REVIEW

Emerging, newly-approved treatments for lower urinary tract symptoms secondary to benign prostatic hypertrophy

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Introduction: *Oral therapy with alpha-blockers or 5-alpha reductase inhibitors remains the most common treatment in men with lower urinary tract symptoms (LUTS) secondary to benign prostatic hypertrophy (BPH). For patients who progress or fail medical therapy, the standard of care surgical treatment continues to be transurethral resection of the prostate (TURP), which has long-studied and durable outcomes. Emerging, minimally invasive options for LUTS secondary to the BPH, however, have been developed over the last decade with promising results and minimal side effects typically associated with TURP, such as retrograde ejaculation and erectile dysfunction.*

Materials and methods: *We performed a literature review on PubMed over the last 10 years using keywords such as "lower urinary tract symptoms," "benign prostatic hypertrophy," "minimally invasive," and "outpatient." All relevant studies that reported on important urinary endpoints were included for each newly-approved treatment option. Available literature across varying prostate volumes was presented.*

Results: *Newly-approved therapies for BPH include new thermal energy sources (Rezum, aquablation), mechanical stenting (UroLift), prostate artery embolization, and injectable agents. These emerging techniques could be considered in patients where preservation of sexual function is a priority since they have demonstrated comparable urinary outcomes to medical therapy while causing no significant sexual dysfunction. Only prostate artery embolization has been extensively analyzed and proven efficacious in patients with > 80 g prostates who cannot undergo surgery.*

Conclusion: *We have summarized the newly-approved treatment options for men with LUTS secondary to BPH as an alternative to traditional medical or surgical therapy. As more minimally invasive, office-based technologies emerge, physician and patients will have the ability to choose a treatment that is more catered to patient expectations.*

Key Words: lower urinary tract symptoms, benign prostate hypertrophy, prostate artery embolization, UroLift, aquablation, Rezum, prostate injectables

Introduction

The goal of novel procedural treatment options for lower urinary tract symptoms (LUTS) secondary to benign prostate hypertrophy (BPH) in men with large prostate glands is to achieve similar outcomes as the gold standard transurethral resection of the prostate (TURP) while minimizing sexual side effects, such as retrograde ejaculation and erectile dysfunction. These emerging therapies also aim to reduce recovery time and hospitalization and minimize the necessity for general anesthesia during treatment and improve postoperative pain control. Although many studies are driven by industry when a new technology is developed, they are still conducted in a scientific manner with appropriate control groups and end points, when applicable. We summarize the emerging, newly-approved treatment options for men with LUTS secondary to BPH as an alternative to traditional medical or surgical therapy (TURP, simple prostatectomy, greenlight laser prostatectomy, holmium laser enucleation of the prostate, etc.).

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Prostate artery embolization

Prostate artery embolization (PAE) is a minimally invasive, radiology-based procedure performed for patients suffering from LUTS including weakened urinary stream, urinary hesitancy, incomplete bladder empyting, nocturia, and post-voidal dribbling secondary to BPH. PAE is typically an outpatient procedure that can be done under local anesthesia. The procedure is performed by first mapping the blood supply of the prostate gland via pelvic computed tomographic (CT) angiography. A specialized catheter is then gently threaded into the prostatic artery from the femoral artery through an initial puncture site in the groin with the help of digital subtraction angiography (DSA) and contrast-enhanced cone-beam CT. Once the catheter is in the optimal position, Embosphere microspheres (Merit Medical Systems Inc., South Jordan, UT, USA) are introduced. These spherical particles aggregate in the arterial lumen and occlude the blood supply to the prostate, causing the gland to shrink with subsequent alleviation of urinary symptoms.[1]

PAE is indicated for patients who do not respond to standard medical treatment for BPH, patients who are not candidates for open surgery or TURP, or patients who refuse surgical treatment. PAE can be performed on all prostate sizes and shapes, including those with an enlarged median lobe. It is contraindicated in patients with severe atherosclerotic changes or tortuosity of the iliac or prostatic arteries.[2]

PAE has demonstrated to be safe and effective in several studies in both smaller and larger prostate glands without significant complications. For patients with larger prostates (> 80 g), the literature demonstrated

TABLE 1. **Clinical outcomes of prostate artery embolization (PAE) in the treatment of lower urinary tract symptoms (LUTS) for men with large (> 80 g) prostate volumes**

Author	N	Results			Follow up
		Urinary	Erectile function	PV change (g)	
Kurbatov et al. 2014[5]	88	IPSS: -13.58 Qmax: +9.61 mL/s PVR: -56.87 mL	IIEF: +0.68	-58.11	12 months
Bagla et al. 2015[6]	36	AUASS: -12.92	IIEF: +3.69		6 months
De Assis et al. 2015[7]	35	IPSS: -15.6 Qmax: +8.1 mL/s		-43.2	3 months
Li et al. 2015[8]	24	IPSS: -19.5 Qmax: +6 mL/s PVR: -100 mL	IIEF: -3	-41	12 months
Wang et al. 2015[9]	64	IPSS: -19 Qmax: +6 mL/s PVR: -95 mL	IIEF: +1	-49.4	24 months
Wang et al. 2015[4]	117	IPSS: -17 Qmax: +6 mL/s PVR: -85 mL	IIEF: -1	-49	24 months
Wang et al. 2016[10]	64	IPSS: -14 Qmax: +6 mL/s PVR: -80 mL	IIEF: +1.5	-54.5	12 months
Isaacson et al. 2016[1]	12	IPSS: -18.2 Qmax: +7.1 mL/s PVR: -46.3 mL	IIEF: +2	-34.4	3 months
Pisco et al. 2016[3]	152	IPSS: -16.27 Qmax: +3.75 mL/s PVR: -13.41 mL	IIEF: +3.55	-54.17	18 months

AUASS = American Urological Association symptom score; IIEF = international index of erectile function; IPSS = international prostate symptom score; PV = prostate volume; PVR = post-void residual volume; Qmax = peak urinary flow

significant improvements in International Prostate Symptom Score (IPSS), peak urinary flow (Qmax), and post-void residual volume (PVR), Table 1. Prostate size was also reduced after PAE, and PSA was decreased an average of 2.8 ng/mL. Sexual function (as measured by the International Index of Erectile Function [IIEF-5]) improved after PAE in some studies, but remaining unchanged in others. The procedure takes an average of 2 hours, and most adverse events, albeit minor, occurred post procedure and included: hematospermia, dysuria, hematuria, urge incontinence, urinary retention, urinary tract infection, prostatitis, rectal bleeding, and inguinal hematoma. The overall complication rate after PAE, however, has been noted to be approximately 10%, and these symptoms generally improved with appropriate antibiotics or resolved spontaneously without treatment.[2] Major adverse events that have been previously reported are associated with erroneous embolization of arteries other than the prostatic artery, leading to ischemia of surrounding organs such as the bladder, rectum, or penis.[3]

A single-center retrospective study by Pisco et al included 152 patients with prostate volumes > 100 g treated with PAE.[3] Clinical success rates with improvement in the patient's LUTS secondary to BPH were 90%, 87.9%, 83.5%, 81.1%, 77.8%, and 72.4% at 1, 3, 6, 12, 18, and 36 months, respectively. IPSS overall decreased 16.27 points (25.27 to 9), Qmax increased 3.75 mL/s (10.02 to 13.77 mL/s), and PVR decreased 13.41 mL (115.18 to 101.77 mL) from baseline after 18 months. Improved sexual function was observed with an average increase in IIEF of 3.55 points (14.45 to 18). Average prostate volumes also decreased 54.17 g (134.17 to 80 g). Overall, the study demonstrated that PAE provided good short-term (< 6 months), medium-term (6 to 24 months), and long-term (> 36 months) results without major complications for the treatment of BPH and LUTS.

A prospective study by Wang et al investigated 117 patients with prostate volumes > 80 g treated with PAE.[4] Clinical success rates at 1, 3, 6, 12, and 24 months were 94.3%, 94.3%, 93.3%, 92.6%, and 91.7%, respectively. LUTS after 24 months showed significant improvement with the average IPSS decreasing 17 points (26 to 9), Qmax increasing 6 mL/s (8.5 to 14.5 mL/s), and PVR decreasing 85 mL (125 to 40 mL) from baseline. Prostate volumes reduced by an average of 49 g from a mean baseline of 118 g. No significant change in sexual function was reported, and no major complications occurred post procedure in their cohort. This study provided further evidence that PAE is safe and effective as an alternative treatment option in patients with LUTS and very large prostate volumes.

Another single-center prospective study by Kurbatov et al examined 88 patients with LUTS and prostate size > 80 g at 1 year post-PAE.[5] The authors reported significant improvements in all urinary variables, with the average IPSS decreasing 13.58 points (23.98 to 10.40), Qmax increasing 9.61 mL/s (7.28 to 16.89 mL/s), and PVR decreasing 56.87 mL (75.25 to 18.38 mL) from baseline. Sexual function did not change significantly from baseline. There were also no reported major or minor complications post procedure, further demonstrating the clinical benefit of PAE on patients with BPH > 80 g.

Other studies with smaller cohort sizes have reported on the use of PAE as a safe and effective treatment option for patients with LUTS and prostate volume > 80 g. Bagla et al compared the outcomes of PAE in patients with small (< 50 g), mid-size (50 to 80 g), and large (> 80 g) prostates.[6] The study found no significant difference in urinary outcomes between the three groups, and patients with large prostates still benefited from PAE. De Assis et al also reported good clinical outcomes for patients with prostate volumes > 90 g 3 months post-PAE.[7] Li et al showed improvement in LUTS in patients with prostate size > 80 g at 12 months, but sexual function worsened in their cohort.[8] Wang et al also demonstrated that patients with large (> 80 g) prostates still benefited from PAE at 24 months, but there were no improvements in sexual function.[9] Isaacson et al reported that PAE was effective in reducing LUTS and improving sexual function in patients with prostates measuring between 80g to 150 g after 3 months.[1] Lastly, Wang et al compared outcomes between medium-sized prostates (50 to 80 g) and large-sized (> 80 g) prostates at 12 months.[10] The authors found that patients with larger prostates had better outcomes than those with smaller prostates with no major complications reported. Despite the small-scale and single-institutional nature of these studies, growing evidence continues to reinforce the feasibility of PAE as alternative treatment option for men with BPH and LUTS regardless of prostate size who are either not surgical candidates or refuse surgery.

Prostatic urethral lift

Prostatic urethral lift (PUL) is a minimally invasive procedure that utilizes permanent nitinol and stainless steel intra-prostatic implants to treat LUTS secondary to BPH.[11] The PUL procedure is performed under local or general anesthesia using the UroLift system (NeoTract, Pleasanton, CA, USA), which consists of a delivery device and small permanent implants. The implants, delivered transurethrally, attach to the lateral prostatic lobes and lift the tissue out of the way to relieve the urinary obstruction. Separation of the enlarging prostatic lobes allows for the rapid relief of LUTS without resection of prostatic tissue or thermal injury to the urethra.[12]

The PUL procedure is suitable for patients who do not desire standard TURP or patients where oral medication was ineffective or not well tolerated. This procedure may appeal to men who wish to preserve their sexual function. The implants work best in smaller or medium sized glands. UroLift is contraindicated in men with prostate volumes > 80 g, an obstructive or protruding median lobe, active urinary tract infection, urethral conditions that may prevent insertion of the delivery system into the bladder (i.e. urethral stricture disease), urinary incontinence, or ongoing gross hematuria.[11]

Due to the contraindication of UroLift in > 80 g prostates, there is no current literature published on the effects of PUL on larger glands. Several studies, however, have demonstrated that PUL is safe and effective in prostates with volumes < 80 g. The literature has demonstrated significant improvements in IPSS, Qmax, PVR in small (< 50 g) and medium (50 g-80 g)

TABLE 2. **Clinical outcomes of prostatic urethral lift in the treatment of lower urinary tract symptoms for men with BPH**

Author	N	Results		Follow up
		Urinary	Erectile function	
Woo et al. 2011[18]	19	IPSS: -9.6 Qmax: +2.5 mL/s PVR: -40 mL		12 months
Chin et al. 2012[19]	64	IPSS: -9.2 Qmax: +2.9 mL/s PVR: +35 mL	SHIM: +1.1	24 months
McNicholas et al. 2013[17]	102	IPSS: -12.3 Qmax: +4.1 mL/s PVR: +3 mL		12 months
Cantwell et al. 2014[20]	53	IPSS: -8.7 Qmax: +2.6 mL/s PVR: -11.4 mL	IIEF-5: +0.9	12 months
Rukstalis et al. 2016[21]	53	IPSS: -9.59 Qmax: +4.18 mL/s PVR: -7.32 mL	SHIM: +0.77	24 months
Sønksen et al. 2015[22]	45	IPSS: -11.3 Qmax: +4 mL/s PVR: +7.4 mL	SHIM: -0.9	12 months
Gratzke et al. 2017[23]	37	IPSS: -9.2 Qmax: +5 mL/s PVR: -10.6 mL	SHIM: -0.1	24 months
Roehrborn et al. 2013[12] McVary et al. 2014[16]	140	AUASS: -10.7 Qmax: +4 mL/s PVR: -12 mL	SHIM: +0.4	12 months
Roehrborn et al. 2015[14]	140	IPSS: -8.83 Qmax: +3.47 mL/s PVR: -7.56 mL	SHIM: +0.54	3 years
Roehrborn et al. 2016[15]	140	IPSS: -8.8 Qmax: +4.2 mL/s	SHIM: +0.3	4 years
Roehrborn et al. 2017[13]	140	IPSS: -7.56 Qmax: +3.48 mL/s	IIEF-5: -0.37	5 years

AUASS = American Urological Association symptom score; IIEF = international index of erectile function; IPSS = international prostate symptom score; PVR = post-void residual volume; Qmax = peak urinary flow; SHIM = sexual heath inventory for men

sized prostates, Table 2. PUL is also known to preserve all aspects of sexual function, which can be seen by minimal changes in IIEF-5 and SHIM scores across all studies. No study to date has reported any incidence of erectile dysfunction or retrograde ejaculation after PUL. The procedure takes an average of 1 hour and typically utilizes 4 implants without any serious adverse effects.[12] All adverse events experienced by patients were typically mild to moderate in severity, resolving within 2 to 4 weeks. The most common complications included: dysuria, hematuria, pelvic pain/discomfort, urgency, bladder spasm, and urge incontinence. The overall complication rate after PUL has been noted to be < 10% with no major adverse event reported.[13]

The L.I.F.T. study (Luminal Improvement Following Prostatic Tissue Approximation for Treatment of LUTS secondary to BPH) conducted by Roehrnborn et al was a prospective, multicenter investigation of 140 patients treated with PUL for BPH and LUTS over a 5-year period.[12-15] IPSS decreased 17.5%, 47.4%, 41.4%, 41.1%, 40.6%, and 35.9% from pre-treatment baseline at 2 weeks, 1 year, 2 years, 3 years, 4 years, and 5 years, respectively. Qmax improved 58.5%, 58.6%, 53.1%, 63.4%, and 44.3% from pre-treatment baseline at 1 year, 2 years, 3 years, 4 years, and 5 years, respectively. McVary et al focused on the effect of PUL on sexual function in this cohort, and they concluded that PUL preserved erectile and ejaculatory function in most men.[16] SHIM scores were no different from pre-treatment baseline at 3 months, and they were significantly improved from baseline at 1 year for men who entered the study with severe erectile dysfunction (SHIM ≤ 7). At 5-year follow up, the IIEF-5 score had a non-significant decrease of 0.37 points in this patient group. Retreatment rate was low at 2%-3% per year (13.6% over 5 years). The L.I.F.T. study demonstrated that symptomatic relief of LUTS secondary to BPH with virtually no sexual dysfunction side effects could be achieved within 2 weeks and sustained up to 5 years after PUL.

A retrospective, multicenter analysis by McNicholas et al included 102 men with prostate volumes < 80 g treated with PUL for LUTS.[17] From baseline, mean IPSS improved 36% at 2 weeks and 52% at 12 months, and mean Qmax improved 38% at 2 weeks and 51% at 12 months. Mean PVR, however, decreased by 10% at 2 weeks, but increased by 3% at 12 months. Although sexual function scores were not included in this study, there were no reports of ejaculation dysfunction or erectile dysfunction in this patient cohort. Overall, this study showed significant, rapid, and durable improvements after PUL in patients with LUTS due to BPH with small and medium sized glands.

Other studies with smaller cohort samples have also demonstrated similar outcomes after PUL for BPH and LUTS. One of the first studies on PUL by Woo et al revealed that it was a safe and durable treatment option for men with BPH that could sustain relief of LUTS up to at least 1 year with minimal morbidity.[18] Additionally, Chin et al demonstrated improvement in LUTS after PUL in men that were sustained through 2 years without decreased sexual function.[19] Cantwell et al conducted a 1-year crossover study with an initial sham rigid cystoscopy procedure followed by the PUL procedure at 3 months.[20] The sham procedure had symptomatic improvement in LUTS at 1 month with significant decline by 3 months, while PUL was able to sustain LUTS relief for 1 year. Rukstalis et al reassessed this cohort at 2 years and determined that PUL was still able to maintain LUTS relief with hardly any sexual compromise.[21] The BPH6 study, conducted by Sønksen and Gratzke et al, compared the PUL procedure to the gold standard TURP. Sønksen and Gratzke et al noted that improvements in IPSS and Qmax were greater with TURP, but PUL was superior in the preservation and quality of recovery of ejaculatory function at 1[22] and 2 years.[23] As can be seen above, the literature unanimously supports the claim that PUL has a modest and rapid effect in treating LUTS for men with BPH while preserving total sexual function in patients with small and medium volume prostates. Although prostatic lift is contraindicated in prostates > 80 g, it could be considered as an early treatment option for prostates that are approaching larger volumes.

Aquablation

Aquablation is a novel minimally invasive, surgical treatment for moderate to severe LUTS as a result of BPH. The AquaBeam system (PROCEPT BioRobotics Inc., Redwood Shores, CA, USA) utilizes a robotic-assisted, high-velocity waterjet under the guidance of transrectal ultrasound to remove prostatic tissue and relieve the obstruction to urine flow. The use of a high-pressure saline stream allows for the controlled resection of tissue without inducing thermal injury to surrounding tissue, which results in less tissue damage and less irritative voiding symptoms experienced by patients when compared to standard TURP.[24]

Aquablation is indicated for patients who do not respond to or tolerate medical therapy for BPH. Because the AquaBeam system is still developing, there is currently a relative contraindication to prostates greater than 100 g and prostates with large median lobes.[25] The entire procedure takes less than 1 hour and is done under general anesthesia.

TABLE 3. **Clinical outcomes of aquablation in the treatment of lower urinary tract symptoms for men with BPH**

Author	N	Results			Follow up
		Urinary	Erectile function	PV change (g)	
Gilling et al. 2016[25]	15	IPSS: -13.7 Qmax: +10 mL/s PVR: -87 mL		-18	6 months
Gilling et al. 2017[26]	21	IPSS: -16 Qmax: +9.6 mL/s PVR: -82 mL	IIEF: +2.5	-22	1 year

IIEF = international index of erectile function; IPSS = international prostate symptom score; PV = prostate volume; PVR = post-void residual volume; Qmax = peak urinary flow

The literature on aquablation has demonstrated the procedure to be safe and effective in treating LUTS caused by small and medium sized prostates, with improvements made to IPSS, Qmax, and IIEF, Table 3. Mean prostate size had approximately a 30% reduction in volume after aquablation. No major complications have been reported, and the adverse events reported post-procedure were minor typical of a transurethral procedure. Dysuria, hematuria, urinary retention, UTI, bladder spasm, and meatal stenosis were the most common post-procedure adverse events, but there were no reports of sexual dysfunction after aquablation.

A prospective, single-center study by Gilling et al observed 15 patients who were treated with aquablation for LUTS secondary to BPH after 6 months.[25] At last follow up, mean IPSS improved from 23.1 to 8.6 and mean Qmax increased from 8.6 to 18.6 mL/s. There were no reports of erectile dysfunction in this small cohort. Another prospective, multicenter study by Gilling et al included 21 men who underwent aquablation with prostate volumes ranging from 30 g-102 g.[26] Mean IPSS improved from 23.0 to 6.8 and mean Qmax increased from 8.7 to 18.3 mL/s at 1 year follow up. IIEF also improved by 2.5 points, demonstrating that this procedure has the potential to preserve sexual function, and no major complications were noted post-procedure. Unfortunately, since the largest prostate treated across both studies was 102 g, the authors claimed that there was a relative contraindication of aquablation for the treatment of prostates greater than 100 g. Aquablation, however, could conceivably be used in a hybrid fashion with another transurethral procedure to treat larger gland sizes. Ultimately, both phase II studies demonstrated that aquablation could be a safe, durable procedure used to treat men with LUTS secondary to BPH that is effective, without compromising sexual function.

The WATER (Waterjet Ablation Therapy for Endoscopic Resection of prostate tissue) study conducted by Roehrborn et al is a multicenter, phase III randomized clinical trial comparing the safety and efficacy of aquablation to standard TURP.[27] Men were randomized to either the TURP or aquablation group, which had similar demographic characteristics, mean baseline IPSS, and mean prostate volumes. After the recruitment of 184 men to the study, preliminary results demonstrated equal efficacy between aquablation and TURP at 3 months in the improvement of Qmax. Mean resection time, however, was significantly shorter in the aquablation arm (4 minutes versus 28 minutes with TURP).

Currently, there is insufficient data supporting the use of aquablation for LUTS in men with prostates > 80 g although it is not entirely contraindicated. To date, patients with 80 g-102 g prostates who underwent aquablation for BPH still have received positive outcomes with minimal complications. Another phase III clinical trial (WATER II study) is underway and expected to be completed by 2020. This emerging study will investigate the safety and effectiveness of aquablation in larger prostates (80 g-150 g) although initial results from prior reports seem promising.

Rezum

Rezum (NxThera Inc., Maple Grove, MN, USA) is a novel treatment option for men with LUTS that targets enlarged prostate glands with steam. It is a transurethral needle ablation technique that injects convective thermal energy in the form of sterile water vapor into the BPH adenoma. The energy delivered by the water vapor disrupts prostate cell membranes, leading to immediate cell death and necrosis. It subsequently takes the body approximately 3 months

to remove the dead cells, shrinking the prostate in the process and relieving typical symptoms of BPH.[28] Because the thermal energy is confined within the zonal boundaries of the prostate, there is a reduced risk of injury to surrounding structures, such as the urinary sphincter, bladder, and rectum, minimizing complication rates.[29]

Rezum is an option for men with LUTS who do not respond to or tolerate traditional BPH medications, but are unwilling to undergo an invasive surgical procedure. This procedure is performed under local anesthesia in an outpatient setting. Differing from other therapies targeting BPH, Rezum is acceptable in patients with hyperplasia of the central zone and/or median lobe of the prostate. This procedure, however, is contraindicated in patients with an artificial urinary sphincter implant or penile prosthesis.[30]

Prior literature has demonstrated that Rezum is a safe and effective treatment option for patients suffering from LUTS secondary to BPH. This procedure has shown to improve IPSS, increase Qmax, and preserve sexual function across many studies, Table 4. Adverse effects that typically occurred were mild to moderate and usually resolved within 3 weeks. These minor complications included: dysuria, hematuria, hematospermia, urinary frequency or urgency, urinary retention, UTI, epididymitis, anejaculation, and pelvic pain/discomfort. One significant disadvantage reported was that after completion of therapy, most patients self-catheterized for up to 1 week in the postoperative period.

A multicenter, randomized, controlled study conducted by McVary et al and Roehrborn et al included 197 men with BPH and LUTS, of which 136 men underwent treatment with Rezum while 61 men underwent sham rigid cystoscopy. McVary et al compared patient outcomes up to 1 year of follow up.[31] At 3 months, mean IPSS dropped by 11.2 versus 4.3 points from baseline for the treatment group versus the control group, respectively. In the Rezum arm, IPSS improved by 11.7 points and Qmax increased by 5.1 mL/s from baseline at 1 year. Roehrborn et al continued to investigate this same cohort, but included a crossover trial.[32] After 3 months, the control arm underwent treatment with Rezum with a significant 10.8 point reduction in IPSS and 5.9 mL/s increase in Qmax from baseline. At 2 years of follow up, the entire patient cohort was able to maintain a mean IPSS score 11.2 points lower than baseline with a Qmax that increased 4.2 mL/s from baseline. No sexual dysfunction was reported at any time period of follow up. Unfortunately, prostate glands > 80 g were not included in the study, but it did demonstrate both the effectiveness and durability of Rezum therapy for LUTS secondary to BPH in small and medium sized glands.

A multicenter, retrospective analysis by Darson et al reviewed the outcomes of 131 men with BPH and LUTS treated with Rezum at 1 year post-therapy.[29] Mean IPSS decreased from a baseline of 19.4 to 10.1, and mean Qmax had a slight 1.5 mL/s increase from baseline. Although larger prostates were not specifically analyzed, this

TABLE 4. **Clinical outcomes of Rezum in the treatment of lower urinary tract symptoms for men with BPH**

Author	N	Results		Follow up
		Urinary	Erectile function	
McVary et al. 2016[31]	136	IPSS: -11.7 Qmax: +5.1 mL/s PVR: -3.4 mL	IIEF: -1.3	1 year
Roehrborn et al. 2017[32]	136	IPSS: -11.2 Qmax: +4.2 mL/s PVR: -0.3 mL	IIEF: -1.1	2 years
Darson et al. 2017[29]	131	IPSS: -9.4 Qmax: +1.5 mL/s PVR: -159.3 mL		1 year
Dixon et al. 2016[33]	65	IPSS: -12.1 Qmax: +3.7 mL/s PVR: -15.7 mL	IIEF: +3.7	2 years

IIEF = international index of erectile function; IPSS = international prostate symptom score; PVR = post-void residual volume; Qmax = peak urinary flow

was the first study to include prostates > 80 g (range: 80 g-183 g). There were successful outcomes across all prostate sizes, including those in larger gland volumes. In a smaller cohort study by Dixon et al, the authors further established the effectiveness and durability of Rezum therapy on prostates of all sizes (20 g-120 g).[33] At 2 years post-treatment, mean IPSS improved from 21.7 to 9.6 and mean Qmax increased from 8.3 to 12 mL/s in this patient group. Sexual function over the 2-year period remained relatively unchanged. Once again, these studies concluded that Rezum therapy provided effective and durable relief of LUTS in men with smaller, medium, and larger prostates.

Intraprostatic injectables and temporary implantable nitinol device

Other minimally invasive therapies for treating LUTS due to BPH from larger glands that are worth mentioning include the intraprostatic injectable PRX302 (Sophiris Bio Inc., La Jolla, CA, USA) and the temporary implantable nitinol device (TiND) (InnoMedicus AG, Switzerland). These options could be considered for patients in whom drug therapy was ineffective, who cannot undergo surgery, or who desire an alternative to medications or other procedures. While the literature is sparse for both techniques, the positive results, Table 5 from several, small cohort studies should warrant further investigation into their clinical utility for the treatment of BPH.

Although the concept of intraprostatic injections is not new, the novel injectable PRX302 has shown to be safe and effective in the treatment of LUTS due to BPH. PRX302 is a precursor protein, derived from an inactive protein produced by the aquatic pathogen Aeromonas hydrophila, that forms pores in the plasma membrane once cleaved.[34] The original cleavage site of the protein is replaced by a PSA-specific sequence, which restricts the toxicity of PRX302 to prostatic tissue. Via the trans-perineal route using guidance from transrectal ultrasound, PRX302 is injected in the transition zone of the prostate, and the procedure is accomplished in an office-based setting.

Denmeade et al conducted a small phase I and II clinical trial on the efficacy and safety of PRX302 injection therapy for BPH and LUTS.[35] This study did not include larger prostates, but mean IPSS decreased by 6.4 and 9.6 points from baseline at 1-year follow up for the phase I and phase II study, respectively. Only the phase II data showed an improvement in Qmax, which increased 3 mL/s from baseline. Prostate volume was also reduced by over 20% in 36% of men in the phase I trial and 63% of men in the phase II trial. Another prospective, multicenter phase IIb trial by Elhilali et al evaluated 92 patients with BPH and LUTS after PRX302 injection treatment at 1 year.[34] This study included prostate glands > 80 g (range: 30 g-100 g). Mean IPSS decreased by 9 points and Qmax increased by 3 mL/s from baseline at 1 year follow up. No significant change in prostate size, however, was observed. Adverse events in these studies were mild to moderate and resolved within 72 hours. The most common complications included hematuria, dysuria, urinary frequency, and urinary urgency, but no sexual dysfunction was reported. These studies confirmed that PRX302 injection therapy could be a safe and effective treatment strategy for LUTS due to BPH as an alternative for medical or surgical therapy, but further investigation is needed to determine its long term efficacy as well as its clinical effectiveness on larger glands.

TABLE 5. **Clinical outcomes of PRX302 injection and TiND in the treatment of lower urinary tract symptoms for men with BPH**

Author	N	Treatment	Results		Follow up
			Urinary	PV change (g)	
Denmeade et al. 2010[35]	Phase I = 15	PRX302	IPSS: -6.4 Qmax: -1 mL/s	-7.1	1 year
	Phase II = 18		IPSS: -9.6 Qmax:+2.9 mL/s	-13	
Elhilali et al. 2013[34]	92	PRX302	IPSS: -9 Qmax = +3 mL/s PVR: +12.2 mL	-2	1 year
Porpiglia et al. 2015[36]	32	TiND	IPSS: -10 Qmax: +4.4 mL/s		1 year

IPSS = international prostate symptom score; PV = prostate volume; PVR = post-void residual volume; Qmax = peak urinary flow

TiND is a unique treatment option that relieves LUTS due to BPH by creating new longitudinal channels in the prostatic urethra and expanding the path for urine flow. Once implanted, the device (made of nitinol- an alloy that retains shape memory) remains in the prostatic urethra for 5 days where it remodels the bladder neck and prostatic urethra by exerting pressure on the urethral walls, inducing ischemia. After 5 days, the device is removed and the patient is left with an increased cross-sectional area of the prostatic urethra.[36] The procedure requires light sedation and lasts approximately 6 minutes.

In a prospective, single center study by Porpiglia et al, the authors assessed the safety and feasibility of TiND on 32 men with BPH and LUTS at 1 year of follow up.[36] Mean IPSS improved 45% from baseline and mean Qmax increased 67% from baseline. Only four postoperative adverse events occurred, which included urinary retention, transient incontinence, prostatic abscess, and UTI. There were no reports of sexual dysfunction, but unfortunately, this study only evaluated prostates < 60 g. This initial observational clinical study demonstrated that TiND is feasible and safe for BPH treatment on smaller glands, but further studies are needed to evaluate the long term efficacy of TiND implantation and its efficacy across a wider range of prostate sizes.

Conclusion

Based on the literature, most of these emerging, newly-approved techniques have demonstrated to be comparable to medical or surgical therapy in treating larger prostates, while causing no significant sexual dysfunction. Majority of the studies reviewed were prospective, randomized trials, which are the gold standard for assessing new treatments. Of all the emerging therapies, prostate artery embolization appears to have the greatest overall impact on urinary outcomes. Embolization is a great alternative to TURP, especially for patients with > 80 g prostates who cannot undergo surgery. While most of the new treatments minimize sexual side effects, aquablation has shown to improve sexual function. This option could be considered in patients where preservation of sexual function is a priority. Depending on availability and patient preference, some of these novel therapies may be suitable options for patients suffering from LUTS secondary to > 80 g prostates. As more minimally invasive options emerge, physician and patients will have the opportunity to choose a treatment that is truly the best fit for the patient. □

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