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Alfuzosin and Its Effect on Ejaculatory Dysfunction: A Systematic Review

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Studies have demonstrated that alfuzosin not only improves lower urinary tract symptoms (LUTS) but also appears to preserve ejaculatory dysfunction (EjD). The objective of this study was to evaluate the impact of alfuzosin on ejaculatory function using the 'Male Sexual Health Questionnaire (MSHQ)-EjD Short Form' – a validated, abridged-version of the 25-item MSHQ specifically assessing EjD. A systematic search of MEDLINE, PubMed, Scopus, Embase, and grey literature was performed in January 2017 to identify relevant cohort studies. Search terms were 'alfuzosin', 'benign prostatic hyperplasia', 'ejaculatory dysfunction' and their synonyms without exclusions. Six cohort studies conducted between 2008 to 2015 were selected for analysis. Three of these were conducted in Korea, one in Thailand, one in China, and one in Tunisia. Overall, 1,371 patients were enrolled in these studies with a median age of 62.3 years. All studies quantified patient LUTS and ejaculatory function using the International Prostate Symptom Score (IPSS) and MSHQ-EjD Short Form, respectively. IPSS had a median decrease of 6.6 while MSHQ-EjD had a median increase of 1.9. This review highlights the very real association between sexual function and LUTS. This systematic review confirms that alfuzosin may improve ejaculatory function in addition to LUTS and should be considered in men who are sexually active or who already complain of deteriorating ejaculation.

Keywords: Alfuzosin; Benign prostatic hyperplasia; Ejaculation; Lower urinary tract symptoms; Sexual dysfunction, Physiological

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 α_1-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 α_1-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 α_1-blockers were made equal. While the mechanism is unclear, alfuzosin's α_1-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 α_1-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', 'alfuzosin', '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
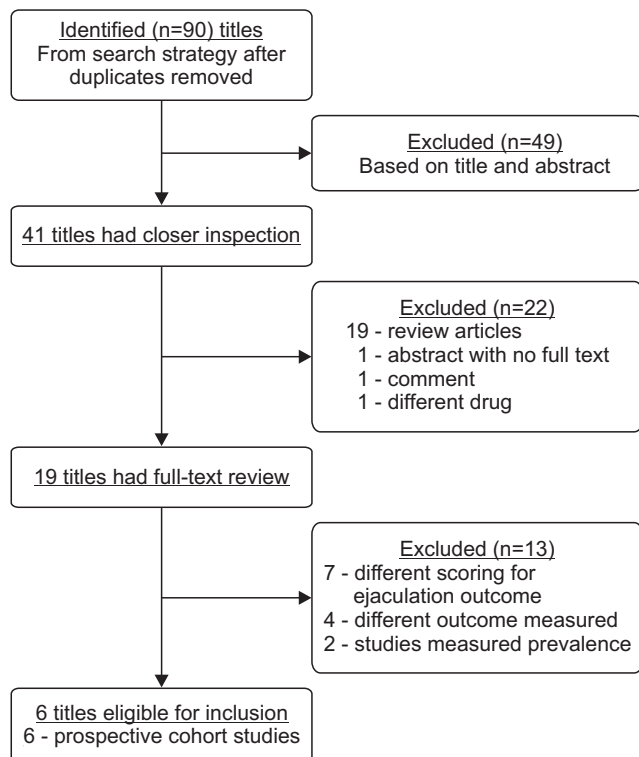

Fig. 1. Search results from systematic search strategy.

Identified (n=90) titles
From search strategy after duplicates removed

Excluded (n=49)
Based on title and abstract

41 titles had closer inspection

Excluded (n=22)
19 - review articles
1 - abstract with no full text
1 - comment
1 - different drug

19 titles had full-text review

Excluded (n=13)
7 - different scoring for ejaculation outcome
4 - different outcome measured
2 - studies measured prevalence

6 titles eligible for inclusion
6 - prospective cohort studies

Table 1. Study characteristics

Study	Ben Rhouma et al [16] (2015)	Yoon et al [15] (2014)	Hwang et al [22] (2012)	Leungwattanakij et al [20] (2010)	Kim et al [17] (2010)	Chung et al [21] (2009)
Type	Open, non-comparative prospective cohort	Open, non-comparative prospective cohort	Open, non-comparative prospective cohort	Open, non-comparative prospective cohort	Open, non-comparative prospective cohort	Open, non-comparative prospective cohort
Size (n)	730 (234 drop out)	30 (18 drop out)	279 (123 drop out)	99	135 (25 drop out)	148 (25 drop out)
Location (no. of center)	Multicenter, Tunisia	Single center, South Korea	Multicenter (9), Taiwan	Multicenter (13), Thailand	Multicenter (9), South Korea	Multicenter (4), South Korea
Intake period	June 2009–Juli 2015	2010–2012	September 2006–May 2008	June 2006–December 2007	Unclear	June 2006–October 2007
Population studied	Male patients with LUTS suggestive of BPH	Male patients with IPSS>8, prostate volume>20, sexually active	Males >40 with moderate to severe LUTS suggestive of BPH, IPSS>8	Males >50 with moderate to severe LUTS suggestive of BPH, IPSS>8, sexually active	Males >40 with mild to moderate LUTS with BPH, prostate volume>20	Males >50 with moderate to severe LUTS suggestive of BPH, IPSS>8, sexually active
Intervention group	Alfuzosin 10 mg daily	Alfuzosin 10 mg daily	Alfuzosin 10 mg daily	Alfuzosin 10 mg daily	Alfuzosin 10 mg daily	Alfuzosin 10 mg daily
Comparator group	Baseline scores	Baseline scores	Baseline scores	Baseline scores	Baseline scores	Baseline scores
Primary outcomes	IPSS and MSHQ-EjD after 6 months	IPSS, IIEF and MSHQ-EjD after 2 years	IPSS, MSHQ-EjD, IIEF after 6 months	IPSS, IIEF, MSHQ-EjD after 6 months	IPSS, MSHQ-EjD after 3 months	IPSS, MSHQ-EjD after 6 months

LUTS: lower urinary tract symptoms, BPH: benign prostatic hyperplasia, IPSS: International Prostate Symptom Score, MSHQ-EjD: Male Sexual Health Questionnaire ejaculatory dysfunction, IIEF: International Index of Erectile Function.

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, Martín-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 2. Study appraisal using ROBINS-1 tool to determine risk of bias in non-randomised studies

Bias due to	Ben Rhouma et al [16] (2015)	Yoon et al [15] (2014)	Hwang et al [22] (2012)	Leungwattanakij et al [20] (2010)	Kim et al [17] (2010)	Chung et al [21] (2009)
Confounding	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk
Selection	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk
Classification of interventions	Low risk	Low risk	Low risk	Low risk	Low risk	Low
Deviations from intended interventions	Low risk	Moderate risk	Low risk	Low risk	Low risk	Moderate risk
Missing data	Low risk	Moderate risk	Moderate risk	Serious risk	Low risk	Low risk
Measurement outcome	Moderate risk	Low risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk
Selection of reported result	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Overall	Moderate risk	Moderate risk	Moderate risk	Serious risk	Moderate risk	Moderate risk
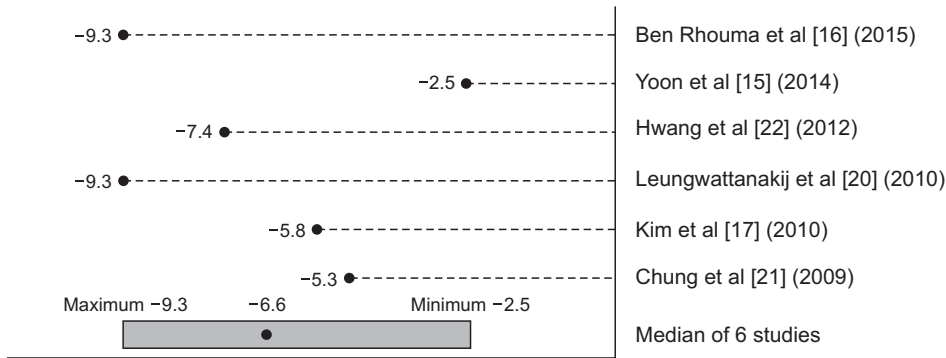
Fig. 2. Graphical summary of mean change from baseline in International Prostate Symptom Score with alfuzosin 10 mg daily treatment.
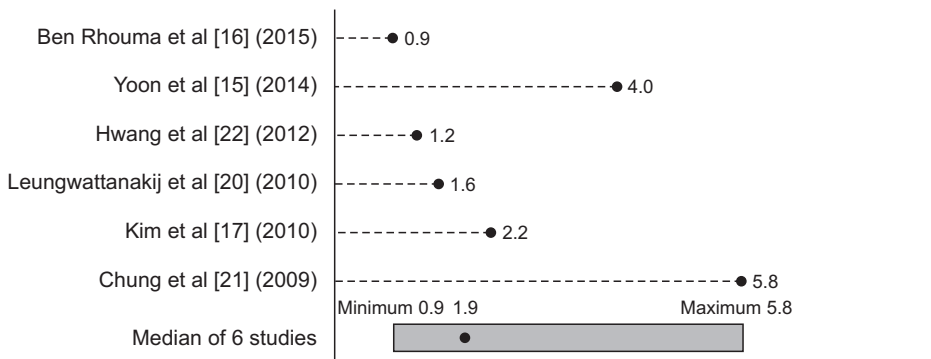
Fig. 3. Graphical summary of mean change from baseline in functional Male Sexual Health Questionnaire ejaculatory dysfunction score with alfuzosin 10 mg daily treatment.

to outliers due to the small sample size.

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 α_1-blockers on EjD is unclear, the effect is likely multifactorial. Alpha1-blocking medications for BPH differentially bind to α_{1A}, α_{1B}, and α_{1D} receptor subtypes thereby producing different side effects. For example, the majority (70%) of the α_1-adrenergic receptors in the prostate are of the α_{1A} subtype [25]. Tamsulosin's differential affinity for α_{1A}-adrenoreceptors in the prostate and α_{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 α_{1A}-receptor compared to α_{1B} 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 $5\text{-}HT_{1A}$ and D_2-like receptors almost 10,000 times greater than other ABs and significantly decreased bulbuspongiosus 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 α_{1B}-adrenoreptor, 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 α_1-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 α_1-blockers by providing LUTS relief without any adverse sexual side effects.

CONCLUSIONS

This novel review of alfuzosin demonstrates a homogenous 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 α_1-blocker therapy.

Conflict of Interest

Henry H. Woo has served on advisory boards for Astellas. The anothor 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.

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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