Review

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

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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, I2 = 55%) and in patients with ureteral stones (OR: 2.88, 95% CI: 1.50-5.44, Z = 3.19, p < 0.001, I2 = 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, I2 = 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.

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-

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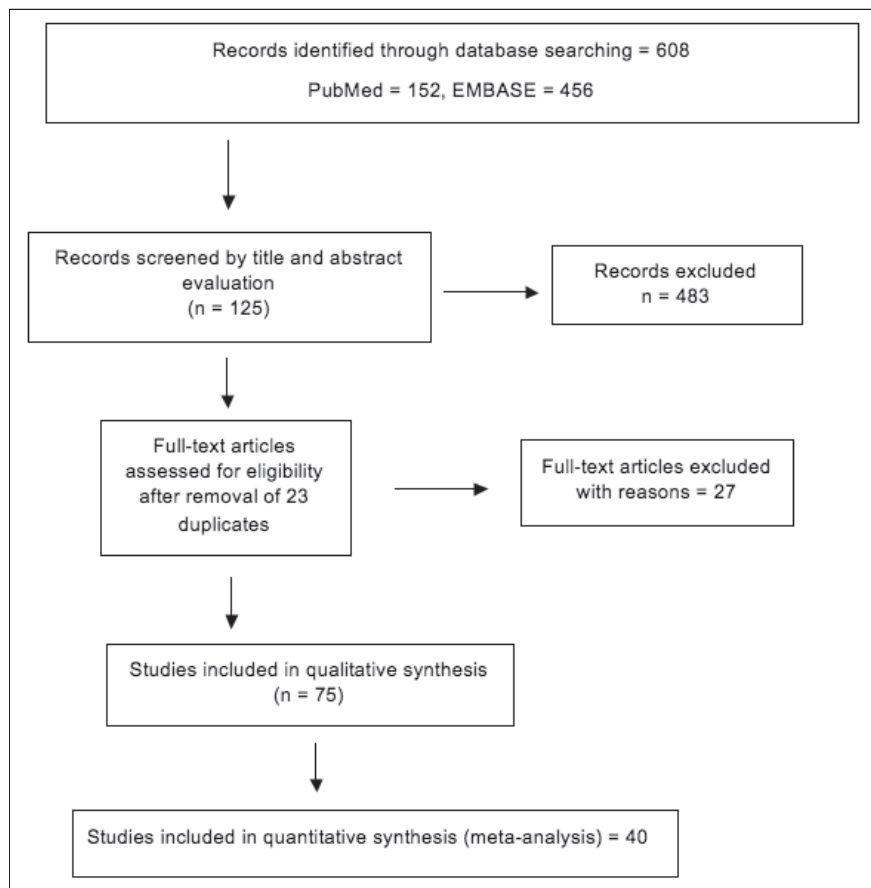
The risk of deviation from the intended intervention was rated as low in 62 studies, unclear in 12 and high in one. The ROB associated to missing outcome data was considered to be low in 63 studies and unclear in 12. The risk of bias in measurement of outcome was considered to be low in 70 studies and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

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

Figure 1.
Flow chart.

studies, 13006 participants, Z = 5.73, p < 0.00001, I2 = 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, I2 = 31%) (Figure 3).
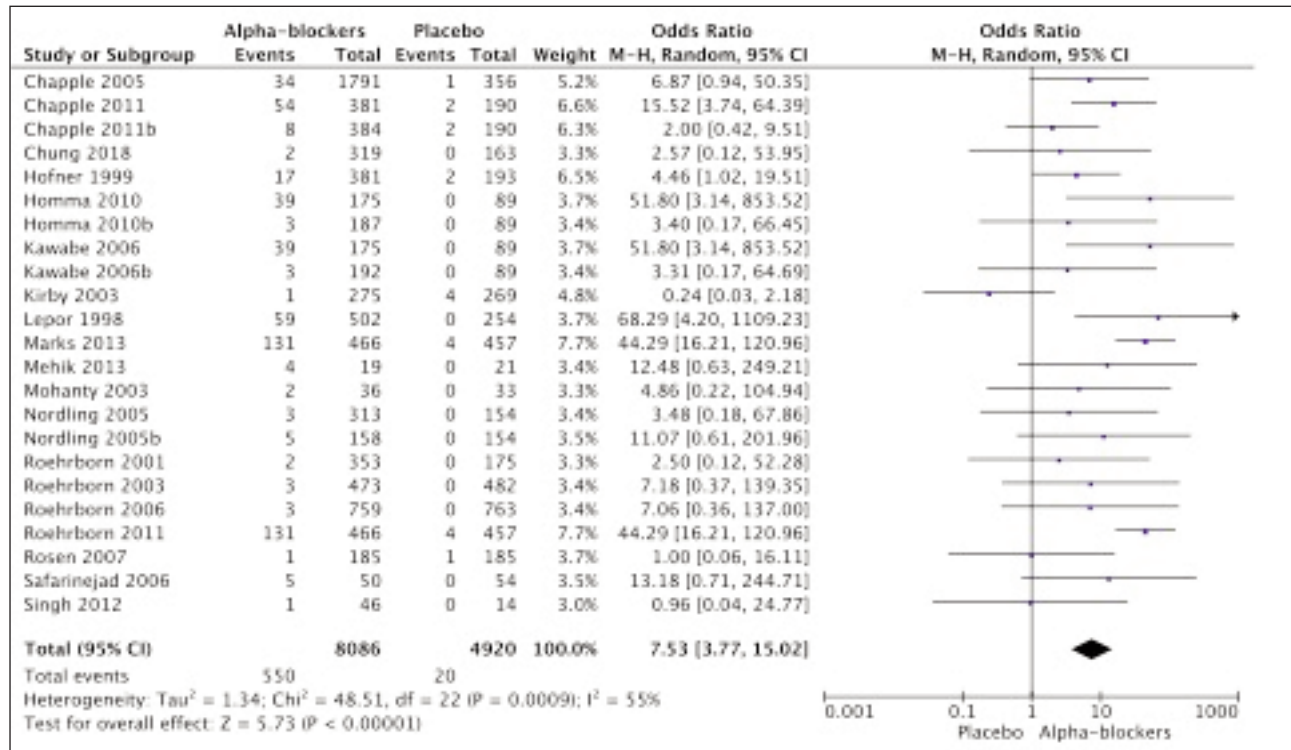
Significantly higher odds for ejaculatory disorders were confirmed in patients with ureteral stones taking alpha-blockers compared to patients either on placebo or on standard treatment (*Forest plots shown in Supplementary Materials - Forest plots Figures 1-2*). Compared to placebo, uroselective alpha-blockers 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, I2 = 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.
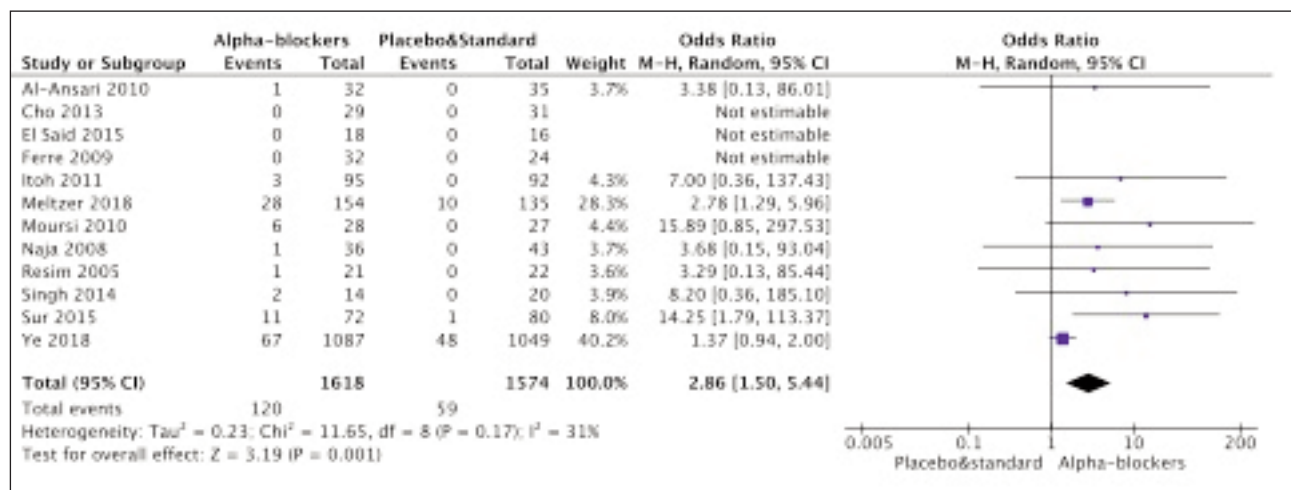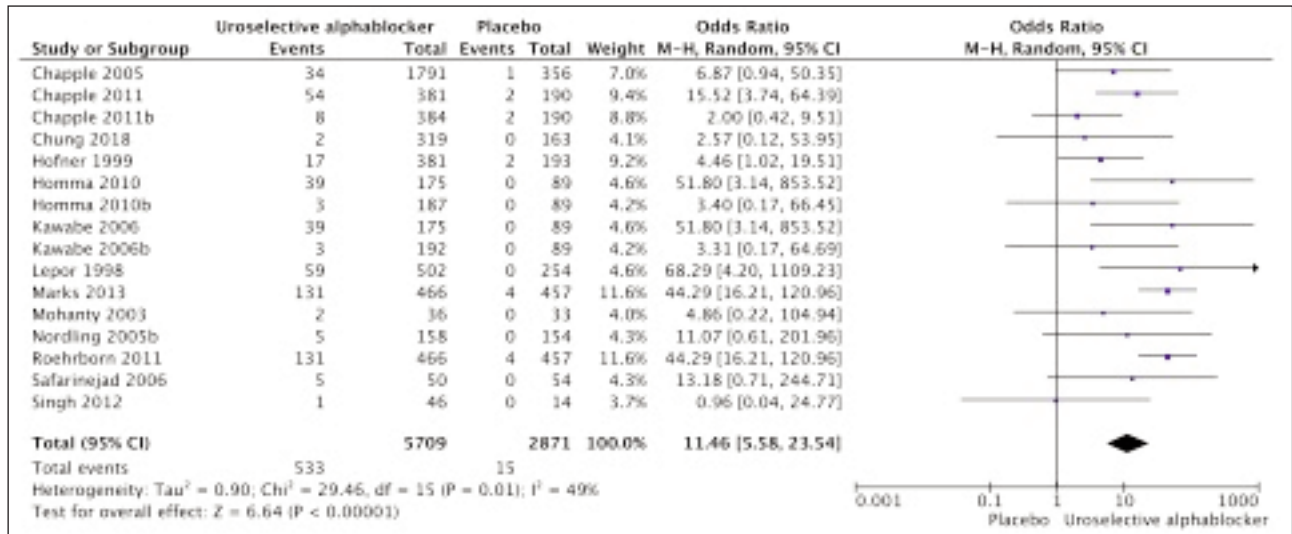*Data to the right of the vertical no-effect axis indicate higher odds for ejaculatory disorders in patients treated with alpha adrenoceptor blockers compared to placebo or standard treatment.*
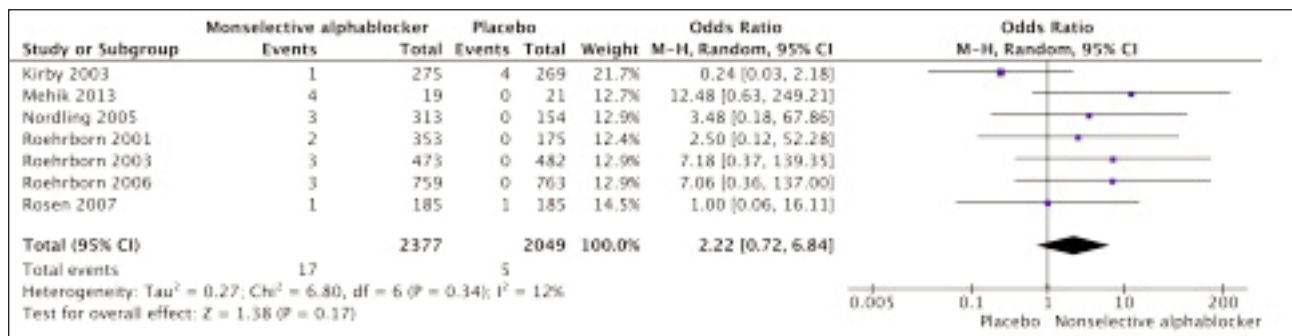
Figure 4.
Odds for ejaculatory disorders in patients in patients with LUTS associated to BPH taking uroselective alpha-blockers.
Data to the right of the vertical no-effect axis indicate higher odds for ejaculatory disorders in patients treated with uroselective alpha adrenoceptor blockers compared to 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, I2 = 12%) (Figure 5).
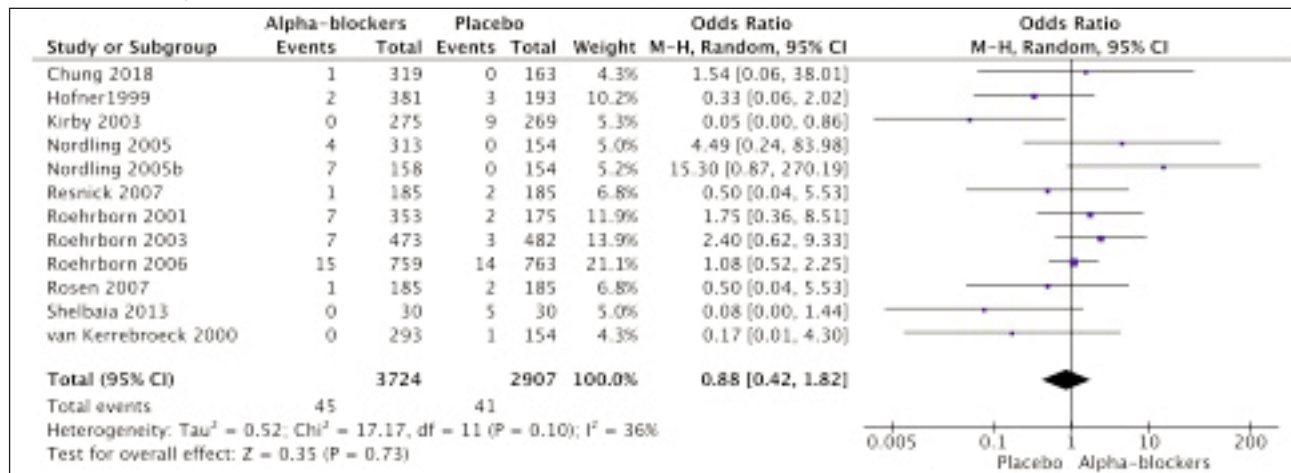
Endpoint: erectile dysfunction
The presence of erectile dysfunction in patients treated with alpha-blockers was investigated in 14 studies. Eleven studies (12 series) reported the rates of erectile dysfunction in patients on treatment with alpha-blockers (any kind) in comparison with placebo (32-39, 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, I2 = 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 alpha1-A-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
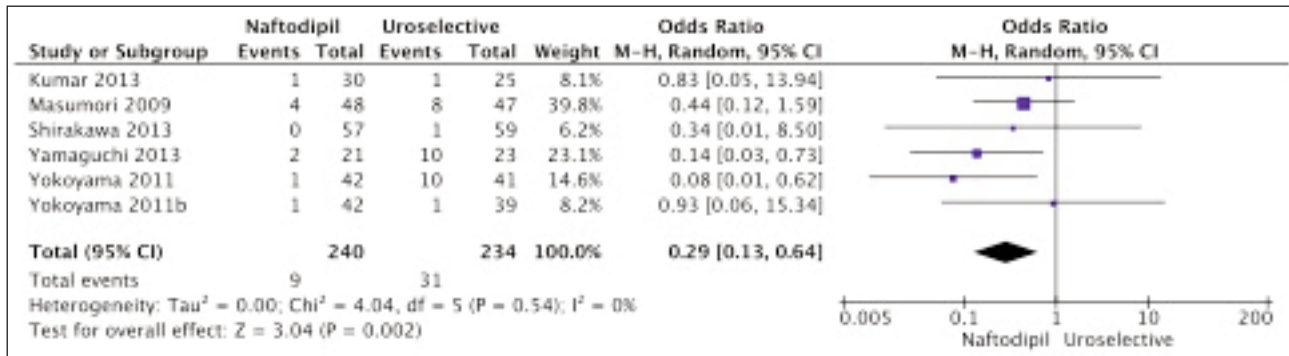
Figure 7.

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.
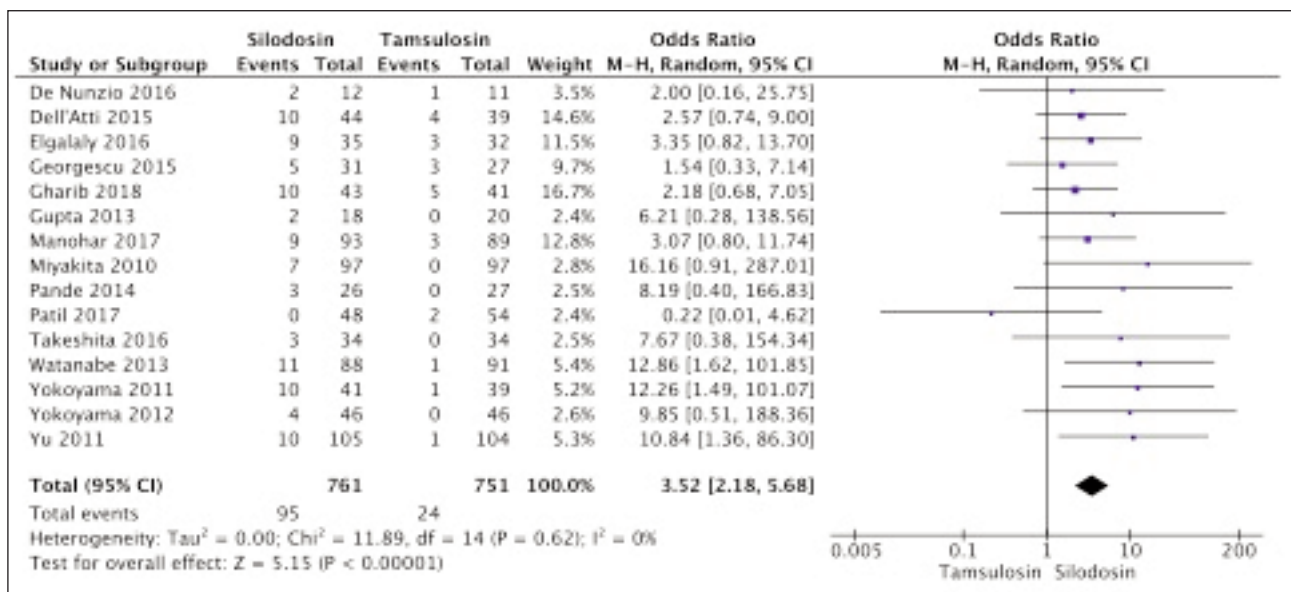
Figure 8.
*Odds for ejaculatory disorders in patients taking naftopidil or uroselective alpha-blockers.*
Data to the left of the vertical no-effect axis indicate lower odds for ejaculatory disorders in patients treated with naftopidil compared to uroselective alpha adrenoceptor blockers.

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.
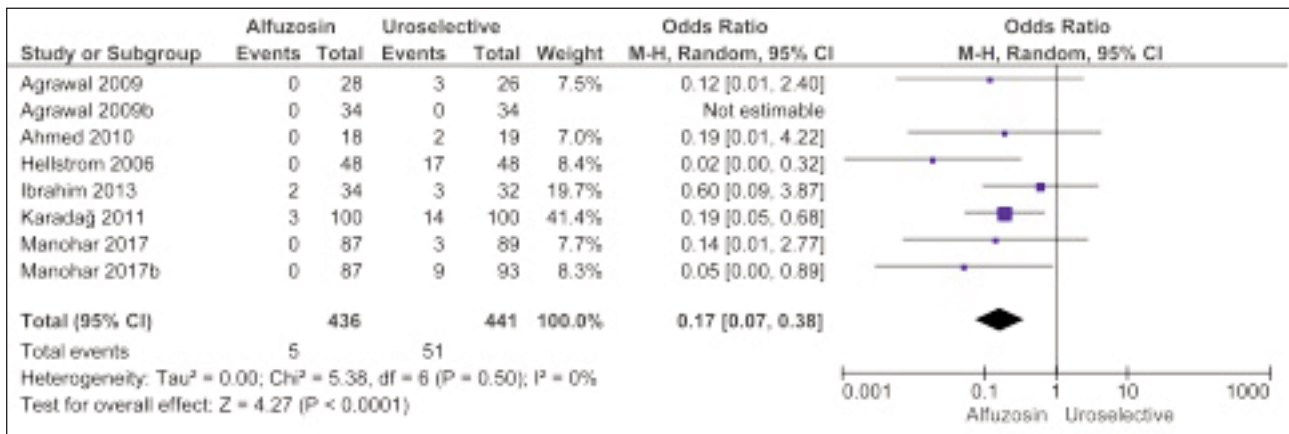
tamsulosin compared with silodosin (49-54, 60, 62, 64, 65, 70, 71, 73-75), 5 studies evaluated the effect of naftopidil compared with a uroselective alpha-blocker on ejaculation (including a study comparing naftopidil with both tamsulosin and silodosin) (59, 61, 68, 72, 73), 7 studies compared alfuzosin 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, $Z = 5.15$, $p < 0.00001$, $I2 = 0\%$) (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, $Z = 3.04$, $p = 0.002$, $I2 = 0\%$) (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, $Z = 4.27$, $p < 0.0001$, $I2 = 0\%$) (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 for 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 alpha1-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.

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