Persistent Sexual and Nonsexual Adverse Effects of Finasteride in Younger Men

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ABSTRACT

Introduction. Recent studies have reported persistent sexual and nonsexual adverse effects associated with the 5α-reductase inhibitor finasteride.

Aims. The first aim was to review the clinical studies of persistent sexual and nonsexual adverse effects associated with finasteride in younger men who took the medication for treatment of male pattern hair loss. The second aim was to place these findings into context with what is known from basic and clinical studies about the hormones and neurosteroids affected by finasteride.

Methods. Relevant published literature on the topic was reviewed. Clinical symptomatology in humans was correlated with findings from rodent models to investigate possible underlying mechanisms.

Main Outcome Measures. Persistent sexual and nonsexual adverse effects were summarized.

Results. Two clinical studies have described persistent side effects associated with finasteride use in otherwise healthy younger men. The sexual side effects are typically present in multiple domains that include erectile dysfunction, low libido, and decreased orgasms. Erectile dysfunction may be related to low levels of dihydrotestosterone, which has been shown to be an important androgen in both human and animal studies. Nonsexual side effects include depression and decreased alcohol consumption that are linked to the neurosteroid allopregnanolone in both human and animal studies. Three men with persistent side effects associated with finasteride were found to have lower plasma and cerebrospinal fluid levels of several neurosteroids.

Conclusions. Persistent adverse effects of finasteride in younger men include erectile dysfunction, low libido, lack of orgasms, depression, and decreased alcohol consumption. One study has found lower levels of several neurosteroids in this population. Out of the various persistent side effects, erectile dysfunction and decreased alcohol consumption have been the most studied in animal models. Further research is needed on who is susceptible to the persistent adverse side effects of finasteride and on the underlying mechanisms of the medication. **Irwig MS. Persistent sexual and non-sexual adverse effects of finasteride in younger men. Sex Med Rev 2014;2:24–35.**

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

Introduction

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

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

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

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

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

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

First Studies

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

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

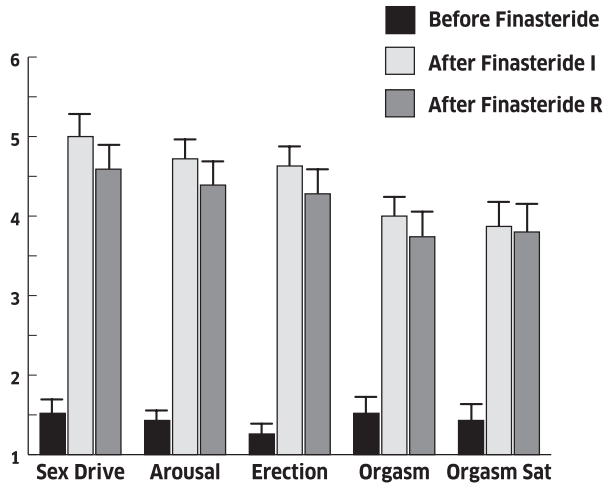

Figure 1 The mean ASEX sexual dysfunction scores (with 95% confidence intervals) fell between 1 (extremely strong/easily/satisfying) and 6 (absent/never). Differences in ASEX variables before finasteride, after finasteride at the interview (I) and after finasteride at reassessment (R) were compared using two tailed paired t-tests. As compared to before finasteride, all five scores at the reassessment were statistically significant with a $P < 0.0001$. Orgasm Sat = orgasm satisfaction. (Adapted from Irwig [66].)

(± standard deviation) were 7.2 ± 2.0 before finasteride, 22.2 ± 2.6 after finasteride at the time of the interview, and 20.8 ± 3.6 at reassessment. Figure 1 shows the mean scores for individual domains before and after finasteride use. Among the former users of finasteride in this study, sexual dysfunction was almost always present in multiple domains: 94% had low libido, 92% had erectile dysfunction, 92% had decreased arousal, and 69% had orgasm problems. In addition to worsening sexual function, subjects reported a dramatic decline in their all-inclusive sexual frequency (including masturbation) from 25.8 episodes per month before finasteride use to 8.8 episodes after finasteride cessation. The minimum duration of the persistent sexual side effects was 3 months with a mean duration of 40 months. The limitations to this study include selection bias, as many subjects were recruited from an Internet forum called Propeciahelp.com, as well as recall bias as subjects had to retrospectively estimate their baseline sexual function prior to starting finasteride.

Finasteride Background

Finasteride is a synthetic steroid that acts as alternative substrate for the 5α-reductase enzymes. 5α-reductase irreversibly reduces the double bond at the 4,5 position in specific androgens, progestins, and glucocorticoids via a nicotinamide adenine dinucleotide phosphate (NADPH) mechanism. Specifically, testosterone is converted into dihydrotestosterone (DHT), progesterone into dihydroprogesterone, and deoxycorticosterone into dihydrodeoxycorticosterone. These hormones then are further metabolized in a reversible reaction by 3α-hydroxysteroid dehydrogenase to 3α-androstanediol, allopregnanolone (ALLO; also known as 3α,5α-tetrahydroprogesterone), and tetrahydrodeoxycorticosterone (THDOC). In adult men treated with finasteride 5 mg daily for 4 months, lower plasma levels of many 5α-reduced steroids were observed, including DHT, ALLO, androsterone, and epiandrosterone [12].

Hulin-Curtis and colleagues have reviewed the metabolism and pharmacogenetics of finasteride [13]. Finasteride is initially metabolized through hydroxylation and oxidation via the cytochrome P450 enzymes. The second phase of metabolism consists of glucuronidation. Finasteride is a lipophilic compound that is able to cross the blood-brain barrier. It is excreted primarily through the gastrointestinal tract and less so through the kidneys.

Thus far three isoforms of 5α-reductase have been described. In humans, Type I is present in the brain, liver, muscle, and skin. Type II is present in epididymis, hair follicles, liver, prostate, and seminal vesicles. Type III was described relatively recently with a distribution in human males in the brain, heart, lung, pancreas, colon, stomach, liver, muscle, prostate, and testicle [14]. Andersson and Russell compared the structure of human and rat 5α-reductases [15]. They found that the human protein contained 259 amino acids and was homologous to the rat protein in only 60% of the amino acid sequence. The enzymes that bind to finasteride have been found to have significant genetic variation that may account for the different affinities for the substrate. For example, SRD5A2, which encodes 5α-reductase type 2, has missense substitutions with at least eight described single-point variants, three compound heterozygotes, and three haplotypes that show different Michaelis constants for testosterone and NADPH, different maximum rates of reaction, and different inhibition constants for finasteride.

In the central nervous system (CNS) of adult male mice, messenger RNA (mRNA) of 5α-reductase type 1 is expressed in neurons but not in glial cells using mRNA in situ hybridization [16]. The specific regions of brain were the amygdala,

cerebellum, cortex, hippocampus, olfactory bulb, striatum, and thalamus. In the adult rat brain, immunohistochemical studies have shown that 5α-reductase type 2 is present in most regions, with the highest presence in the prefrontal and somatosensory cortex, olfactory bulb, thalamus, hippocampus, amygdala, and cerebellum. Lower levels were present in the midbrain and hypothalamus. Using double immunofluorescence labeling, the authors found that 5α-reductase type 2 localized in the neurons but not the glia [17].

Neurosteroids

Finasteride alters the concentrations of several neurosteroids, a term that refers to steroids that are locally synthesized in the brain or are metabolized in the brain from steroids produced within the gonads or adrenal glands. In general, neurosteroid concentrations are higher in brain tissue than in plasma and cerebrospinal fluid (CSF) [18]. In male rats, plasma levels of most neurosteroids correlated with their levels in the CSF. The plasma levels of the following neurosteroids correlated with their corresponding levels in most CNS structures studied: dihydroprogesterone, ALLO, testosterone, DHT, and 3α-androstanediol [18]. As the authors acknowledge, the measurements of neurosteroids do not provide the full picture as they are rapidly interconverted in the brain tissue.

Neurosteroids have been found to play a wide variety of roles in neurogenesis, neuroprotection, plasticity, and synaptic formation and function. In the brain, γ aminobutyric acid (GABA) is the major inhibitory neurotransmitter. Two important neurosteroids are ALLO and THDOC that are modulators of the GABA receptor [19]. Using a model of the hippocampus in mice, Ge and colleagues have described the process of synaptic integration of new granule cells in the dentate gyrus [20]. Depending on the developmental stage of the mice, GABA signaling by neurosteroids underlies how new synapses are formed. The sensitivity of the $GABA_A$ receptor to ALLO can be altered by withdrawal of neurosteroids, chronic steroid administration, age, stress, and social isolation [21].

Charalampopoulos and colleagues have reviewed the effects of neurosteroids on neuronal survival and neurogenesis [22]. In one of their own experiments, they describe the signaling pathway in which ALLO activates the prosurvival transcription factors cAMP response element-binding protein and nuclear factor kappa B that control the transcription of antiapoptotic Bcl-2 and Bcl-xL genes [23]. Another relevant neurosteroid linked to neurogenesis is DHT. In castrated male rats, injections of DHT for 30 days led to increased cell survival in the dentate gyrus of the hippocampus [24].

5α Reductase, Finasteride, and Neurosteroids

A small ground-breaking human study looked at plasma and CSF levels of neurosteroids in three men with persistent symptoms associated with finasteride use [25]. In addition to the sexual symptoms, the men suffered from anxious/depressive symptomatology, chronic fatigue, and muscle ache and tension. As compared with a control group of five subjects, those with persistent symptoms had lower CSF levels of ALLO, isopregnanolone, and DHT, and higher levels of testosterone and estradiol. The neurosteroids were measured by liquid chromatography-tandem mass spectrometry.

In male mice, finasteride has been found to alter neuronal plasticity on a structural level [26]. Specifically, there were fewer newborn cells and young neurons in the adult hippocampus region of finasteride-treated mice. By lowering brain levels of DHT (and possibly other neurosteriods), finasteride decreases the rate of neurogenesis and the proliferation of neural precursor cells.

In a mouse model of Niemann-Pick type C disease, neurosteroids were found to play an important role in neuroprotection and in the longevity of the animals. Shortly after birth, mice with Niemann-Pick type C disease experience a progressive reduction in 5α reductase activity over 10 weeks [27]. Consequently, the brains of these mice have lower levels of neurosteroids such as dihydroprogesterone and ALLO. When mice with Niemann-Pick type C disease were administered ALLO from post-natal days 21–23, their mean lifespan significantly increased from 67 to 80 days. As compared with mice that received an inactive ALLO homolog, the administration of ALLO markedly increased the survival of Purkinje cells in the cerebellum. This survival was blocked with bicuculline an antagonist of the $GABA_A$ receptor. This implies that the effects of ALLO are at least partially mediated by the $GABA_A$ receptor.

Progesterone and its metabolites are neurosteroids that also play an important role in myelination. Consequently, blocking the production of the metabolites of progesterone has been

found to have an adverse effect on the myelination process. Using cultured cerebellum slices from 7-day-old rats, a 5α-reductase inhibitor partially inhibited myelination as measured by myelin basic protein immunostaining [28]. The inhibitory effect of the 5α-reductase inhibitor was reversed by administering ALLO, demonstrating the important role of this progesterone metabolite.

Erectile Dysfunction

Out of the various persistent sexual side effects associated with finasteride, erectile dysfunction has been the best studied thus far. The most likely culprit is DHT, which that has been shown to play an important role in the erectile function of both humans and rodents.

Long before the development of finasteride, a different 5α-reductase inhibitor was shown to be harmful in the erectile function of male rats [29]. Using castrated animals, erection frequency was higher in the group treated with a combination of DHT, T, and a 5α-reductase inhibitor than the groups treated with testosterone only or testosterone plus a 5α-reductase inhibitor. A second study showed that erectile response to electric field stimulation of the cavernosal nerve was higher in castrated rats treated with DHT and finasteride as compared with T and finasteride [30]. A third study demonstrated that DHT treatment markedly improved erectile function in rats that had been castrated and adrenalectomized [31]. These studies point to an important physiological role for DHT in erectile function.

In older rats, there are age-related declines in both erectile function and in serum testosterone concentrations. To determine the role of androgens in erectile function in older rats (20 months old), the animals were treated with either testosterone or DHT for 45 days via Silastic tubing [32]. As compared with control groups of younger rats (5 months old) and untreated older rats, older rats in both the testosterone and DHT treatment groups showed restoration of erectile response as measured by intracavernosal pressure with electrical field stimulation of the cavernosal nerve. This demonstrates the important role of DHT in erectile function as DHT cannot be converted into testosterone. This study found no differences in nitric oxide levels or activity between the treated and untreated older rats.

Using a 5α-reductase inhibitor, Pinsky and colleagues found that dutasteride had detrimental effects on erectile function in rats [33]. In one experiment, rats treated with dutasteride had a decrease in vivo erectile response with cavernosal nerve stimulation. A second experiment used strips of smooth muscle from the corpora cavernosa in tissue baths to demonstrate changes in contraction and relaxation. The dutasteride-treated group exhibited less relaxation when subjected to electrical stimulation and acetylcholine. A third experiment used immunohistochemistry to show increased collagen deposition, decreased staining intensity of neuronal nitric oxide synthase, and intense staining of inducible nitric oxide synthase in the dutasteride group (Figure 2).

A second research group using finasteride also confirmed worsening erectile function and histological changes in male rats treated with a 5α-reductase inhibitor. The weights of the corpora cavernosa were 26% and 22% lower in younger and older finasteride-treated rats, respectively, as compared with controls [34,35]. In addition, the smooth muscle cells of finasteride-treated rats showed fewer autophagosomes as shown by transmission electron microscopy, increased apoptosis, decreased smooth muscle, increased collagen deposition, and decreased endothelial nitric oxide synthase. Another study involving castrated male rats found that nitric oxide activity was significantly higher in the T- and DHT-treated groups as compared with the T plus finasteride group [30].

To study persistent erectile dysfunction in a rat model using a 5α-reductase inhibitor, Oztekin and colleagues compared a control group with a group on treatment with dutasteride for 8 weeks and a group on treatment with dutasteride for 6 weeks followed by a 2-week washout period [36]. They found that certain parameters of decreased erectile function persisted after the washout period. First, there was decreased in vivo erectile activity as measured by intracavernosal pressure/mean arterial pressure and decreased total intracavernosal pressure. Second, there was decreased relaxation of smooth muscle after acetylcholine. There were no changes to relaxation of smooth muscle after electrical field stimulation or sodium nitroprusside.

To complement the animal studies, two human studies demonstrated that treatment with DHT resulted in clinical improvement in erectile function. The first was an RCT of men aged 50–70 with ≤1 nocturnal penile tumescence per week, an andropause symptom, and a total testosterone ≤15 nmol/L [37]. As compared with the placebo

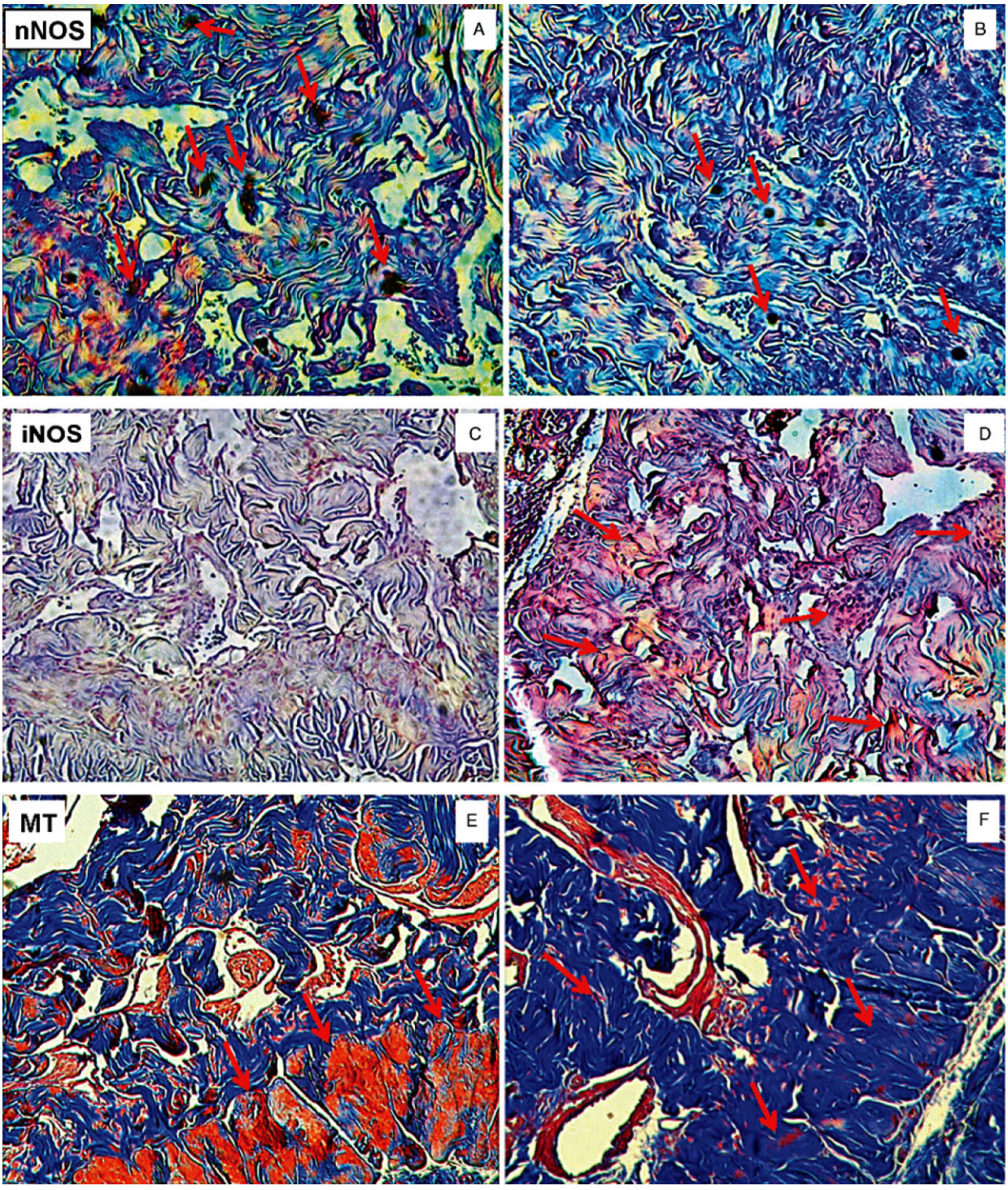

Figure 2 Immunohistochemical localization of nNOS and iNOS in rat penis (40× magnification). (A and B): nNOS staining (dark brown) with decreased localization to the nerves of the corpus cavernosal smooth muscle from control (A) to treatment (B) groups. (C and D): iNOS staining (dark brown) enhanced in the corpus cavernosal smooth muscle from the treatment group. The negative control section processed without antibodies did not stain (data not shown). (E and F): Masson's trichrome (MT) staining results. MT staining is presented as ratio of smooth muscle : collagen in a percentage (mean ± standard deviation), which is markedly different between control (E) and treatment (F) groups. Quantitative analysis of collagen, and smooth muscle content in cavernosal tissue was performed with an image analyzer. nNOS = neuronal nitric oxide synthase; iNOS = inducible nitric oxide synthase. (Adapted from Pinsky et al. [33].)

group, men treated with topical DHT for 6 months showed improvement in ability to maintain erection during intercourse. The second study enrolled elderly men with total testosterone concentrations <10 nmol/L. In this study, treatment with DHT increased the number of erections and maximum rigidity to levels similar to those of older men with testosterone concentrations >10 nmol/L [38].

Low Libido and Decreased Orgasms

As compared with erectile function, low libido is much more difficult to study, especially in humans. Whereas erectile function and frequency can be objectively measured, assessment of libido in humans relies more heavily upon subjective data. Pfaus has reviewed the complexities of the brain systems and pathways involved in sexual excitation and inhibition [39]. A central player in excitation is the neurotransmitter dopamine. One dopaminergic system is the diencephalic with terminals in the medical preoptic area of the hypothalamus. A second dopaminergic system is the mesolimbic/mesocortical with projections to the nucleus accumbens, amygdala, and frontal cortex. A third dopaminergic system is the nigrostriatal with cell bodies in the substantia nigra and terminals in the striatum. Another excitatory neurotransmitter is norepinephrine in which the cell bodies arise in the locus ceruleus and project to a wide variety of areas including the hypothalamus, cerebellum, cortex, and limbic systems. Furthermore, other excitatory systems involve melanocortins and oxytocin that both arise in the hypothalamus and project to different areas of the hypothalamus, as well as the limbic forebrain regions and posterior pituitary. On the other side, inhibitory mechanisms of sexual desire and arousal include serotonin, opioids, and endocannabanoids.

Although the mechanisms between finasteride and low libido and orgasm problems are less clear than that of erectile function, 5α-reductase is present in many of the important brain regions linked to sexual desire. It is plausible to hypothesize that the reduction in neurosteroid levels has a negative effect on sexual desire because of a loss of normal neuroprotection and changes in plasticity based on several animal studies [26,27]. In a fascinating study using intracerebral microdialysis in freely moving rats, infusion of ALLO increased extracellular concentrations of dopamine in the nucleus accumbens, a region important to sexual desire [40].

Depression

Although Irwig's original case series set out to examine persistent sexual side effects associated with finasteride, it became apparent during the interviews that many of the subjects had developed depressive symptomatology, as well. In order to formally study these symptoms using a validated instrument, Irwig recruited 61 subjects to self-administer the Beck Depression Inventory II (BDI-II) [41,42]. To serve as a control group were 29 men with male pattern hair loss but no history of finasteride use and no history of psychiatric diagnoses or medication use. The prevalence of depressive symptoms, as defined by a score of ≥14 on the BDI-II, was 75% in the finasteride group as compared with 10% in the control group ($P < 0.0001$). Furthermore, rates of moderate or severe depressive symptoms, as defined by a score of ≥20 on the BDI-II, were 64% in the finasteride group vs. 0% in the control group. Finally, suicidal thoughts were expressed by 44% of the finasteride group and 3% of the control group ($P < 0.0001$). Among the 27 former finasteride users with suicidal thoughts, three chose the statement "I would like to kill myself." The author is aware of several cases of suicide in younger men who have taken and developed persistent side effects associated with finasteride.

Prior to this case series, there were two human studies that examined the relationship between finasteride use and depression. One was a retrospective study of 23 men and women treated with finasteride in whom 19 developed depression that resolved after medication discontinuation [43]. In an attempt to determine causality, two of these 19 subjects were rechallenged with finasteride, and both redeveloped depression within 2 weeks. The second study measured scores on the BDI before and during finasteride treatment in 128 men with male pattern hair loss [44]. In this uncontrolled study, mean scores were significantly higher after having been on finasteride treatment for 2 months.

Depression has been associated with lower concentrations of neurosteroids in humans. Using CSF, researchers found lower levels of ALLO in depressed adults as compared with nondepressed controls [45]. Likewise, serum ALLO concentrations were lower in patients during a severe major depressive episode as compared with when fully recovered [46]. One study even found lower concentrations of serum GABAergic neurosteroids in women in remission for several years from previous depression [47].

To complement the human studies, finasteride has also been linked to depression in rodents. One behavioral method to assess depression in rodents is the forced swim test in which the animal is placed into a cylinder containing water. The time spent immobile, as opposed to swimming, is considered depressive behavior. As compared with female rats that were administered vehicle, rats that received either subcutaneous finasteride or an intrahippocampal implant of finasteride both showed increased durations of immobility in the forced swim test [48]. A similar study found that finasteride increased depressive behavior in pregnant rats administered the forced swim test [49]. These rats were shown to have lower levels of ALLO in both the plasma and hippocampus as compared with a control group. A third study by the same research group found that female rats that received finasteride in the amygdala also had increased depressive behavior as measured by the forced swim test [50].

Decrease in Alcohol Consumption

In addition to assessing sexual function before and after finasteride use, Irwig's case series also collected data on the number of alcoholic beverages consumed prior to starting finasteride and after discontinuing finasteride [51]. At baseline, 63 out of 83 subjects consumed at least one alcoholic drink/week. Among this group, 65% noted a decrease in alcohol consumption before and after finasteride use. The mean (±standard error) number of drinks consumed per week dropped from 5.2 ± 0.7 to 2.0 ± 0.3 ($P < 0.0001$). The largest decline was observed among the eight subjects who consumed at least 10 drinks/week prior to finasteride. Equally noteworthy, 18 out of 63 men reported quitting drinking entirely as a result of the effects that alcohol had on their mental functions. These subjects described that after finasteride, they had a lowered tolerance for alcohol as well as decreased euphoria.

In a placebo-controlled RCT of healthy human social drinkers homozygous for the A-allele of $GABA_A$ receptor α-2 subunit, pretreatment with finasteride (two doses of 100 mg) resulted in changes in the subjective response to three alcoholic drinks [52]. Finasteride reduced the number of stimulant effects of alcohol and numbing effects of alcohol. Likewise, finasteride pretreatment in male mice led the animals to drink less ethanol, which varied during the treatment and withdrawal phases [53–55].

The effects of finasteride on alcohol appear to be modulated by ALLO. Different doses of ALLO have been shown to influence the intake patterns of alcohol in male mice and rats [56,57]. Acute alcohol intoxication in humans results in increased levels of plasma ALLO [58]. In rats, a similar phenomenon is observed, whereby ethanol increases the levels of ALLO and THDOC in the plasma, cortex, and hippocampus [59]. In male rats, pretreatment with finasteride decreased the levels of ALLO in the cerebral cortex [60]. This study also looked at the electrophysiological actions of ethanol and found that finasteride pretreatment prevented the ethanol-induced inhibition of spontaneous firing rates in neurons of the medial septum/diagonal band of Broca. Finasteride was also shown to inhibit the effects of alcohol by decreasing the amplitude of miniature inhibitory post-synaptic currents in rat hippocampus [61]. On a cellular level, one area that finasteride affects is the pyramidal neurons of the CA1 region of the hippocampus in rats [62]. After administration of alcohol, finasteride blocked the staining of ALLO in this region. This same group found that finasteride treatment to rat hippocampal slices altered the effects of ethanol on a form of synaptic plasticity known as long-term potentiation [63].

Medication Warnings

Some might wonder why it has taken over 10 years since the approval of Propecia for the persistence of sexual and other side effects to be reported in the medical literature. One major factor is the incidence of the persistent side effects that is probably quite low, likely to be less than 1%. Because only a few thousand patients were studied in the RCTs of finasteride for male pattern hair loss, these studies were not adequately powered to detect an uncommon or rare adverse effect. For this reason, post-marketing studies are critically important to identify less common adverse effects. It stands to follow that a medication's complete safety profile is not fully established until it has been on the market for several years and until a large enough population has been exposed. Another well-described factor is the underreporting of adverse effects of medications. In a systematic review of 45 studies, reasons noted for not reporting adverse medication events included ignorance, diffidence, lack of interest or time, indifference, insecurity about being incorrect, and complacency [64].

Although the most plausible adverse effects of finasteride would be sexual in nature because of

lower concentrations of the potent androgen DHT, most of the RCTs of the 5α-reductase inhibitor did not use a validated instrument to assess sexual function before and during treatment with the medication. Reliance of self-reporting and yes/no questions to ascertain adverse events creates limitations to studying safety as these studies likely would not detect minor or mild decreases in sexual function.

Based on the published post-marketing reports of persistent sexual side effects associated with finasteride, as well as the significant media coverage of the topic, the U.S. Food and Drug Administration (FDA) conducted an investigation that included several hundred adverse effect reports in its database. In 2012, the FDA mandated changes to the product labeling of finasteride (Propecia and Proscar®) to broaden the list of persistent sexual side effects [65]. Of note, depression was added to the product labeling of Propecia in the United States in 2010.

Future Avenues for Research

Unraveling the mechanisms behind the persistent sexual and nonsexual effects of finasteride in humans will be quite challenging for two obvious reasons. First, finasteride alters the levels of multiple hormones and neurosteroids, making it difficult to tease apart the individual roles of a particular hormone or neurosteroid. Second, studying the inner workings of the brains of live humans will be difficult because of anatomic constraints and risks.

One of the most intriguing aspects of this field is the persistent nature of the adverse effects. A pressing question for men suffering from the persistent adverse effects is whether the effects will ever go away. Irwig prospectively followed 54 men with persistent sexual side effects who were reassessed after a mean of 14 months after completing the first study [66]. According to the Arizona Sexual Experience Scale, 89% of subjects continued to fulfill the criteria for sexual dysfunction. The changes in scores of sexual function were not related to the length of finasteride use or the duration of the persistent sexual side effects.

In addition to the rat model described in the erectile dysfunction section, finasteride treatment for 30 days resulted in persistent changes in prostate morphology in the epithelial and stromal compartments of male gerbils of different ages [67]. Similar to the studies of corpora cavernosa in rats, there was an increased amount of collagen among the smooth muscle cells in the gerbil study. Although the mechanism underlying the persistence of tardive dyskinesias associated with the phenothiazines has still yet to be definitively solved, one study has implicated the neurosteroid ALLO [68]. Perhaps finasteride and the phenothiazines will share a common pathway for some their neurotoxicities.

In addition to further elucidating the mechanisms of the adverse effects, another important avenue for research pertains to who is susceptible to the persistent side effects of finasteride. Presumably, genetics would determine an individual's risk for a particular side effect. Ideally, a genetic test would be developed in which a potential user of a 5α-reductase inhibitor could be informed of whether he would be at risk before making the decision on whether to use the medication.

While calculating the incidence of persistent adverse effects of finasteride would be helpful, this question is less important clinically as an individual contemplating the use of the medication cannot predict if he will be unlucky. In addition, a study to ascertain the incidence would need to enroll thousands of men who would need to be followed for several years as many subjects only developed persistent effects after having been on the medication for years at a time. Such a study realistically is unlikely to be funded due to the high cost.

Conclusion

Persistent adverse effects of finasteride in younger men include erectile dysfunction, low libido, lack of orgasms, depression, and decreased alcohol consumption. One study has found lower levels of several neurosteroids (ALLO, DHT, and isopregnanolone) in the CSF of this population. Out of the various persistent side effects, erectile dysfunction and decreased alcohol consumption have been the most extensively studied in animal models. Further research is needed on who is susceptible to the persistent adverse side effects of finasteride and on the underlying mechanisms of the medication. Although there are still many unanswered questions, the basic and clinical studies published thus far will provide a solid foundation upon which to make further research discoveries.

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References

1 Lowe FC, McConnell JD, Hudson PB, Romas NA, Boake R, Lieber M, Elhilali M, Geller J, Imperto-McGinely J, Andriole GL, Bruskewitz RC, Walsh PC, Bartsch G, Nacey JN, Shah S, Pappas F, Ko A, Cook T, Stoner E, Waldstreicher J; Finasteride Study Group. Long-term 6-year experience with finasteride in patients with benign prostatic hyperplasia. Urology 2003;61:791–6.

2 Nickel JC, Fradet Y, Boake RC, Pommerville PJ, Perreault JP, Afridi SK, Elhilali MM. Efficacy and safety of finasteride therapy for benign prostatic hyperplasia: Results of a 2-year randomized controlled trial (the PROSPECT study). PROscar Safety Plus Efficacy Canadian two year study. CMAJ 1996;155:1251–9.

3 Wessells H, Roy J, Bannow J, Grayhack J, Matsumoto AM, Tenover L, Herlihy R, Fitch W, Labasky R, Auerbach S, Parra R, Rajfer J, Culbertson J, Lee M, Bach MA, Waldstreicher J; PLESS Study Group. Incidence and severity of sexual adverse experiences in finasteride and placebo-treated men with benign prostatic hyperplasia. Urology 2003;61:579–84.

4 Olsen EA, Hordinsky M, Whiting D, Stough D, Hobbs S, Ellis ML, Wilson T, Rittmaster RS. The importance of dual 5alpha-reductase inhibition in the treatment of male pattern hair loss: Results of a randomized placebo-controlled study of dutasteride versus finasteride. J Am Acad Dermatol 2006; 55:1014–23.

5 Medicines and Healthcare products Regulatory Agency. Public Assessment Report Decentralised Procedure. Finasteride 1 mg film-coated tablets. 2009. Available at: http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con054522.pdf (accessed November 16, 2013).

6 Traish AM, Hassani J, Guay AT, Zitzmann M, Hansen ML. 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;8:872–84.

7 Irwig MS, Kolukula S. Persistent sexual side effects of finasteride for male pattern hair loss. J Sex Med 2011;8:1747–53.

8 Hunter R, Earl CJ, Thornicroft S. Apparently irreversible syndrome of abnormal movements following phenothiazine medication. Proc R Soc Med 1964;57:758–62.

9 Whiting DA, Olsen EA, Savin R, Halper L, Rodgers A, Wang L, Hustad C, Palmisano J; Male Pattern Hair Loss Study Group. Efficacy and tolerability of finasteride 1 mg in men aged 41 to 60 years with male pattern hair loss. Eur J Dermatol 2003;13:150–60.

10 McGahuey CA, Gelenberg AJ, Laukes CA, Moreno FA, Delgado PL, McKnight KM, Manber R. The Arizona Sexual Experience Scale (ASEX): Reliability and validity. J Sex Marital Ther 2000;26:25–40.

11 DeRogatis LR. Assessment of sexual function/dysfunction via patient reported outcomes. Int J Impot Res 2008;20:35–44.

12 Duskova M, Hill M, Hanus M, Matousková M, Stárka L. Finasteride treatment and neuroactive steroid formation. Prague Med Rep 2009;110:222–30.

13 Hulin-Curtis SL, Petit D, Figg WD, Hsing AW, Reichardt JK. Finasteride metabolism and pharmacogenetics: New approaches to personalized prevention of prostate cancer. Future Oncol 2010;6:1897–913.

14 Yamana K, Labrie F, Luu-The V. 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;2:293–9.

15 Andersson S, Russell DW. Structural and biochemical properties of cloned and expressed human and rat steroid 5 alpha-reductases. Proc Natl Acad Sci U S A 1990;87:3640–4.

16 Agís-Balboa RC, Pinna G, Zhubi A, Maloku E, Veldic M, Costa E, Guidotti A. Characterization of brain neurons that express enzymes mediating neurosteroid biosynthesis. Proc Natl Acad Sci U S A 2006;103:14602–7.

17 Castelli MP, Casti A, Casu A, Frau R, Bortolato M, Spiga S, Ennas MG. Regional distribution of 5α-reductase type 2 in the adult rat brain: An immunohistochemical analysis. Psychoneuroendocrinology 2013;38:281–93.

18 Caruso D, Pesaresi M, Abbiati F, Calabrese D, Giatti S, Garcia-Segura LM, Melcangi RC. Comparison of plasma and cerebrospinal fluid levels of neuroactive steroids with their brain, spinal cord and peripheral nerve levels in male and female rats. Psychoneuroendocrinology 2013;38:2278–90.

19 Majewska MD, Harrison NL, Schwartz RD, Barker JL, Paul SM. Steroid hormone metabolites are barbiturate-like modulators of the GABA receptor. Science 1986;232:1004–7.

20 Ge S, Sailor KA, Ming GL, Song H. Synaptic integration and plasticity of new neurons in the adult hippocampus. J Physiol 2008;586:3759–65.

21 Mellon SH. Neurosteroid regulation of central nervous system development. Pharmacol Ther 2007;116:107–24.

22 Charalampopoulos I, Remboutsika E, Margioris AN, Gravanis A. Neurosteroids as modulators of neurogenesis and neuronal survival. Trends Endocrinol Metab 2008;19:300–7.

23 Charalampopoulos I, Tsatsanis C, Dermitzaki E, Alexaki VI, Castanas E, Margioris AN, Gravanis A. Dehydroepiandrosterone and allopregnanolone protect sympathoadrenal medulla cells against apoptosis via antiapoptotic Bcl-2 proteins. Proc Natl Acad Sci U S A 2004;101:8209–14.

24 Spritzer MD, Galea LA. Testosterone and dihydrotestosterone, but not estradiol, enhance survival of new hippocampal neurons in adult male rats. Dev Neurobiol 2007; 67:1321–33.

25 Melcangi RC, Caruso D, Abbiati F, Giatti S, Calabrese D, Piazza F, Cavaletti G. Neuroactive steroid levels are modified in cerebrospinal fluid and plasma of post-finasteride patients showing persistent sexual side effects and anxious/depressive symptomatology. J Sex Med 2013;10:2598–603.

26 Römer B, Pfeiffer N, Lewicka S, Ben-Abdallah N, Vogt MA, Deuschle M, Vollmayr B, Gass P. Finasteride treatment inhibits adult hippocampal neurogenesis in male mice. Pharmacopsychiatry 2010;43:174–8.

27 Griffin LD, Gong W, Verot L, Mellon SH. Niemann-Pick type C disease involves disrupted neurosteroidogenesis and responds to allopregnanolone. Nat Med 2004;10:704–11.
28 Ghoumari AM, Ibanez C, El-Etr M, Leclerc P, Eychenne B, O'Malley BW, Baulieu EE, Schumacher M. Progesterone and its metabolites increase myelin basic protein expression in organotypic slice cultures of rat cerebellum. J Neurochem 2003;86:848–59.
29 Bradshaw WG, Baum MJ, Awh CC. Attenuation by a 5 alpha-reductase inhibitor of the activational effect of testosterone propionate on penile erections in castrated male rats. Endocrinology 1981;109:1047–51.
30 Lugg JA, Rajfer J, González-Cadavid NF. Dihydrotestosterone is the active androgen in the maintenance of nitric oxide-mediated penile erection in the rat. Endocrinology 1995;136:1495–501.
31 Penson DF, Ng C, Rajfer J, Gonzalez-Cadavid NF. Adrenal control of erectile function and nitric oxide synthase in the rat penis. Endocrinology 1997;138:3925–32.
32 Garban H, Marquez D, Cai L, Rajfer J, Gonzalez-Cadavid NF. Restoration of normal adult penile erectile response in aged rats by long-term treatment with androgens. Biol Reprod 1995;53:1365–72.
33 Pinsky MR, Gur S, Tracey AJ, Harbin A, Hellstrom WJ. The effects of chronic 5-alpha-reductase inhibitor (dutasteride) treatment on rat erectile function. J Sex Med 2011;8:3066–74.
34 Zhang MG, Wu W, Zhang CM, Wang XJ, Gao PJ, Lu YL, Shen ZJ. Effects of oral finasteride on erectile function in a rat model. J Sex Med 2012;9:1328–36.
35 Zhang MG, Wang XJ, Shen ZJ, Gao PJ. 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;82:743.e9–743.
36 Oztekin CV, Gur S, Abdulkadir NA, Lokman U, Akdemir AÖ, Cetinkaya M, Hellstrom WJ. Incomplete recovery of erectile function in rat after discontinuation of dual 5-alpha reductase inhibitor therapy. J Sex Med 2012;9:1773–81.
37 Kunelius P, Lukkarinen O, Hannuksela ML, Itkonen O, Tapanainen JS. The effects of transdermal dihydrotestosterone in the aging male: A prospective, randomized, double blind study. J Clin Endocrinol Metab 2002;87:1467–72.
38 Foresta C, Caretta N, Garolla A, Rossato M. Erectile function in elderly: Role of androgens. J Endocrinol Invest 2003;26:77–81.
39 Pfaus JG. Pathways of sexual desire. J Sex Med 2009;6:1506–33.
40 Rougé-Pont F, Mayo W, Marinelli M, Gingras M, Le Moal M, Piazza PV. The neurosteroid allopregnanolone increases dopamine release and dopaminergic response to morphine in the rat nucleus accumbens. Eur J Neurosci 2002;16:169–73.
41 Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory II. San Antonio, TX: Pearson; 1996.
42 Irwig MS. Depressive symptoms and suicidal thoughts among former users of finasteride with persistent sexual side effects. J Clin Psychiatry 2012;73:1220–3.
43 Altomare G, Capella GL. Depression circumstantially related to the administration of finasteride for androgenetic alopecia. J Dermatol 2002;29:665–9.
44 Rahimi-Ardabili B, Pourandarjani R, Habibollahi P, Mualeki A. Finasteride induced depression: A prospective study. BMC Clin Pharmacol 2006;6:7.
45 Uzunova V, Sheline Y, Davis JM, Rasmusson A, Uzunov DP, Costa E, Guidotti A. Increase in the cerebrospinal fluid content of neurosteroids in patients with unipolar major depression who are receiving fluoxetine or fluvoxamine. Proc Natl Acad Sci U S A 1998;95:3239–44.
46 Romeo E, Ströhle A, Spalletta G, di Michele F, Hermann B, Holsboer F, Pasini A, Rupprecht R. Effects of antidepressant treatment on neuroactive steroids in major depression. Am J Psychiatry 1998;155:910–3.
47 Girdler SS, Lindgren M, Porcu P, Rubinow DR, Johnson JL, Morrow AL. A history of depression in women is associated with an altered GABAergic neuroactive steroid profile. Psychoneuroendocrinology 2012;37:543–53.
48 Frye CA, Walf AA. Changes in progesterone metabolites in the hippocampus can modulate open field and forced swim test behavior of proestrous rats. Horm Behav 2002;41:306–15.
49 Frye CA, Walf AA. Hippocampal 3alpha, 5alpha-THP may alter depressive behavior of pregnant and lactating rats. Pharmacol Biochem Behav 2004;78:531–40.
50 Walf AA, Sumida K, Frye CA. Inhibiting 5alpha-reductase in the amygdala attenuates antianxiety and antidepressive behavior of naturally receptive and hormone-primed ovariectomized rats. Psychopharmacology (Berl) 2006;186:302–11.
51 Irwig MS. Decreased alcohol consumption among former male users of finasteride with persistent sexual side effects: A preliminary report. Alcohol Clin Exp Res 2013;37:1823–6.
52 Pierucci-Lagha A, Covault J, Feinn R, Nellissery M, Hernandez-Avila C, Oncken C, Morrow AL, Kranzler HR. GABRA2 alleles moderate the subjective effects of alcohol, which are attenuated by finasteride. Neuropsychopharmacology 2005;30:1193–203.
53 Ford MM, Nickel JD, Finn DA. Treatment with and withdrawal from finasteride alter ethanol intake patterns in male C57BL/6J mice: Potential role of endogenous neurosteroids? Alcohol 2005;37:23–33.
54 Ford MM, Yoneyama N, Strong MN, Fretwell A, Tanchuck M, Finn DA. Inhibition of 5alpha-reduced steroid biosynthesis impedes acquisition of ethanol drinking in male C57BL/6J mice. Alcohol Clin Exp Res 2008;32:1408–16.
55 Ramaker MJ, Ford MM, Fretwell AM, Finn DA. Alteration of ethanol drinking in mice via modulation of the GABA(A) receptor with ganaxolone, finasteride, and gaboxadol. Alcohol Clin Exp Res 2011;35:1994–2007.
56 Ford MM, Nickel JD, Phillips TJ, Finn DA. Neurosteroid modulators of GABA(A) receptors differentially modulate ethanol intake patterns in male C57BL/6J mice. Alcohol Clin Exp Res 2005;29:1630–40.
57 Janak PH, Redfern JE, Samson HH. The reinforcing effects of ethanol are altered by the endogenous neurosteroid, allopregnanolone. Alcohol Clin Exp Res 1998;22:1106–12.
58 Torres JM, Ortega E. Alcohol intoxication increases allopregnanolone levels in male adolescent humans. Psychopharmacology (Berl) 2004;172:352–5.
59 Barbaccia ML, Affricano D, Trabucchi M, Purdy RH, Colombo G, Agabio R, Gessa GL. Ethanol markedly increases "GABAergic" neurosteroids in alcohol-preferring rats. Eur J Pharmacol 1999;384:R1–2.
60 VanDoren MJ, Matthews DB, Janis GC, Grobin AC, Devaud LL, Morrow AL. Neuroactive steroid 3alpha-hydroxy-5alpha-pregnan-20-one modulates electrophysiological and behavioral actions of ethanol. J Neurosci 2000;20:1982–9.
61 Sanna E, Talani G, Busonero F, Pisu MG, Purdy RH, Serra M, Biggio G. Brain steroidogenesis mediates ethanol modulation of GABAA receptor activity in rat hippocampus. J Neurosci 2004;24:6521–30.
62 Tokuda K, Izumi Y, Zorumski CF. Ethanol enhances neurosteroidogenesis in hippocampal pyramidal neurons by paradoxical NMDA receptor activation. J Neurosci 2011; 31:9905–9.
63 Izumi Y, Murayama K, Tokuda K, Krishnan K, Covey DF, Zorumski CF. GABAergic neurosteroids mediate the effects of

ethanol on long-term potentiation in rat hippocampal slices. Eur J Neurosci 2007;26:1881–8.
64 Lopez-Gonzalez E, Herdeiro MT, Figueiras A. Determinants of under-reporting of adverse drug reactions: A systematic review. Drug Saf 2009;32:19–31.
65 US Food and Drug Administration. Questions and answers: Finasteride label changes. 2012. Available at: http://www.fda.gov/safety/medwatch/safetyinformation/ucm303257.htm (accessed November 16, 2013).
66 Irwig MS. Persistent sexual side effects of finasteride: Could they be permanent? J Sex Med 2012;9:2927–32.
67 Corradi LS, Campos SG, Santos FC, Vilamaior PS, Góes RM, Taboga SR. Long-term inhibition of 5-alpha reductase and aromatase changes the cellular and extracellular compartments in gerbil ventral prostate at different postnatal ages. Int J Exp Pathol 2009;90:79–94.
68 Bishnoi M, Chopra K, Kulkarni SK. Progesterone attenuates neuroleptic-induced orofacial dyskinesia via the activity of its metabolite, allopregnanolone, a positive GABA(A) modulating neurosteroid. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:451–61.