From BPH to Male LUTS: A 20-year journey of the EAU guidelines

European Association of Urology Non-neurogenic Male LUTS Guidelines Panel

Word count (without Abstract): 3172
Word count (with Abstract): 3,438

Abstract

Context

The European Association of Urology (EAU) clinical practice guidelines aim to improve quality of care, decrease variation in clinical practice and improve patient safety. Central to achieving this aim is the robust, systematic literature review process and regular guideline updates to incorporate new evidence in a timely fashion. The EAU guideline on non-neurogenic male lower urinary tract symptoms (LUTS) was first developed 20 years ago and has undergone considerable developments in its concept and philosophy over this time.

Objective

This paper discusses the changes in methodology and content of the EAU guideline on non-neurogenic male LUTS over the past 20 years, highlighting the evolution of the guideline over this time.

Key messages

The most significant development over the past 20 years has been an evolution in the philosophy of the guideline, changing from one on benign prostatic hyperplasia to one on non-neurogenic male LUTS, thereby highlighting the multifactorial nature of LUTS in men. The methodology has become robust and transparent to ensure that recommendations are formulated based on the highest levels of evidence, with removal of treatments that were found to be unsuccessful following increasing evidence. The concept of the guideline, and the field of surgery for benign prostatic obstruction, has evolved with a move away from the traditional energy-based classification of surgical procedures to a more conceptual classification (e.g., endoscopic enucleation procedures), irrespective of the energy source used.

Patient summary

The EAU guideline on non-neurogenic male LUTS has evolved considerably over the past 20 years, with changes in philosophy, methodology and content. This paper discusses these changes and highlights how the guideline has evolved.

1. Introduction

The European Association of Urology (EAU) aims to promote the highest standards of urological care throughout Europe. Fundamental to achieving this aim has been the development of evidence-based clinical practice guidelines. These guidelines are intended to improve quality of care, decrease variation in clinical practice and improve patient safety, as well as empowering patients to make informed health choices. Hence the guidelines may be instrumental to influence healthcare policy (1). These guidelines are widely perceived to be amongst the most important publications that the EAU produce, and adherence to EAU guidelines has been shown to result in improved patient outcomes (2). The first EAU guideline on benign prostatic hyperplasia (BPH) was published in 2001. Over the past 20 years there have been considerable developments in its concept and philosophy, changing from a guideline on BPH to one on non-neurogenic male lower urinary tract symptoms (LUTS), thereby highlighting the importance of looking beyond the prostate when trying to assess the underlying functional basis for a patient's symptoms. Changes related to methodology and content have ensured that the breadth of conditions leading to male LUTS are included and that guideline recommendations are based upon the highest quality evidence, incorporating patient's perspectives, values and preferences. This paper discusses these changes and highlights the evolution of the guideline over the past 20 years.

2. Evolution in methodology

The principles of the EAU guidelines are that they should be based on the highest quality evidence, presenting a balanced view of risks and benefits that is free from bias, should be regularly updated and be widely disseminated and implemented. Over the last 20 years, the methodology involved in the guideline development process has been continuously refined, leading to greater transparency, and enabling trust in the resulting guideline recommendations. The first EAU guideline on BPH was published in 2001. Due to the relative paucity of well-conducted randomised controlled trials (RCTs) and meta-analyses at the time, guideline recommendations were based predominantly on expert opinion in combination with an unstructured literature search of relevant scientific evidence using the Medline database (3). Recommendations for investigation and follow-up of men with BPH were classified as mandatory, recommended, optional, and not recommended, and recommendations for treatment were provided but not graded or classified. Reliance on the guideline group members' knowledge of the literature to ensure that all relevant evidence had been captured meant that the process lacked transparency and risked article selection bias. Furthermore, the levels of evidence used to formulate the guideline recommendations were not included, and so it was not possible for the reader to judge the validity of the statements made. It should be noted that the number of RCTs

were limited in the first years of Guidelines development, and this gap in the literature was disclosed and subsequently led to the performance of more studies with high levels of evidence. In 2004, in an attempt to provide greater clarity, the updated guideline was based upon a systematic literature search of the Medline database encompassing the preceding 4 years (4). It changed the categorisation of recommendations into 3 (instead of 4) categories and introduced recommendations for the different treatment options (Figure 1). Definitions for the different categories were also specified, as follows: recommended (there is evidence to support routine use of this test), optional (not required during initial assessment but may aid in the decision-making process), and not recommended (there is no evidence to support the routine use of this test for the average patient). However, the recommendations were not graded, and the strength of the evidence used to inform these recommendations was not provided. Furthermore, the criteria for selecting the evidence and the methods used for formulating the recommendations were not clearly described. Therefore, in 2010, in line with the EAU guidelines office's new structure and recommendations for the development of the Guideline, a major methodological change was introduced (5). A new multidisciplinary panel (consisting of urologists, a pharmacologist, an epidemiologist and a statistician) was formed and the literature search criteria were clearly defined. The search was limited to randomised controlled trials and meta-analyses from 3 different databases (Pubmed-Medline, Web of Science, and Cochrane databases) between 1966 to 2009, but in the absence of level 1 evidence studies with lower levels of evidence were used for the development of recommendations. Each included article was assigned a level of evidence based on a modification of the Oxford Centre For Evidence-based Medicine Levels of Evidence, from Level 1a (meta-analysis) to Level 4 (expert opinion) (6), and this was summarised in tables of evidence so that the reader could clearly see the evidence upon which recommendations were made; each recommendation was graded from strong (Grade A) to weak (Grade C) (Figure 1). The methodology continued to evolve to reduce risk of bias, aid transparency, and ensure that the guideline recommendations were formulated based on the highest levels of evidence. In the 2012 update, the search criteria were clearly specified and in 2014 a Delphi process was introduced to achieve consensus more systematically on the assessment of male LUTS where high level of evidence was lacking (7). In order to ensure that guideline recommendations were based on the best evidence, the EAU started to focus on the development of high-quality systematic reviews and meta-analyses on which to base recommendations (8). In the subsequent guideline updates, the first recommendations based on the panel's systematic reviews were included on nocturia and non-invasive tests in diagnosing bladder outlet obstruction (9, 10). In 2017, special caution was taken to avoid ambiguous wording (e.g. 'consider', 'may be used', 'seems to be feasible', etc.) and properly formulate the recommendations

to make them actionable and guide users what to do, to whom, and under what specific circumstances.

Another methodological change was introduced in 2018 with the use of strength ratings assigned to each recommendation, as opposed to grades of recommendation. The strength of the rating (strong or weak) is now based on a modified GRADE methodology encompassing the following key elements:

1. the level of evidence (modified Oxford Centre for Evidence-Based Medicine Levels of Evidence)
2. the magnitude of effect
3. the certainty of results
4. the balance between desirable and undesirable outcomes
5. the impact of patient values and preferences on the intervention
6. the certainty of those values and preferences

The criteria used to formulate the strength ratings are published online allowing the reader to clearly understand the reason behind each guideline recommendation.

In 2012, in an effort to translate the evidence-based guideline recommendations into a clear and practical approach for the practitioner, assessment and treatment algorithms were introduced into the guideline (Figure 2).

3. Evolution in content

The content of the guideline has evolved considerably over the past 20 years, reflecting changes in our understanding of the pathogenesis, assessment, and treatment of LUTS. It was long believed that LUTS in men were due, either directly or indirectly, to benign prostatic enlargement (BPE) related to histological BPH. However, the causal link between prostatic enlargement and the pathogenesis of LUTS was called into question with increasing evidence that only half of men referred with LUTS actually had urodynamically-proven bladder outlet obstruction (BOO), and that the cause of LUTS in an individual man may be multifactorial (including urethral, bladder, renal and non-urological conditions) (11, 12). This broader, more complex approach to the management of LUTS was reflected in the change of the title of the guideline, from BPH to male LUTS, with a symptom-oriented guideline providing a more practical and user-friendly guide than the previous disease-specific approach. The complex relationship between BPH, BPE and LUTS was highlighted in the 2004 guideline (4), but it was in 2012 that a significant change was made with the introduction of

a diagram highlighting the multifactorial aetiology of LUTS (Figure 3). A systematic LUTS assessment algorithm was also created to provide a practical guide to aid the practitioner in excluding other causes of LUTS beyond prostatic enlargement, and a treatment algorithm was provided to ensure that practitioners considered nocturnal polyuria and overactive bladder in the differential diagnosis of men with LUTS. In line with this change in perspective, the 2010 guideline introduced new sections dedicated to muscarinic receptor antagonists and desmopressin for nocturnal polyuria (5). Prior to this, only pharmacological and surgical treatments for LUTS secondary to BPE had been included. The yearly guideline update allowed for new therapies to be incorporated if the evidence met the inclusion criteria, and in 2015 a section on beta-3 agonists for overactive bladder was added (13). With increasing evidence that nocturia is one of the most bothersome lower urinary tract symptoms in men, the first nocturia treatment guideline was incorporated in 2016 based on a panel-led systematic review of the evidence (10, 14). These changes allowed the guideline to continually evolve, emphasising the fact that LUTS may be the consequence of a complex interplay of pathophysiological processes, including prostatic pathology and bladder dysfunction.

A fundamental change to the guideline, and to the whole field of BPO (benign prostatic obstruction) surgery, was seen in 2016 with the introduction of the concept of endoscopic enucleation of the prostate (EEP). This term allowed a move away from the traditional energy-based classification of surgical procedures to a more conceptual classification, irrespective of the energy source used (e.g. enucleation with holmium laser, bipolar diathermy etc), thereby facilitating broader access to this treatment for the global community. Over the past few decades, a large number of minimally invasive interventional and surgical treatments for benign prostatic enlargement have been developed, each with a slightly different mechanism of action. Although these were previously listed by type of technology (e.g., TURP, TUNA, open prostatectomy, laser treatments etc), the clinical reality is primarily reflected by surgical approach and so in 2021 a major restructuring of the surgical treatment section was undertaken to reflect this. Surgical treatments were listed based on mechanism of action, as follows:

1. Resection
2. Enucleation
3. Vaporisation
4. Alternative ablative techniques
5. Non-ablative techniques

This has provided a more structured and clear review of the evidence so that readers can clearly see the relative merits of each surgical approach, irrespective of the technology used.

4. Treatment recommendations

A key strength of the EAU guideline process is the systematic yearly update to incorporate any new efficacy and safety evidence. This allows the guideline to remain contemporary and relevant, allowing beneficial treatments to be recommended whilst those proven to be ineffective can be withdrawn in a timely way. This is particularly important in the treatment of BPO, for which a large number of minimally invasive and surgical treatments have been introduced over the past few decades, and where technology is rapidly developing. Not all treatments have stood the test of time, and as new evidence has emerged several initially promising treatments have fallen out of favour, or worse, been shown to be harmful. Over the last 20 years, there have been successes and failures in the treatments that have been developed for BPO, highlighting the importance of careful evaluation of the quality and certainty of the evidence when formulating guideline recommendations.

4.1 Successful treatments

Several well-established treatments that are now given strong recommendations were initially included in the guideline as emerging or promising therapies until the quality of evidence was at a sufficient level to assign definitive recommendations. Holmium laser resection and enucleation of the prostate is a good example of a treatment that has been given stronger recommendations with increasing evidence and is now one of the mainstays of surgical treatment for BPO. Although the procedure had been described almost a decade earlier (15), the use of holmium laser to treat BPO was only introduced into the guideline in 2004 following publication of RCTs and comparative studies against the standard of care, monopolar transurethral resection of the prostate (TURP), showing equivalent short-term symptomatic improvements with shorter length of hospital stay (16). Following the publication of high-quality long-term safety and efficacy data, as well as meta-analyses of RCTs, HoLEP was assigned a grade A recommendation in 2011 as an alternative to TURP (17, 18). Similarly, bipolar TURP was briefly introduced into the guideline in 2004 as a promising technique. However, it was 7 years later, once increasing evidence from systematic reviews of RCTs demonstrating comparable short-term efficacy and lower morbidity compared to monopolar TURP was published, that bipolar TURP was recommended as an alternative to monopolar TURP with the caution that there was a lack of sufficient long-term data and so conclusions regarding durability could not be drawn (19). With the publication of outcomes at longer than 12 months, the guideline recommendation was initially modified to incorporate the mid-term efficacy of bipolar TURP, and

then following publication of long-term outcomes a strong recommendation to offer bipolar TURP was ultimately assigned.

4.2 Unsuccessful treatments

The importance of well-conducted, high-quality RCTs comparing investigational treatments to the standard of care is highlighted by the fate of several treatments that were once considered to be promising but were eventually shown to be ineffective. Transurethral needle ablation of the prostate (TUNA), a minimally-invasive treatment which causes coagulative necrosis through the delivery of radiofrequency energy to the prostate, was initially promoted based on several non-randomised studies demonstrating symptomatic improvement in 40-70% of patients (20, 21). The results of short-term RCTs comparing TUNA to TURP had been reported, as well as with 5-year follow-up, and so TUNA was given a grade A recommendation as an alternative to TURP (22). However, despite the presence of RCTs, the overall quality of the evidence was low and subsequent studies reported high retreatment rates and concerns regarding durability, and so TUNA was withdrawn from the guideline in 2019 (23). Similarly, intra-prostatic injections of botulinum toxin A (BTX-A) were studied in numerous non-randomised trials, all of which reported significant improvements in IPSS and urinary flow rates (24). In men with retention, it was reported that 80-100% could void spontaneously within one month following injection (25, 26). It was therefore described as a promising and quick minimally invasive treatment modality with low morbidity for patients that were refractory to medical treatment or in urinary retention and was introduced into the guideline as an emerging option in 2011. However, subsequent evidence from well-conducted RCT's and a systematic review, showed that there was no significant difference in efficacy between intra-prostatic BTX-A and placebo (27, 28). As a result, in 2017 the guideline panel made a strong recommendation that intra-prostatic BTX-A should not be offered to treat male LUTS.

These examples serve to highlight the importance of a critical and systematic evaluation of the literature before assigning recommendations to new devices or interventions. A single RCT should not mandate a guideline recommendation, and certain minimum standards should be met before widespread implementation of new surgical procedures. To aid transparency, the guideline panel have published their position on the minimum standards required for an interventional procedure to be included in the guideline (29). Initial proof of concept studies should be followed by sham controlled RCTs, and then RCTs against the standard of care, or other suitable comparator, focussing on efficacy and safety. Ideally these should be multicentre to demonstrate reproducibility and should be with long-term follow-up (>36 months). Importantly, evidence from high-quality, large,

prospective cohort studies, databases or registries should also be considered when forming guideline recommendations. RCTs are often restricted to a well-selected, 'index' population, whereas cohort studies provide greater insight into the safety and efficacy of a treatment in the general unselected population (including those with significant comorbidity, anticoagulation use, and elderly). These studies are important for understanding long-term outcomes, re-treatment rates, and adverse events, and can be used to evaluate the generalisability of an intervention. For novel treatments that appear promising, but do not yet meet these criteria, the guideline continues to include a 'techniques under investigation' section. This allows the reader to see the current evidence available, but with the awareness that these treatments remain under investigation until the required certainty of evidence has been provided.

5. Future

The EAU guideline on non-neurogenic male LUTS has changed considerably over the past 20 years and will continue to evolve in order to meet future expectations. In terms of content, the new guideline update will, for the first time, include a section on male urinary incontinence (stress incontinence, overactive bladder and urgency incontinence, and mixed incontinence). Future additions will include a section on detrusor underactivity/underactive bladder. The guideline will therefore need to be dynamic to keep abreast of the latest evidence, with regular updates to ensure that the guideline recommendations are up-to-date, but not so frequent that treatments are included before they have achieved the required certainty of evidence. Incorporating 'real life' data from cohort or registry studies will make guideline recommendations more robust but assessing the quality of this evidence will remain a challenge for future guideline updates. As an international guideline, a limitation is that cost-effectiveness analyses and recommendations cannot be made due to the varying reimbursement systems in place between different European countries.

The methodology will also continue to evolve. An important challenge is ensuring that the guideline is relevant to patients and focusses on the outcomes that they value most. For the first time in the history of the EAU guidelines, our guideline group recently completed a systematic review on values, preferences and expectations for the diagnosis and treatment of male LUTS. Our review can facilitate the treatment decision-making process and improve the trustworthiness of guideline recommendations. Importantly, as the first values and preferences systematic review, it will be an example for other EAU guidelines (30). It is important that all stakeholders are involved in the guideline development process. Stakeholder engagement is important in creating patient-focussed guidelines, and so a patient advocate will start to be included on the guideline panel. The aim is to

facilitate discussions regarding outcomes of importance, patient values and preferences, and weighing up benefits and risks of treatments, thereby continuing to make guideline recommendations relevant to patients (31). Another important future challenge is to ensure that these evidence-based guideline recommendations are implemented and adhered to across Europe, thereby enabling optimal care to be accessible to all patients. There is evidence that adherence to clinical practice guidelines is suboptimal throughout Europe, and so the EAU Guidelines Office have launched the 'IMAGINE' (IMpact Assessment of Guidelines Implementation and Education) project to identify reasons for non-adherence to guideline recommendations and to design solutions to improve implementation of these evidence-based recommendations (32).

6. Conclusions

The past 20 years have seen considerable changes in the EAU non-neurogenic male LUTS guideline, primarily in terms of philosophy and concept. The original focus was on BPH, but this has evolved to encompass the multifactorial causes of LUTS in men. The methodology has developed to become more systematic, transparent, and rigorous, with future inclusion of a patient advocate ensuring that patient-focussed care remains at the centre of the guideline recommendation process. Clear criteria for the certainty of evidence required for new interventions to be included in the guideline will ensure that recommendations are only assigned, and treatments only widely adopted once they are proven to be safe and effective.

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Figure 1. Example of how the presentation of guideline recommendations has evolved from 2004 (upper) to 2021 (lower)

4.2.1.4 CONCLUSIONS

1. It has been shown in numerous randomized, placebo-controlled clinical trials that 5-alpha reductase inhibitors are capable of reducing prostate volume and improving symptom scores and flow rates. Maximum benefits are seen at a mean period after 6 months.
2. Men with small prostates (< 40 mL) are less likely to benefit from finasteride.
3. 5-alpha reductase inhibitors can alter the natural history of symptomatic BPH by influencing prostatectomy and acute urinary retention rates. The costs of such protocols, however, should be further evaluated.
4. The long-term (up to 10 years) effects of 5- alpha reductase inhibitors are substantial.
5. The combination of a 5-alpha reductase inhibitor with an alpha-blocker seems beneficial according to the data currently available.
6. Side-effects of 5-alpha reductase inhibitors are minimal
7. Treatment with 5-alpha reductase inhibitors does not mask the detection of prostate carcinoma. By doubling PSA serum levels, an accurate estimation can be expected.

Recommendation	Strength rating
Offer combination treatment with an α1-blocker and a 5α-reductase inhibitor to men with moderate-to-severe LUTS and an increased risk of disease progression (e.g. prostate volume > 40 mL).	Strong

Figure 2. Treatment algorithm of male LUTS (from 2012 EAU Guideline).

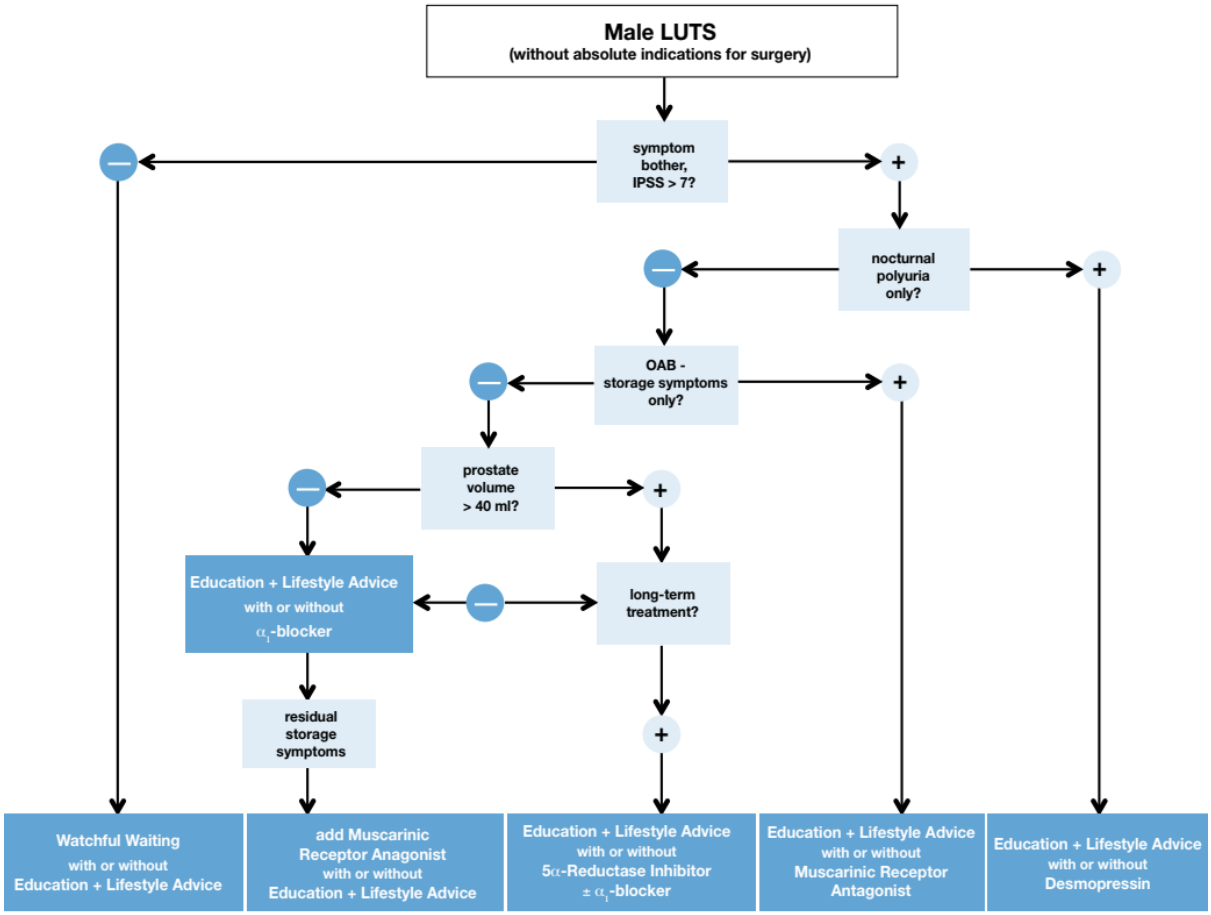

Figure 3. Multifactorial aetiology of LUTS (From 2012 Guideline).