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ORIGINAL RESEARCH

Is Sexual Function Better Preserved After Water Vapor Thermal Therapy or Medical Therapy for Lower Urinary Tract Symptoms due to Benign Prostatic Hyperplasia?

Kevin T. McVary, MD,[1] Tyson Rogers, MS,[2] Joseph Mahon, MD,[1] and Nikhil K. Gupta, MD[3]

ABSTRACT

Background: Men often experience deterioration of sexual function after the use of α-blockers and 5-α reductase inhibitors for the treatment of lower urinary tract symptoms (LUTS) attributed to benign prostatic hyperplasia. Thus, an alternative treatment with water vapor thermal therapy (Rezūm System, Boston Scientific, Marlborough, MA, USA) which is an efficacious minimally invasive surgical treatment that preserves sexual function was examined.

Aim: To compare sexual function over 3 years after continuous daily treatment with pharmaceutical agents in the Medical Therapy of Prostatic Symptoms (MTOPS) study vs a single thermal therapy procedure (Rezūm study) in subjects with matched criteria for LUTS severity and prostate size.

Methods: We used sexual function data from sexually active cohorts in the MTOPS study (1,209) randomized to doxazosin, finasteride, combination drugs and placebo, and sexually active men who received thermal therapy (86). MTOPS study participants completed the Brief Male Sexual Function Inventory; men in the Rezūm trial completed the International Index of Erectile Function and Male Sexual Health Questionnaire.

Main Outcome Measure: Estimated mean changes from baseline for sexual function variables were compared using a linear mixed repeated measures model with fixed effects for treatment and follow-up visits.

Results: With continued daily drug use, men experienced significant worsening of sexual desire, erectile and ejaculatory function with finasteride and combination drug therapy, and reduced desire and erectile function with doxazosin. Thermal therapy was not associated with significant negative changes in sexual function throughout 3 years after treatment.

Clinical Implications: Water vapor thermal therapy can result in greater LUTS improvements than either doxazosin or finasteride alone, whereas combination drug therapy may equal that of this Rezūm procedure, but all drug therapies did have a significant negative impact on sexual function in contrast to the preservation of libido, erectile, and ejaculatory function after thermal therapy.

Strength & Limitations: The report includes high-quality data from 2 large randomized controlled trials in subjects with similar baseline inclusion criteria for LUTS severity and prostate size. It is the first longitudinal assessment of sexual function domains restricted to sexually active men treated with drugs or a single minimally invasive surgical treatment with the Rezūm procedure. A limitation of the study is the use of 2 different, although validated sexual function inventories (Brief Male Sexual Function Inventory and International Index of Erectile Function).

Conclusion: A single water vapor thermal therapy procedure for targeted prostate tissue ablation for LUTS/ benign prostatic hyperplasia had no deleterious effect on 4 sexual function domains compared with appreciable worsening of sexual function after long-term single or combination drug use. **McVary KT, Rogers T, Mahon J, et al. Is Sexual Function Better Preserved After Water Vapor Thermal Therapy or Medical Therapy for Lower Urinary Tract Symptoms due to Benign Prostatic Hyperplasia? J Sex Med 2018;XX:XXX–XXX.**

Key Words: Benign Prostatic Hyperplasia; Medical Therapy; Lower Urinary Tract Symptoms; Sexual Function; Water Vapor Thermal Therapy

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[1]Division of Urology, Stritch School of Medicine, Loyola University Medical Center, Maywood, IL, USA;

[2]NAMSA, Minneapolis, MN, USA;

[3]Division of Urology, Robert Wood Johnson Medical School, New Brunswick, NJ, USA

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INTRODUCTION

Men with lower urinary tract symptoms (LUTS) attributed to benign prostatic hyperplasia (BPH) often experience deterioration in sexual function as an independent risk factor in the natural history and progression of the disease.[1−4] α-Blockers and 5-α reductase inhibitors are the typical first-line treatment for men with moderate-to-severe LUTS. Although these agents used alone or in combination are efficacious,[5−7] they have also been shown to adversely affect erectile and ejaculatory function and overall sexual quality of life.[8−12]

Men with bothersome LUTS/BPH who need treatment beyond watchful waiting, or use of pharmacologic agents but wish to avoid conventional surgical intervention, may consider an alternative minimally invasive surgical therapy (MIST). Decisions regarding adoption of new technologies for the treatment of LUTS/BPH require understanding of any impact on sexual quality of life as well as treatment duration and expense. This report assesses the long-term outcomes related to sexual function 3 years after continuous medical therapy for LUTS/BPH in cohorts from the Medical Therapy of Prostatic Symptoms (MTOPS) study vs a one-time thermal therapy procedure. The outpatient procedure was performed with the novel technology of convective radiofrequency (RF)-generated water vapor energy (Rezūm System, Boston Scientific, Marlborough, MA, USA) to ablate obstructive prostatic tissue including the median lobe. This therapy provides rapid, significant, and durable relief of LUTS as well as preservation of sexual function.[13−17] Our primary objective is to evaluate reported treatment effects on sexual function in otherwise sexually active men with LUTS/BPH.

PATIENTS AND METHODS

Medical Therapy of Prostatic Symptoms and Rezūm Trial Designs and Participants

Details of design and primary outcomes of the MTOPS study have been published.[6] Briefly, men ≥50 years of age with an International Prostate Symptom Score (IPSS) ranging from 8 to 30, maximum urinary flow rate of 4−15 mL/s with a voided volume of ≥125 mL were eligible for MTOPS study inclusion. A total of 3,047 men were enrolled in 17 centers in the United States and equally randomized to placebo, α-blocker (doxazosin, 4−8 mg), a 5α-reductase inhibitor (finasteride 5 mg), or combination therapy with doxazosin and finasteride. The primary objective of the double-blind study was the effect of drug therapy on long-term delay or prevention of BPH clinical progression. Sexual function, a secondary outcome, was evaluated at baseline and annually. Changes in sexual function over 4 years for MTOPS study subjects have been reported.[9]

The study design of the prospective, randomized, controlled trial (RCT) of water vapor thermal therapy was conducted at 15 U.S. centers (Clinicaltrials.gov: NCT01912339) and outcomes over 3 years were reported.[13,15,17]. Men ≥50 years of age with a prostate volume of 30−80 cm^3, IPSS ≥13, and a maximum urinary flow rate of ≤15 mL/s with a voided volume of ≥125 mL were eligible for enrollment. A total of 197 participants with moderate-to-severe LUTS/ BPH were randomly assigned 2:1 for a single treatment thermal therapy or sham control rigid cystoscopy with simulated active treatment sounds. The primary outcome for comparison was change in IPSS at 3 months; active treatment group follow-up is intended annually for 5 years. Current follow-up has been completed through 3 years. Sexual function was a secondary outcome evaluated at baseline and annually. In both trials, the institutional review board at each center approved the protocols, and all men gave written informed consent.

For the comparison of subjects treated with thermal therapy and medical therapies, only men in the MTOPS study who met the limited enrollment eligibility criteria of the Rezūm RCT for prostate size and limitations of IPSS severity in both studies were included. Thus, the MTOPS study cohorts included were men with a prostate volume of 30−80 cm^3 (vs 8.8−181.0 cm^3 in the original MTOPS study) and IPSS ≥13 to ≤30 (vs 8−30 in MTOPS study). Subjects who reported no sexual intercourse in both RCTs were excluded for sexual function analysis.

Procedures

The MTOPS study medications (either placebo, doxazosin, finasteride, or a combination of both drugs) were taken daily, and there was provision for α-blocker dose modifications based on tolerability.[6]

The water vapor thermal therapy subjects were treated in a single setting, in the office or ambulatory outpatient clinic with management of potential discomfort/pain and anxiety based on the urologist's preference and discretion. General anesthesia is not required. In the RCT, anesthesia was variable, 69% received oral sedation only, 10% intravenous sedation, and 21% received a prostate block.[13] Minimal transient perioperative side effects may occur, are anticipated, and can occur after routine rigid cystoscopy. Adverse events reported were infrequent and of short duration.

The Rezūm System includes an RF generator power supply, system controls, and a single-use transurethral cystoscopic delivery mechanism, which incorporates a standard retractable treatment needle. Water vapor (steam) thermal energy is created through the application of RF current against an inductive coil heater in the handle of the device. The delivery device tip is initially positioned approximately 1 cm distal to the bladder. The water vapor (0.5 mL) is convectively delivered in 9-second injections and dispersed circumferentially to create a 1.5−2.0-cm lesion, remaining confined within the prostate zones. The needle is retracted after each treatment and repositioned in 1-cm increments distal from the previous site to the end of the prostatic tissue just proximal to the verumontanum. The objective of the treatment is to create contiguous, overlapping lesions running parallel to the natural slope of the urethra. The total number of treatments in each lobe of the prostate is determined by the length of the hypertrophied prostatic tissue and can be

Table 1. Comparison of Rezūm and MTOPS cohort subjects with baseline IPSS 13–30 and prostate volume 30–80 cm^3

	Rezūm	Doxazosin	*P* vs Rezūm	Finasteride	*P* vs Rezūm	Combo	*P* vs Rezūm	Placebo	*P* vs Rezūm
No. patients	129	370	—	391	—	385	—	331	—
Age, y	63.3 ± 7.0	63.0 ± 7.3	.63	63.0 ± 6.9	.62	63.1 ± 6.9	.73	62.7 ± 7.1	.41
Race/ethnicity %									
White	82.2%	83.6%	.72	83.5%	.72	82.1%	.993	86.1%	.29
Black	10.1%	8.1%	.49	8.1%	.49	8.5%	.60	6.0%	.14
Other	7.8%	8.4%	.83	8.4%	.83	9.3%	.59	7.9%	.98
Clinical assessments									
Body mass index	28.7 ± 4.5	27.7 ± 3.8)	.02	28.1 ± 4.8	.23	28.1 ± 4.5	.17	27.7 ± 4.1	.03
Serum prostate-specific antigen (ng/mL)	2.1 ± 1.6	2.8 ± 2.3	< .001	2.6 ± 2.2	< .010	2.6 ± 2.1	< .01	2.8 ± 2.3	< .001
IPSS	21.5 ± 4.3	19.5 ± 4.4	< .0001	20.1 ± 4.4	< .002	19.4 ± 4.8	< .0001	20.0 ± 4.6	< .002
Quality of life (IPSS)	4.4 ± 1.0	3.2 ± 1.1	< .0001	3.4 ± 1.2	< .0001	3.3 ± 1.2	< .0001	3.4 ± 1.2	< .001
BPH impact index	6.2 ± 2.8	4.4 ± 2.5	< .0001	4.7 ± 2.8	< .0001	4.6 ± 2.7	< .0001	4.7 ± 2.7	< .001
Prostate vol, cm^3	46.0 ± 13.1	39.4 ± 10.5	< .0001	38.6 ± 11.0	< .0001	37.8 ± 9.8	< .0001	37.8 ± 8.4	< .001
Voided vol (mL)	237 ± 87.1	237 ± 95.9	.93	231 ± 92.6	.513	236 ± 101	.89	238 ± 95.9	.95
Maximum urinary flow rate (mL/s)	9.9 ± 2.3	10.3 ± 2.6	.20	10.4 ± 2.7	< .05	10.3 ± 2.6	.17	10.3 ± 2.8	.20
Postvoid residual vol (mL)	82.0 ± 52.3	76.5 ± 97.4	.42	72.7 ± 86.1	.147	73.2 ± 82.7	.16	82.3 ± 95.6	.97
Sexual function assessments									
MTOPS subjects only									
BMSFI completed at baseline and once during follow-up	—	356		369		361		316	
Sexually active throughout follow-up*		304		319		214		272	
Impotence† —yes	—	21.7%	—	19.7%	—	19.1%	—	22.4%	—
Impotence† —intermittent	—	18.8%	—	19.7%	—	24.2%	—	20.2%	—
BMSFI total score (range 1–34)	—	24.5 ± 10.6	—	24.3 ± 10.2	—	24.4 ± 10.3	—	24.2 ± 11.0	—
BMSFI domain scores									
Sexual drive (range 0–8)	—	3.8 ± 1.8	—	3.8 ± 1.8	—	3.7 ± 1.8	—	3.7 ± 1.9	
Erectile function (range 0–12)	—	6.1 ± 3.6	—	6.0 ± 3.6	—	6.2 ± 3.5	—	5.9 ± 3.7	—
Ejaculatory function (range 0–8)	—	5.4 ± 2.7	—	6.0 ± 3.6	—	5.5 ± 2.6	—	5.4 ± 2.6	—
Sexual problem assessment (range 0–12)	—	7.3 ± 3.8	—	7.1 ± 3.8		7.2 ± 3.8	—	7.2 ± 3.9	—
Overall sexual satisfaction (range 0–4)	—	1.9 ± 1.2	—	1.9 ± 1.2		1.9 ± 1.2	—	2.0 ± 1.3	—

(continued)

Table 1. Continued

	Rezūm	Doxazosin	*P* vs Rezūm	Finasteride	*P* vs Rezūm	Combo	*P* vs Rezūm	Placebo	*P* vs Rezūm
BMSFI domain, n (%) Cut-off points for sexual dysfunction‡									
Sexual drive ≤2	—	100 (28.1)	—	89 (24.3)	—	88 (24.4)	—	94 (29.9)	—
Erectile function ≤3	—	94 (26.5)	—	96 (26.3)	—	86 (23.9)	—	87 (27.5)	—
Ejaculatory function ≤2	—	57 (15.9)	—	58 (15.9)	—	55 (15.3)	—	52 (16.3)	—
Sexual problem assessment ≤3	—	66 (18.6)	—	73 (19.9)	—	70 (19.5)	—	64 (20.2)	—
Overall sexual satisfaction ≤1	—	122 (34.3)	—	124 (33.8)	—	125 (34.8)	—	109 (34.4)	—
Rezūm subjects only									
IIEF-15 completed at baseline	90								
Sexually active throughout follow-up*	86	—	—	—	—	—	—	—	-
History of ED, n/129 (%)	68 (52.7)	—	—	—	—	—	—		
Duration of ED, y (range)	5.2 ± 5.7 (0.5–42)	—	—	—	—	—	—	—	—
IIEF-15 total score (1–75)	41.5 ± 21.4	—	—	—	—	—	—	—	—
IIEF-EF score (1–30)	17.2 ± 10.2	—	—	—	—	—	—	—	—
History of EjD, n/129 (%)	32 (24.8)	—	—	—	—	—	—	—	—
Duration of EjD, y (range)	4.6 ± 3.7 (0.3–15.0)	—	—	—	—	—	—	—	—
MSQH-EjD function (range 0–15)	7.7 ± 4.1 (1.0–15.0)	—	—	—	—	—	—	—	—
MSQH-EjD bother (range 0–5)	2.6 ± 1.7 (0–5.0)	—	—	—	—	—	—	—	—

BMSFI = Brief Male Sexual Function Inventory; BPH = benign prostatic hyperplasia; ED = erectile dysfunction; IIEF-15 = International Index of Erectile Function; IPSS = International Prostate Symptom Score; MSHQ-EjD = Male Sexual Health Questionnaire for Ejaculatory Dysfunction (EjD); MTOPS = medical therapy of prostatic symptoms; Rezūm = water vapor thermal therapy.
Data are presented as mean ± SD.
*Sexual function assessments included men who were identified as sexually active at baseline on BMSFI or IIEF-15 and remained active throughout follow-up evaluations.
†Medical history case report form as part of the screening visit for MTOPS trial subjects included a question on impotence; possible answers are yes, no, or intermittent.
‡The BMSFI inventory does not categorize sexual dysfunction; however, previously reported cut-off points are used to describe baseline sexual dysfunction in each domain.[22,23]

Table 2. Comparison of sexual function questionnaires

	IIEF-15 or MSHQ-EjD Rezūm RCT		BMSFI MTOPS RCT	
Domains	Question number	Domain total score range	Question number	Domain total score range
Sexual desire/interest*	11, 12	0–10	1, 2	0–8
Erectile function*	1–5, 15	0–30	3, 4 ,5	0–12
Ejaculatory function*	MSHQ-EjD, 1–3	0–15	6, 7	0–8
Orgasmic function	9, 10	0–10	Not included	—
Sexual problem assessment	Not included	—	8, 9, 10	0–12
Intercourse satisfaction	6, 7, 8	0–15	Not included	—
Overall sexual satisfaction*	13, 14	0–10	11	0–4

BMSFI = Brief Male Sexual Function Inventory; IIEF-15 = International Index of Erectile Function (EF); MSHQ-EjD = Male Sexual Health Questionnaire for Ejaculatory Dysfunction; MTOPS = medical therapy of prostatic symptoms; RCT = randomized controlled trial; Rezūm = water vapor thermal therapy.
*Sexual function categories included in both questionnaires or with MSHQ-EjD function score to assess ejaculatory function are not included in the IIEF-15. BMSFI assessments for each domain are a continuous score ranging from 0 (lack/none) to total of 4–12 (normal). The inventory does not categorize sexual dysfunction. With the IIEF-15, the EF domain score ranging from 1 to 30 is divided into categories to define the level of erectile dysfunction.

customized to the configuration of the gland including the median lobe. There are no morphologic contraindications.[13,16,18]

Sexual Function Measures

2 validated, self-administered questionnaires were used for clinical assessment of pretreatment sexual function and treatment outcomes in the clinical trials, each querying experiences over the past 30 days. Questionnaires were completed at baseline and at each follow-up clinical visit. The MTOPS study used the 11-item Brief Male Sexual Function Inventory (BMSFI)[19]; whereas the Rezūm RCT used the 15-item International Index of Erectile Function (IIEF-15) Questionnaire[20] and 3-item Male Sexual Health Questionnaire for Ejaculatory Function (MSHQ-EjD)-Short Form to assess ejaculation dysfunction (EjD).[21] Excluded from evaluation were subjects who had no sexual activity or did not attempt intercourse as indicated by responses to question 6 on the BMSFI and question 6 on the IIEF-15.

Statistical Analysis

Descriptive statistics were calculated for baseline variables and presented as mean ± SD. Outcomes were compared at 1, 2, and 3 years using a linear mixed repeated measures model with fixed effects for treatment and follow-up visit; data are presented as mean and 95% CI. Estimation used maximum likelihood, the Satterthwaite method for denominator degrees of freedom, and an unstructured covariance matrix to adjust for missing longitudinal data, including subjects lost to follow-up. Due to the use of different sexual function scales, comparative analyses of MTOPS and thermal therapy subjects are descriptive in nature. For each of 4 key domains of male sexual responses at baseline and throughout annual evaluations over 3 years, profiles of change from baseline are presented for men who remained sexually active. At each time point, the mean change from baseline in each group is reported on a percentage scale by dividing the mean change by the baseline mean. For statistical comparisons, a P value $<.05$ was considered statistically significant. All calculations were carried out using SAS statistical software version 9.3 or greater (SAS Institute, Inc, Cary, NC, USA).

RESULTS

Baseline Characteristics

A total of 1,477 from the original 3,047 (48.5%) MTOPS subjects met baseline eligibility criteria of the Rezūm subjects. Of these, 370 subjects were treated with doxazosin, 391 with finasteride, 385 with combination drugs, and 331 were treated with placebo. The BMSFI was completed at baseline and at least once during follow-up by 1,402 of 1,477 (94.9%) subjects, and of these, 1,209 of 1,402 (81.9%) were sexually active. Among the 129 thermal therapy subjects, 86 (66.6%) were sexually active.

Table 1 shows baseline demographic characteristics of the MTOPS cohorts and Rezūm subjects, restricted to men with prostate volumes of 30–80 cm^3 and IPSS $\geq$13 to $\leq$30. Compared to MTOPS study cohorts, the Rezūm subjects had slightly larger average prostate volumes and higher (worse) scores for LUTS severity on the IPSS, quality of life, and BPH Impact Index ($P < .0001$ on all items), although with a lower prostate specific antigen value ($P \leq .0062$). Among the thermal therapy subjects, an approximate 5-year history of erectile dysfunction (ED) was reported by 52.7% (68 of 129) and EjD by 24.8% (32 of 129). Using cut-off points of the BMSFI to identify sexual dysfunction[22,23] at baseline, a mean of 26.1% of each cohort had ED and 15.9% had EjD. MTOPS trial subjects were asked if they had a history of impotence. An average 20.7% of men answered "yes" and an additional 20.8% described impotence as "intermittent."

Sexual Function Outcomes

Multiple aspects of male sexual function were examined for domains common to both BMSFI and IIEF-15 or MSHQ-EjD questionnaires: sexual desire, erectile function (EF), ejaculatory

Table 3. IIEF-15 or MSHQ and BMSFI domain questions with similar wording

IIEF-15 or MSHQ	BMSFI
Sexual Desire	
Q11: **How often have you felt sexual desire?**	Q1: **On how many days have you felt sexual drive?**
Q12: **How would you rate your level of sexual desire?**	Q2: **How would you rate your level of sexual drive?**
Commonality = Frequency of desire (Q11 & 1); level of desire (Q12 & 2)	
Erectile Function	
Q1: **How often were you able to get an erection during sexual activity?**	Q3: **How often have you had partial or full sexual erections when you were sexually stimulated in any way?**
Q2: When you had erections with sexual stimulation, **how often** were your **erections hard enough** for penetration?	Q4: When you had **erections, how often** were they **firm enough** to have sexual intercourse?
Q3: When you attempted intercourse, how often were you **able to penetrate** (enter) your partner?	Q5: How much **difficulty** did you have getting an erection during the past 30 days?
Q4: During sexual intercourse, how often were you able to **maintain** your erection **after you had penetrated** (entered) your partner?	—
Q5: During sexual intercourse, how difficult was it to **maintain your erection to completion of intercourse**?	—
Q15: How do you rate your confidence that you could get and keep an erection?	—
Commonalities = Frequency of erections (Q1 & 3); firmness of erection (Q2 & 4)	
Overall sexual satisfaction	
Q13: How **satisfied** have you been **with your overall sex life?**	Q11: **Overall,** how **satisfied** have you been **with your sex life?**
Q14: How satisfied have you been with your sexual relationship with your partner?	—————
Commonality = Satisfaction with sex life (Q13 & 11)	
Ejaculatory function—MSHQ-EjD	BMSFI
MSHQ-Q1: How often have you **been able to ejaculate** when having sexual activity	Q6: How much **difficulty** have **you had ejaculating** when you have been sexually stimulated?
MSHQ-Q2: How would you rate the **strength** or force of your ejaculation?	Q7: How much did you consider the **amount of semen** you ejaculate to be a problem for you?
MSHQ- Q3: How would you rate the **amount** or volume **of semen** or fluid when you ejaculate?	—
Commonality = Ability to ejaculate (Q1 & 6); amount of semen (Q3 & 7)	

BMSFI = Brief Male Sexual Function Inventory; IIEF-15 = International Index of Erectile Function; MSHQ-EjD = Male Sexual Health Questionnaire for Ejaculatory Dysfunction.
Questionnaire responses are in reference to subjects' experiences during the past 30 days.

function, and overall sexual satisfaction (Table 2). Table 3 shows the similarity of wording in the 4 domains common to both questionnaires. The integrity of domain questions in each questionnaire has been preserved, and as such, changes relative to baseline are reported. The profiles of percent changes in domain scores from baseline scores (mean change/mean baseline score) for thermal therapy subjects and MTOPS cohorts are presented in Figure 1. The profiles of change are relative to each sexual function inventory (BMSFI for MTOPS and IIEF/MSH-EjD for Rezūm), and thus profiles remain independent and are not compared statistically with one another.

Sexual Desire

Men in the 3 drug groups had a worsening of sexual desire scores through 3 years including −6.7% for doxazosin, −10.7% for finasteride, and −8.6% for the combination drug group by 3 years (all $P < .001$) (Figure 1A). After treatment with water vapor thermal therapy, subjects showed slight improvements, however, no significant estimated mean percent changes (%Δ) in sexual desire domain scores compared with baseline at year 3 (%Δ = 1.8% [−5.6, 9.2], $P = .62$). The profile of the MTOPS placebo remained unchanged (%Δ = −1.2% [−6.0, 3.6], $P = .61$).

Erectile Function

The profiles of the 3 drug groups showed significantly worsening EF scores over time (Figure 1B). Men receiving combination drug therapy had the greatest %Δ in EF at 1 year of −10.5%, compared with −6.4% for doxazosin and −5.3% for finasteride; these estimated %Δ in mean scores continued at a similar level, or with further score decreases over 3 years (all $P \leq .004$). The profiles

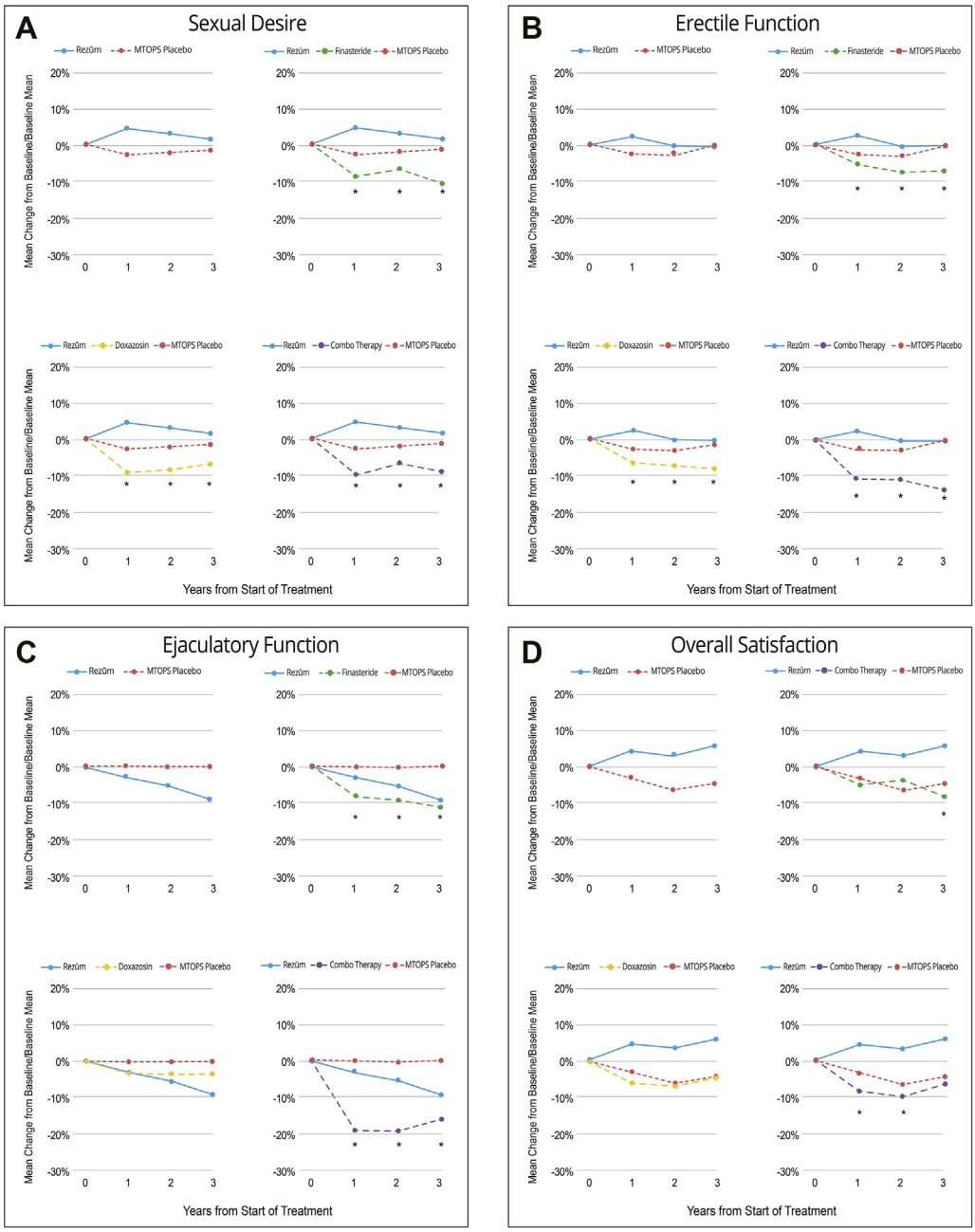

Figure 1. Profiles of mean percentage changes from baseline over 3 years in sexual function domains with time after treatment with a single water vapor therapy procedure or continued treatment with doxazosin, finasteride, or a combination of both drugs. The domains are sexual desire (A), erectile function (B), ejaculatory function (C), and overall sexual satisfaction (D). Rezūm study (water vapor thermal therapy) evaluations were measured with the International Index of Erectile Function-15 and Male Sexual Health Questionnaire for Ejaculatory Dysfunction inventories and those for medical therapy of prostatic symptoms study were evaluated with the Brief Male Sexual Function Inventory. Asterisk denotes treatment is significantly different from baseline at follow-up ($P < .05$ to $< .001$).

of EF scores for Rezūm and MTOPS placebo were similar and without significant mean changes over 3 years relative to baseline scores for the respective inventories ($P = .90$ and $P = .94$, respectively). Of note are minimal clinically important differences of improved EF scores for water vapor thermal therapy, which occurred in 20 of 63 (32%) men at year 1 and 10 of 48 (21%) at year 3 (Table 4).

Ejaculatory Function

Ejaculatory function worsened significantly in finasteride and combination drug groups over 3 years, whereas the slight score decreases with doxazosin were not significant (Figure 1C). Men receiving combination therapy experienced the greatest estimated mean %Δ relative to baseline of −18.9% at year 1 to −16% (−20.6, −11.4) at year 3 ($P < .001$). The score decreased at −8.2%

Table 4. Improved erectile function over 3 years after water vapor thermal therapy in sexually active men evidenced by minimal clinically important differences

		Year 1 N = 63		Year 2 N = 59		Year 3 N = 48	
ED severity category (score range)	Baseline N = 86	n/N	MCID increase Median (range)	n/N	MCID increase Median (range)	n/N	MCID Increase Median (range)
Severe (1–10)	7	2/2	11.5 (9–14)	1/2	20	1/2	17
Moderate (11–16)	14	5/10	11 (7–18)	5/10	11 (6–15)	2/7	13 (13–13)
Mild (17 to ≤25)	65	13/51	5 (2–12)	10/47	4.5 (2–11)	7/39	7 (2–11)
n/N, % with improved EF scores		20/63 32%		16/59 27%		10/48 21%	

ED = erectile dysfunction; IIEF-EF = International Index of Erectile Function (IIEF)-erectile function (EF) domain; MCID = minimal clinically important differences.

Improvement in EF or decreased severity is indicated by an increase in IIEF-EF domain score in each baseline severity category. Change in EF score was evaluated using the criterion of the MCID, which represents the amount of change in the EF domain needed to be clinically meaningful and perceptible as a benefit to the patient.[14,24] For each EF severity category, the MCID would require a minimal EF score increase of 2 for men with mild ED, an increase of 5 for moderate ED, and an increase of 7 for severe ED. The MCID helps define responses to interventions benefitting EF.

after finasteride and further decreased at year 3 with %Δ = −11.3% (−15.3, −7.3), $P < .001$. The natural history of ejaculatory function as reflected by the MTOPS placebo cohort showed no appreciable changes compared with baseline scores throughout 3 years; the %Δ = 0.1% (−3.8, 4.0), $P = .95$ at year 3. Subjects treated with thermal therapy showed a profile of decreasing, but no significant mean change in ejaculatory function at year 3, %Δ = −9.2% (−18.4, −0.0), $P = .05$.

Overall Sexual Satisfaction

The combination drug group had decreases in overall sexual satisfaction at 1 and 2 years, %Δ = −8.3% (−15.0, −1.6), $P < .01$ to %Δ = −9.8% (−17.4, −1.7), $P = 0.01$, respectively; whereas profiles for subjects receiving placebo and doxazosin over 3 years and placebo and finasteride over 2 years had slight but insignificant changes. At 3 years, the score for subjects receiving finasteride had a %Δ = −8.5% (−15.5, −1.7), $P = .01$ (Figure 1D). Subjects treated with water vapor thermal therapy showed slight, non-significant improvements (4.6–6.0%) in the overall satisfaction domain score on the IIEF-15 compared with baseline ($P \geq .17$).

DISCUSSION

This report extends our understanding of effects on sexual function after long-term daily medical therapy for LUTS/BPH vs outcomes after a one-time water vapor thermal therapy procedure. A prior study evaluated MTOPS and thermal therapy in men propensity matched for baseline LUTS severity and prostate size.[25] Symptom improvement was significantly greater with thermal therapy than either doxazosin or finasteride alone but similar to outcomes with a combination drug therapy. The observed rates of clinical progression over 3 years were approximately 5 times greater for any of the medical therapies vs a single thermal therapy procedure. In this report, we provide additional observations evaluating mean changes in various domains of sexual function between MTOPS and Rezūm cohorts.

Profiles of worsening sexual desire and EF occurred over 3 years for all drug treatments. Men treated with finasteride and combination drugs also experienced worsening of ejaculatory function; scores were approximately 2 times worse with combination drugs including significant decreases in overall sexual satisfaction. In contrast, men treated once with the Rezūm procedure had on average no worsening in any domain; slight improvements occurred in profiles for sexual desire and satisfaction. An earlier report of MTOPS subject sexual function included all men without characterization of sexual activity.[9] The placebo group had worsening scores for desire, erectile and ejaculatory function, whereas in our study, restricted to men continuing to be sexually active, no significant changes in placebo profiles were observed.

Medications for LUTS/BPH do not provide immediate satisfaction and may take up to 2 years of continuous use to obtain maximum benefit. Whether it is due to drug side effects or dissatisfaction with the level of urinary symptom relief, patients often interrupt therapy, change prescriptions, or discontinue therapy completely.[26,27] In real-life situations, after 12 months of medication use, the discontinuation rate ranges from 62–91%.[26–28] In the MTOPS study, medication adherence was remarkably good due to the nature of the NIH protocol. Daily medication regimens used for extended periods can be costly. The water vapor thermal procedure was positioned favorably in a cost-effectiveness comparison with generic and prescription combination drugs and other MISTs.[29]

This report has several positive aspects including utilization of high-quality data from 2 large RCTs with subjects restricted to those with the same baseline inclusion criteria for symptom severity and prostate size. It presents the first longitudinal evaluation and comparison of sexual function domains restricted to sexually active men treated with drugs or a single MIST procedure. With the minimal clinically important differences assessment, we identified subjects with mild-to-severe ED who had meaningful clinical improvements in ED that were durable

for 36 months after thermal therapy. Thus, the water vapor thermal procedure intended to alleviate obstructive and irritative urinary symptoms also occurred in conjunction with improved EF in some patients.[14] A limitation of this study is the use of 2 different, although validated sexual function inventories, the BMSFI, which was the state of art at the time of MTOPS study recruitment, and the subsequently developed IIEF-15. To overcome this limitation, we examined the independent profiles of change relative to baseline for each of the inventories, thus preserving the integrity of each questionnaire. Neither the MTOPS nor Rezūm RCT collected sufficient data to address confounding factors (eg, diabetes, metabolic syndrome, tobacco use) that may influence EF. Although a contemporary RCT comparing medical therapy and Rezūm or with any other MIST might be ideal, it is highly unlikely. As one might recall, the NIDDK embarked on such an RCT (NIDDK: ClinicalTrials.gov Identifier: NCT00064649 Minimally Invasive Surgical Therapy for BPH [MIST]), a combination of medical therapy vs transurethral needle ablation vs microwave thermotherapy, which was terminated after nearly 3 years of futile enrollment. Because such an RCT is unlikely to be revisited, our assessments provide an important insight that otherwise is likely to remain elusive. Water vapor thermal therapy can result in greater LUTS improvements than either doxazosin or finasteride alone, whereas combination drug therapy may equal that of this MIST,[25] but all drug therapies come at the cost of a significant negative impact on sexual function. An additional limitation is that outcomes of this study may not be generalizable to sexual function effects after the use of other α-blockers (eg, alfuzosin, silodosin, tamsulosin, terazosin) and 5-α reductase inhibitors (eg, dutasteride), alone or in combination, for various treatment periods and with outcomes evaluated with different sexual function questionnaires. A fixed-dose combination of dutasteride/tamsulosin resulted in worsening of the ejaculatory and satisfaction domains of the male sexual health questionnaire but not the EF domain.[12]

CONCLUSION

A single water vapor thermal therapy procedure had no negative impact on sexual function over a 3-year period after treatment in sexually active men in contrast to worsening desire, erectile and ejaculatory function with the daily use of finasteride and combination drugs, and reduced libido and EF with doxazosin. As value and quality-based payment programs continue to evolve, technologies such as water vapor thermal therapy that demonstrate cost effectiveness, circumvent the need for long-term use, and provide good outcomes with preservation of sexual function will continue to have great appeal and provide a benefit to physicians and patients. Clinicians should consider this therapeutic option to improve LUTS while preserving libido, erectile, and ejaculatory function in men.

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Corresponding Author: Kevin T. McVary, MD, Division of Urology, Southern Illinois University School of Medicine, St. John's Pavilion, 301 North Eighth Street, PO Box 19665, Springfield, IL 62794-9665, USA. Tel: 217-545-8860; Fax: 217-545-7305; E-mail: kmcvary@gmail.com

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STATEMENT OF AUTHORSHIP

Category 1

(a) **Conception and Design**
Kevin T. McVary; Tyson Rogers
(b) **Acquisition of Data**
Kevin T. McVary; Tyson Rogers
(c) **Analysis and Interpretation of Data**
Kevin T. McVary; Tyson Rogers; Joseph Mahon; Nikhil K. Gupta

Category 2

(a) **Drafting the Article**
Kevin T. McVary; Tyson Rogers
(b) **Revising It for Intellectual Content**
Kevin T. McVary; Tyson Rogers; Joseph Mahon; Nikhil K. Gupta

Category 3

(a) **Final Approval of the Completed Article**
Kevin T. McVary; Tyson Rogers; Joseph Mahon; Nikhil K. Gupta

REFERENCES

1. Rosen R, Altwein J, Boyle P, et al. Lower urinary tract symptoms and male sexual dysfunction: The multinational survey of the aging male (MSAM-7). **Eur Urol 2003;44:637-649.**
2. Vallancien G, Emberton M, Harving N, et al. Sexual dysfunction in 1,274 European men suffering from lower urinary tract symptoms. **J Urol 2003;169:2257-2261.**
3. McVary K, Foley KA, Long SR, et al. Identifying patients with benign prostatic hyperplasia through a diagnosis of, or treatment for, erectile dysfunction. **Curr Med Res Opin 2008;24:775-784.**
4. Gacci M, Eardley I, Giuliano F, et al. Critical analysis of the relationship between sexual dysfunctions and lower urinary

tract symptoms due to benign prostatic hyperplasia. **Eur Urol 2011;60:809-825.**

5. Kirby RS, Roehrborn C, Boyle P, et al. 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 (PREDICT) trial. **Urology 2003;61:119-126.**
6. McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. **New Engl J Med 2003;49:2387-2398.**
7. Roehrborn CG, Siami P, Barkin J, et al. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. **Eur Urol 2010; 57:123-131.**
8. Erdemir F, Harbin A, Hellstrom WJ. 5-alpha reductase inhibitors and erectile dysfunction: The connection. **J Sex Med 2008;5:2917-2924.**
9. Fwu CW, Eggers PW, Kirkali Z, et al. Change in sexual function in men with lower urinary tract symptoms/benign prostatic hyperplasia associated with long-term treatment with doxazosin, finasteride and combined therapy. **J Urol 2014; 191:1828-1834.**
10. Welliver C, Butcher M, Potini Y, et al. Impact of alpha blockers, 5-alpha reductase inhibitors and combination therapy on sexual function. **Curr Urol Rep 2014;15:441-448.**
11. Favilla V, Russo GI, Privitera S, et al. Impact of combination therapy 5-alpha reductase inhibitors (5-ARI) plus alpha-blockers (AB) on erectile dysfunction and decrease of libido in patients with LUTS/BPH: A systematic review with meta-analysis. **Aging Male 2016;19:175-181.**
12. Roehrborn CG, Manyak MJ, Palacios-Moreno JM, et al. A prospective, randomised placebo-controlled study of the impact of dutasteride/tamsulosin combination therapy on sexual function domains in sexually active men with lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH). **BJU Int 2018;121:647-658.**
13. McVary KT, Gange SN, Gittelman MC, et al. Minimally invasive prostate convective water vapor energy (WAVE) ablation: A multicenter, randomized, controlled study for treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. **J Urol 2016;195:1529-1538.**
14. McVary KT, Gange SN, Gittelman MC, et al. Erectile and ejaculatory function preserved with convective water vapor energy treatment of LUTS secondary to BPH: Randomized controlled study. **J Sex Med 2016;13:924-933.**
15. Roehrborn CG, Gange SN, Gittelman MC, et al. Convective water vapor energy (WAVE) ablation therapy: Durable two-year results and prospective blinded crossover study for treatment of lower urinary tract symptoms due to benign prostatic hyperplasia. **J Urol 2017;197:1507-1516.**
16. Darson MF, Alexander EE, Schiffman ZJ, et al. Procedural techniques and multicenter post-market experience using minimally invasive convective radiofrequency thermal therapy with Rezūm System for treatment of lower urinary tract symptoms due to benign prostatic hyperplasia. **Res Rep Urol 2017;9:159-168.**
17. McVary KT, Roehrborn CG. Three-year outcomes of the prospective, randomized controlled Rezūm System study: Convective radiofrequency thermal therapy for treatment of lower urinary tract symptoms due to benign prostatic hyperplasia. **Urology 2018;111:1-9.**
18. Woo HH, Gonzalez RR. Perspective on the Rezūm System: A minimally invasive treatment strategy for benign prostatic hyperplasia using convective radiofrequency water vapor thermal therapy. **Med Dev (Auckl) 2017;10:71-80.**
19. O'Leary MP, Lenderking WR, Barber B, et al. A brief male sexual function inventory for urology. **Urology 1995;46:697-706.**
20. Rosen RC, Riley A, Wagner G, et al. The International Index of Erectile Function (IIEF): A multidimensional scale for assessment of erectile dysfunction. **Urology 1997;49:822-830.**
21. Rosen RC, Catania JA, Althof SE, et al. Development and validation of four-item version of Male Sexual Health Questionnaire to assess ejaculatory dysfunction. **Urology 2007; 69:805-809.**
22. Burke JP, Jacobson DJ, McGree ME, et al. Diabetes and sexual dysfunction: Results from the Olmsted County study of urinary symptoms and health status among men. **J Urol 2007; 177:1438-1442.**
23. Gades NM, Jacobson DJ, McGree ME, et al. Longitudinal evaluation of sexual function in a male cohort: The Olmsted county study of urinary symptoms and health status among men. **J Sex Med 2009;6:2455-2466.**
24. Rosen RC, Allen KR, Ni X, et al. Minimal clinically important differences in the erectile function domain of the International Index of Erectile Function Scale. **Eur Urol 2011;60:1010-1016.**
25. Gupta N, Rogers T, Holland B, et al. Three-year treatment outcomes of water vapor thermal therapy (Rezūm System) compared to doxazosin, finasteride and combination drug therapy for men with benign prostatic hyperplasia: Cohort data from the Medical Therapy of Prostatic Symptoms (MTOPS) Trial. **J Urol 2018;200:405-413.**
26. Verhamme KM, Dieleman JP, Bleumink GS, et al. Treatment strategies, patterns of drug use and treatment discontinuation in men with LUTS suggestive of benign prostatic hyperplasia: The Triumph Project. **Eur Urol 2003;44:539-545.**
27. Cindolo L, Pirozzi L, Fanizza C, et al. Drug adherence and clinical outcomes for patients under pharmacological therapy for lower urinary tract symptoms related to benign prostatic hyperplasia: Population-based cohort study. **Eur Urol 2015; 68:418-425.**
28. Issa MM, Lin P-J, Eaddy MT, et al. Comparative analysis of alpha-blocker utilization in combination with 5-alpha reductase inhibitors for enlarged prostate in a managed care setting among Medicare-aged men. **Am J Manag Care 2008;14(5 Suppl. 2):S160-S166.**
29. Ulchaker JC, Martinson M. Cost-effectiveness analysis of six therapies for the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia. **ClinicoEconomics Outcomes Res 2018;11:29-43.**