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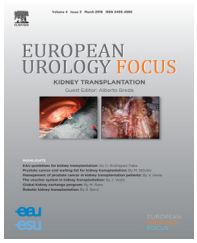

Guidelines

What Is the Required Certainty of Evidence for the Implementation of Novel Techniques for the Treatment of Benign Prostatic Obstruction?

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Abstract

Context: A large number of minimally invasive techniques have been developed for the surgical management of male lower urinary tract symptoms (LUTS) presumed to be secondary to benign prostatic obstruction (BPO) over the last 3 decades. Many have not stood the test of time often because they were overpromoted before there were sufficient data.
Objective: The scope of this paper is to consider whether new devices, for the treatment of male LUTS/BPO, have been implemented prematurely in the past. We also examine the relative certainty of evidence (CoE) that is currently available for newer developing technologies and make recommendations about the CoE that should be demanded in the future before widespread implementation.
Key messages: This evidence must provide adequate length of follow-up to allow proper information to be provided for patients before treatment choices are made and to be able to create recommendations in high-quality guidelines such as those of the European Association of Urology. It is not just within the domain of LUTS treatments that this is important, other urological devices, such as mesh devices, have been equally "guilty" and likewise devices in most other (surgical) specialities. We believe that there is a need for a set of requirements built around primary randomised controlled trials (RCTs) looking at both efficacy and safety, and secondary studies to confirm the reproducibility and generalisability of the first pivotal studies. Otherwise, there is a danger that a single pivotal study can be overexploited by device manufacturers. Studies that are needed include (1) proof of concept, (2) RCTs on efficacy and safety, as well as (3) cohort studies with a broad range of inclusion and exclusion criteria to confirm both reproducibility and generalisability of the benefits and harms. It is not the purpose of this paper to make judgements about individual treatments but simply to look at different treatments to provide verification for this debate.

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Patient summary: Many new treatment devices have been developed over the last 20–30 yr, often with inadequate medium- to long-term results. Many have not stood the test of time, but were heavily promoted by manufacturers, the press, and some doctors when they were first released, meaning that many patients had unsatisfactory results. This paper proposes minimum standards for the investigation of new treatments before their widespread promotion to patients.

1. Introduction

It is a common perception that surgical rather than medical intervention becomes appropriate in patients with bothersome lower urinary tract symptoms (LUTS) due to benign prostatic obstruction (BPO), who are unwilling to try medical therapies, or in cases where medical therapies are ineffective or not well tolerated, and in cases of complicated LUTS. However, with the advent of more minimally invasive treatments, the threshold for surgical intervention has become much lower [1].

This paper is the opinion of the current European Association of Urology (EAU) male LUTS guideline development group and has been developed after a considerable review of the current literature on novel treatment devices.

A large number of minimally invasive techniques (MITs) have been developed for the management of male LUTS/BPO, in the last 3 decades or so. From the middle of the 1980s onwards, attempts to use balloon dilation of the prostate, prostatic stents, prostate hyperthermia and cryotherapy, neodymium:YAG-based therapies of the prostate-like interstitial laser coagulation or visual laser ablation of the prostate, transurethral needle ablation (TUNA), transurethral microwave therapy, and high-intensity focused ultrasound have all had strong advocates, but over time many devices have not stood the test of time and have fallen out of favour. These may have disappeared for a variety of reasons, such as lack of long-term efficacy, adverse events, poor cost effectiveness, or development of newer versions (the "industrial/commercial circle"), which again dilute the data available on the latest or current version of the device.

It is important to bear in mind, from the start, that patients' and clinicians' expectations of outcomes may differ. For instance, patients (compared with clinicians) may prefer treatment options that are less effective if they result in a lower risk of complications or a faster return to normal activities. There is little doubt that there is a desire from patients for MITs. Unfortunately, sometimes the eagerness for these new MITs, in the popular press—the commonest source of direct patient information—but sometimes also from the early adopters of the treatment, has meant that this enthusiasm has often outstripped the clinical evidence. Early and aggressive company marketing can also overpower clinical evidence. Unlike pharmaceutical interventions, implementation of novel devices and techniques into clinical practice is not governed by the same strict regulatory mechanisms [2].

Therefore, the quality of the studies must remain high: (1) there must be adequate control arms (eg, compared with sham treatment or other established comparable therapies); (2) outcomes, including patient-reported outcome measurements, should be important to patients; and (3) studies should include a relevant study population that is generalisable.

We also need to remember that behind the tool, there is also a concept: ablation, resection, enucleation, etc.; therefore, a new device for resection is not a new device for vaporisation. Some of the principles behind these "failed" treatments have been generated again using newer or more powerful devices. It is therefore important that unlike their predecessors, sufficient controlled trials are carried out before their widespread application. Certain concepts, however, such as (laser) enucleation, have resulted in a paradigm change in the surgical management of LUTS/BPO.

2. Long-term unsuccessful treatments

In 1988, transurethral balloon dilatation of the prostate was reported as a safe and simple procedure that could be performed on an outpatient basis using topical anaesthesia and sedation with minimal morbidity [3]. Two years later, however, another series claimed that significant improvement in objective measurement of outflow obstruction was noted in only two out of 14 patients [4].

Another example was TUNA, where again early results promised significant improvements in both subjective and objective outcomes: "TUNA is a promising, anaesthesia-free alternative treatment for men with symptomatic BPH" [5]. Yet a few years later, a study reported that "TUNA produced an unsatisfactory clinical result" [6]. The overall retreatment rate after TUNA was 19%, based on an analysis of 17 noncomparative studies (median follow-up unreported; only three out of 17 studies had follow-up exceeding 2 yr)—a rate considerably higher than that seen with transurethral resection of the prostate (TURP) [7]. A very high reintervention rate for BPO was also reported in another French study of TUNA [8].

Many of these and similar studies, in their conclusions, promised prospective randomised studies to determine the role of treatment "*x*" in the management of LUTS, but these rarely materialised.

3. How to assess certainty of evidence

The certainty of evidence (CoE) in urological clinical research literature is generally very low, and the reporting is inadequate [9]. The Idea, Development, Exploration, Assessment, Long-term (IDEAL) study recommendations

have been established as a potential solution by serving as guidelines tailored to surgical research and as a platform for systematic data generation from well-designed, conducted, and reported trials; it provides a regulatory protective framework against potential harms of novel procedures before incorporation into practice [10].

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) is a transparent approach for assessing the CoE (also known as quality of evidence). The GRADE approach is adopted and/or endorsed by >100 organisations, including Cochrane and World Health Organization. The EAU Guidelines Office use modified GRADE for rating guidelines recommendations.

According to GRADE, the outcomes included in a systematic review (SR) are scored on a scale of 1–9 (slightly important to critically important for decision making). Evidence from randomised controlled trials (RCTs) starts as "high" certainty, whereas evidence from nonrandomised studies start as "low" certainty. There can be five reasons to possibly rate down the CoE: (1) methodological limitation of study design (risk of bias), (2) inconsistency, (3) indirectness, (4) imprecision, and (5) publication bias. There are three possible reasons to rate up the CoE (from nonrandomised studies): (1) large magnitude of effect, (2) opposing plausible residual bias or confounders, and (3) dose-response gradient. The guideline recommendations are based upon CoE of the critical outcomes; balance of benefits and harms; patients' values, preferences, and acceptability; and resource implication. By considering the above factors, a "strong" or "weak" recommendation "for" or "against" an intervention can be made [11].

4. Safe and appropriate implementation of new treatments

To safely and effectively introduce novel techniques in the future, there needs to be a systematic way of studying these new devices.

The studies should start with the publication of a proof of concept or "first in man" trial followed by an RCT against a sham (placebo) treatment (Table 1). It is likely, although not essential, that these will come from experienced centres of excellence and need to follow established criteria including the usage of risk of bias assessment tools [11–13].

These studies should be followed by RCTs against TURP or a well-recognised and accepted MIT. The issue is what should be the comparator. For instance, an MIT such as Rezum is perhaps a competitor between medical treatment and an ablative technique for BPO relief. Thus, does it require to be as safe as a drug, or just safer than a more invasive ablative therapy, with a trade-off about reduced efficacy?

Ideally, two RCTs would be presented (a noninferiority trial on efficacy and another on safety), although these could come from a single study if it is of a sufficiently high-quality design. It would be preferable to conduct multicentre studies with several surgeons, rather than single-centre or single-surgeon studies, to confirm the reproducibility of the principle.

Table 1 – Requirements for widespread implementation.

- Proof of concept study
- Placebo/sham comparison study
- Randomised controlled trial against accepted alternative treatment
- Cohort studies: to understand the generalisability and potential harms
- Systematic reviews and meta-analysis of high-quality primary studies
- How many patients should be included?—A sample size determination is needed
- What should be the length of follow-up?
- ○ Short term: <12 months, medium- 12–36 months and long-term > 36 months
- Inclusion and exclusion criteria need to allow good generalisability
- Relevant outcomes—varied and need to be clearly outlined from the start

These should be followed by cohort studies, which will help in understanding the generalisability of the concept, allow secondary centres to gain experience, and investigate for harms not necessarily shown in trials with selected study populations or short-duration follow-up. These should be mandatory for gaining the right to penetrate the market.

Finally, RCT-based SRs and/or meta-analyses are acceptable, but this is on the proviso that there are sufficient high-quality RCTs in the first place. One reasonable question is: are SRs currently performed too soon before there are sufficient high-quality RCTs?

The next question is: how many patients should be included? Clearly, sample size determination must be performed; this does not guarantee, however, that the study will be powered for all the primary outcomes of interest. This calculation would be influenced by the expected difference between treatments and also by what we could call the "margin of inferiority" that might be accepted for a less invasive treatment. Systematic reviewers are encouraged to calculate the "optimal information size" (OIS). OIS is the minimum threshold of pooled estimate obtained from a meta-analysis that is required for drawing reliable conclusions.

What should be the length of follow-up? This has been one of the greatest weaknesses in past trials. This is amplified in an SR of transurethral ablative procedures (techniques that have often been evaluated better than other MITs) [14]. It identified 69 studies on LUTS/BPO ablative surgical treatments over a 20-yr period. The follow-up of these studies ranged from 1 to 100 mo with a median follow-up of just 12 mo. Unsurprisingly, the longer the duration of follow-up, the fewer the number of trials available (Fig. 1).

As noted by the authors " . . . further studies are needed to provide long-term comparative data and head-to head comparisons of emerging techniques". Reasonable suggestions therefore from the EAU Non-neurogenic Male LUTS

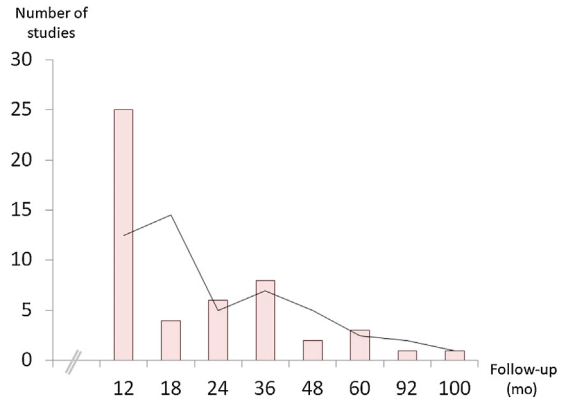

Fig. 1 – Follow-up of LUTS/BPO ablative studies. BPO = benign prostatic obstruction; LUTS = lower urinary tract symptoms. Adapted from Cornu et al [14].

Guideline Panel would be the following: (1) short term, <12 mo of follow-up; (2) medium term, 12–36 mo of follow-up; and (3) long term, >36 mo of follow-up [15]. Outcome expectations of these studies may vary. If a therapy is very safe, although with limited efficacy over time, and can be performed again, it is more a trade-off with the patient. However, these facts must be clear. This could be reflected in a guideline recommendation.

Inclusion and exclusion criteria need to be broad enough to allow good generalisability of the technique. Sometimes, the inclusion and exclusion criteria have been too stringent, making the studies not applicable to all the populations. These must, therefore, include factors such as variable prostate size and configuration, and patients with or without retention after failed trial without a catheter. Larger postvoid residual volumes could be considered, but may reflect more on poor detrusor function than on BPO. Patients with a range of comorbidities need to be included, certainly in the cohort studies, to note potential treatment options with less morbidity for such patients. This would include patients with a variety of anticoagulant needs.

Before starting a clinical trial or a study, it is strongly recommended to check whether there is an agreed minimum set of outcomes or outcome measures known as a "core outcome set" (COS). The COS should be measured and reported by all new clinical trials and studies. "Core Outcome Measures in Effectiveness Trials" (COMET) [16] and the "International Consortium for Health Outcomes Measurement" (ICHOM) have developed COS for various medical conditions. In a recent SR on the management of urinary retention in patients with LUTS/BPO, a broad search of the COMET database for a COS using the term "urology" in the disease category yielded no directly applicable COS for the disease or treatments dealt with in that SR [17]. Outcomes important to all stakeholders, patients, the public, doctors, and healthcare decision makers need to be developed [18]. COS should be checked first, and if it does not exist, then the following outcomes should be considered for measurement and reporting (Table 2). Inconsistency in the measurement of outcomes and outcome-reporting bias add further to the problems faced by users of research who wish to make well-informed decisions about health care.

The appropriateness of some of these is obvious and will depend on the device being tested.

The ability to preserve both erectile and ejaculatory function has been one of the potential positive benefits of many of the new MITs. Others such as the need for supplemental medical treatment will reflect on the success of treatment, but may, in the case of overactive bladder symptoms, not be a sign of device failure. Overall however, we have to recognise that concentrating on patient-important factors such as return to all normal activities can be more important to patients than a dramatic improvement in flow rate. The minimally important difference (MID) is the smallest change in a clinical outcome that patients perceive as important, either beneficial or harmful, which could result

Table 2 – Potential recordable outcomes.

• Symptom assessment (eg, IPSS, bladder diary)
• Objective measurements (eg, flow rate, PVR, and pressure flow studies)
• Quality of life questionnaire (eg, SF-36)
• Patient satisfaction
• Erectile and ejaculatory function (eg, IIEF and MSHQ-EjD)
• Complications associated with the intervention
• Length of stay and other hospital factors
• Speed of return to normal activities
• Need for additional medical treatment
• Reoperation rates
• Cost effectiveness (eg, QALYs)

IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; MSHQ-EjD = Male Sexual Health Questionnaire for assessing ejaculatory dysfunction; PVR = postvoid residual; QALY = quality-adjusted life year; SF-36 = 36-Item Short Form Survey.

Table 3 – Emerging technologies reviewed in the EAU LUTS guideline over three iterations of the guideline from 2009 to 2019.

Treatment	EAU2009	EAU2015	EAU2019
Bipolar TURP	ND	R	R
GreenLight	ND	R	R
PUL	ND	E	R*
Intraprostatic Botox	ND	E	NR
Minimally invasive simple prostatectomy	ND	E	UI
Aquablation	ND	ND	UI
Rezum	ND	ND	UI
iTIND	ND	ND	UI
Prostate artery embolisation	ND	ND	UI

E = emerging; EAU = European Association of Urology; LUTS = lower urinary tract symptoms; NR = not recommended; R = recommended; R* = under conditions; ND = not discussed; PUL = prostatic urethral lift; TURP = transurethral resection of the prostate; UI = under investigation.

in the patient or doctor considering a change in treatment [19]. It has always represented a challenging concept in the management of LUTS. It is generally accepted that patients will perceive a difference if their International Prostate Symptom Score improves or deteriorates by three or more points; however, this varied considerably in the original paper and depended greatly on the baseline symptom score [20]. In addition, the MID is not an immutable characteristic, but may vary by population and context [21]. The authors emphatically support the need for a clinical significance aspiration and not merely statistical significance.

Currently in the literature, bipolar TURP is the most investigated of the newer modalities with 56 RCTs and >6500 patients. However, CoE is still not perfect for many of the investigated outcomes [22,23], and it is much lower indeed for many of the other MIT procedures [15]. A simple PubMed search reveals 54 references for Urolift, 39 for Rezum, 248 for prostate artery embolisation (because of many radiological technique papers), 42 for aquablation, and six for iTIND devices. The very large majority of these papers, of course, are not RCTs.

As a result of the quality of the information, devices and techniques will have varying recommendations in international guidelines over the years, such as those of the EAU (Table 3).

5. Conclusions

New modalities, therefore, need to achieve improvements in patient-important outcomes that are similar to or better than those of established treatments, such as bipolar TURP, or have lower risks of complications and side effects, or similar costs and shorter hospital stays. Evidence should include studies with long-term (>3 yr) follow-up. Preferably, they should also improve urodynamic parameters such as maximum urinary flow rate and postvoid residual volumes [24]. There is clearly a difference, however, between the ideal treatment (which might be cost effective, a day case, and with few complications, good relief of BPO, and good durability) and the ideal standard of evaluation (which is all about safety and clinical effectiveness). These trade-offs are clearly value and preference sensitive, and shared decision making between patients and clinicians is therefore necessary.

National organisations, for example, the British, French, and German Urological Associations, and the international ones such as the EAU should refuse to sanction new treatments (as they do when they devise patient information leaflets and procedure-specific consent forms) until an agreed minimum threshold of CoE for the implementation of novel techniques for surgical treatment of LUTS/BPO is available.

However, we do not want an extended delay until effective treatments are fully implemented, and therefore a national or better still a European initiative would allow new techniques to be used only in research settings, such as structured cohort studies or registries, to collect crucial data about these early patients, and avoid or reduce the misuse under commercial pressure, particularly in private healthcare centres.

This paper presents in a transparent way how the EAU Guideline Panel on non-neurogenic male LUTS evaluates new invasive treatments, and proposes the requirements and CoE that a new therapy should meet in order to be included in the guidelines. It is our strong belief that the paper should trigger further discussions about the optimal way to assess new technology across all surgical disciplines, but that these devices should not be broadly implemented until at least quality RCTs on both safety and efficacy with adequate follow-up are completed. Contributions from patients' organisations, device manufacturers, and other stakeholders would be extremely important to formulate the optimal guidance.

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Study concept and design: Speakman, Gravas.
Acquisition of data: Speakman, Cornu, Gacci, Gratzke, Mamoulakis, Herrmann, Omar, Rieken, Tikkinen, Gravas.
Analysis and interpretation of data: Speakman, Cornu, Gacci, Gratzke, Mamoulakis, Herrmann, Omar, Rieken, Tikkinen, Gravas.
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