Post Finasteride Syndrome
Fact or Fiction?

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Disclosures

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Physiological role of Type I and II 5a-Reductase

- 5AR are enzymes involved in steroid metabolism
- 5AR participate in 3 metabolic pathways:
  - bile acid biosynthesis
  - androgen and estrogen metabolism
  - prostate cancer
- There are two main isoenzymes of 5 AR (5AR-1 and 5AR-2), which vary in different tissues with age
- 5 AR-2 is the predominant isoenzyme in the human prostate

Iehle et al. J Steroid Biochem Mol Bio, 1999.68(5-6):189-95
Physiological role of Type I and II 5α-Reductase

• Finasteride is a potent inhibitor of human 5AR2 but is much less effective inhibiting human 5AR1

• Dutasteride inhibits both 5AR1 and 5AR2 to a similar extent and to a greater degree than finasteride

Iehle et al. J Steroid Biochem Mol Bio, 1999.68(5-6):189-95
Localization of Type 1 and Type 2 5-AR

Iehle et al. J Steroid Biochem Mol Bio, 1999.68(5-6):189-95
5α-Reductases

Testosterone → 5α-Dihydrotestosterone → 3α,5α-Androstanediol

4-Androstenedione → 5α-Dihydroandrostanedione → 3α, 5α-Androstanedione

3α-HSD

Neurosteroids

5α-Dihydrotestosterone
Corticosterone → 5α-Dihydrocorticosterone → 3α, 5α-Tetrahydrocorticosterone

Aldosterone → 5α-Dihydroaldosterone → 3α, 5α-Tetrahydroaldosterone

5α-Reductases

3α-HSD

Neurosteroids
5α-Reductases

- Progesterone → 5α-Dihydroprogesterone
- Deoxycorticosterone (DOC) → 5α-Dihydro-Deoxycorticosterone (5αDH-DOC)

3α-HSD

- 5α-Dihydroprogesterone → 3α, 5α-Dihydroprogesterone (Allopregnenolone)
- 5α-Dihydro-Deoxycorticosterone (5αDH-DOC) → 3α, 5α-Tetrahydrodoxycorticosterone

Neurosteroids

Deoxycorticosterone (DOC)
Role of Neurosteroids

- Pregnenolone
  - Depression
  - Anxiolysis

- Progesterone (direct or indirect)
  - Depression
  - Anxiolysis
  - Sexual function

- 3α-5α-reduced neurosteroids
  - Depression
  - Anxiolysis
  - PTSD
  - Alzheimer’s disease
  - Cognition
  - Sexual function
History of 5 ARIs

1992

1997

2002

2010
Dutasteride Package Insert: Sexual Adverse Effects

Table 1. Adverse Reactions Reported in ≥1% of Subjects over a 24-Month Period and More Frequently in the Group Receiving AVODART than the Placebo Group (Randomized, Double-blind, Placebo-controlled Trials Pooled) by Time of Onset

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>AVODART (n)</th>
<th>Placebo (n)</th>
<th>Adverse Reaction Time of Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Months 0-6</td>
<td>Months 7-12</td>
<td>Months 13-18</td>
</tr>
<tr>
<td></td>
<td>(n = 2,167)</td>
<td>(n = 1,901)</td>
<td>(n = 1,725)</td>
</tr>
<tr>
<td>Impotence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVODART</td>
<td>4.7%</td>
<td>1.4%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.7%</td>
<td>1.5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Decreased libido</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVODART</td>
<td>3.0%</td>
<td>0.7%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.4%</td>
<td>0.6%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Ejaculation disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVODART</td>
<td>1.4%</td>
<td>0.5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.5%</td>
<td>0.3%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Breast disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVODART</td>
<td>0.5%</td>
<td>0.8%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.2%</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

*a These sexual adverse reactions are associated with dutasteride treatment (including monotherapy and combination with tamsulosin). These adverse reactions may persist after treatment discontinuation. The role of dutasteride in this persistence is unknown.

*b Includes breast tenderness and breast enlargement.
## Table 1: Drug-Related Adverse Experiences

<table>
<thead>
<tr>
<th></th>
<th>Year 1 (%)</th>
<th>Years 2, 3 and 4* (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Finasteride</td>
<td>Placebo</td>
<td>Finasteride</td>
<td>Placebo</td>
</tr>
<tr>
<td>Impotence</td>
<td>8.1</td>
<td>3.7</td>
<td>5.1</td>
<td>5.1</td>
</tr>
<tr>
<td>Decreased Libido</td>
<td>6.4</td>
<td>3.4</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Decreased Volume of Ejaculate</td>
<td>3.7</td>
<td>0.8</td>
<td>1.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Ejaculation Disorder</td>
<td>0.8</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Breast Enlargement</td>
<td>0.5</td>
<td>0.1</td>
<td>1.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Breast Tenderness</td>
<td>0.4</td>
<td>0.1</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Rash</td>
<td>0.5</td>
<td>0.2</td>
<td>0.5</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*Combined Years 2-4
N = 1524 and 1516, finasteride vs placebo, respectively
Permanent Side Effects?
Finasteride 5mg and Persistent Sexual Adverse Events

• 1992-2010 (sponsor’s worldwide safety database):
  • 131 cases erectile dysfunction (most confounded by pre-existing conditions, other medications)
  • 68 cases decreased libido
  • In some cases, duration up to several weeks after drug discontinued
Finasteride 1 mg Persistent Sexual Adverse Events

• Post-Marketing Reports (1998-2011):
  • 421 reports of sexual dysfunction
  • 14% lasting ≥3 months following discontinuation of Propecia
    • 34% lasted 1-2 years
  • Young population, lack of confounding factors in most cases
There is no evidence of increased sexual adverse experiences with increased duration of treatment with PROSCAR. New reports of drug-related sexual adverse experiences decreased with duration of therapy.

6.2 Postmarketing Experience

The following additional adverse events have been reported in postmarketing experience with PROSCAR. Because these events 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:

- hypersensitivity reactions, such as pruritus, urticaria, and angioedema (including swelling of the lips, tongue, throat, and face)
- testicular pain
- sexual dysfunction that continued after discontinuation of treatment, including erectile dysfunction, decreased libido and ejaculation disorders (e.g. reduced ejaculate volume). These events were reported rarely in men taking PROSCAR for the treatment of BPH. Most men were older and were taking concomitant medications and/or had co-morbid conditions. The independent role of PROSCAR in these events is unknown.
- male infertility and/or poor seminal quality were reported rarely in men taking PROSCAR for the treatment of BPH. Normalization or improvement of poor seminal quality has been reported after discontinuation of finasteride. The independent role of PROSCAR in these events is unknown.
  - depression
  - male breast cancer.

The following additional adverse event related to sexual dysfunction that continued after discontinuation of treatment has been reported in postmarketing experience with finasteride at lower doses used to treat male pattern baldness. Because the event is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate its frequency or establish a causal relationship to drug exposure:

- orgasm disorders
The Medicines and Healthcare Products Regulatory Agency of the UK and the Swedish Medical Products Agency both updated their patient information leaflets to include the following statement:

“Persistence of Erectile Dysfunction after Discontinuation of Treatment with Propecia Has Been Reported in Post-Marketing Use.”
• Interviews with 71 healthy men aged 21–46 years who reported new onset sexual side effects associated with finasteride use

• Symptoms persisted for at least 3 months despite the discontinuation of finasteride

• The indication for finasteride was MPHL and all subjects began and finished finasteride use prior to age 40

• Arizona Sexual Experience Scale (ASEX)
  • Five core elements of sexual function
  • Each domain measured with 6-point Likert scale ranging from 1 to 6 (higher the number the worse)
Results

54 men with persistent sexual side effects associated with finasteride used for male pattern hair loss

Reassessed (R) after 9–16 months (mean 14 months) after their initial interview (I)

- Mean age at reassessment 31 y/o
- Healthy young men without any baseline sexual dysfunction, medical conditions, psychiatric conditions, or use of oral prescription medications prior to taking finasteride

Arizona Sexual Experience Scale (ASEX)

**Results at reassessment:**
- Persistent sexual side effects reported in 96% of men
- 89% of subjects met ASEX definition of sexual dysfunction
- Length of finasteride use did not correlate to changes in scores of sexual dysfunction

5 ARI and Permanent Sexual Side Effects?

- Wessells et al.¹
  - Only 50% of patients experienced resolution of their sexual adverse events after discontinuation
- Erdemir et al.²
  - “While sexual dysfunction induced by finasteride and dutasteride diminishes over time, resolving completely with discontinuation of therapy in only up to 4% of patients.”

¹Wessells et al. Urology 2003;61:579–84
DHT and Erectile Dysfunction
5α-Reductase Inhibitor Attenuates Erectile Function

Lugg et al 1995; Endocrinology 136: 1495-1501
Incomplete Recovery of Erectile Function in the Rat After Discontinuation of a Dual 5 Alpha Reductase Inhibitor Therapy

DHT and Erectile Function

- Double-blind randomized clinical trial with 120 men (aged 50–70) with low DHT levels given 5a-DHT transdermal gel
- Nocturnal penile tumescence improved in the 5a-DHT group during the first 3 months of treatment
- DHT gel alone demonstrated significant improvement in IIEF-EF at 3 and 6 months

Effects of 5ARIs on the CNS
Role of neurosteroids in regulating cell death and proliferation in the late gestation fetal brain

Photomicrographs showing activated caspase-3 immunoreactivity in the granular layer of the cerebellum of a fetus at 24 h after infusion with vehicle (control; A), finasteride (B),

Allopregnanolone levels are reduced in temporal cortex in patients with Alzheimer's disease compared to cognitively intact control subjects.
Patients treated for male pattern hair loss with finasteride show, after discontinuation of the drug, altered levels of neuroactive steroids in cerebrospinal fluid and plasma

- 7 patients diagnosed with PFS and 12 healthy controls
- CSF and plasma collected in all patients
- Mean age of PFS patients 38 y/o
- Mean finasteride treatment duration 727 days
- Interval between finasteride withdrawal and CSF sampling 1635 days (range 171-5000 days)

Fig. 1. Pregnenolone (PREG), progesterone (PROG), dihydroprogesterone (DHP), tetrahydroprogesterone (THP) and isopregnanolone levels in cerebrospinal fluid (CSF) and in plasma of controls (CTRL) and post-intensive patients (PFS). Data (n = 12 for CTRL and 7 for PFS) are expressed as pg/μl ± SEM. *p < 0.05; **p < 0.01; ***p < 0.001; the detection limit for DHP is <0.25 pg/μl, that for THP and isopregnanolone is <0.1 pg/μl.
5 ARI and Depression Clinical Trials

• Rahimi-Ardabili et al
  • 128 men with alopecia treated with finasteride 1mg daily
  • Finasteride treatment increased both Beck Depression Index (BDI) \( (P < 0.001) \) and Hospital Anxiety and Depression Scale (HADS) depression scores significantly \( (P = 0.005) \)

• Altomare et al
  • 19 patients developed mood disturbance during treatment with finasteride for alopecia
  • Depression developed after 9–19 weeks of treatment
  • Depression resolved after stopping use of finasteride in all patients

Why?
Development of Resistance to 5ARI Therapy

• At least 25-30% of patients do not respond to 5ARI therapy

• “Resistance to medical therapy with finasteride may occur through silencing of the 5AR2 gene by DNA methylation, leading to a state in which 30% of adult prostates do not express 5AR2”

Nocebo Effect

- Randomized 120 patients with BPH and IIEF scores >24 to receive finasteride 5 mg for 12 months, with or without specific counseling of potential sexual AEs

- Patients who were counseled on sexual AEs experienced a higher rate of AEs compared to no counseling on sexual AEs:
  - Decreased libido: 15.3% vs 7.7%
  - ED: 43.6 vs 9.65
  - EjD: 15.3 vs 5.7%

- Nocebo effect - symptoms were due to factors other than medication itself

Mondaini et al J Sex Med 2007;4:1708
Genetic Predisposition
Baylor Genetic and Epigenetic Studies on Post-Finasteride Syndrome Patients

- 25 men with history of PFS
  - Penile biopsy taken in clinic
- 25 men undergoing circumcision
  - Foreskin sent to lab for analysis
- Microarray of RNA in all 50 patients
- Primary culture of fibroblasts from all tissue samples to assess androgen receptor expression
Summary

• Permanent adverse effects described with 5ARIs include ED, EjD, and decreased libido

• Reduction in $3\alpha$, $5\alpha$ neurosteroids can result in anxiety, depression, declining cognition and sexual dysfunction

• Future research through registries and clinical trials are needed to better understand the etiology of PFS in young men