Chapter 2: Methodology

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Introduction

The clinical recommendations presented in this report are based on a systematic review and synthesis of the clinical literature on current and emerging therapies for the treatment of benign prostatic hyperplasia (BPH). The methodology follows the same process used in the development of the 2003 Guideline and, as such, did not include an evaluation of the strength of the body of evidence as will be done in future Guidelines produced by the American Urological Association (AUA).

The expert Panel examined three overarching key questions for pharmacotherapeutic, surgical, and alternative medicine therapies:

1. What is the comparative efficacy and effectiveness of currently available and emerging treatments for BPH? What are the predictors of beneficial effects from treatments?
2. What are the adverse events associated with each of the included treatments and how do the adverse events compare across treatments?
3. Are there subpopulations in which the efficacy, effectiveness, and adverse event rates vary from those in general populations? Efficacy measures the extent to which an intervention produces a beneficial result under ideal conditions, such as clinical trials, whereas effectiveness measures the extent to which an intervention in ordinary conditions produces the intended result.

Study Selection and Data Abstraction

To identify relevant citations, the AUA research librarian searched Ovid Medline® from January 1, 1999 through February 28, 2008. The search period overlapped with that of the prior AUA Guideline for BPH (2003) in order to capture any citations that were in the process of being indexed for Medline prior to June 30, 1999. The search strategy included the Medical Subject Headings (MeSH) for BPH and LUTS: "Prostatic Hyperplasia"[MesH] AND Benign NOT Case reports NOT Editorials NOT Comments NOT Abstracts NOT Letters to editor NOT Author replies (Limits: Entrez Date from 2006/06/01 to 2008/03/31, Humans, Male, English); "Urinary Tract"[MeSH] AND Symptoms AND Lower NOT Case reports NOT Editorials NOT Comments NOT Abstracts NOT Letters to editor NOT Author replies (Limits: Entrez Date from 2006/06/01 to 2008/04/22, Humans, Male, English).

Study inclusion and exclusion criteria (Table 2.1) were determined by the Panel chair, co-chair, and the methodologist in order to clearly define the scope and to achieve a reproducible and explicit process. All titles and abstracts from the bibliographic searches were reviewed by the Panel chair and the co-chair and the relevant articles were selected and then the full-text reviewed for inclusion. To update the search from January 2007 through February 2008, titles, abstracts and full-text were dual reviewed by either the Panel chair or co-chair and the methodologist, and consensus was achieved at the full-text level. Descriptive data were abstracted into Microsoft Word and numeric data into Microsoft Excel by a reviewer on the methodologist's staff and checked by a second reviewer. Abstracted data included study design, setting, population characteristics (including, age, AUA-Symptom Index (SI) score, Quality of Life (QoL) question, peak urine flow [Qmax; mL/sec], and for procedural studies, prostate volume and percentage of subjects in urinary retention) and details of the intervention

(device, procedure, drug dosage and formulation). The Panel chair and co-chair selected outcomes for abstraction and synthesis that were relevant to the clinician such as urinary flow and volume outcomes, as well as outcomes important to patients, such as symptoms and QoL. Also abstracted were data on adverse events for both pharmacotherapy and procedural interventions. For the latter, intraoperative, peri-operative, as well as short-term (<30 days) and longer-term adverse events were examined.

Table 2.1 Study inclusion and exclusion criteria

Domain	Inclusion criteria	Exclusion criteria
Population	- Men ≥ 45 years of age without significant risk of non-benign prostatic hyperplasia (BPH) causes of lower urinary tract symptoms (LUTS)	- Men with polyuria, underlying neurologic disease, or prior lower urinary tract disease - Men <45 years of age with voiding dysfunction
Interventions	**Procedures** 1. Open prostatectomy: transvesical, perineal, retropubic, suprapubic 2. Laparoscopic prostatectomy 3. Transurethral procedures a. Laser coagulation b. Holmium laser resection/enucleation (HoLRP; HoLEP) c. Vaporization of tissue i.KTP green light laser photoselective vaporization of the prostate (KTP-PVP) ii.Thulium: YAG laser iii.PlasmaKinetic vaporization of the prostate (PKVP) iv. Transurethral vaporization of the prostate (TUVP)	**Procedures** 1. Water-induced thermal therapy 2. Plasmakinetic Tissue Management System 3. Interstitial laser coagulation (ILC) 4. High intensity focused ultrasound (HIFU) 5. Absolute ethanol injection 6. Botox 7. Stent placement (e.g., UroLume®) 8. Balloon dilation 9. Rotoresection of the prostate

	v.Holmium laser ablation of prostate (HoLAP) d. Transurethral resection of the prostate (TURP): monopolar, bipolar e. Transurethral incision of the prostate (TUIP) f. Transurethral radiofrequency needle ablation (TUNA) g. Thermal-based therapies i.Transurethral microwave treatments 1. CoreTherm® 2. Prostatron® 3. Targis® 4. TherMatrx® 5. Prolieve™ **Pharmacotherapy** 1. Anticholinergic agents a. Monotherapy: tolterodine b. Combination therapy with alpha blockers 2. Alpha-adrenergic blockers: alfuzosin, doxazosin, tamsulosin, terazosin, 3. 5 alpha-reductase inhibitors (5-ARIs): dutasteride, finasteride	10. Nd:YAG laser 11. Visual laser ablation of the prostate (VLAP), contact laser ablation of the prostate (CLAP) **Drugs** 1. Naftopidil (investigational) 2. Silodosin* 3. Immediate-release alfuzosin (2.5 mg TID) 4. Sustained release alfuzosin (5 mg BID) 5. Alfuzosin 15 mg QD (10 mg QD) 6. Tamsulosin oral controlled absorption system 7. Antidiuretic hormone (vasopressin)

	4. Combination therapy of alpha blockers and 5-ARIs **Complementary and Alternative Medicines (CAM)** a. Saw palmetto b. Urtica dioica c. Combination phytotherapies **Watchful waiting**	
Comparators	1. Interventions will be compared among each other, including the strategy of watchful waiting. 2. Different techniques for the same surgical procedure will be compared 3. Dose-ranging studies for pharmacotherapeutic agents and CAM	1. Studies with an included intervention compared to another intervention not included in this review
Efficacy and effectiveness outcomes	1. Morbidity 2. Mortality 3. Pressure, flow, volume a. Voided volume b. Maximum flow rate c. Post-void residual d. Prostate volume measured by transrectal ultrasonography or magnetic resonance imaging	1. Pressure, flow volume a. Percent of residual (%) b. Bladder capacity at first desire to void c. Bladder capacity at strong desire to void d. Detrusor pressure at cystometric capacity e. Bladder compliance f. Detrusor opening

	e. Transition zone prostate volume f. Detrusor pressure at maximum flow 4. Symptoms a. American Urological Association Symptom Index/International Prostate Symptom Score (AUA-SI/IPSS) (total) b. Boyarsky symptom index c. Madsen-Iversen symptom index d. Other study-specific scores 5. Quality of life, function a. Disease-specific measures i. Quality of life measure from IPSS ii. BPH impact index iii. Other custom measures b. Generic measures 6. Other: a. Prostate-specific antigen b. Prostate cancer on histology c. Resected weight	pressure g. Amplitude of overactive detrusor contractions h. Invasive pressure-flow studies i. Prostate volume assessed by digital rectal exam 2. Symptoms a. Partial symptom scores b. Symptom diaries with unvalidated scoring systems 3. Other a. Dihydrotestosterone b. Estradiol c. Blood pressure

Harms and withdrawals	1. Total withdrawals or loss to follow-up 2. Withdrawals due to adverse effects 3. Mortality 4. Surgical complications i. Intraoperative ii. Immediate postoperative complications (<24 h) iii. Short-term complications (<30 d) iv. Long-term complications 5. Secondary procedures 6. Sexual function 7. Drug adverse events a. Symptomatic hypotension; postural change, dizziness b. Sexual function c. Significant morbidity	1. Intraoperative and immediate postoperative a. Serum sodium b. Expired ethanol levels c. Irrigation fluid used
Setting	There were no restrictions based on geographic location of the study or on other study setting characteristics.	
Study design	1. Key Question 1: efficacy/ effectiveness: a. Pharmacotherapy, CAM: randomized controlled trials (RCTs) and controlled comparative trials (CCTs) b. Procedures, watchful waiting: RCTs, CCTs, observational studies	1. Case reports for both benefit and adverse events

	2. Key Question 2: Adverse events: RCTs, CCTs, observational studies 3. Key Question 3: Subpopulations: study designs as noted above Minimum duration of follow-up 1. Procedures: no restrictions 2. Pharmacotherapy and alternative and CAM: 12 weeks 3. Watchful waiting: 12 weeks	
Publication characteristics	1. Studies in which the full text is available in English	1. Studies with an English abstract but non-English full text 2. Studies not published in English 3. Studies where publication is available in abstract form only 4. Letters, commentaries, opinion pieces 5. Theses and dissertations 6. Narrative reviews

*Silodosin had been approved by the U.S. Food and Drug Administration but there were no relevant published articles in the peer-reviewed literature prior to the cut-off date for the literature search.

Data Synthesis

A qualitative analysis of the available evidence was performed on all interventions and outcomes. A narrative synthesis was presented, along with in-text tables summarizing important study and population characteristics, outcomes and adverse events. Forest plots of study effect sizes were prepared when there were at least three to four points for an intervention. Studies were stratified by

study design, comparator, follow-up interval, and intensity of intervention. Meta-analyses (quantitative synthesis) of outcomes of randomized controlled trials were planned; however, data were either sparse (i.e., there were small numbers of studies in certain categories), or not sufficiently homogeneous for the pooled effect to be meaningful.

The studies varied with respect to patient selection; randomization; blinding mechanism; run-in periods; patient demographics, comorbidities, prostate characteristics, and symptoms; drug doses; other intervention characteristics; comparators; rigor of follow-up; follow-up intervals; trial duration; timing of the trial; suspected lack of applicability to current practice in the United Sates; and techniques of outcomes measurement. These data limitations affected the quality of the materials available for review, making formal meta-analysis impractical or futile. Thus, the Panel and extractors were required to review the material in a systematic fashion rather than one with statistical rigor.

Detailed efficacy, effectiveness and complications outcomes are found in Chapter 3 of the guideline.

Guideline Development and Approvals

The treatment guideline was drafted by the Panel based on the outcomes data and tempered by the Panel's expert opinion. As in the previous Guideline, the guideline statements were graded with respect to the degree of flexibility in their application. The three levels are essentially the same as in the previous guideline. A "standard" has the least flexibility as a treatment policy; a "recommendation" has significantly more flexibility; and an "option" is even more flexible. These three levels of flexibility are defined as follows:

1. **Standard**: A guideline statement is a standard if: (1) the health outcomes of the alternative interventions are sufficiently well known to permit meaningful decisions and (2) there is virtual unanimity about which intervention is preferred.
2. **Recommendation**: A guideline statement is a recommendation if: (1) the health outcomes of the alternative intervention are sufficiently well known to permit meaningful decisions, and (2) an appreciable but not unanimous majority agrees on which intervention is preferred.
3. **Option**: A guideline statement is an option if: (1) the health outcomes of the interventions are not sufficiently well known to permit meaningful decisions, or (2) preferences are unknown or equivocal. Options can exist because of insufficient evidence or because patient preferences are divided and may/should influence choices made.

The draft was reviewed by the Panel, examined by 69 peer reviewers, and approved by the Practice Guidelines Committee and the Board of Directors of the AUA. A full description of the methodology is presented in Chapter 2 of this guideline. The Guideline is published on the AUA website (http://www.auanet.org). A version of Chapter 1 will be published in *The Journal of Urology.*

Conflict of Interest

All authors, staff and consultants self-reported potential financial conflicts of interest in accordance with AUA policy. Disclosures were made available to all Panel members prior to meetings, and at the beginning of each meeting, AUA staff reviewed the AUA conflict of interest policy, which requires recusal of individuals with potential conflict of interest.

