

Effect of alpha-adrenoceptor antagonists on sexual function. A systematic review and meta-analysis

Rawa Bapir^{1, 13}, Kamran Hassan Bhatti^{2, 13}, Ahmed Eliwa^{3, 13}, Herney Andrés García-Perdomo^{4, 13}, Nazim Gherabi^{5, 13}, Derek Hennessey^{6, 13}, Vittorio Magri^{7, 13}, Panagiotis Mourmouris^{8, 13}, Adama Ouattara^{9, 13}, Gianpaolo Perletti^{10, 13}, Joseph Philipraj^{11, 13}, Alberto Trinchieri^{12, 13}, Noor Buchholz¹³

¹ Smart Health Tower, Sulaymaniyah, Kurdistan region, Iraq;

² Urology Department, HMC, Hamad Medical Corporation, Qatar;

³ Department of Urology, Zagazig University, Zagazig, Sharkia, Egypt;

⁴ Universidad del Valle, Cali, Colombia;

⁵ Faculty of Medicine Algiers 1, Algiers, Algeria;

⁶ Department of Urology, Mercy University Hospital, Cork, Ireland;

⁷ ASST Nord Milano, Milan, Italy;

⁸ 2nd Department of Urology, National and Kapodistrian University of Athens, Sismanoglio Hospital, Athens, Greece;

⁹ Division of Urology, Souro Sanou University Teaching Hospital, Bobo-Dioulasso, Burkina Faso;

¹⁰ Department of Biotechnology and Life Sciences, Section of Medical and Surgical Sciences, University of Insubria, Varese, Italy;

¹¹ Department of Urology, Mahatma Gandhi Medical College and Research Institute, Sri Balaji Vidyapeeth, Puducherry, India;

¹² Urology School, University of Milan, Milan, Italy;

¹³ U-merge Ltd. (Urology for emerging countries), London-Athens-Dubai *.

Authors 1-12 have equally contributed to the paper and share first authorship.

*U-merge Ltd. (Urology for Emerging Countries) is an academic urological platform dedicated to facilitate knowledge transfer in urology on all levels from developed to emerging countries. U-merge Ltd. is registered with the Companies House in London/ UK. www.U-merge.com.

Summary

Background: Alpha-adrenoreceptor antagonists or alpha-blockers are used in the treatment of hypertension, in the therapy of benign prostatic hyperplasia and in medical expulsive treatment of ureteral stones. These agents may affect the sexual function, with differences between drugs within the same class, depending on their selectivity for receptor subtypes. The aim of this review was to analyze the effects of alpha-blockers on sexual function.

Materials and methods: We conducted a systematic review and meta-analysis by searching PubMed, EMBASE and other databases for randomized controlled trials (RCTs) reporting sexual adverse effects in patients treated with alpha-blockers. Odds ratios for sexual dysfunction were calculated using random effects Mantel-Haenszel statistics.

Results: Out of 608 records retrieved, 75 eligible RCTs were included in the meta-analysis. Compared with placebo, alpha-blockers were associated with increased odds of ejaculatory disorders both in patients with lower urinary tract symptoms (LUTS) associated to benign prostatic hyperplasia (BPH) (OR: 7.53, 95% CI: 3.77-15.02, $Z = 5.73$, $p < 0.00001$, $I^2 = 55\%$) and in patients with ureteral stones (OR: 2.88, 95% CI: 1.50-5.44, $Z = 3.19$, $p < 0.001$, $I^2 = 31\%$).

Uroselective alpha-blockers showed higher odds of ejaculatory disorders. Conversely, nonselective alpha-blockers were not associated with higher odds of ejaculatory dysfunction. Silodosin was associated with increased odds of ejaculatory dysfunction compared with tamsulosin (OR: 3.52, 95% CI: 2.18-5.68, 15 series, 1512 participants, $Z = 5.15$, $p < 0.00001$, $I^2 = 0\%$). Naftopidil and alfuzosin showed lower odds of ejaculatory dysfunction compared to uroselective alpha-blockers.

No statistically significant differences in the odds of erectile dysfunction were observed when alpha-blockers were compared to placebo.

KEY WORDS: Alpha-blockers; Ejaculation; Erectile dysfunction; Silodosin; Tamsulosin; Alfuzosin; Doxazosin; Terazosin.

Submitted 11 February 2022; Accepted 24 March 2022

INTRODUCTION

Alpha adrenergic receptor (or adrenoreceptor) antagonists, also known as alpha-blockers, are a class of pharmacological agents acting as antagonists on various alpha-adrenergic receptors. Depending on receptor specificity, they bind and inhibit alpha1-receptors, alpha2-receptors, or both (1).

Alpha-1 adrenergic antagonists bind to type-1 alpha-adrenergic receptors, thus inhibiting smooth muscle contraction. Several subtypes of postsynaptic alpha1 receptors are present in vascular and nonvascular smooth muscle. Alpha 1A receptors are predominantly located in the smooth muscle of the genitourinary tract, where they regulate the tone of the bladder neck and of the smooth muscle fibers within the prostate. Alpha 1B receptors are more represented in the vascular smooth muscle, and are involved in the regulation of the vascular tone. Receptors belonging to the alpha1D subtype regulate the contraction of the urinary bladder (2). The effects of alpha-

No conflict of interest declared.

adrenergic blocking agents depend on their selectivity (or non-selectivity) for specific receptor subtypes.

Nonselective alpha-1-adrenergic antagonists have been used for decades against hypertension. Blockade of alpha1B receptors can decrease vascular resistance in peripheral arterioles and increase venous capacitance, ultimately lowering blood pressure (3). At present, alpha1 adrenergic antagonists are no longer recommended as monotherapy, but only as adjunctive treatment of hypertension (4). Alpha-1-blockers are used for the treatment of symptoms of urinary obstruction due to benign prostatic hyperplasia because they can relax the smooth muscle fiber in the bladder neck and in the prostate acting on alpha1A receptors. Initially, nonselective alpha-1 adrenergic antagonists such as doxazosin, terazosin and alfuzosin were used for the management of bladder neck obstruction (5). Selective alpha1A blockers with high affinity for the alpha1A adrenergic receptor, as tamsulosin and silodosin, have been subsequently developed to be specifically used in benign prostatic hyperplasia. Selectivity of these agents was aimed at decreasing their effect on blood pressure and at reducing the risk of unwanted effects, such as postural hypotension.

Alpha1D-adrenoceptor antagonists have also been shown to be effective in alleviating both voiding and storage LUTS associated with BPH. Naftopidil is an alpha-1 adrenoceptor antagonist with a distinct selectivity for the alpha1D receptor showing a threefold selectivity for the alpha1D-adrenoceptor compared to the alpha1A-adrenoceptor (6). It is used for BPH management in Japan because of its fewer side effects, but there is limited evidence of its effectiveness in other populations (7).

Alpha-1-adrenergic antagonists are also used to facilitate the spontaneous passage of stones in the distal ureter.

When alpha-1-adrenergic antagonists are administered for benign prostatic hyperplasia and for medical expulsive therapy, their effect at various sites of the uro-genital tract may affect sexual function, with differences between drugs within the same class.

The aim of this study is to review the existing evidence on the effect of alpha-1-adrenergic antagonists on sexual function.

MATERIALS AND METHODS

The review was conducted in accordance with PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) guidelines (8). It was registered on the PROSPERO platform as CRD42021283385.

We included in this review *randomized controlled trials* (RCTs), with single/double blinded design involving participants of any age or ethnicity who were treated with alpha adrenergic receptor antagonists for different conditions such as arterial hypertension, bladder neck obstruction by *benign prostatic hyperplasia* (BPH) or ureteral obstruction by ureteral stones (medical expulsive treatment or MET).

The following outcomes were considered: (i) rate of ejaculatory disorders, (ii) rate of erectile disorders, (iii) scores of tests measuring erectile (IIEF-5) or ejaculatory activity (MSHQ-EJD, DAN-PSSsex).

Two electronic databases (PubMed and EMBASE) were

searched for articles published up to September 30th, 2021. Database interrogation was performed using specific search strings; for example, the PubMed search was preferentially based on MeSH terms (('adrenergic alpha-antagonists/exp OR 'adrenergic alpha-antagonists' OR (adrenergic AND 'alpha antagonists') OR 'alfuzosin'/exp OR alfuzosin OR 'silodosin'/exp OR silodosin OR 'tamsulosin'/exp OR tamsulosin) AND ('ejaculation'/exp OR ejaculation OR 'erectile dysfunction'/exp OR 'erectile dysfunction' OR (erectile AND dysfunction)) AND [randomized controlled trial]/lim).

Relevant data were also hand searched by browsing various sources (e.g., reference lists from reviews and study reports, congress abstracts, clinical trial registers such as www.clinicaltrials.gov, www.clinicaltrialsregister.eu, etc.).

Title and abstract screening to exclude documents that did not meet the inclusion criteria was performed independently by two authors. Duplicate references were deleted. Controversies were resolved by a third researcher.

Full texts were downloaded to confirm or reject inclusion and to extract relevant information. Data extraction was conducted by two authors using a standardized form.

The following information was obtained from each study: authors, publication year, study design, population, intervention, effect on sexual function (erectile, ejaculatory). In case of missing or insufficient information, we analyzed the impact of missing data on the meta-analysis results and evaluated the potential risk of bias.

Two authors independently performed the quality assessment by identifying potential biases using the *Risk of Bias* (ROB)-2 assessment tool of the Cochrane Collaboration (9). Study quality was evaluated based on pre-defined criteria in relation to randomization process (D1), deviations from the intended interventions (D1), missing outcome data (D3), measurement of the outcome (D4) and selection of the reported result (D5). For each ROB domain, an evaluation was given, based on a specific algorithm, resulting in the following rating: low risk, some concern, high risk. Disagreements were resolved by discussion. The presence of risk of bias did not influence the decision to include/exclude a study from quantitative analysis.

Statistical analysis

Statistical analysis was performed using the RevMan5 software. Dichotomous data (presence/absence of sexual dysfunction) and number of per-protocol or intent-to-treat patients were extracted to calculate *odds ratios* (OR), 95% *confidence intervals* (CI) to odds-ratios, and Z statistics (Random-effects model, Mantel-Haenszel method). Study heterogeneity was assessed by calculating I^2 (and 95% CI), which was interpreted as of lesser importance ($I^2 \leq 40\%$), moderate ($I^2 = 30\%-60\%$), substantial ($I^2 = 50\%-90\%$) or considerable ($I^2 \geq 75\%$), according to Cochrane criteria.

Funnel plots were drawn and visually evaluated to detect publication bias and small study effects. If publication bias was suspected, the Egger's and Begg's tests were implemented to assess funnel plot symmetry or asymmetry. Asymmetry tests were performed using the MetaEssentials-1 software (Rotterdam School of Management, Erasmus University, The Netherlands). The 'trim and fill' missing study imputation approach was applied to funnel plots; if

missing studies were imputed by this procedure, adjusted overall effect sizes (odds ratios) were calculated.

RESULTS

A PRISMA flow diagram illustrates the results of study selection process (Figure 1). We retrieved 612 records (PubMed, 152; EMBASE, 456; other sources, 4). After title and abstract screening, we selected 125 articles by title and abstract screening (PubMed = 45 papers, EMBASE = 80). Following removal of 23 duplicates, the full text of the remaining 102 articles were examined. Twenty-seven articles were excluded (2 because alpha-blockers were expressly used to treat premature ejaculation or as male oral contraceptives, 6 open-label studies, 5 non-controlled studies, 4 studies not reported in English, 3 reviews, 4 short term experimental studies in healthy subjects, 3 studies not reporting sexual function outcomes).

The remaining 75 papers were included in three analyses: alpha-blockers versus placebo (N=36) (10-45), comparison of different alpha-blockers (N=31) (46-76) and comparison of alpha-blockers administered at different dosages (N=8) (77-84) (**Supplementary Materials - PICO Tables**).

Risk of bias

Among the 75 studies included in qualitative analysis, the method of randomization was deemed to be at low risk of bias in 46 cases, and to unclear risk in 29.

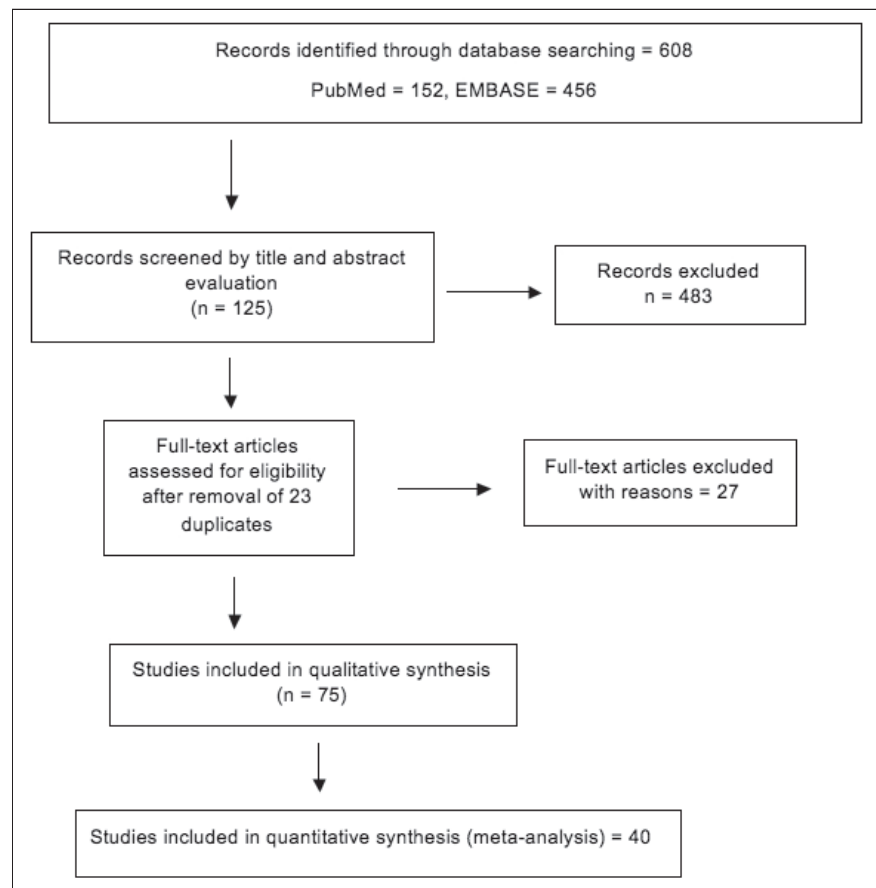
The risk of deviation from the intended intervention was rated as low in 62 studies, unclear in 12 and high in one. The ROB associated to missing outcome data was considered to be low in 63 studies and unclear in 12. The risk of bias in measurement of outcome was considered to be low in 70 studies and unclear in 5. The risk of bias generated by selection of the reported results was rated as low in 73 studies and as unclear in 2.

In total risk of bias was considered low in 37 studies, unclear in 35 and high in 3 (**Supplementary Materials - Risk of Bias**).

Analysis of funnel plots symmetry by Egger's and Begg's tests, and adjusted odds ratios when missing studies were imputed by the trim-and-fill procedure are shown in the (**Supplementary Materials - Funnel plots & Symmetry tests**). Significant asymmetry was detected by at least one test for any kind of alpha blockers (uroselective, non-uroselective or both) compared to placebo in BPH patients (endpoint: ejaculation), in the alpha blockers vs. standard care comparison in stone patients (endpoint: ejaculation), and in the alpha blockers vs. standard care or placebo comparison in stone patients (endpoint: ejaculation). Imputation of missing studies by the trim-and-fill procedure was implemented in 4 comparisons. In 3 cases, the significance or non-significance of adjusted odds ratios was not modified by imputation.

Conversely, the adjusted odds ratio for ejaculatory disorders in stone patients treated with alpha adrenoceptor blockers compared to placebo lost statistical significance.

Figure 1.
Flow chart.



Alpha-blockers versus placebo

A total of 36 studies were included in this analysis: 15 studies evaluated ejaculatory disorders secondary to treatment with alpha-blockers compared to placebo (9 in patients with BPH, 1 in patients with CP/CPPS, 5 in patients with ureteral stones) (10-24). In 7 studies ejaculatory disorders were compared in patients on treatment with alpha-blockers compared with standard conservative treatment of ureteral stones (25-31). In 9 studies, both ejaculatory and erectile dysfunction after treatment with alpha-blockers were compared to placebo in patients with BPH (32-40). Finally, 5 studies reported the effect on erectile function of alpha-blockers compared to placebo in BPH patients (41-45).

Endpoint: ejaculatory disorders

Compared to placebo, alpha-blockers were associated with significantly increased odds of ejaculatory disorders in patients with LUTS associated to BPH (OR: 7.53, 95% CI: 3.77 to 15.02, 23 series from 19

studies, 13006 participants, $Z = 5.73$, $p < 0.00001$, $I^2 = 55\%$ (Figure 2).

Similarly, in patients with ureteral stones, patients taking alpha-blockers showed significantly higher odds for ejaculatory disorders, compared to patients receiving placebo or standard care (OR: 2.86, 95% CI: 1.50 to 5.44, 12 series from 12 studies, 3192 participants, $Z = 3.19$, $p < 0.001$, $I^2 = 31\%$) (Figure 3).

Significantly higher odds for ejaculatory disorders were

confirmed in patients with ureteral stones taking alpha-blockers compared to patients either on placebo or on standard treatment (*Forest plots shown in Supplementary Materials - Forest plots Figures 1-2*). Compared to placebo, uroselective alpha-blockers showed significantly higher odds of ejaculatory disorders (OR: 11.46, 95% CI: 5.58 to 23.54, 16 series from 13 studies, 8580 participants, $Z = 6.64$, $p < 0.00001$, $I^2 = 49\%$ (Figure 4), whereas non-selective alpha-blockers were not associated with higher

Figure 2.

Odds for ejaculatory disorders in patients with LUTS associated to BPH taking alpha-blockers.

Data to the right of the vertical no-effect axis indicate higher odds for ejaculatory disorders in patients treated with alpha adrenoceptor blockers (both uroselective and non-uroselective), compared to placebo.

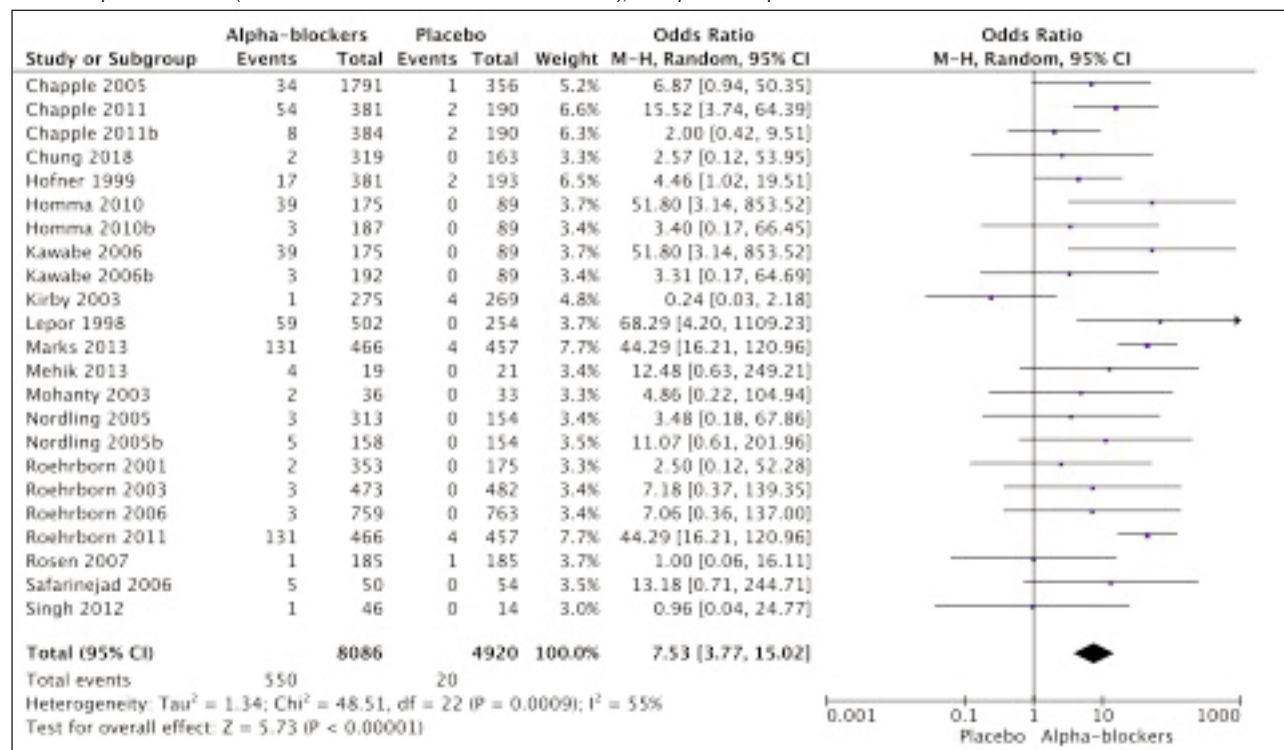


Figure 3.

Odds for ejaculatory disorders in patients with ureteral stones taking alpha-blockers for medical expulsive treatment.

Data to the right of the vertical no-effect axis indicate higher odds for ejaculatory disorders in patients treated with alpha adrenoceptor blockers compared to placebo or standard treatment.

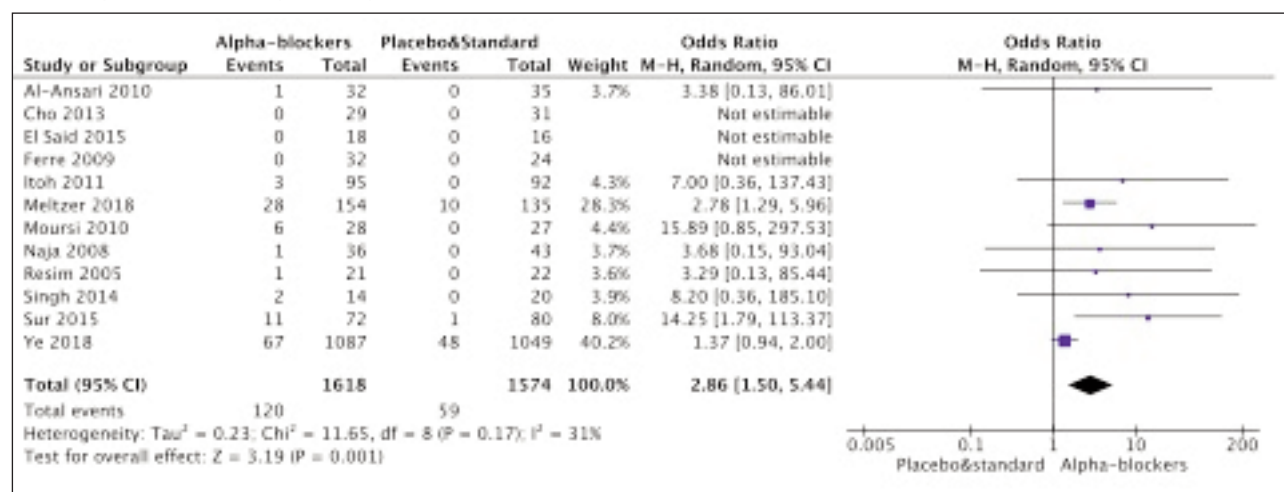
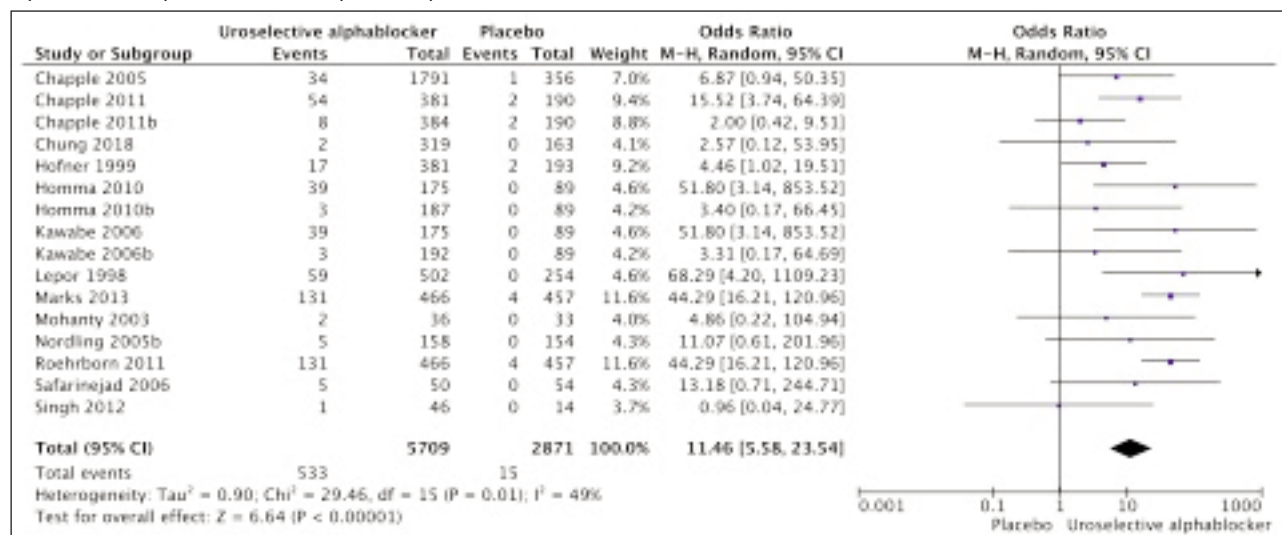
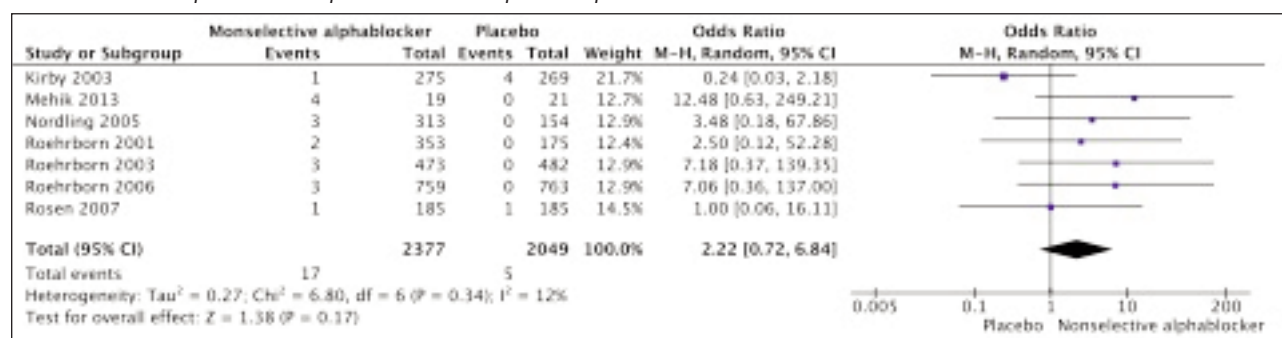


Figure 4.

Odds for ejaculatory disorders in patients in patients with LUTS associated to BPH taking uroselective alpha-blockers. Data to the right of the vertical no-effect axis indicate higher odds for ejaculatory disorders in patients treated with uroselective alpha adrenoceptor blockers compared to placebo.

**Figure 5.**

Odds for ejaculatory disorders in patients in patients with LUTS associated to BPH taking non-uroselective alpha-blockers. Data to the right of the vertical no-effect axis indicate higher odds for ejaculatory disorders in patients treated with non-uroselective alpha adrenoceptor blockers compared to placebo.



odds of ejaculatory dysfunction (OR: 2.22, 95% CI: 0.72 to 6.84, 7 series, 4426 participants, $Z = 1.38$, $p = 0.17$, $I^2 = 12\%$) (Figure 5).

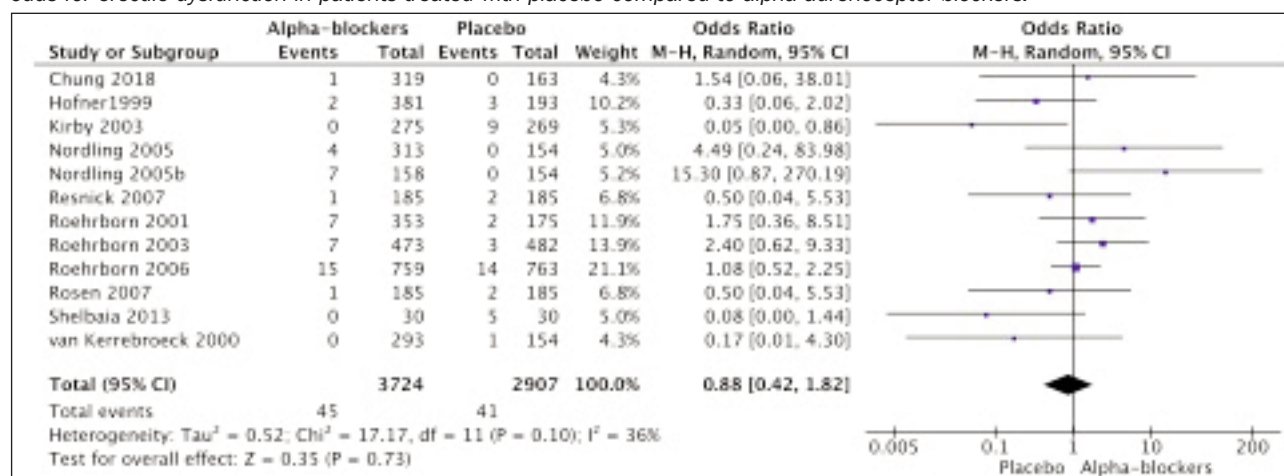
Endpoint: erectile dysfunction

The presence of erectile dysfunction in patients treated with alpha-blockers was investigated in 14 studies. Eleven studies (12 series) reported the rates of erectile dysfunction in patients on treatment with alpha-blockers (any kind) in comparison with placebo (32-39, 43-45). There was no statistically significant difference between the odds of erectile dysfunction assessed in the alpha-blocker treatment arm compared to placebo (OR: 0.88, 95% CI: 0.42 to 1.82, 12 series, 6631 participants, $Z = 0.35$, $p = 0.73$, $I^2 = 36\%$) (Figure 6). The lack of a significant inter-arm difference versus placebo was confirmed when uroselective and non-selective alpha-blockers were analyzed separately (**Forest plots shown in Supplementary Materials - Forest plots Figures 3, 4**). In three of the above reported studies, erectile function alterations were also evaluated by administering questionnaires to enrolled patients. Hofner *et al.* (33) evaluat-

ed the effect of alpha-blockers on sexual function by administering a quality-of-life assessment questionnaire including three questions on sexual function (interest in sex, erection, ejaculation). The authors reported the overall evaluation of sexual function without showing the results of the three separate domains. A trend to improvement of the overall sexual function was observed after tamsulosin ($p = 0.042$), whereas no differences were observed when tamsulosin was compared to alfuzosin. Rosen *et al.* (39) reported changes of the DAN-PSSsex score after alfuzosin treatment. The DAN-PSSsex tool includes questions on erectile and ejaculatory function, and on bother associated with these two functions. Alfuzosin treatment was associated with a significant improvement of erectile function compared with placebo ($p = 0.02$), whereas treatment didn't appear to influence the ejaculatory function. Shelbaia *et al.* (44) observed that the use of tamsulosin was associated with increased IIEF scores ($p = 0.047$) in patients with LUTS and erectile dysfunction. Three additional studies were not included in our quantitative analysis. One study evaluated the effects of the oral administration of the nonselective alpha-

Figure 6.

Odds for erectile dysfunction in BPH patients taking alpha-blockers. Data to the left of the vertical no-effect axis indicate lower odds for erectile dysfunction in patients treated with placebo compared to alpha adrenoceptor blockers.



adrenergic antagonist phentolamine in patients with erectile dysfunction. Full erection was achieved after on-demand administration of phentolamine at different doses (from 20 to 60 mg) more frequently than after placebo. However, the sample size was too small for statistical analysis (41). Another study evaluated the effect of a single dose of the selective, orally-active alpha-1-adrenoceptor antagonist Ro70-0004 on the erectile function in a group of men with erectile dysfunction. Ro70-0004 did not improve the erectile function when compared to placebo (42). Finally, in patients with painful ejaculation, Safarinejad *et al.* (40) found that the intercourse satisfaction domain IIEF scores were not significantly improved after tamsulosin ($p = 0.08$).

Other endpoints

Few studies reported about the alterations of sexual desire

after administration of alpha-blockers. No significant differences of desire after alfuzosin or tamsulosin and placebo were reported. Kirby *et al.* (34) reported similar decreases of libido after alfuzosin or placebo (-3.6% vs -1.9%, $P = 0.58$). Van Kerrebroeck *et al.* (45) reported no cases of decreased desire after alfuzosin 10 mg/day, 0.7% cases after alfuzosin 2.5 mg t.i.d. and 0.7% cases after placebo. Hofner *et al.* (33) reported no differences between tamsulosin and placebo (0.8% vs 0%, $p = 0.306$) and Singh *et al.* (19) no cases of decreased desire after both tamsulosin or placebo. Hofner *et al.* (33) found no cases of decreased libido after tamsulosin or alfuzosin.

Comparisons between alpha-blockers

A total of 31 studies compared the effect of different alpha-blockers on sexual function (46-76). Out of 31 trials, 15 compared the risk of ejaculatory disorders after

Figure 7.

Odds for ejaculatory disorders in patients taking silodosin or tamsulosin. Data to the right of the vertical no-effect axis indicate higher odds for ejaculatory disorders in patients treated with silodosin.

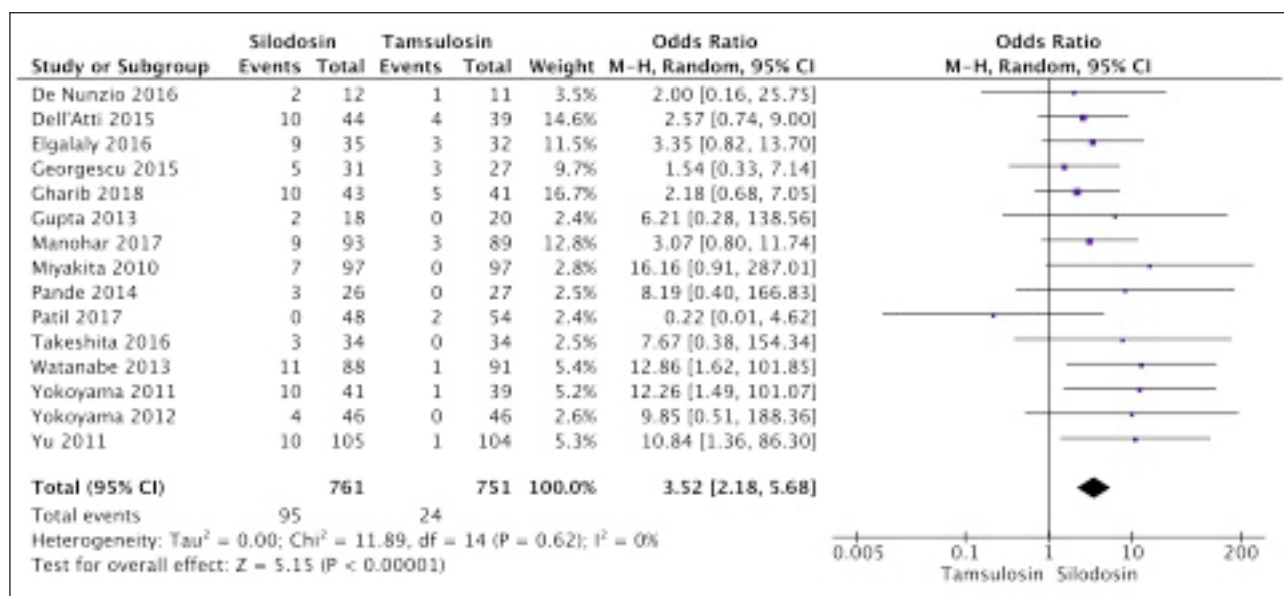
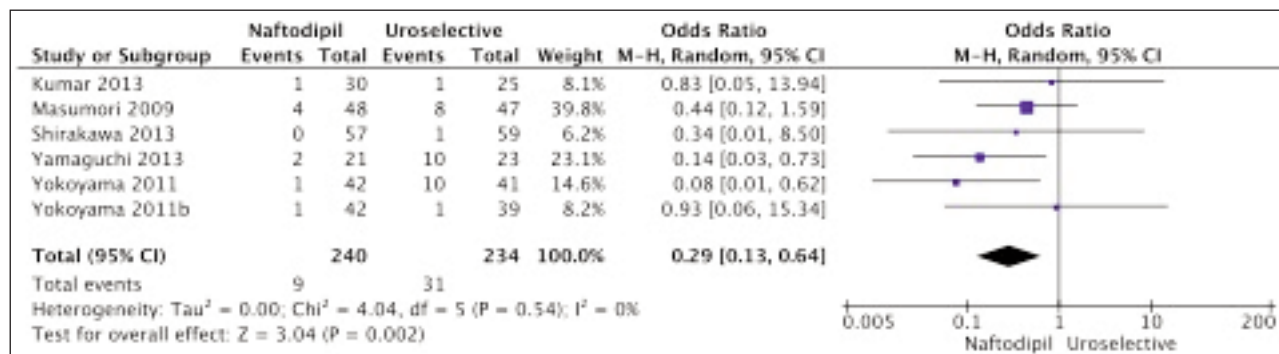


Figure 8.

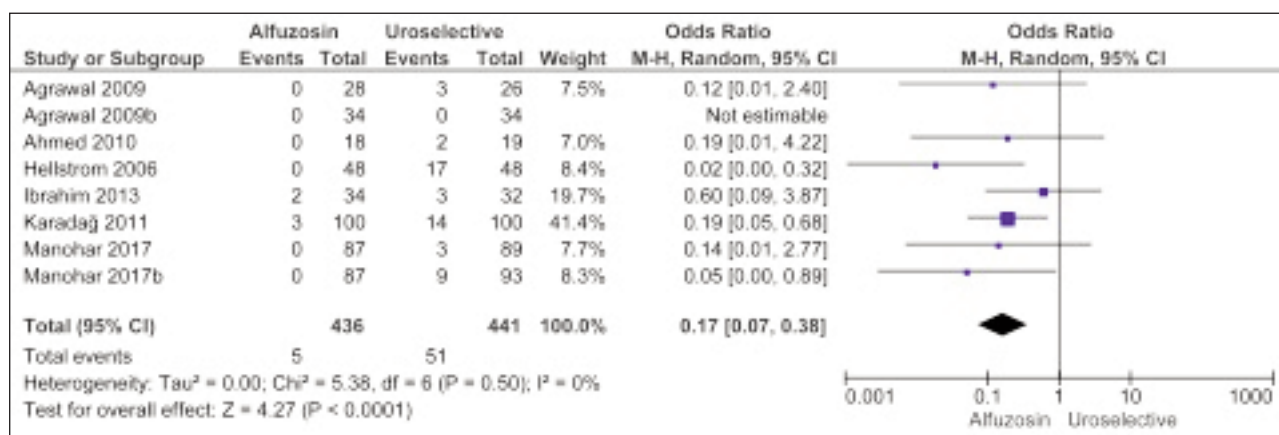
Odds for ejaculatory disorders in patients taking naftopidil or uroselective alpha-blockers.

Data to the left of the vertical no-effect axis indicate lower odds for ejaculatory disorders in patients treated with naftopidil compared to uroselective alpha adrenoceptor blockers.

**Figure 9.**

Odds for ejaculatory disorders in patients taking alfuzosin compared to uroselective alpha-blockers.

Data to the left of the vertical no-effect axis indicate lower odds for ejaculatory disorders in patients treated with alfuzosin.



tamsulosin compared with silodosin (49-54, 60, 62, 64, 65, 70, 71, 73-75), 5 studies evaluated the effect of naftopidil compared with a uroselective alpha-blocker on ejaculation (including a study comparing naftopidil with both tamsulosin and silodosin) (59, 61, 68, 72, 73), 7 studies compared alfuzosin with uroselective alpha-blockers (46-48, 55-57, 60), 4 studies compared terazosin or doxazosin with tamsulosin (58, 63, 66, 76) and one study terazosin with doxazosin (67).

Silodosin was associated with significantly increased odds of ejaculatory dysfunction compared with tamsulosin (OR: 3.52, 95% CI: 2.18 to 5.68, 15 series, 1512 participants, $Z = 5.15$, $p < 0.00001$, $I^2 = 0\%$) (Figure 7).

Naftopidil showed significantly lower odds of ejaculatory dysfunction compared to uroselective alpha-blockers (OR: 0.29, 95% CI: 0.13 to 0.64, 6 series from 5 studies, 474 participants, $Z = 3.04$, $p = 0.002$, $I^2 = 0\%$) (Figure 8).

Alfuzosin was associated with significantly lower odds of ejaculatory disorders compared to uroselective alpha-blockers (OR: 0.17, 95% CI: 0.07 to 0.38, 8 series from 7 studies, 877 participants, $Z = 4.27$, $p < 0.0001$, $I^2 = 0\%$) (Figure 9).

Summary of findings

Summary of finding (SOF) tables, containing illustrative

comparative risks (assumed control risks and corresponding intervention risks) and odds ratios relative to each single meta-analysis are presented as **Supplementary Materials. SOF tables** also contain evaluations of the quality of the evidence relative to each meta-analysis, rated according to GRADE criteria.

Single studies not included in quantitative analysis

Zaytoun *et al.* (2/50 vs 0/50) (76), Pompeo *et al.* (4/83 vs 2/82) (66) and Kirby *et al.* (2/50 vs 0/48) (58) observed more frequently ejaculatory disorders after tamsulosin compared to doxazosin.

Narayan *et al.* (63) described higher rates of ejaculatory dysfunction after tamsulosin compared to terazosin [37/1002 (3.7%) vs 3/981 (0.3%)].

Samli *et al.* (67) observed similar rates of erectile dysfunction after doxazosin versus terazosin (0/25 vs 1/25).

Comparison between different dosages of alpha-blockers We retrieved 8 studies (77-84) designed to compare the clinical efficacy and tolerability of different alpha-blockers administered at different doses and time intervals.

The designs of the studies were too heterogenous for quantitative analysis.

No differences in the rate of ejaculatory disorders were observed with different formulations and different doses

of doxazosin (4 mg vs 8 mg) (77, 78). The improvement in IIEF scores after extended-release doxazosin (4 or 8 mg once daily) was similar to the one observed after fast-release doxazosin (1-8 mg once daily) (78).

Similarly, the administration of tamsulosin at different doses resulted in similar effects on ejaculatory function (81-83). Rates of ejaculatory disorders were not different after tamsulosin 0.4 mg versus 0.2 mg (81, 82), or 0.4 mg once daily every other day (83).

The timing of administration of silodosin appears to change the effects of the drug on sexual function. Silodosin 4 mg twice-daily induced a higher rate of ejaculatory disorders compared to silodosin 4 mg taken once a day (10/115 vs 67/115) or silodosin 8 mg administered after breakfast (46/208 vs 32/212) (79, 80).

Discussion

Alpha-1 adrenoceptor blockers have been shown to be very effective in counteracting lower urinary tract symptoms associated with benign prostatic hyperplasia (85, 86), as well as in facilitating the spontaneous passage of stones from the distal ureter (87, 88). However, this class of drugs can lead to cardiovascular side effects and sexual dysfunction, thus potentially worsening the quality of life of patients and possibly causing a reduction in the compliance to long-term treatment. Since alpha-adrenergic receptors are highly expressed in male genital organs, adrenergic blockade can potentially affect erection, ejaculation, and sexual desire.

Ejaculation

The influence of alpha-blockers on ejaculation is well known, although the underlying physiological mechanism for such effect is not yet well defined. Our analysis confirms that the odds for ejaculation disorders are greater in patients taking alpha-blockers of any kind, compared to placebo. Moreover, when the effects of different alpha-blocking agents are analyzed separately, the odds for abnormal ejaculation are greater upon administration of uroselective alpha blockers (tamsulosin and silodosin). Conversely, comparison between alfuzosin and placebo does not result in statistically significant results. The comparison between different alpha-blocking agents showed that silodosin and tamsulosin were more frequently associated with ejaculation disorders when compared to non-selective alpha-blockers.

Tamsulosin and, to a greater extent, silodosin, show super-selective binding with the alpha1A receptor, while alfuzosin, doxazosin and terazosin show comparable affinity with the three subtypes of alpha1-adrenergic receptors. Naftopidil on the other hand exhibits a unique selectivity for alpha1B receptors. The different binding affinity (or selectivity) for alpha1-adrenergic receptor subtypes explains the different effects of alpha-blockers on ejaculation. Ejaculatory disorders associated with administration of alpha-1 blockers were initially thought to be a consequence of bladder neck relaxation, causing in turn retrograde ejaculation. Further studies clarified the mechanisms whereby ejaculation disorders occur following the use of uroselective alpha-blockers. Disorders of ejaculation after tamsulosin and silodosin have been

related to both a peripheral effect on the vas deferens and/or seminal vesicles and a central effect in the coordination of ejaculation (89). At the peripheral level, ejaculation disorders have been related to the decreased capacity of contraction of the seminal vesicles and of the vas deferens. This is supported by the evidence that alpha-1A adrenoceptor subtype mRNA is predominant in human seminal vesicles, and that spermatic cells are not detected in the urine after ejaculation following silodosin administration. This shows that ejaculatory dysfunction caused by silodosin is not related to retrograde ejaculation but rather to a loss of seminal emission (90, 91). Similarly, administration of 0.8 mg tamsulosin to healthy volunteers resulted in reduction of the ejaculatory volume in almost all subjects, without causing a significant difference in post-ejaculation urinary sperm concentrations when compared to placebo or alfuzosin (92). Unlike other alpha1-blockers, tamsulosin can cross the blood-brain barrier and bind to dopaminergic and/or serotonergic receptors that are involved in the central coordination of ejaculation (93). A strong affinity of alpha1-adrenoceptor antagonists for D2- and 5HT1A-like receptors has been demonstrated, suggesting that these drugs may act as antagonists of dopaminergic receptors mediating the contraction of the vas deferens (94).

Erection

There are conflicting data about the effect of alpha-blockers on erection, mainly because the erectile function is the result of a complex interplay between multiple biochemical signals responding to several neurotransmitters and vasoactive agents. Basically, penile tumescence is associated with relaxation of the erectile tissue whereas detumescence is caused by contraction of the erectile tissue. Postsynaptic alpha1-adrenoceptor activation causes the contraction of the erectile tissue, leading to penile flaccidity and detumescence. For this reason, alpha-adrenoceptor antagonists can promote the relaxation of the muscles of the trabeculae of the corpora cavernosa and induce erection, as demonstrated by erection induced by intra-cavernous injection of alpha-adrenoceptor antagonists (95, 96).

In addition, alpha-blocker-induced priapism is a rare but well documented side effect of treatment (97).

At the systemic level, blockage of adrenergic receptors has a more complex effect on the regulation of erectile function because it can occur at both peripheral and central levels (through ascending pathways to the brain and descending pathways to the spinal cord) and involve various alpha1- or alpha2-adrenoceptor subtypes. The effect of each drug will depend on the central and peripheral effects exerted on the different receptors, causing in turn specific effects on erectile function (98). Finally, hemodynamic effects of non-selective alpha-blockers may harm erectile function because of symptomatic hypotension side effects (99).

Our meta-analysis demonstrated neither greater odds of erectile dysfunction or impotence upon exposure to alpha-blockers, nor differences of odds of erectile dysfunction evoked by treatment with uroselective or non-selective alpha-blockers compared to placebo.

Thus, the potential effect of alpha-blockers on erectile

function therefore remains unknown. In our analysis we excluded studies that evaluated the effects of combination therapy with alpha-1 adrenergic antagonists and phosphodiesterase-5 (PDE5) inhibitors on sexual function.

Interestingly, some studies have shown an additive favorable effect of the combined use of alpha-blockers and PDE5 inhibitors on erectile dysfunction (100).

In 2014, a meta-analysis demonstrated that alpha-blockers may enhance the efficacy of PDE5 inhibitors on erectile dysfunction in men with LUTS suggestive of BPH (101). However, a more recent review found no significant difference of the mean change of IIEF between combination therapy and PDE5 inhibitors-monotherapy concluding that benefits regarding the treatment of ED are not clear (102).

Limitations

A limitation of this meta-analysis is the disparity of assessment criteria and definitions used to describe sexual dysfunction associated with alpha-blockers.

Ejaculation disorders have been defined indifferently as abnormal ejaculation, ejaculatory disorders, decreased ejaculatory volume, anejaculation, and retrograde ejaculation. Some of these terms are generic, others imply specific pathophysiological alterations that may not correspond to clinically observable manifestations.

The presence of retrograde ejaculation has been questioned by recent studies which have shown that the ejaculatory alterations caused by alpha-blockers are due to a lack of semen emission, that should be better defined as anejaculation. The different physiological mechanisms that are at the origin of failure of semen emission, or of retrograde ejaculation, can be associated with different orgasmic dysfunctions. On the other hand, ejaculation disorders have rarely been evaluated with specific questionnaires such as DAN-PSS or MSQH.

Erectile dysfunction was also not uniquely defined in the different studies that used both the term impotence and erectile dysfunction, with only a few studies assessing the latter with the IIEF questionnaire.

In order to take into account the diversity of diagnostic methods and tools used to ascertain ejaculatory or erectile dysfunction in included studies, we have used in all metanalyses a random-effect model (103).

CONCLUSIONS

In conclusion, because of the different effects of alpha-1 adrenergic antagonists on sexuality, the sexual function of each patient should be assessed and discussed when alpha-blocker therapy is planned, and patients should be informed about the potential side effects of such treatment. When prescribing a specific alpha-blocker, the specialist should consider the needs and expectations of the patient, to ensure the best possible quality of life.

REFERENCES

1. Frishman WH, Kotob F. Alpha-adrenergic blocking drugs in clinical medicine. *J Clin Pharmacol*. 1999; 39:7-16.
2. Civantos Calzada B, Alexandre de Artiñano A. Alpha-adrenoceptor subtypes. *Pharmacol Res*. 2001; 44:195-208.

3. Graham RM. Selective alpha 1-adrenergic antagonists: therapeutically relevant antihypertensive agents. *Am J Cardiol*. 1984; 53:16A-20A.
4. Heran BS, Galm BP, Wright JM. Blood pressure lowering efficacy of alpha blockers for primary hypertension. *Cochrane Database Syst Rev*. 2012; (8):CD004643.
5. Lepor H. Alpha-blockers for the Treatment of Benign Prostatic Hyperplasia. *Urol Clin North Am*. 2016; 43:311-23.
6. Ishihama H, Momota Y, Yanase H, et al. Activation of alpha1D adrenergic receptors in the rat urothelium facilitates the micturition reflex. *J Urol*. 2006; 175:358-64.
7. Hwang EC, Gandhi S, Jung JH, et al. Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia. *Cochrane Database Syst Rev*. 2018; 10:CD007360.
8. Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med*. 2009; 6:e1000097.
9. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366:l4898.
10. Chapple CR, Al-Shukri SH, Gattegno B, et al. Tamsulosin oral controlled absorption system (OCAS) in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH): Efficacy and tolerability in a placebo and active comparator controlled phase 3^a study *Eur Urol*. (Supplements) 2005; 4:33-44.
11. Chapple CR, Montorsi F, Tammela TL, et al. European Silodosin Study Group. Silodosin therapy for lower urinary tract symptoms in men with suspected benign prostatic hyperplasia: results of an international, randomized, double-blind, placebo- and active-controlled clinical trial performed in Europe. *Eur Urol*. 2011; 59:342-52.
12. Homma Y, Kawabe K, Takeda M, Yoshida M. Ejaculation disorder is associated with increased efficacy of silodosin for benign prostatic hyperplasia. *Urology* 2010; 76:1446-1450.
13. Kawabe K, Yoshida M, Homma Y, Silodosin Clinical Study Group. Silodosin, a new alpha1A-adrenoceptor-selective antagonist for treating benign prostatic hyperplasia: results of a phase III randomized, placebo-controlled, double-blind study in Japanese men. *BJU Int*. 2006; 98:1019-24.
14. Lepor H. Phase III multicenter placebo-controlled study of tamsulosin in benign prostatic hyperplasia. Tamsulosin Investigator Group. *Urology*. 1998; 51:892-900.
15. Marks LS, Gittelman MC, Hill LA, et al. Rapid efficacy of the highly selective alpha(1A)-adrenoceptor antagonist silodosin in men with signs and symptoms of benign prostatic hyperplasia: pooled results of 2 phase 3 studies. *J Urol*. 2013; 189(1 Suppl):S122-8.
16. Mehik A, Alas P, Nickel JC, et al. Alfuzosin treatment for chronic prostatitis/chronic pelvic pain syndrome: a prospective, randomized, double-blind, placebo-controlled, pilot study. *Urology*. 2003; 62:425-9.
17. Mohanty NK, Nayak RL, Malhotra V, Arora RP. A double-blind placebo controlled study of tamsulosin in the management of benign prostatic hyperplasia in an Indian population. *Ann College of Surgeons of Hong Kong*. 2003; 7:88-93.
18. Roehrborn CG, Kaplan SA, Lepor H, Volinn W. Symptomatic and urodynamic responses in patients with reduced or no seminal emission during silodosin treatment for LUTS and BPH. *Prostate Cancer Prostatic Dis*. 2011; 14:143-8.
19. Singh P, Singh A, Indurkar M, Raj B. Efficacy and safety of tamsulosin (0.4 mg) once daily for treating symptomatic benign prostatic

- hyperplasia. *Asian Journal of Pharmaceutical and Clinical Research* 2012; 5(Suppl 4):87-91.
20. Al-Ansari A, Al-Naimi A, Alobaidy A, et al. Efficacy of tamsulosin in the management of lower ureteral stones: a randomized double-blind placebo-controlled study of 100 patients *Urology*. 2010; 75:4-7.
 21. Meltzer AC, Burrows PK, Wolfson AB, et al. Effect of tamsulosin on passage of symptomatic ureteral stones: A randomized clinical trial *JAMA Intern Med*. 2018; 178:1051-1057.
 22. Singh I, Tripathy S, Agrawal V. Efficacy of tamsulosin hydrochloride in relieving "double-J ureteral stent-related morbidity": a randomized placebo controlled clinical study. *Int Urol Nephrol*. 2014; 46:2279-83.
 23. Sur RL, Shore N, L'Esperance J, et al. Silodosin to facilitate passage of ureteral stones: a multi-institutional, randomized, double-blinded, placebo-controlled trial. *Eur Urol*. 2015; 67:959-64.
 24. Ye Z, Zeng G, Yang H, et al. Efficacy and safety of tamsulosin in medical expulsive therapy for distal ureteral stones with renal colic: a multicenter, randomized, double-blind, placebo-controlled trial. *Eur Urol*. 2018; 73:385-391.
 25. Cho HJ, Shin SC, Seo DY, et al. Efficacy of alfuzosin after shock wave lithotripsy for the treatment of ureteral calculi *Korean J Urol*. 2013; 54:106-110.
 26. El Said NO, El Wakeel L, Kamal KM, Morad Ael R. Alfuzosin treatment improves the rate and time for stone expulsion in patients with distal ureteral stones: a prospective randomized controlled study. *Pharmacotherapy*. 2015; 35:470-6.
 27. Ferre RM, Wasielewski JN, Strout TD, Perron AD. Tamsulosin for ureteral stones in the emergency department: a randomized, controlled trial. *Ann Emerg Med*. 2009; 54:432-9, 439.e1-2.
 28. Itoh Y, Okada A, Yasui T, et al. Efficacy of selective alpha1A adrenoceptor antagonist silodosin in the medical expulsive therapy for ureteral stones. *Int J Urol*. 2011; 18:672-4.
 29. Moursy E, Gamal WM, Abuzeid A. Tamsulosin as an expulsive therapy for steinstrasse after extracorporeal shock wave lithotripsy: a randomized controlled study. *Scand J Urol Nephrol*. 2010; 44:315-9.
 30. Naja V, Agarwal MM, Mandal AK, et al. Tamsulosin facilitates earlier clearance of stone fragments and reduces pain after shock-wave lithotripsy for renal calculi: results from an open-label randomized study. *Urology*. 2008; 72:1006-11.
 31. Resim S, Ekerbicer HC, Ciftci A. Role of tamsulosin in treatment of patients with steinstrasse developing after extracorporeal shock wave lithotripsy. *Urology*. 2005; 66:945-8.
 32. Chung JH, Oh CY, Kim JH, et al. Efficacy and safety of tamsulosin 0.4mg single pills for treatment of Asian patients with symptomatic benign prostatic hyperplasia with lower urinary tract symptoms: a randomized, double-blind, phase 3 trial. *Curr Med Res Opin*. 2018; 34:1793-1801.
 33. Höfner K, Claes H, De Reijke TM, et al. Tamsulosin 0.4 mg once daily: effect on sexual function in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. *Eur Urol*. 1999; 36:335-41.
 34. Kirby RS, Roehrborn C, Boyle P, et al. Prospective European Doxazosin and Combination Therapy Study Investigators. Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PRE-DICT) trial. *Urology*. 2003; 61:119-26.
 35. Nordling J. Efficacy and safety of two doses (10 and 15 mg) of alfuzosin or tamsulosin (0.4 mg) once daily for treating symptomatic benign prostatic hyperplasia. *BJU Int*. 2005; 95:1006-12.
 36. Roehrborn CG. Efficacy and safety of once-daily alfuzosin in the treatment of lower urinary tract symptoms and clinical benign prostatic hyperplasia: a randomized, placebo-controlled trial. *Urology*. 2001; 58:953-9.
 37. Roehrborn CG, Van Kerrebroeck P, Nordling J. Safety and efficacy of alfuzosin 10 mg once-daily in the treatment of lower urinary tract symptoms and clinical benign prostatic hyperplasia: a pooled analysis of three double-blind, placebo-controlled studies. *BJU Int*. 2003; 92:257-61.
 38. Roehrborn C.G. Alfuzosin 10 mg once daily prevents overall clinical progression of benign prostatic hyperplasia but not acute urinary retention: Results of a 2-year placebo-controlled study *BJU Int*. 2006; 97:734-741.
 39. Rosen R, Seftel A, Roehrborn CG. Effects of alfuzosin 10 mg once daily on sexual function in men treated for symptomatic benign prostatic hyperplasia. *Int J Impot Res*. 2007; 19:480-5.
 40. Safarinejad MR. Safety and efficacy of tamsulosin in the treatment of painful ejaculation: a randomized, double-blind, placebo-controlled study. *Int J Impot Res*. 2006; 18:527-33.
 41. Becker AJ, Stief CG, Machtens S, et al. Oral phentolamine as treatment for erectile dysfunction. *J Urol*. 1998; 159:1214-6.
 42. Choppin A, Blue DR, Hegde SS, et al. Evaluation of oral ro70-0004/003, an alpha1A-adrenoceptor antagonist, in the treatment of male erectile dysfunction. *Int J Impot Res*. 2001; 13:157-61.
 43. Resnick MI, Roehrborn CG. Rapid onset of action with alfuzosin 10 mg once daily in men with benign prostatic hyperplasia: A randomized, placebo-controlled trial *Prostate Cancer Prostatic Dis*. 2007; 10:155-159.
 44. Shelbaia A, Elsaied WM, Elghamrawy H, et al. Effect of selective alpha-blocker tamsulosin on erectile function in patients with lower urinary tract symptoms due to benign prostatic hyperplasia. *Urology*. 2013; 82:130-5.
 45. van Kerrebroeck P, Jardin A, Laval KU, van Cangh P. Efficacy and safety of a new prolonged release formulation of alfuzosin 10 mg once daily versus alfuzosin 2.5 mg thrice daily and placebo in patients with symptomatic benign prostatic hyperplasia. ALFORTI Study Group. *Eur Urol*. 2000; 37:306-13.
 46. Agrawal M, Gupta M, Gupta A, et al. Prospective randomized trial comparing efficacy of alfuzosin and tamsulosin in management of lower ureteral stones. *Urology*. 2009; 73:706-9.
 47. Agrawal MS, Yadav A, Yadav H, et al. A prospective randomized study comparing efficacy of alfuzosin and tamsulosin in the management of patients suffering from acute urinary retention caused by benign prostatic hyperplasia. *Indian J Urol*. 2009; 25:474-478.
 48. Ahmed A.-F.A.-M., Al-sayed A.-Y.S. Tamsulosin versus alfuzosin in the treatment of patients with distal ureteral stones: Prospective, randomized, comparative study. *Korean J Urol*. 2010; 51:193-197.
 49. Dell'Atti L. Silodosin versus tamsulosin as medical expulsive therapy for distal ureteral stones: a prospective randomized study. *Urologia*. 2015; 82:54-7.
 50. De Nunzio C, Brassetti A, Bellangino M, et al. Tamsulosin or silodosin adjuvant treatment is ineffective in improving shockwave lithotripsy outcome: A short-term follow-up randomized, placebo-controlled study *J Endourol*. 2016; 30: 817-821.
 51. Elgalaly H, Sakr A, Fawzi A, et al. Silodosin vs tamsulosin in the management of distal ureteric stones: A prospective randomised study. *Arab J Urol*. 2016; 14:12-17.

52. Georgescu D, Ionita-Radu F, Multescu R, et al. The role of alpha1-blockers in the medical expulsive therapy for ureteral calculi - a prospective controlled randomized study comparing tamsulosin and silodosin. *Farmacia* 2015; 63:184-188.
53. Gharib T, Mohey A, Fathi A, et al. Comparative study between silodosin and tamsulosin in expectant therapy of distal ureteral stones. *Urol Int.* 2018; 101:161-166.
54. Gupta S, Lodh B, Kaku Singh A, et al. Comparing the efficacy of tamsulosin and silodosin in the medical expulsion therapy for ureteral calculi. *J Clin Diagn Res.* 2013; 7:1672-1674.
55. Hellstrom WJ, Sikka SC. Effects of acute treatment with tamsulosin versus alfuzosin on ejaculatory function in normal volunteers. *J Urol.* 2006; 176:1529-33.
56. Ibrahim AK, Mahmood IH, Mahmood NS. Efficacy and safety of tamsulosin vs. alfuzosin as medical expulsive therapy for ureteric stones. *Arab J Urol.* 2013 11:142-147.
57. Karadag E, Öner S, Budak YU, Atahan O. Randomized crossover comparison of tamsulosin and alfuzosin in patients with urinary disturbances caused by benign prostatic hyperplasia. *Int Urol Nephrol.* 2011; 43:949-954.
58. Kirby RS. A randomized, double-blind crossover study of tamsulosin and controlled-release doxazosin in patients with benign prostatic hyperplasia. *BJU Int.* 2003; 91:41-4.
59. Kumar S, Kurdia KC, Ganesamoni R, et al. Randomized controlled trial to compare the safety and efficacy of naftopidil and tamsulosin as medical expulsive therapy in combination with prednisolone for distal ureteral stones. *Korean J Urol.* 2013; 54:311-315.
60. Manohar CMS, Nagabhushana M, Karthikeyan VS, et al. Safety and efficacy of tamsulosin, alfuzosin or silodosin as monotherapy for LUTS in BPH - a double-blind randomized trial. *Cent European J Urol.* 2017; 70:148-153.
61. Masumori N, Tsukamoto T, Iwasawa A, et al. Hokkaido Urological Disorders Conference Writing Group. Ejaculatory disorders caused by alpha-1 blockers for patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: comparison of naftopidil and tamsulosin in a randomized multicenter study. *Urol Int.* 2009; 83:49-54.
62. Miyakita H, Yokoyama E, Onodera Y, et al. Short-term effects of crossover treatment with silodosin and tamsulosin hydrochloride for lower urinary tract symptoms associated with benign prostatic hyperplasia. *Int J Urol.* 2010; 17:869-875.
63. Narayan P, O'Leary MP, Davidai G. Early efficacy of tamsulosin versus terazosin in the treatment of men with benign prostatic hyperplasia: A randomized, open-label trial. *The Journal of Applied Research* 2005; 5:237-245.
64. Pande S, Hazra A, Kundu AK. Evaluation of silodosin in comparison to tamsulosin in benign prostatic hyperplasia: A randomized controlled trial *Indian J Pharmacol* 2014; 46: 601-607.
65. Patil SB, Ranka K, Kundargi VS, Guru N. Comparison of tamsulosin and silodosin in the management of acute urinary retention secondary to benign prostatic hyperplasia in patients planned for trial without catheter. A prospective randomized study *Cent European J Urol.* 2017; 70:259-263.
66. Pompeo AC, Rosenblatt C, Bertero E, et al. Doxazosin and Tamsulosin Study Investigator Group. A randomised, double-blind study comparing the efficacy and tolerability of controlled-release doxazosin and tamsulosin in the treatment of benign prostatic hyperplasia in Brazil. *Int J Clin Pract.* 2006; 60:1172-7.
67. Samli MM, Dincel C. Terazosin and doxazosin in the treatment of BPH: Results of a randomized study with crossover in non-responders. *Urol Int.* 2004; 73:125-129.
68. Shirakawa T, Haraguchi T, Shigemura K, et al. Silodosin versus naftopidil in Japanese patients with lower urinary tract symptoms associated with benign prostatic hyperplasia: A randomized multicenter study *International J Urol.* 2013; 20:903-910.
69. Takahashi S, Yamaguchi K. Treatment of benign prostatic hyperplasia and aging: Impacts of alpha-1 blockers on sexual function. *Journal of Men's Health.* 2011; 8 (Suppl 1):S25-S28.
70. Takeshita H, Moriyama S, Arai Y, et al. Randomized Crossover Comparison of the Short-Term Efficacy and Safety of Single Half-Dose Silodosin and Tamsulosin Hydrochloride in Men With Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia. *Low Urin Tract Symptoms.* 2016; 8:38-43.
71. Watanabe T, Ozono S, Kageyama S. A randomized crossover study comparing patient preference for tamsulosin and silodosin in patients with lower urinary tract symptoms associated with benign prostatic hyperplasia. *J Int Med Res.* 2011; 39:129-142.
72. Yamaguchi K, Aoki Y, Yoshikawa T, et al. Silodosin versus naftopidil for the treatment of benign prostatic hyperplasia: a multicenter randomized trial. *Int J Urol.* 2013; 20:1234-8.
73. Yokoyama T, Hara R, Fukumoto K, et al. Effects of three types of alpha-1 adrenoceptor blocker on lower urinary tract symptoms and sexual function in males with benign prostatic hyperplasia. *Int J Urol.* 2011; 18:225-30.
74. Yokoyama T, Hara R, Fujii T, et al. Comparison of Two Different alpha1-Adrenoceptor Antagonists, Tamsulosin and Silodosin, in the Treatment of Male Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia: A Prospective Randomized Crossover Study LUTS: Lower Urinary Tract Symptoms 2012; 4:14-18.
75. Yu HJ, Lin AT, Yang SS, et al. Non-inferiority of silodosin to tamsulosin in treating patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). *BJU Int.* 2011; 108:1843-8.
76. Zaytoun OM, Yakoubi R, Zahran ARM, et al. Tamsulosin and doxazosin as adjunctive therapy following shock-wave lithotripsy of renal calculi: Randomized controlled trial. *Urological Research.* 2012; 40:327-332.
77. Keten T, Aslan Y, Balci M, et al. Determination of the efficiency of 8 mg doxazosin XL treatment in patients with an inadequate response to 4 mg doxazosin XL treatment for benign prostatic hyperplasia *Urology.* 2015; 85:189-194.
78. Kirby RS, O'Leary MP, Carson C. Efficacy of extended-release doxazosin and doxazosin standard in patients with concomitant benign prostatic hyperplasia and sexual dysfunction. *BJU Int.* 2005; 95:103-9.
79. Choo MS, Song M, Kim JH, et al. Safety and efficacy of 8-mg once-daily vs 4-mg twice-daily silodosin in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (SILVER Study): a 12-week, double-blind, randomized, parallel, multicenter study. *Urology.* 2014; 83:875-81.
80. Seki N, Takahashi R, Yamaguchi A, et al. Non-inferiority of silodosin 4 mg once daily to twice daily for storage symptoms score evaluated by the International Prostate Symptom Score in Japanese patients with benign prostatic hyperplasia: a multicenter, randomized, parallel-group study. *Int J Urol.* 2015; 22:311-6.
81. Kim JJ, Han DH, Sung HH, et al. Efficacy and tolerability of tamsulosin 0.4 mg in Asian patients with lower urinary tract symptoms secondary to benign prostatic hyperplasia refractory to tamsulosin 0.2 mg: a randomized placebo controlled trial. *Int J Urol.* 2014; 21:677-82.

82. Lojanapiwat B, Kochakarn W, Suparatchatpan N, Lertwuttichaiikul K. Effectiveness of low-dose and standard-dose tamsulosin in the treatment of distal ureteric stones: a randomized controlled study. *J Int Med Res.* 2008; 36:529-36.
83. Yanardag H, Goktas S, Kibar Y, et al. Intermittent tamsulosin therapy in men with lower urinary tract symptoms. *J Urol.* 2005; 173:155-7.
84. Hareendran A, Abraham L. Using a treatment satisfaction measure in an early trial to inform the evaluation of a new treatment for benign prostatic hyperplasia. *Value Health.* 2005; 8(Suppl 1):S35-40.
85. Lepor H. Alpha-blockers for the Treatment of Benign Prostatic Hyperplasia. *Urol Clin North Am.* 2016; 43:311-23.
86. Nickel JC, Sander S, Moon TD. A meta-analysis of the vascular-related safety profile and efficacy of alpha-adrenergic blockers for symptoms related to benign prostatic hyperplasia. *Int J Clin Pract.* 2008; 62:1547-59.
87. Hollingsworth JM, Canales BK, Rogers MA, et al. Alpha blockers for treatment of ureteric stones: systematic review and meta-analysis. *BMJ.* 2016; 355:i6112.
88. Sentürk AB, Aydin C, Ekici M, et al. Comparison of three most frequently used alpha blocker agents in medical expulsive therapy for distal ureteral calculi, result of a retrospective observational study. *Arch Ital Urol Androl.* 2018; 90:25-28.
89. Giuliano F. Impact of medical treatments for benign prostatic hyperplasia on sexual function. *BJU Int.* 2006; 97 (Suppl 2):34-8; discussion 44-5.
90. Hisasue S, Furuya R, Itoh N, et al. Ejaculatory disorder caused by alpha-1 adrenoceptor antagonists is not retrograde ejaculation but a loss of seminal emission. *Int J Urol.* 2006; 13:1311-6.
91. Kobayashi K, Masumori N, Hisasue S, et al. Inhibition of seminal emission is the main cause of anejaculation induced by a new highly selective alpha1A-blocker in normal volunteers. *J Sex Med.* 2008; 5:2185-90.
92. Hellstrom WJ, Sikka SC. Effects of acute treatment with tamsulosin versus alfuzosin on ejaculatory function in normal volunteers. *J Urol.* 2006; 176:1529-1533.
93. Yeung HEL, Sena SJ, Calopedos RJ, Woo HH. Alfuzosin and its effect on ejaculatory dysfunction: a systematic review. *World J Mens Health.* 2021; 39:186-194.
94. Britto-Júnior J, Ribeiro A, Ximenes L, et al. Alpha1-adrenergic antagonists block 6-nitrodopamine contractions on the rat isolated epididymal vas deferens. *Eur J Pharmacol.* 2022; 915:174716.
95. Blum MD, Bahnson RR, Porter TN, Carter MF. Effect of local alpha-adrenergic blockade on human penile erection. *J Urol.* 1985; 134:479-481.
96. Brindley GS. Pilot experiments on the actions of drugs injected into the human corpus cavernosum penis. *Br J Pharmacol.* 1986; 87:495-500.
97. Marconi M, Pavez P, San Francisco I, Narvaez P. Priapism induced by use of tamsulosin: A case report and review of the literature. *Arch Ital Urol Androl.* 2019; 91:193.
98. Rampin O. Pharmacology of alpha-adrenoceptors in male sexual function. *Eur Urol.* 1999; 36 Suppl 1:103-6.
99. van Dijk MM, de la Rosette JJ, Michel MC. Effects of alpha(1)-adrenoceptor antagonists on male sexual function. *Drugs.* 2006; 66:287-301.
100. Kaplan SA, Gonzalez RR, Te AE. Combination of alfuzosin and sildenafil is superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction. *Eur Urol.* 2007; 51:1717-1723.
101. Yan H, Zong H, Cui Y, et al. The efficacy of PDE5 inhibitors alone or in combination with alpha-blockers for the treatment of erectile dysfunction and lower urinary tract symptoms due to benign prostatic hyperplasia: a systematic review and meta-analysis. *J Sex Med.* 2014; 11:1539-45.
102. Kallidonis P, Adamou C, Kotsiris D, et al. Young Academic Urologists of the European Association of Urology-Endourology Working Party. Combination therapy with alpha-blocker and phosphodiesterase-5 inhibitor for improving lower urinary tract symptoms and erectile dysfunction in comparison with monotherapy: a systematic review and meta-analysis. *Eur Urol Focus.* 2020; 6:537-558.
103. Tufanaru C, Munn Z, Stephenson M, Aromataris E. Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. *Int J Evid Based Healthc.* 2015; 13:196-207.

Correspondence

Rawa Bapir
Dr.rawa@yahoo.com
Smart Health Tower, Sulaymaniyah, Kurdistan region, Iraq

Kamran Hassan Bhatti
kamibhatti92@gmail.com
Urology Department, HMC, Hamad Medical Corporation, Qatar.

Ahmed Eliwa
ahmedeliwafarag@gmail.com
Department of Urology, Zagazig University, Zagazig, Sharkia, Egypt.

Herney Andrés García-Perdomo
herney.garcia@correounivalle.edu.co
Universidad del Valle, Cali, Colombia

Nazim Gherabi, MD
ngherabi@gmail.com
Faculty of Medicine Algiers 1, Algiers, Algeria

Derek Hennessey, MD
derek.hennessey@gmail.com
Department of Urology, Mercy University Hospital, Cork, Ireland

Vittorio Magri, MD
vittorio.magri@virgilio.it
ASST Nord Milano, Milan, Italy

Panagiotis Mourmouris, MD
thodoros13@yahoo.com
2nd Department of Urology, National and Kapodistrian University of Athens, Sismanoglio Hospital, Athens, Greece

Adama Ouattara, MD
adamsouat1@hotmail.com
Division of Urology, Souro Sanou University Teaching Hospital, Bobo-Dioulasso, Burkina Faso

Gianpaolo Perletti
gianpaolo.perletti@uninsubria.it
Department of Biotechnology and Life Sciences, Section of Medical and Surgical Sciences, University of Insubria, Varese, Italy

Joseph Philipraj, MD
josephphilipraj@gmail.com
Department of Urology, Mahatma Gandhi Medical College and Research Institute, Sri Balaji Vidyapeeth, Puducherry, India.

Alberto Trinchieri, MD (Corresponding Author)
alberto.trinchieri@gmail.com
Urology School, University of Milan, Milan (Italy)

Noor Buchholz
noor.buchholz@gmail.com
Sobeh's Vascular and Medical Center, Dubai Health Care City, Dubai, United Arab Emirates