Sexual Dysfunction and Medical Treatment for LUTS/BPH

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Randomised, controlled trials demonstrate that standard medical therapies for LUTS/BPH are associated with sexual adverse effects (AEs) such as:

- decreased or loss of libido
- erectile dysfunction (ED)
- ejaculatory disorder (EjD)
Drug therapy licensed for LUTS/BPH

- a1-adrenoceptor antagonists
- 5a-reductase inhibitors
- Antimuscarinic drugs
- Vasopressin analogue
- Phosphodiesterase type 5 inhibitors
- Combination therapies
- Beta-3 agonist
α1-adrenoceptor antagonists (α1-blockers)

First-line drug treatment of male LUTS/BPH

Five types of α1-blockers are currently in mainstream use: alfuzosin, doxazosin, silodosin, tamsulosin, and terazosin (naftopidil).

Efficacy: similar (equally effective)
Adverse effects: different (in terms of the uroselectivity)

α1-Adrenoceptors in blood vessels, other nonprostatic smooth muscle cells, and the CNS are considered mediators of adverse events during α1-blocker treatment.
Subtypes of α1-Adrenoceptors

There are **three subtypes** of α1-Adrenoceptors in humans: α1A, α1B, and α1D.

- **α1A** – prostate, bladder neck, prostatic urethra
- **α1D** – detrusor muscle, sacral spinal cord, afferent n.
- **α1B** – blood vessels (ageing: α1B/α1A ratio↑)

In the prostate, 70% of α1-Adrenoceptors are of the α1A subtype.
Receptor Selectivity of $\alpha_1$-blockers

Terazosin, doxazosin, alfuzosin ($\alpha_{1A} = \alpha_{1B} = \alpha_{1D}$)

Tamsulosin ($\alpha_{1A} = \alpha_{1D} > \alpha_{1B}$)
$\alpha_{1A}, \alpha_{1D} - 10$ times vs $\alpha_{1B}$

Silodosin ($\alpha_{1A} > \alpha_{1D} > \alpha_{1B}$)
$\alpha_{1A} - 50$ times vs $\alpha_{1D}, 160$ times vs $\alpha_{1B}$

Naftopidil ($\alpha_{1D} \geq \alpha_{1A} > \alpha_{1B}$)
$\alpha_{1D} - 3$ times vs $\alpha_{1A}, 17$ times vs $\alpha_{1B}$
Adverse events of a1-blockers

- Asthenia
- Dizziness
- Orthostatic hypotension
- Intra-operative floppy iris syndrome (IFIS)
- **Ejaculatory disorder (EjD)**

Non-selective a1-blockers may be associated with side effects related to *vasodilation*.

However, **selective a1-blockers** have a higher incidence of ejaculatory disorders.
Adverse events of α1–blockers

A systematic review concluded that α1–blockers:

- do not adversely affect libido
- have a small beneficial effect on erectile function
- sometimes cause abnormal ejaculation

EAU Guidelines 2013

α1–blockers have mixed effects on sexual function in that evidence shows both improved erectile function and ejaculatory dysfunction, although different α–blockers have different effects on ejaculation.

van Dijk et al. Drugs 2006; 66:287–301
Adverse events of a1–blockers: ED

A community–based study suggested that a1–blockers were associated with improved sexual function.

Kumar et al. Drugs Urology 2009;74:82–7

The meta–analysis by Van Dijk et al. appears to confirm a beneficial effect on erectile function.

van Dijk et al. Drugs 2006; 66:287–301

Moreover, a retrospective analysis of the doxazosin database suggested a beneficial effect on erectile function.

MacDonald et al. BJU Int 2004;94:1263–70

The positive effect of a1–blockers on erectile function

← relax the cavernosal smooth muscle and enhance erections.

← improvement in QoL following relief of BPH–associated LUTS
Adverse events of $\alpha_1$-blockers: EjD

The exact mechanisms are not clear.

One suggestion is that these agents, particularly those selective for the $\alpha_1A$-adrenoceptor that is widely distributed in organs involved in the emission phase of ejaculation, may effect this first phase of the ejaculation process. (a direct effect on the vas and seminal vesicles leading to anejaculation)

A second hypothesis involves an effect of alpha-blockers on the CNS, possibly via binding to serotonin and/or dopamine receptors, to block signals controlling ejaculation.

Giuliano et al. BJU Int 2006; 97 (Suppl. 2): 34–8

??? Bladder neck relaxation with retrograde ejaculation
Adverse events of α1-blockers: EjD

Uroselective drugs have a high affinity for the α1A-adrenoreceptor, with tamsulosin (α1a and α1d) and particularly silodosin (α1a) being the most uroselective.

EjD occurs more commonly with tamsulosin and silodosin.

Silodosin has the highest incidence of abnormal ejaculation; however, efficacy seems to be increased in patients experiencing abnormal ejaculation.

Roehrborn et al. Prostate Cancer Prostatic Dis 2011;14:143–8
Adverse events of a1-blockers: EjD

[ Incidence ]

**Tamsulosin**: 4% – 26%
*dose-dependently* increasing the incidence (0.8mg – 35%) & reducing the amount of ejaculate)

**Silodosin**: 22–29%

**Doxazosin, Terazosin and Alfuzosin**: < 1.5%
*(was not statistically different from the placebo)*
Adverse events of α1-blockers: EjD

[ Degree of bother ]

In a multicentre trial with 1228 men with LUTS/BPH:

- Only **1.3%** of men in the silodosin arm discontinued treatment because of ejaculatory dysfunction.
- Although the side-effect might be relatively prevalent, the degree of bother is relatively minor.


This conclusion may reflect:

- the maintained sensation of orgasm
- the presence of ejaculatory dysfunction is associated with a relatively good symptomatic response of LUTS
5α-reductase inhibitors (5α-ARIs)

Dutasteride and finasteride are available for clinical use.

Finasteride inhibits only 5α-reductase type 2, dutasteride inhibits types 1 and 2 with similar potency (dual 5α-ARI). However, the clinical benefit of dual inhibition remains unclear.

The most relevant adverse effects are related to sexual function and include reduced libido, erectile dysfunction, and, less frequently, ejaculation disorders. The incidence of sexual dysfunction and other adverse events is low and decreased with trial duration. Gynaecomastia develops in approximately 1–2% of patients.

EAU Guidelines 2013
The underlying mechanism 5ARI–induced sexual dysfunction is not fully understood but presumably is related to:

- the decrease of dihydrotestosterone
- a reduction of NO or NOS in the corpus cavernosum (inhibition of androgen–stimulated NOS expression)

5-ARIs

- Side effects related to sexual function do occur.
- The profile and incidence of sexual AEs is similar for both (finasteride and dutasteride) treatments.
- 5-ARIs have sexual effects, including ED in 3–16% of patients, decrease of libido in 2–10%, and EjD in 0–8%.

### Table 2: Effects of 5α-reductase inhibitors on sexual function

<table>
<thead>
<tr>
<th>Study [ref.]</th>
<th>Drug used</th>
<th>Drug</th>
<th>Drug related sexual adverse events (%)</th>
<th>Placebo</th>
<th>Placebo related sexual adverse events (%)</th>
<th>Comments/remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Libido</td>
<td>ED</td>
<td>EJD</td>
<td>Libido</td>
</tr>
<tr>
<td>Nickel et al. (1996)</td>
<td>Finasteride</td>
<td>310</td>
<td>10.0</td>
<td>15.8</td>
<td>7.7</td>
<td>303</td>
</tr>
<tr>
<td>Tenover et al. (1997)</td>
<td>Finasteride</td>
<td>1,736</td>
<td>5.4</td>
<td>8.1</td>
<td>4.0</td>
<td>579</td>
</tr>
<tr>
<td>Hudson et al. (1999)</td>
<td>Dutasteride</td>
<td>259</td>
<td>7.7</td>
<td>6.7</td>
<td>4.7</td>
<td>NA</td>
</tr>
<tr>
<td>Wessells et al. (2003)</td>
<td>Finasteride</td>
<td>1,524</td>
<td>6.0</td>
<td>8.0</td>
<td>3.0</td>
<td>1,516</td>
</tr>
<tr>
<td>Thompson et al. (2003)</td>
<td>Finasteride</td>
<td>9,423</td>
<td>65.4</td>
<td>67.4</td>
<td>60.4</td>
<td>9,457</td>
</tr>
<tr>
<td>Andriole et al. (2010)</td>
<td>Dutasteride</td>
<td>4,105</td>
<td>5.2</td>
<td>9.0</td>
<td>1.4</td>
<td>4,126</td>
</tr>
<tr>
<td>Kaplan et al. (2012)</td>
<td>Finasteride</td>
<td>197</td>
<td>3.1</td>
<td>3.6</td>
<td>3.6</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Dutasteride</td>
<td>211</td>
<td>5.2</td>
<td>7.1</td>
<td>4.7</td>
<td>NA</td>
</tr>
<tr>
<td>Gubelin et al. (2014)</td>
<td>Dutasteride</td>
<td>184</td>
<td>3.3</td>
<td>5.4</td>
<td>3.3</td>
<td>181</td>
</tr>
<tr>
<td></td>
<td>Finasteride</td>
<td>179</td>
<td>5.0</td>
<td>5.6</td>
<td>3.9</td>
<td>181</td>
</tr>
</tbody>
</table>
Kaplan et al.: finasteride vs. **dutasteride**

- ED – 3.6% vs. **7.1%**
- EjD – 3.6% vs. **4.7%**
- Decreased libido – 3.1% vs. **5.2%**.
- Discontinued treatment – 42.6% vs. **57.5%**

The authors suggested that dutasteride elicits **more** sexual side effects and breast complications than finasteride.

5–ARIs

New sexual AEs with 5ARI treatment decreases with longer duration of therapy.

✔ Analysis of 4–year data from Proscar Long–term Efficacy and Safety Study (PLESS): men treated with finasteride experienced new drug–related sexual AEs with an increased frequency only during the first year of therapy.

✔ Analysis of the 4–year safety and tolerability of dutasteride: similarly, the incidence of drug–related sexual AEs decreased with longer duration of therapy.

Schulman et al. BJU Int 2005; 97: 73–80
5–ARIs

However, a recent study by Traish et al demonstrated persistent ED and diminished libido in users of 5ARIs.


Chi and Kim investigated the effects of dutasteride treatment during a 1–year follow-up period in Korean men:

- **After 1 month** of treatment, dutasteride therapy resulted in a significant reduction in all investigated sexual functions.
- **Overall**, recovery in sexual function was noted at 3 months.
- **EF of the IIEF remained** significantly reduced even after 12 months of treatment.
- **Orgasmic function and sexual desire** were significantly reduced but slowly recovered after six months.

Nocebo effect

In a study of 120 sexually active men with BPH, blinded administration of finasteride: a significantly higher proportion of sexual dysfunction in men informed about potential sexual side effects compared with those who were not counselled.

Several factors have been identified that appear to be associated with this phenomenon, including

- a patient’s expectations of adverse effects at the start of Tx.
- psychological characteristics such as anxiety and depression
- a patient’s susceptibility to suggestions of possible adverse effects associated with treatment.

Combination therapies (5ARI plus alpha-blocker)

In both the **MTOPS and CombAT studies**, the incidence of sexual AEs was higher with combination therapy than with monotherapies.

Table 2  Sexual adverse event rates for 5ARIs, alpha-blockers and the combination reported in randomised, controlled trials

<table>
<thead>
<tr>
<th>Patients with AE (%)</th>
<th>Alpha-blocker</th>
<th>Combination therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CombAT (45)</strong>: dutasteride and tamsulosin</td>
<td>-Decreased libido</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>ED</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Semen volume decreased</td>
<td>&lt; 1</td>
</tr>
<tr>
<td></td>
<td>Retrograde ejaculation</td>
<td>&lt; 1</td>
</tr>
<tr>
<td><strong>MTOPS (46)</strong>: finasteride and doxazosin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased libido</td>
<td>2.36</td>
<td>1.56</td>
</tr>
<tr>
<td>ED</td>
<td>4.53</td>
<td>3.56</td>
</tr>
<tr>
<td>EjD (abnormal ejaculation)</td>
<td>1.78</td>
<td>1.10</td>
</tr>
</tbody>
</table>

data expressed as rate per 100 person-years (incidence density)

For **EjD**, the rate reported in the combination therapy arms was **higher than the sum** of the rates reported in the monotherapy arms.
In both MTOPS and CombAT studies the discontinuation rates in the combination therapy arms were similar to those in the monotherapy arms.

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✓ drug-related sexual dysfunction does not represent a clinically significant cause of treatment withdrawal, 
✓ the benefits of therapy outweigh the impact of drug-related sexual AEs.
A substantial proportion of men who present with BPH/ LUTS will already have some degree of sexual dysfunction. It is therefore important to thoroughly assess sexual function before initiating pharmacotherapy for BPH/ LUTS.

1) The IIEF (15–question tool)
2) A validated abbreviated version, the IIEF–5 (The IIEF does not adequately address EjD therefore an additional tool is required.)
3) A four item version of the Male Sexual Health Questionnaire has been developed and validated for the assessment of EjD.
4) Male Sexual Function–4 (MSF–4) (Another shorter 4–item questionnaire)
Evaluation of sexual dysfunction in men requiring treatment for BPH/LUTS

Male Sexual Function–4 (MSF–4) (4–item questionnaire)

| How would you rate the following aspects of your life? (Circle one answer for each question) |
|---------------------------------|-----------------|-----------------|--------|--------|---------|-------|
|                                 | Very strong     | Strong          | Moderate | Weak   | Very weak | None |
| 1. Your interest in sex         | 0               | 1               | 2       | 3      | 4        | 5     |
| 2. The quality of your erection | 0               | 1               | 2       | 3      | 4        | 5     |
| 3. Achieving orgasm             | 0               | 1               | 2       | 3      | 4        | 5     |
| 4. Achieving ejaculation        | 0               | 1               | 2       | 3      | 4        | 5     |
Management of sexual dysfunction in men treated for BPH/LUTS

Assess sexual function before initiating pharmacotherapy for BPH/LUTS, using a validated questionnaire or enquiry.
(e.g. the international index of erectile function, male sexual health questionnaire)

Assess co-morbidities and concomitant medications before initiating pharmacotherapy for BPH/LUTS, with particular focus on those that may effect erectile capacity.
Address any risk factors for cardiovascular disease.

Before initiating pharmacotherapy for BPH/LUTS, advise on lifestyle interventions to improve sexual dysfunction e.g. physical activity, weight loss. Consider PDE5 inhibitors if necessary.

ED
Consider pharmacotherapy for ED if required e.g. PDE5 inhibitors

EjD
Consider switching BPH/LUTS therapy (e.g alternative alpha-blocker or 5ARI) if EjD are a major problem

Provide adequate and appropriate counselling on the safety and tolerability of medical therapies for BPH/LUTS

Provide review date for 4–8 weeks time.
Review regularly at 6-month intervals.
Management of sexual dysfunction in men treated for BPH/LUTS

It is important to understand the **impact** of any sexual dysfunction on the patient and their partner; the impact **is likely to be less** in men who **are not sexually active** and in men whose LUTS are most serious and bothersome.

It is also important to obtain information on **comorbidities and concomitant medications**, and be aware of medications that can affect erectile capacity.

Many men with ED will also have **hypertension** and some **antihypertensive drugs** (e.g. **thiazide diuretics**) have ED as a potential side effect; in such cases, **switching** to a medication that is less likely to cause ED (e.g. angiotensin receptor blocker) may help to alleviate the problem. Other drug classes that can interfere with male sexual function include **antihistamines**, **psychotherapeutics**, **Parkinson’s disease drugs** and **muscle relaxants**, as well as **alcohol**.
Management of sexual dysfunction in men treated for BPH/LUTS

Sexual function should be assessed thoroughly before initiating medical therapy for BPH/ LUTS.

If sexual dysfunction is identified, non–pharmacological interventions such as lifestyle changes should be considered. As well as improving erectile function, interventions such as weight loss and increased physical activity may have a positive impact on LUTS as well as improving overall cardiovascular health.

If drug therapy is considered necessary, PDE5 inhibitors are a highly effective treatment option.
Management of sexual dysfunction in men treated for BPH/LUTS

If sexual dysfunction emerges after initiation of pharmacotherapy for BPH/ LUTS, the options available depend on the type of sexual dysfunction and the BPH/ LUTS treatment regimen.

**ED**: PDE5 inhibitors should be considered.
**EjD**: switching to an alternative drug (such as a 5ARI or an alternative alpha-blocker) may be an option.

Adequate and appropriate counselling is a key element of the management of sexual dysfunction in men with BPH/ LUTS.