

The use of 5 alpha-reductase in the era of minimally invasive surgical therapies (MISTs): Is it still valuable?

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Benign prostatic hyperplasia (BPH) represents one of the most common urologic diseases among elderly men, with a major impact on quality of life (QoL) and a substantial economic burden [1]. Epidemiological studies suggest that age, genetic factors, and sex hormones play major roles as risk factors for BPH, and the only known factors associated with BPH progression are age and prostate volume. The incidence of BPH among men is approximately 50% at 50 years of age and is as high as 90% at 80 years of age. Of these individuals, approximately 50% will develop age-related sexual dysfunction considering that lower urinary tract symptoms (LUTS) are one of the strongest predictors of male sexual dysfunction [1].

Current guidelines recommend the use of alpha-blockers (ABs) and 5-alpha reductase (5-ARIs) as monotherapy or in combination for the treatment of BPH-associated LUTS [2]. Nevertheless, although combination therapy with ABs and 5-alpha reductase (5-ARIs) has been shown to be beneficial in terms of symptom control and disease progression, patient adherence to pharmacotherapy for BPH-associated LUTS remains low, which is often associated with the collateral effects that these therapies may have on quality of life [3]. Both finasteride and dutasteride are usually well-tolerated medications with mild and transient adverse effects. Nevertheless, when the patient experiences side effects associated with this therapy occur, they can strongly impact a male patient's sexual life by causing sexual dysfunction, mainly decreased sexual libido, impotence, and ejaculatory disorders [3]. Liu *et al.* published a meta-analysis, suggesting that patients taking 5-ARIs for BPH had a 156% increased risk of experiencing sexual side effects. Furthermore, the incidence of adverse sexual side effects was increased for dutasteride compared with finasteride [4]. Several other adverse effects associated

with 5-ARIs have been described, including depression, infertility, breast swelling/tenderness, breast cancer, rash, testicular pain, allergic reaction, and anaphylaxis. In July 2022, France's National Agency for the Safety of Medicines and Health Products released new information related to side effects caused by 5-ARIs, including "suicidal thoughts that could lead to suicide" [5].

Based on the recent actual findings, urologists prescribing 5-ARIs should be aware not only of sexual disorders but also of suicide and suicidal ideation, which could be associated with the therapy. Moreover, when considering patients with chronic heart failure, brain natriuretic peptide >100 pg/mL and with severely abnormal (< 30%) and moderately abnormal ($\geq 30 \leq 40\%$) left ventricular ejection fraction, dutasteride and finasteride had no effect on prostate volume in patients by exposing these fragile patients to adverse effects [6].

On the other hand, up to a few years ago, the only therapeutic alternative to medical treatment for BPH was represented by surgery, such as transurethral resection of the prostate (TURP), which still represents the first choice in most patients, and it is responsible for sexual dysfunction in a considerable number of patients (4–35%) [6]. Several efforts have been made to find new surgical solutions that could improve lower urinary symptoms associated with BPH without sacrificing sexual function.

The introduction of new ultraminimally invasive surgical therapies (MISTs) for BPH, including Rezum, Urolift, and prostatic artery embolization, has turned this aim into reality, reducing hospitalization rates, complication rates, and the convalescence period and improving patients' quality of life [7]. In 2019, McVary *et al.* conducted a double-blind RCT, reporting significant and long-term improvement in the mean IPSS score after Rezum therapy [8]. Furthermore, there was an improvement in QoL (42.9%, $P < 0.0001$) and Q_{max} (49.5%, $P < 0.0001$) at the 4-year follow-up, with a surgical failure rate of 4.4%. No patient reported any disturbances in sexual function. Similar results were also confirmed in an Italian multicentre series including 135 consecutive patients treated by Rezum at 5 institutions. In this experience, in addition to an improvement in urinary symptoms, the authors also reported a slight but statistically significant increase in the IIEF-5

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score from baseline to 6 months ($P = 0.04$) [9]. Finally, Rezūm could also be performed under local anaesthesia in an outpatient setting, thus drastically reducing the risk of complications and convalescence.

Urolift represents another MIST that can be performed under local anaesthesia. The Urolift device is placed through the obstructed urethra to access the enlarged prostate; the device compresses the tissue and places tiny implants to lift and hold the prostate tissue, thus helping to restore a free urethral canal for urination while maintaining antegrade ejaculations. A prospective randomized study reported efficient functional outcomes associated with lasting improvements in ejaculatory function confirmed at 5 years of follow-up [10].

Even PAE procedure is a MIST performed under local anaesthesia and offered in cases of LUTS resistant to medical treatment, in the presence of adverse side effects, or in patients who desire to maintain antegrade ejaculations. A prospective study of 32 patients reported antegrade ejaculation in all patients, with a 7-month follow-up [11], whereas a randomized study comparing PAE and TURP evidenced retrograde ejaculation in 10% of patients in the PAE group versus 100% in the TURP group. All these MISTs show promising results in significantly improving LUTS and the quality of life of treated patients without sacrificing sexual life.

Even if the conclusions of these pilot studies need to be confirmed in larger randomized trials with long-term results, we should reflect on whether medical therapy, especially with 5-ARIs, still represents a valid option in the treatment of BPH, considering how it can negatively impact the quality of life of patients and the recent supposed effects on mental health. Life expectancy has increased, and similarly, the period of sexual activity has been lengthened in elderly patients. The time has come to tailor medical therapies and personalize scientific guidelines to the individual characteristics of each patient.

Take home message

Patient adherence to pharmacotherapy for BPH-associated LUTS remains low, because of the collateral effects that these therapies may have on quality of life, whereas the new MISTs show promising results in significantly improving LUTS and the quality of life of treated patients without sacrificing sexual life. The time has come to tailor medical therapies and personalize scientific guidelines to the individual characteristics of each patient.

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