INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most common causes of lower urinary tract symptoms (LUTS) with an incidence greater than 80% in men older than age 80 years affected [1]. From longitudinal population-based studies, we know that BPH is an age-related, progressive disease with moderate-severe LUTS noted in 26% of men aged 40 to 49 years and 46% aged 70 to 79 years [2]. While complications, such as acute urinary retention, are relatively low at 2% to 7% with 6% to 10% of men requiring surgery for BPH [2-4]. Despite these low rates, BPH-related LUTS do significantly impact a man's quality of life and has led to the ubiquitous use of α₁-blocker pharmacotherapy to ameliorate symptoms and reduce the risk of disease progression. While effectively improving LUTS, these benefits often come at a cost of other adverse effects, including sexual dysfunction. Sexual dysfunction is a complex phenomenon characterised not only by erectile dysfunction (ED) but also ejaculatory dysfunction (EjD) and other orgasmic disorders [5-7]. The adverse event of...
EjD is a well recognised amongst α₁-blockers. Surveys have shown that up to 70% of sexually active men said they would discontinue BPH therapy that would negatively impact their sex-life [8]. Furthermore, men with LUTS may already complain of significant pre-morbid sexual dysfunction. A large multinational study highlights that EjD was very prominent in men with LUTS in all geographical regions (including Europe, Asia, Latin America, and Russia) with 77.9% complaining of decreased force of ejaculation, 74.4% decreased amount of semen and half of these men considering EjD a significant problem [9]. In one trial, the incidence of EjD in BPH patients treated with Silodosin was up to 22.3% [10]. Another study observing the effect of 0.8 mg tamsulosin revealed that up to 90% of men had reduce ejaculate volume and over one third reported anejaculation [11]. While patients may not be forthcoming about their ejaculations, urologists should carefully consider sexual effects and appropriately counsel patients before initiating therapy.

Interestingly, it appears that not all α₁-blockers were made equal. While the mechanism is unclear, alfuzosin’s α₁-uroselectivity seems to produce less EjD compared to its counterparts that also effect vascular smooth-muscle tone [12]. While the drug shows promise for sexually active men with BPH, the vast majority of available literature lacks a standardised score for quantification of EjD. Most studies simply report rates of ‘abnormal’ ejaculation or utilise the Danish Prostatic Symptom Score (DAN-PSS-1), which is relatively limited in its evaluation of ejaculatory function. Unlike reviews of ED effects of α₁-blockers that use the standardised International Index of Erectile Function (IIEF), no such review had been performed on EjD due to lack of standardised quantification.

The Male Sexual Health Questionnaire Ejaculatory Function Short Form (MSHQ-EjD-SF) is a validated abridged version of the 25-item MSHQ, first introduced in 2007 [13]. It is a four-item questionnaire that assesses EjD, with three questions on function and one question on bother. Compared to the DAN-PSS-1 and International Continence Society sex questionnaire, the MSHQ also evaluates psychometric properties such as force, delay and pleasure of ejaculation addressing the previous limitations of these scores [9,14]. The aim of the present review is to evaluate clinical trials assessing ejaculatory function and alfuzosin treatment using the MSHQ-EjD-SF.

METHODS

We conducted a systematic review of Medline, PubMed, Pre-Medline, Embase, Scopus, and ‘grey literature’ (sourced from scientific meeting abstracts and Google Scholar) to identify original research articles that measured the outcomes of LUTS and EjD using validated questionnaires (International Prostate Symptom Score [IPSS] and MSHQ-EjD-SF) in men with BPH after treatment with alfuzosin. Keywords used included ‘benign prostatic hyperplasia’, ‘lower urinary tract symptoms’, ‘alpha blockers’, ‘ejaculatory dysfunction’ and their synonyms (Appendix). The reference lists of identified studies were also manually searched to see if they met the inclusion criteria.

Given that the 25-item MSHQ was only validated for use in 2004 [14], and the abridged MSHQ-EjD-SF in 2007 [13], the present systematic review was limited to studies published between January 2007 and January 2017. There was no restriction on language and non-English publications were translated via Google Translate (Google LLC, Mountain View, CA, USA). Studies were excluded if only qualitative descriptors of EjD were used, if they were non-human studies or if conference abstracts did not have access to full-text. All studies were reviewed independently by two reviewers and any discrepancies resolved by consensus.

The primary outcome measure was change in MSHQ-EjD-SF scores following treatment with alfuzosin in males with BPH. Data extracted from selected studies included study design and sample size, demographic and patient characteristics information, inclusion/exclusion criteria used, duration of treatment, and the mean change in symptom scores from baseline to after treatment with alfuzosin. These changes were derived from ‘overall’ score, rather than the specific domains of the SHQ-EjD-SF (ability to ejaculate during sexual activity, force of ejaculation, volume of ejaculation, bother). If data required for the review was not published, authors were contacted to clarify these results. Statistical imputation was not used for any missing data.

As a systematic review of the literature, institutional research ethics review approval was not required.

RESULTS

The initial search strategy yielded 90 original articles. After removal of duplicates, 13 studies were
included for a full text review. Six of these 13 studies satisfied the final inclusion criteria (Fig. 1) with combined sample size of 1,371 men.

1. Study characteristics

The characteristics and methodology of these cohort studies are summarised in Table 1. All six studies were open labelled, non-comparative prospective cohort studies that solely investigated changes in LUTS and ejaculatory function after treatment with alfuzosin. Ejaculatory function, erectile function and LUTS were measured in these studies using the MSHQ-EjD SF, the IIEF-5 and IPSS, respectively. The treatment protocol was identical across all studies with 10 mg of alfuzosin taken once daily. MSHQ-EjD and IPSS were measured at baseline and after treatment was commenced, however follow-up time varied. All trials were conducted over multiple centres across Asia with the exception of Yoon et al [15]. Individual sample sizes varied with largest trial in Tunisia assessing 730 patients [16], while the others had less than 200 patients each. A number of similarities between these studies regarding patient selection criteria, intervention protocol and outcomes measured was observed. Kim et al [17] had the shortest intervention time, re-assessing men after just 3 months

<table>
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<tr>
<th>Study</th>
<th>Type</th>
<th>Size (n)</th>
<th>Location (no. of center)</th>
<th>Intake period</th>
<th>Population studied</th>
<th>Intervention group</th>
<th>Comparator group</th>
<th>Primary outcomes</th>
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<tr>
<td>Hwang et al [22] (2012)</td>
<td>Open, non-comparative prospective cohort</td>
<td>279 (123 drop out)</td>
<td>Multicenter (9), Taiwan</td>
<td>September 2006–May 2008</td>
<td>Males &gt;40 with moderate to severe LUTS suggestive of BPH volume &gt;20, sexually active</td>
<td>Baseline scores</td>
<td>Alfuzosin 10 mg daily</td>
<td>IPSS, MSHQ-EjD after 6 months</td>
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Table 1. Study characteristics

Fig. 1. Search results from systematic search strategy.

of treatment, while Yoon et al [15] followed their patients up to 2 years after commencement of treatment. In addition to the above six papers, Martin-Morales et al [18] also met inclusion criteria, however published data was incomplete. Reasonable efforts were made to contact the authors unsuccessfully, thereby excluding this study from final selection.

2. Study appraisal

Each cohort study was appraised via the Cochrane Risk of Bias Tool for Non-Randomised Trials (ROBIN-1) (Table 2). This tool stratifies a trial’s overall risk of bias using domain-based assessments of different bias types [19]. All the trials except Leungwattanakij et al [20] were deemed to have an overall moderate risk of bias. Leungwattanakij et al [20] did not report the proportion of missing patients, their reasons for drop out and whether they were included in analysis. Ben Rhouma et al [16] did not specify what their patient inclusion criteria was and whether it was developed retrospectively or prospectively. None of the studies identified relevant cofounding factors or explicitly state whether adjustments were made on this basis. Despite this, the studies were consistent in so far as their results were likely effected by similar biases. For example, Kim et al [17], Chung et al [21], and Hwang et al [22] had near identical patient selection criteria, treatment protocol, and treatment length. All studies reported their patient exclusion criteria.

3. Changes in International Prostate Symptom Score after treatment

Change in LUTS scores from baseline demonstrated a significant decrease in IPSS score after commencement of alfuzosin treatment, with a median decrease of 6.6 points, range: 2.5 to 9.3 points (Fig. 2). All studies showed that LUTS improved after treatment of 6 months (except Kim et al [17] which demonstrated improvement after 3 months). While the change in score after 6 months was used for Yoon et al’s study [15] for uniformity, their results showed a continuous improvement in IPSS score at 2 years of treatment. In this study, the mean IPSS at month of treatment was 20, compared to 11.5 after 2 years of treatment. A visual summary detailing the spread of means was used rather than a meta-analysis given the studies were mostly descriptive ordinal scales and lacked measures of variability. The median of all six studies is less susceptible

<table>
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<tr>
<th>Bias due to</th>
<th>Confounding</th>
<th>Selection</th>
<th>Classification of interventions</th>
<th>Deviations from intended interventions</th>
<th>Missing Data</th>
<th>Measurement Outcome</th>
<th>Selection of Reported Result</th>
<th>Overall</th>
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Table 2. Study appraisal using ROBINS-I tool to determine risk of bias in non-randomised studies
4. Changes in Male Sexual Health Questionnaire ejaculatory dysfunction after treatment

MSHQ-EjD scores also increased after alfuzosin treatment, correlating to an improvement in ejaculatory function. Median increase of MSHQ-EjD SF score was 1.9, range: 0.9 to 5.8 (Fig. 3). As above, Yoon et al [15] also demonstrated a continued improvement in MSHQ-EjD-SF scores from 6 months to 2 years with a mean increase of 5.

DISCUSSION

The present study is the first review that links alfuzosin and improved ejaculatory function using the validated MSHQ-EjD questionnaire. As well as providing a more ejaculate-friendly option to the medical management of BPH, the review further consolidates the growing body of evidence that BPH and sexual dysfunction are inherently linked. In order to better appreciate the reason why these symptoms coexist, it is imperative to expel the idea that EjD is merely an effect of ‘retrograde’ ejaculation. While 0.8 mg of tamsulosin resulted in anejaculation in one third of patients and reduced ejaculatory volume in 90%, there was no significantly difference in post-ejaculation urinary sperm concentrations when compared to placebo or patients prescribed alfuzosin [11]. Another study performed by 17 Korean urologists also demonstrated that daily 0.2 to 0.4 mg tamsulosin significantly decreased ejaculate volume with no sperm found in mid-stream urine samples collected after ejaculation [23]. While some may consider this reduced post-coital ‘clean-up’ an advantage, decreased stimuli in the posterior urethra can significantly dampen the male orgasm and have pervasive effects on relationships and quality of life [24].

While the precise mechanism of alfuzosin and other \( \alpha_1 \)-blockers on EjD is unclear, the effect is likely multifactorial. Alpha1-blocking medications for BPH differentially bind to \( \alpha_{1A} \), \( \alpha_{1B} \) and \( \alpha_{1D} \) receptor subtypes thereby producing different side effects. For example, the majority (70%) of the \( \alpha_1 \)-adrenergic receptors in the prostate are of the \( \alpha_{1A} \) subtype [25]. Tamsulosin’s differential affinity for \( \alpha_{1A} \)-adrenoreceptors in the prostate and \( \alpha_{1B} \) receptors of cardiovascular smooth muscle is approximately 15.8:1 [26], thereby improving LUTS without significant hypotensive effects. As such, tam-
sulosin is thought to reduce pressure generated within the vas deferens and seminal vesicles thereby impairing emission phase of ejaculation [27]. This was demonstrated in animal models, where tamsulosin administration significantly decreased intra-seminal vesicle pressure of rats, compared to placebo [28]. Interestingly, this effect was not observed when our rodent relatives where given alfuzosin [28], even though alfuzosin’s selectivity for α1A-receptor compared to α1B is significantly lower than tamsulosin (0.31:1 versus 15.8:1, respectively) [26].

A differential central inhibitory effect of ejaculation may account for this discrepancy between uroselective alpha blockers. Unlike alfuzosin, tamsulosin readily crosses the blood-brain barrier and bind to dopaminergic and/or serotonergic receptors that are integrally involved in the central coordination of ejaculation [28]. In animal models, tamsulosin demonstrated a binding affinity for 5-HT1A and D2-like receptors almost 10,000 times greater than other ABs and significantly decreased bulbospongious contractions in male rats [29]. While it is conceivable that alfuzosin has less sexual side effects due less central inhibition, the mechanism behind improved ejaculatory function is only speculative. In one study, alfuzosin was found to fully relax rodent cavernosal tissue in vitro [30], highlighting the potential link between EjD and ED. Other studies have also demonstrated IPSS-score improvements using tadalafil for men with BPH [31]. While the vasodilatory effect is similar between tadalafil’s phosphodiesterase 5-inhibiting mechanism and alfuzosin’s blockage of peripheral α1-adrenoceptor, an explanation for the improvement in MSHQ-EjD scores remains elusive.

The strengths of the present review include its demonstration of homogenous results, showing similar trends in both IPSS and MSHQ-EjD-SF scores. The review was also based on a predefined and specific search strategy undertaken separately by two reviewers. Despite this, there are a number of limiting factors that this systematic review was unable to address. As there are no randomised control trials measuring ejaculatory function using validated scoring systems, all selected studies were open, non-comparator cohort studies with a single treatment arm. Meta-analysis was therefore unable to be performed and confounding factors for ejaculatory function, such as age and other comorbidities, could not be controlled for. It is also important to note that a proportion of patients lost to follow-up experienced adverse effects that lead to alfuzosin discontinuation. This may indicate that certain population groups may have different results with alfuzosin. Interpretation of the findings in publications of non-English language may also be affected by the use of an online translator rather than professional interpreter.

We were only able to quantify change of IPSS and MSHQ-EjD-SF after a certain duration of treatment, given that included trials report variable length of follow-up. As α1-blocker therapy is known to provide maximum symptom control anywhere from weeks to months after treatment initiation, shorter trials like Kim et al [17] may not accurately reflect true treatment effect. Conversely, Yoon et al [15] demonstrated continual improvement of LUTS and ejaculatory function from 6 months to 2 years of treatment.

Despite using a validated questionnaire, the review assumes that a given change in score represents a similar improvement in ejaculatory function. For example, a score from 1 to 3 is assumed to have the same impact for a patient with a score increase from 15 to 17. Unlike the IPSS which has 3 clinical categories of severity, the MSHQ-EjD-SF does not. Rather, it is a combination of different aspects of EjD with one bother item, Question 4: “If you have had any ejaculation difficulties or have been unable to ejaculate, have you been bothered by this?” Minimal clinically important difference (MCID) based on MSHQ-EjD-SF score changes have not been formally established or published and therefore must be interpreted with caution. Therefore, a median score increase of 1.9 in this review, may or may not correlate to clinical improvement. Furthermore, the studies inconsistently assessed ejaculatory bother with only Hwang et al [22] documenting changes in the different domains included within the MSQH-EjD-SF.

Despite this, we can consider total MSHQ-EjD-SF scores as an acceptable, albeit imperfect, quantification of an otherwise subjective experience. While the baseline severity of symptoms was variable in this patient group, influencing the outcome of MCID, none of the studies indicated a decrease in ejaculatory function. This result shows that alfuzosin is arguably superior to other α1-blockers by providing LUTS relief without any adverse sexual side effects.
CONCLUSIONS

This novel review of alfuzosin demonstrates a homogeneous improvement of LUTS without a detrimental effect on ejaculatory function. While we lack a precise understanding of how LUTS is linked with ejaculatory function, alfuzosin appears to even ameliorate ejaculatory function. Although, the conclusions of this review should be interpreted with caution given the overall moderate risk of bias. Importantly, the present findings serve as a firm reminder that urologists should discuss the different sexual side effects of available α₁-blocker therapy.

Disclosure

Henry H. Woo has served on advisory boards for Astellas. The other authors have no potential conflicts of interest to disclose.

Author Contribution

Conceptualisation, data curation, formal analysis, investigation, methodology: HELY, SJS, HHW. Supervision: RJC, HHW. Writing – original draft: HELY, HHW. Writing – review and editing: all authors.

REFERENCES


Appendix. Male Sexual Health Questionnaire Ejaculatory Function (MSHQ-EjD) Short Form

In the past month:
How often have you been able to ejaculate or ‘cum’ when having sexual activity?

- All the time 5
- Most of the time 4
- About half the time 3
- Less than half the time 2
- None of the time/could not ejaculate 1

How would you rate the strength or force of your ejaculation?

- As strong as it always was 5
- A little less strong than it used to be 4
- Somewhat less strong than it used to be 3
- Much less strong than it used to be 2
- Very much less strong than it used to be 1
- Could not ejaculate 0

How would you rate the amount of volume of semen or fluid when you ejaculate?

- As much as it always was 5
- A little less than it used to be 4
- Somewhat less than it used to be 3
- Much less than it used to be 2
- Very much less than it used to be 1
- Could not ejaculate 0

If you have had any ejaculation difficulties or have been unable to ejaculate, have you been bothered by this?

- No problem with ejaculation 0
- Not at all bothered 1
- A little bothered 2
- Moderately bothered 3
- Very bothered 4
- Extremely bothered 5