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Critical Review of Guidelines for BPH Diagnosis and Treatment Strategy

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Abstract

Objectives: To provide a critical overview of the currently available guidelines on benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS).

Methods: Through a nonsystematic review of MEDLINE, we identified the guidelines produced by the following institutions: American Urological Association (AUA), Australian National Health and Medical Research Council (NHMRC), British Association of Urological Surgeons (BAUS), Canadian Urological Association, European Association of Urology (EAU), and the 5th International Consultation on BPH. All the guidelines were evaluated by the international appraisal instrument provided by the Appraisal of Guidelines, Research and Evaluation (AGREE) collaboration. Moreover, the recommendations concerning diagnosis and treatment from the different guidelines were compared.

Results: A wide discrepancy was observed among the overall quality of the guidelines. The guidelines from the Australian NHMRC and from the AUA yielded the highest overall scores, with 86 and 72 points, respectively. According to the domains of the AGREE appraisal instrument, the scores concerning ''scope and purpose'' and ''clarity and presentation'' were quite high and quite similar among the different documents, whereas the most relevant differences were observed in domains concerning the methodology of development of the guidelines.

Conclusion: Although all the texts had some good aspects, we found considerable differences in the overall quality of the available guidelines, especially with regard to the methodologic issues. The guidelines from the Australian NHMRC and AUA were most adherent to the standards of quality suggested by the AGREE appraisal instrument. In cases of controversial issues, clinicians could use the summarised data to select the guidelines they trusted the most to be used in their clinical practice.

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1. Introduction

Evidence-based medicine (EBM) has been defined as ''the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients'' [1]. In the era of EBM, ''high-quality healthcare implies a practice that is consistent with the best available evidence'' [2]. However, obtaining and critically appraising the current evidence, as well as considering that evidence in the context of an individual's circumstances, is beyond the time, skills, and resources of most clinicians. To overcome those limitations, clinical practice guidelines have been developed with the aim of providing ''an evidence-based framework on which clinicians base their practice, with the purpose of reducing unwanted variations by setting agreed standards based on the best available evidence'' [3].

Clinical practice guidelines have been defined as systematically developed statements designed to assist practitioner and patient decisions about appropriate health care for specific clinical conditions and/or circumstances [4]. In the most relevant clinical areas several guidelines have been published and significant differences are often present among the different documents, with frequent conflicting recommendations, raising concerns about the overall quality of the process that led to the generation of the guidelines.

1.1. *What makes a good clinical guideline?*

The development of a guideline is a very long task, involving different kinds of expertise and including several relevant steps, such as planning of the objectives, search, extraction, rating and analysis of the evidence, cost analysis, draft of the recommendations, draft reviewing, guideline piloting, dissemination, and implementation, and so on. Each step may be impaired by several methodologic biases. A few papers demonstrated clearly that most of the guidelines published in the peer-reviewed medical literature did not adhere to basic methodologic standards [5,6]. Consequently, the establishment of internationally recognised standards to improve the development and reporting of clinical guidelines has become a major medical issue, which has been addressed by both national health providers (National Institutes of Health [NIH] from the United States and National Health Service [NHS] from the United Kingdom) and independent multinational groups, such as the Appraisal of Guidelines, Research and Evaluation (AGREE) collaboration. The NHS executive group identified nine different major issues, which should identify a good-quality guideline (Table 1), including the steps of methodologic development and a plan for updating the guidelines [7]. Moreover, a few algorithms have been developed to analyse step by step the quality of a guideline, such as the checklist of the Health Care Evaluation Unit at St George's Hospital Medical School, London, United Kingdom [8] and the appraisal instrument provided by the AGREE collaboration [9].

Lower urinary tract symptoms (LUTS) are a major health problem. That terminology, initially suggested by Abrams in 1994 [10], was recommended by the 5th International Consultation on BPH to replace imprecise terms such as ''clinical BPH,'' ''symptomatic BPH,'' and ''prostatism'' [11]. The same consultation recommended the use of the terms benign prostatic hyperplasia (BPH) only in case of histologic confirmation and benign prostatic enlargement (BPE) when such pathologic data were lacking. Moreover, considering the weak correlation between urinary symptoms and urodynamic observations, the term bladder outlet obstruction (BOO) was suggested to be used when a reduced urine flow rate was associated with increased detrusor pressure [11]. LUTS are highly prevalent. By the age of 60 yr, nearly 60% of the cohort of the Baltimore

Table 1 – Major characteristics of good clinical practice guidelines

Characteristic	Description
Validity	Leads to the results expected of them
Reproducibility	If using the same evidence, other guideline groups would come to the same results
Cost-efficacy	Reduce the inappropriate use of resources
Representativity/multidisciplinarity	Needs to involve key groups and their interests
Clinical applicability	Patient populations affected should be unambiguously defined
Flexibility	Needs to identify the expectations relating to recommendations as well as patient preferences
Clearness	Unambiguous language, which is readily understood by clinicians and patients, should be used
Reviewability	The date and process of review should be stated
Amenability to clinical audit	The guidelines should be capable of translation into explicit audit criteria

Modified from ref. [7].

Longitudinal Study of Aging had some degree of urinary symptoms due to BPE [12]. Further data from the United States showed that moderate-to-severe symptoms can occur among 13% of men aged 40–49 yr and among 28% of those older than 70 yr [13]. Similar trends were reported in Europe as well [14]. Moreover, with the changing demographic profile and the increasingly aging population in all western societies, this disorder will become even more prevalent and a major challenge for all health care systems in the future [15]. Those figures, as well as variations in the patterns of practice, high cost of treatment, and the increasing number of treatment options made BPH an optimal topic for guidelines development.

To date, several guidelines are available on diagnosis, management, and follow-up of BPH/BPE and LUTS. The aim of this review is to provide a critical overview of both the quality and contents of the published guidelines.

2. Materials and methods

We performed a nonsystematic review of the literature. Data were identified by a search of MEDLINE using a complex search strategy including both ''MeSH'' (Medical Subject Heading) and ''free text'' protocols. Specifically, the MeSH search was conducted by the term ''Prostatic Hyperplasia'' retrieved from the MeSH browser provided by MEDLINE. Multiple ''free text'' searches were performed by applying the following terms one by one through all fields of the records: ''benign prostatic hyperplasia,'' ''benign prostatic enlargement,'' ''lower urinary tract symptoms,'' and ''LUTS.'' All the MEDLINE searches were pooled together, collecting 25,603 records. Subsequently, the following search limits were used: publication type (''Practice Guideline'') and languages (''English''). Twenty records were finally identified, whose abstracts were reviewed by three of the authors (G.N., A.G., V.F.). In addition, other significant studies cited in the reference lists of the selected papers were considered.

After excluding the papers regarding standardisations of terminology of the International Consultation on Incontinence (3 records), LUTS in female (2 records) or paediatric (one record) patients, urinary tract infections (1 record), and prostate cancer (1 record), we identified the guidelines produced by the following institutions: American Urological Association (AUA) [16], Australian National Health and Medical Research Council (NHMRC) [17], British Association of Urological Surgeons (BAUS) [18], Canadian Urological Association [19], European Association of Urology (EAU) [15], and World Health Organization (WHO) [20]. When multiple editions of the guidelines were available (AUA, BAUS, EAU), we elected to analyse the most recent one. Although not indexed in MEDLINE, we included in the review the 5th International Consultation on Benign Prostatic Hyperplasia [11]. Since the consultation was patronized by WHO, we considered its text an update of the WHO guideline published in 1991, which, consequently, was excluded from the present study.

The retrieved guidelines were evaluated by the AGREE appraisal instrument by three of the authors (G.N., A.G., V.F.), with any discrepancies solved by open discussion. The AGREE collaboration scale includes 23 questions grouped in six domains: scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence. A score from 1 to 4 can be assigned for each question, 23 and 92 being the lowest and the highest possible scores [9]. The English version and several validated translations of the appraisal instrument, including instructions for the users, are available free at http://www.agreecollaboration.org.

3. Results

3.1. *Quality of guidelines*

Table 2 summarizes our findings after application of the AGREE appraisal instrument to the analysed guidelines.

A wide discrepancy was observed among the overall quality of the guidelines. The guidelines from the Australian NHMRC and from the AUA

Table 2 – AGREE appraisal instrument for clinical practice guidelines: summary of six domains and overall scores for the analysed guidelines

Domains	Australian NHMRC	5th IC on BPH	AUA	BAUS	EAU	Canadian Urological Association
Year of publication	2000	2001	2003	2004	2004	2005
Scope and purpose	12	10	11	12	11	11
Stakeholder involvement	14	6	12	12	8	8
Rigor of development	24	9	23	15	12	12
Clarity and presentation	16	14	16	16	15	14
Applicability	12	5	5	5	5	4
Editorial independence	8	5	5	8	5	5
Overall score	86	49	72	68	56	54

Guidelines are listed according to the year of publication; 23 and 92 were the lowest and highest possible scores, respectively.
NHMRC = National Health and Medical Research Council; IC = International Consultation; BPH = benign prostatic hyperplasia; AUA, American Urological Association; BAUS = British Association of Urological Surgeons; EAU, European Association of Urology.

yielded the highest overall scores, being definitely the most ''evidence-based.'' The worst scores were obtained by EAU, the Canadian guidelines, and the 5th International Consultation on BPH.

According to the domains of the AGREE appraisal instrument, the scores concerning ''scope and purpose'' and ''clarity and presentation'' were quite high and quite similar among the different documents, meaning that the aims of the guideline, specific clinical questions, target patient population as well as format and languages of the guidelines were addressed adequately in all cases. The most relevant differences were actually observed in the domains concerning the methodology followed during the guideline development.

First of all, with regard to the ''stakeholder involvement'' domain, the steering groups of the best-ranked guidelines were multidisciplinary, including urologists, general practitioners, experts in general medicine and family medicine [16], health economists [17], nurses [18], and patients [17,18].

As far as the ''rigor of development'' domain was concerned, AUA and NHMRC had extremely high scores (23 and 24, respectively, of a maximum possible score of 28). The AUA text depicted step by step the 3-yr work done to carry out an excellent meta-analysis of the available evidence, which was closely related to the guideline recommendations. The Australian NHMRC was the text that better rated the level of the gathered evidence, applying a system similar to the most widely accepted scale from the Oxford Centre for Evidence-Based Medicine [21]. Moreover, the panel of the Australian guidelines provided a straightforward cost analysis and was the only one to include a plan for updating the guidelines in the final document. Those were two of the best qualities of that excellent text [17].

Regarding the ''applicability'' domain, the Australian NHMRC guideline was the only one to propose a series of indicators for guideline dissemination (e.g., 80% of general practitioners being aware of the LUTS guidelines and 40% of men aged $\geq$50 yr with bothersome urinary symptoms aware of the consumer guidelines within a year of publication) and implementation (e.g., reduction of prostate-specific antigen [PSA] test ordering; reduction of referral to urologists for investigation and management of men not bothered by urinary symptoms; increase of watchful waiting programs; decrease in transurethral resections of the prostate [TURPs] performed on men 'not at all' or only 'mildly' bothered by uncomplicated urinary symptoms) [17]. These latest issues justified the maximum score in the ''applicability'' domain. In contrast, most of those issues were ignored in the other guidelines.

The differences in the overall quality of the guidelines as assessed by the AGREE appraisal instrument were paralleled by the suggested diagnostic recommendation, with the best scoring guidelines being those that recommend the lowest numbers of tests (Table 3).

3.2. *Diagnostic recommendations*

Table 3 summarises the recommended procedures in the routine assessment of patients with LUTS due to BPE.

All the guidelines agreed in recommending medical history, physical examination, symptom assessment by a validated score, and urinalysis.

Table 3 – Diagnostic tests recommended by the analysed guidelines in the evaluation of male lower urinary tract symptoms

	Australian NHMRC	5th IC on BPH	AUA	BAUS	EAU	Canadian Urological Association
History, physical exam and DRE	R	R	R	R	R	M
Symptom score	R	R	R	R	R	R
Voiding diary	O	R	O	O	O	O
Urine analysis	R	R	R	R	R	M
Uroflowmetry	NR	O	O	O	R	O
PVR measurement	NR	O	O	O	R	O
Serum creatinine	NR	ND	NR	O	R	O
Serum PSA	NR	R	O	O	R	R
Upper urinary tract imaging	NR	O	NR	NR	O	NR
Prostate ultrasound scans	NR	O	O	NR	O	NR
Pressure-flow study	NR	O	O	O	O	NR
Cysto-uretroscopy	NR	O	O	NR	O	NR
Total recommended or mandatory procedures	3	5	3	3	7	4

Guidelines are listed according to the year of publication.
R = recommended; M = mandatory; O = optional; NR = not recommended; ND = not discussed; DRE = digital rectal examination; PVR = postvoiding residual urine; PSA = prostate-specific antigen. Other abbreviations are defined in Table 2.

Medical history should be focused on the urinary tract and, in addiction, address general health issues that might cause bladder dysfunction or polyuria, as well as disease that might impair general health conditions for eventual surgical procedures. Family history of prostatic disease as well as personal history of previous surgical procedures should be taken into account. The Australian NHMRC provided a clear list of conditions that should be assessed, such as bowel habit, comorbidity (neurologic or psychiatric conditions, diabetes, cardiac disease, or poor mobility), drug intakes (diuretics, antidepressants, and antihypertensives), social/employment and psychological issues relevant to the management of LUTS, and mental state with specific attention to dementia, anxiety, and depression [17].

Similarly, all the documents suggested a careful physical examination, including a digital rectal examination (DRE). Moreover, AUA guidelines highlighted the need for a focused neurologic examination to assess general mental status, ambulatory status, lower extremity neuromuscular function, and anal sphincter tone [16]. The DRE was aimed at detecting gross distortion of the anatomy suggestive of a diagnosis of locally advanced prostate cancer, at estimating prostate volume, and excluding other anorectal pathologies. Although the DRE tends to underestimate the real prostate size, it is usually recognised that prostates that feel enlarged at rectal examination are usually confirmed to be large through imaging techniques [22]. Moreover, even if the correlation between prostate size and symptoms is not so strict, the Olmsted study showed that the odds of having moderate to severe LUTS were 1.5 and 3.5 times higher for patients with prostates larger than 30 ml and 50 ml, respectively [23].

Further agreement among the guidelines was found in the use of a symptom score, the International Prostate Symptom Score (IPSS) being the most commonly applied. The index has a high internal consistency and test-retest reliability [17], and it has been translated and validated in several languages. Although that score does not appropriately address urinary continence and bother due to LUTS as well as their interference with daily activities, it is considered a fundamental tool for planning therapeutic strategy and assessing response to therapy or disease progression during the follow-up. In the AUA guidelines further attention was given to other questionnaires (such as the International Continence Society male questionnaire, Danish Prostatic Symptom Score, BPH Impact Index), which, however, were all considered optional.

Urinalysis was similarly recommended by all the guidelines, with the aim of detecting microhematuria or pyuria, which might be clues to bladder carcinoma, urinary tract infections, urethral strictures, bladder stones, and other conditions that might be causes of LUTS.

Those listed above were the only procedures recommended by the guidelines of AUA, Australian NHMRC, and BAUS in the initial assessment of patients with LUTS. However, the EAU, Canadian, and 5th International Consultation on BPH guidelines suggested the use of further tests.

Guidelines from Canadian Urological Association, EAU, and the 5th Consultation on BPH recommended having a PSA sample in patients with LUTS. Wisely, AUA guidelines, which considered PSA an optional test, highlighted the need to offer a PSA test to those patients with ''at least a 10-year life expectancy and for whom knowledge of the presence of prostate cancer would change management'' or ''for whom the PSA measurement may change the management of their voiding symptoms'' [16]. Similar caveats were also included in the EAU guidelines and in the International Consultation on BPH. In contrast, Australian NHMRC guidelines underscored that early prostate cancer was a silent disease and that ''men with uncomplicated LUTS should be advised that current data suggest that they have little or no increased risk of prostate cancer'' [17]. Hence, the Australian document discouraged the use of PSA testing and advised informing patients that ''there is no scientific evidence of a relationship between LUTS and presence of early prostate cancer'' [17]. Moreover, the AUA and Australian guidelines recommended extensively informing patients of the consequence of PSA testing.

Determination of serum creatinine levels was also advocated by EAU guideline documents, with the aim of diagnosing renal insufficiency. However, analysing >10,000 patients enrolled in randomised clinical trials, the panel of AUA guidelines reported a rate of silent renal insufficiency <2%, mostly unrelated to BPH, discouraging the routine testing of creatinine [17]. Wisely, BAUS guidelines suggested having creatinine tested in cases where chronic urinary retention was suspected. EAU guidelines recommended, besides, uroflowmetry and postvoiding residual (PVR) urine measurement. The panel of the 5th International Consultation on BPH highlighted the value of uroflowmetry as a screening test, even though the test is unable to distinguish lower urinary tract obstruction from poor bladder contraction. Even with a peak flow rate (Q_{max}) >15 ml/s, 30% of the patients had urodynamically proven BOO, where those figures were as

low as 10% for Q_{max} <10 ml/s [24]. Moreover, flow rates have to be considered inaccurate for voided volumes <125–150 ml and a learning effect has been shown, which suggests the value of at least two separate flow rates [17]. Indeed, the diagnostic role of uroflowmetry is far from being optimal. Although several papers showed that the lower the Q_{max}, the higher the chances of symptom improvement after surgery, Jensen reported that 71% of the patients who underwent TURP with Q_{max} >15 ml/s had symptom relief, compared to 92% for those with Q_{max} <10 mL/s [25].

Similarly, several limitations impaired the use of PVR urine measurement. Several studies highlighted that the reproducibility of the test was poor, as suggested by considerable intraindividual variations in residual urine values. Moreover, the magnitude of PVR volume was not or was only weakly correlated with the severity of urinary symptoms and with urodynamic parameters such as voiding pressures and peak urine flow rate. Most importantly, however, pretreatment PVR volume is at best only weakly associated with treatment outcome and residual urine is not a contraindication to watchful waiting or medical therapy. Although large PVR volumes may indicate bladder dysfunction and predict a slightly less favourable response to treatment, major disagreement was evident among the guidelines, with each document suggesting different cut-points (200 ml for EAU, 300 ml for BAUS, and 350 ml for AUA guidelines). Interestingly, BAUS guidelines suggested performing upper urinary tract imaging and pressure-flow study in all the patients with persistently large PVR values.

Higher level of agreement was seen among the different guidelines concerning further diagnostic tests. Pressure-flow studies were considered optional by all the guidelines, with the exception of the Australian NHMRC, which did not recommend their use. According to the EAU text, they might be indicated before surgery in patients with Q_{max} >15 ml/s, in the elderly (e.g., >80 yr), in younger men (e.g., <50 yr), in the presence of large PVR (>300 ml), in patients with suspicion of neurogenic bladder dysfunction (e.g., neurologic disease such as Parkinson disease), or after radical pelvic surgery or unsuccessful invasive BPH treatment [15]. The aim of the invasive urodynamic test is to identify patients without a clear BOO, who have the lowest chance to benefit from surgery.

Similarly, almost all the guidelines considered the use of frequency-volume charts or voiding diaries optional, to be indicated in case of predominant storage symptoms (especially nocturia).

Most of the guidelines did not recommend the use of imaging techniques of the upper urinary tract because in patients with apparently uncomplicated LUTS, the prevalence of upper tract dilatation has been estimated to range from 0.8% to 2.5%. Indication for such imaging may, however, include haematuria, urinary tract infections, renal insufficiency, history of urolithiasis, and history of urinary tract surgery. Similarly, all the guidelines did not recommended the routine use of prostate imaging (e.g., transrectal ultrasound scan), which might be indicated only in the case of minimally invasive surgery (where prostate volume might be a limiting factor) or for selecting the most appropriate conventional surgical therapy (transurethral incision of the prostate [TUIP], TURP, or open prostatectomy). In that context, anatomic features of the prostate, such the presence of an intravesical middle lobe, may affect the choice of therapy. Although few papers showed an interesting diagnostic role of the bladder wall thickness as a marker of BOO [26], measurement of bladder wall thickness is currently not part of the recommended diagnostic work-up of patients with LUTS.

Finally, urethrocystoscopy was not recommended in the initial assessment of patients with LUTS prior to watchful waiting or medical therapy, but it has to be considered in patients with a history of microscopic or gross haematuria, urethral strictures (or risk factors, such as history of urethritis or urethral trauma), bladder cancer, previous lower urinary tract surgery, or before surgery.

3.3. *Treatment recommendations*

The major outcomes of BPE/BPH treatment are relief of patients' symptoms and improvement of quality of life, and, more recently added, altering the disease progression [27]. Most of the treatment recommendations provided by the guidelines were focused on the first two objectives, although those more recently developed provided further insights on disease progression.

In most of the clinical cases, the cornerstone of treatment planning was established on symptom severity and the degree of bother. Patients with mild (IPSS $\leq$ 7), not bothersome, or slightly bothersome symptoms are considered candidates for a watchful waiting program.

Watchful waiting is a management strategy in which the patient is monitored by his physician without receiving any active intervention for LUTS. Various conservative measures may be used to reduce the degree of bother, such as minor lifestyle modifications and bladder training. Lifestyle mod-

ifications consist of the reduction of fluid intake, toilet scheduling, reviewing patient's medication and changing the time of administration or substituting drugs for others that have fewer urinary effects, treatment of constipation, and reversal, where possible, of polyuria [15,17].

In patients with moderate to severe (IPSS $\geq$ 8) or bothersome symptoms, almost all the guidelines indicated the central role of the patient in selecting the kind of treatment he accepted the most, once clearly informed about efficacy and side-effect profiles. The currently available options include medical therapy, minimally invasive surgical therapy, and conventional surgical therapies.

The mainstays of drug therapy are currently α-blockers and 5-α-reductase inhibitors. α-Blocker therapy is based on the hypothesis that LUTS are partly caused by α_1-adrenergic–mediated contraction of prostatic smooth muscle and bladder neck, resulting in BOO [28]. α-Adrenergic receptor antagonists, such as doxazosin, tamsulosin, alfuzosin, and terazosin, reduce this process, relieving BOO. The use of those drugs has been widely studied. Meta-analytical data from AUA guidelines suggest that alfuzosin, doxazosin, tamsulosin, and terazosin are similarly effective in partially relieving symptoms, producing a 4-to-6 point improvement in the AUA Symptom Index. The most relevant adverse events reported with α-blocker therapy are orthostatic hypotension, dizziness, tiredness, asthenia, ejaculatory problems, and nasal congestion. The adverse event profile appears slightly different between the four α-blocking agents, with tamsulosin having a lower probability of orthostatic hypotension but a higher probability of ejaculatory dysfunction than the other α-blockers [29–31].

Finasteride and dutasteride are the currently available 5-α-reductase inhibitors. Both of them impair the intraprostatic conversion of testosterone in dihydrotestosterone, reducing the size of the prostate, increasing the peak urinary flow rate, and relieving LUTS within 6–9 mo of therapy. The reported adverse events are primarily sexually related and include decreased libido, ejaculatory dysfunction, and erectile dysfunction. However, those adverse events are reversible and uncommon after the first year of therapy. Relevant analyses of both the Proscar Long-term Efficacy and Safety Study (PLESS) [32] and Medical Therapy of Prostatic Symptoms (MTOPS) [33] randomised controlled trials, moreover, allowed further insights on finasteride efficacy. MTOPS trial randomised 3047 men to placebo, doxazosin, finasteride, or the combination therapy of doxazosin and finasteride. The trial showed a significant reduction in both the incidence of acute urinary retention and need of surgery for LUTS in patients treated with finasteride, whereas doxazosin was only able to delay these events for about 2–2.5 yr, without preventing them in the end [33]. Similar data were reported in the studies on dutasteride as well [34–36]. Those data clarified the key role of 5-α-reductase inhibitors in preventing disease progression. All the guidelines published after the MTOPS trial discussed the option to offer 5-α-reductase inhibitors or combination therapy of 5-α-reductase inhibitors and α-blockers as appropriate treatment for patients with LUTS with demonstrated prostatic enlargement. AUA guidelines reported, moreover, that ''patients with symptomatic prostatic enlargement but without signs of bother may be offered 5-α-reductase inhibitor to prevent disease progression'' after a clear presentation of advantages and disadvantages of that kind of therapy [16]. In addiction, BAUS guidelines highlighted the possible use of 5-α-reductase inhibitors in patients at high risk of disease progression (PSA $>$1.4 ng/ml, prostate volume $>$30 cc), regardless of the presence of bothersome symptoms [18].

All the guidelines agreed in not recommending phytotherapeutic agents (*Pygeum africanum*, *Serenoa repens*). Although several randomised clinical trials and a few meta-analyses demonstrated clearly the efficacy of *Serenoa repens* in improving both IPSS score and maximum flow rate [37,38], all the guidelines did not recommended the routinely use of plants extracts because of the lack of long-term studies. However, long-term randomised controlled studies are ongoing. Table 4 summarises the recommendations for the pharmacologic therapeutic options.

All the guidelines agreed in recommending surgical treatment for patients with complicated LUTS, such as those with refractory urinary retention who had failed at least one trial of catheter removal, renal insufficiency, recurrent urinary tract infections, persistent gross hematuria, or bladder stones due to BOO and refractory to other therapies. Other candidates for surgery are the patients who refuse medical therapy or achieve unsatisfactory benefit or have unacceptable side-effects following drug therapies. All guidelines agreed in considering TURP as the gold standard of treatment, excluding cases with small prostate, suitable for TUIP, or very large glands, suitable for open prostatectomy.

Moreover, several minimally invasive therapies have been developed for LUTS/BPE management, which are considered as alternatives to either surgical or medical treatments. Most of those treatment modalities use the thermal effects of different sources of energy on the prostate tissue, with the aim

Table 4 – Pharmacologic therapies recommended by the analysed guidelines for male lower urinary tract symptoms

	Australian NHMRC	5th IC on BPH	AUA	BAUS	EAU	Canadian Urological Association
α-blockers						
Alfuzosin	ND	R	R	R	R	R
Doxazosin	R	R	R	R	R	R
Phenoxybenzamine	ND	ND	NR	ND	ND	ND
Prazosin	NR	ND	NR	ND	ND	NR
Tamsulosin	R	R	R	R	R	R
Terazosin	R	R	R	R	R	R
5-α reductase inhibitors						
Dutasteride	ND	NR	R	R	R	R
Finasteride	R	R	R	R	R	R
Combination therapy	ND	ND	R	R	R	R
Phytotherapeutic drugs	NR	NR	NR	NR	NR	NR
Anticholinergic drugs	R	ND	ND	ND	ND	ND

Guidelines were listed according to the year of publication. Abbreviations are defined in Tables 2 and 3.

of producing irreversible tissue damage [39]. Transurethral microwave thermotherapy (TUMT) and transurethral needle ablation (TUNA) are those that have been more extensively tested and are currently recommended by several guidelines. On the other hand, interstitial laser coagulation (ILC), water-induced thermal therapy (WIT), and high-intensity focused ultrasound (HIFU) are still considered investigational. Table 5 summarises the recommendations for the nonpharmacologic therapeutic options.

Extensive insights on minimally invasive therapy and surgery are beyond the purpose of the present review.

4. Discussion

The present study provided a quality ranking of the most commonly used clinical practice guidelines on male LUTS by the application of a validated appraisal instrument. Although all the texts presented some good aspects, we found considerable differences in the overall quality of the available guidelines, especially with regard to the methodologic issues. The texts from the Australian NHMRC and AUA were those that adhered most to the standards of quality suggested by the AGREE appraisal instrument.

Table 5 – Nonpharmacologic therapies recommended by the analysed guidelines for male lower urinary tract symptoms

	Australian NHMRC	5th IC on BPH	AUA	EAU	Canadian Urological Association
Minimally invasive therapies					
TUMT	R with caveat	R	R with caveat	R	R
TUNA	NR	R	R	R	R
Prostatic stent	R with caveat	R with caveat	R with caveat	R with caveat	R with caveat
Balloon dilatation	NR	NR	NR	NR	NR
ILC	ND	R	NR	R	NR
WIT	ND	NR	NR	NR	NR
HIFU	NR	ND	NR	NR	NR
Surgical therapies					
TUIP	R	R	R	R	R
TURP	R	R	R	R	R
Open prostatectomy	R	R	R	R	R
TUVP	NR	R	R	R	R
HoLEP	R with caveat	R	R	R	R
VLAP	R	R	R	R	ND

BAUS guidelines were not included in the table because of the lack of specific considerations on nonpharmacological therapeutic options.
TUMT = transurethral microwave thermotherapy; TUNA = transurethral needle ablation; ILC = interstitial laser coagulation; WIT = water-induced thermal therapy; HIFU = high-intensity focused ultrasound; TUIP = transurethral incision of the prostate; TURP = transurethral resection of the prostate; TUVP = transurethral (electro)vaporization of the prostate; HoLEP = transurethral holmium laser enucleation of the prostate; VLAP = visual laser ablation of the prostate. Other abbreviations are defined in Tables 2 and 3.

The assessment of guideline quality is an increasing health problem, given that hundreds of guidelines are currently available in the medical literature. A few papers addressed the quality of the published guidelines, mostly in the fields of general medicine, with urology only marginally involved. In 2003 Irani et al. performed a study similar to the present one, assessing quality of the BPH guidelines through the checklist of the St George's Hospital Health Care Evaluation Unit [40]. However, because of the rapid development of new guidelines and updating of older editions, only the text from the Australian NHMRC was analysed in both Irani's and our papers, which was rated as the best guideline. However, different appraisal instruments were used in the two papers. We used the instrument provided by the AGREE collaboration because its rigorous development process, involving more than 250 appraisers from 11 nations, led to a powerful tool, recognised worldwide and adopted by several health agencies (WHO, National Institute for Clinical Excellence in the United Kingdom, National Federation of Cancer Centers in France, the Agency for Quality in Medicine in Germany) [9].

Slight differences were evident within the titles of the guidelines. Only the guidelines of Australian NHMRC [17], BAUS [18], and EAU [15] were appropriately focused on male LUTS, whereas the other one was aimed at BPH management.

With regard to the content of the guidelines, as stated, the most relevant differences were found in the diagnostic recommendations, with the low-ranked guidelines advising more procedures (Table 3). Although all the appraisal instruments assessing the quality of a guideline relied heavily on how well documented the guideline development process was, it did not guarantee excellent recommendations because unsystematically (''opinion-based'') developed guidelines might provide wise recommendations and, vice versa, a well-reported one may include imperfect advice. Notwithstanding, to date, those criteria are largely accepted among methodologists and experts on guideline development and implementation. Moreover, Irani et al. reported a linear relationship among the number of recommended diagnostic tests and the overall guideline score, with the high-score guidelines recommending the lowest number of tests [40].

The choice to offer a PSA test is the most critical issue in the initial assessment of patients with LUTS due to BPE. Beyond prostate cancer diagnosis, recent studies are suggesting a new role for PSA in patients with BPH. Analysis of the placebo arm of PLESS, a double-blind, randomised, placebo-controlled trial, in which 3040 men with LUTS and enlarged prostate glands were randomised to finasteride 5 mg or placebo [32], highlighted the possible role of PSA as a marker of disease progression. Specifically, the baseline PSA level was a powerful predictor of long-term changes in the IPSS score and Q_{max}, as well as of the risk of acute urinary retention and the need for surgery. The studies suggested that the patients above the lowest tertile of PSA distribution ($\geq$ 1.4 ng/ml) were those with the worst long-term outcome [41–44]. Similar data were reconfirmed in the MTOPS study [33] and the dutasteride phase 3 study, highlighting the new dimension of PSA as a biomarker for disease progression [45,46]. Those issues were included in the most recently published guidelines (AUA, BAUS, and EAU) and can have a major role in therapy planning.

Other, less relevant, differences were observed in the treatment recommendations. The most recently published guidelines addressed more deeply the possible role of 5-α-reductase inhibitors in preventing BPH progression. That was mostly related to the publication of MTOPS data in 2003 [33]. Two of the latest texts, the guideline from the AUA and BAUS recommended the use of 5-α-reductase inhibitors in patients at high risk of disease progression, regardless of symptoms [18]. The possible advantages in terms of BPH progression, however, have to be weighed against both oncologic and economic issues. Data from the Prostate Cancer Prevention Trial showed clearly that long-term treatment with finasteride reduced the overall incidence of prostate cancer but, meanwhile, seemed to increase the risk of high-grade tumours [47]. Although those data might be seen as biased by the effects of finasteride on prostate volume and Gleason score system reliability, those concerns have not been unequivocally dispelled. Moreover, according to the MTOPS data, 29 patients (confidence interval, 19–59) had to be treated with combination therapy and 31 (confidence interval, 20–74) with finasteride alone to prevent a single patient from undergoing surgery. Although the cut-points of PSA and prostate volume suggested by the BAUS guideline identified high-risk patients, where the benefit might be higher and the number needed to treat lower, further studies would be desirable to address those health economic issues.

Excluding the guidelines from the Australian NHMRC, all the other guidelines did not take into consideration antimuscarinic drugs. Although less prevalent, ''storage'' LUTS are, indeed, highly bothersome and few papers suggested the concomitant use of anticholinergic drugs with α-blockers [48,49]. Moreover, recent experimental data suggested a

possible action for acetylcholine on the afferent nerves within the detrusor and the sub-urothelium, which could help to explain the role of antimuscarinic drugs in patients with LUTS [50].

The present review might be useful in several ways. Clinicians could use the summarised data to select the guidelines they trust the most to be used in their clinical practice. On the other hand, the limitations highlighted for the low-score guidelines might be useful to support their update. In that scenario, the use of an appraisal instrument such as the one provided by the AGREE collaboration might be fundamental for improving the overall quality of the upcoming guidelines.

5. Conclusion

Our study provided a quality ranking of the most commonly used clinical practice guidelines on male LUTS by the AGREE appraisal instrument. Although all the texts had some good aspects, we found that considerable differences were evident in the overall quality of the available guidelines, especially with regard to the methodologic issues. The text from the Australian NHMRC and AUA were those most adherent to the standards of quality suggested by the AGREE appraisal instrument. In cases where controversial recommendations were evident among the different guidelines, clinicians could use the summarised data to select the guidelines they trust the most to be used in their clinical practice. Methodologic considerations suggested the need to consider the quality of a guideline as a significant parameter to be assessed.

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Suggested links

Complete Australian NHMRC Guideline is available at http://www.nhmrc.gov.au/publications/synopses/cp42syn.htm

Complete AUA Guideline is available at http://www.auanet.org/guidelines/bph.cfm

BAUS Guideline is available at http://www.baus.org.uk

Complete EAU Guideline is available at http://www.uroweb.org/index.php?structure_id=140#EAU_guidelines_online

The English version and several validated translations of the AGREE appraisal instrument, including instruction for users, are freely available at http://www.agreecollaboration.org