

# Sexual Dysfunction Related to Drugs: a Critical Review. Part V: $\alpha$ -Blocker and 5-ARI Drugs

## Authors

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## Key words

- $\alpha$ -blockers
- 5-ARIs
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- LUTS (lower urinary tract symptoms) drugs
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- sexual side effects
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## Abstract

Sexual dysfunction is a potential side effect of BPH (benign prostatic hyperplasia) and LUTS (lower urinary tract symptoms) drugs: this article is a critical review of the current literature. Many studies have been published on this topic. Methodological flaws limit the conclusions of these studies, mainly because of the lack of diagnostic criteria for ejaculatory and sexual desire dysfunction. Few of these studies are RCTs.

The  $\alpha$ -blocker (also called  $\alpha$ 1-adrenergic antagonist, alpha-adrenoceptor antagonist, alpha-blocker or AB) and 5-ARI (also called 5 $\alpha$ -reductase inhibitor or testosterone-5-alpha reductase inhibitor) drugs can in particular cause erectile dysfunction, ejaculatory disorders and reduction of sexual desire. The sexual side effect profile of these drugs is different. Among the  $\alpha$ -blockers, silodosin appears have the highest incidence of ejaculatory disorders. Persistent sexual side effects after discontinuation of finasteride has recently been reported, however further studies are needed to clarify the true incidence and the significance of this finding.

It is desirable that future studies include validated tools to assess and diagnose sexual dysfunction induced by these medications, especially for ejaculation and sexual desire disorders. Only a small amount of research has intentionally set out to investigate sexual dysfunction caused by  $\alpha$ -blocker and 5-ARI drugs: studies to specifically assess sexual dysfunction induced by these drugs are needed. Further studies are also needed to assess in the long term the role

of combined therapy of phosphodiesterase type 5 inhibitors and  $\alpha$ -blockers or 5-ARIs in treating LUTS/BPH.

**Methods:** This study was conducted in 2014 using the paper and electronic resources of the library of the "Azienda Provinciale per i Servizi Sanitari (APSS)" in Trento, Italy (<http://atoz.ebsco.com/Titles/2793>). The library has access to a wide range of databases including DYNAMED, MEDLINE Full Text, CINAHL Plus Full Text, The Cochrane Library, Micromedex healthcare series, BMJ Clinical Evidence. The full list of available journals can be viewed at <http://atoz.ebsco.com/Titles/2793>, or at the APSS web site (<http://www.apss.tn.it>).

In completing this review, a literature search was conducted using the key words "benign prostatic hyperplasia drugs", "lower urinary tract symptoms drugs", " $\alpha$ -blockers", "5-ARIs", "sexual dysfunction", "sexual side effects", "treatment-emergent sexual dysfunction", "phosphodiesterase type 5 (PDE5) inhibitors". All resulting listed articles were reviewed. Studies published between 2002 and December 2014 were included in the review.

We included all studies that explicitly reported data on sexual dysfunction during treatment with  $\alpha$ -blockers and 5-ARIs. We also reviewed studies that have evaluated the use of phosphodiesterase type 5 (PDE5) inhibitors in combination with these drugs.

The purpose was to identify possible intervention strategies for sexual dysfunction related to these drugs.

published) [1–4], many other drugs have been identified as causing sexual dysfunction.

In this review, we will deal with sexual dysfunction induced by the  $\alpha$ -blockers and the 5-ARIs.

## Introduction

In addition to antidepressant, antipsychotic, antiepileptic, benzodiazepine and antihypertensive drugs (for which, see the reviews already

It was considered useful to list them according to the ATC system used by the World Health Organization. ATC is an acronym for “Anatomical Therapeutic Chemical” classification system, which can be viewed in detail on the web site of the WHO [5].

In the following table (Table 1) we have summarized the Anatomical Therapeutic Chemical classification system for  $\alpha$ -blocker and 5-ARI drugs.

These pharmacologic therapies are employed alone or in combination for the clinical treatment of BPH (Benign Prostatic Hypertrophy), a common disorder among middle-aged and elderly men, which often results in urethral obstruction and LUTS (lower urinary tract symptoms).

Numerous studies have shown that sexual dysfunction is common in older men [6–10].

Also, several clinical and epidemiological studies have clearly demonstrated a consistent and independent association between LUTS/BPH and sexual function in males [9, 11–15]. In particular, the severity of LUTS has been shown to correlate with erectile dysfunction and ejaculatory dysfunction in large-scale epidemiological studies [6–8, 16–18]. Erectile dysfunction and ejaculatory dysfunction are also side effects of some medical therapies used for the treatment of LUTS caused BPH [8, 19–25]. A large volume of clinical research has been based on the use of questionnaires for clinical assessment of sexual dysfunction in urological patients. Among these questionnaires, the International Index of Erectile Function (IIEF: a 15-item self-report inventory developed and psychometrically validated to assess the efficacy of pharmacological treatments for erectile dysfunction) is one of the most commonly used [26]. The Sexual Health Inventory for Men (SHIM) is an abridged 5-item version of the IIEF [26]. The Male Sexual Health Questionnaire (MSHQ) contains 25 items in total, which includes a 7-item domain for assessment of ejaculatory dysfunction [27]. An abbreviated version of the MSHQ has recently been published: this short form questionnaire has only a 4-item domain on ejaculation; 3 ejaculatory function items (“force”, “volume”, and “frequency of ejaculation”)

and one “ejaculation bother” item [28]. Other self-administered questionnaires or patient-reported outcome measures used in the assessment of sexual function of urological patients also include the Brief Sexual Function Inventory (BSFI: 11 items that focus on sexual function) [29], the International Continence Society Sex Questionnaire (ICS: includes 4 items assessing erectile function, ejaculatory function, pain/discomfort during ejaculation and the extent to which urinary symptoms interfere with sexual function) [30], the Danish Prostate Symptom Score (DAN-PSS: questionnaire used to assess erection, ejaculation, pain/discomfort during ejaculation and the bothersomeness of each of these items) [31] and the Structured Interview on Erectile Dysfunction (SIEDY: a validated, 13-item structured interview that assesses the organic, relational, and psychological components of erectile dysfunction) [32].

## Results



We collected all of the articles listed in the following 2 tables (Table 2, 3). In the first table we have indicated the articles on sexual dysfunction related to LUTS and/or BPH drugs, while in the second table we have indicated the articles on PDE5 inhibitors used in LUTS and/or BPH.

As demonstrated in Table 2, the majority of articles are reviews and there are few RCTs (randomized clinical trials, i.e., randomized, double-blind, placebo-controlled studies). The conclusions reached by the various reviews and studies are similar [11–15, 18–21, 24–26, 33–73]. Surprisingly, of the 21 RCTs [74–94] reviewed on  $\alpha$ -blockers and 5-ARIs, only 2 of them [89, 93] used a specific and validated rating scale for measuring sexual functioning. In contrast, of the 38 [6–10, 16, 95–126] non-RCT studies outlined in Table 2, most of them used a specific questionnaire (IIEF mainly) to detect sexual dysfunction, while 9 studies [101, 103, 105, 106, 115, 120, 124–126] did not use any validated rating scale.

**Table 1** “Anatomical Therapeutic Chemical” Classification System:  $\alpha$ -blocker and 5-ARI drugs.

Anatomical Main Group	Therapeutic Subgroup	Pharmacological Subgroup	Chemical Subgroup	Chemical substance	Main therapeutic use
G Genito Urinary System and Sex Hormones	G04 Urologicals	G04C Drugs Used in Benign Prostatic Hypertrophy	G04CA Alpha- Adrenoreceptor Antagonists	Alfuzosin Tamsulosin Terazosin Doxazosin Silodosin	Drugs Used in Benign Prostatic Hypertrophy
G Genito Urinary System and Sex Hormones	G04 Urologicals	G04C Drugs Used in Benign Prostatic Hypertrophy	G04CB Testosterone-5- Alpha reductase inhibitors	Dutasteride Finasteride (*)	Drugs Used in Benign Prostatic Hypertrophy

(\*) The 5-ARI inhibitor finasteride is also approved for male pattern hair loss. In the ATC Classification System, this drug is even classified in another group called “other dermatologicals”

**Table 2** Total articles on Sexual dysfunction related to LUTS and/or BPH drugs: 154.

	Reviews and meta-analysis: 53	RCTs (Randomized Clinical Trials): 21	Observational studies (Prospective, Retrospective or Case Controls), Open labels, Surveys and Case reports: 38	Other articles: 42
<b>References</b>	[11–15, 18–21, 24–26, 33–73]	[74–94]	[6–10, 16, 95–126]	[1–5, 17, 22, 23, 27–32, 127–154]

The bibliography entries from number 33 onwards have been listed by the year of publication (or by the date of on line access): this order will also be maintained in the text

The  $\alpha$ -blocker and 5-ARI drugs in particular can cause erectile dysfunction, ejaculatory disorders and reduction of sexual desire [59].

We have summarized the main conclusions in the following tables (see Table 4–7).

The sexual side effect profile of these drugs differs. Among the  $\alpha$ -blockers, silodosin (followed by tamsulosin) appears to have the highest incidence of ejaculatory disorders, up to 28.1% [92] (for details, see Table 4).

The different sexual side effect profile of  $\alpha$ -blockers could be related to their chemical structure, binding affinity/selectivity for  $\alpha$ 1-adrenergic receptor subtypes, other receptor-mediated mechanisms, and differential tissue distribution. Alfuzosin, doxazosin, and terazosin demonstrate equal binding to the 3  $\alpha$ 1-adrenergic receptor subtypes, while tamsulosin and silodosin exhibit superselective binding to the  $\alpha$ 1A-receptor [9, 20, 54].

**Table 3** Total articles on PDE-5 inhibitors used in LUTS and/or BPH: 60.

	Reviews and meta-analysis: 28	RCTs: 23	Other Studies (non RCTs): 9
References	[155–182]	[183–205]	[206–214]

The bibliography entries have been listed by the year of publication: this order will also be maintained in the text

The most uroselective  $\alpha$ -blocker is silodosin, which also has the most marked effect on ejaculation [11].

The sexual side effect profile of dutasteride appears to be similar to that of finasteride with regards to erectile dysfunction (ED), ejaculatory dysfunction (EjD) and decreased libido [39, 112, 144]: both are associated with a greater risk of ED, EjD, and decreased libido than placebo [39, 66]. Recently however, Corona et al. [117] found that 5-ARI was associated with a greater risk of decreased libido and spontaneous nocturnal erection, whereas no relationship was found with erectile dysfunction and ejaculation disturbance.

The rate of adverse sexual effects of 5-ARIs becomes comparable to placebo after treatment has been continued for more than 2 years [33, 39, 76, 103]. In contrast to these findings, Kaplan et al. [119] recently found that in the long term (5 years), dutasteride resulted in significantly more sexual side effects and breast complications (gynecomastia) than finasteride.

Recently there have been reports of persistent sexual dysfunction after discontinuation of treatment with finasteride [69, 113, 118, 125, 126]. Irwig and coll. [113] conducted retrospective interviews with 71 otherwise healthy men (age 21–46) who had used finasteride for the treatment of male pattern hair loss, using the validated ASEX (Arizona Sexual Experience Scale) questionnaire. Based on ASEX score results, these researchers found an extremely high incidence of sexual dysfunction in

**Table 4**  $\alpha$ -blockers: Type of effect on Sexual function.

negative (inhibitory) effect	(–)				
no significant effect (comparable to placebo)	(±)				
positive (beneficial or excitatory) effect	(+)				
uncertain results	(?)				
We have defined the effect of drugs on sexuality as “positive” (+) “negative” (–) or “neutral” (±); “uncertain results” (?) refers to findings difficult to interpret. In square brackets we have indicated the reference.					
	<b>Silodosin</b>	<b>Tamsulosin (¶) (▼)</b>	<b>Alfuzosin (¶)</b>	<b>Terazosin</b>	<b>Doxazosin (¶)</b>
Effect on Erectile function	(±) [89]	(±) [22, 23, 72, 79, 97, 98, 122, 144] (+) [104, 111, 121, 123]	(±) [22, 23, 72, 77, 79, 80, 144] (+) [43, 57, 83, 97, 100, 102, 107, 108, 110, 114, 121]	(±) [22, 23, 72, 144] (+) [111]	(±) [22, 23, 72, 98, 144] (+) [40, 74, 95, 99, 109, 111]
Effect on Ejaculatory function	(–) (1 **) [20, 54, 82, 85, 87–90, 92, 94, 105, 106, 115, 120]	(–) (2 **) [20, 56, 80, 81, 101, 116, 123, 124]	(±) [72, 80, 83] (+) [97, 100, 102, 107, 108]	(±) [20, 72]	(±) [20, 72] (+) [99]
Effect on sexual desire	No data	(+) [123] (±) [55, 72, 122]	(+) [97, 108] (±) [55, 72]	(±) [55, 72]	(+) [99] (±) [55, 72, 75]

(¶) There appears to be conflicting data about the effect on sexual function of alfuzosin, doxazosin and tamsulosin: some research suggests an effect similar to placebo, while other research suggests an improvement. The methodological issues concerning the various studies are detailed in the review by van Dijk et al. [41]. Methodological issues are probably responsible for some of the contradictory findings on sexual adverse events [57]

(▼) In the study by Hellstrom et al. almost 90% of subjects (healthy volunteers) taking 0.8 mg of tamsulosin had at least a 20% decreased semen volume [81]

(1 \*\*) The prevalence of ejaculation dysfunction (EjD) induced by silodosin is between 5 to 28.1%, with a median value of about 20% [148]: silodosin appears to be the drug with the highest risk of EjD [11, 20]. Efficacy of silodosin seems to be increased in patients experiencing abnormal ejaculation [115]

(2 \*\*) The prevalence of ejaculation dysfunction induced by tamsulosin ranges between 3–11% [56, 72]: tamsulosin is associated with a significantly lower risk of ejaculatory disorders than silodosin [20]. In the studies by Hellstrom et al. [81] and Hisasue et al. 2006 [101], ejaculation disorders due to tamsulosin (decreased ejaculate volume and anejaculation) were not attributed to retrograde ejaculation

Rare instances of priapism have been reported during treatment with  $\alpha$ -blockers [49]

The study of Liefeld et al. [96] reaches uncertain results: the  $\alpha$ -blockers “showed mixed results, but for all aspects there was both improvement and deterioration”

Several authors have considered gynaecomastia as a sexual dysfunction. This side effect has been reported in some research on  $\alpha$ -blockers [39, 103]

**Table 5** 5-ARIs: Type of effect on Sexual function.

negative (inhibitory) effect	(-)	
no significant effect (comparable to placebo)	(±)	
positive (beneficial or excitatory) effect	(+)	
uncertain results	(?)	
We have defined the effect of drugs on sexuality as “positive” (+) “negative” (-) or “neutral” (±); “uncertain results” (?) refers to findings difficult to interpret. In square brackets we have indicated the reference.		
	<b>Dutasteride (*), (**), (***)</b>	<b>Finasteride (*), (**), (***), (****)</b>
Effect on Erectile function	(-) [33, 47, 67, 71, 78, 84, 86, 91, 112, 144] (±) [117]	(-) [47, 67, 71, 74–76, 93, 144] (±) [117] (?) [50]
Effect on Ejaculatory function	(-) [20, 33, 47, 67, 71, 78, 84, 86, 112, 144] (±) [117]	(-) [20, 47, 50, 67, 71, 74–76, 93, 144] (±) [117]
Effect on sexual desire	(-) [33, 67, 71, 78, 84, 86, 91, 112, 117, 144]	(-) [67, 71, 74–76, 93, 117, 144]

(\*) Both finasteride and dutasteride are associated with comparable adverse effects on sexual function [39, 144]

(\*\*) The rates of these adverse effects become comparable to placebo after treatment is continued for 2 or more years [103, 144]. In contrast to this data, Kaplan et al. [119] recently found that long-term (5-years) dutasteride resulted in significantly more sexual side effects and breast complications (gynecomastia) than finasteride

(\*\*\*) In a review of clinical studies by Anitha et al. [50], the authors concluded that there was no clear evidence of finasteride (5 mg or 1 mg/day) having a negative effect on erectile function. Analogous conclusions were also reached by Canguven et al. [46]. Anitha et al. found that older non controlled studies reported high rates of erectile dysfunction during treatment with finasteride (0.8–33%), while randomized controlled studies reported erectile dysfunction between 0.8–15.8%. However, the findings of these clinical studies were not considered reliable because they did not either assess the baseline sexual function or use a validated questionnaire. Probably for similar reasons, the review by Erdemir et al. [47] reported high rates of sexual dysfunction with 5-ARI (between 2,1–38%), however they conclude that the rate of erectile dysfunction in clinical trials with 5-ARI ranges from 5 to 9%. Similar conclusions are also reached by Ponholzer et al. [45]: “5 $\alpha$ -Reductase inhibitors are associated with ED, loss of libido and reduction of ejaculate volume in up to 10%”. With regard to 5-ARIs, Gacci et al. [20] found “an overall prevalence of ejaculation disorder as low as 3%, although about 3-times higher than with placebo”. In the review by Trost et al. [67], a pooled summary of all randomized, placebo-controlled trials evaluating 5-ARIs revealed slightly increased rates over placebo for decreased libido (1.5%), erectile dysfunction (1.6%) and ejaculatory dysfunction (3.4%). The recent review by Traish et al. [71] shows slightly different percentages of sexual dysfunction. Gur et al. [66] instead report that the true prevalence of sexual side effects with 5-ARI treatment is currently unknown

(\*\*\*\*) Recently there have been reports of persistent sexual dysfunction after discontinuation of treatment with finasteride [69, 113, 118, 125–126]

Several authors have considered gynaecomastia as a sexual dysfunction. This side effect has been reported in several researches on 5-ARIs [38, 39, 44, 61, 67, 78, 91, 103, 119]

**Table 6** 5-ARIs: rates (minimum and maximum percentages) of Sexual Dysfunction in double-blind, randomized, placebo-controlled clinical trials for benign prostatic hyperplasia.

	<b>finasteride</b>	<b>Dutasteride</b>
ED (Erectile Dysfunction)	3.4–15.8% (1.7–6.3%)	1.7–11% (1.2–3%)
EjD (Ejaculatory Dysfunction)	0.2–7.7% (0.1–1.7%)	0.5–2% (0.1–1%)
Diminished Sexual Desire	2.4–13% (1.4–2%)	0.6–4% (0.3–2%)

Placebo effects in studies are shown in parenthesis. Data from Gur et al. [66]

patients in this group: between 69 and 94% of the people interviewed had sexual dysfunction in several categories including “low libido” (94%), “erectile dysfunction” (92%), “decreased arousal” (92%) and “problem with orgasm” (69%). However, the same authors have acknowledged the limitations of their study, stating that “the true incidence of these events is unknown as this is a post hoc approach” and that in previous randomized, placebo-controlled studies, the incidence of sexual side effects was less than 8% in the finasteride group and less than 3% in the control group. “Assuming that the vast majority of these events resolved, the incidence of persistent sexual events in finasteride users would probably be less than 1%” [113]. In fact, some methodological biases could limit the findings of Irwig et al. Firstly, the study was conducted only through “telephone or spoken Skype standardized interviews”. Secondly, the study was carried out on a sample of patients recruited from a website for people complaining of sexual dysfunction. Finally, the study by Irwig et

al. was an observational survey (without control groups) and only involved a small number of patients.

The pathophysiology of sexual function produced by 5-ARIs may be related to reduction of dihydrotestosterone levels and probably other neurosteroids such as the metabolites of progesterone [61, 69, 147]. Psychological factors (“nocebo effect”) have also been implicated as being responsible for sexual dysfunction in patients treated with 5-ARI drugs [141]. Nevertheless, to date little is known about the exact mechanisms behind 5-ARI-related sexual dysfunction [47, 63].

There is a cumulative risk of sexual side effects with combination therapy (by giving an  $\alpha$ -blocker with a 5-ARI) when compared to monotherapy or placebo [37, 75, 84, 86, 93]. Gacci and co-writers [20] found that combination therapy with  $\alpha$ -blockers and 5-ARIs resulted in a 3-fold increase in the risk of ejaculation disorder as compared with either monotherapies.

Numerous clinical trials seem to confirm that a combination treatment of  $\alpha$ -blocker and phosphodiesterase type 5 (PDE5) inhibitor is more effective in improving both LUTS and erectile dysfunction, compared to treatment with  $\alpha$ -blocker alone [48, 165, 182, 209]. The results of studies on combination treatment with  $\alpha$ -blocker and phosphodiesterase type 5 inhibitors in men with ED and BPH have suggested a beneficial synergistic effect of these medications on erectile dysfunction and LUTS [11, 49, 152, 165].

In this review, among the studies of combination treatment with  $\alpha$ -blockers or 5-ARIs and phosphodiesterase type 5 inhibitors,

**Table 7** summary of the main conclusions in the literature on sexual dysfunction in patients treated with  $\alpha$ -blockers and 5-ARIs.

	<b>Ejaculatory dysfunction (EjD): odds ratio (OR) with a 95% confidence interval (C.I.). Data from Gacci et al. [20]</b>
$\alpha$ -blockers vs. placebo	OR: 5.88; P<0.0001
Tamsulosin vs. placebo	OR: 8.58; P=0.006
Silodosin vs. placebo	OR: 32.5; P<0.0001
5-ARIs vs. placebo	OR: 2.73; P<0.0001
Finasteride vs. placebo	OR: 2.70; P<0.0001
Dutasteride vs. placebo	OR: 2.81; P=0.0002
Combination therapy vs. $\alpha$ -blockers alone	OR: 3.75; P<0.0001
Combination therapy vs. 5-ARIs alone	OR: 2.76; P=0.02
– Tamsulosin was associated with significantly lower risk of EjD than Silodosin (OR: 0.09; P<0.00001)	
– Alfuzosin, Doxazosin and Terazosin were associated with a risk of EjD similar to placebo	
– Both Finasteride and Dutasteride were associated with significantly higher risk of EjD than placebo	
– EjD was significantly more common with combination therapy as compared with $\alpha$ -blockers alone, or with 5-ARIs alone [20]	
– $\alpha$ -blockers (alfuzosin, doxazosin, tamsulosin, terazosin) show an incidence of decreased libido and of erectile dysfunction (ED) closely similar to placebo [39, 111]	
– 5-ARIs (finasteride and dutasteride) are associated with a greater risk of erectile dysfunction (ED), ejaculatory dysfunction (EjD) and decreased libido than is placebo [39]	
– the rate of ED in clinical trials on 5-ARIs ranges from 5 to 9% [47]	

we found 16 RCTs on tadalafil [184, 185, 187, 188, 192–195, 198–205], 3 RCTs on sildenafil [183, 191, 196], 2 RCTs on vardenafil [186, 197] and 2 RCTs on UK-369,003 [189, 190]. The PDE5 inhibitors are used alone or in combination mostly with  $\alpha$ -blocker alfuzosin or tamsulosin. More recently, PDE5 inhibitors are also used in combination with finasteride [203, 204].

These studies reveal the alleviating effect of phosphodiesterase-5 inhibitors on LUTS, as expressed by a reduction of IPSS score (International Prostate Symptom Score), which except for the study by Oelke et al. [195], was not followed by a change in  $Q_{max}$  (“*maximum urinary flow rate*”, which is the urodynamic parameter for assessment of LUTS). The Oelke et al. study [195] is in fact the first to report a significant increase in  $Q_{max}$ , and as such, this finding must be interpreted with caution until confirmed by other studies [149].

The link between erectile dysfunction and LUTS is based on 4 theories: 1) decreased or altered nitrous oxide synthase/nitric oxide levels in the prostate and penile smooth muscle; 2) autonomic hyperactivity effects on LUTS, prostate growth, and erectile dysfunction; 3) increased Rho kinase activation/endothelin activity; and 4) pelvic atherosclerosis [14, 58, 60]. As reported in a recent review, all these major mechanisms of BPH/LUTS could be counteracted by PDE5 inhibitors [160]. Inhibition of PDE5 has been demonstrated to have an effect on several pathogenetic pathways contributing to LUTS, although the exact mechanism of action remains to be clarified [165].

Excluding specific contraindications, all of the studies reviewed and listed in **Table 3** [155–214] conclude that the use of PDE5 is both well tolerated and safe in patients with LUTS and/or BPH.

## Discussion



In this review study we found different and seemingly conflicting epidemiological data on sexual dysfunction induced by  $\alpha$ -blocker and 5-ARI drugs. Several problems make it difficult to quantify and qualify sexual dysfunctions induced by  $\alpha$ -blocker and 5-ARI drugs. These problems mainly concern the diagnostic criteria of ejaculatory disorders.

None of the studies that we reviewed used the diagnostic criteria for sexual dysfunction proposed by ICD-10 [154], DSM-IV-TR [133] and DSM5 [150] (which receive the greatest international consensus). Other proposed classifications, such as that of NIH (National Institutes of Health) [128], are rarely used.

To date no clear consensus exists on the classification of “non-premature ejaculatory dysfunction” [153]. There are no clear diagnostic criteria for delayed ejaculation, as operationalized criteria do not exist [213].

In 2005 Hartman and Waldinger [138] wrote that “a major problem that we should solve is to find consensus on operational definitions of ejaculatory disorders”. To the best of our knowledge, the classification of delayed ejaculatory dysfunction is still far from precise. Retarded ejaculation, delayed ejaculation, inadequate ejaculation, inhibited ejaculation, idiopathic anejaculation, (primary) “*impotentia ejaculatiois*”, and psychogenic anejaculation have all been used synonymously to describe a delay or absence of male orgasmic response [145]. Furthermore some authors have also included orgasm disorders as ejaculatory disorders [139], while other authors have considered ejaculatory dysfunction as orgasmic dysfunction [72].

The lack of consensus on the diagnostic criteria of ejaculatory disorders makes it difficult to compare the conclusions of the various studies because it is not always clear what the different authors intended.

It is still important to distinguish anejaculation from retrograde ejaculation. Jannini and colleagues [139] have argued that “it is important not to confuse the classification of anejaculation with that of retrograde ejaculation. In the latter, orgasm is usually present, even if blunted, while anejaculation always coincides with anorgasmia (even if the reverse is not true)”. Hellstrom et al. [12] and Rosen et al. [143] defined “severe ejaculatory dysfunction as ejaculation with decreased amount of semen or loss of ejaculation”. Retrograde ejaculation (or dry ejaculation) occurs when there is entry of semen into the bladder instead of emerging through the penis [153].

Despite this important difference, many studies do not differentiate between anejaculation and retrograde ejaculation.

Examination of “post-ejaculate urine sperm concentration” serves as a reliable indicator of retrograde ejaculation. Nevertheless, only a few studies have researched this data [81, 85, 101].

Other methodological issues include the definition of reduced ejaculatory volume. Previous studies that assessed a reduction in the semen volume could be limited by some methodological bias. Several physiological factors can cause decreased semen volume. For instance, low semen volume can be the result of a short period of sexual abstinence (<2 days) or frequent ejaculations in the period preceding the seminal collection [146]. Therefore the results of any questionnaire or survey can be compromised if you do not define the basic conditions, such as the time period of abstinence prior to analysis of the semen volume. In many studies the period of abstinence prior to the semen analysis was not specified.

Another possible methodological bias may be due to the fact that in most studies there was no objective measurement of the semen volume and they relied instead on a subjective assessment of semen volume provided by the volunteers (or patients), which carries the risk of incorrect subjective assessment of reduced semen volume. According to Hellstrom et al. [81], “the subjective evaluation of EjD in clinical studies may lead to underestimates of the disorder”.

A further methodological bias depends on the lack of definition of semen volume reduction. For example, WHO [146] indicates that the lower reference limit for semen volume is 1.5 ml, but none of the studies we reviewed indicated a benchmark for the definition of the reduced volume of ejaculate, except Hellstrom et al. [81], who have defined “ejaculate volume decrease” as “a greater than 20% decrease from baseline”.

The Danish Prostatic Symptom Score (DAN-PSS), a questionnaire published by Hald et al. in 1991 [31] was often used for the detection of ejaculatory disorders. The DAN-PSS is another questionnaire which includes 12 questions related to voiding problems and the perceived bother of each individual symptom and 3 questions concerning sexuality (erection, ejaculation volume, pain/discomfort during ejaculation). This questionnaire has been validated and used in many epidemiologic surveys and clinical trials [127, 129–131, 137, 140]. However, to the best of our knowledge it has only been validated for assessing urinary symptoms and not sexual function [30]. This may be a potential limit of studies that have used the DAN-PSS, in that it may have led to an overestimation (or underestimation) of ejaculatory disorders. Rosen et al. [8] found that not only the DAN-PSS, but also the ICS questionnaire have not been psychometrically validated for sexual dysfunction. Both of these questionnaires evaluate only 2 ejaculatory dysfunctions (a reduced amount of semen and pain/discomfort on ejaculation). Rosen et al. [27] have proposed the use of the MSHQ questionnaire (“the only psychometrically and linguistically validated self-administered measure evaluating all components of ejaculation”), but unfortunately there are few studies that have used this questionnaire. As it has been previously highlighted, among the RCTs reviewed on  $\alpha$ -blockers and 5-ARIs, only 2 [89, 93] of these used a specific and validated rating scale for measuring sexual functioning. In those studies that did not use a patient self-administered questionnaire or patient-reported outcomes, the identification of sexual dysfunction often relies on the spontaneous disclosure by patients, but previous studies have shown that spontaneous reports from patients are infrequent, even though sexual side effects can considerably influence drug compliance [135]. Therefore, failure to use rating scales compromises the accurate assessment of the true rate of sexual dysfunction.

Most researchers have used the term “libido”, which unfortunately does not determine which specific phase (desire, arousal or orgasm) of the human sexual response is affected by the sexual dysfunction. In fact, the term “libido” is very generic and does not discriminate between the various phases of the sexual response cycle [136].

In the literature we have found the apparent use of similar expressions of sexual function, which however have probably been interpreted as having different meanings: “loss of sexual desire”, “hypoactive sexual desire (HSD)”, “hypoactive sexual desire disorder (HSDD)”, “low sexual desire”, “decreased sex drive (libido)”, “loss of libido (sex drive)”, “decreased libido”. See for example table 2 (“Adverse Events”) in the study by Roehrborn et al. [84]. These authors distinguished between “altered

(decreased) libido” and “loss of libido”, but do not explain the actual difference between these 2 (very similar) terms or why they have differentiated this side effect. Again, in table 1 described in the review by Skolarus et al. [53], “erectile function” is defined in terms of 1) “quality of erection”, 2) “libido/drive” and 3) “satisfaction”. However defining erectile function in terms of “libido/drive” can be confusing and difficult to understand for the patient.

## Conclusion



There have been few rigorous studies utilizing both control groups and validated questionnaires to evaluate the sexual side effects of  $\alpha$ -blocker and 5-ARI drugs [72].

It is desirable that future studies include validated tools to assess and diagnose sexual dysfunction induced by these medications, especially for ejaculation and sexual desire disorders. Failure to use such assessment questionnaires, reduces the detection of sexual dysfunction and the probability of accurately diagnosing the specific type of sexual dysfunction involved, as well as preventing an objective monitoring of symptom improvement or worsening during the course of drug treatment. MSHQ is a validated questionnaire for the evaluation of sexual dysfunction, in particular for the assessment of the force, delay and pleasure with ejaculation [8, 143]. Other specific rating scales such as the ASEX [134] or the CSFQ [132] could also be used for patients with LUTS/BPH.

Only a small amount of research has intentionally set out to investigate sexual dysfunction caused by  $\alpha$ -blocker and 5-ARI drugs. Studies specifically assessing sexual dysfunction induced by these drugs are needed.

Numerous studies show that sexual dysfunction is both highly prevalent and bothersome in sexually active men with LUTS [9]. This implies that sexual dysfunction should be carefully assessed and diagnosed before treating LUTS, as some treatments might further exacerbate it. Additional studies are needed to determine the pathophysiological mechanisms involved in the link between LUTS and sexual dysfunction (especially ejaculation disorders) and the optimal management strategies for men with these concomitant conditions [8, 12].

The sexual side effect profile of these urologic drugs is different. Among the  $\alpha$ -blockers, silodosin (followed by tamsulosin) appears to be the drug with the highest incidence of ejaculatory disorders. Alfuzosin has no deleterious effect on sexual function and is well tolerated when used in combination with low doses of phosphodiesterase type 5 inhibitors for the treatment of ED. Studies suggest that combination treatment with  $\alpha$ -blocker and phosphodiesterase type 5 inhibitors may act synergistically to improve both LUTS and sexual function [11, 49, 152, 165].

With the only exception of silodosin and, to a lesser extent of tamsulosin, the effect of the  $\alpha$ -blockers on sexual function appears similar to placebo.

The sexual adverse event profile of dutasteride appears to be similar to that of finasteride.

Recent reports of persistent sexual dysfunction after discontinuation of treatment with finasteride require further studies to assess causality [67].

Further studies are also needed to assess the long-term role of combined therapy of phosphodiesterase type 5 inhibitors and  $\alpha$ -blockers or 5-ARIs in the treatment LUTS/BPH [180, 197].

## Conflict of Interest



Andres Conca has served as consultant for Lilly, Pfizer and on the speakers' bureau of Lilly, BMS, Astra Zeneca, Lundbeck, Italfarma and Janssen. He reports no conflict of interest with this publication.

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**Important Note:**

This contribution has been corrected on November 30th, 2015 and downloaded on ..... ■■■  
 The name of the author was not correct: Torre AL,  
 now: La Torre A