Permanent Adverse Effects After 5ARI Treatment

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Discussion

• Physiology of 5 alpha-reductase inhibitors (ARIs)
• Adverse effects
  • Permanent adverse effects
    • Erectile dysfunction
    • Ejaculatory dysfunction
    • Decreased libido
  • Other potential permanent adverse effects
    • Depression
    • Gynecomastia/breast cancer
    • High grade prostate cancer
• Etiology of permanent AE
• Future research
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
  - 5AR-3 recently detected and described in hormone refractory prostate cancer
- 5 AR-2 is the predominant isozyme 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 in 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

Type 1 5aR
- Brain
- Sebaceous Gland
- Scalp
- Face
- Chest/Back Skin
- Liver
- Adrenal Gland
- Kidney
- Visceral Adipose Tissue

Type 2 5aR
- Scalp - Hair Follicle
- Beard
- Chest Skin
- Liver
- Visceral Adipose Tissue
- Seminal Vesicle
- Prostate
- Epididymis
- Foreskin/Scrotum

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

3α–HSD

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

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

Neurosteroids
**Neurosteroids**

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

**5α-Reductases**

**3α-HSD**
Neurosteroids

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

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

5α-Reductases 3α-HSD
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
AVODART or other 5 alpha-reductase inhibitors. (4)

WARNINGS AND PRECAUTIONS

- AVODART reduces serum prostate-specific antigen (PSA) concentration by approximately 50%. However, any confirmed increase in PSA while on AVODART may signal the presence of prostate cancer and should be evaluated, even if those values are still within the normal range for untreated men. (5.1)
- AVODART may increase the risk of high-grade prostate cancer. (5.2, 6.1)
- Prior to initiating treatment with AVODART, consideration should be given to other urological conditions that may cause similar symptoms. (5.3)
- Women who are pregnant or could become pregnant should not handle AVODART Capsules due to potential risk to a male fetus. (5.4, 8.1)
- Patients should not donate blood until 6 months after their last dose of AVODART. (5.5)
## Dutasteride Package Insert: 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>Months 0-6 (n = 2,167)</th>
<th>Months 7-12 (n = 1,901)</th>
<th>Months 13-18 (n = 1,725)</th>
<th>Months 19-24 (n = 1,605)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVODART (n)</td>
<td>(n = 2,158)</td>
<td>(n = 1,922)</td>
<td>(n = 1,714)</td>
<td>(n = 1,555)</td>
</tr>
<tr>
<td>Placebo (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impotence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVODART</td>
<td>4.7%</td>
<td>1.4%</td>
<td>1.0%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.7%</td>
<td>1.5%</td>
<td>0.5%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Decreased libido</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVODART</td>
<td>3.0%</td>
<td>0.7%</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.4%</td>
<td>0.6%</td>
<td>0.2%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Ejaculation disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVODART</td>
<td>1.4%</td>
<td>0.5%</td>
<td>0.5%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.5%</td>
<td>0.3%</td>
<td>0.1%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Breast disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVODART</td>
<td>0.5%</td>
<td>0.8%</td>
<td>1.1%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.2%</td>
<td>0.3%</td>
<td>0.3%</td>
<td>0.1%</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.
Warnings and Precautions

- PROSCAR reduces serum prostate specific antigen (PSA) levels by approximately 50%. However, any confirmed increase in PSA while on PROSCAR may signal the presence of prostate cancer and should be evaluated, even if those values are still within the normal range for men not taking a 5α-reductase inhibitor (5.1).
- PROSCAR may increase the risk of high-grade prostate cancer (5.2, 6.1).
- Women should not handle crushed or broken PROSCAR tablets when they are pregnant or may potentially be pregnant due to potential risk to a male fetus (5.3, 8.1, 16).
- PROSCAR is not indicated for use in pediatric patients or women (5.4, 8.1, 8.3, 8.4, 12.3).
- Prior to initiating treatment with PROSCAR for BPH, consideration should be given to other urological conditions that may cause similar symptoms (5.6).
### Table 1: Drug-Related Adverse Experiences

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

*Combined Years 2-4
N = 1524 and 1516, finasteride vs placebo, respectively
Warnings and Precautions

- PROPECIA is not indicated for use in women or pediatric patients (5.1, 5.4).
- Women should not handle crushed or broken PROPECIA tablets when they are pregnant or may potentially be pregnant due to potential risk to a male fetus (5.1, 8.1, 16).
- PROPECIA causes a decrease in serum PSA levels. Any confirmed increase in PSA while on PROPECIA may signal the presence of prostate cancer and should be evaluated, even if those values are still within the normal range for men not taking a 5α-reductase inhibitor (5.2).
- 5α-reductase inhibitors may increase the risk of high-grade prostate cancer (5.3, 6.1).

### TABLE 1: Drug-Related Adverse Experiences for PROPECIA (finasteride 1 mg) in Year 1 (%)

<table>
<thead>
<tr>
<th>Male Pattern Hair Loss</th>
<th>PROPECIA N=945</th>
<th>Placebo N=934</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased Libido</td>
<td>1.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Erectile Dysfunction</td>
<td>1.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Ejaculation Disorder</td>
<td>1.2 (0.8)</td>
<td>0.7 (0.4)</td>
</tr>
<tr>
<td>Discontinuation due to drug-related sexual adverse experiences</td>
<td>1.2</td>
<td>0.9</td>
</tr>
</tbody>
</table>
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
  - 59/421 lasting ≥3 months following discontinuation of Propecia
  - 20/59 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 hyperfunction (1) to hypofunction (6)

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 and mean age of beginning finasteride was 26 y/o
  • White (80%), Asian (13%), Other (7%)

• 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 continued to be present in 96% of men
  • 89% of subjects met the definition of sexual dysfunction
  • Neither the length of finasteride use nor the duration of the sexual side effects correlated to changes in scores of sexual dysfunction
Results

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.”
• Medicine health care products regulatory agency (MHRA) public assessment report on the risk of finasteride published in December of 2009 in Section 4.8 Undesirable Effects: “In addition, the following have been reported in post-marketing use: persistence of ED after discontinuation of treatment with PROPECIA.”

¹Wessells et al. Urology 2003;61:579–84
5ARI and Erectile Dysfunction
# Effects of 5ARI on NOS, SMC and Erections in Vivo

Table 1: Effects of 5α Reductase inhibitors on nitric oxide synthase expression and activity, trabecular smooth muscle content and erections in vivo as assessed by intracavernosal pressure (ICP) or by behavioral observations.

<table>
<thead>
<tr>
<th>Study [Ref.]</th>
<th>5α Reductase inhibitor</th>
<th>Penile Nitric Oxide Synthase Expression or Activity</th>
<th>Penile Smooth Muscle Content</th>
<th>In Vivo Assessment of Erections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradshaw et al 1981 [23]</td>
<td>17β-testosterone carboxylic acid</td>
<td>Not Measured</td>
<td>Not Measured</td>
<td>Significant Decrease a</td>
</tr>
<tr>
<td>Pinsky et al 2011 [39]</td>
<td>Dutasteride</td>
<td>Significant Decrease</td>
<td>Significant Decrease</td>
<td>Significant Decrease b</td>
</tr>
<tr>
<td>Oztekin et al 2012 [38]</td>
<td>Dutasteride</td>
<td>Significant Decrease</td>
<td>Significant Decrease</td>
<td>Significant Decrease b</td>
</tr>
<tr>
<td>Seo et al 1999 [37]</td>
<td>MK-434</td>
<td>Significant Decrease</td>
<td>-----</td>
<td>Significant Decrease b</td>
</tr>
<tr>
<td>Zhang et al 2013 [40]</td>
<td>Finasteride</td>
<td>Significant Decrease</td>
<td>Significant Decrease</td>
<td>Significant Decrease b</td>
</tr>
</tbody>
</table>

a. Erections were monitored visually during behavior studies.
b. Penile erection was assessed by electric field stimulation (EFS) of the cavernosal nerve and measurement of the intracavernosal pressure.

Testosterone $\rightarrow$ 5α-Reductase $\rightarrow$ 5α-DHT

Androgen Receptor

Biochemical Markers
- eNOS
- nNOS
- PDE 5

Structural Changes in Tissue Components:
- Nerve fibers
- Endothelial cells
- Smooth muscle content
- Connective tissue
- Adipogenesis

Veno-occlusion

Slide courtesy of Dr. Abdul Traish
NOS Activity is Reduced by 5α-Reductase Inhibitors in Erectile Tissue

Lugg et al 1995; Endocrinology 136: 1495-1501
Effects of long-term Finasteride treatment on smooth muscle content and eNOS in Rat CC

Masson’s trichrome staining showing reduced smooth muscle in the finasteride treated group (B) compared to the control group (A). Endothelial nitric oxide synthase protein immunohistochemically staining. Control group (C) and Finasteride treated group (D).

Zhang et al., UROLOGY 82: 743.e9e743.e15, 2013.
Effects of $5\alpha$RI on eNOS, iNOS and SM content in the penis


- Reduced nNOS expression
- Increased iNOS expression
- Reduced smooth muscle content
Quantification of apoptotic index of cavernous smooth muscle cells from rats treated with or without finasteride. (Left) Apoptotic indexes (ratio of apoptotic cells to all cells). Black arrows indicate apoptotic cells with dark brown-stained nuclei: (A) control group and (B) Finasteride-treated group.

Zhang et al., UROLOGY 82: 743.e9e743.e15, 2013.

weight of the corpus cavernosum decreased by 22.4%
5a-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

### Table 2: Effect of 5-α Reductase Inhibitors on Sexual Function in Clinical Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug Used</th>
<th>Drug N =</th>
<th>Drug Related Sexual Adverse Events (%)</th>
<th>Placebo N =</th>
<th>Placebo Related Sexual Adverse Events (%)</th>
<th>Comments/Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nickel et al., 1996</td>
<td>Finasteride 310</td>
<td>10</td>
<td>15.8</td>
<td>7.7</td>
<td>303</td>
<td>6.3</td>
</tr>
<tr>
<td>Tenover et al., 1997</td>
<td>Finasteride 1736</td>
<td>5.4</td>
<td>8.1</td>
<td>4.0</td>
<td>579</td>
<td>3.3</td>
</tr>
<tr>
<td>Hudson et al., 1999</td>
<td>Dutasteride 259</td>
<td>7.7</td>
<td>6.7</td>
<td>4.7</td>
<td>NA</td>
<td>3.3</td>
</tr>
<tr>
<td>Wessells et al., 2003</td>
<td>Finasteride 1524</td>
<td>6.0</td>
<td>8.0</td>
<td>3.0</td>
<td>1516</td>
<td>3.0</td>
</tr>
<tr>
<td>Thompson et al., 2003</td>
<td>Finasteride 9423</td>
<td>65.4</td>
<td>67.4</td>
<td>60.4</td>
<td>9457</td>
<td>59.6</td>
</tr>
<tr>
<td>Androilo et al., 2010</td>
<td>Dutasteride 4105</td>
<td>5.2</td>
<td>9.0</td>
<td>1.4</td>
<td>4126</td>
<td>2.9</td>
</tr>
<tr>
<td>Kaplan et al., 2012</td>
<td>Finasteride 197</td>
<td>3.1</td>
<td>3.6</td>
<td>3.6</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kaplan et al., 2012</td>
<td>Dutasteride 211</td>
<td>5.2</td>
<td>7.1</td>
<td>4.7</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Gubelin et al., 2013</td>
<td>Dutasteride 184</td>
<td>3.3</td>
<td>5.4</td>
<td>3.3</td>
<td>181</td>
<td>1.1</td>
</tr>
<tr>
<td>Gubelin et al., 2013</td>
<td>Finasteride 179</td>
<td>5.0</td>
<td>5.6</td>
<td>3.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DHT and Erectile Function

- Double-blind randomized clinical trial with 120 men (aged 50–70) 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 modified IIEF at 3 and 6 months

<table>
<thead>
<tr>
<th>TABLE 3. Ability to maintain erection during intercourse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>DHT</td>
</tr>
</tbody>
</table>

## 5 ARIs and Ejaculatory Dysfunction

### Table 2: Effect of 5-α Reductase Inhibitors on Sexual Function in Clinical Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug Used</th>
<th>Drug N =</th>
<th>Drug Related Sexual Adverse Events (%)</th>
<th>Placebo N =</th>
<th>Placebo Related Sexual Adverse Events (%)</th>
<th>Comments/Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nickel et al., 1996 [42]</td>
<td>Finasteride 310</td>
<td>Libido 10, ED 15.8, EJD 7.7</td>
<td>Placebo 303, Libido 6.3, ED 6.3, EJD 1.7</td>
<td>Comment a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenover et al., 1997 [43]</td>
<td>Finasteride 1736</td>
<td>Libido 5.4, ED 8.1, EJD 4.0</td>
<td>Placebo 579, Libido 3.3, ED 3.8, EJD 0.9</td>
<td>Comment b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hudson et al., 1999 [44]</td>
<td>Dutasteride 259</td>
<td>Libido 7.7, ED 6.7, EJD 4.7</td>
<td>Placebo NA, Libido 3.3, ED 4.0, EJD 1.7</td>
<td>Comment c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wessells et al., 2003 [19]</td>
<td>Finasteride 1524</td>
<td>Libido 6.0, ED 8.0, EJD 3.0</td>
<td>Placebo 1516, Libido 3.0, ED 3.0, EJD 0.5</td>
<td>Comment d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thompson et al., 2003 [14]</td>
<td>Finasteride 9423</td>
<td>Libido 65.4, ED 67.4, EJD 60.4</td>
<td>Placebo 9457, Libido 59.6, ED 61.5, EJD 47.3</td>
<td>Comment e</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andriole et al., 2010 [13]</td>
<td>Dutasteride 4105</td>
<td>Libido 5.2, ED 9.0, EJD 1.4</td>
<td>Placebo 4126, Libido 2.9, ED 5.7, EJD 0.2</td>
<td>Comment f</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaplan et al., 2012 [53]</td>
<td>Finasteride 197</td>
<td>Libido 3.1, ED 3.6, EJD 3.6</td>
<td>Placebo NA, Libido NA, ED NA, EJD NA</td>
<td>Comment g</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dutasteride 211</td>
<td>Libido 5.2, ED 7.1, EJD 4.7</td>
<td>Placebo NA, Libido NA, ED NA, EJD NA</td>
<td>Comment h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gubelin et al., 2013 [90]</td>
<td>Dutasteride 184</td>
<td>Libido 3.3, ED 5.4, EJD 3.3</td>
<td>Placebo 181, Libido 1.1, ED 3.9, EJD 3.3</td>
<td>Comment i</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ejaculatory Dysfunction

- The CombAT study observed 0.6% retrograde ejaculations, 0.5% ejaculation failure, and 0.3% semen volume decrease in patients\(^1\)

- The AUA clinical practice guidelines:\(^2\)
  - 4% taking finasteride and 1% taking placebo had ejaculatory dysfunction
  - “Results pertaining to ejaculatory function are mixed and additional data are needed to ascertain the drug impact on ejaculation.”

\(^1\)Roehrborn et al J Urol 2008;179:616–21
# 5 ARIs and Libido

## Table 2: Effect of 5-α Reductase Inhibitors on Sexual Function in Clinical Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug Used</th>
<th>Drug N =</th>
<th>Drug Related Sexual Adverse Events (%)</th>
<th>Placebo N =</th>
<th>Placebo Related Sexual Adverse Events (%)</th>
<th>Comments/Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nickel et al., 1996 [42]</td>
<td>Finasteride</td>
<td>310</td>
<td>Libido 10, ED 15.8, EJD 7.7</td>
<td>303</td>
<td>Libido 6.3, ED 6.3, EJD 1.7</td>
<td>Comment a</td>
</tr>
<tr>
<td>Tener et al., 1997 [43]</td>
<td>Finasteride</td>
<td>1736</td>
<td>Libido 5.4, ED 8.1, EJD 4.0</td>
<td>579</td>
<td>Libido 3.3, ED 3.8, EJD 0.9</td>
<td>Comment b</td>
</tr>
<tr>
<td>Hudson et al., 1999 [44]</td>
<td>Dutasteride</td>
<td>259</td>
<td>Libido 7.7, ED 6.7, EJD 4.7</td>
<td>NA</td>
<td>Libido 3.3, ED 4.0, EJD 1.7</td>
<td>Comment c</td>
</tr>
<tr>
<td>Wessells et al., 2003 [19]</td>
<td>Finasteride</td>
<td>1524</td>
<td>Libido 6.0, ED 8.0, EJD 3.0</td>
<td>1516</td>
<td>Libido 3.0, ED 3.0, EJD 0.5</td>
<td>Comment d</td>
</tr>
<tr>
<td>Thompson et al., 2003 [14]</td>
<td>Finasteride</td>
<td>9423</td>
<td>Libido 65.4, ED 67.4, EJD 60.4</td>
<td>9457</td>
<td>Libido 59.6, ED 61.5, EJD 47.3</td>
<td>Comment e</td>
</tr>
<tr>
<td>Andriole et al., 2010 [13]</td>
<td>Dutasteride</td>
<td>4105</td>
<td>Libido 5.2, ED 9.0, EJD 1.4</td>
<td>4126</td>
<td>Libido 2.9, ED 5.7, EJD 0.2</td>
<td>Comment f</td>
</tr>
<tr>
<td>Kaplan et al., 2012 [53]</td>
<td>Finasteride</td>
<td>197</td>
<td>Libido 3.1, ED 3.6, EJD 3.6</td>
<td>NA</td>
<td>Libido NA, ED NA, EJD NA</td>
<td>Comment g</td>
</tr>
<tr>
<td>Kaplan et al., 2012 [53]</td>
<td>Dutasteride</td>
<td>211</td>
<td>Libido 5.2, ED 7.1, EJD 4.7</td>
<td>NA</td>
<td>Libido NA, ED NA, EJD NA</td>
<td>Comment g</td>
</tr>
<tr>
<td>Gubelin et al., 2013 [99]</td>
<td>Dutasteride</td>
<td>184</td>
<td>Libido 3.3, ED 5.4, EJD 3.3</td>
<td>181</td>
<td>Libido 1.1, ED 3.9, EJD 3.3</td>
<td>Comment h</td>
</tr>
<tr>
<td>Gubelin et al., 2013 [99]</td>
<td>Finasteride</td>
<td>179</td>
<td>Libido 5.0, ED 5.6, EJD 3.9</td>
<td>NA</td>
<td>Libido NA, ED NA, EJD NA</td>
<td>Comment h</td>
</tr>
</tbody>
</table>

Libido

- American Urological Association (AUA) clinical practice guideline reported that 5% finasteride and 3% placebo patients experienced reduced libido
- CombAT trial 2-year follow-up 2.8% of the dutasteride group and 1.3% of placebo group experienced complete loss of libido

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.

Figure 2.
Allopregnanolone levels in temporal cortex are significantly decreased in subjects with Alzheimer's disease (median 2.68 ng/g, n=40) compared to cognitively intact control subjects (median 5.64 ng/g, n=41). Mann-Whitney p=0.0002.

Naylor et al., Biochim Biophys Acta. 2010; 1801: 951–959
Patients treated for male pattern hair 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-finasteride 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.
Neurosteroids and Depression

• Neurosteroids play an important role in memory enhancement, sedation, anxiety, stress, sleep modulation, anticonvulption, and antidepressant properties¹

• 5 ARI therapy may reduce neurosteroid biosynthesis significantly and predispose them to onset or progression of depression²

• Allopregnenolone has been shown to have anti-anxiety effects, as well as anti-depressant effects³

¹Finn et al. Pharmacol Biochem Behav 2004;78:435–43
GABA Receptors

• Finasteride significantly decreases all 5α-reduced steroid metabolites in the brain

• These neurosteroids are known to modulate GABA and N-methyl D-Aspartate (NMAD) receptors in the brain

• Decreased concentration of circulating neuroactive steroids with known inhibitory activity on GABA-ergic excitation in the brain likely contributing to depression

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

5 ARI Effects on Breast Tissue

Conversion and Metabolism

Estradiol-17\(^B\)

5-alpha-Dihydrotestosterone

Active metabolites

Aromatase

5-alpha-Reductase

Testosterone
### Finasteride 5mg Package Insert: Adverse Effects

<table>
<thead>
<tr>
<th>Table 1: Drug-Related Adverse Experiences</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Impotence</td>
</tr>
<tr>
<td>Decreased Libido</td>
</tr>
<tr>
<td>Decreased Volume of Ejaculate</td>
</tr>
<tr>
<td>Ejaculation Disorder</td>
</tr>
<tr>
<td>Breast Enlargement</td>
</tr>
<tr>
<td>Breast Tenderness</td>
</tr>
<tr>
<td>Rash</td>
</tr>
</tbody>
</table>

*Combined Years 2-4

N = 1524 and 1516, finasteride vs placebo, respectively
5 ARI Effects on Breast Tissue

• Gynecomastia observed in 214 men receiving finasteride according to reports to the U.S. Food and Drug Administration from 1992 to 1995¹

• Prostate Cancer Prevention Trial (PCPT), approximately 426 of 9,423 subjects (4.5%) in the finasteride arm had gynecomastia compared with 261 of 9,457 subjects (2.8%) in the placebo arm²

• In men taking finasteride alone or with doxazosin, 4 out of 1,554 developed breast cancer, a rate approximately 200 times that of the general population³

¹ Greene et al N Engl J Med 1996;335:823
² Thompson et al N Engl J Med 2003;349:21
Finasteride and Prostate Cancer

- The PCPT enrolled 18,882 men and randomized to placebo vs. finasteride 5 mg daily for 7 years.
- Reduction of prostate cancer by 24.6% in the treatment arm, with an increased rate of development of Gleason 7–10 prostate cancers (37% treatment vs 22.2% placebo).
- Subsequent reanalysis found multiple counterarguments against the increased risk for HGPC:
  - Lack of reliability of Gleason scoring following 5ARI treatment.
  - Reduction in prostate volume and subsequent increased detection of malignancy.
  - Increased sensitivity of PSA as a prostate cancer detection marker in the finasteride group.

Dutasteride and Prostate Cancer

- REDUCE TRIAL - RCT of 8,231 men aged 50 to 75 years taking dutasteride 0.5mg over 4 years demonstrated relative risk reduction of prostate cancer of 22.8% with no increased risk of high-grade malignancy in years 1 to 4.

- Retrospective analysis there was a statistically significant difference in the development of high risk prostate cancer between years 3 to 4.

5.2 Increased Risk of High-grade Prostate Cancer

In men aged 50 to 75 years with a prior negative biopsy for prostate cancer and a baseline PSA between 2.5 ng/mL and 10.0 ng/mL taking AVODART in the 4-year Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, there was an increased incidence of Gleason score 8-10 prostate cancer compared with men taking placebo (AVODART 1.0% versus placebo 0.5%).

[see Indications and Usage (1.3), Adverse Reactions (6.1)]. In a 7-year placebo-controlled clinical trial with another 5 alpha-reductase inhibitor (finasteride 5 mg, PROSCAR®), similar results for Gleason score 8-10 prostate cancer were observed (finasteride 1.8% versus placebo 1.1%).

5 alpha-reductase inhibitors may increase the risk of development of high-grade prostate cancer.

Whether the effect of 5 alpha-reductase inhibitors to reduce prostate volume or trial-related factors impacted the results of these trials has not been established.

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 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
A Colloquium on Research Avenues to Explore In Defining The Link Between 5-Alpha Reductase Inhibitors And Sexual Dysfunction

Registry Working Group
• Gerald Brock
• Mohit Khera
• John Mulhall
• Gregory Broderick
• Lawrence Hakim
• Claus Roehrborn

Neurosteroid Working Group
• Abdul Traish
• Roberto Melcangi
• Marco Bortalato
• Cheryl Frye
• Luis Garcia-Segura
• Wayne Hellstrom
• Mario Maggi
• Vassilios Papadopoulos
• Michael Zitzmann
• Arthur Burnett
• Francois Giuliano
• Irwin Goldstein
• Ziya Kirkali
• Kevin McKenna
• Jim Pfaus
Summary

• Permanent adverse effects described with 5ARIs include ED, EjD, and decreased libido
• Other potentially permanent adverse effects associated with 5 ARIs include depression, gynecomastia/breast cancer, and prostate cancer
• 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
Thank you for your attention
5-Alpha Reductase Inhibitors and Erectile Dysfunction: The Connection

Fikret Erdemir, MD, Andrew Harbin, BA, and Wayne JG Hellstrom, MD
Tulane University-Department of Urology, New Orleans, LA, USA
They also more frequently reported sexual adverse events, including erectile dysfunction, decreased libido, and gynecomastia (RR 1.83, 95% CI 1.42–2.36, RR 2.00, 95% CI 1.42–2.83, respectively).

**Park T, Choi JY. World J Urol. 2014 Feb 6**
Changes in Sexual Function in Benign Prostatic Hyperplasia Patients Taking Dutasteride: 1-Year Follow-Up Results

Animal Studies

- In castrated and adrenalectomized rats, treatment with 5a-DHT for 7 days restored erectile function to levels similar to that of control animals [58]. Other studies demonstrated that 5a-DHT treatment in castrated rats improved the erectile response to electrical field stimulation [59,60].
Dark side

• 38
FIG. 3. Effects of long-term treatment with finasteride on corpus cavernosum smooth muscle death. Terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end labeling quantification of apoptotic index of cavernous smooth muscle cells in rats with or without 5α-reductase inhibitor (5α-RI) treatment. (Left) Apoptotic indexes (ratio of apoptotic cells to all cells) of 2 groups were assessed. For each corpus cavernosum sample, 5 randomly obtained fields were selected, and the mean ratio of apoptotic cells to all cells was used to calculate the apoptotic index. Values for 5 samples in each group presented as ratio ± standard deviation. **p < 0.001 compared with 5α-RI-treatment group (unpaired t-test); (A) control group and (B) 5α-RI-treated group. Black arrows indicate apoptotic cells with dark brown-stained nuclei: (A) control group and (B) 5α-RI-treated group (ApopTag Peroxidase In Situ Apoptosis Detection Kit, Scale bar=100 μm, ×200). Adapted from Zhang MC, et al. Urology 2013;82:743.e9-15, with permission of Elsevier Inc. [40].
4 week treatment with finasteride reduced penile weight (25.9%) and prostatic weight (92.3%) compared to control. No decrease in Smooth muscle content. No deficit in erectile function was observed.
Erectile Dysfunction

- Approximately 6–8% of patients reported ED in several trials [33,41,44,45,48,49]. In an observational cohort of 14,772 taking finasteride [50], ED was the most common adverse event, leading to withdrawal (143 patients). The AUA clinical practice guideline reported erectile problems in 8% and 4% of patients taking finasteride and placebo, respectively [46].
The effect of 5-alpha reductase inhibitor on expression of TGF-β1. Lat. means lateral portion of the prostate and Ant. means anterior wall. Each value is expressed as the mean ± SD of six independent experiments. *P < 0.05 versus control.

Important Animal Study

• Rat studies showed a 50% reduction in erectile response was noted after castration which was reversed by T [64]. However, treatment with T and finasteride together did not restore erectile response in castrated rats. Administration of 5a-DHT, however, restored nitric oxide synthase.
The effects of chronic dutasteride treatment on rat erectile function

Pinsky et al., J. Sexual Medicine 2011; 8: 3066-3074
Androgens
- Androstenedione
  - testosterone

Progestins
- Progesterone

Glucocorticoids
- Cortisol, corticosterone, & deoxycorticosterone

5α-Reductases

Finasteride or dutasteride
- Inhibits

5α-Dihydro-derivatives

3α-Hydroxy-steroid dehydrogenases

3α, 5α-Tetrahydro-derivatives
- Neuro-active steroids

Play role in:
- Neuro-protection
- Seizure
- Anxiety
- Stress
- Depression
eNOS in the CC before and After Finasteride Treatment

Zhang et al., UROLOGY 82: 743.e9e743.e15, 2013.