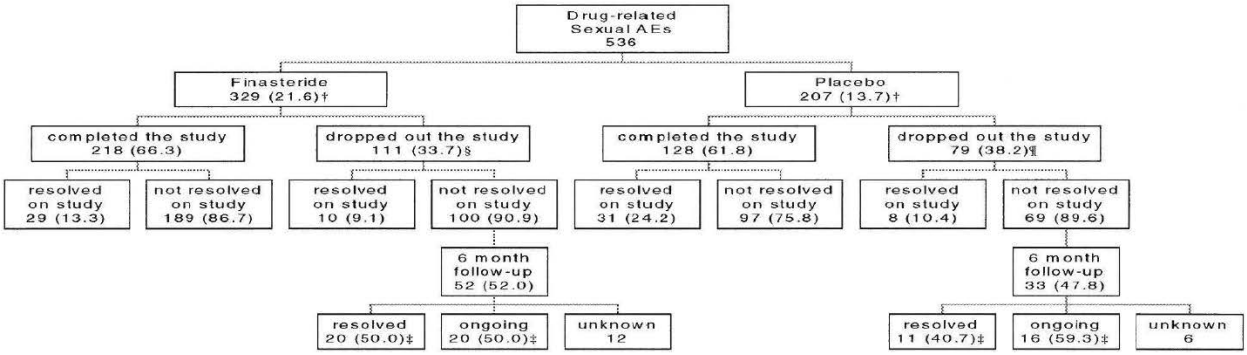
- Significant increases in any sexual AEs, decreased libido, impotence, decreased ejaculation volume and other ejaculation disorders were reported for the finasteride patients ($p < 0.001$ for all groups). Persistence data for each of these specific types of sexual AEs were not reported in the Clinical Study Report Synopsis. This reporting omission may have biased the reported study results.

- The PLESS study was not designed to do a six-month follow-up of men who completed the 4-year study to evaluate whether their sexual AEs were reversible after discontinuation of therapy. This is another design flaw in the PLESS trial that prevents any conclusion about the persistence of sexual AEs with finasteride.

Figure 12 below reports the Drug-Related Sexual Adverse Experiences by Treatment Group and the Adverse Experience Status at the End of the Study and the 6-Month Follow-up Contact.

Figure 12

Drug-Related Sexual Adverse Experiences by Treatment Group and the Adverse Experience Status at the End of the Study and the 6-Month Follow-up Contact



Nearly twice as many finasteride as placebo patients had unresolved, drug-related sexual AEs at the end of the study. Of the 218 finasteride patients with drug-related sexual AEs who completed the PLESS study, 189 (86.7%) had sexual AEs that were not resolved at the end of the study. Of the 128 placebo patients with drug-related sexual AEs who completed the study, 97 (75.8%) had sexual AEs that were not resolved at the end of the study. The Clinical Study Report Synopsis did not report a statistical analysis of these large differences. This reporting omission may have biased the study results.

- Significant increases in testicular pain (p = 0.018) and penis disorder (p = 0.041) sexual AEs were observed in the finasteride patients. Penis disorders and testicular pain are significant findings that need to be disclosed in the **ADVERSE REACTIONS, Clinical Trials Experience** section (6.1) of the Propecia product label.

Penis disorders occurred in 15 (1.0%) finasteride patients and 5 (0.3%) placebo patients. The most common penis disorders in finasteride patients were curvature of the penis (4 patients) and decreased penile sensation (5 patients). Eight of the 15 finasteride patients and 1 of the 5 placebo patients had a penis disorder that was considered to be drug-related by the investigators.

There is no disclosure of the significant increase in penis disorders in the men taking finasteride in the Propecia product label or in the medical literature, yet these are sexual AEs that are commonly reported by PFS patients.

The increase in testicular pain in men taking finasteride was not disclosed in the original Propecia product label through December 2001,[192] and was only added to the **ADVERSE REACTIONS**, *Postmarketing experience* section of the Propecia product label in April 2002.[193]

- Significant increases in breast enlargement (p = 0.03) and breast tenderness (p = 0.03) AEs were observed in the finasteride patients.

Breast enlargement and tenderness are estrogenic effects of finasteride. The Propecia product label needs to disclose these significant breast AEs in the **ADVERSE REACTIONS, Clinical Trials Experience** section (6.1) and should not state that finasteride has no estrogenic effects.

- Medical professionals often cite Wessells et al. as proof that sexual AEs with finasteride resolve after discontinuation of treatment. Despite the impression given by Wessells et al. that the PLESS trial demonstrated no difference in persistent sexual AEs in the finasteride v. placebo group, the Conclusion section of the PLESS Clinical Study Report Synopsis does not discuss any findings or conclusion regarding the persistence of sexual AEs after discontinuation of treatment.

- The Clinical Study Report Synopsis of the PLESS trial was submitted to the FDA on July 31, 1997,[194] well before FDA approval of the Propecia NDA in December 1997, yet Merck has never publicly disclosed material data from the PLESS trial. It is not clear whether material data from the PLESS trial was withheld from the FDA Advisory Committee reviewing Merck's NDA for Propecia.

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[192] *Propecia® Full Prescribing Information* (2001) *op. cit.*
[193] *Propecia® Full Prescribing Information* (2002). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/20788S4lbl.pdf.
[194] Waldstreicher *op. cit.* (July 31, 1997).

b. Meta-analyses and Systematic Reviews.

While there have been numerous studies and meta-analyses that have evaluated the risk of developing sexual dysfunction during the treatment of BPH or AGA with finasteride, none of these studies have evaluated the risk of sexual dysfunction that started during finasteride use and persisted after the discontinuation of finasteride. A couple of meta-analyses have evaluated the quality of sexual AE reporting in finasteride for AGA RCTs.

Mella J et al, *Efficacy and Safety of Finasteride Therapy for Androgenetic Alopecia: A Systematic Review* (2010).[195]

Mella et al. evaluated the risk of sexual AEs in finasteride AGA RCTs, but did not evaluate persistent sexual AEs following discontinuation of finasteride. Out of 128 possibly relevant articles, Mella included 12 studies of finasteride v. placebo for AGA in a meta-analysis. Nine of the 12 trials were sponsored by Merck. Moderate-quality evidence suggested an increase in ED (relative risk (RR) = 2.22; number needed to harm (NNH) = 82.1). There was no significant difference between the use of 1 mg and 5 mg of finasteride in any of the outcomes.

Mella et al. concluded, "The major problems with the quality of evidence included imprecision, inconsistency, and likelihood of publication bias. The likelihood of publication bias was suggested by the asymmetrical funnel plots but also by the fact that all trials were relatively small and almost all were funded by industry sponsors."

Belknap S et al, *Adverse Event Reporting in Clinical Trials of Finasteride for Androgenic Alopecia: A Meta-analysis* (2015).[196]

Belknap et al. published the only meta-analysis in the medical literature that evaluated the quality of finasteride for AGA clinical trial reporting for both the risk of sexual AEs with finasteride use and the risk of persistent sexual AEs following discontinuation of finasteride. Belknap et al. evaluated 34 finasteride for AGA clinical trial publications (9,751 participants, mean age of 35.5 years) for study design, drug dosage, sample size, average age, study duration, quality of AE reporting, adequacy of blinding, treatment indication, withdrawal rate, inclusion and exclusion criteria, conflicts of interest, and funding source.

Using the criteria of Ioannidis and Lau[197] for adequate safety reporting, the authors concluded, "None [of the 34 clinical trials] had adequate safety reporting, 19 were partially adequate, 12 were inadequate, and 3 reported no AEs." Most studies provided

[195] Mella J et al, *Efficacy and Safety of Finasteride Therapy for Androgenetic Alopecia: A Systematic Review*, Arch Derm (2010), Vol. 146(10), pp. 1141-1150.
[196] Belknap S et al, *Adverse Event Reporting in Clinical Trials of Finasteride for Androgenic Alopecia: A Meta-analysis*" JAMA Dermatol (2015), Vol. 151(6), pp. 600-606.
[197] Ioannidis J and Lau J, *Completeness of Safety Reporting in Randomized Trials, An Evaluation of 7 Medical Areas*, JAMA (2001), Vol. 285(4), pp. 437-443.

no description of the duration or severity of sexual dysfunction and failed to distinguish between mild, reversible sexual dysfunction and severe, permanent sexual dysfunction.

To assess generalizability, the medical histories of 5,704 men treated for AGA with finasteride from Northwestern's clinical data repository were compared to the exclusion criteria of Merck's 3 pivotal finasteride for AGA clinical trials. There were 69% of men in the Northwestern repository who would have been excluded from the clinical trials that supported the Propecia NDA. The authors explained, "Lack of generalizability represents another serious limitation of the available clinical trial data because … 69% of such men met exclusion criteria for the 3 clinical trials that supported FDA approval of [Propecia]."

In studies where odds ratios could be calculated, funnel plots of odds ratios for sexual dysfunction, impotence and decreased libido v. sample size were "asymmetric with a bias toward lower odds ratios, suggesting possible under-detection or under-reporting of sexual AEs in these trials, perhaps owing to publication bias."

No reports assessed adequacy of blinding. Since study subjects taking finasteride would likely notice cessation or reversal of balding and AE assessments were based on participant reports, the authors commented, "The lack of assessment of adequacy of blinding is a serious flaw in the reporting of these 34 clinical trials."

Belknap et al. concluded, "Available toxicity information from clinical trials of finasteride in men with AGA is very limited, is of poor quality, and seems to be systematically biased. … Published reports of clinical trials provide insufficient information to establish the safety profile for finasteride in the treatment of AGA."

Moore T, *Finasteride and the Uncertainties of Establishing Harm* (2015).[198]

Moore commented that the findings reported by Belknap and colleagues "are best understood as 3 separate issues woven together. (1) What is the evidence that use of finasteride for AGA impairs sexual function, especially persistently? (2) How adequate were clinical trials for assessing these harms? (3) How well reported was this evidence in scientific journals, especially in meta-analyses?"

Moore explained, "Clinical trials are a modest and limited tool for assessing harms." RCTs are designed and powered as small as possible to determine whether a validated, primary endpoint is sensitive to a drug's effects. As a result, the trial may be too small to identify important AEs. How AEs were ascertained in RCTs is essential to know and this information is rarely disclosed in publicly available documents. "The persistence of drug-induced harms is rarely measured." For finasteride, persistent sexual AEs were only reported by Wessells et al.[199] and "only spontaneously self-reported sexual AEs were recorded."

[198] Moore T, *Finasteride and the Uncertainties of Establishing Harm*, JAMA Dermatol (2015), Vol. 151(6), pp. 585-586.
[199] Wessells *op. cit.*, pp. 579-584.

Moore concluded that meta-analyses are usually a weak assessment tool for the assessment of harms because of the inadequacy of data in the underlying journal articles. "Belknap and colleagues remind us that drug harms are not systematically assessed with the quality, scientific rigor, and objectivity available to measure drug benefits."

c. Observational Epidemiologic Studies.

Over the last year, 2 observational epidemiologic studies evaluating persistence of sexual AEs after discontinuation of therapy in men using finasteride for AGA have been published.[200,201] Together, these studies provide the best available evidence in the medical literature that evaluates the association between the use of finasteride and sexual AEs that persist after discontinuation of therapy. There are no other similar observational epidemiologic studies evaluating persistent sexual dysfunction following discontinuation of finasteride for AGA that provides data which is inconsistent with the results of these 2 studies.

When Kiguradze et al.[202] is interpreted together with Guo et al,[203] the voluminous medical literature that conclusively establishes biological plausibility, hundreds of case reports of persistent ED following discontinuation of finasteride in the medical literature and FAERS database, and controlled studies documenting objective findings in patients with persistent sexual dysfunction following discontinuation of finasteride, the scientific case supporting the causation of persistent ED by finasteride is clear.

Together, these studies provide strong support for the immediate withdrawal of marketing approval for Propecia, or the addition of **WARNINGS**, **PRECAUTIONS**, **HIGHLIGHTS OF PRESCRIBING INFORMATION** and a **BOXED WARNING** to the Propecia product label for persistent and permanent ED that develops with Propecia use, results in the substantial or complete inability to engage in sexual relations, and continues indefinitely for many years after discontinuation of Propecia.

Guo M et al, *Persistent Sexual Dysfunction with Finasteride 1 mg Taken for Hair Loss* (2016).[204]

Persistent sexual dysfunction was evaluated using the IMS U.S. health claims database in a cohort of 6,110,723 patients 15 to 60 years old, identifying 1,390 men who discontinued finasteride, 1 mg, and 20,000 randomly selected, age-matched users of omeprazole from 2006 to 2014. A "first persistent sexual dysfunction event was defined as (1) the first persistent sexual dysfunction diagnosis through the first ICD-9-CM code for sexual dysfunction and (2) use of a PDE_5 inhibitor." Cox proportional hazard models computed hazard ratios (HRs) and adjusted for covariate variables, including

[200] Guo *op. cit.*, pp. 1180-1184.
[201] Kiguradze *op. cit.*, pp. 1-31.
[202] Ibid.
[203] Guo *op. cit.*, pp. 1180-1184.
[204] Ibid.

hypertension, diabetes, stroke, coronary artery disease, antidepressant use, anxiety, prior ED, and prior physician visit.

Guo et al. reported, "The mean time to first persistent sexual dysfunction events among persistent sexual dysfunction cases with the finasteride users was 391 days (SD, 357 days)." The rate of persistent sexual dysfunction for finasteride and omeprazole users was 37.9 and 15.0 per 1000 person-years, respectively. For persistent sexual dysfunction, the crude and adjusted HRs comparing finasteride to omeprazole users were 2.19 (95% CI, 1.64–2.92) and 1.62 (95% CI, 1.14–2.29), respectively. The crude and adjusted HRs comparing finasteride to omeprazole users for persistent sexual dysfunction defined as a PDE_5 inhibitor prescription post-exposure were 2.41 (95% CI, 1.78–3.26) and 2.73 (95% CI, 2.01–3.69), respectively.

The authors explained, "The results of our cohort study demonstrate an increased risk of persistent sexual dysfunction with finasteride use. … The time from the last finasteride prescription to the last sexual dysfunction ICD-9-CM code was 1,680 days. … It is possible our findings underestimate the true risk of persistent sexual dysfunction with finasteride since men with persistent sexual dysfunction may not necessarily receive an ICD-9-CM code and are likely to under-report symptoms of persistent sexual dysfunction to their physician."

Guo et al. concluded, "This is the first epidemiologic study quantifying the risk of persistent sexual dysfunction with finasteride in a real clinical setting. Strengths of this study include the large sample size, inclusion of a control group, and adjustment for potential confounding variables."

Kiguradze T et al, *Persistent erectile dysfunction in men exposed to the 5α–reductase inhibitors finasteride or dutasteride* (2017).[205]

With the publication of Kiguradze et al, a strong, statistically significant association between the use of low dose finasteride (1.0 to 1.25 mg/day) to treat AGA and persistent ED that continues after drug discontinuation has now been conclusively established in a large, well-designed epidemiological study.

Strengths of Kiguradze et al. include: (i) Strength of Association - a large relative risk was observed for the association between the use of low-dose finasteride for AGA and persistent ED, (ii) Specificity of Association – a stronger association between the use of low-dose finasteride for AGA and persistent ED was observed than for all other known risk factors for ED, (iii) Dose Response – an increased time of exposure to low-dose finasteride for AGA was accompanied by increased risk of persistent ED, and (iv) Temporal Relationship – exposure to low-dose finasteride for AGA preceded the onset of persistent ED.

Kiguradze et al. also established a significant association between new persistent ED and the use of all 5αRIs at all doses. Electronic medical records (EMRs) for 691,268 men

[205] Kiguradze *op. cit.*, pp. 1-31.

age 16 to 89 years were reviewed. Of these men, 17,475 had exposure to 5αRIs. A subset of EMRs for 327,437 men 16 to 42 years old were independently reviewed and 5,582 (1.7%) of these men were exposed to finasteride ≤ 1.25 mg/day.

The charts of all men with persistent ED were manually evaluated by two independent reviewers. Men with new persistent ED met strict diagnostic criteria defined as (i) new ED lasting ≥ 90 days after discontinuation of 5αRI use, and (ii) treatment with a PDE_5 inhibitor. To reduce heterogeneity, a single group experimental design was used, excluding men not prescribed a 5αRI. Men with shorter 5αRI exposure served as a comparison control group for those with longer exposure. Multivariable analyses using classification tree analysis software identified the model that maximized predictive accuracy.

There were 11,909 men with no prior sexual dysfunction who were exposed to a 5αRI and evaluated for persistent ED. Among these men, 167 (1.4%) developed new persistent ED with a median duration of 1,348 days after drug discontinuation. Of the 530 men with new ED, 167 (31.5%) had new persistent ED. The number of men with new ED and continued exposure to a 5αRI was not determined which suggests an actual rate of new persistent ED among men with new ED who discontinued finasteride treatment that is greater than 31.5%. The best multivariable model predicting new persistent ED had four variables: prostate disease, duration of 5αRI exposure, age, and non-steroidal anti-inflammatory drug (NSAID) use (effect strength for sensitivity (ESS) = 42.4%, all p-values ≤ 0.002). Men without prostate disease who combined NSAID use with > 208.5 days of 5αRI exposure had a 4.8–fold higher risk of persistent ED (NNH = 59.8, all p values < 0.002) than men with shorter exposure.

There were 4,284 men 16 to 42 years old without prior sexual dysfunction who were exposed to finasteride ≤ 1.25 mg/day. Of these men, 34 (0.8%) developed persistent ED with a median duration of 1,534 days after drug discontinuation. Of the 103 young men with new ED, 34 (33%) had new persistent ED. The number of young men with new ED and continued exposure to finasteride ≤ 1.25 mg/day was not determined which suggests an actual rate of new persistent ED among men with new ED who discontinued finasteride treatment that is greater than 33%. The optimally predictive multivariable model predicting new persistent ED had one variable: duration of finasteride exposure. Men with > 205 days of finasteride exposure had a 4.9-fold higher risk of developing persistent ED than men with shorter exposure (NNH = 108.2, p < 0.004). Persistent ED developed in 1.19% of men with > 205 days of exposure.

Kiguradze et al. explained, “Our finding of a consistent effect provides evidence of an intrinsic relationship between duration of 5αRI exposure and persistent ED. … The predictor cut-points for 5αRI exposure duration do not establish a safe threshold for exposure duration. Our use of a single group design for the primary analysis means that the observed NNH must be considered as an upper bound, as all men in the study cohort were exposed to 5αRIs. … We expect that a clinical trial using randomization, placebo-control, universal evaluation, and a validated measure of ED would likely give a higher attributable risk and therefore a lower NNH. … Among men with 5αRI exposure,

duration of 5αRI exposure was a more accurate predictor of persistent ED than all other assessed risk factors except prostate disease and prostate surgery. Among young men with 5αRI exposure, duration of 5αRI exposure was a more accurate predictor of persistent ED than all other assessed risk factors."

An estimated 2.1 million men with BPH used 5αRIs in 2010. An estimated 500,000 men were prescribed Propecia for AGA in 2011. Among all men exposed to 5αRIs, the authors commented that "the duration of 5αRI exposure was a more accurate predictor of persistent ED than many known risk factors, including age, hypertension, diabetes mellitus, cigarette smoking, ethanol abuse, obesity, and depression. … Duration of finasteride exposure proved to be a more accurate predictor of sexual dysfunction than higher dose vs lower dose of finasteride, likely reflecting that finasteride exerts near maximal inhibition of DHT synthesis at a dose of 1 mg."

Kiguradze et al. concluded, "Risk of persistent ED was higher in men with longer exposure to 5αRIs. Among young men, longer exposure to finasteride posed a greater risk of persistent ED than all other assessed risk factors."

d. Studies in Men with Persistent Sexual Dysfunction after Discontinuation of Finasteride Use for AGA.

There have been several studies which have identified objective findings in men with sexual AEs that developed during finasteride use for AGA and persisted following discontinuation of finasteride treatment. Some of the abnormal objective findings include AR overexpression in androgen responsive tissues, abnormal brain circuitry consistent with decreased sexual arousal and major depression, altered levels of multiple neurosteroids in plasma and CSF, pudendal nerve neuropathy, and altered T/LH ratios.

La Marra F et al, *Preliminary Evidence of a Peculiar Hormonal Profile in Men with Adverse Effects after Use of Finasteride against Androgenetic Alopecia* (2012).[206]

La Marra et al. measured T, LH, and FSH levels in (i) 9 men age 31 to 41 years who previously used ≤ 1.25 mg finasteride for AGA and developed persistent AEs (including ED, infertility and depression) lasting > 6 months after discontinuation of finasteride, and (ii) 10 controls. LH was 2-fold lower in cases ($p = 0.03$) and the T/LH ratio was 1.8-fold higher in cases than controls ($p = 0.04$). T and FSH did not differ between cases and controls. The hormonal profile in these PFS patients suggests an impairment of the hypothalamic-pituitary-gonadal (HPG) axis.

La Marra et al. concluded, "We were the first to determine a peculiar hormonal profile in these patients suggesting an impairment of the endocrine interplay of hypothalamus, pituitary and the testis, which specifically dampens only one of the gonadotrophins released from the pituitary gland, i.e. LH."

[206] La Marra F et al, *Preliminary Evidence of a Peculiar Hormonal Profile in Men with Adverse Effects after Use of Finasteride against Androgenetic Alopecia,* Amer J Pathol (2012), Vol. 181, Suppl., Abstract EMD3.

Di Loreto C et al, *Immunohistochemical Evaluation of Androgen Receptor and Nerve Structure Density in Human Prepuce from Patients with Persistent Sexual Side Effects after Finasteride Use for Androgenetic Alopecia* (2014).[207]

Di Loreto et al. published the first molecular evidence of an impairment of androgen regulation and gene expression in the foreskin of PFS patients, suggesting that modulation of local AR levels might be implicated in the long-term sexual side effects of finasteride use.

This case control study of 8 PFS patients (age 29 to 43 years) and 11 healthy controls (age 23 to 40 years) assessed AR expression by IHC and structural nerve density in foreskin specimens. PFS patients took ≤ 1.25 mg per day finasteride for an average of 32 months and were evaluated an average of 56 months after discontinuation of finasteride. All PFS patients in the study had ED and complained of genital skin discomfort or paresthesia, including loss of penis sensitivity and loss of pleasurable response to touch. Controls were more frequently married than cases ($p = 0.045$).

A significant increase of nuclear AR levels was found in stromal and epithelial cells of the foreskins of PFS patients. Density of nuclear AR in stromal cells was higher in PFS patients than controls (40.0% v. 23.4% positive cells, respectively; $p = 0.023$). Density of nuclear AR in epithelial cells was higher in PFS patients than controls (80.6% v. 65.0% positive cells, respectively; $p = 0.043$). The ratio of AR positive stromal cells to serum total T was almost 2-fold higher in PFS patients than controls (3.47 v. 1.86; $p = 0.001$). The ratio of AR positive stromal cells to serum free T was 2-fold higher in PFS patients than controls (0.192 v. 0.096; $p = 0.005$).

Di Loreto et al. reported, "This finding could indicate the presence in former finasteride users of an augmented regulatory feedback loop that normally serves to modulate hormonal responses. … We cannot presently exclude that this apparent upregulation of AR expression is due to low local levels of androgens (particularly DHT)."

The authors commented, "Our unexpected observation that [the] percentage of AR positive stromal cells is inversely related to Arizona Sexual Experience Scale (ASEX) score suggests that [PFS] patients less able to raise AR are those with more severe side effects related to sexual dysfunction. This seems to support the hypothesis that the body tries to compensate [for] local androgen deprivation by producing more ARs."

Di Loreto et al. concluded, "Our findings revealed that modulation of local AR levels might be implicated in long-term side effects of finasteride use. This provides the first evidence of a molecular objective difference between patients with long-term adverse sexual effects after finasteride use versus drug untreated healthy controls in certain tissues."

[207] Di Loreto C et al, *Immunohistochemical Evaluation of Androgen Receptor and Nerve Structure Density in Human Prepuce from Patients with Persistent Sexual Side Effects after Finasteride use for Androgenetic Alopecia*, PLoS One (2014), Vol. 9(6), e100237, pp. e1-e7.

Increased androgen receptor expression has also been observed in hormone refractory prostate cancer patients who had previously been treated with androgen deprivation therapy,[208] the prostate gland of gerbils chronically treated with finasteride,[209] BPH patients treated with finasteride for 30-180 days,[210] an androgen-dependent prostate cancer cell line (LNCaP) treated with finasteride,[211] and the cerebral cortex of the brain in rats treated subchronically with finasteride.[212] AR overexpression was not reversible in any of these examples (when evaluated) with discontinuation of finasteride treatment.

Basaria S et al, *Characteristics of Men Who Report Persistent Sexual Symptoms after Finasteride Use for Hair Loss* (2016).[213]

Basaria et al. studied three groups of men 18 to 50 years old: (i) symptomatic former Propecia users with persistent sexual dysfunction (N=25); (ii) non-symptomatic former Propecia users (N=13); and (iii) healthy controls (N=18). Former Propecia users had no history of sexual dysfunction or depression prior to finasteride use.

Symptomatic finasteride users had significantly lower International Index of Erectile Function (IIEF) composite scores ($p < 0.001$), significantly lower scores for each domain of erectile function, sexual desire, orgasmic function, intercourse satisfaction, and overall satisfaction ($p < 0.001$ for each domain), as well as significantly fewer vaginal penetrations ($p = 0.01$) and satisfactory sexual encounters ($p < 0.001$). Symptomatic finasteride users had significantly lower Male Sexual Health Questionnaire (MSHQ) scores for sexual desire ($p < 0.001$) and ejaculatory function ($p < 0.001$).

The authors explained, "Studies of the neurobiology of sexual arousal have converged on a multidimensional network comprising cognitive (parietal, anterior cingulate, thalamus, insula), emotional (amygdala, insula), motivational (precentral gyrus, parietal cortex) and physiological (hypothalamus, thalamus, insula) components."

Functional magnetic resonance imaging (fMRI) activation tasks for sexual arousal were conducted. A correlation analysis assessed the association between blood oxygen level dependent (BOLD) activation levels during exposure to erotic images and IIEF scores. Negative correlations between IIEF scores and BOLD activity were identified in the hypothalamus ($p = 0.014$), bilateral thalamus, right thalamus ($p = 0.008$), and right posterior cingulate cortex ($p < 0.01$). Positive correlations between IIEF scores and BOLD activity were observed in the right mid cingulate cortex ($p = 0.005$), right posterior cingulate, left insula, right precentral gyrus, left inferior parietal, left caudate ($p < 0.01$) and left putamen ($p < 0.05$).

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[208] Visakorpi T et al, *In vivo amplification of the androgen receptor gene and progression of human prostate cancer*, Nature Genetics (1995), Vol. 9, pp. 401-406.
[209] Corradi (2009) Microsc Res and Technique *op. cit.*, pp. 939-950.
[210] Hsieh JT et al, *Finasteride Upregulates Androgen Receptor in Hyperplastic Prostate and LNCaP Cells: Implications for Chemoprevention of Prostate Cancer*, The Prostate (2011), Vol. 71, pp. 1115-1121.
[211] Ibid.
[212] Giatti *op. cit.*, pp. 746-757.
[213] Basaria S et al, *Characteristics of Men Who Report Persistent Sexual Symptoms after Finasteride Use for Hair Loss*. J Clin Endocrinol Metab (2016), Vol. 101(12), pp. 4669-4680.

Basaria et al. concluded that fMRI BOLD responses to erotic stimuli "suggest that there are underlying neurobiological abnormalities in symptomatic finasteride users, which can be linked to circuitry that has been implicated … in sexual arousal."

Cauci S et al, *Androgen Receptor (AR) Gene (CAG)n and (GGN)n Length Polymorphisms and Symptoms in Young Males With Long-Lasting Adverse Effects After Finasteride Use Against Androgenic Alopecia* (2016).[214]

The relationship of AR polymorphisms to specific PFS symptoms was studied in 66 PFS patients 18 to 50 years old by ASEX, Aging Males Symptoms (AMS) and ad hoc questionnaires. (CAG)n and (GGN)n repeats were categorized as short (CAG 9-19, GGN < 23), medium (CAG 20-24, GGN 23), or long (CAG 25-37, GGN > 23). The results demonstrated that short and/or long (CAG)n and (GGN)n repeats had different frequencies according to symptoms reported by PFS patients, likely reflecting the vast array of genes modulated by the AR.

The AR expression level and amino acid protein sequence can be affected by AR polymorphisms. Cauci et al. concluded, "Longer or shorter amino acid repeat stretches could modify optimal protein folding, leading to suboptimal activity of the [AR] protein. … Our data showed that short and long (CAG)n and (GGN)n repeats correlate in an unpredictable way with several conditions related to male androgenicity; this could derive from the vast array of genes that are up- or down-modulated by the AR."

Melcangi RC et al, *Neuroactive steroid levels and psychiatric and andrological features in post-finasteride patients* (2017).[215]

Melcangi et al. performed a multicentric, prospective, longitudinal clinical trial that evaluated andrological features in 16 PFS patients 22 to 44 years old with a negative history for sexual and psychiatric problems prior to finasteride use. The interval between finasteride withdrawal and clinical evaluation of PFS patients ranged from 1.2 to 12.9 years with a median of 5.4 years. Sexual function was evaluated by the IIEF-15, pelvic somatosensory evoked potentials (SSEP) of the pudendal nerve, and testicular ultrasound.

The authors explained, "All patients (100%) showed some degree of ED, with a mean score [on] the erectile function domain of 10.31 ± 9.48. In particular, we found 10 men with severe ED (62.50%) and six with mild-moderate forms (37.5%)." The PFS patients also scored low on the IIEF for orgasmic function, sexual desire and overall satisfaction domains compared to the general population.

Abnormal SSEPs of the pudendal nerve were found in 25% (4/16) PFS patients with no evoked response in 3 PFS patients and increased P1 wave latency in the other PFS

[214] Cauci S et al, *Androgen Receptor (AR) Gene (CAG)n and (GGN)n Length Polymorphisms and Symptoms in Young Males With Long-Lasting Adverse Effects After Finasteride Use Against Androgenic Alopecia*, Sex Med (2016), pp. 5e1-e11.
[215] Melcangi (2017) *op. cit.*, pp. 229-235.

patient. Pudendal SSEPs were significantly abnormal in PFS patients with severe ED as compared to those with mild-moderate ED ($p = 0.032$). Testicular volume was normal in all PFS patients.

Melcangi et al. reported "abnormal SSEPs of the pudendal nerve in PFS patients with severe ED, the first objective evidence of a neuropathy involving the peripheral neurogenic control of erection."

e. Case Reports and FAERS Database.

As early as the first year after FDA approval of Propecia, patients started to submit AE reports to Merck and the FDA for persistent sexual dysfunction. Together with the cases of persistent sexual dysfunction in the Propecia clinical trials, it was becoming increasingly clear shortly after FDA approval that Propecia might cause persistent sexual dysfunction that would not resolve after discontinuation of treatment.

The following is an example of one of these AE reports:

MedWatch FDA Form 3500A, 98060961, submitted December 11, 1998.[216]

The patient was a 19-year-old man who took ® from April 1, 1998 until June 10, 1998. While on therapy with finasteride, he had difficulty achieving an erection and less desire for sex. A follow-up AE report from the patient submitted to Merck 6 months after discontinuation of finasteride treatment indicated he was still experiencing erection problems and had less desire for sex.

Traish AM et al, *Adverse Side Effects of 5α-Reductase Inhibitors Therapy: Persistent Diminished Libido and Erectile Dysfunction and Depression in a Subset of Patients* (2011).[217]

In January 2011, Traish et al. published the first case report of persistent sexual side effects in a patient who used Propecia for AGA. In 1999, a 24-year-old male started treatment with Propecia for AGA. Within 2 to 5 days, he had onset of testicular pain, loss of sex drive, ED, difficulty concentrating and depression. After about 1 month, he discontinued treatment. Eleven years later, he still suffered from ED and loss of libido. The authors explained, "In some patients, these sexual side effects are persistent with regard to sexual function and with an emotional toll including decreased quality of life."

ED subsequent to use of 5αRIs may be explained by the role of androgens in erectile physiology. Androgens are integral to maintaining the structural integrity of the penile dorsal and cavernosal nerves, the smooth muscle and connective tissue of the corpus cavernosum, and the neurologic pathways in the penis. Androgen deficiency induced by

[216] MedWatch FDA Form 3500A, WAES 98060961, submitted December 11, 1998.
[217] Traish AM et al, *Adverse Side Effects of 5α-Reductase Inhibitors Therapy: Persistent Diminished Libido and Erectile Dysfunction and Depression in a Subset of Patients*, J Sex Med (2011), Vol. 8, pp. 872-884.

5αRIs may contribute to ED. Animal and human studies suggest that DHT plays an important role in erectile physiology.

Traish et al. concluded, "Honest and open discussion with patients to educate them on these serious issues must be pursued prior to commencing therapy because, in some patients, these AEs are persistent and may be prolonged, and patients do not recover after discontinuation from drug use. These issues must be addressed in detail with the patients."

Irwig M and Kolukula S, *Persistent Sexual Side Effects of Finasteride for Male Pattern Hair Loss* (2011).[218]

In April 2011, Irwig and Kolukula published the first case series of what is now known as PFS. Standardized interviews were conducted with 71 healthy men (age 21 to 46) who reported new onset of sexual side effects associated with the use of finasteride for AGA that persisted for at least 3 months after discontinuation of use. Exclusion criteria included baseline sexual dysfunction, baseline psychiatric or medical conditions, or chronic use of nontopical prescription medications.

Symptoms included low libido (94%), ED (92%), decreased arousal (92%) and orgasm problems (69%). The number of sexual episodes per month decreased ($p < 0.0001$) and the total sexual dysfunction score increased ($p < 0.0001$) from before v. after finasteride with the ASEX questionnaire. The mean duration of finasteride use was 28 months and the mean duration of persistent sexual side effects was 40 months from the time of finasteride cessation. Subjects volunteered other side effects that they believed were associated with finasteride use, including fatigue (27), cognitive difficulties (26), depression (20), anxiety (20), and decreased semen volume (9). Study limitations include a post hoc approach, selection bias, recall bias for before finasteride use data, and no serum hormone levels.

Irwig and Kolukula explained, "Libido and orgasm are perceived in the brain, where receptors for androgens and progesterones are widely distributed, particularly in the hypothalamus and amygdala. … Finasteride does cross the blood-brain barrier and can inhibit the production of DHT throughout the CNS. It is biologically plausible that a lack of DHT or another 5α-reduced hormone is responsible for a decrease in libido and/or orgasm. … Although the conversion of T to DHT may play a key role in normal sexual function, another possible player could be progesterone and its metabolites. … Both human and rat 5αRs showed a greater preference for progesterone as a substrate over T and androstenedione. … The validity of our findings is supported by the known sexual side effects of finasteride in RCTs, the temporal association of the onset of sexual dysfunction with the use of finasteride in otherwise healthy men, and the biological plausibility of the role of androgens and progestins in areas of the brain and peripheral nervous system associated with libido, orgasm, and erectile function."

[218] Irwig MS and Kolukula S, *Persistent Sexual Side Effects of Finasteride for Male Pattern Hair Loss*, J Sex Med (2011), Vol. 8, pp. 1747-1753.

Kothary N et al, *Pharmacovigilance Review (Sexual Dysfunction with Propecia®)* (2011).[219]

Kothary et al. from the FDA's Office of Surveillance and Epidemiology performed a Pharmacovigilance Review of the FAERS database for finasteride and "identified 59 cases of sexual dysfunction that persisted at least 3 months after discontinuing finasteride, 1 mg." Erectile disorders and libido disorders were reported in 86% and 71% of the cases, respectively. The reviewers explained, "The relatively young population and lack of confounded cases in this case series further supports a possible association between finasteride use and persistent sexual dysfunction." Of the 59 cases, 30% reported events persisting for 3 to 5 months, 30% reported events persisting for 7 to 11 months, 34% reported events persisting for 1 to 2 years, and 2 cases reported events persisting for "years."

Kothary et al. concluded, "Although the current Propecia label includes sexual dysfunction, it does not indicate that these events may be persistent. … Based on this review, we recommend changing the finasteride 1 mg label [by] updating the Adverse Events, Postmarketing Experience section to reflect the potential risk for persistent sexual dysfunction, including ED, libido disorders, ejaculation disorders, and orgasm disorders."

Kothary et al. explained, "Although our analysis was limited by the information provided in the cases and lack of long-term follow up, we identified cases of persistent sexual dysfunction despite discontinuation of Propecia. This is inconsistent with the current language in the label that states, '*Resolution occurred in men who discontinued therapy with Propecia due to these side effects and in most of those who continued therapy*.' Therefore, the Propecia label should be updated to reflect the potential risk of persistent sexual dysfunction after discontinuation of therapy."

Irwig MS, *Persistent Sexual Side Effects of Finasteride: Could They Be Permanent?* (2012).[220]

Irwig re-evaluated 54 of his original clinical series of 71 post-finasteride patients with persistent sexual dysfunction 9 to 16 months after their initial assessment. Persistent sexual side effects continued to be present in 96% subjects (mean length of finasteride use was 23 months). There were 20% of subjects who reported persistent sexual dysfunction for ≥ 6 years, suggesting the possibility that the sexual dysfunction may be permanent. According to the ASEX scores, 89% of subjects met the definition of sexual dysfunction. In addition to sexual side effects, some of the men volunteered other symptoms, including changes in semen quality and volume (11%), changes in penis size, curvature of the penis or reduced penile sensation (19%), decrease in spontaneous

[219] Kothary N et al, *Pharmacovigilance Review (Sexual Dysfunction with Propecia®)*, FDA Division of Pharmacovigilance, Office of Surveillance and Epidemiology (June 2, 2011), Reference ID: 2954995, pp. 1-19.
[220] Irwig MS, *Persistent Sexual Side Effects of Finasteride: Could They Be Permanent?*, J Sex Med (2012), Vol. 9, pp. 2927-2932.

erections (9%), changes in testicular size or pain (15%), and changes to mental abilities and/or depressive symptoms (17%).

Irwig explained, "Finasteride crosses the blood-brain barrier and blocks 5αR1 which reduces the concentration of three neuroactive steroids (DHT, DHP and DHDOC) and their downstream metabolites. Sexual desire is related to brain dopamine systems in the hypothalamus and limbic areas, especially the MPOA, amygdala and nucleus accumbens. In adult male mice, 5αR1 and 3α-HSD colocalize in glutamatergic and GABAergic neurons in the cerebral cortex, hippocampus, olfactory bulb, amygdala, cerebellum, and thalamus. Neuroactive steroids have been shown to modulate neurogenesis and neuronal survival. Neuroactive steroids protect neurons from apoptosis or programmed cell death."

Moore T, *Finasteride (PROPECIA®) and Persistent Side Effects* (2013).[221]

In the 2nd quarter 2012, Moore identified 46 serious AE reports to the FDA for finasteride that indicated a sexual problem. In 28 patients (46%), sexual AEs had not resolved when the report was prepared. Side effects were possibly persistent in 27 cases, and 20 cases reported a significant or persistent disability. Side effects included penile curvature, testicular pain, scrotal pain, gynecomastia, testicular atrophy, reduced penile size, and anorgasmia.

Moore stated, "Persistent side effects – those that don't resolve after a drug is stopped - are among the most elusive, difficult to detect and to measure, and are often overlooked" and evidence generally emerges many years after approval. "The Medical Dictionary for Regulatory Activities provides more than 29,000 terms to describe drug side effects. But not a single term or phrase is provided to highlight persistent side effects. Identification of persistent side effects is rare."

Moore explained, "Although both the FDA and company reported that these side effects mostly resolved upon discontinuation, the number of treated patients (N = 934) was relatively small, the treatment period was six months to one year, and the follow up was not clear. Yet, it seems plausible that a drug which causes enduring changes in the anatomy of the prostate and the pattern of hair growth might also make changes in sexual desire and function that are long lasting."

Moore concluded, "This signal for persistent sexual side effects in the adverse event data is consistent with more detailed published and FDA studies, and not rendered less likely by the clinical trials' results. Effects on sexual function are biologically plausible and clearly evident in several clinical trials. … The clinical trials were neither powered nor designed to detect persistent side effects. … The number of reported adverse events may be increased by media coverage, internet forums, and other factors. However, this signal amplification may be quite valuable in uncovering side effects not clearly observed or overlooked through limitations in the clinical testing process."

[221] Moore T et al, *Finasteride (PROPECIA®) and Persistent Side Effects*, Inst Safe Medication Pract, Quarter Watch (2013), Data from 2012 Quarter 2, pp. 7-10.

Ganzer C et al, *Persistent Sexual, Emotional, and Cognitive Impairment Post-Finasteride: A Survey of Men Reporting Symptoms* (2015).[222]

Ganzer et al. surveyed by questionnaire 131 healthy men (mean age, 24 years) who had taken finasteride for AGA and experienced sexual and non-sexual AEs lasting at least 3 months after discontinuation. There were 105 men (80%) who were recruited from an author's private practice.

Persistent sexual changes included decreased libido (93%), complete loss of sex drive (63%), intermittent ED (83%), complete impotence (40%), loss of morning and spontaneous erections (89%), loss of pleasurable orgasm (70%), and diminished semen volume or ejaculatory force (82%). Persistent physical effects include lethargy and fatigue (69%), gynecomastia (70%), penile shrinkage or penile sensory changes (79%), scrotal shrinkage or numbness (51%), and Peyronie's disease (20%).

Ganzer et al. explained, "Respondents described that their physicians generally attributed physical symptoms as psychological in nature and encouraged them to seek out psychiatric consultation (69%). Overall, men reported that they were frustrated and dissatisfied with the medical care that they received and their physicians' lack of awareness and recognition of their symptoms as being valid (93%)."

Their physicians' lack of awareness and recognition of their symptoms as being valid is understandable in light of the inadequate, false and misleading disclosures in the Propecia product label.

Ali AK et al, *Persistent Sexual Dysfunction and Suicidal Ideation in Young Men Treated with Low-Dose Finasteride: A Pharmacovigilance Study* (2015).[223]

Ali et al. applied disproportionality analysis to the FDA Adverse Event Reporting System database to calculate the empirical Bayes geometric mean (EBGM) for an association between low-dose finasteride and persistent sexual dysfunction using the Medical Dictionary for Regulatory Activities Preferred Terms. A signal was defined as a CI lower limit of 2.0. Pharmacovigilance studies using this algorithm show similar results to pharmacoepidemiologic studies.

Persistent sexual dysfunction accounted for 11.8% (577 reports) of 4,910 total reports. Low-dose finasteride was associated with more than expected sexual dysfunction compared with other drugs (EBGM 28.0, 95% CI 26.1 – 30.0). Sexual dysfunction continued for 5.4 months after finasteride cessation.

"Approximately 60% of the sexual dysfunction AEs were serious in nature. … Among serious sexual dysfunction events, 43% led to disability; 28% required medical

[222] Ganzer C et al, *Persistent Sexual, Emotional, and Cognitive Impairment Post-Finasteride: A Survey of Men Reporting Symptoms*, Amer J Men Health (2015), Vol. 9(3), pp. 222-228.
[223] Ali AK et al, *Persistent Sexual Dysfunction and Suicidal Ideation in Young Men Treated with Low-Dose Finasteride: A Pharmacovigilance Study*, Pharmacother (2015), Vol. 35(7), pp. 687-695.

intervention, including hospitalization; and 5% were life-threatening. Six fatal sexual dysfunction reports were identified."

Chiriaco G et al, *An observational retrospective evaluation of 79 young men with long-term adverse effects after use of finasteride against androgenetic alopecia* (2016).[224]

Chiriaco et al. published a case series of 79 AGA patients (age 18 to 48 years at first finasteride use) who complained of persistent sexual side effects lasting > 6 months after discontinuation of finasteride, consulted a physician, and obtained at least one blood test. Exclusion criteria were sexual dysfunction and/or mental disease prior to finasteride treatment, obesity, acute or chronic disease (diabetes mellitus, cardiovascular, liver, auto-immune or thyroid disease, and malignancies), use of drugs capable of altering hormonal status prior to finasteride use, and involvement in any lawsuit. Mean age, duration of finasteride use and time from finasteride discontinuation was 33.4 years, 27.3 months and 44.1 months, respectively.

Each participant provided medical records and was evaluated by ad hoc, ASEX and AMS questionnaires. By the ad hoc questionnaire, the participants declared 'getting and keeping erection very difficult' (40.5%), 'erection never achieved' (3.8%), 'reaching orgasm very difficult' (16.5%), and 'orgasm never achieved' (2.5%). The most frequent sexual symptoms referred were loss of penis sensitivity (87.3%), decreased ejaculatory force (82.3%), and low penile temperature (78.5%). The most frequent non-sexual symptoms were reduced feeling of life pleasure or emotions (anhedonia) (75.9%), lack of mental concentration (72.2%), and loss of muscle tone/mass (51.9%). All pre-ASEX vs. post-ASEX differences were highly significant ($p < 0.001$).

Reported AMS scores demonstrated that 5.1% participants had slight androgen deficiency, 34.6% had moderate androgen deficiency, and 60.3% had severe androgen deficiency.

The authors concluded, "Symptoms reported by our PFS patients are suggestive of androgen deficiency in several different tissues where 5αR is expressed. The intriguing finding is that this occurred long after finasteride discontinuation (on average 44 month; i.e., almost 4 years), thus, this phenomenon seems to indicate that some … permanent changes occurred."

f. Testimony of Key Merck Employees.

Mass tort litigation was filed in 2011 against Merck for persistent sexual AEs associated with the use of Propecia for AGA (In re: Propecia (Finasteride) Products Liability Litigation MDL 2331). Certain documents of interest have been made publicly available via the Public Access to Court Electronic Records (PACER) database for the U.S. District Court for the Eastern District of New York (https://ecf.nyed.uscourts.gov/cgi-

[224] Chiriaco G et al, *An observational retrospective evaluation of 79 young men with long-term adverse effects after use of finasteride against androgenetic alopecia*, Andrology (2016), Vol. 4, pp. 245-250.

bin/ShowIndex.pl) which can be downloaded after registering online for a PACER account (https://pacer.psc.uscourts.gov/pscof/registration.jsf).

In the Propecia mass tort litigation, a Motion to Amend PPO No. 10 and Extend Discovery Deadline to Allow for Requests for Admission was filed by Becker and the plaintiffs' attorneys on July 20, 2016.[225] Becker et al. stated, "Discovery to date revealed credible facts evidencing Merck was aware of the following: 1) persistent ongoing sexual dysfunction stemming from both post-marketing reports and the clinical trials themselves; 2) the existence of a safety-signal identifying a causal association between Propecia and ongoing sexual dysfunction; 3) flaws in Merck's regulatory conduct; and 4) motive - i.e., that Merck intentionally ignored signs of harm so as to increase sales.

By way of example only:

- Dr. Elizabeth Round conceded the label was deficient in that it failed to identify a temporal nexus from the time of discontinuation to the time of resolution. …
- Charlotte Merritt, the person at Merck who oversaw regulatory activity related to Propecia conceded that Merck changed the label from: 'Resolution occurred in **all** men who discontinuation therapy with Propecia' to 'Resolution occurred in men who discontinued therapy with Propecia.' (emphasis supplied) … She further testified Merck eliminated the word 'all' due to evidence *from the clinical trials* of persistent ongoing erectile dysfunction following discontinuation of use. She also testified that Merck made no others changes to the label at that time. …
- Dr. Cynthia Silber, the person at Merck who oversaw post-marketing safety and surveillance, conceded that Merck identified a 'safety-signal' related to persistent ongoing ED as early as 2006, but did not amend the label until 2012. …
- Paul Howes, the head of marketing for Merck related to Propecia from 1998 through 2002, conceded that between 1997 and 2002 Merck was on track to lose patent protection for several key drugs resulting in the potential loss of billions of dollars of revenue; … that Propecia was distributed, in part, to plug the gap in lost revenue; … and that Merck was keenly aware that references to sexual side effects—particularly persistent to permanent side effects—would have a devastating impact on sales."

Deposition Testimony of Elizabeth Round (December 17, 2015).[226]

Dr. Round had primary responsibility for the Propecia clinical trials prior to FDA approval of Propecia.

Round was asked, "Would you agree that if the symptoms did not resolve for a month, that Merck should alert patients who take the drug that it may take up to a month for their sexual dysfunction – for their sexual function to return?"

She replied, "If we had that information, yes."

[225] Becker *op. cit.*, pp. 1-7, Exhibits A-F.
[226] Becker *op. cit.* Exhibit A.

A follow-up question asked, "If the data demonstrates that resolution took a long time following discontinuation of use, shouldn't you have told patients and doctors that?"

She answered, "It may have been useful to put that in."

Deposition Testimony of Charlotte Merritt (May 19, 2016).[227]

Charlotte Merritt oversaw regulatory activity at Merck related to Propecia.

In response to cases of persistent sexual dysfunction despite drug discontinuation that emerged during the extension phase of the phase 3 Propecia clinical trials, Merck appears to have intentionally concealed these findings. Merck made a change to the Propecia product label in 2002 that did not disclose these cases of persistent sexual function. Instead, they merely deleted the word 'all' from the disclosure in the product label that stated, "Resolution occurred in all men who discontinued therapy with PROPECIA due to these [sexual] side effects."

The 2001 Propecia product label[228] stated, "Resolution occurred in all men who discontinued therapy with PROPECIA due to these [sexual] side effects and in 58% who continued therapy."

The 2002 Propecia product label[229] stated, "Resolution occurred in men who discontinued therapy with PROPECIA due to these [sexual] side effects and in most who continued therapy."

Merritt was asked, "So the word 'all' has been removed in this label?"

She replied, "Yes, it has."

A follow-up question asked, "Why was that?"

Merritt answered, "Well, as you saw, there were some men in whom after some period of time the AEs did not resolve so this is – so the word 'all' was no longer factual as relates to the longer-term data."

Merritt was asked, "And you would agree with me that the only change that reflects the fact there were in fact men who had – who did not have resolution upon discontinuation, the only thing that reflects that here is the taking out of the word 'all,' right? … It doesn't also say there were men who did not experience resolution upon discontinuation, right?"

She responded, "No, it doesn't say that."

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[227] Becker *op. cit.* Exhibit B.
[228] *Propecia® Full Prescribing Information* (2001) *op. cit.*
[229] *Propecia® Full Prescribing Information* (2002). *op. cit.*

A follow-up question asked, "In changing this label in 2002 from the one we looked at in 2001, there was nothing that prevented Merck from disclosing the details … about patients continuing to experience sexual adverse events upon discontinuation, right? … There was nothing that prevented Merck, which as we agreed earlier is responsible at all times for its label, from putting into this 2002 label what it now had information about for over a year … about the lack of resolution upon discontinuation in some patients in the clinical data, right?"

> Merritt answered, "Merck didn't feel at the time that that was something that needed to be – that needed to be put in the label. FDA apparently agreed. This is the label that was – you know, that was the result of that submission, and we can't comment any further."

Another follow-up question asked, "With respect to the label language itself, Merck could have developed this language and made it more clear that there were instances of patients developing sexual adverse events in the clinical data, in the clinical trials, whose sexual adverse events did not resolve upon discontinuation, right?"

> Merritt responded, "It could have been done if Merck felt that that was an appropriate thing to label based on the data. I can't comment on why – why it was done the way it was done."

Regarding the cases of persistent sexual dysfunction that did not resolve following drug discontinuation in the Propecia clinical trials, the statement in the product label that "resolution occurred in men who discontinued therapy with PROPECIA due to these [sexual] side effects and in most who continued therapy" is an untrue statement of a material fact.

21 U.S.C. §355(e) provides that the Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds the application contains any untrue statement of a material fact.

Deposition Testimony of Cynthia Silber (April 19, 2016).[230]

Cynthia Silber oversaw post-marketing safety and surveillance at Merck related to Propecia. She testified that Merck had identified a safety signal for persistent sexual dysfunction with Propecia at least as early as the mid-2000's.

Silber was asked, "What did you do to determine whether or not a signal existed [for persistent sexual dysfunction]?"

> She replied, "When I picked up the product, the issue was already one that was under ongoing analysis in the program, so I did not do signal detection for this particular adverse event."

[230] Becker *op. cit.* Exhibit E.

A follow-up question asked, "Is it your testimony you never engaged in signal detection related to Propecia and persistent ongoing sexual dysfunction?"

> Silber responded, "I engaged in signal evaluation. The signal had been identified by the time I joined the program. … The outcome when I joined the team was that persistent erectile dysfunction was not causally associated with Propecia."

Another follow-up question asked, "You testified earlier that somebody had established a signal between Propecia and persistent ongoing sexual dysfunction prior to you joining the team in the mid-2000's; correct?"

> Silber answered, "Yes."

21 C.F.R. 201 §201.80(e) states that labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved.

Testimony of Paul Howes (June 7, 2016).[231]

Paul Howes was head of marketing at Merck for Propecia from 1998 to 2002. Howes acknowledged that Merck was aware during the first year of product launch of a marketing challenge due to Propecia's sexual side effects and needed to figure out how to minimize this problem.

Howes was asked, "So Merck saw a large opportunity with lots of potential consumers or customers to buy this particular product that, really, nobody else was in this area at the time. Correct?"

> He responded, "Correct."

A follow-up question asked, "And [Merck] thought at the time that if it could capture a significant portion of those 33 million men [in its targeting audience], it could, in fact, develop a blockbuster drug. Correct?"

> Howes answered, "Yes."

In reference to a Wall Street Journal article dated January 6, 1998 at the time that Propecia was being launched as a product, Howes was asked, "There's a quote by Mr. Casola. … So, he was in charge of it from a marketing standpoint?"

> He replied, "Yes."

[231] Becker *op. cit.* Exhibit F.

A follow-up question asked, “So Mr. Casola states, quote, ‘There is definitely a large group of men searching for help. We just need to communicate the benefits of Propecia to them and motivate them to see their physicians. Did I read that correctly?’”

Howes responded, “Yes.”

Howes was asked, “So you knew internally that if these sexual adverse events were prolonged or lengthened or never went away, that that would be something that would impact sales in a negative way”

He answered, “Yes”.

Regarding a Marketing Information Center (MIC) report dated March 15, 1999 entitled ‘Evaluation of the 1998 Direct-to-Consumer [DTC] Advertising Campaign for Propecia, End-of-Year Report on the Consumer Awareness and Action [A & A] Study,’ Howes was asked, “The fifth [bullet point] says, ‘Sexual side effects and side effects associated with pregnant women (women not handling Propecia) are the side effects recalled by respondents.’ Did I read that correctly?”

He replied, “Yes.”

A follow-up question asked, “And then the bullet point above that says, ‘40 percent of those men aware of Propecia are aware of [sexual] side effects associated with taking the product. Of those, side effects would prevent 50 percent of the men from taking the product.’ Correct?”

Howes responded, “Yes.”

Another follow-up question asked, “Does it stand to reason that if 20 percent of the men who were in the pool of guys who could use the drug would not touch it, recognizing that the symptoms could go away, that that percentage would have gone even higher if they thought that use of the drug could cause permanent, persistent problems for them?”

Howes answered, “Yes.”

Regarding the MIC report, Howes was asked, “Do you see the heading that says, ‘Next Step’? … It says, ‘Fear of side effects is one barrier of action that the TBG is interested in better understanding. A & A questions have been revised to understand the role of side effects in preventing men from acting and how the – and how the product in DTC campaign can be revised to minimize these concerns. Do you see that there?”

He replied, “Yes.”

A follow-up query stated, “So the walk-away from this was that we understand we have a problem with sexual side effects, and we, as a company, have to figure out how to address that.”

Howes affirmed, "Yes."

6. Persistent/Permanent Sexual Side Effects with Finasteride during Drug Use

Language in the **ADVERSE REACTIONS, Clinical Trials Experience section** (6.1) of the product label states, "Resolution [of sexual adverse reactions with PROPECIA] occurs … in most who continued therapy."

Language in the **ADVERSE REACTIONS, Clinical Trials Experience section** (6.1) of the product label also states, "There is no evidence of increased sexual adverse experiences with increased duration of treatment with PROSCAR 5 mg."

These are both misleading statements because they give the false impression that it is safe for men who develop sexual AEs during Propecia use to continue using the drug.

Sexual AEs did not resolve during continued drug use for a large majority of men who developed a sexual AE during several Proscar RCTs. Studies with 5αR inhibitors that evaluated sexual function at regular intervals using a validated sexual function questionnaire have demonstrated sustained and progressive decreases in sexual function with continued 5αR inhibitor drug use over time.

a. Randomized Controlled Trials.

Stoner et al, *Maintenance of Clinical Efficacy with Finasteride Therapy for 24 Months in Patients with Benign Prostatic Hyperplasia* (1994).[232]

Stoner et al. presented evidence that sexual AEs did not resolve for a large majority of men with increased duration of treatment with Proscar.

Men with BPH in Merck's North American and international BPH phase 3 clinical trials were followed in a 1 year open-extension phase (after the initial 1-year controlled study) in which all patients received finasteride, 5 mg. Sexual adverse experiences during the first year of the controlled study were reported by 5.2% (placebo), 12.8% (1 mg finasteride), and 10.8% (5 mg finasteride) of patients.

Of patients reporting a sexual AE during the controlled study, two-thirds of those sexual AEs did not resolve with continued treatment.

[232] Stoner E et al, *Maintenance of Clinical Efficacy with Finasteride Therapy for 24 Months in Patients with Benign Prostatic Hyperplasia,* Arch Intern Med (1994), Vol. 154, pp. 83-88.

Hudson P et al, *Efficacy of Finasteride is Maintained in Patients with Benign Prostatic Hyperplasia Treated for 5 Years* (1999).[233]

Hudson et al. (and Stoner) presented evidence of an increased prevalence of impotence with increased duration of treatment with Proscar.

Merck's pivotal U.S. phase 3 BPH clinical trial enrolled 895 men. Of the 297 patients who initially received finasteride, 5 mg, 186 completed 48 months of open-label therapy. The authors stated that there was no significant increase in the prevalence of sexual AEs over time.

The prevalence of impotence in men treated with finasteride in Table II below was 6.7% at year 1 and 9.6% at year 5. In the 1st year, 2.0 % of men receiving finasteride withdrew due to a sexual AE. An additional 1.7% men withdrew due to a sexual AE during the 48-month open label period.

TABLE II. *Prevalence of sexual adverse events (percent of patients)*

	Year 1 (Double-Blind)		Open Extension (Finasteride 5 mg)			
Sexual Adverse Event	Finasteride 5 mg	Placebo	Year 2	Year 3	Year 4	Year 5
Ejaculation disorder	4.7	1.7	3.2	2.2	1.9	2.7
Impotence	6.7	4.0	10.4	6.7	7.3	9.6
Decreased libido	7.7	3.3	4.8	2.7	3.9	3.7
Any sexual adverse event	15.5	8.3	15.3	9.4	9.7	10.1

Hudson et al. presented evidence that is inconsistent with the representation in the Propecia product label that states, "There is no evidence of increased sexual adverse experiences with increased duration of treatment with PROSCAR 5 mg."

The 43% increase in prevalence of impotence from year 1 to year 5 may not have been statistically significant due to Type II error (only 186 men completed the 4-year extension phase), and the exclusion of men who withdrew from the study due to a sexual AE from the prevalence statistics, but the prevalence of impotence was greater after 5 years (9.6%) than after 1 year (6.7%) of treatment with Proscar.

Finasteride (MK-906) Clinical Study Report Synopsis for the PLESS Trial (1997).[234]

Contrary to the disclosure in the Propecia product label, the PLESS data contains evidence of increased sexual adverse experiences with increased duration of treatment with PROSCAR 5 mg. The 4-year PLESS trial enrolled 3,040 men aged 45 to 78 years with moderate to severe BPH of whom 1,524 men received 5 mg finasteride and 1,516 received placebo.

[233] Hudson P et al, *Efficacy of Finasteride is Maintained in Patients with Benign Prostatic Hyperplasia Treated for 5 Years*, Urology (1999), Vol. 53, pp. 690-695.
[234] Waldstreicher *op. cit.* (July 31, 1997).

Sexual AEs did not resolve during continued drug use for most men who developed a sexual AE during the PLESS trial. Of the 218 men with drug-related sexual AEs who completed the study, 189 men (86.7%) did not have resolution of their sexual AEs with increased duration of treatment. Of the 111 men with drug-related sexual AEs who dropped out of the study, 100 men (90.9%) did not have resolution of their sexual AE while still on study drug.

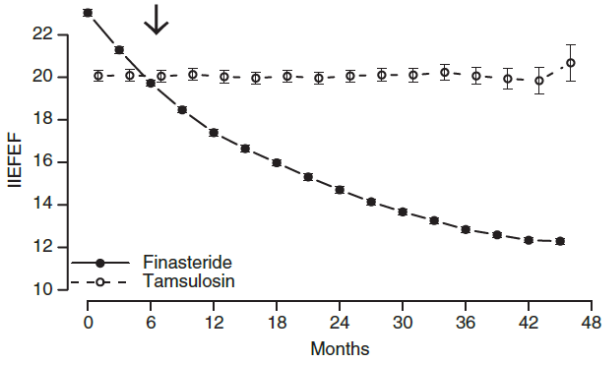
There were more men with drug-related sexual AEs with increased duration of treatment than after year 1 of the study. There were 289 men (189 + 100) with drug-related sexual AEs who did not have resolution of their sexual AE with increased duration of treatment, a 28% increase of 64 men over the 225 men who experienced drug-related sexual AEs in year 1 of the study.

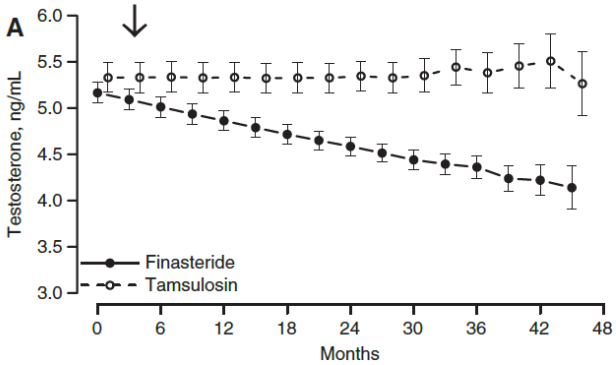
Nearly twice as many finasteride as placebo patients had unresolved, drug-related sexual AEs at the end of the study. Of the 218 men with drug-related sexual AEs who completed the study, 189 men (86.7%) did not have resolution of their sexual AEs with increased duration of treatment. Of the 128 placebo patients with drug-related sexual AEs who completed the study, 97 (75.8%) had sexual AEs that were not resolved at the end of the study. The Clinical Study Report Synopsis did not report a statistical analysis of these large differences.

b. Observational Studies.

Traish AM et al, *Finasteride, not tamulosin, increases severity of erectile dysfunction and decreases testosterone levels in men with benign prostatic hyperplasia* (2015).[235]

Traish et al. published the first retrospective observational study to demonstrate that sexual dysfunction gets progressively worse and T levels progressively decrease with continued finasteride treatment. Traish et al. studied 470 men with BPH who were treated with finasteride (5 mg/day) or tamsulosin (0.4 mg/day), and followed at 3-month intervals for 45 months.





[235] Traish AM et al, *Finasteride, not tamulosin, increases severity of erectile dysfunction and decreases testosterone levels in men with benign prostatic hyperplasia*, Horm Mol Biol Clin Invest (2015), Vol. 23(3), pp. 85-96.

Compared to tamsulosin, men treated with finasteride had (i) worsening of ED over time with significant, progressive decreases in IIEF-Erectile Function domain (IIEF-EF) scores that did not resolve with continued treatment, (ii) significant, progressive reduction in total T levels, and (iii) a significant, progressive decline in AMS scores. A reduction in the IIEF-EF score by > 6 to 8 points is clinically meaningful.

Kiguradze T et al, *Persistent erectile dysfunction in men exposed to the 5α–reductase inhibitors finasteride or dutasteride* (2017).[236]

Kiguradze et al. conclusively established that the risk of persistent ED increases with increased duration of treatment for all 5αRIs (finasteride and dutasteride) at all doses and across all clinical indications (AGA and BPH).

Electronic medical records (EMRs) for 691,268 men age 16 to 89 years were reviewed. Of these men, 17,475 had exposure to 5αRIs. A subset of EMRs for 327,437 men 16 to 42 years old were independently reviewed and 5,582 (1.7%) of these men were exposed to finasteride ≤ 1.25 mg/day.

There were 11,909 men with no prior sexual dysfunction who were exposed to a 5αRI and evaluated for persistent ED. Among these men, 167 (1.4%) developed new persistent ED. Men without prostate disease who combined NSAID use with > 208.5 days of 5αRI exposure had a 4.8–fold higher risk of persistent ED (NNH = 59.8, all p values < 0.002) than men with shorter exposure.

There were 4,284 men 16 to 42 years old without prior sexual dysfunction who were exposed to finasteride ≤ 1.25 mg/day. Of these men, 34 (0.8%) developed persistent ED. Persistent ED developed in 1.19% of men with > 205 days of exposure. Men with > 205 days of finasteride exposure had a 4.9-fold higher risk of developing persistent ED than men with shorter exposure (NNH = 108.2, p < 0.004).

Traish AM et al, *Long-term dutasteride therapy in men with benign prostatic hyperplasia alters glucose and lipid profiles and increases severity of erectile dysfunction* (2017).[237]

Traish et al. published the first retrospective observational study to demonstrate that sexual dysfunction gets progressively worse and T levels progressively decrease with continued dutasteride treatment.

This retrospective observational study in men with lower urinary tract symptoms and BPH treated 230 men with dutasteride (0.5 mg/day) and 230 men with tamsulosin (0.4 mg). The patients were followed at 3- to 6-month intervals for 36 to 42 months and evaluated for (i) blood glucose, (ii) T levels, (iii) hemoglobin A1c (HbA1c), (iv) total,

[236] Kiguradze *op. cit.*, pp. 1-31.

[237] Traish AM et al, *Long-term dutasteride therapy in men with benign prostatic hyperplasia alters glucose and lipid profiles and increases severity of erectile dysfunction*, Horm Mol Biol Clin Invest (2017), Vol. 30(3), Epub ahead of print June 21, 2017.

LDL and HDL cholesterol, and (v) liver ALT and AST transaminases, and by (iv) IIEF and AMS questionnaires. The choice of treatment drug was based on patient preference after discussion with their urologist.

Patients receiving long-term dutasteride treatment had a progressive and sustained decline in T levels ($p < 0.0001$), erectile function/IIEF-EF scores ($p < 0.0001$) and AMS scores ($p < 0.0001$). No decrease in T levels, AMS scores or IIEF-EF scores were observed with tamsulosin treatment.

Long-term dutasteride treatment resulted in increased HbA1c ($p < 0.0001$) and a progressive rise in fasting blood glucose ($p < 0.0001$). No changes in HbA1c and blood glucose were observed in the tamsulosin group. Dutasteride therapy also resulted in increased LDL and total cholesterol ($p < 0.0001$), as well as AST and ALT throughout the treatment period.

The authors suggest that long-term dutasteride treatment induces (i) a progressive and sustained decrease in T levels, erectile function and quality of life, (ii) an imbalance in glucose and lipid metabolic function, and (iii) biochemical changes or inflammation of the liver.

7. Depression and Suicidality with Propecia

The **CLINICAL PHARMACOLOGY, Mechanism of Action** section (12.1) of the product label is misleading because it does not disclose critically important information about Propecia's mechanism of action. Propecia globally affects the metabolism of C_{19} and C_{21} steroid substrates into neuroactive steroids with mood-regulating, neurogenesis-modulating, anxiolytic, analgesic, sedative, anticonvulsant and hypnotic properties that are critical for normal behavioral regulation.

Depression with suicidal ideation that develops during Propecia use and persists indefinitely for years after drug discontinuation occasionally leads to completed suicide. PFS patients have altered neuroactive steroid levels in plasma and CSF. Decreased allopregnanolone levels in CSF correlate with major depression and a positive depression treatment response. PFS patients have neurobiological abnormalities in the CNS that are observed in major depression.

a. Randomized Controlled Trials.

No RCTs have been designed to evaluate depression and suicidality in men taking finasteride for either BPH or AGA.

b. Observational Epidemiologic Studies.

One observational epidemiologic study has been designed to evaluate suicidality in men taking finasteride for BPH. None have been designed in men taking finasteride for AGA.

Welk B et al, *Association of Suicidality and Depression With 5α-Reductase Inhibitors* (2017).[238]

This is the first study to firmly establish a statistically significant association between the use of 5αRIs and depression/suicidality in an observational epidemiologic study. This population-based, retrospective, matched cohort study evaluated (i) completed suicide, (ii) suicidality defined as a hospital visit/admission for self-harm and (iii) depression using linked administrative data for 93,197 men with BPH ≥ 66 years old who filled a new prescription for finasteride or dutasteride from 2003 through 2013. Participants were matched to an equal number of men not prescribed a 5αRI.

The primary outcome was death registered as a suicide on the death certificate by the coroner and entered in the Ontario Registrar General-Death database. Secondary outcomes were self-harm and incident depression using a validated definition. The definition of self-harm was narrow and included either emergency department visits for a suicide attempt or parasuicide behavior, or psychiatric hospital admission for recent self-harm or thoughts of self-harm. To identify incident cases of depression, patients with an existing history of depression in the 5 years prior to the index date were excluded from the analysis of this outcome.

The absolute risk of suicide was low in both exposed and unexposed men (0.04%). Men who used 5αRIs were not at a significantly increased risk of suicide (HR, 0.88; 95% CI, 0.53-1.45). Risk of self-harm was significantly increased during the initial 18 months after 5αRI initiation (HR, 1.88; 95% CI, 1.34-2.64), but not thereafter. Incident depression risk was elevated during the initial 18 months after 5αRI initiation (HR, 1.94; 95% CI, 1.73-2.16) and for the remainder of the follow-up period (HR, 1.22; 95% CI, 1.08-1.37). The absolute increases in the event rates for self-harm and depression were 17 per 100,000 patient-years and 237 per 100,000 patient-years, respectively.

Welk et al. explained, "Although the absolute risk of self-harm is low, this is still potentially important given the increasing rate of self-harm in adults, the high costs associated with subsequent treatment, and the strength of this as a risk factor for future self-harm and suicide."

c. Other Studies, FAERS Database and Case Reports.

Uzunova V et al, *Increase in the CSF content of neurosteroids in patients with unipolar major depression who are receiving fluoxetine or fluvoxamine* (1998).[239]

Uzunova et al. first demonstrated that CSF allopregnanolone levels are reduced in patients with major depression and CSF allopregnanolone levels normalize in patients

[238] Welk B et al, *Association of Suicidality and Depression With 5α-Reductase Inhibitors*, JAMA Intern Med (2017), Vol. 177(5), pp. 683-691.
[239] Uzunova V et al, *Increase in the CSF content of neurosteroids in patients with unipolar major depression who are receiving fluoxetine or fluvoxamine*, Proc Natl Acad Sci (1998), Vol. 95, pp. 3239-3244.

responding to selective serotonin reuptake inhibitor (SSRI) therapy. Allopregnanolone levels were measured in the CSF of 15 patients age 18 to 65 years diagnosed with major depression before and after treatment for 8 to 10 weeks with the SSRIs, fluoxetine and fluvoxamine.

Baseline CSF allopregnanolone levels were 60% lower in depressed patients than 3 healthy control subjects ($p < 0.0001$). A significant negative correlation ($r = - 0.82$; $p = 0.001$) was found between severity of depression as assessed by the Hamilton Rating Scale for Depression (HAM-D) and CSF allopregnanolone levels. The SSRIs significantly increased CSF allopregnanolone levels 2-fold in responding patients with significant correlation ($r = 0.58$; $p < 0.023$) between % symptom improvement (HAM-D scores) and increase in CSF allopregnanolone.

Altomare G and Capella GL, *Depression Circumstantially Related to the Administration of Finasteride for Androgenetic Alopecia* (2002).[240]

This is the first case report of 19 patients (14 males, 5 females; mean age 28 years) out of a series of 23 (17 males, 5 females) who developed a mood disturbance (moderate to severe depression) during treatment with 1 mg finasteride for AGA. Depression which significantly impaired sociofamilial relations, sleep and eating behavior (and was associated with marked anxiety in some cases) developed after 9 to 19 weeks of treatment with finasteride, and promptly resolved after suspension of the drug. Two patients accepted reintroduction of the drug, and depression relapsed within 2 weeks. Depression as an adverse effect of finasteride has been reported only once.

Rahimi-Ardabili B et al, *Finasteride induced depression: a prospective study* (2006).[241]

Rahimi-Ardabili et al. evaluated Beck Depression Inventory (BDI) and Hospital Anxiety and Depression Scale (HADS) questionnaires 2 months after the start of Propecia treatment in 128 men (mean age 26) with AGA. Finasteride increased BDI ($p < 0.001$) and HADS ($p = 0.005$) depression scores significantly. HADS anxiety scores increased, but the difference was not significant ($p = 0.061$). Transient loss of libido was reported by 9.4% (12) of the subjects. A limitation of the study is that it didn't have a control group.

Duskova M et al, *Finasteride Treatment and Neuroactive Steroid Formation* (2009).[242]

Duskova et al. gave finasteride 5 mg to 20 men with BPH for 4 months and measured plasma neuroactive steroid levels. Finasteride treatment significantly decreased all

[240] Altomare G and Capella GL, *Depression Circumstantially Related to the Administration of Finasteride for Androgenetic Alopecia,* J Dermatol (2002), Vol. 29, pp. 665-669.
[241] Rahimi-Ardabili B et al, *Finasteride induced depression: a prospective study*, BMC Clin Pharmacol (2006), Vol. 6(7), pp. 1-6.
[242] Duskova M et al, *Finasteride Treatment and Neuroactive Steroid Formation*, Prague Med Rep (2009), Vol. 110(3), pp. 222-230.

α-reduced neuroactive steroid metabolites of T (3α-diol) and progesterone (allopregnanolone) which modulate $GABA_A$ receptors in the brain. Plasma concentrations of androgen and progesterone neuroactive steroid derivatives are profoundly changed after finasteride treatment.

Duskova et al. concluded, "The decrease of the concentration of circulating steroids with known inhibitory activity on GABA-ergic excitation in the brain is very probably an important factor contributing to the development of symptoms of depression seen in some isolated cases of finasteride administration."

Duskova M et al, *The influence of low dose finasteride, a type II 5α-reductase inhibitor, on circulating neuroactive steroids* (2010).[243]

Duskova et al. measured plasma neuroactive steroid levels in 12 men (age 22 to 37) with AGA treated with finasteride 1 mg for 1 year. 5α-reduced steroids, including DHT, androsterone, 3α-diol, isopregnanolone and allopregnanolone, decreased gradually during treatment. Prolonged treatment induced a further decrease in these neurosteroids.

Duskova et al. concluded, "The decrease of 5α-reduced neurosteroids, especially allopregnanolone, DHT and pregnenolone, is probably one of the factors responsible for the increased occurrence of depression in men treated with finasteride, even at low doses."

Irwig MS, *Depressive Symptoms and Suicidal Thoughts Among Former Users of Finasteride with Persistent Sexual Side Effects* (2012).[244]

Irwig administered standardized interviews that gathered medical and psychiatric histories of 61 men (mean age of 26 years prior to mean length of finasteride use of 27 months) who were former users of finasteride for AGA with persistent sexual side effects for ≥ 3 months after finasteride discontinuation. Exclusion criteria included baseline sexual dysfunction, baseline psychiatric or medical conditions, or chronic use of non-topical prescription medications. A control group of 29 men had AGA, but had never used finasteride and denied any history of psychiatric conditions or use of psychiatric medications.

Depressive symptoms (BDI-II score) were present in 75% former finasteride users and 10% of the controls ($P < 0.0001$). Moderate or severe depressive symptoms were present in 64% of the finasteride group and 0% of the controls. Suicidal thoughts were present in 44% of the former finasteride users and in 3% of the controls ($P < 0.0001$). Comparing

[243] Duskova M et al, *The influence of low dose finasteride, a type II 5α-reductase inhibitor, on circulating neuroactive steroids*, Horm Mol Biol Clin Invest (2010), Vol. 1(2), pp. 95-102.
[244] Irwig MS, *Depressive Symptoms and Suicidal Thoughts Among Former Users of Finasteride with Persistent Sexual Side Effects*, J Clin Psych (2012), Vol. 73(9), pp. 1220-1223.

the lower rates of depression in two published studies of older men with ED[245,246] with the high rates of suicidality in PFS patients, Irwig suggests, "It is therefore reasonable to hypothesize that finasteride is associated with depression independently of the sexual dysfunction."

Melcangi RC et al, *Neuroactive Steroid Levels are Modified in CSF and Plasma of Post-Finasteride Patients Showing Persistent Sexual Side Effects and Anxious/Depressive Symptomatology* (2013).[247]

Melcangi et al. published the first objective evidence of altered plasma and CSF neuroactive steroid levels in PFS patients with depressive/anxious symptomatology. Neuroactive steroid levels were evaluated in 3 PFS patients with depressive/anxious symptomatology and chronic fatigue, and 5 healthy controls. Significantly decreased levels of allopregnanolone, isopregnanolone (3β-isomer of allopregnanolone) and DHT, and significantly increased levels of T and 17β-estradiol were reported in CSF of PFS patients. Significantly decreased levels of DHP, and significantly increased levels of 3α-diol and 17β-estradiol, were observed in plasma of PFS patients.

CSF levels of allopregnanolone and isopregnanolone were under detection limits in all 3 PFS patients (allopregnanolone, $p < 0.01$; isopregnanolone, $p = 0.05$). Allopregnanolone levels were also under detection limits in plasma of PFS patients. Plasma levels of DHP were under detection limits in all 3 PFS patients ($p < 0.001$).

Melcangi et al. concluded, "Altogether, these results provide a molecular basis for the anxious/depressive symptomatology occurring despite discontinuation of finasteride treatment in male patients with [AGA]."

Caruso D et al, *Patients treated for male pattern hair with finasteride show, after discontinuation of the drug, altered levels of neuroactive steroids in CSF and plasma* (2014).[248]

Caruso et al. published a 2nd article demonstrating altered CSF neurosteroid levels in PFS patients. Neuroactive steroid levels in CSF and plasma were evaluated in 7 PFS patients with anxious/depressive symptomatology and a complex neuropsychiatric pattern, and 12 age-matched, healthy controls. In the CSF of PFS patients, there was a significant decrease in progesterone, DHP, allopregnanolone and DHT, and a significant increase in pregnenolone, T and 3α-diol. In plasma of PFS patients, there was a

[245] Shabsigh R et al, *Increased Incidence of Depressive Symptoms in Men with Erectile Dysfunction*, Urology (1998), Vol. 52(5), pp. 848-852.
[246] Lee IC et al, *The prevalence and influence of psychiatric abnormalities in men undergoing comprehensive management of organic erectile dysfunction*, Intl J Impot Res (2000), Vol. 12(1), pp. 47-51.
[247] Melcangi RC et al, *Neuroactive Steroid Levels are Modified in CSF and Plasma of Post-Finasteride Patients Showing Persistent Sexual Side Effects and Anxious/Depressive Symptomatology*, J Sex Med (2013), Vol. 10, pp. 2598-2603.
[248] Caruso D et al, *Patients treated for male pattern hair with finasteride show, after discontinuation of the drug, altered levels of neuroactive steroids in CSF and plasma*, J Ster Biochem Mol Biol (2014), Vol. 146, pp. 74-9.

significant decrease in DHP and allopregnanolone, and a significant increase in pregnenolone, T, 3α-diol, 3β-diol and 17β-estradiol.

Reported symptoms in the PFS patients included decreased initiative and concentration (71%), loss of short-term memory (43%), irritability (57%), depression (86%), suicidal thoughts (14%), anxiety (57%), panic attacks (14%) and sleep problems (86%). Loss of libido (86%), ED (71%), and decreased genital sensation (57%) were reported. Patients also reported chronic fatigue (86%) and joint pain/muscle aches (86%). None of these symptoms were present before treatment with finasteride, except for 2 subjects who reported sleep problems before treatment with finasteride.

Ganzer C et al, *Persistent Sexual, Emotional, and Cognitive Impairment Post-Finasteride: A Survey of Men Reporting Symptoms* (2015).[249]

Ganzer et al. surveyed by questionnaire 131 healthy men (mean age, 24 years) who had taken finasteride for AGA and experienced sexual and non-sexual AEs lasting at least 3 months after discontinuation. Persistent psychological effects included elevated anxiety (74%), depressed mood (73%), anhedonia (73%), sleep disturbance (58%), and suicidal ideation (63%) leading to functional decline. Persistent cognitive effects included severe memory impairment (56%), mental cloudiness or brain fog (75%), and attentional difficulties (74%).

Ganzer et al. concluded, "Of particular concern was suicidality in our population. Targeted questions asked men if they experienced suicidal ideations once they discontinued finasteride therapy. In our sample, 63% (n = 82) acknowledged that they had experienced negative thoughts and felt that they could not continue living with the extreme side effects on a daily basis."

Ali AK et al, *Persistent Sexual Dysfunction and Suicidal Ideation in Young Men Treated with Low-Dose Finasteride: A Pharmacovigilance Study* (2015).[250]

Ali et al. applied disproportionality analysis to the FAERS database to calculate the EBGM for an association between low-dose finasteride and suicidal ideation using the Medical Dictionary for Regulatory Activities Preferred Terms. A signal was defined as a CI lower limit of 2.0. Pharmacovigilance studies using this algorithm show similar results to pharmacoepidemiologic studies.

Suicidal ideation AEs accounted for 0.79% (39 reports) of 4,910 total reports. Approximately 87% men with suicidal ideation (34/39 men) also reported sexual dysfunction. Disproportional reporting in suicidal ideation events was noted, but did not reach signal threshold (EBGM 1.72; 95% CI 1.31 – 2.23). Suicidal ideation could be considered a signal if a 95% CI lower limit > 1.0 was used instead of ≥ 2.0.

[249] Ganzer *op. cit.*, pp. 222-228.
[250] Ali *op. cit.*, pp. 687-695.

Ali et al. explained, "Suicidal ideation continued for 2.4 years after low-dose finasteride cessation among those who experienced sexual dysfunction. ... Among men who experienced sexual dysfunction and suicidal ideation, 88% of the suicidal ideation events were serious (disability [36.7%], hospitalization [20%], life-threatening events [16.7%], and required intervention [13.3%])."

Wu M et al, *Differences in reproductive toxicology between alopecia drugs: an analysis of adverse events among female and male cases* (2016).[251]

Alopecia FAERS reports were retrieved by openFDA from 2004 to 2014 and proportional reporting ratios (PRRs) comparing AEs with finasteride and minoxidil were calculated. Warnings for certain psychiatric and other AEs associated with increased PRRs for finasteride, including anxiety, cognitive disorder and fatigue, are not disclosed in the FDA-approved prescribing information for Propecia. Among male cases, psychiatric AEs were reported more frequently with finasteride than minoxidil for anxiety (PRR = 29.74; $p = 4.17 \times 10^{-10}$), depression (PRR = 10.74; $p = 5.55 \times 10^{-9}$), cognitive disorder (no reports for minoxidil; $p = 1.75 \times 10^{-10}$), and fatigue (PRR = 5.14; $p = 6.88 \times 10^{-3}$).

Warnings for anxiety, cognitive dysfunction and fatigue need to be added to the **ADVERSE REACTIONS, Postmarketing Experience** section (6.2) of the Propecia product label.

Basaria S et al, *Characteristics of Men Who Report Persistent Sexual Symptoms after Finasteride Use for Hair Loss* (2016).[252]

Three groups of men 18 to 50 years old were studied: (i) symptomatic former Propecia users with persistent sexual dysfunction (N=25); (ii) non-symptomatic former Propecia users (N=13); and (iii) healthy controls (N=18). Former Propecia users had no history of sexual dysfunction or depression prior to finasteride use.

Patient Health Questionnaire-9 (PHQ-9) depression scores were significantly higher in symptomatic finasteride users ($p < 0.001$). Hamilton Depression Inventory ($p < 0.001$) and BDI ($p < 0.001$) scores were significantly higher in symptomatic finasteride users. The authors explained, "The average scores of symptomatic finasteride users on the three depression scales were in the range exhibited by men with moderately severe depression."

fMRI activation tasks for affective dysfunction were conducted. A correlation analysis assessed the association between blood oxygen level dependent activation levels and BDI scores. Significant positive correlations between negative attitude scores on the BDI and BOLD activity levels were observed in brain regions associated with major depression, including the right nucleus accumbens ($p = 0.049$), right insula, left

[251] Wu M et al, *Differences in reproductive toxicology between alopecia drugs: an analysis of adverse events among female and male cases*, Oncotarget (2016), pp. e1-e11.
[252] Basaria *op. cit.*, pp. 4669-4680.

pregenual anterior cingulate cortex ($p = 0.040$), right lateral orbito-frontal cortex, and left posterior cingulate ($p < 0.01$). A negative correlation between the BDI subscores and BOLD activity in the right parahippocampal/fusiform gyrus ($p = 0.005$) was observed.

Basaria et al. concluded, "This neural circuitry overlaps with functional abnormalities that have been identified in major depression. [This] fMRI experiment suggests that there are underlying neurobiological abnormalities in symptomatic finasteride users, which can be linked to circuitry that has been implicated in … depression."

Melcangi RC et al, *Neuroactive steroid levels and psychiatric and andrological features in post-finasteride patients* (2017).[253]

A multicentric, prospective, longitudinal, case-control clinical trial evaluated psychiatric features in 16 PFS patients 22 to 44 years old with a negative history for psychiatric or sexual problems prior to finasteride use. CSF and plasma levels of 11 neuroactive steroids were determined in 14 PFS patients and 25 healthy controls undergoing spinal anesthesia for lower limb, orthopedic surgery. The interval between finasteride withdrawal and clinical evaluation of PFS patients ranged from 1.2 to 12.9 years with a median of 5.4 years. Depression and anxiety were evaluated by the K-10 questionnaire, the Mini-International Neuropsychiatric Interview (MINI), the BDI and the Beck Anxiety Inventory (BAI). Neuroactive steroids levels were measured by liquid chromatography-tandem mass spectroscopy.

Fifty percent (8/16) of PFS patients had DSM-IV major depressive disorder (MDD) as diagnosed by MINI. PFS patients with MDD had significantly elevated BAI scores compared to PFS patients without MDD.

CSF levels of DHT, pregnenolone, progesterone, DHP and 17β-estradiol were significantly decreased in PFS patients v. controls. CSF levels of allopregnanolone were 9% of the allopregnanolone levels in control subjects, but these differences were not statistically significant due to a large standard deviation (personal communication with R.M. Melcangi). CSF levels of T, DHEA and 3α-diol were significantly increased in PFS patients v. controls. Not surprisingly, plasma neuroactive steroid levels did not reflect CSF levels. Plasma levels of DHP and allopregnanolone were significantly decreased, while levels of pregnenolone, DHEA and T were significantly increased, in PFS patients v. controls.

Melcangi et al. concluded, "Finasteride did not only affect, as expected, the levels of 5α-reduced metabolites of progesterone and T, but also the further metabolites and precursors suggesting that this drug has broad consequences on neuroactive steroid levels of PFS patients."

[253] Melcangi (2017) *op. cit.*, pp. 229-235.

d. Medwatch Reports of Suicides in PFS Patients.

The depth of depression that PFS patients experience can be profound. After the application of a software algorithm designed to eliminate duplicate AE reports, the VigiBase database of the Uppsala Monitoring Centre and the World Health Organization's Programme for International Drug Monitoring reports 212 AE cases of suicidal ideation, 31 AE cases of suicide attempt, and 46 AE cases of completed suicides among former and current finasteride users.[254]

The Post-Finasteride Syndrome Foundation has provided intensive emotional support to a dozen PFS patients who attempted suicide, more than a dozen PFS patients (or their family members) who have committed suicide, and dozens of other PFS patients who were seriously contemplating suicide.

The PFS Foundation recently submitted MedWatch reports directly to the FDA for 8 Propecia suicide victims together with detailed supporting documentation, including all available medical records, medical examiner/autopsy reports, personal diaries and/or suicide notes of the deceased, and personal narratives of family members. Family members of the Propecia suicide victims obtained all records and documents of their deceased family member and forwarded these records and documents to the PFS Foundation.

Family members consented in writing (i) to having the PFS Foundation submit MedWatch reports of their family member's suicide to the FDA on their behalf, together with detailed supporting documentation, and (ii) for inclusion of a summary of the clinical course of their family member's suicide in this citizen petition for the express purpose of providing information to the FDA that might result in either withdrawal of Propecia from the market or amended labeling of the Propecia product label that more accurately reflects the serious risk of suicide in patients using Propecia.

The following are brief summaries of the clinical courses of these Propecia suicide victims:

<u>PFS Patient Suicide #1 (PFSS#1)</u>.[255]

The deceased was a 42-year-old former user of Propecia for AGA who developed psychoneurocognitive and sexual symptoms starting 2 years after initiation of treatment that never abated after discontinuation of finasteride and culminated in suicide. He was treated with Propecia for about 6 years, but had discontinued Propecia for about 4 years prior to committing suicide. The patient had no pre-existing sexual dysfunction, psychiatric or medical conditions prior to initiation of treatment with finasteride.

[254] *Propecia Adverse Drug Reactions*, VigiAccess Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, accessed August 16, 2017. Available from: http://www.vigiaccess.org/.
[255] MedWatch FDA Form 3500, PFSS#1, submitted May 24, 2017.

Symptoms and diagnoses included ED, loss of libido, perineal burning/numbness, dysuria, loss of sensitivity of genitals, hypogonadism, decreased penile length, non-bacterial chronic prostatitis, severe depression, severe insomnia, vertigo, anxiety, panic attacks, cognitive confusion, social isolation, fatigue, muscle spasms/wasting, hand tremors, and numbness/tingling in hands and feet. His symptoms were unsuccessfully treated with PDE_5 inhibitors, Clomid, Arimidex, Lunesta, Valium, Klonopin, and propanolol.

The Medical Examiner determined suicide to be the cause of death. The Autopsy Report noted evidence of hanging by a belt with no other significant external or internal injuries or histopathologic findings. The brain and spinal cord were fixed in formalin prior to further examination and donated to medical researchers for studies currently underway.

Excerpts from a personal narrative of the deceased's parents stated, "Our awareness of [our son's] symptoms first became evident to us in 2006. ... Eventually, through his own research and physical exams, he determined his use of Propecia (finasteride) to be the source of his problem. He entered a study at Baylor University for the research of the effects of finasteride. ... To the best of our memory, [our son] spent eight years suffering from the adverse effects of what he eventually concluded were caused by finasteride use."

PFS Patient Suicide #2 (PFSS#2).[256]

The deceased was a 37-year-old man who used Propecia for AGA for only 8 days. After taking Propecia for 3 days, he developed ED, depression, cognitive dysfunction, and muscle spasms. He had no pre-existing sexual dysfunction, psychiatric or medical conditions prior to initiation of treatment with Propecia.

He also developed low libido, testicular pain, penile discomfort, insomnia, and muscle wasting. None of these symptoms resolved after discontinuing Propecia and he was diagnosed with hypogonadism. Penile duplex ultrasound diagnosed venous leak.

An email that the deceased sent to the PFS Foundation stated, "I am writing this short message to let your foundation know how important its work is to the thousands of men affected by finasteride. But for your efforts providing hope, I probably wouldn't be alive today. Six months ago (after taking only 9 pills), I found myself afflicted with post-finasteride syndrome, and since then my life has been fundamentally altered."

The deceased committed suicide 11 months after discontinuing Propecia. The deceased's autopsy report described hanging as the cause of death and suicide as the manner of death. Gross anatomy and internal exam were otherwise unremarkable.

[256] MedWatch FDA Form 3500, PFSS#2, submitted May 24, 2017.

PFS Patient Suicide #3 (PFSS#3).[257]

The deceased was a 25-year-old man who used Propecia for AGA for 2 years, 7 months. He had no pre-existing sexual dysfunction, psychiatric or medical conditions prior to initiation of treatment with Propecia. He developed psychoneurocognitive and sexual symptoms starting almost immediately after initiation of treatment that never abated. He committed suicide 3 years, 2 months after discontinuation of treatment with Propecia.

Symptoms and diagnoses included ED, loss of libido, gynecomastia, severe depression, anxiety, fatigue, insomnia, muscle pain, memory loss, difficulty concentrating, social withdrawal, and flat emotions. His symptoms were unsuccessfully treated with Viagra, Clomid, intrapenile alprostadil, Griffonia (serotonin), Valdoxan (antidepressant), bupropion, and zopliclone.

A note from the deceased to his prescribing dermatologist stated, "I am one of your former patients. I am contacting you because you prescribed fina[asteride] for me for hair loss. ... I am contacting you to add my support to these critics of Propecia, in the hope that it will no longer be prescribed."

The Police Report for Discovery of a Body noted that they found a handwritten sign outside the tent where the body was found that stated, “DEADLY GAS DO NOT ENTER”. A gas detector noted the presence of carbon monoxide. A noose was found in a nearby bag and the deceased’s wrists were tied together with slip knots and ankles were tied with single knots. The report concluded that the direct cause of death was acute poisoning by carbon monoxide.

The deceased signed his suicide note to his family, “Your [son], grateful to all of you for all the happiness and support you gave me. [Name of deceased], a victim of Merck and Propecia.”

PFS Patient Suicide #4 (PFSS#4).[258]

The deceased was a 33-year-old man who used Propecia 1 mg for 4 months followed by Propecia 2 mg for another 4 months to treat AGA. He had no pre-existing sexual dysfunction, psychiatric or medical conditions prior to initiation of treatment with Propecia, and had lived independently, supporting himself financially ever since leaving home for college. He developed psychoneurocognitive and sexual symptoms starting several months after initiation of treatment that never abated. When he discontinued Propecia, he moved back into his parents’ house and never again moved out. He committed suicide 7 years, 3 months after discontinuation of Propecia.

Symptoms and diagnoses included ED, loss of libido, yellow jelly-like ejaculate, decreased ejaculatory volume, decreased intensity of orgasm, decreased penile sensitivity, penile and testicular shrinkage/pain, cognitive dysfunction, depression,

[257] MedWatch FDA Form 3500, PFSS#3, submitted May 20, 2017.
[258] MedWatch FDA Form 3500, PFSS#4, submitted May 26, 2017.

suicidal ideation, anxiety, mood swings, flat affect, social isolation, insomnia, extreme fatigue, and muscle spasms/pain. His symptoms were unsuccessfully treated with Ambien, Andractim (topical DHT), pregnenolone, Advil, Aromasin, and Femara.

The Medical Examiner's Case Report stated the deceased was found on a boat with a gunshot wound to the head from a 9-mm handgun due to an apparent suicide.

A personal narrative from the deceased's mother stated, "[Our son] said that he had taken a prescribed medicine named Propecia for hair loss. That he took it for 8 months and it has ruined his life."

PFS Patient Suicide #5 (PFSS#5).[259]

The deceased was a 31-year-old former user of Propecia for AGA. He first took Propecia for 2 years and then discontinued Propecia for about 3 years. He took Propecia a second time for 15 months before discontinuing therapy. He had no pre-existing sexual dysfunction, psychiatric or medical conditions prior to initiation of treatment with finasteride. He developed psychoneurocognitive and sexual symptoms starting about a year after initiation of his second course of treatment that never abated. The deceased was living with his fiancé when he discontinued Propecia for the second time. He committed suicide about 3 to 4 months later.

Symptoms and diagnoses included ED, loss of libido, testicular pain, depression, suicidal ideation, anxiety, panic attacks, insomnia, and cognitive dysfunction. His symptoms were unsuccessfully treated with citalopram, zopiclone, mirtazapine, sertraline, propanolol and paracetamol.

A blog posting by the deceased stated, "I've spent the last day or so looking over pre-fin pics on Facebook and the great life I once had. … I will in my suicide note lay it all bare in death I hope I can stop this drug from ruining more lives."

The deceased took his own life by hanging with a ligature causing hypoxic brain injury. He was found still alive by his family, but died in the hospital 2 days later.

Following the conclusion of an inquest, the Senior Coroner wrote a letter to the Medicines and Healthcare Products Regulatory Agency describing the clinical course of the deceased that stated, "The Senior Coroner felt that this was important information that should be shared with you to assist in your Regulatory Role. She further hopes that the information will assist in updating the Patient Information leaflets that are distributed to those prescribed Finasteride."

PFS Patient Suicide #6 (PFSS#6).[260]

The deceased was a married 40-year-old who had used Propecia for AGA for 3 years,

[259] MedWatch FDA Form 3500, PFSS#5, submitted May 27, 2017.
[260] MedWatch FDA Form 3500, PFSS#6, submitted May 29, 2017.

9 months. The deceased and his wife had 2 young children. He was the founder and CEO of a tech company. The deceased had no pre-existing sexual dysfunction, psychiatric or medical conditions prior to initiation of treatment with Propecia. He developed psychoneurocognitive and sexual symptoms starting 2 years after initiation of treatment that never abated. He committed suicide just over a year after discontinuation of Propecia.

Symptoms and diagnoses included sexual dysfunction, loss of libido, depression, suicidal ideation, anxiety, panic attacks, mood swings, cognitive dysfunction, fatigue, severe insomnia, and dry skin. His symptoms were unsuccessfully treated with psychological counseling. Prior to committing suicide, he was unable to sleep for 42 straight days.

The deceased committed suicide by stepping in front of an Amtrak train. The autopsy report listed the cause of death was blunt force injuries of the torso by suicide.

An excerpt of an interview with the deceased's wife stated, "If [Propecia] could do something to someone like my husband, that is very – that makes my stomach hurt. And if this drug it out there now doing that, that's really scary and should be properly labeled. … But, yes, Merck should either take this drug off the market until they figure out the gray area. Or, yeah, they should be coming up with a big research side of this where they help people who now have the syndrome. They should be donating to PFS."

A personal narrative of the deceased's mother stated, "Soon after [my son's] death, I began piecing together all these symptoms and became concerned about the hair loss drug he had been taking. Doing research on Propecia led me to the PFS Foundation which has opened all our eyes to this drug which, for [my son], was a poisonous, dangerous drug."

PFS Patient Suicide #7 (PFSS#7).[261]

The deceased was a 22-year-old who used Propecia for 1 year, 7 months followed by Avodart 0.5 mg for 3 months. He had no pre-existing sexual dysfunction, medical or diagnosed psychiatric conditions prior to initiation of treatment with Propecia. He developed psychoneurocognitive and sexual symptoms starting almost immediately after initiation of treatment that never abated. He committed suicide 1 to 2 months after discontinuation of Propecia and Avodart.

Symptoms and diagnoses included ED, loss of libido, Peyronie's disease, decreased semen volume/force of ejaculation, loss of pleasurable orgasm, shrinkage/numbness of the penis/scrotum, gynecomastia, deep depression, flat affect, extreme anxiety, psychosis, severe insomnia, dry skin, cognitive dysfunction, and muscle weakness.

[261] MedWatch FDA Form 3500, PFSS#7, submitted May 30, 2017.

The deceased's symptoms were unsuccessfully treated with various benzodiazepines, antidepressants and anti-psychotic medications, and the deceased self-medicated with alcohol to treat his severe insomnia.

He was admitted briefly to a psychiatric hospital a few weeks before he committed suicide. The deceased's rehab clinic journal several weeks before his death stated, "I can still find someone loving and caring and special if [Propecia's] mental effects wear off, but things will never be the same. … There are a lot of aspects to sexuality and although it will never be OK, life is still worth living if I can even pretend to be a sexually normal person."

The Medical Examiner's Report found that the cause of death was suicide from asphyxia due to helium inhalation.

PFS Patient Suicide #8 (PFSS#8).[262]

The deceased was a 29-year-old who used Propecia for AGA for 5 years. He had no pre-existing medical or psychiatric conditions prior to initiation of treatment with Propecia. The deceased developed psychiatric symptoms within months after initiation of treatment that never abated and culminated in suicide. He was still taking Propecia at the time of his death.

Symptoms and diagnoses included depression, suicidal ideation, attempted suicide, anxiety, and low self-esteem. The deceased was unsuccessfully treated briefly with an antidepressant, and over a longer period with psychotherapy, exercise, relaxation tapes, SAD lights, lifestyle changes and a career change.

A personal narrative of the deceased's parents stated, "The fact that [our son] battled in this way whilst taking a drug supplied by Merck who had openly identified depression amongst its side effects for a sub-set of young men in other parts of the world, is inexcusable. Why was this information not available to [our son] and all users world-wide? We have raised the issue of lack of global consistency in patient information leaflets, notably the very limited listing of Finasteride side effects in the UK, with the MHRA (Medical Health Regulatory Authority) in London."

e. Propecia Product Label Actions by Regulatory Authorities Outside of U.S.

Recently, several drug regulatory authorities around the world have added warnings for suicidal ideation in association with the use of Propecia. The FDA is currently out of step with the actions taken by these other drug products regulatory authorities. The current Propecia product label does not reflect the significantly increased risk of suicidality (self-harm) with finasteride that has been recently reported in a large epidemiological study[263] and other studies in the scientific literature.

[262] MedWatch FDA Form 3500, PFSS#8, submitted May 28, 2017.
[263] Welk *op. cit.*, pp. 683-691.

Prescriber Update, *Post-Finasteride Syndrome*, New Zealand Medicines and Medical Devices Safety Authority (2016).[264]

"Key Messages

- Post-Finasteride Syndrome can occur in some men who have taken finasteride.
- Symptoms (sexual, physical, and mental and neurological) often persist after the patient has stopped taking finasteride.
- Patients should be informed of the risks of taking finasteride prior to treatment initiation.
- The symptoms associated with Post-Finasteride Syndrome should be discussed with patients prior to treatment."

"Importantly, some patients can experience suicidal ideation and depression after stopping finasteride treatment. Patients and their families should be advised about these symptoms and to seek medical advice as soon as possible if they occur."

Amendments to the Propecia Marketing Authorisation, European Medicines Agency (2017).[265]

Taking into account the Pharmacovigilance Risk Assessment Committee (PRAC) for the Periodic Safety Update Reports for finasteride, the scientific conclusions of the Co-ordination Group for Mutual Recognition and Decentralised Procedure – Human (CMDh) are as follows:

"Cumulatively 51 cases of suicidal ideation have been received according to the information in the summary tabulation of adverse drug reactions from post-marketing sources. Taking into account the serious reported cases and that depression is already included in section 4.8 of the summary of product characteristics (SmPC) of finasteride 5 mg, the PRAC recommended to include a warning in section 4.4 of the SmPC to inform about mood alterations, depression and suicidal ideation that have been reported with finasteride. In addition, an advice to monitor patients and remind them to seek medical advice should they develop psychiatric symptoms should also be included. … To the extent that additional medicinal products containing finasteride are currently authorized in the EU or are subject to future authorization procedures in the EU, the CMDh recommends that the concerned Member States and applicant/marketing authorization holders take due consideration of this CMDh position."

"Amendments to be included in the relevant sections of the Product Information of finasteride 1 mg:"

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[264] Prescriber Update, *Post-Finasteride Syndrome*, New Zealand Medicines and Medical Devices Safety Authority (March 2016). Available from: http://medsafe.govt.nz/profs/PUArticles/March2016/PostFinasterideSyndrome.htm.
[265] Amendments to the Propecia Marketing Authorisation, Co-ordination Group for Mutual Recognition and Decentralised Procedure - Human (April 2017). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Periodic_safety_update_single_assessment/2017/05/WC500228684.pdf.

- "Summary of Product Characteristics (Section 4.4)

A warning should be added as follows: Mood alterations including depressed mood, depression and, less frequently, suicidal ideation have been reported in patients treated with finasteride, 1 mg. Patients should be monitored for psychiatric symptoms and if these occur, treatment with finasteride should be discontinued and the patient advised to seek medical advice."

- "Package leaflet (Section 2)

Warnings and precautions

Mood alterations and depression
Mood alterations such as depressed mood, depression and, less frequently, suicidal thoughts have been reported in patients treated with <product name>. If you experience any of these symptoms stop taking <product name> and contact your doctor for further medical advice as soon as possible."

"Timetable for the implementation of this position

- Adoption of CMDh position: April 2017 CMDh meeting
- Transmission to National Competent Authorities of the translations of the annexes to the position: 04 June 2017
- Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder): 03 August 2017"

Drug Safety Update, *Finasteride: rare reports of depression and suicidal thoughts*, Medicines and Healthcare products Regulatory Agency (2017).[266]

The MHRA has "received reports of depression and, in rare cases, suicidal thoughts in men taking finasteride 1 mg (Propecia) for male pattern hair loss. … Depression and suicidal thoughts have been reported in men with and without a previous history of depression. Depressed mood has been previously recognized with Propecia. A recent review of the evidence has suggested more significant depression can occur."

"Advice for healthcare professionals:

- Since finasteride has been marketed, there have been a number of spontaneous adverse drug reaction reports suggesting a possible link to depression, and in rare cases, suicidal thoughts.
- Advise patients to stop finasteride 1 mg (Propecia) immediately if they develop depression and inform a healthcare professional."

[266] Drug Safety Update, *Finasteride: rare reports of depression and suicidal thoughts*, Medicines and Healthcare products Regulatory Agency (May 24, 2017). Available from: https://www.gov.uk/drug-safety-update/finasteride-rare-reports-of-depression-and-suicidal-thoughts.

Directive for Revised Approval, *Finasteride 1 mg*, Korean Ministry of Food and Drug Safety, Pharmaceutical Safety Assessment Division (2017).[267]

A newly added 'Warning' will be added to Finasteride Single-Drug (Tablet) to include, "Mood swings, including gloomy mood, depression and suicidal thoughts, were reported from patients who had been given 1 mg of Finasteride. Please make sure to observe the patient for psychological symptoms. If any of the above symptoms has been found in a patient, stop the treatment with Finasteride and consult a medical provider."

Propecia Summary of Product Characteristics, Medicines and Healthcare products Regulatory Agency (July 28, 2017).[268]

Section 4.4 (Special warnings and precautions for use) states, "Mood alterations and depression. Mood alterations including depressed mood, depression and, less frequently, suicidal ideation have been reported in patients treated with finasteride 1 mg. Patients should be monitored for psychiatric symptoms and if these occur, treatment with finasteride should be discontinued and the patient advised to seek medical advice."

8. Impaired Spermatogenesis and Infertility with Finasteride

The **ADVERSE REACTIONS, Postmarketing Experience** section (6.2) of the product label states, "The following adverse reactions have been identified during post approval use of PROPECIA. … *Reproductive System*: … male infertility and/or poor seminal quality (normalization or improvement of seminal quality has been reported after discontinuation of finasteride)."

This language is misleading because it does not accurately reflect the scientific literature which documents the important role of DHT in spermatogenesis, the adverse effects of Propecia on fertility, and reports of abnormal sperm parameters that continue after discontinuation of Propecia.

[267] Pharmaceutical Safety Assessment, *Finasteride 1 mg*, Korean Ministry of Food and Drug Safety, English translation (June 29, 2017). Available in Korean from: http://www.mfds.go.kr/index.do?mid=1042&seq=37801&cmd=v.
[268] Summary of Product Characteristics, *Propecia 1 mg tablets* (28-Jul-2017). Available from: https://www.medicines.org.uk/EMC/medicine/3680/SPC/Propecia+1mg+tablets/.

a. Role of DHT and 5α-Reductase in Spermatogenesis.

Payne A et al, *Formation of Dihydrotestosterone and Other 5α-Reduced Metabolites by Isolated Seminiferous Tubules and Suspension of Interstitial Cells in a Human Testis* (1973).[269]

In 1973, Payne et al. discovered that the seminiferous tubules (where spermatocytes are formed) in a testis from of a 17-year-old male converted androgens to DHT at a 50-fold greater rate than interstitial cells. DHT was not detected in interstitial cells.

Payne et al. concluded, "The data suggest that DHT may be the mediator of androgen action in human seminiferous tubules. … Since only seminiferous tubules and not interstitial cells from human testis convert androstenedione and T to DHT and 5α-androstanediols, it is likely that either or both of these 5α-reduced compounds may be necessary in the human testis to maintain normal spermatogenesis."

Dorrington J and Fritz I, *Cellular localization of 5alpha-reductase and 3alpha-hydroxysteroid dehydrogenase in the seminiferous tubule of the rat testis* (1975).[270]

In the seminiferous tubules of normal adult rats, spermatocytes and Sertoli cells (whose main function is to nourish the developing sperm cells through the stages of spermatogenesis) metabolize T to DHT. DHT is the major product formed by spermatocytes.

Mahony M et al, *Regional distribution of 5α-reductase type 1 and 2 mRNA along the human epididymis* (1998).[271]

The epididymis is the site of final maturation of spermatozoa where the sperm acquires the ability to swim, fertilize oocytes (eggs) and produce viable offspring. Experiments to identify the regional distribution and expression of 5αR2 mRNA in the human epididymis demonstrated 5αR2 in the midcaput, distal caput, corpus and proximal cauda of the epididymis.

Mahony et al. explained, "In addition to mediating overall maintenance of the epididymis, DHT is thought to be the primary androgen regulating sperm maturation and subsequent storage in the distal regions of that organ."

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[269] Payne A et al, *Formation of Dihydrotestosterone and Other 5α-Reduced Metabolites by Isolated Seminiferous Tubules and Suspension of Interstitial Cells in a Human Testis*, J Clin Endocrinol Metab (1973), Vol. 37, pp. 448-453.
[270] Dorrington J and Fritz I, *Cellular localization of 5alpha-reductase and 3alpha-hydroxysteroid dehydrogenase in the seminiferous tubule of the rat testis*, Endocrinology (1975), Vol. 96(4), pp. 897-899.
[271] Mahony M et al, *Regional distribution of 5α-reductase type 1 and 2 mRNA along the human epididymis*, Fertil Steril (1998), Vol. 69(6), pp. 1116-1121.

O'Donnell L et al, *Testosterone-Dependent Restoration of Spermatogenesis in Adult Rats is Impaired by a 5α-Reductase Inhibitor* (J Androl 1999).[272]

Spermatogenesis in adult rats was suppressed for 8 weeks with T and estradiol. After discontinuation of T and estradiol, spermatogenesis was then restored by administration of increasing doses of T with or without a 5αRI (L685,273 supplied by Dr. Rasmusson of Merck). The authors concluded that "the 5α-reduction of T is particularly important for the progression of spermatogenesis through midspermiogenesis, because this phase of germ cell development is more sensitive to withdrawal of androgens. … DHT is important for T-mediated short-term restoration of spermiogenesis, specifically for the conversion of round spermatids between stages VII and VIII."

Trybek G et al, *Immunolocalization of androgen receptor in the epididymis of rats with dihydrotestosterone deficiency* (2005).[273]

Trybek et al. examined the morphology of epididymis and localization of the AR in the epididymis of rats treated with finasteride for 56 days. The epididymis is necessary for maturation, storage, and survival of spermatozoa. T and DHT maintain the structure, secretory and absorptive functions of the epididymis.

The authors explained, "In humans and rats, finasteride inhibits DHT production in a similar way to castration. … DHT deficiency resulted in sloughing of germ cells – mainly spermatids in different developmental steps and, rarely, late pachytene spermatocytes. The amount of spermatozoa visible in the lumen of caput, especially in cauda epididymis, decreased. This may be caused by the sloughing of immature germ cells into the lumen of seminiferous tubules in the finasteride-treated rats."

Trybek et al. concluded, "It has been shown that finasteride … affected the expression of a wide range of genes in the rat epididymis. For this reason, DHT is regarded as a global modulator of many epididymal functions."

Kolasa A et al, *DHT deficiency perturbs the integrity of the rat seminiferous epithelium by disrupting right and adherens junctions* (2011).[274]

Kolasa et al. treated rats with finasteride, resulting in structural alterations in the seminiferous epithelium with premature germ cells sloughing into the lumen of seminiferous tubules, a pathologic condition which ultimately could impair fertility. The etiology of this disorder could be connected with intercellular junction disintegration of the blood-testis-barrier (BTB). The testis is an immunologically privileged organ because of the normal function of the BTB. The integrity of the BTB is essential for separation of germ cells from immunocompetent cells.

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[272] O'Donnell L, *Testosterone-Dependent Restoration of Spermatogenesis in Adult Rats is Impaired by a 5α-Reductase Inhibitor*, J Androl (1999), Vol. 20(1), pp. 109-117.
[273] Trybek G et al, *Immunolocalization of androgen receptor in the epididymis of rats with dihydrotestosterone deficiency*, Reproductive Biology (2005), Vol. 5(3), pp. 291-301.
[274] Kolasa A et al, *DHT deficiency perturbs the integrity of the rat seminiferous epithelium by disrupting right and adherens junctions*, Folia Histochem Cytobiol (2011), Vol. 49(1), pp. 62-71.

Kolasa et al. concluded, "Our data indicates that finasteride-induced DHT deficiency changes the expression of junctional proteins involved in the building of tight and adherens junctions in the seminiferous epithelium of rats. Therefore, it can be expected that the structure and function of the BTB can be regulated by DHT."

b. Spermatogenesis and Fertility in Genetic 5α-Reductase Deficiency.

Virtually all pseudohermaphrodites with genetic 5αR2 deficiency are infertile, have impaired spermatogenesis and require invasive infertility procedures to have any possibility of achieving paternity.

Cai L et al, *Dihydrotestosterone Regulation of Semen in Male Pseudohermaphrodites with 5α-Reductase-2 Deficiency* (1994).[275]

Cai et al. (and Imperato-McGinley) characterized the semen from 9 male pseudohermaphrodites with genetic 5αR2 deficiency as having extremely low volume (range, < 0.05 to 1.0 mL), increased viscosity and poor liquefaction (Table 1 below). Semen from 8 of the 9 subjects was oligospermic or azoospermic (no sperm in semen) with subnormal motility and morphology.

TABLE 1. Baseline semen analyses in adult male pseudohermaphrodites with 5αRD

Location of testes	Semen vol (mL)	Sperm conc. ($\times 10^6$/mL)	Total sperm count ($\times 10^6$/ejaculate)	% Motile cells	Morphology (%)			Liquefaction
					Normal	H. defect	T. defect	
I. Bilaterally descended								
Patient 1	0.15	321	48.2	56	71	23	3	No
Patient 2	0.5	2	1	0	36	55	9	No
Patient 3	0.4	12	4.8	10	59	34	4	No
Patient 4	0.8	<1	<1	ND	ND			ND
Patient 5	0.1	<1	<1	0	<1			No
Patient 6	1.0	0	0	0	0	0	0	No
II. Unilaterally undescended								
Patient 7	<0.05	<1	<1	0	4	86	10	No
Patient 8	0.5	0	0	0	0	0	0	No
III. Bilaterally retractile								
Patient 9	0.2	0	0	0	0	0	0	No
Mean	0.4							
SE	0.1							
Normal values	>2	>20	>40	>50	>45	>34	>20	Yes

ND, Not done.

DHT regulates semen volume and viscosity through its action on the prostate and seminal vesicles. Together, the prostate and seminal vesicles account for over 95% of semen volume.

The testes of 4 of the pseudohermaphrodites were biopsied (Table 3 below). Findings from the testicular biopsies of 3 subjects with bilateral descended testes showed decreased spermatogenesis, few mature sperm, no germs cells seen, sloughing of spermatogonia, generalized atrophy, immature appearing Sertoli cells, seminiferous tubule basement membrane sclerosis, etc. Even the one subject with a normal sperm

[275] Cai L et al, *Dihydrotestosterone Regulation of Semen in Male Pseudohermaphrodites with 5α-Reductase-2 Deficiency*, J Clin Endocrinol Metab (1994), Vol. 79, pp. 409-414.

count had decreased spermatogenesis overall, few mature sperm, and sloughing of spermatogonia with seminiferous basement membrane thickening. The affected subjects had different degrees of maturation arrest and tubular sclerosis.

TABLE 3. Histology from testicular biopsies with corresponding semen analyses and testicular location in male pseudohermaphrodites with 5αRD

Subject no.	Testicular biopsy histology	Semen analysis (see Table I)	Testes location
1	Decreased spermatogenesis overall Few mature sperm Sloughing of spermatogonia Low lying appearance of germinal epithelium, Seminiferous tubule basement membrane thickening	Normal conc., motility, morphology	Scrotal
3	Generalized atrophy Immature appearing Sertoli cells No germ cells seen Seminiferous tubule basement membrane sclerosis	Oligospermia, hypomotility, borderline morphology	Scrotal
4	Moderately severe hypospermatogenesis Some fully mature spermatozoa seen Some luminal sloughing of immature spermatocytes Prominent tunica propria	Severe oligospermia	Scrotal
8	Markedly decreased germ cell number Spermatogonia and primary spermatocytes seen More mature forms only rarely seen No fully mature spermatids seen Diffuse mild peritubular fibrosis	Azoospermia	Distal inbuinal canal

Cai et al. stated, "It is puzzling that eight of the nine patients studied demonstrated oligo- or azoospermia at baseline despite the fact that six patients had bilaterally descended testes, and one had bilaterally retractile testes." The authors explained the oligospermia and azoospermia by hypothesizing that there may have been delayed descent of the testes prior to puberty that could have caused seminiferous tubule damage.

The authors concluded, "The finding of normal sperm concentrations in two subjects with genetic 5αR2 deficiency suggests that DHT does not play a major role in spermatogenesis. However, the possibility that low levels of DHT might be sufficient for normal spermatogenesis must also be considered."

Contrary to the assertion of Cai et al. that two subjects had normal sperm concentrations, the data presented in Table 1 above shows that only one subject with genetic 5αR2 deficiency had a normal sperm concentration. The one subject with a normal sperm count had a DHT level (1.0 nmol/L) that was borderline normal (normal DHT range of 1.03-2.41 nmol/L).

Katz et al, *Paternity by Intrauterine Insemination with Sperm from a Man with 5α-Reductase-2 Deficiency* (1997).[276]

Katz et al. (and Imperato-McGinley) published the first case report of a man with genetic 5αR2 deficiency who was able to achieve biological fatherhood almost 25 years after Imperato-McGinley's discovery of pseudohermaphrodites in the Dominican Republic with genetic 5αR2 deficiency.

[276] Katz M et al, *Paternity by Intrauterine Insemination with Sperm from a Man with 5α-Reductase-2 Deficiency,* New Engl J Med (1997), Vol. 336(14), pp. 994-997.

Intrauterine insemination was necessary for this man to achieve paternity. After preparation by multiple cycles of washing, centrifugation (concentration) through a medium of artificial human tubal fluid and resuspension, 2 semen samples had sperm concentrations of 23 million and 43 million sperm per mL. Washing the semen before insemination rids the sample of abnormal sperm.

The authors concluded, "Paternity by intrauterine insemination is feasible in men with 5αR2 deficiency."

Nordenskjold A and Ivarsson S et al, *Molecular Characterization of 5α-Reductase Type 2 Deficiency and Fertility in a Swedish Family* (1998).[277]

Nordenskjold and Ivarsson published the first case report of proven fertility and natural paternity in 2 brothers with a mild clinical presentation of genetic 5αR2 deficiency. At birth, these patients manifested a male phenotype with hypospadias, well-developed scrotum and cryptorchidism. The authors stated, "Early correction of cryptorchidism and hypospadias is crucial to prevent damage to the seminiferous tubules and to preserve spermatogenesis and future fertility."

Molecular analysis showed the brothers to be compound heterozygotes with 2 mutations (H231R and G196S) that code for partially functioning 5αR2 enzymes. Partially functional 5αR2 may explain the male phenotype and fertility in these patients. The H231R mutant protein possesses 15% of the activity of normal 5αR2 and the G196S mutant protein has 10% of normal 5αR2 activity.

Stoner E, *Testimony during Dermatologic and Ophthalmic Drugs Advisory Committee Meeting No. 48* (November 13, 1997).[278]

Elizabeth Stoner, head of Merck's finasteride clinical research program, made a representation to the Advisory Committee reviewing the Propecia NDA that cannot be reconciled with the scientific literature when she asserted, "In fact, even though these patients have congenital anatomical abnormalities, several pregnancies have been reported with the fathers being the men with 5-alpha-Reductase, demonstrating that even *lifelong inhibition of DHT does not appear to alter spermatogenesis*." [emphasis supplied]

Men with genetic 5αR2 deficiency have low, but present, circulating levels of DHT from 5αR1 activity in the liver, and partial activity of the 5αR2 enzyme in many cases. They virtually all have impairments in spermatogenesis, even in the absence of undescended testes.[279]

[277] Nordenskjold A and Ivarsson S, *Molecular Characterization of 5α-Reductase Type 2 Deficiency and Fertility in a Swedish Family*, J Clin Endocrinol Metab (1998), Vol. 83, pp. 3236-3238.
[278] Advisory Committee Meeting No. 48 *op. cit.*, pp. 95-96.
[279] Cai *op. cit.*, pp. 409-414.

Steger K et al, *Reversion of the differentiated phenotype and maturation block in Sertoli cells in pathological human testis* (1999).[280]

Steger et al. published the first study evaluating the persistence of immature Sertoli cells (nurse cells) in the testis of adult men with genetic 5αR2 deficiency. Sertoli cell differentiation and spermatogenic impairment was studied in 3 children, 50 adults (aged 19–45 years) with azoospermia or oligospermia, and 6 patients (aged 1–18 years) with genetic 5αR2 deficiency.

Steger et al. explained, "The maturation of Sertoli cells at puberty [in response to hormones] is critical for the initiation and maintenance of spermatogenesis." In adults with genetic 5αR2 deficiency, the persistence of immature Sertoli cells was associated with prepubertal seminiferous cords and impaired spermatogenesis. Genetic 5αR2 deficiency prevents the maturation of Sertoli cells, resulting in impaired spermatogenesis.

Steger et al. concluded, "In 5αR2 deficiency, the failure of Sertoli cells to progress fully to a mature functional state at puberty is a primary defect, which, in turn, does not allow normal spermatogenic progression. In this respect, our description of immature Sertoli cells in two adults with this genetic defect represents the first report of the persistence of immature, rather than de-differentiated Sertoli cells in adult testis."

Hadziselimovic F and Dessouky N, *Differences in Testicular Development Between 5α-Reductase 2 Deficiency and Isolated Bilateral Cryptorchidism* (2008).[281]

Hadziselimovic and Dessouky provided direct evidence that the primary defect responsible for the high infertility rate in genetic 5αR2 deficiency is the intrinsic failure of Sertoli cells to mature at puberty, not undescended testes. They compared the testicular histopathology of 5 boys with genetic 5αR2 deficiency (mean age 5.36 years) to 49 boys with bilateral undescended testes (mean age 5.4 years). The position of the undescended testis had no major impact on the development of germ cells in patients with genetic 5αR2 deficiency.

In the genetic 5αR2 deficiency patients, there were no primary spermatocytes in all prepubertal testes, but typical germ stem cells were found and the number of germ cells was normal. All patients with genetic 5αR2 deficiency had normal germ cell counts, but not a single patient with isolated bilateral cryptorchidism had a normal germ cell count ($p < 0.000000001$). Only 29% of all cryptorchid testes exhibited Ad spermatogonia compared to 100% of 5αR2 deficient testes ($p < 0.001$). Mean number of Ad spermatogonia in cryptorchid testes was 0.0064, while the mean number of Ad spermatogonia in 5αR2 deficient testes was 0.1 ($p < 0.001$). Leydig cells of the testis produce T. Juvenile Leydig cells were observed in all genetic 5αR2 deficiency patients, but cryptorchid testes had prominent atrophy of juvenile Leydig cells.

[280] Steger *op. cit.*, pp. 136-143.
[281] Hadziselimovic *op. cit.*, pp. 1116-1120.

Studies have convincingly shown that 5αR2 is important in the maintenance of spermatogenesis and 5αR2 indirectly influences growth and differentiation of spermatocytes.[282] Moreover, DHT is a major product formed by spermatocytes.[283]

The authors concluded, "In patients with steroid 5αR2 deficiency, the impaired second step of germ cell maturation results in defective transformation of spermatogonia into spermatocytes. The position of the undescended testis appears to have no major pathological impact on the development of germ cells in patients with steroid 5αR2 deficiency. … Infertility in subjects with [genetic 5αR2 deficiency] is likely to be a direct consequence of the gene mutation, rather than a result of the undescended testes."

c. Effects on Fertility in Men Treated with Finasteride.

Semen Production Study #012 (5 mg finasteride and placebo, 47 subjects).[284]

Ejaculate volume decreased by 29.8% after 12 weeks ($p = 0.009$) and 23.9% after discontinuation for 12 weeks ($p = 0.031$). Total sperm per ejaculate decreased non-significantly by 46.9% after 12 weeks and was still decreased by 26.1% after discontinuation for 12 weeks. Percent motile sperm was decreased non-significantly by 11.1% after 12 weeks of use. One subject in the finasteride group developed oligospermia.

The results of study #012 have never been published. The adverse effects of finasteride on these fertility parameters (other than ejaculate volume) are not disclosed in the Propecia product label.

Semen Production Study #056 (5 mg finasteride and placebo, 138 subjects).[285]

Ejaculate volume decreased by 7.8% and 18.0% at weeks 12 and 24 ($p = 0.002$ and < 0.001, respectively), and remained decreased by 14.0% and 7.2% after discontinuation for 12 and 36 weeks ($p = 0.001$ and 0.002, respectively). After discontinuation for 60 weeks, ejaculate volume was still decreased by 4.4%, but not significantly ($p = 0.151$). The Propecia product label fails to state that it took about one year after discontinuation of finasteride for decreases in ejaculate volume to reverse to within non-significant limits and that small decreases in ejaculate volume were still detected 84 weeks after discontinuation of treatment.

Total sperm per ejaculate was decreased by 17.5% at week 12 ($p = 0.039$) and 30.4% at week 24 ($p < 0.001$), and remained decreased by 7.7% after discontinuation for 12 weeks. Percent motile sperm was significantly decreased by 4.4% and 3.9% at weeks 12 and 24 ($p = 0.002$ and 0.014).

[282] O'Donnell *op. cit.*, pp. 109-117.
[283] Dorrington *op. cit.*, pp. 897-899.
[284] Ko Medical Review *op. cit.*, page 87.
[285] Ko Medical Review *op. cit.*, page 87.

Study #056 had a larger sample size than Merck's other FDA-approved semen studies #012 and #092, and was the only one of the 3 studies to demonstrate statistically significant decreases in total sperm per ejaculate and percent motile sperm.

The results of study #056 have never been published. The adverse effects of finasteride on these fertility parameters (other than ejaculate volume) are not disclosed in the Propecia product label. Although this study was conducted with 5 mg finasteride, these results are highly relevant because the effects of 1 mg and 5 mg finasteride on all measured parameters in all other studies are substantially equivalent.[286]

Kaufman K, *Testimony during Dermatologic and Ophthalmic Drugs Advisory Committee Meeting No. 48* (November 13, 1997).[287]

Keith Kaufman, head of Merck's clinical development program for Propecia, testified before the Advisory Committee reviewing the Propecia NDA, "There is no evidence to support that finasteride would have any effect on male fertility." This assertion cannot be reconciled with the scientific literature or data from two of Merck's finasteride RCTs. The results from semen production studies #012 and #056,[288] and from other studies in men,[289,290] are evidence that finasteride should have been expected to affect male fertility.

Overstreet J et al, *Chronic treatment with finasteride daily does not affect spermatogenesis or semen production in young men* (1999).[291]

In Merck's long-term reversibility-of-effect study (FDA Protocol # 094), sequential semen samples were analyzed in 79 men (age 19 to 41) who received 1 mg finasteride or placebo for 48 weeks followed by a 60-week, off-drug period. There were no significant effects of finasteride on sperm concentration, total sperm per ejaculate, sperm motility or morphology. Total sperm per ejaculate in the finasteride group decreased from 160 million at baseline to 125 million after the 60-week, off-drug period (-22%), but this change was not statistically significant.

Overstreet et al. concluded, "Treatment with 1 mg finasteride does not affect spermatogenesis or semen production in young men. … While there is 5αR activity in the human testis and accessory sex organs, DHT does not appear to be important for spermatogenesis or the sperm maturation process."

[286] Shukla (April 28, 2011) *op. cit.*, pp. 1-13.
[287] Advisory Committee Meeting No. 48 *op. cit.*, pg. 73.
[288] Ko Medical Review *op. cit.*, page 87.
[289] Payne *op. cit.*, pp. 448-453.
[290] Cai *op. cit.*, pp. 409-414.
[291] Overstreet *op. cit.*, pp. 1295-1300.

Overstreet et al. excluded patients with abnormal screening semen analyses, a history of subfertility, etc.[292] Due to the small sample size of the semen study (79 men at initiation of the study), the likelihood of Type II statistical error must be considered.

In the FDA's Medical Review of the Propecia NDA, Ko comments, "The Applicant concludes that the negative findings on semen parameters (apart from ejaculatory volume) suggested that treatment with finasteride 1 mg/day had little detectable effect on spermatogenesis. This conclusion is premature, as (a) current methodology may not be able to evaluate all aspects of spermatogenesis and (b) long-term effects beyond 48 weeks are unknown."[293]

Glina S et al, *Finasteride-Associated Male Infertility* (2004).[294]

Glina et al. reported the first case series of Propecia-associated male infertility. Three cases were reported of men age 31, 32 and 33 years with poor seminal quality during Propecia use whose seminal quality improved after discontinuation. In 2 men, semen normalized 3 to 4 months after discontinuation of Propecia. In the 3rd man, semen parameters improved, but the improved sperm concentration was still abnormal. The couple was treated with intrauterine insemination (sperm is injected directly into the uterus) instead of intra-cytoplasmic sperm injection (a single sperm is injected into a single egg).

Collodel G et al, *Spermatozoa and Chronic Treatment with Finasteride: A TEM and FISH Study* (2007).[295]

Collodel et al. published the first case series demonstrating impaired meiosis and sperm damage during Propecia treatment that persisted after discontinuation. Three male patients (age 29, 34 and 36 years) on Propecia with abnormal semen parameters (1 with azoospermia and 2 with reduced progressive motility) had elevated diploidy and sex chromosome disomy frequencies by transmission electron microscopy (TEM). Serum hormone levels (T, estradiol, FSH, LH and prolactin) were normal in all patients.

After discontinuation of Propecia, spermatogenesis, morphology and motility improved, but abnormal meiosis in both fertile and infertile men did not improve. The authors explained, "Light microscopy is very superficial and TEM is the only tool able to evaluate fine structural sperm alterations."

Among sperm pathologies, all patients had a high number of sperm with necrosis. The high number of sperm with ultrastructural defects indicated severe fertility problems.

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[292] Samplaski MK et al, *Finasteride use in the male infertility population: effects on semen and hormone parameters*, Fertil Steril (2013), Vol. 100(6), pp. 1542-1546.
[293] Ko Medical Review *op. cit.*, page 93.
[294] Glina S et al, *Finasteride-Associated Male Infertility*, Revista do Hospital das Clínicas (2004), Vol. 59(4), pp. 203-205.
[295] Collodel G et al, *Spermatozoa and Chronic Treatment with Finasteride: A TEM and FISH Study*, Arch Androl: J Reproduct Syst (2007), Vol. 53, pp. 229-233.

Sperm analysis for aneuploidy frequency was significantly elevated in all patients compared to controls (p = 0.001 to 0.003 with different analytical techniques), even after discontinuation of Propecia. The patient with azoospermia improved, but was still oligospermic (1.23 million sperm per mL) 1 year after discontinuation of Propecia.

Prior studies[296,297] used less sensitive standard methods to evaluate sperm quality.

Amory J et al, *The Effect of 5α-Reductase Inhibition with Dutasteride and Finasteride on Semen Parameters and Serum Hormones in Healthy Men* (2007).[298]

Amory et al. (research supported by Glaxo Smith Kline) analyzed blood and semen in 99 healthy men age 18 to 55 years who received dutasteride, finasteride 5 mg, or placebo for 1 year with follow-up 24 weeks after discontinuation.

Total sperm count was significantly decreased by 34.3% (p = 0.004) at 26 weeks in the finasteride group. Total sperm counts were decreased in the finasteride group by 16.2% at 52 weeks and by 6.2% at the 24-week follow-up, but these changes were not statistically significant. At 26 weeks in the finasteride group, semen volume was significantly decreased by 21.1% (p = 0.01) and sperm concentration was significantly decreased by 21.5% (p = 0.032). At 52 weeks in the finasteride group, semen volume was decreased by 14.5% and sperm concentration was decreased by 7.4%, but these changes were not statistically significant.

There was a significant decrease in sperm motility during treatment (-10.5%; $p \leq 0.01$) and at follow-up 24 weeks after discontinuation (-9.7%; p = 0.006) in the finasteride group.

One finasteride subject had a decline in total sperm count to less than 10% of baseline at 26 weeks and 52 weeks of therapy. At the 24-week follow-up, this individual had recovered to 18.8% of his baseline values. Amory et al. concluded, "The marked sensitivity of some individuals to these compounds [finasteride and dutasteride] could be of importance for some men with infertility and reduced semen quality while using these medications. Indeed, these compounds should be considered as possible etiological agents when evaluating men for infertility."

Liu KF et al, *Propecia-induced spermatogenic failure: a report of two cases* (2008).[299]

Liu et al. reported cases of azoospermia and severe oligospermia in two men age 32 and 34 years during and after cessation of Propecia.

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[296] Overstreet *op. cit.*, pp. 1295-1300.
[297] Glina *op. cit.*, pp. 203-205.
[298] Amory, J et al, *The Effect of 5α-Reductase Inhibition with Dutasteride and Finasteride on Semen Parameters and Serum Hormones in Healthy Men*, J Clin Endocrinol Metab (2007), Vol. 92, pp. 1659-1665.
[299] Liu KE et al, *Propecia-induced spermatogenic failure: a report of two cases,* Fertil Steril (2008); Vol. 90(3), pp. 849.e17-e19.

The first patient had only rare sperm while on Propecia, but had 5.5 million sperm per mL after stopping Propecia for 7 months. The second patient had 4 million sperm per mL while on Propecia, but had 18.7 million sperm per mL after stopping Propecia for 6 months. Motility and normal morphology also improved after discontinuation of Propecia. In both cases, semen parameters did not return to normal.

Tu H and Zini A, *Finasteride-induced secondary infertility associated with sperm DNA damage* (2011).[300]

Tu and Zini published the first case report of finasteride-associated sperm damage with an elevated DNA fragmentation index (DFI) and recurrent pregnancy losses. Sperm DNA damage is associated with male infertility and sperm DFI is an estimate of sperm DNA breaks.

A 48-year-old man on low-dose finasteride with secondary infertility had an abnormal sperm DFI of 30% and otherwise normal semen parameters. The DFI decreased to 21% three months after discontinuing finasteride, and the DFI improved to 16.5% after another 3 months, but the couple remained infertile. A sperm DFI of 27% to 30% has shown a statistically significant relationship with increased pregnancy losses.

Tu and Zini concluded, "The significant reduction in DFI within 3 months of finasteride cessation and continued improvement suggests a causal link between finasteride and sperm DNA damage."

Samplaski et al, *Finasteride use in the male infertility population: effects on semen and hormone parameters* (2013).[301]

Samplaski et al. analyzed a prospective database of men on Propecia evaluated for infertility from 2008 to 2012 for semen parameters before and after discontinuation of Propecia. There were 14 men who had 'before' and 'after' semen analyses with mean time between measurements of 6.45 months.

Sperm counts increased significantly 11.6-fold after discontinuing Propecia ($p = 0.002$). Mean sperm concentration significantly increased from 13.2 to 42.25 M/mL ($p = 0.003$). Mean sperm motility increased from 16.8% to 25.9%, but not significantly ($p = 0.183$). The degree of recovery was variable, but was reversible for most of the men who presented with infertility. There were 57% of men with severe oligospermia who had sperm counts that increased to > 15 M/mL after cessation.

Samplaski et al. concluded, "It has now become increasingly clear that some men on finasteride have reduced fertility, and stopping the drug results in improved sperm parameters. … The discontinuation of finasteride may not bring the sperm parameters to levels where a spontaneous pregnancy is likely, but it may allow for less invasive

[300] Tu H and Zini A, *Finasteride-induced secondary infertility associated with sperm DNA damage*, Fertil Steril (2011), Vol. 95(6), pp. 2125.e13-14.
[301] Samplaski *op. cit.*, pp. 1542-1546.

fertility therapy (intrauterine insemination versus intracytoplasmic injection). In addition, caution and appropriate counseling should be exercised when [finasteride is] given to men of reproductive age who desire fertility. … Finasteride should be discontinued in subfertile men with oligospermia, and used with caution in men who desire fertility."

Irwig MS, *Androgen Levels and Semen Parameters Among Former Users of Finasteride with Persistent Sexual Adverse Events* (2014).[302]

Irwig evaluated T levels, DHT levels and semen parameters in otherwise healthy young men (N = 24) who developed sexual AEs during finasteride use for AGA that persisted after discontinuation of treatment.

Low total T and DHT levels were found in 3 (13%) and 3 (13%) participants, respectively. Two of 23 participants (9%) had 2 low levels of both T and DHT. Mean and median sperm concentrations were normal, but 3 of 19 participants (16%) had severe oligospermia (< 5 million sperm/mL). Mean and median sperm motilities were normal, but 4 of 9 participants (44%) had 2 low motility values. Four of 8 participants (50%) had 2 low sperm morphology values.

9. Finasteride and the Hypothalamic-Pituitary-Gonadal Axis

The **CLINICAL PHARMACOLOGY, Pharmacodynamics** section (12.2) of the product label states, "In studies with finasteride, no clinically meaningful changes in luteinizing hormone (LH), follicle-stimulating hormone (FSH) or prolactin were detected. In healthy volunteers, treatment with finasteride did not alter the response of LH and FSH to gonadotropin-releasing hormone indicating that the hypothalamic-pituitary-testicular axis was not affected."

The first sentence is misleading because Merck's phase 3 clinical trial with finasteride for BPH demonstrated a significant 15% increase in serum LH levels in the 1 mg finasteride group.[303] A 15% increase in serum LH levels is clinically meaningful because the increased LH levels were associated with an 8-10% increase in serum T levels. Grino et al. (and Stoner) concluded that an 8-12% increase in serum T levels in Merck's phase 3 finasteride RCTs for BPH suggests the negative feedback by DHT at the hypothalamic-pituitary level.[304] Asserting that a 15% increase in LH levels is not clinically meaningful arbitrarily obscures Merck's own evidence of the effects of finasteride on the HPT axis.

The second sentence is misleading because it presents data from an uncontrolled clinical trial lasting only 28 days that enrolled only 20 men[305] while failing to disclose inconsistent data from Merck's phase 3 RCT with finasteride for BPH that enrolled

[302] Irwig MS, *Androgen Levels and Semen Parameters Among Former Users of Finasteride with Persistent Sexual Adverse Events*, JAMA Dermatol (2014), Vol. 150(12), pp.1361-1363.
[303] Gormley (1992) *op. cit.*, pp. 1185-1191.
[304] Grino (1994) *op. cit.*, pp. 24-28.
[305] Rittmaster R et al, *Effect of Finasteride, A 5α-Reductase Inhibitor, on Serum Gonadotropins in Normal Men,*

895 men.[306]

Kuhn J et al, *Effects of 10 Days Administration of Percutaneous Dihydrotestosterone on the Pituitary-Testicular Axis in Normal Men* (1984).[307]

DHT given to 12 normal men (age 25 to 45) for 10 days decreased LH levels significantly ($p < 0.001$). The correlation between changes in LH levels with DHT treatment suggests a direct negative feedback effect on LH release via a suppressive effect on LH-RH secretion.

Kuhn et al. concluded, "The results of this study demonstrate that 10-days DHT administration has an inhibitory effect on the HPT axis in normal men. … DHT, at least in pharmacological amounts, directly alters the regulation of the HPT axis in men."

Gormley GJ et al, *The Effect of Finasteride in Men with Benign Prostatic Hyperplasia* (1992).[308]

Merck's pivotal phase 3 clinical trial with finasteride for BPH enrolled 895 men who were given 1 mg or 5 mg finasteride, or placebo. Serum T and LH levels in the finasteride groups increased by 8-10% and 15%, respectively. The 1 mg and 5 mg finasteride groups each had significantly higher LH levels than placebo ($p < 0.05$).

Rittmaster R et al, *Effect of Finasteride, A 5α-Reductase Inhibitor, on Serum Gonadotropins in Normal Men* (1992).[309]

Rittmaster et al. conducted a study in 20 healthy men (age 25 to 38) who were given finasteride, 5 mg, for 28 days to determine whether suppression of DHT alters gonadotropin (LH and FSH) secretion. No significant changes were seen in either basal or GnRH-stimulated LH or FSH levels.

The authors concluded "that suppression of serum DHT levels with 5 mg finasteride daily in healthy young men has no discernible effect on serum gonadotropin levels. … The lack of effect of finasteride on both basal and GnRH-stimulated gonadotropin levels indicates that physiological levels of circulating DHT do not modulate LH and FSH secretion. … A final distinct possibility is that 5αR plays no role in the modulation of gonadotropin secretion."

The authors acknowledge that men with 5αR2 deficiency have "modestly increased serum FSH, LH and T levels, in spite of reductions in serum DHT that are less than were found in the present study."

J Clin Endocrinol Metab (1992), Vol. 75, pp. 484-488.

[306] Gormley (1992) *op. cit.*, pp. 1185-1191.

[307] Kuhn J et al, *Effects of 10 Days Administration of Percutaneous Dihydrotestosterone on the Pituitary-Testicular Axis in Normal Men*, J Clin Endocrinol Metab (1984), Vol. 58, pp. 231-235.

[308] Gormley (1992) *op. cit.*, pp. 1185-1191.

[309] Rittmaster (1992) *op. cit.*, pp. 484-488.

Grino P et al, *Finasteride for the Treatment and Control of Benign Prostatic Hyperplasia: Summary of Phase III Controlled Studies* (1994).[310]

Grino et al. (and Stoner) tested finasteride, 1 mg and 5 mg, in pivotal phase 3 BPH clinical trials that enrolled 1,645 patients over a 12-month period. Serum T levels increased an average of 8-12% in the finasteride groups. Grino et al. concluded, "This suggests that DHT plays some role in the negative feedback of androgens at the hypothalamic-pituitary level, which may explain, at least in part, the slight rise in serum T levels."

Canovatchel W et al, *LH Pulsatility in Subjects with 5α-Reductase Deficiency and Decreased Dihydrotestosterone Production* (1994).[311]

Canovatchel et al. (and Imperato-McGinley) compared LH pulsatility in 16 men with genetic 5αR2 deficiency to 18 normal males. Analysis of plasma LH sampling every 10 minutes over 10 or 24 hours demonstrated that subjects with genetic 5αR2 deficiency had a 2-fold increase in plasma LH level ($p < 0.0008$), LH pulse amplitude ($p < 0.002$) and plasma LH nadir ($p < 0.004$). Increased plasma LH response to LH-RH ($p < 0.01$) was also demonstrated.

The authors explained, "The findings suggest that a deficiency of DHT results in decreased negative feedback at the level of the hypothalamus and/or pituitary, resulting in increased mean plasma LH, LH pulse amplitude, and LH responsiveness to GnRH. In response to increased LH, mean plasma T, free T, and plasma estradiol are increased. … The pulse amplitude is increased despite elevated plasma T and estradiol levels; this underscores the importance of DHT in [LH] pulse amplitude regulation."

Canovatchel et al. concluded, "Males with 5αR2 deficiency and deficient plasma DHT levels have markedly elevated mean plasma LH levels and significantly increased LH pulse amplitude; pulse frequency is normal. This study suggests a role for DHT in the modulation of the pulsatile release of LH in males."

Andriole G et al, *Treatment with Finasteride following Radical Prostatectomy for Prostate Cancer* (1995).[312]

Andriole et al. (and Gormley) treated 120 men (age 48 to 89) with prostate cancer with 10 mg finasteride or placebo for 2 years after radical prostatectomy. During the 2 years on finasteride, serum T levels increased 20%, serum LH increased 25%, and FSH increased by about 15%.

[310] Grino (1994) *op. cit.*, pp. 24-28.
[311] Canovatchel W et al, *LH Pulsatility in Subjects with 5α-Reductase Deficiency and Decreased Dihydrotestosterone Production*, J Clin Endocrinol Metab (1994), Vol. 78, pp. 916-921.
[312] Andriole G et al, *Treatment with Finasteride following Radical Prostatectomy for Prostate Cancer*, Urology (1995), Vol. 45(3), pp. 491-497.

Castro-Magana M et al, *Effect of Finasteride on Human Testicular Steroidogenesis* (1996).[313]

Castro-Magana et al. studied testicular function in 22 men (age 16 to 30) with AGA treated with finasteride (10 mg) for 2 years. Finasteride caused a significant increase in serum T. LH levels increased by 33% at 24 months, but these changes were not significant.

Roberts J, *Clinical dose ranging studies with finasteride, type 2 5α-reductase inhibitor, in men with male pattern hair loss* (1999).[314]

In two of Merck's phase 2 clinical trials for AGA, 693 men age 18 to 36 years received 5, 1, 0.2 or 0.01 mg/day finasteride or placebo. Reductions in serum DHT at doses of finasteride ≥ 0.2 mg/day were associated with significant increases in serum T (mean increase of 18.3%, 19.4%, and 18.1% for the 5, 1, and 0.2 mg groups, respectively; $p < 0.01$ v. placebo) at month 6.

The increases in serum T and decreases in serum DHT were not associated with significant changes in serum LH or FSH from baseline. The authors concluded, "The absence of significant effect on serum LH or FSH baseline levels indicates that finasteride treatment had no significant effect on the HPG axis." The article does not report actual LH or FSH levels either before or after finasteride treatment.

If LH release is not affected by finasteride administration, what alternative explanation might account for the significant 18-19% increases in T levels? Grino et al. (and Stoner) concluded that the 8-12% increase in T levels with finasteride in the phase 3 clinical trials for BPH "suggests that DHT plays some role in the negative feedback of androgens at the hypothalamic-pituitary level."[315]

Overstreet J et al, *Chronic treatment with finasteride daily does not affect spermatogenesis or semen production in young men* (1999).[316]

In Merck's long-term reversibility-of-effect study (FDA Protocol # 094), 181 men (age 19 to 41) received 1 mg finasteride or placebo for 48 weeks followed by a 60-week, off-drug period. LH and FSH increased nonsignificantly from 6.7 to 7.1 (+6%) and 3.9 to 4.3 (+10%), respectively, after 48 weeks of finasteride treatment.

[313] Castro-Magana M et al, *Effect of Finasteride on Human Testicular Steroidogenesis*, J Androl (1996), Vol. 17(5), pp. 516-521.
[314] Roberts *op. cit.*, pp. 555-563.
[315] Grino (1994) *op. cit.*, pp. 24-28.
[316] Overstreet *op. cit.*, pp. 1295-1300.

Kaufman K et al, *Finasteride in the treatment of men with androgenetic alopecia* (1998).[317]

In two of Merck's 1-year pivotal phase 3 clinical trials, 1,553 men (age 18 to 41) with AGA received finasteride, 1 mg, or placebo, and 1,215 men continued in extension studies for a second year. Finasteride significantly increased serum T by 9.1% after 1 year ($p < 0.001$), but had no significant effects on serum LH or FSH after 1 year. The article does not report actual LH or FSH levels before or after finasteride treatment.

If LH release is not affected by finasteride administration, what alternative explanation might account for the significant 9% increase in T levels? Grino et al. (and Stoner) concluded that the 8-12% increase in T levels with finasteride in the phase 3 clinical trials for BPH "suggests that DHT plays some role in the negative feedback of androgens at the hypothalamic-pituitary level.[318]

Poletti A et al, *5α-reductase isozymes in the central nervous system* (1998),[319] Poletti A and Martini L, *Androgen-activating enzymes in the central nervous system* (1999),[320] and Poletti A et al, *5α-Reductase Type 2 and Androgen Receptor Expression in Gonadotropin Releasing Hormone GT1-1 Cells* (2001).[321]

5αR2 is expressed in hypothalamus and LH-RH secreting neurons of the hypothalamus of the brain. 5αR2 expression in the hypothalamus is controlled by the interaction of the AR with T and DHT. 5αR1, 5αR2 and the AR were all detected in a GnRH-secreting cell line with 5αR2 being the predominant 5αR isozyme. In GnRH neurons, DHT down-regulates transcription of the GnRH gene in a negative feedback manner.

Shakil T et al, *Differential Regulation of Gonadotropin-Releasing Hormone Secretion and Gene Expression by Androgen: Membrane versus Nuclear Receptor Activation* (2002).[322]

Shakil et al. examined the membrane receptor-mediated effects of androgens on GT1-7 GnRH-secreting neurons. GnRH mRNA levels were down-regulated by DHT and T. DHT is capable of mediating signal transduction initiated at the cell membrane of GnRH-secreting neurons via what appears to be the classic form of the AR in the plasma membrane.

[317] Kaufman *op. cit.*, pp. 578-589.
[318] Grino (1994) *op. cit.*, pp. 24-28.
[319] Poletti A et al, *5α-reductase isozymes in the central nervous system*, Steroids (1998), Vol. 63, pp. 246-251.
[320] Poletti A and Martini L, *Androgen-activating enzymes in the central nervous system*, J Ster Biochem Mol Biol (1999), Vol. 69, pp. 117-122.
[321] Poletti A et al, *5α-Reductase Type 2 and Androgen Receptor Expression in Gonadotropin Releasing Hormone GT1-1 Cells*, J Neuroendocrinol (2001), Vol. 13, pp. 353-357.
[322] Shakil T et al, *Differential Regulation of Gonadotropin-Releasing Hormone Secretion and Gene Expression by Androgen: Membrane versus Nuclear Receptor Activation*, Molec Endocrinol (2002), Vol. 16, pp. 2592-2602.

10. Off-Label Uses of Finasteride as an Antiandrogen

The Propecia product label states that finasteride has no antiandrogenic effects. This is an untrue statement of a material fact.

The antiandrogenic effects of finasteride are the theoretical foundation for its off-label uses. Finasteride is used to induce transitioning and maintain female characteristics in male-to-female transgender patients because of its antiandrogenic effects. For the same reason, finasteride has been explored as a potential treatment for prostate cancer.

The antiandrogenic effects of Propecia are highly undesirable characteristics for young men in their sexual and reproductive prime. This explains why Merck would want to deny that Propecia has antiandrogenic effects in the Propecia product label.

a. Prostate Cancer.

Based on its potent antiandrogenic effects, its ability to induce androgen deprivation and its comparison to castration, finasteride has been studied for its potential to treat prostate cancer either as a single agent or in combination with other antiandrogens.

Schmidt L and Tindall D, *Androgen Receptor: Past, Present and Future* (2013).[323]

Schmidt and Tindall reviewed the role of androgens and the AR as the focus of prostate cancer research. In the early 1940s, Huggins first showed that removal of androgens caused advanced prostate cancer to regress. Since 1941, many androgen deprivation therapies (ADTs), including surgical castration, 5αRIs (finasteride, dutasteride), anti-androgens that bind the AR, and GnRH agonists and antagonists have been developed as an effort to cure prostate cancer. Since 1988, new ADTs have been developed to find medical alternatives to surgical castration. Following a remission of about 2-3 years from initiation of ADT, prostate cancer recurs in most patients and is termed castration-recurrent prostate cancer (CRPC) for which there is no cure.

Efforts to disrupt androgen pathways at the level of androgen production, conversion of T to DHT (5αRIs) and competitive binding of drugs to the AR have all been employed to treat CRPC with limited success. A number of cellular mechanisms allow prostate cancer to escape the effects of ADT and progress to CRPC, including amplification of the AR both at the genomic and mRNA level.

In 1995, Visakorpi et al. showed that amplification of the AR is a critical factor in progression to CRPC.[324] In 2014, Di Loreto et al. demonstrated amplification of nuclear AR in stromal and epithelial cells of the foreskins of PFS patients.[325]

[323] Schmidt *op. cit.*, pp. 401-407.
[324] Visakorpi *op. cit.*, pp. 401-406.
[325] Di Loreto *op. cit.*, pp. e1-e7.

Presti JC et al, *Multicenter, randomized, double-blind, placebo controlled study to investigate the effect of finasteride (MK-906) on stage D prostate cancer* (1992).[326]

Presti et al. (and Gormley) investigated the use of finasteride to treat prostate cancer. Patients with stage D prostate cancer received 10 mg/day finasteride (N = 13) or placebo (N = 15) and were evaluated with serum PSA and prostatic acid phosphatase levels, bone scan, and ultrasound for prostatic volume. A significant decrease in PSA at weeks 3 and 6 occurred with finasteride v. placebo ($p < 0.05$), but all other parameters were unchanged.

Presti et al. concluded, "A decrease in serum PSA in the finasteride treatment group suggests that finasteride exerts a minor effect in patients with prostate cancer. This effect does not approach that seen with medical or surgical castration yet because of the potency preserving feature and the lack of toxicity finasteride may warrant further study in the treatment of prostate cancer."

Andriole G et al, *Treatment with Finasteride following Radical Prostatectomy for Prostate Cancer* (1995).[327]

Andriole et al. (and Gormley) treated 120 men (age 48 to 89) with prostate cancer with 10 mg finasteride or placebo for 2 years after radical prostatectomy. After ADT or surgery for the primary treatment of prostate cancer, a rise in serum PSA is the most widely used biomarker to indicate a prostate cancer recurrence.

Andriole et al. concluded, "The results of this study indicate that treatment with finasteride delays but does not prevent the rise in serum PSA observed in untreated patients with detectable PSA levels after radical prostatectomy. The reduction in local and distant recurrences in the finasteride group suggests that the effect on PSA reflects a direct effect on tumor growth without affecting the initial response to subsequent hormonal therapy."

Tay M et al, *Finasteride and bicalutamide as primary hormonal therapy in patients with advanced adenocarcinoma of the prostate* (2004).[328]

Tay et al. treated 41 patients with advanced prostate cancer with bicalutamide (an antiandrogen that binds to the AR) and 5 mg finasteride as primary hormonal therapy. Enhanced disease control was evaluated by serum PSA. Medical or surgical castration is effective in advanced prostate cancer, but has profound sexual side effects. Finasteride provided additional androgen blockade when added to bicalutamide and duration of prostate cancer disease control was comparable to castration with preserved sexual function in some patients.

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[326] Presti JC et al, *Multicenter, randomized, double-blind, placebo controlled study to investigate the effect of finasteride (MK-906) on stage D prostate cancer*, J Urol (1992), Vol. 148(4), pp. 1201-1204.
[327] Andriole *op. cit.*, pp. 491-497.
[328] Tay M et al, *Finasteride and bicalutamide as primary hormonal therapy in patients with advanced adenocarcinoma of the prostate*, Ann Oncol (2004), Vol. 15, pp. 974-978.

Tay et al. concluded, "This pilot study demonstrates that bicalutamide and finasteride may be given as primary hormonal therapy for advanced prostate cancer with few side effects. In addition, this study shows an additive effect of finasteride to the androgen-suppressive effect of bicalutamide. Overall duration of hormone responsiveness in this study appears comparable to standard ADT but this should be confirmed in a prospective randomized trial. Thus, this therapy may represent a promising approach for men with advanced prostate cancer and minimal disease burden and who desire potency sparing therapy."

Tindall D and Rittmaster R, *The Rationale for Inhibiting 5α-Reductase Isoenzymes in the Prevention and Treatment of Prostate Cancer* (2008).[329]

Tindall and Rittmaster conducted a medical literature review to examine the evidence supporting the treatment of prostate cancer with 5αRIs. 5αR1 and 5αR2 expression is increased in localized high-grade prostate cancer.

Treatment of early prostate cancer with a 5αR inhibitor has the potential to delay the progression of prostate cancer. Dutasteride pretreatment in men undergoing radical prostatectomy for prostate cancer increased apoptosis, decreased tumor volume and increased atrophic epithelium. Finasteride caused similar, but less prominent, atrophic effects. Finasteride treatment in men post-radical prostatectomy at high risk for clinical relapse delayed an increase in PSA by 9 months over 1 year of treatment and by 14 months over 2 years of treatment. Finasteride treatment in men with metastatic prostate cancer significantly decreased serum PSA.

The authors stated, "The inhibition of 5αR represents a valid target for prostate cancer risk reduction and treatment strategies." DHT, not T, is primarily responsible for the AR-mediated growth and survival of prostate cancer. Tindall and Rittmaster concluded, "Given the lower potency of T v. DHT, 5αRI treatment *significantly decreases the total androgen effect*. [emphasis supplied] … The effect of 5αR inhibition on prostate function is not as great as castration and the combination of the 2 methods has been shown to be more effective than either alone in an animal model of prostate cancer."

b. Male-to-Female Transgenderism.

Dahl M et al, *Physical Aspects of Transgender Therapy* (2006).[330]

Dahl et al. explained, "The goal of transgender endocrine therapy is to change secondary sex characteristics to reduce gender dysphoria and/or facilitate a gender presentation consistent with the felt sense of self. … Endocrine-induced feminization is achieved by direct or indirect *suppression of the effects of androgens* and induction of female physical characteristics. [emphasis supplied] Androgen suppression can be achieved" by several drug classes, including drugs "interfering with the … metabolism of T to DHT."

[329] Tindall D and Rittmaster R, *The Rationale for Inhibiting 5α-Reductase Isoenzymes in the Prevention and Treatment of Prostate Cancer*, J Urol (2008), Vol. 179(4), pp. 1235-1242.
[330] Dahl M et al, *Physical Aspects of Transgender Therapy*, Intl J Transgender (2006), Vol. 9:3-4, pp. 111-134.

The recommended dose of finasteride is 2.5-5.0 mg qd for "*systemic antiandrogen effect*." [emphasis supplied] Feminizing effects include decreased libido, possible difficulty reaching orgasm, reduction of ejaculate, decreased spontaneous/morning erections and reduced testicular volume.

Spack NP, *Management of Transgenderism* (2013).[331]

Transgenderism refers to individuals whose gender identity (inherent sense of being male or female) differs from their biologic sex. Therapeutic options for transgenderism include hormone and surgical treatments. For patients seeking male-to-female change who desire medical therapy, hormone treatment includes finasteride.

11. Risk-Benefit Relationship of Propecia

AGA is a cosmetic condition. The development of permanent sexual dysfunction and psychoneurocognitive side effects in young men (as young as their teens) who use Propecia is life-altering and results in a level of disability that can be devastating. The majority of PFS patients report that they had no sexual dysfunction or psychological issues prior to Propecia use.

Patients using Propecia unknowingly have assumed unacceptable risks because they were not adequately informed by their prescribing physician of Propecia's risks. If the Propecia product label contained truthful and transparent disclosures of Propecia's risks, prescribing physicians would be able to give their patients an adequate informed consent and undoubtedly many fewer patients would decide to take Propecia. Men taking Propecia for AGA have risked permanent sexual and psychoneurocognitive side effects for the potential promise of a 10% increase in the hair counts of their balding scalp.[332]

We believe the risk-benefit relationship for Propecia use should demand its immediate removal from the market.

a. Summary of the Benefits of Propecia.

Kaufman KD et al, *Finasteride in the treatment of men with androgenetic alopecia* (1998).[333]

Merck's two 1-year pivotal phase 3 clinical trials with finasteride for AGA (U.S. Study #087 and International Study #089) enrolled 1,553 men 18 to 41 years old who received finasteride 1 mg, or placebo, and 1,215 men continued in blinded extension studies for a second year.

Statistically significant increases in hair count (baseline = 876 hairs) in a 1-inch diameter circular area of balding vertex scalp were observed with finasteride treatment

[331] Spack NP, *Management of Transgenderism*, J Amer Med Assn (2013), Vol. 309(5), pp. 478-484.
[332] Kaufman *op. cit.*, pp. 578-589.
[333] Ibid.

at 1 and 2 years ($p < 0.001$). At 12 months, finasteride increased hair count by 86 hairs (10%). At month 24, men taking finasteride maintained the hair count observed at month 12. Treatment with placebo resulted in progressive hair loss with a decrease of 21 hairs at 12 months and 37 hairs at 24 months. At month 24, 17% of men continuing finasteride treatment had fewer hairs than at baseline.

The 2001 Propecia Patient Information[334] stated, "If you stop taking PROPECIA, you will likely lose the hair you have gained within 12 months of stopping treatment." The decision to take Propecia with the potential promise of increasing the hair count in your balding scalp by 10% is a lifelong commitment.

b. Summary of the Risks of Propecia.

The major risks of Propecia involve the potential for permanent impairments in the function of one's sexual organs, CNS and peripheral nerves.

- Finasteride causes atrophy of the prostate glands of men by apoptosis,[335] and increased apoptosis and decreased autophagy in the corpus cavernosum of male rats that results in a 25% decrease in cavernosal weight.[336,337] There is every reason to believe that finasteride would cause similar changes in all tissues where 5αR2 and the AR are present.

- In humans, 5αR2 localizes in the prostate, hair follicles, liver, seminal vesicles and epididymides.[338] 5αR2 in humans is also found in genital skin and organs,[339,340] the spermatogonia, seminiferous tubules and Sertoli cells of the testes,[341,342,343] and the cerebral cortex, medulla oblongata, pons, hypothalamus and pituitary gland of the brain.[344,345,346,347] In humans, the AR is found in the corpus cavernosum of the penis.[348] In mammals, 5αR2 has also been found to be present in the penis,[349] spinal cord,[350] and the

[334] *Propecia® Full Prescribing Information* (2001) *op. cit.*
[335] Rittmaster (1996) *op. cit.*, pp. 814-819.
[336] Zhang (2012) *op. cit.*, 1328-1336.
[337] Zhang (2013) *op. cit.*, pp. 743.e9-743.e15.
[338] *Propecia® Full Prescribing Information* (2014) *op. cit.*
[339] Hellwinkel *op. cit.*, pp. 217-225.
[340] Eicheler *op. cit.*, pp. 667-675.
[341] Aumuller *op. cit.*, pp. 241-252.
[342] Steger *op. cit.*, pp. 136-143.
[343] Hadziselimovic *op. cit.*, pp. 1116-1120.
[344] Thigpen *op. cit.*, pp. 903-910.
[345] Eicheler *op. cit.*, pp. 667-675.
[346]Aumuller *op. cit.*, pp. 241-252.
[347] McPhaul *op. cit.*, pp. 466-472.
[348] Schultheiss *op. cit.*, pp. 320-324.
[349] Nonomura *op. cit.*, pp. 152-155.
[350] Schirar *op. cit.*, pp. 3093-3102.

nucleus accumbens, locus coerulus, amygdala, cerebellum and hippocampus of the brain.[351]

Studies in mammals have demonstrated structural and physiological abnormalities with finasteride use in many 5αR2-containing tissues that persisted after withdrawal of finasteride which strongly suggests that these changes may be permanent.[352,353] Multiple mammal studies have demonstrated reduced smooth muscle, increased collagen deposition and other ultrastructural abnormalities in the corpus cavernosum of animals treated with finasteride.[354,355,356,357,358]

- Finasteride is an irreversible inhibitor of both 5αR1 and 5αR2.[359,360,361] Finasteride inhibits 5αR3 with similar potency as 5αR2.[362]

The deficiency of 5αR2 activity induced by finasteride is not specific for androgen metabolism, but is a general deficiency in steroid metabolism affecting C_{19} and C_{21} steroids, including T, progesterone, androstenedione, epitestosterone, cortisol, cortisone, corticosterone, DOC and aldosterone.[363,364,365] The downstream metabolites of these steroid substrates are biologically active and include DHP, allopregnanolone, DHDOC and THDOC, neurosteroids that play critical roles in CNS function in many brain regions that are necessary for normal sexual function and behavioral regulation.[366,367]

- Finasteride is a potent antiandrogen that has frequently been compared to castration[368] and induces a state of androgen deprivation.[369] The antiandrogenic effects of finasteride and resulting androgen deprivation form the basis of its efficacy in treating BPH and AGA. However, the antiandrogenic effects of finasteride and the similarity of these effects to castration have also provided the theoretical basis for Merck to conduct

[351] Castelli *op. cit.*, pp. 281-293.
[352] Corradi (2009) Microsc Res and Technique *op. cit.*, pp. 939-950.
[353] Corradi (2009) Intl J Exp Path *op. cit.*, pp. 79-94
[354] Shen *op. cit.*, pp. 33-36.
[355] Zhang (2012) *op. cit.*, 1328-1336.
[356] Zhang (2013) *op. cit.*, pp. 743.e9-743.e15.
[357] Traish (2005) *op cit.*, pp. 759-770.
[358] Traish (2009) *op. cit.*, pp. 363-369.
[359]Tian *op. cit.*, pp. 2291-2296.
[360] Bull (1996) *op. cit.*, pp. 2359-2365.
[361] Bull (1999) *op. cit.*
[362] Yamana *op. cit.*, pp. 293-299.
[363] Stoner (1990) *op. cit.*, pp. 375-378.
[364] Imperato-McGinley (1990) *op. cit.*, pp. 777-782.
[365] Traish (2015) Rev Endocr Metab Dis *op. cit.*, pp. 177-198.
[366] Ibid.
[367] Azzouni *op. cit.*, pp. 1-18.
[368] Stoner (1990) *op. cit.*, pp. 375-378.
[369] Rasmusson (1988) *op. cit.*

clinical trials with finasteride for both the prevention[370] and treatment[371,372,373] of prostate cancer. The antiandrogenic effects of finasteride have also provided the basis for its use in the transitioning of male-to-female transgender patients.[374,375]

- Recent observational epidemiological studies have conclusively demonstrated that low-dose finasteride (≤ 1.25 mg/day) is associated with a significant increase in persistent ED and sexual dysfunction.[376,377] One of these studies conclusively demonstrated that the risk of persistent ED after drug discontinuation with low-dose finasteride (≤ 1.25 mg/day), high-dose (5 mg/day) finasteride and dutasteride increases with increased duration of use.[378] This study determined that persistent ED developed in 1.2% of men with AGA with more than 205 days exposure to ≤ 1.25 mg finasteride per day. With longer duration of use, higher incidence rates for persistent ED would be expected. This study also demonstrated that at least 33% of men who developed new ED with ≤ 1.25 mg finasteride per day eventually developed persistent ED after drug discontinuation.

A 4-year, FDA-approved RCT in men with BPH demonstrated statistically significant increases in penile disorders, testicular pain, gynecomastia and breast tenderness in men taking finasteride.[379]

Several case series and controlled studies have been published identifying persistent sexual and psychoneurocognitive side effects in a total of several hundred men who have used finasteride (1.0 to 1.25 mg/day) for AGA and who had no prior history of either sexual dysfunction or psychiatric issues.[380,381,382,383,384,385]

Recent observational studies with both finasteride[386] and dutasteride[387] have demonstrated a sustained and progressive decline in sexual function and T levels with increased duration of therapy in men with BPH.

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[370] *Propecia® Full Prescribing Information* (2014) *op. cit.*
[371] Presti *op. cit.*, pp. 1201-1204.
[372] Andriole *op. cit.*, pp. 491-497.
[373] Tindall *op. cit.*, pp. 1235-1242.
[374] Dahl *op. cit.*, pp. 111-134.
[375] Spack *op. cit.*, pp. 478-484.
[376] Guo *op. cit.*, pp. 1180-1184.
[377] Kiguradze *op. cit.*, pp. 1-31.
[378] Ibid.
[379] Waldstreicher *op. cit.* (July 31, 1997).
[380] Irwig (2011) *op. cit.*, pp. 1747-1753
[381] Kothary *op. cit.*, pp. 1-19.
[382] Ganzer *op. cit.*, pp. 222-228.
[383] Ali *op. cit.*, pp. 687-695.
[384] Chiriaco *op. cit.*, pp. 245-250.
[385] Basaria *op. cit.*, pp. 4669-4680.
[386] Traish (2015) Horm Mol Biol Clin Invest *op. cit.*, pp. 85-96.
[387] Traish (2017) *op. cit.*, Epub ahead of print.

Recent controlled studies in men with persistent sexual dysfunction that developed during and did not resolve following discontinuation of low-dose finasteride for AGA, and control subjects, have demonstrated significant decreases in sexual function and changes consistent with major depression in the former finasteride users.[388,389] fMRI studies in former Propecia users with persistent sexual dysfunction and control subjects have revealed abnormal brain circuitry in the former Propecia users linked to diminished sexual arousal and overlapping with abnormalities seen in major depression which suggests there are neurobiological abnormalities in the CNS of former Propecia users with persistent sexual dysfunction.[390]

Another controlled study found a significant increase of nuclear AR levels in stromal and epithelial cells of the foreskins of PFS patients.[391]

- A recent observational epidemiological study has demonstrated a significantly increased risk of depression and suicidality (self-harm) in men with BPH who used finasteride or dutasteride.[392]

Studies in men taking finasteride for BPH[393] and AGA[394] have demonstrated reduced plasma neuroactive steroid levels during finasteride use. Several studies in men with PFS and control subjects have revealed significant changes in the levels of multiple neuroactive steroids in both plasma and CSF.[395,396,397] One of these studies demonstrated SSEP abnormalities indicative of a pudendal nerve neuropathy in 25% of PFS patients.[398]

The PFS Foundation recently submitted MedWatch reports to FDA for 8 men who took Propecia for AGA, developed depression, and committed suicide.[399,400,401,,402,403,404,405,406] None of the 8 cases reported pre-existing sexual dysfunction, psychiatric or medical conditions prior to use of Propecia. Extensive case documentation with medical records, medical examiner and autopsy reports, suicide notes and family narratives were submitted with the MedWatch reports. Seven of the eight men also reported persistent

[388] Melcangi (2017) *op. cit.*, pp. 229-235.
[389] Basaria *op. cit.*, pp. 4669-4680.
[390] Ibid.
[391] Di Loreto *op. cit.*, e1-e7.
[392] Welk *op. cit.*, pp. 683-691.
[393] Duskova (2009) *op. cit.*, pp. 222-230.
[394] Duskova (2010) *op. cit.*, pp. 95-102.
[395] Melcangi (2013) *op. cit.*, pp. 2598-2603
[396] Caruso *op. cit.*, pp. 74-9.
[397] Melcangi (2017) *op. cit.*, pp. 229-235.
[398] Ibid.
[399] MedWatch FDA Form 3500, PFSS#1 *op. cit.*
[400] MedWatch FDA Form 3500, PFSS#2 *op. cit.*
[401] MedWatch FDA Form 3500, PFSS#3 *op. cit.*
[402] MedWatch FDA Form 3500, PFSS#4 *op. cit.*
[403] MedWatch FDA Form 3500, PFSS#5 *op. cit.*
[404] MedWatch FDA Form 3500, PFSS#6 *op. cit.*
[405] MedWatch FDA Form 3500, PFSS#7 *op. cit.*
[406] MedWatch FDA Form 3500, PFSS#8 *op. cit.*

sexual dysfunction, and had discontinued finasteride therapy prior to committing suicide. The eighth man reported only depression and other psychoneurocognitive symptoms that developed with Propecia use. He committed suicide while still using Propecia.

- The seminiferous tubules in humans convert T to DHT at a 50-fold greater rate than interstitial cells[407] and DHT is the major product formed by spermatocytes in rats.[408]

Virtually all men with genetic 5αR2 deficiency are infertile although paternity has been achieved in rare cases with the employment of invasive infertility procedures[409,410] and naturally in one case of two siblings from Sweden with a male phenotype at birth and partially functional 5αR2 enzyme.[411] Testicular biopsies of 4 men with 5αR2 deficiency demonstrated abnormal spermatogenesis in 100% of these subjects, including in one man with a normal sperm count.[412] Men with 5αR2 deficiency have immature Sertoli cells which is a primary defect that does not allow normal spermatogenesis.[413,414]

Semen production study #056 demonstrated statistically significant decreases in ejaculate volume, total sperm per ejaculate and percent motile sperm with finasteride.[415]

Several case series report spermatogenic failure, infertility and poor seminal quality in men taking Propecia for AGA. While semen parameters improve with discontinuation of Propecia, many men continue to have abnormal semen parameters even after discontinuation of Propecia.[416] Reported spermatozoa abnormalities with the use of Propecia include azoospermia, oligospermia, abnormal sperm concentration and morphology, impaired meiosis, sperm damage, reduced progressive motility, elevated diploidy and sex chromosome disomy frequencies by TEM, and elevated DNA fragmentation index.[417,418,419,420,421,422]

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[407] Payne *op. cit.*, pp. 448-453.
[408] Dorrington *op. cit.*, pp. 897-899.
[409] Katz *op. cit.*, pp. 994-997.
[410] Kang H et al, *The first successful paternity through in vitro fertilization-intracytoplasmic sperm injection with a man homozygous for the 5α-reductase-2 gene mutation*, Fertil Steril (2011), Vol. 95(6), 2125.e5-e8.
[411] Nordenskjold *op. cit.*, pp. 3236-3238.
[412] Cai *op. cit.*, pp. 409-414.
[413] Steger *op. cit.*, pp. 136-143.
[414] Hadziselimovic *op. cit.*, pp. 1116-1120.
[415] Ko Medical Review *op. cit.*, page 87.
[416] Samplaski *op. cit.*, pp. 1542-1546.
[417] Glina *op. cit.*, pp. 203-205.
[418] Collodel *op. cit.*, pp. 229-233.
[419] Liu *op. cit.*, 849.e17-e19.
[420] Tu *op. cit.*, 2125.e13-14.
[421] Samplaski *op. cit.*, pp. 1542-1546
[422] Irwig (2014) *op. cit.*, pp.1361-1363.

12. Conclusion

Propecia is an unacceptably dangerous drug that can cause life-altering adverse drug reactions in individuals leading to severe permanent disability, and in rare cases death by suicide.

Weighing the potential serious risks against the limited benefits of Propecia should mandate its immediate removal from the market to protect the public health. The public health concerns regarding Propecia are especially problematic considering that Propecia is a cosmetic drug that does not treat a medical condition.

If patients and prescribing physicians realized that Propecia (i) is a potent antiandrogen with effects that have frequently been compared to castration, (ii) was developed to mimic a genetic mutation in pseudohermaphrodites with congenital urogenital defects and infertility, (iii) has been used to treat male-to-female transgenderism and prostate cancer, and (iv) can cause permanent loss of sexual function with depression and/or suicidality that persists after drug discontinuation, very few young men in their sexual and reproductive prime would assume those risks just to treat their hair loss.

The current labeling of Propecia is dangerously deficient. Not only are the warnings of serious side effects grossly inadequate, but several material disclosures are either false or misleading. Most disquieting is evidence suggesting that some of the false or misleading disclosures may have been made with fraudulent intent.

If a patient develops a sexual or psychoneurocognitive AE during Propecia treatment, there is no information in the Propecia product label that recommends discontinuation of the drug, or steps that should be taken to mitigate the risk that these side effects will eventually become persistent or permanent.

Finally, the Propecia product label needs to warn that the drug is contraindicated in men with sexual dysfunction or depression. Providing such a contraindication to use in the Propecia product label could prevent persistent sexual and psychoneurocognitive AEs in some patients, but it would do nothing to prevent healthy men from developing PFS.

C. ENVIRONMENTAL IMPACT STATEMENT

We claim categorical exclusion under 21 C.F.R §25.31(a) from the environmental assessment requirement. An assessment is not required because the requested action would not increase the use of the active moiety that is the subject of this petition.

D. ECONOMIC IMPACT

Will be submitted upon request.

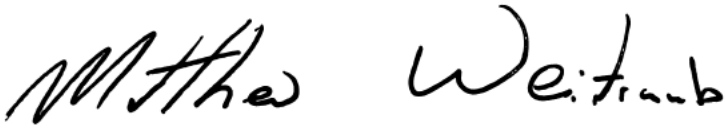
E. CERTIFICATION

I certify that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Sincerely,

John Santmann, M.D.
Chief Executive Officer
Post-Finasteride Syndrome Foundation

Rosemary McGeady, M.D., J.D.
General Counsel
Post-Finasteride Syndrome Foundation



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