Chapter 3: Results of the Treatment Outcomes Analyses

Introduction

To determine the appropriateness of individual therapies, as well as to develop practice recommendations, the American Urological Association (AUA) Benign Prostatic Hyperplasia Guideline Update Panel (hereafter, the Panel) analyzed clinical management study outcomes data for the potential benefits and complications associated with the treatment of lower urinary tract symptoms (LUTS) and clinical benign prostatic hyperplasia (BPH). Outcomes data extracted from the literature were combined. Sufficient evidence was produced for the majority of treatments to allow for the calculation of probability estimates for most outcomes. These probability estimates are summarized in Simplified Outcomes Tables by treatment category (Appendix 1-C) to facilitate direct comparisons. Discussion of these data with the patient will ensure that he has the opportunity to participate actively in the shared decision-making process and that he is aware not only of the best estimates of therapeutic outcomes as presented in the outcomes tables but also of the range of uncertainty associated with these estimates (reflected in the confidence intervals when known). This chapter summarizes the differences found in treatment outcomes upon analysis of the evidence.

Types of treatment outcomes

Two types of treatment outcomes were evaluated in the development of this guideline, efficacy and adverse events. Because efficacy outcomes were measured on a scale that could change with treatment and time course while adverse events were measured as occurrences, restrictions were imposed on the data requirements and the analytic methods used for each type of outcome. Data presentation in the outcomes tables reflects these measurement differences.

Analytical distinctions are discussed in Chapter 2 and in the Methodologic Appendix (Appendix 2-C) and the outcomes table structures are summarized later in this chapter and in Appendix 3.

Efficacy Outcomes

Efficacy outcome measures evaluate the efficacy of the treatment in relieving the symptoms or sequelae of BPH. In the past, the direct outcomes (i.e., those that patients can directly perceive) of BPH therapies have been measured in a qualitative fashion (i.e., as improved, unchanged, or worsened) and/or by global subjective assessment either by physicians or patients. More recently, quantitative measurement tools have been developed and validated. Symptom scores and quality-of-life questionnaires are examples of instruments that provide an objective assessment of subjective phenomena and that allow a numerical estimate of the severity of LUTS, the bother induced, interference with daily activities, and impact on disease-specific quality of life.

Symptom Scores

A variety of symptom scores utilized to evaluate BPH therapies is discussed below. The current international standard, the AUA Symptom Index/International Prostate Symptom Score (IPSS; Appendix 1-A), is in widespread use. Early studies conducted before 1990 employed questions that were not as well validated.

Validated symptom scores

The AUA commissioned the development of a quantitative symptom severity and frequency score. The resulting instrument is a 7-question questionnaire with a response scheme from 0 to 5 for each question for a total score ranging from 0 to 35 in the order of increasing symptom severity and frequency. Symptoms of both irritative and obstructive LUTS are addressed. The AUA Symptom Index has been culturally and linguistically validated, has been translated into

many languages, and is identical to the first 7 symptom questions of the IPSS that is used worldwide.

The Danish Prostatic Symptom Score is another validated symptom scoring instrument that incorporates the concept of bother due to symptoms in addition to simple enumeration of symptom severity and frequency. The International Continence Society's questionnaire evaluates the issues surrounding incontinence as well as irritative and obstructive LUTS.

Nonvalidated symptom scores

Nonvalidated symptom scores are quantitative measurements of symptom severity and frequency that have not been properly validated and tested. Classic examples are the Boyarsky and Madsen-Iversen symptom indices[102, 103]. These instruments were used extensively in studies of LUTS and BPH management in the 1980s and early 1990s. A number of pivotal trials conducted in both the United States and Europe have reported results using these instruments.

Custom-made symptom scores

A number of investigators in the United States and Europe have developed and employed customized scoring systems using individual questions from the Boyarsky or Madsen-Iversen symptom indices. Similar to the nonvalidated symptom scores, these instruments were used extensively in studies of LUTS and BPH management (including several pivotal trials) in the 1980s and early 1990s.

Modified symptom scores

Modified symptom scores are slight modifications of recognized but not necessarily validated scoring systems. An example of a modified scoring system that has been utilized extensively in trials of the 5 alpha-reductase inhibitor finasteride is the Quasi-AUA Symptom Score.

While the AUA/IPSS is most commonly used, for reasons of completeness and because several pivotal trials used the Boyarsky and Madsen-Iversen symptom indices, or modified versions of these scores, attempts were made to mathematically adjust scores to fit the AUA/IPSS 0-to-35 point scale for this meta-analysis. Only studies that employed complete symptom scores were included; those that used partial scales (e.g., bothersomeness or irritability scales) were excluded. Studies using the AUA or IPSS with scoring based on ranges other than 0 to 35 were rescaled for consistency. (For specifics regarding the mathematical computation, see the Methodologic Appendix [Appendix 2-C].)

Peak Urinary Flow Rate

The urinary flow rate is the strength or intensity of the urinary stream over time determined by measurement of the voided volume and the voiding or micturition time. Units are expressed as mL/sec. Dividing the voided volume by the voiding or micturition time yields the average urinary flow rate (e.g., 200 mL [voided volume] divided by 20 seconds [voiding time] yields an average urinary flow rate of 10 mL/sec). The most commonly reported measure is the peak or maximal urinary flow rate (Qmax). This parameter, however, is nonspecific in that peak urinary flow rate decreases with advancing age in both sexes. In addition, a lower than expected urinary flow rate can be caused by bladder muscle weakness, subvesical or bladder outlet obstruction, or urethral stricture.

In the interpretation of the peak urinary flow rate, a minimum voided volume usually is required for the flow rate recording to be valid. A flow rate of less than 10 mL/sec is more suggestive of an obstructed state while a flow rate above 15 mL/sec is more suggestive of a nonobstructed state. Flow rates between 10 and 15 mL/sec are considered equivocal. The interpretation of this measurement is based on the correlation between free flow rates and invasive pressure-flow studies, which suggests that the probability of obstruction is very low if

the maximum flow rate is over 15 mL/sec while the probability is relatively high if the maximum flow rate is under 10 mL/sec.

Unfortunately, peak urinary flow rates correlate poorly with subjective symptoms such as severity and frequency of bother, quality of life, residual urine or prostate size. Peak urinary flow is a weak patient-oriented outcome in that the patient only marginally experiences flow-rate differences (primarily based on urination time). Although peak urinary flow rate is not particularly useful from a diagnostic point of view, it is recommended as an optional test prior to treatment discussion because the result may predict the natural history as well as the response to certain therapeutic interventions. The Panel elected to include this outcome in the analysis because repeated urinary flow-rate recordings are useful for patient follow-up and in comparing treatment outcomes among trials using the same or different treatments.

Quality-of-life Scoring Instruments

Quality-of-life scoring instruments can be classified under two broad categories: 1) generic instruments, such as the Short Form-36 Health Survey (SF-36), that do not focus on the impact of a particular disease state or a set of symptoms, and 2) disease-specific quality-of-life instruments, which measure the impact of specific diseases or sets of symptoms on the health of a given individual. Of all generic and disease-specific quality-of-life scoring instruments, the BPH Impact Index (Appendix 1-B) and the Disease Specific Quality of Life (QoL) Question (Appendix 1-A) have been validated and were used herein.

The BPH Impact Index was developed and validated by the AUA Measurement Committee with the objective of determining the degrees to which urinary problems affect various domains of health and impact the perception of health in a given individual. Three questions are scored on a scale from 0 to 3 and one question on a scale from 0 to 4, for a total score ranging from 0 to 13

in order of increasing severity[4]. The BPH Impact Index has been used in studies of medical as well as in many invasive therapies, thus providing comparative data.

A single global question complements the 7 individual symptom severity and frequency questions of the AUA/IPSS Symptom Index by adding a disease-specific quality-of-life (Disease Specific QoL Question) dimension. This question initially was recommended by the 1st International Consultation on BPH cosponsored by the World Health Organization in 1991 and its use has been confirmed at each meeting, with the latest held in the year 2000[33]. Clearly, a single question cannot possibly capture the global impact of LUTS on the quality of an individual's life; however, it has been accepted as a valuable beginning for a patient/physician conversation regarding this issue. The question simply asks, "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?" The answer scheme ranges from "delighted" to "terrible" on a score from 0 to 6, in order of increasing severity.

Efficacy Outcomes Not Analyzed

Other outcome measures used by investigators are indirect measures, that is, measures of outcomes that patients do not experience directly and that do not impact the patient perception of health. Often they are related to outcomes that affect patients or that can be used to predict outcomes, hence, the term indirect outcomes. Postvoid residual urine (PVR) volume, invasive pressure-flow studies, prostate volume, and serum prostate-specific antigen (PSA) are indirect measures that were not analyzed in detail by the Panel.

Postvoid residual urine

Although healthy men have less than 1 ounce of residual urine, the presence of PVR volume is neither specific nor diagnostic for LUTS and clinical BPH. The amount of residual urine correlates poorly with subjective parameters such as symptom severity and frequency, bother,

quality of life, peak urinary flow rate, and prostate size. No thresholds have been identified that would be predictive of long-term outcome and/or that would be pathognomonic for the diagnosis of BPH. In addition, PVR is subject to significant intraindividual variability, thus limiting its usefulness. Although recent data suggest that very high amounts of PVR may predict the natural history of the condition and outcomes such as acute urinary retention and surgery[105], the Panel elected not to formally analyze this parameter.

Invasive pressure-flow studies

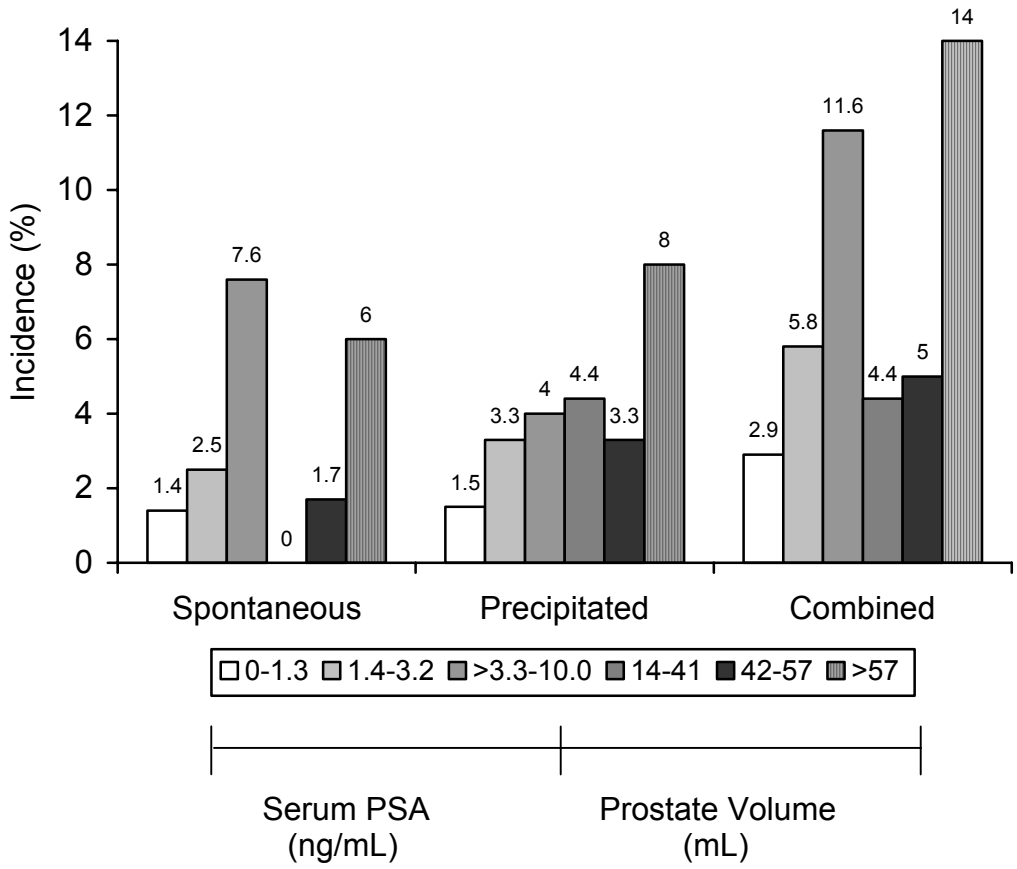
The invasive pressure-flow urodynamic study is considered to be the "gold standard" for the diagnosis of subvesical or outlet obstruction; this is the only test that can clearly differentiate between detrusor muscle weakness and obstruction at the level of the bladder neck or below. Because placement of a transurethral catheter as well as a transrectal pressure sensor is necessary, this test is less commonly conducted both in clinical practice and in trials. While the pressure-flow study has been used as an outcomes measure in efficacy trials of most treatment modalities, the Panel did not conduct a formal meta-analysis of these data because it is not generally an outcome of which the patient is aware.

Prostate volume

While in past decades an increase in prostate size was assumed to be the single most important pathophysiological entity underlying the onset of LUTS in aging men, this assertion is no longer supportable. In both a cohort of men from a community setting[106] and in patients enrolled in clinical BPH trials, there is a poor correlation between prostate size, as measured by transrectal ultrasound or magnetic resonance imaging, and other parameters, such as symptom severity, frequency, bother, quality of life, urinary flow rate, residual urine, or pressure-flow parameters.

The absence of significant correlation between prostate volume and other physiological measures of BPH at *baseline*, however, does not preclude the possibility of a significant correlation between *baseline* prostate volume and *subsequent* changes in such parameters or ultimate outcomes such as acute urinary retention and/or surgery. In the "Olmsted County Study of Urinary Symptoms in Men" the relative risk of acute urinary retention in patients with prostate volumes >30 mL was three times greater than that in patients with a prostate volume of <30 mL[107]. In the placebo-treated patients in the Proscar Long-term Efficacy and Safety Study (PLESS), the incidence of spontaneous acute urinary retention increased with increasing prostate volume divided into tertiles (14 to 41 mL; 42 to 57 mL; >57 mL) from 0% to 1.7% and 6.0%, respectively, over a 4-year period (Figure 3.1)[34]. The incidence of combined, spontaneous, and precipitated acute urinary retention increased from 4.4% to 14.0%, from the smallest to the largest volume tertile. Additional data from PLESS suggest that prostate volume at baseline also predicts the rate of progression of the disease as measured by symptom severity, bother, interference, and peak urinary flow rate[108, 109]. Lastly, prostate volume has been found to be a predictor of future prostate growth in the Olmsted County Study[110].

Figure 3.1. Spontaneous, precipitated or combined acute urinary retention incidence over 4 years in the Proscar Long-term Efficacy and Safety Study (Roehrborn, McConnell, Lieber, et al., 1999). PSA = prostate-specific antigen.



Serum prostate-specific antigen

Prostate-specific antigen is a serine protease that is produced by the glandular epithelial cells in the prostate and released into the circulation where it is measured as a serum marker for prostatic diseases. Prostate-specific antigen is neither sensitive nor specific enough to be a reliable marker for prostatic carcinoma. However, it has been shown in recent years to correlate with the size or volume of the prostate in men with BPH [109]. Since volume alterations are associated with serum level changes, baseline levels often are compared to levels measured during follow-up in treatment trials evaluating medical, minimally invasive, and surgical therapies. It also has been found to be useful as a baseline parameter to predict natural history as well as ultimate outcomes and future prostate growth[109, 19, 20, 34].

In the PLESS, the incidence of spontaneous and precipitated acute urinary retention episodes increased from 2.9% of placebo-treated patients in the lowest PSA tertile (0 to 1.3 ng/mL) to 11.6% in the highest PSA tertile (3.3 to 10.0 ng/mL) (see Figure 3.1). For the three tertiles of serum PSA, the incidence of prostate-related surgery increased from 6.2% to 14.6% and for the three prostate volume tertiles from 6.7% to 14.0%.

Many therapeutic interventions alter PSA; therefore, this outcome is measured commonly in clinical trials. A formal meta-analysis was not performed by the Panel because it is an indirect outcome measure and because there is a poor correlation with outcomes of importance to the patient. Of the medical interventions, only hormonal therapy by 5 alpha-reductase inhibition appears to induce a significant volume reduction in serum PSA over time. The minimally invasive and surgical therapeutic modalities can be differentiated by whether or not they reliably induce changes in serum PSA. Evidence, though, has shown that there is a poor correlation, at best, between the magnitude of PSA changes and symptomatic improvement, and, in fact, many

of the treatments that have been found to be effective in improving symptoms have little or no impact on serum PSA.

Adverse Events Outcomes

The adverse events outcomes include side effects and complications of treatment and disease progression (e.g., development of urinary retention). Adverse events have been grouped together since there are no consistent reporting standards or naming standards for such events. A listing of adverse event categories is presented in Appendices 2-Ea and 2-Eb.

Types of treatment interventions

The treatment interventions analyzed in the preparation of this guideline were categorized as watchful waiting, medical, minimally invasive and surgical. The following specific therapies were included:

- medical therapies — alpha-adrenergic blockers, 5 alpha-reductase inhibitors, alpha blocker/5 alpha-reductase inhibitor combinations, and placebo;
- minimally invasive therapies — transurethral microwave heat treatment, transurethral needle ablation (TUNA®; Medtronics, Minneapolis, Minnesota), stents, and sham; and
- surgical therapies — transurethral resection of the prostate (TURP), transurethral electrovaporization, transurethral incision of the prostate (TUIP), transurethral holmium laser resection/enucleation prostatectomy, transurethral laser vaporization, transurethral laser coagulation, and open prostatectomy.

Because evidence for the recommended interventions, dutasteride, CoreTherm™ (Prostalund, Lund, Sweden), and TherMatrx™ (TherMatrx, Inc., Northbrook, Illinois), became available after the formal meta-analysis was complete, outcomes estimates for these therapies are not presented in the outcomes tables. Furthermore, several therapies recognized by the Panel as emerging, that

is, having insufficient evidence to recommend use also were not included in the analysis: absolute ethanol injection, high-intensity focused ultrasound (HIFU; Ablatherm®, EDAP Technomed, France), interstitial laser coagulation (ILC; Indigo Optima Laser System, Ethicon Endo-Surgery, Cincinnati, Ohio), phytotherapies, the PlasmaKinetic™ Tissue Management System (Gyrus, Maple Grove, Minnesota), and water-induced thermotherapy (WIT; Thermoflex® System, ACMI, Southborough, Massachusetts), also were not included in the analysis.

Watchful Waiting

The expectant management of BPH is defined as "watchful waiting." Many men with BPH and LUTS do not require treatment because their symptoms are not significantly interfering with their quality of life. Moreover, progression of symptoms or deterioration of quality of life occurs in only a portion of men, and treatment intervention is still effective, even when delayed.

Watchful waiting studies, such as the Veterans Affairs Cooperative Study [30], demonstrate slight symptom improvement in up to one third of men. However, the magnitude of the symptom improvement is small. Even placebo, arguably more effective than watchful waiting, produces no more than a 1- to 2-point improvement in symptom score in men followed for 4 years [111, 17].

Acute urinary retention and invasive treatment occur in a certain subset of men followed conservatively. These complications are more frequent in men with larger prostates and higher serum PSA levels than in other men. For example, men with a PSA of 3.3 ng/mL or greater have approximately a 5% annual risk of acute urinary retention or surgery compared to less than a 2% annual risk for men with a PSA less than 1.3 ng/mL. Even in the highest risk groups, not all men develop acute urinary retention or require surgery[109, 112, 34]. Therefore, serum PSA and prostate size can be used as parameters to advise men on their overall risk but are not to be used as the sole basis for treatment recommendations.

Summary: Watchful waiting is an appropriate strategy for most men with BPH. It is the recommended management for men who do not have bothersome symptoms and have not developed complications of BPH. Serum PSA and prostate size are helpful to predict the risk of acute urinary retention and need for surgery in men managed by watchful waiting. However, neither prostate size nor serum PSA should be used as the sole determinant of the need for active therapy. The overall benefit and risks of therapy also must be considered.

Medical Therapies

The alpha blockers analyzed included alfuzosin, doxazosin, tamsulosin, and terazosin. Alfuzosin has been used extensively in Europe for several years in two dose regimens (2.5 mg thrice daily and 5 mg twice daily). A 10 mg once daily sustained-release formulation has been approved by the FDA on June 12, 2003, and the data presented are for the new preparation only. Doxazosin and terazosin typically were studied in doses titrated to response although a few studies used specific doses. Tamsulosin is available as a 0.4 mg tablet. While 0.4 mg once a day is the most common prescribed dose, some patients receive 0.4 mg twice a day for a total daily dose of 0.8 mg. For each drug, study outcomes were combined regardless of daily dose.

One hormonal therapy, the 5 alpha-reductase inhibitor finasteride, was analyzed in detail alone and in combination with the alpha blockers alfuzosin, doxazosin, and terazosin. No studies were found that used tamsulosin in combination with finasteride.

The new 5 alpha-reductase enzyme inhibitor dutasteride has been studied in three placebo-controlled trials of 2-year duration in more than 4,000 men with LUTS and BPH. In general, efficacy and safety are similar to that of finasteride, and specific data are given in the individual section discussing outcomes by intervention.

After reviewing the evidence supporting the use of phytotherapies, the Panel decided that lack of clinical trials and product formulation standardization precluded inclusion of these therapies in the outcomes tables.

Minimally Invasive Therapies

Evidence supporting the efficacy and safety of the transurethral microwave heat treatment devices (Prostatron® [Prostasoft®, 2.0 and 2.5; Urologix, Minneapolis, Minnesota], Targis® [Urologix, Minneapolis, Minnesota], CoreTherm and TherMatrx) with their various software modifications was reviewed. Data on the use of TherMatrx and CoreTherm were published after the cutoff for analysis and therefore were reviewed by the Panel but not included in the outcomes tables. Prostatron and Targis are considered high-energy devices with an output of 60 watts or greater featuring water cooling; CoreTherm is a high-energy device with no water cooling; and TherMatrx uses low energy (6 watts) with no water cooling. Some studies used sham controls while others used TURP controls and thus are presented in separate sections of the outcomes tables. Studies evaluating TUNA and stents also were analyzed.

Study outcomes for a number of other minimally invasive therapies that are either currently marketed or under investigation were not included in the outcomes tables due either to the general unavailability of the evidence or to the lack of sufficient credible data to provide outcome estimates. Water-induced thermal therapy is a type of transurethral, catheter-based heat therapy that utilizes warm circulating water to heat the prostatic tissue. Interstitial laser coagulation of the prostate by the transurethral route has been attempted using several laser sources and delivery devices. In the United States (and worldwide), a diode laser device, the Indigo 830e (Ethicon Endo-Surgery, Cincinnati, Ohio), has been evaluated [55, 56]. At present, a multicenter trial is under way using this technology in men with BPH. High-intensity focused ultrasound uses timed bursts of ultrasound to create coagulation necrosis in a targeted area of

tissue. Frequencies can range as high as 10 MHz depending on the device, heating tissue to 70°C or higher. High-intensity focused ultrasound therapy is still investigational. Using plasma energy in a saline environment to achieve tissue vaporization with minimal thermal spread and enhanced hemostasis, the PlasmaKinetic Tissue Management System has the potential to increase safety by eliminating potential hyponatremia and TURP syndrome. The Panel believed that there was insufficient data to consider any of these treatments as recommended options at this time. Additional multicenter trials with independent data analysis are required.

Summary: In preliminary studies, WIT, ILC, HIFU, and the PlasmaKinetic Tissue Management System, newer forms of heat-based, transurethral therapy, produce symptom score and flow-rate improvements similar to other minimally invasive treatments. Currently, there is insufficient evidence to consider these interventions as recommended treatment options.

Surgical Therapies

Surgical therapies have been the reference standards for BPH treatment. Transurethral resection of the prostate is the control therapy for most studies of nonmedical therapies. Surgical therapies evaluated in this analysis include TURP, transurethral electrovaporization, transurethral holmium laser resection/enucleation prostatectomy, transurethral laser vaporization, transurethral laser coagulation, TUIP, and open prostatectomy. In addition, watchful waiting is included in this category in the outcomes tables because it has been compared most often to TURP.

Outcomes Analyzed

The remainder of this chapter describes the results of the Panel's analysis of the literature and provides estimates of the outcomes of the alternative therapies for BPH. The presentation is divided into sections based on outcome type: efficacy outcomes, analyzed with respect to changes in measurement scales, and adverse event outcomes, analyzed with regard to probability

of occurrence. The specific efficacy and adverse events outcomes analyzed for the three therapeutic interventions follow:

- Efficacy outcomes:

  AUA Symptom Index

  Peak Urinary Flow Rate

  BPH Impact Index (except for surgical therapies)

  Disease Specific QoL Question

- Adverse event outcomes of medical therapies:

  Acute urinary retention, asthenia, breast, cardiovascular adverse events, dizziness, gastrointestinal disorders/events, headache, hypotension, respiratory/nasal congestion, and sexual dysfunction

- Adverse event outcomes of invasive therapies:

  Short term: Aborted procedure/device failures, acute urinary retention, intraoperative complications, cardiovascular adverse events, hematuria, transfusion, infections/urinary tract infections (UTIs), and irritative voiding symptoms

  Long term: Urinary incontinence, secondary procedures, bladder neck contracture/urethral stricture, and sexual dysfunction

In each of the following two chapter sections, a brief description of the analytic approach is presented. Next, the key outcomes are discussed with reference to graphs which correspond to the relevant sections of the Detailed Outcomes Tables (Appendix 3). Note that the Simplified Outcomes Tables in Appendix 1-C represent a subset of the full analytic results; detailed findings

are provided in Appendix 3. Evidence published after the cutoff year (2000) was not included in the outcomes tables.

Efficacy outcomes — results of analyses

Each efficacy outcome has been analyzed with regard to expected change after treatment with either an active or control therapy. Changes were estimated for three different time periods: 3 to 9 months (6-month data used preferentially), 10 to 16 months (1-year data used preferentially), and >16 months (2-year data used preferentially).

Efficacy outcomes were estimated using two different techniques:

- The first technique used a single-arm weighted average (SAWA) of all study arms from studies evaluating a particular treatment or control. Study results were weighted by study size on the average. Single-arm weighted average was determined instead of using meta-analysis because appropriate variance data were lacking in most studies.
- A second technique was used when randomized, controlled trials (RCTs) with variance of change data were available. In those cases, RCTs were meta-analyzed to estimate the difference between the active treatment and the control. To estimate the treatment effect, the SAWA estimate for the control was added to this difference.

The Detailed Outcomes Tables (see Appendix 3) provide the results of the second method when available; otherwise, they present SAWA estimates. In either case, the result shown is the total effect expected from the treatment (i.e., the combined treatment and placebo effect). Given the use of SAWA estimates, no confidence intervals could be computed for any of the efficacy estimates.

Efficacy outcomes tables for all therapies for which data were analyzed are presented in Appendix 1-C (simplified data) and Appendix 3 (detailed data). A discussion of each outcome

for the therapeutic interventions analyzed, that is, medical therapies, minimally invasive therapies and surgical therapies, follows. At the end of each outcome discussion, a bar graph corresponding to the relevant portions of the outcomes tables in Appendix 1-C is included for reference. For each efficacy outcome, the discussion content is organized consistently:

- introduction
- discussion of the analysis of RCT data (if available)
- discussion of SAWA data (if appropriate)
- summary statement
- graph comparing outcomes across therapies (if appropriate)

Medical Therapies

AUA Symptom Index

Alpha blockers

Alfuzosin, doxazosin, tamsulosin and terazosin produce significant improvement in LUTS compared to placebo (Figure 3.2). Because of the significant variation in the duration of randomized, clinical trials, the alpha-blocker data were pooled into two groups: studies of 3- to 9-month duration and studies of 10- to 16-month duration. No longer term data were available for analysis. The placebo data represent a SAWA of 5960 patients in the 3- to 9-month group and 6679 patients in the 10- to 16-month group. This analysis demonstrates a symptom score improvement of approximately 2 to 2.5 points from placebo (see Figure 3.2).

In general, doxazosin trials have used a titration-to-response scheme. Patients usually are titrated to a dose of 4 or 8 mg, with the median dose in the analyzed trials being between 6 and 7 mg per day. Similarly, most terazosin studies used a titration to response design, with doses generally ranging between 5 and 10 mg. The median terazosin dose in the reported studies is between 6 and 7 mg. In the reported tamsulosin studies, patients were treated at a dose of either

0.4 or 0.8 mg. The RCT net improvement for tamsulosin 0.4 mg was -1.92 compared to -3.12 for the 0.8 mg dose. Data for all dosages were combined for presentation in the tables and graphs. In general, the 10- to 16-month data report demonstrates similar symptom score improvement compared to the 3- to 9-month trials.

The Panel performed SAWA of all the available alpha-blocker study arms. In general, this analytical approach yielded symptom score improvements of 5 to 7 points (see Appendix 1-C; Appendix 3). Although the SAWA yields a greater magnitude of symptom score improvement, the Panel feels that the RCT net improvement (as illustrated in Figure 3.2, net is added to placebo) is a more precise depiction of expected outcomes.

A comparative analysis of alpha blockers revealed minimal differences in symptom improvement. At 3 to 9 months, alfuzosin is slightly less effective than terazosin ($p < .10$). There were no differences among the other three agents. However, the 0.4 mg dose of tamsulosin appears to be slightly less effective than doxazosin or terazosin titrated to response. In other words, some patients require two 0.4 mg tablets of tamsulosin to achieve the maximal responses seen with doxazosin and terazosin. Superior symptom improvement most likely is related to dosing and not to any inherent pharmacologic advantage of the agent itself.

Summary: Alpha blockers produce a significant symptom improvement that the average patient will appreciate as a moderate improvement The minor differences in efficacy noted are not statistically or clinically significant. It does appear that some patients treated with tamsulosin require the 0.8 mg dose to achieve the results obtained with doxazosin and terazosin titrated to response. This presents a cost-effectiveness problem for tamsulosin (which is not available generically) because the 0.8 mg daily dose requires two tablets and thus twice the expense of the

lower dose while the terazosin and doxazosin recommended dosages are available as one unit generic products and priced accordingly.

5 Alpha-reductase inhibitors

Finasteride was the first 5 alpha-reductase inhibitor approved by the FDA. Meta-analysis of RCT data shows that finasteride produces an additional 1.00 point reduction at 1 year over the 2.44-point reduction produced with placebo (Figure 3.2). The Panel's combined analysis found that the incremental effect over placebo was equal to approximately one half of the incremental effect of alpha blockers. The net efficacy of finasteride compared to placebo is superior for patients with a prostate volume greater than 30 mL and a serum PSA greater than 1.3 ng/mL. However, the absolute magnitude of symptom improvement for patients who respond to finasteride is not statistically superior in men with larger prostates or higher PSA levels. In these patients there seems to be less of a placebo effect, though, producing a more significant net benefit. The symptom improvement seen with finasteride has been demonstrated to be durable in a randomized trial setting for up to 4 years and an open-label setting for up to 8 years[34, 113, 111, 114].

Dutasteride is the second 5 alpha-reductase inhibitor approved by the FDA for use in men with LUTS and BPH. Three phase 3 studies, which included more than 4000 men with BPH treated with either dutasteride or placebo, found a net difference of 2 points on the AUA Symptom Index favoring dutasteride[50]. The reduction in risk for acute urinary retention and surgery was 57% and 48%, respectively, which is comparable to the effect of finasteride. The adverse-event profile of dutasteride is also very similar to finasteride, with erectile dysfunction, loss of libido, and decreased ejaculate volume being the most common adverse events. Because key evidence supporting the use of dutasteride became available after the outcomes analysis was complete, it was not presented as outcomes estimates in the outcomes tables.

Summary: Finasteride produces a statistically significant improvement in symptom score that the average patient will appreciate as a mild improvement. The symptom improvement is durable for up to 6 years in patients who are maintained on therapy. Finasteride is less effective than alpha blocker therapy in alleviating LUTS. Although the net benefit of finasteride (placebo versus active treatment) is superior for men with larger prostates (and higher PSA levels), the absolute level of symptom improvement is not significantly different. Preliminary analysis suggests that dutasteride has similar efficacy and safety.

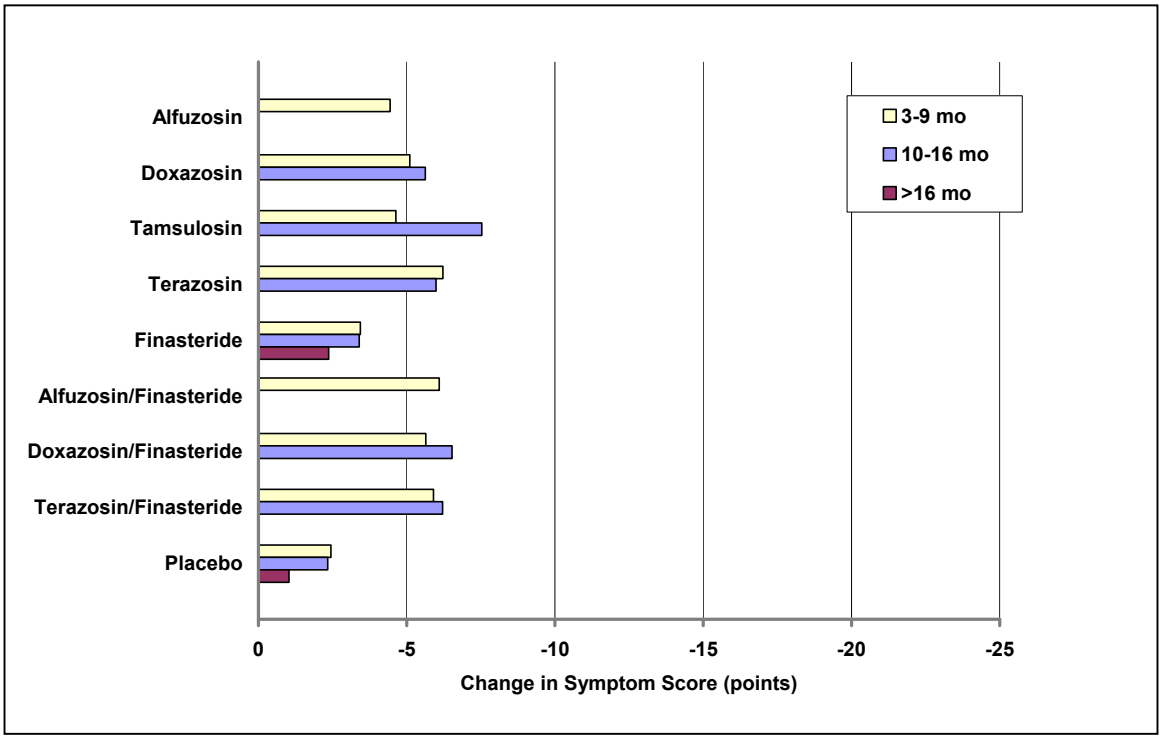
Combination therapy

It is reasonable to assume that the combination of a 5 alpha-reductase inhibitor such as finasteride and an alpha blocker would produce symptom improvement superior to monotherapy with either class of drug. However, the Panel's analysis of studies of 1-year duration or less demonstrated no benefit of combination therapy over alpha-blocker monotherapy (Figure 3.2). This observation is consistent with the results of two RCTs in which combination therapy was compared directly to an alpha blocker and finasteride[53, 115, 52].

The Medical Therapy of Prostatic Symptoms (MTOPS) study of five-year duration compared combination therapy, doxazosin, finasteride and placebo. Results that only recently became available suggest that long-term combination therapy is significantly superior to either single therapies in preventing the progression of LUTS and BPH as defined by either one of the following events: symptom worsening, acute urinary retention, UTI, incontinence, or need for surgery[51]. In addition, combination therapy provided superior improvement in symptoms and urinary flow rate compared to single therapies. Because key evidence supporting the use of dutasteride became available after the outcomes analysis was complete, it was not presented as outcomes estimates in the outcomes tables.

Summary: While in previous studies of 1-year duration or less, combination therapy proved equal to alpha-blocker therapy but superior to 5 alpha-reductase therapy. MTOPS demonstrated that in the long term, combination therapy is superior to either alpha-blocker or 5 alpha-reductase therapy in preventing progression and improving symptoms. Issues such as cost-effectiveness and continued combination therapy versus selective discontinuation require further analyses of the MTOPS data and/or additional studies.

Figure 3.2. AUA Symptom Index score improvements for medical therapies by duration of follow-up. Missing bars indicate that data were not available.



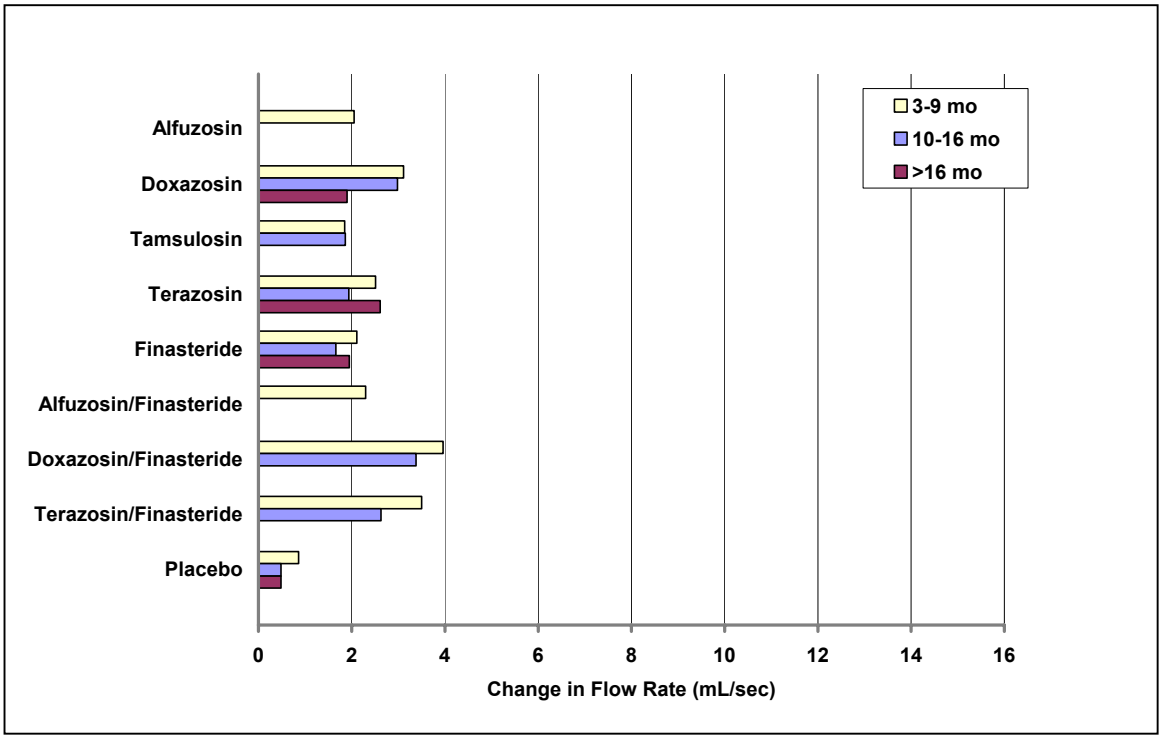
Peak Urinary Flow Rate

Increases in peak urinary flow rate are most likely due to treatment-related decreases in outflow resistance. However, improvement in detrusor function may contribute. In the SAWA of placebo arms, the peak urinary flow rate increased approximately 0.5 mL at 12 months or longer (Figure 3.3). Men with larger prostates (and higher serum PSA levels) have less of a placebo response[111]. As a group, alpha blockers produce flow rate improvement of approximately 2 to 3 mL/sec. In the comparative analysis of the 3- to 9- month data, doxazosin was more effective than tamsulosin ($p < .05$). Doxazosin also tended to be more effective than alfuzosin ($p < .10$). In the studies conducted for at least 12 months, though, there were no statistically significant differences found between doxazosin, tamsulosin and terazosin. There is a slight trend for combination therapy to be more effective than monotherapy in flow-rate improvement. Long-

term studies with doxazosin, terazosin and finasteride demonstrate maintenance of flow-rate improvement in the range of 2.0 to 2.5 mL/sec. Alpha blockers do not appear to be superior to finasteride in producing flow rate improvement. Flow-rate improvement with dutasteride is comparable to finasteride.

Summary: Alpha blockers, 5 alpha-reductase inhibitors, and combination therapy produce improvements in peak urinary flow rate that are sustained over time. In the available studies, doxazosin appears to be more effective than tamsulosin and alfuzosin (Figure 3.3). Combination therapy of finasteride with doxazosin or terazosin appears to be slightly more effective than monotherapy. The results of MTOPS corroborate this finding, at least in the case of finasteride and doxazosin combination[51].

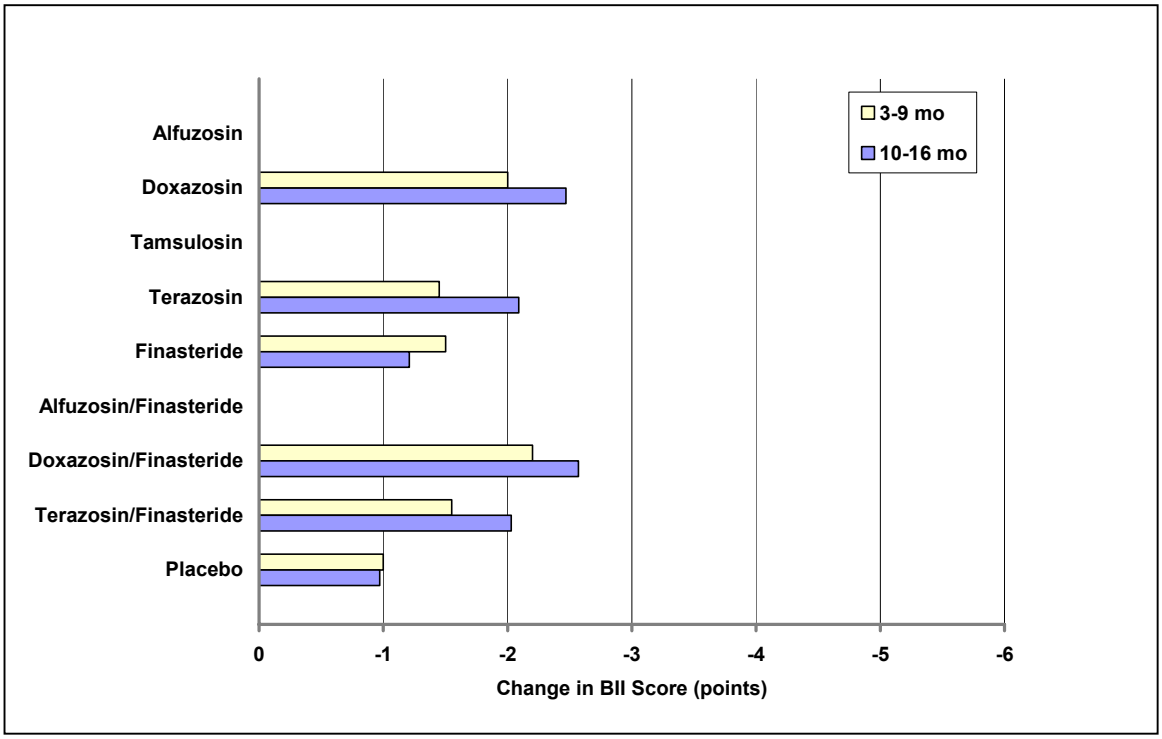
Figure 3.3. Peak urinary flow-rate improvements for medical therapies by duration of follow-up. Missing bars indicate that data were not available.



BPH Impact Index

Few studies report the effect of medical therapy on the BPH Impact Index. The SAWA of placebo arms demonstrated a decrease of approximately 1 point in the BPH Impact Index overall score (Figure 3.4), which ranges from 0 to 13. Doxazosin, terazosin, finasteride and combination therapy studies report roughly equivalent benefits in the BPH Impact Index, although the trend was for finasteride to be slightly less beneficial than alpha blockers. The effect of dutasteride appears to be similar to that seen with finasteride.

Figure 3.4. BPH Impact Index (BII) score improvements for medical therapies by duration of follow-up. Missing bars indicate that data were not available.

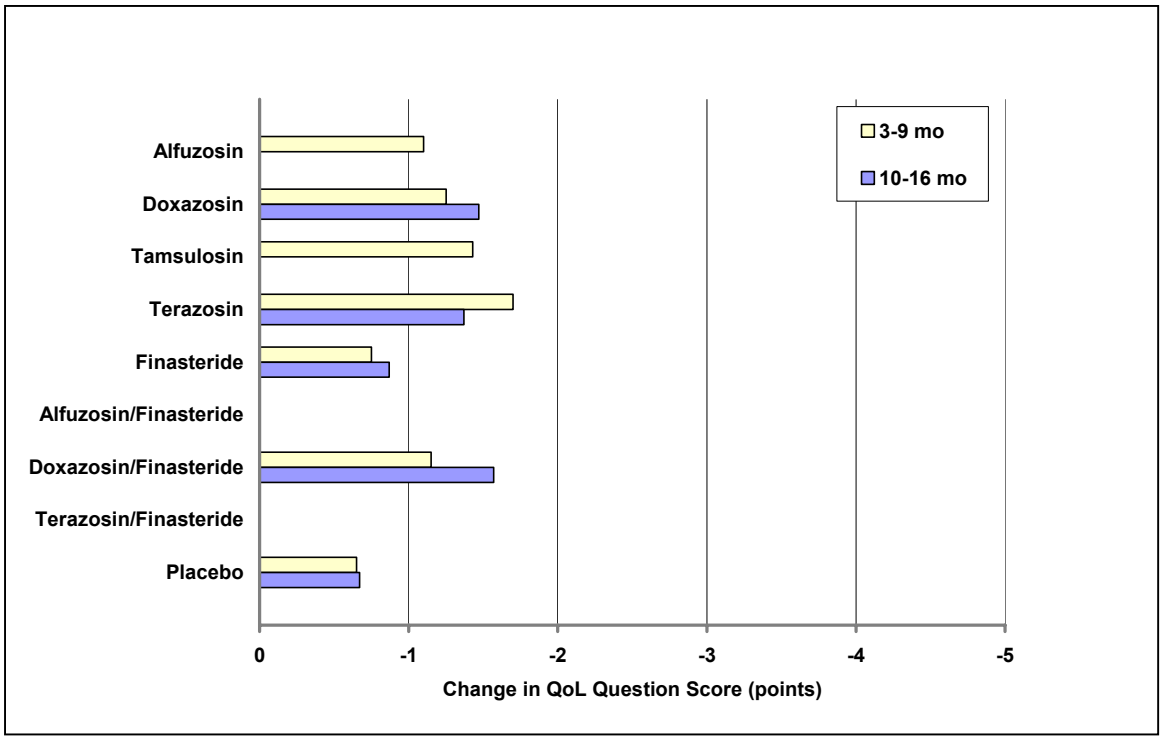


Disease Specific Quality of Life Question

All four alpha blockers reviewed demonstrated QoL Question score improvements compared to placebo (Figure 3.5). The SAWA of placebo treatment yields a decrease (improvement) in QoL Question score of 0.65. In general, alpha blockers demonstrated QoL Question score improvement roughly twice that of placebo. Although the QoL Question score improvement in the reported finasteride studies was superior to placebo within those studies, in the combined analysis, finasteride was not demonstratively better than placebo. Finasteride was less effective than alpha blockers in improved quality of life. The one study for which combination therapy data were available (doxazosin plus finasteride) reported QoL Question score improvement similar to alpha-blocker monotherapy. The effect of dutasteride appears to be similar to that seen with finasteride.

Summary: Medical therapy improves quality of life, with alpha blockers being significantly more effective than 5 alpha-reductase inhibitors. There is no advantage to combination therapy in improving QoL Question score. It is important to note, however, that the QoL Question score does not capture all quality-of-life issues related to BPH (e.g., urinary retention and need for surgery).

Figure 3.5. Disease Specific Quality of Life (QoL) Question score improvements for medical therapies by duration of follow-up. Missing bars indicate that data were not available.



Minimally Invasive Therapies

The following minimally invasive therapies were included in the analysis:

- the transurethral microwave heat treatment devices, Prostatron (Prostasoft Versions 2.0 and 2.5) and Targis; both are transurethral microwave thermotherapies (TUMT®);
- TUNA based on radiofrequency energy;

- UroLume® Endoprosthesis Stent (American Medical Systems, Minnetonka, Minnesota); UroLume stent is included with this group of interventions because it is minimally invasive even though it is only recommended for a subset of the target patient group.

Data for CoreTherm and TherMatrx became available after the data cutoff date and are therefore not included in the analysis.

AUA Symptom Index

The majority of the TUMT-controlled studies compared active intervention with sham treatment, where the microwave device is inserted into the urethra but only warmed to body temperature. The remainder compared TUMT to TURP. The minimally invasive treatment data were compared to a pooled analysis of all sham control arms, as well as a pooled analysis of all TURP control arms.

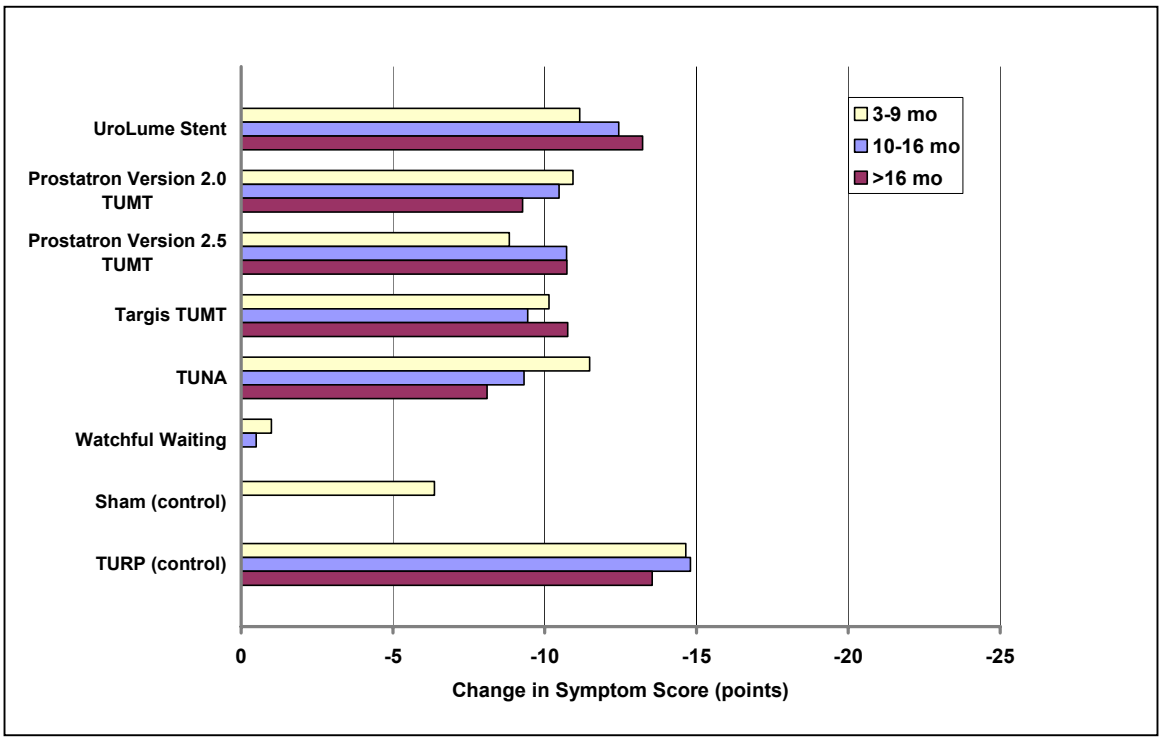
In general, TUMT reduces the symptom score by approximately 9 to 11 points (Figure 3.6). This improvement is clearly superior to sham treatment, which produces an average 6-point reduction in symptom score. TUMT is less effective than TURP in reducing symptoms but more effective than any form of medical therapy (Figure 3.2). Outcomes reported with the use of TUMT appear to be durable out to 12 to 24 months, although the long-term retreatment rates are still uncertain. Although TUNA appears slightly less effective in reducing symptoms than TUMT, the confidence intervals between TUNA and all forms of TUMT overlap and the differences do not reach statistical significance. The UroLume stent is reserved for a subset of patients but appears to have results similar to the other minimally invasive therapies.

In a randomized, multicenter, TURP-comparison trial, the CoreTherm device provided similar symptom and flow-rate improvement[59]. When compared to sham-treated patients in a randomized, multicenter trial, the TherMatrx device provided superior symptom improvement at 3 months postprocedure. Twelve months after study initiation, significant improvements in

symptoms and flow rate were measured both in patients originally treated with TherMatrx and in sham-treated patients who were offered open-label, active therapy after the initial 3-month trial period[60].

Summary: All forms of minimally invasive therapies produce significant symptom score improvement. In general, minimally invasive therapies produce greater symptom score improvements than medical therapies but lesser symptom score improvements than surgical therapies. Transurethral microwave thermotherapies and TUNA appear to be effective in the range of 12 to 24 months, but longer term effectiveness and retreatment rates have not been clearly defined.

Figure 3.6. AUA Symptom Index score improvements for minimally invasive therapies by duration of follow-up. Missing bars indicate that data were not available.



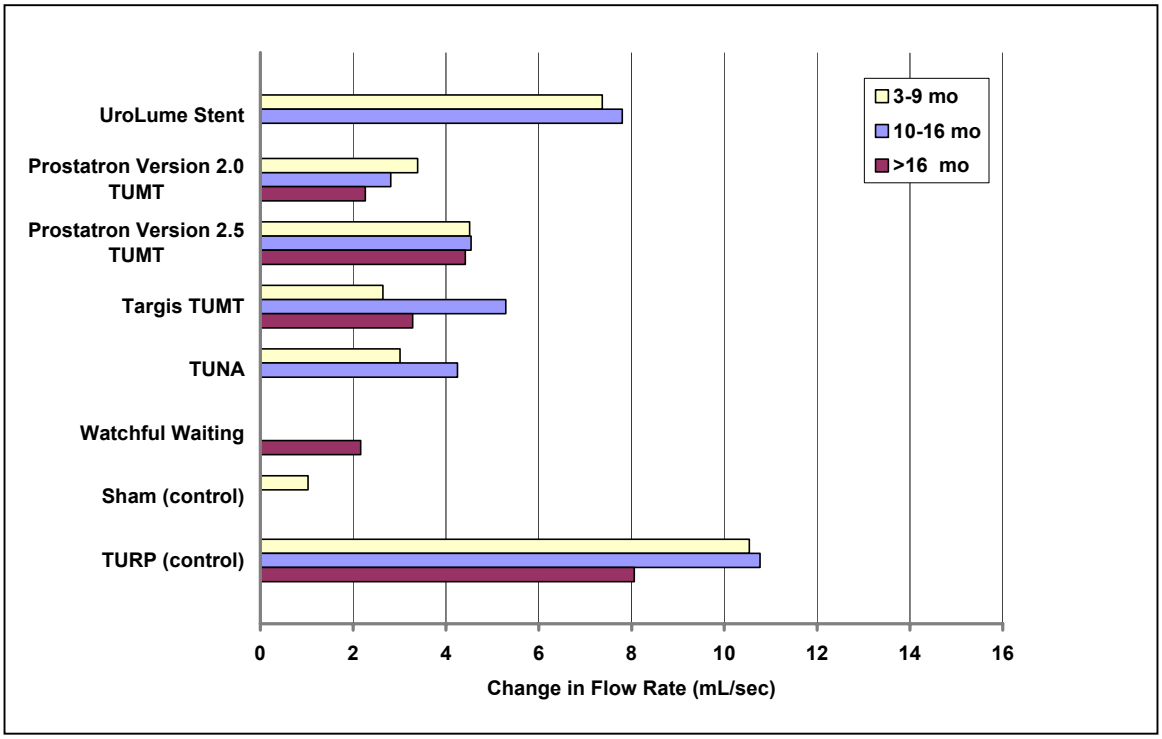
Peak Urinary Flow Rate

The average peak urinary flow-rate improvement of sham therapy is approximately 1 mL/sec (Figure 3.7). Given the minimal flow-rate improvement in watchful waiting and sham (which is more likely due to regression to the mean than improvement being part of the natural history of BPH), there appears to be little placebo effect of interventional therapy on the peak urinary flow rate. In general, TUMT and TUNA produce urinary flow-rate improvements between 3 and 5 mL/sec. The confidence intervals for TUMT peak urinary flow rates overlap, suggesting there is no significant difference between these interventions. Outcomes with the use of TUIP, TURP, open surgery, and other ablative techniques are clearly superior to TUMT and TUNA. On average, the flow-rate improvement for TUMT and TUNA is roughly half that seen with more invasive therapies.

The CoreTherm device provided flow-rate improvement comparable to the TURP-treated patients in a randomized trial while the TherMatrx device did not provide flow-rate improvement superior to placebo in a randomized trial.

Summary: Transurethral microwave thermotherapies and TUNA improve the peak urinary flow rate from baseline compared to a sham intervention. These minimally invasive approaches are more effective than medical therapy but generally less effective than surgery.

Figure 3.7. Peak urinary flow-rate improvements for minimally invasive therapies by duration of follow-up. Missing bars indicate that data were not available.



BPH Impact Index

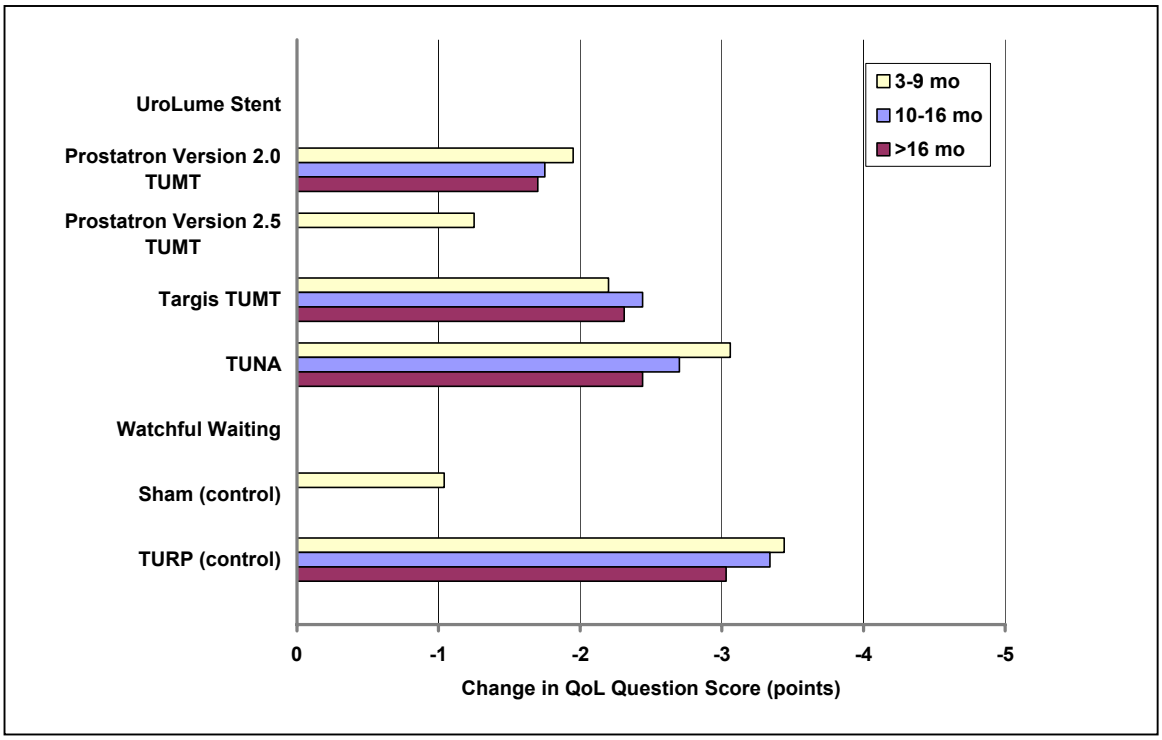
The BPH Impact Index was not used in any controlled trials of minimally invasive therapies. It was included in a few case series only. The only data available show roughly a 5-point drop for TUNA that extends to the 12- to 16-month time frame.

Disease Specific Quality of Life Question

Few studies monitored QoL Question score improvements. Sham (control) treatment produces, on average, a 1-point drop in the QoL Question score (Figure 3.8). Transurethral microwave thermotherapies and TUNA produce a 1- to 3-point improvement in the QoL Question score. There were insufficient data for comparative analysis between minimally invasive treatments.

Summary: Transurethral microwave thermotherapies and TUNA produce improvements in QoL Question scores that are superior to sham treatment. Quality of Life Question score data were not available for stents in any study.

Figure 3.8 Disease Specific Quality of Life (QoL) Question score improvements for minimally invasive therapies by duration of follow-up. Missing bars indicate that data were not available.



Surgical Therapies

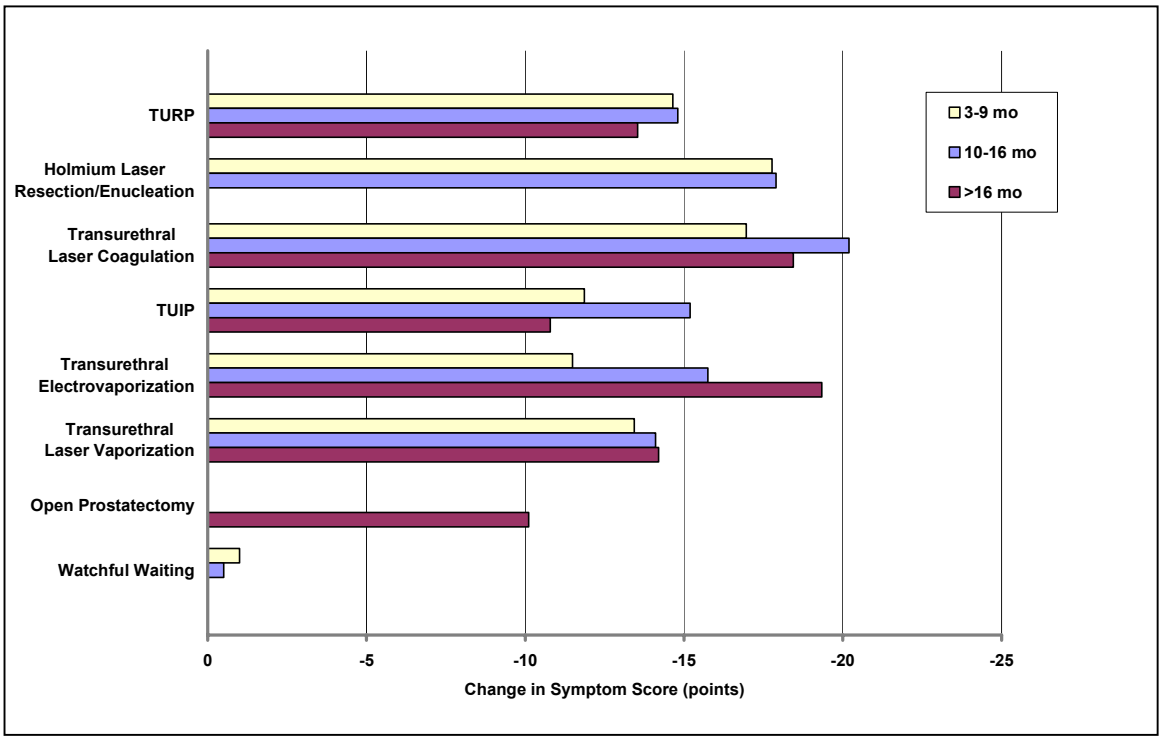
Symptom score and peak-flow data were available for all surgical treatments and QoL Question scores were available for most treatments. The BPH Impact Index scores were not recorded for any surgical trials. Transurethral resection of the prostate is considered the standard of comparison in all surgical controlled trials and is still considered by many to be the "gold standard" treatment. Other surgical procedures appear to offer similar results in this analysis.

AUA Symptom Index

Outcomes of studies evaluating symptom improvement with TURP over 3 to 9 months and >10 months were similar, showing reductions in symptom scores of approximately 15 points (Figure 3.9). Laser coagulation, with a ≥ 17 point score reduction, was superior to all other surgical treatments in studies of 3- to 16-month duration. Data from RCTs are only available, however, for laser coagulation, and the difference from TURP did not reach statistical significance.

Summary: All surgical therapies produce major improvements in the AUA Symptom Index score with holmium laser resection/enucleation and laser coagulation producing improvements of the greatest magnitude at 1 year.

Figure 3.9. AUA Symptom Index score improvements for surgical therapies by duration of follow-up. Missing bars indicate that data were not available.

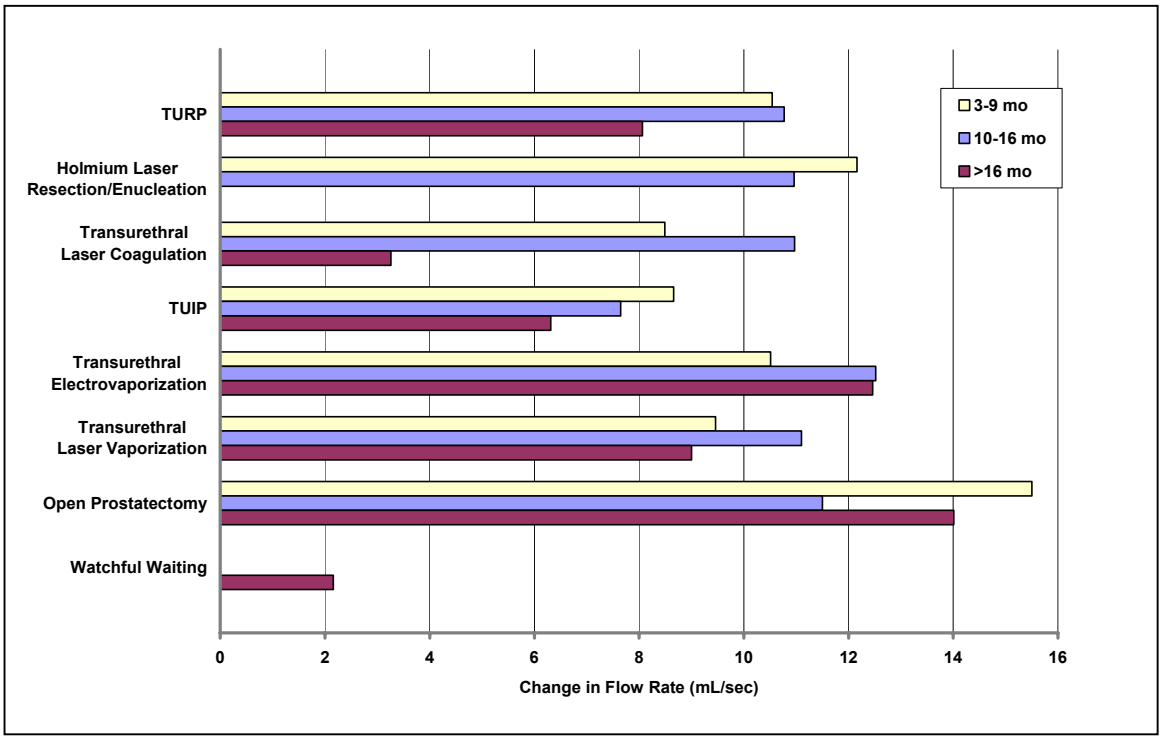


Peak Urinary Flow Rate

Overall, within the initial 3- to 9-month postsurgical period, peak urinary flow rate improved by at least 7.5 mL/sec with any surgical treatment modality (Figure 3.10). From 10 months forward, though, this improvement decreases in magnitude with some treatments but surprisingly increases in some. Transurethral resection of the prostate, holmium laser resection/enucleation and open prostatectomy have the best outcomes over the 3-monthe through >16-month study periods, with the lowest mean flow rate of 8 mL/sec reported with TURP >16 months postsurgery.

Summary: Outcomes of RCTs, where available, yielded no statistically significant differences among surgical therapies. All surgical therapies provided similar outcomes over time with regard to peak flow.

Figure 3.10. Peak urinary flow-rate improvements for surgical therapies by duration of follow-up. Missing bars indicate that data were not available.

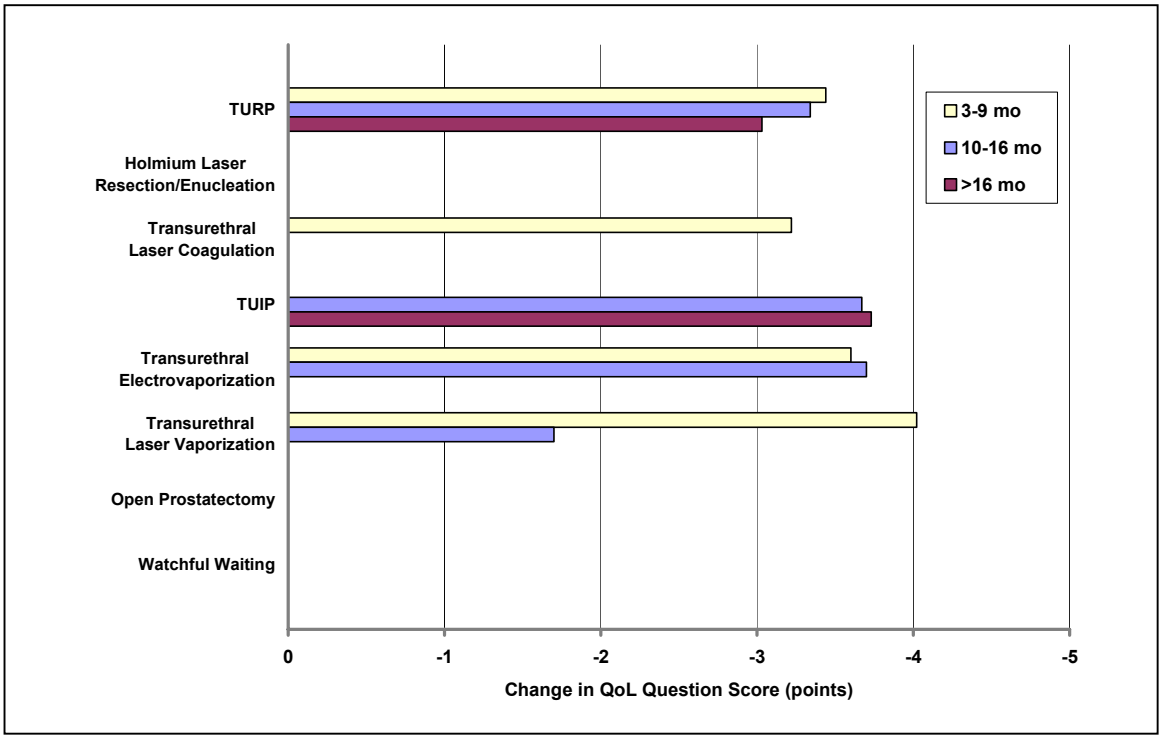


Disease Specific Quality of Life Question

Few data are available regarding the impact of surgical therapies on the QoL Question score in patients with BPH. Based on four groups comprising 136 patients, TURP has been shown to induce an improvement in the QoL Question score by approximately 3 points as early as 3 months postprocedure (Figure 3.11). This improvement persists in studies of >16 months duration. Similarly, other surgical treatments for which scores are available, for example, transurethral laser coagulation, transurethral electrovaporization and transurethral laser vaporization induce QoL Question score improvements by approximately 3 to 4 points at 3 to 9 months. Generally, improvements are maintained for the 10- to 16-month time frame. Data from studies of 10- to >16-month duration show TUIP associated with similar QoL Question score improvements.

Summary: Although data are limited, the QoL Question score improved by at least 3 points postsurgery, regardless of the procedure type. These improvements also were shown in the mid- and long-term time periods where data were available.

Figure 3.11. Disease Specific Quality of Life (QoL) Question score improvements for surgical therapies by duration of follow-up. Missing bars indicate that data were not available.



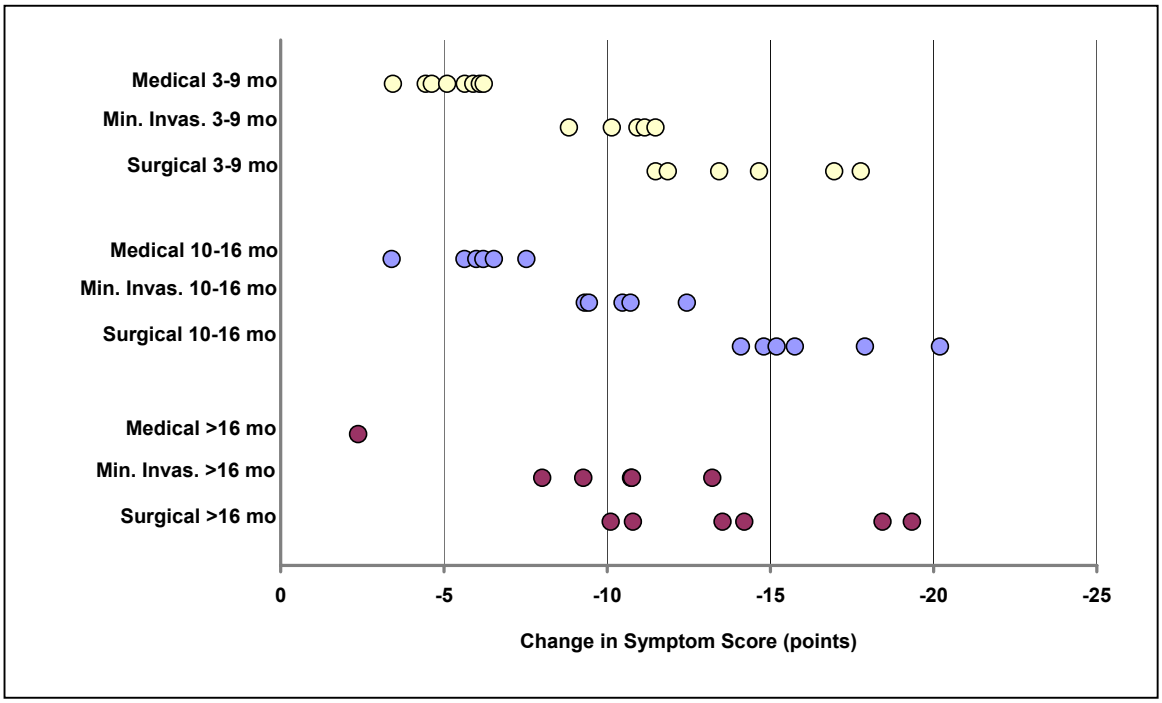
Comparison of Efficacy Outcomes by Treatment Intervention

Because the patient's initial decision usually concerns the selection of a treatment intervention, graphs have been constructed to present the range of efficacy outcomes among the three classes of interventions: medical, minimally invasive, and surgical. Each symbol represents the median estimate for a treatment in the group (as shown in the Simplified Outcomes Tables, Appendix 1-C). Confidence intervals are not presented because meaningful confidence intervals cannot be computed for these efficacy outcomes. Thus, the range of values should not be interpreted as bounding the value for the class. Because there are no BPH Impact Index data for surgical therapies, no comparison graphs for that outcome are presented here. The comparisons implied by these graphs and the discussion below should be viewed with caution.

True head-to-head comparisons have not been performed, and the patients selected for the varying treatment classes almost certainly vary significantly.

Surgical therapies clearly provide the best symptom score improvement of the three groups of interventions, with maximum improvement of approximately four times that of the average medical therapies (Figure 3.12). In addition, the effects on symptom improvement are consistently better than the effects of other interventions throughout the follow-up periods. Minimally invasive therapies also produce greater symptom relief than medical therapies. Although medical therapy did produce a consistent symptom relief up to a maximum change of 6 points, it had the poorest efficacy through the 16-month follow-up period.

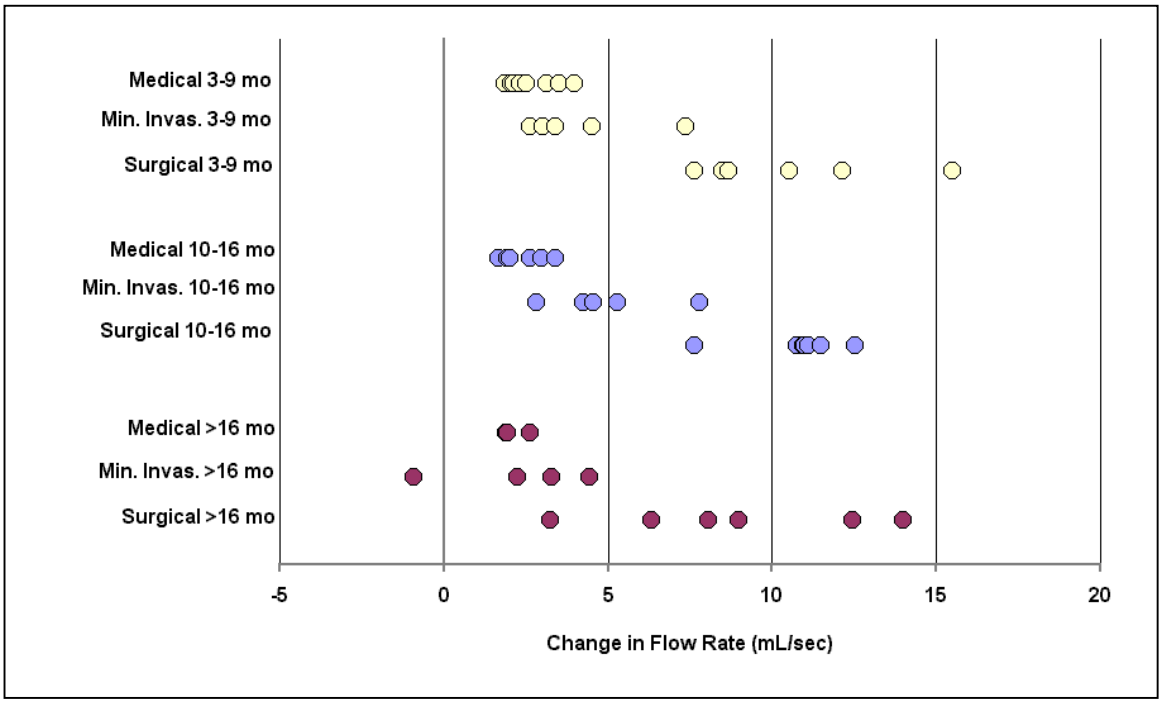
Figure 3.12. Range of AUA Symptom Index score improvements by treatment intervention and duration of follow-up.



Like the comparisons of other efficacy outcomes, it appears that the surgical therapies also provide the best estimated changes in peak urinary flow rate of the three classes of interventions

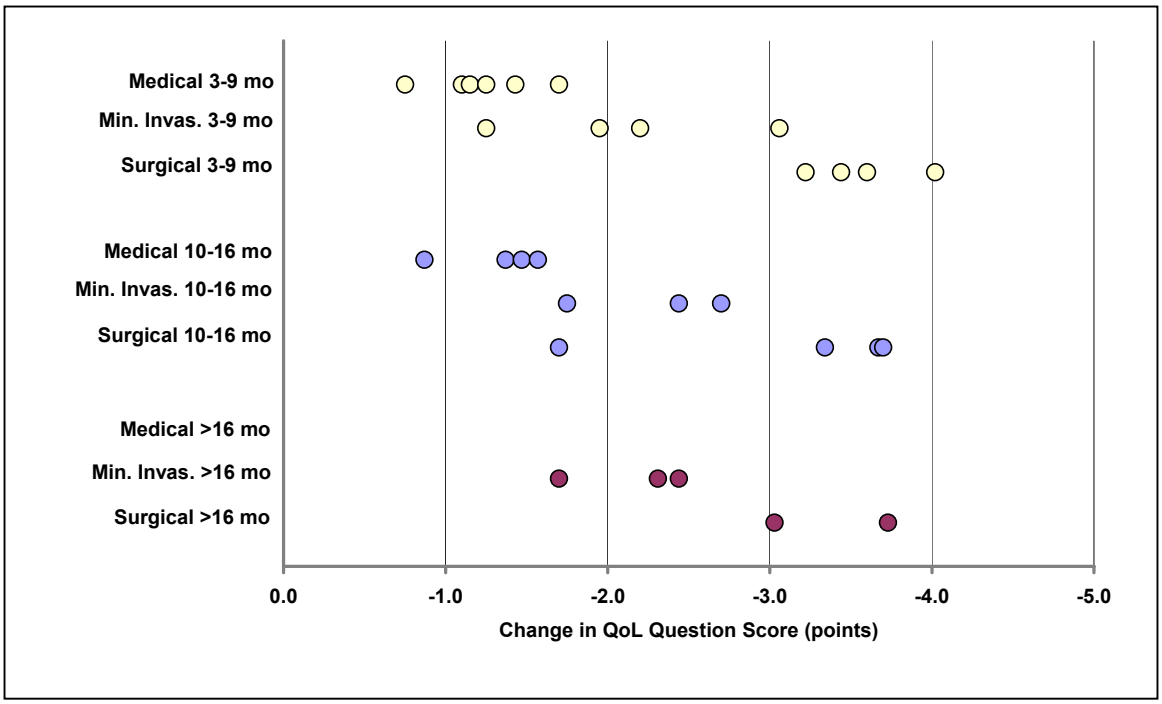
for each time period (Figure 3.13). Medical therapies are associated with the smallest change in improvement. Maximum improvements of 8 mL/min to approximately 16 mL/min are produced within 3 to 9 months postsurgery and decline somewhat over a 1- to 2-year period. The change in peak flow rate appears to decrease over time with all treatment classes.

Figure 3.13. Range of peak urinary flow-rate improvements by treatment intervention and duration of follow-up.



Similar to the results of the other efficacy outcomes, it appears that the surgical therapies provide the best QoL Question score improvement for every time period measured (Figure 3.14). Minimally invasive therapies also produce greater changes in the QoL Question score than do medical therapies. Although medical therapies did produce some improvement in the QoL Question score, this class had the poorest impact of the three classes of treatment interventions.

Figure 3.14. Range of Disease Specific Quality of Life (QoL) Question score improvements by treatment intervention and duration of follow-up. Data not available for long-term use of medical therapy.



Adverse events outcomes — results of analyses

The analysis and presentation of adverse event outcome data were unlike those for the efficacy outcomes due primarily to differences in assessment methods. In particular, the efficacy outcomes described above are measured on numeric scales. Adverse events typically do not have such measures — they either occur or do not occur. Thus, the adverse event outcome measure presented in the Simplified Outcomes Tables (Appendix 1-C) is the probability that the patient will experience the event. The numbers in the adverse event outcomes tables represent the results of single-arm meta-analysis (SAMA) of all study groups using the given therapy and show the estimated frequency of occurrence for each adverse event group. In addition, a meta-analysis of RCTs was performed. Results of RCT analyses are not included in the Simplified Outcomes Tables (Appendix 1-C) but are included in the Detailed Outcomes Tables in Appendix 3. In

addition, results of meta-analyses of RCTs are referenced in the text of the present chapter when these allow determination of whether event rates for treatments differ from controls at statistically significant levels. A further analysis of selected outcomes of alpha blockers also was performed to determine whether the differences between pairs of alpha blockers reached statistical significance.

It is important to note that a number of methodologic deficiencies could have reduced the accuracy of the reported adverse event estimates. The first deficiency is that data are reported as frequency of occurrence in populations of patients studied. This is a reasonable surrogate for probability of occurrence but may overestimate the chance of an event occurring in an individual patient. This overestimate can occur because some patients may have experienced the event multiple times. While an investigator may or may not count multiple events in a single patient separately, the present analysis combines similar events into categories and thus increases the likelihood of counting such multiple events. The second deficiency is that the collection of adverse event data was not standardized. Different authors elicit adverse events differently. Some rely on spontaneous patient reports while others explicitly elicit such reports. The third methodologic problem relates to the definition of complications. Authors use varied terms for similar adverse events or count similar adverse events in different categories. For some events, the level of effect, which triggers recording, may be important. For example, nearly all patients have some increased urgency and/or frequency of urination shortly after an invasive procedure. Some authors record these early irritability symptoms while others only record such symptoms if they continue for some longer (usually unspecified) period. The fourth deficiency concerns the time of initiation of the adverse event. Some authors only record events that occur shortly after

treatment while other authors record data for longer terms. For this guideline, all recorded adverse events were included if possible.

For the purposes of analysis, adverse events were clustered into categories. The definition of each category and the list of included adverse events are shown in Appendices 2-Ea and 2-Eb.

In the following sections, selected adverse event outcomes are discussed for medical, minimally invasive, and surgical therapies. For each adverse event outcome, the content is organized as follows:

- introduction (if appropriate);
- discussion of the results of RCT (if available) and SAMA data (in the case of medical therapies, alpha blockers are discussed first followed by finasteride and finasteride/alpha-blocker combinations);
- summary statement (if appropriate); and
- graph comparing outcomes across therapies (if appropriate).

Note that the graph may not exactly match the corresponding Simplified Outcomes Table because the values in the outcomes tables presented in Appendix 1-C have been rounded to the nearest whole percent while the graphs are based on unrounded values. Unrounded values can be found in the detailed tables in Appendix 3.

Perioperative Mortality

Estimating perioperative mortality (or any infrequent outcome) from small clinical series is problematic. Obstacles include the following:

- the lack of reporting of mortality data by investigators in publications;

- an insufficient study size to yield an estimate of the actual probability for a given patient; when mortality is reported, it is usually a single incident in a relatively small sample of patients;
- patient variation that produces divergent perioperative death rates; patients with BPH vary significantly in age and comorbidities; older or sicker patients have a higher probability of dying from other causes during the perioperative period; and
- significant site-to-site or surgeon-to-surgeon variation in mortality rates.

For the above reasons, the Panel determined that it was not possible to estimate either perioperative or distant mortality by treatment. The major obstacle was that the majority of articles lacked appropriate data to estimate rates. With the exception of TURP and watchful waiting, a total of only five deaths was reported.

Although the 1994 AHCPR guideline provided an extensive discussion of the perioperative mortality of TURP as compared to open prostatectomy, follow-up of several large series have updated these data. These studies uniformly demonstrated a reduction over time in BPH mortality and particularly in perioperative mortality in patients who underwent TURP. Boyle and colleagues examined the World Health Organization database for trends in BPH mortality between 1950 and 1990[116]. The death rate due to BPH per 100,000 patients dropped from 7.47 between 1950 and 1954 to 0.26 between 1995 and 1999. The rate had dropped continuously over the entire period; for example, the mortality rate from 1970 to 1974 was 1.37. The Patient Outcomes Research Team for Prostatic Diseases studied perioperative mortality rates[117, 118] by age cohort during two time periods, 1984 to 1990 and 1991 to 1997. The 30-day mortality rate remained constant for the 65- to 69-year-old cohort at 0.39% and decreased from 3.54% to 2.52% for patients 85 years of age and greater. Thorpe and associates studied TURP mortality

rates over an 8 month period in 1991 in 12 hospitals in northern England and reported a 30-day rate of 0.9% with a variation between hospitals ranging from 0% to 3.7%[119]. A significant correlation was found between perioperative mortality and the American Society of Anesthesiology comorbidity score. Finally, in the Veterans Affairs Cooperative Study Group[30] RCT of TURP compared to watchful waiting, no perioperative deaths in the surgical cohort (n=280) were reported. At 3 years, the mortality rates per 100 patient-years were similar: 1.7 for the surgical group versus 1.3 for the watchful waiting group (p=0.55).

Medical Therapies

Asthenia

Adverse events categorized as asthenia, including fatigue, tiredness, or a general feeling of malaise, are reported by some patients receiving alpha$_1$-adrenergic receptor blockers. (See Appendix 2-E-a for a comprehensive list of adverse events categorized as asthenia in this analysis.) Although the occurrence of asthenia has been attributed to the vascular changes produced by these agents, findings of the Veterans Affairs Cooperative Study Group suggest that this side effect may not be associated with the alpha$_1$-adrenergic receptor-mediated reduction in blood pressure[120].

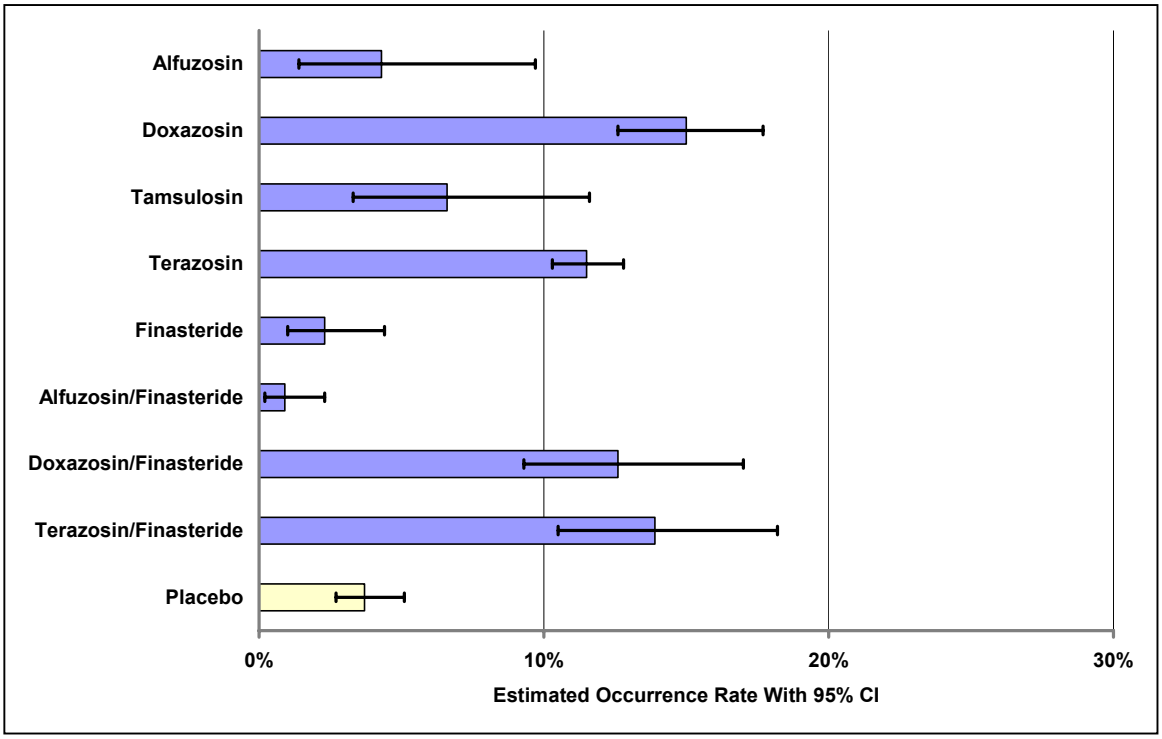
The meta-analysis of RCTs showed statistically significantly higher rates of asthenia in patients treated with doxazosin, tamsulosin, or terazosin compared to placebo. While those analyses showed a trend to more asthenia in alfuzosin- than placebo-treated patients, the results did not reach statistical significance. Results of SAMAs of available alpha-blocker study arms revealed rates of asthenia with terazosin (12%) between those of doxazosin (15%) and alfuzosin and tamsulosin (4% and 7%, respectively) (Figure 3.15). Comparative analysis of meta-analytic results of RCTs showed that doxazosin produced asthenia in a significantly greater proportion of

patients than either alfuzosin or tamsulosin ($p < .05$); the asthenia rate in patients treated with terazosin was not significantly different from that of any other alpha blocker.

Meta-analysis of RCTs of finasteride yielded rates of asthenia comparable to placebo while studies including patients treated with terazosin/finasteride and doxazosin/finasteride found rates for the combination therapies to be statistically significantly greater than that in placebo-treated patients. Single-arm studies of the alpha-blocker/finasteride combinations found similar rates for combinations using terazosin (14%) or doxazosin (13%) but a negligible frequency for the combination with alfuzosin (0.9%). (No RCT reports were found for alfuzosin/finasteride.)

Assessing asthenia frequency from the literature is complicated for two reasons. First, no agreed-upon definition exists, and several terms have been used in the literature yielding inconsistent assessments. Second, some studies used multiple terms, and it is unclear if any patients were double counted.

Figure 3.15. Asthenia rates for medical therapies (based on single-arm meta-analysis).



Dizziness

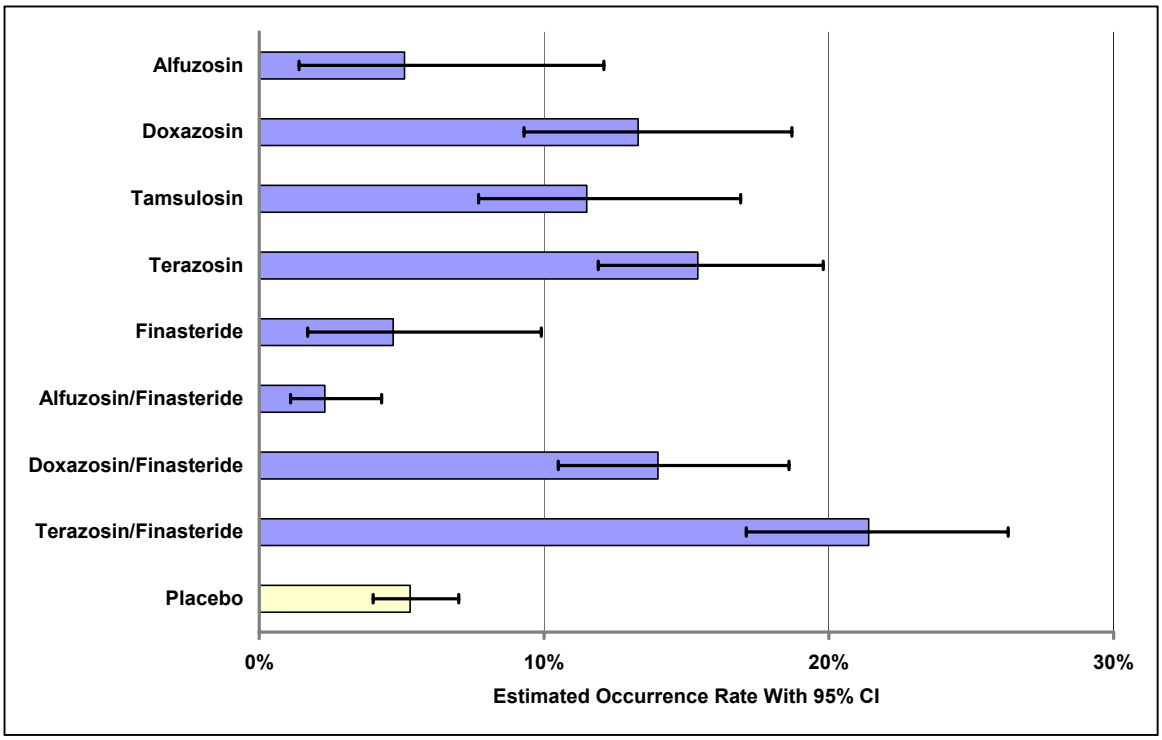
Adverse events categorized as dizziness, such as faintness and light-headedness, are commonly reported by patients receiving alpha$_1$-adrenergic receptor blockers. (See Appendix 2-E-a for a comprehensive list of adverse events categorized as dizziness in this analysis.) Like asthenia, the occurrence of dizziness has been attributed to the vascular changes produced by these agents. Results of the Veterans Affairs Cooperative Study, however, suggest that this side effect may not be associated with the alpha$_1$-adrenergic receptor-mediated reduction in blood pressure[120].

Meta-analysis of available RCTs showed dizziness was statistically significantly more common in patients treated with doxazosin, tamsulosin, or terazosin than in those treated with placebo; rates in placebo- and alfuzosin-treated patients were not statistically significantly

different. Results of SAMAs were consistent with RCT data. Thus, patients receiving alfuzosin or tamsulosin had lower rates of dizziness than did those treated with terazosin (5%, 12%, and 15%, respectively; Figure 3.16). Pairwise comparisons of alpha blockers using meta-analytic results of RCT data found differences between alfuzosin and terazosin and between tamsulosin and terazosin to be marginally significant ($p < .10$); the rate for doxazosin-treated patients was not significantly different from any other alpha blocker.

In meta-analyses of RCT data, rates of dizziness in finasteride- versus placebo-treated patients were similar. Conversely, combinations of finasteride with terazosin or doxazosin yielded dizziness rates that were statistically significantly greater than those reported for patients receiving placebo. Estimated rates based on single-arm studies for terazosin/finasteride and doxazosin/finasteride were 21% and 14%, respectively, compared with 2% in patients treated with alfuzosin/finasteride and 5% in placebo-treated patients (Figure 3.16). (No RCTs reported dizziness associated with alfuzosin/finasteride.)

Figure 3.16. Dizziness rates for medical therapies (based on single-arm meta-analysis).



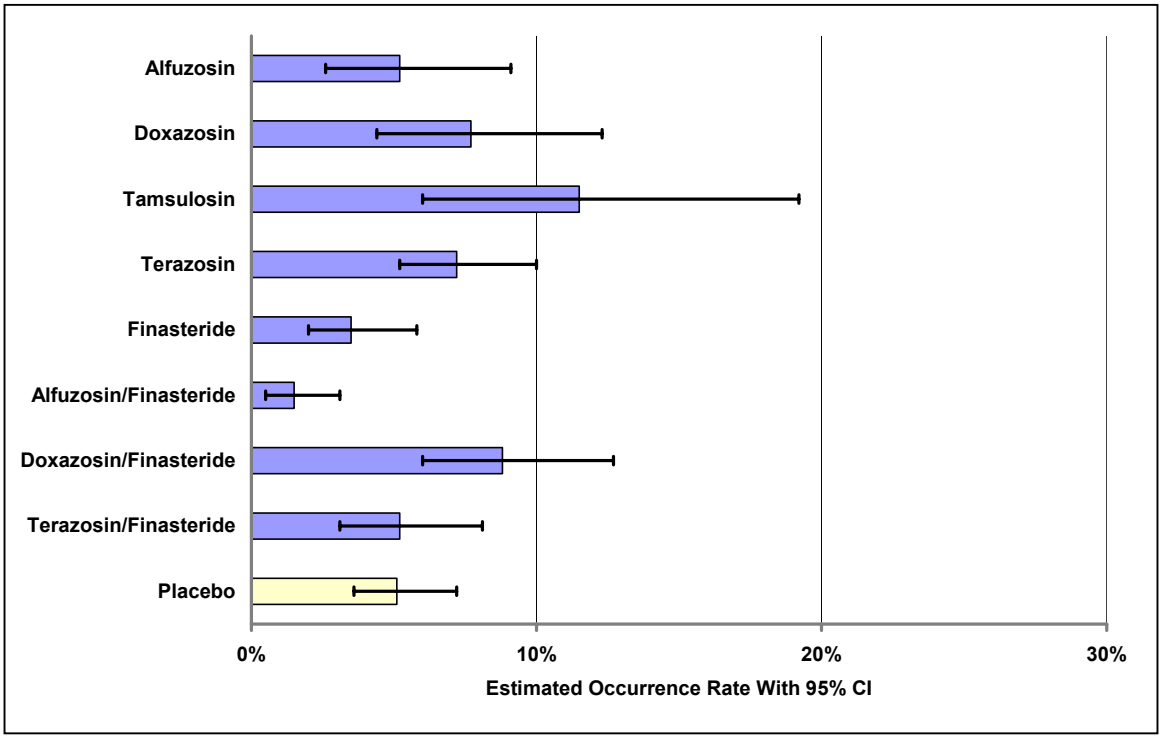
Headache

Headache is a nonspecific adverse event reported in nearly all medical intervention trials for LUTS and BPH; an estimated median frequency of 5% was calculated from reports of placebo-treated patients in RCTs (which included 24 treatment groups). Results of meta-analyses of RCTs revealed that the frequency of headache was similar in patients treated with placebo versus doxazosin, tamsulosin, or terazosin; a single RCT found the rate for alfuzosin also to be similar to that for placebo. Rates based on SAMAs ranged from 7% (terazosin) to 12% (tamsulosin) (Figure 3.17); one single-arm study reported a 5% rate for alfuzosin. These differences could be due to differences in adverse-event reporting across studies.

Treatments with finasteride and terazosin/finasteride and alfuzosin/finasteride combinations also were not associated with increased rates of headache over that reported for placebo (Figure

3.17). Although only one patient group was included in each of these analyses, headache rates generally were consistent in patients treated with terazosin/finasteride and doxazosin/finasteride with those found for patients treated with the alpha blockers alone. (No RCT data on headache was found for alfuzosin/finasteride.)

Figure 3.17. Headache rates for medical therapies (based on single-arm meta-analysis).



Hypotension

Because the majority of alpha blockers were developed to treat hypertension, hypotension is expected to occur frequently in patients with LUTS and BPH who receive these agents. For the current analyses, reports of hypotension were classified as: asymptomatic hypotension, symptomatic hypotension, symptomatic postural hypotension and syncope. Hypotension reports were divided into these categories primarily by following the term used by the study authors. There may be considerable overlap in the symptomatic and symptomatic postural groups. (See

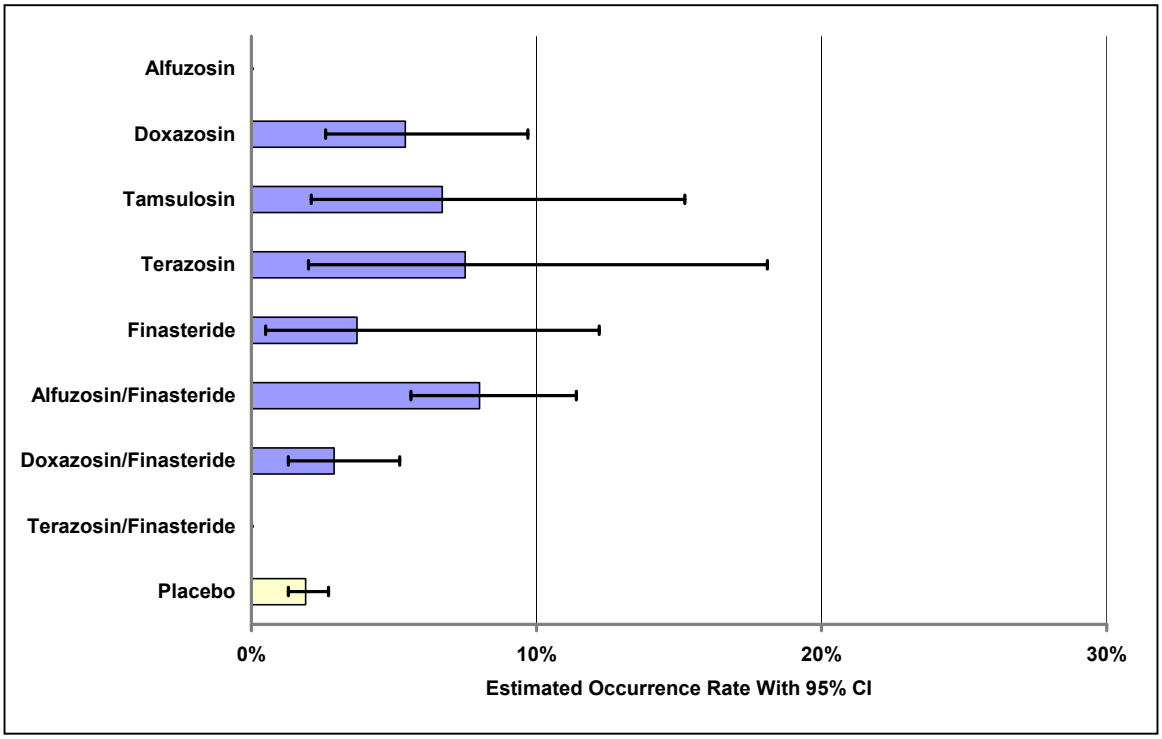
Appendix 2-E-a for a comprehensive list of adverse events classified in these categories.) Results of the SAMA of frequency rates for each category are presented in Figures 3.18 through 3.21. Note that investigators most likely interpreted the categories differently and that not all studies reported the same categories.

Asymptomatic hypotension

Based on meta-analyses of RCTs, patients treated with tamsulosin experienced asymptomatic hypotension at statistically significantly higher rates than did those receiving placebo while those treated with doxazosin had rates similar to placebo-treated groups. A single RCT found the rate for terazosin to be statistically significantly higher than that for placebo. Results of SAMAs confirmed the RCT results yielding somewhat higher rates in patients treated with terazosin or tamsulosin compared with those in patients receiving doxazosin (8%, 7%, and 5%, respectively; Figure 3.18); these differences are unlikely to be clinically significant.

Neither finasteride nor the combination of doxazosin/finasteride was associated with increased rates of asymptomatic hypotension compared with placebo. (No RCTs reported on asymptomatic hypotension for alfuzosin/finasteride; no studies reporting on asymptomatic hypotension were found for alfuzosin or for the combination terazosin/finasteride.)

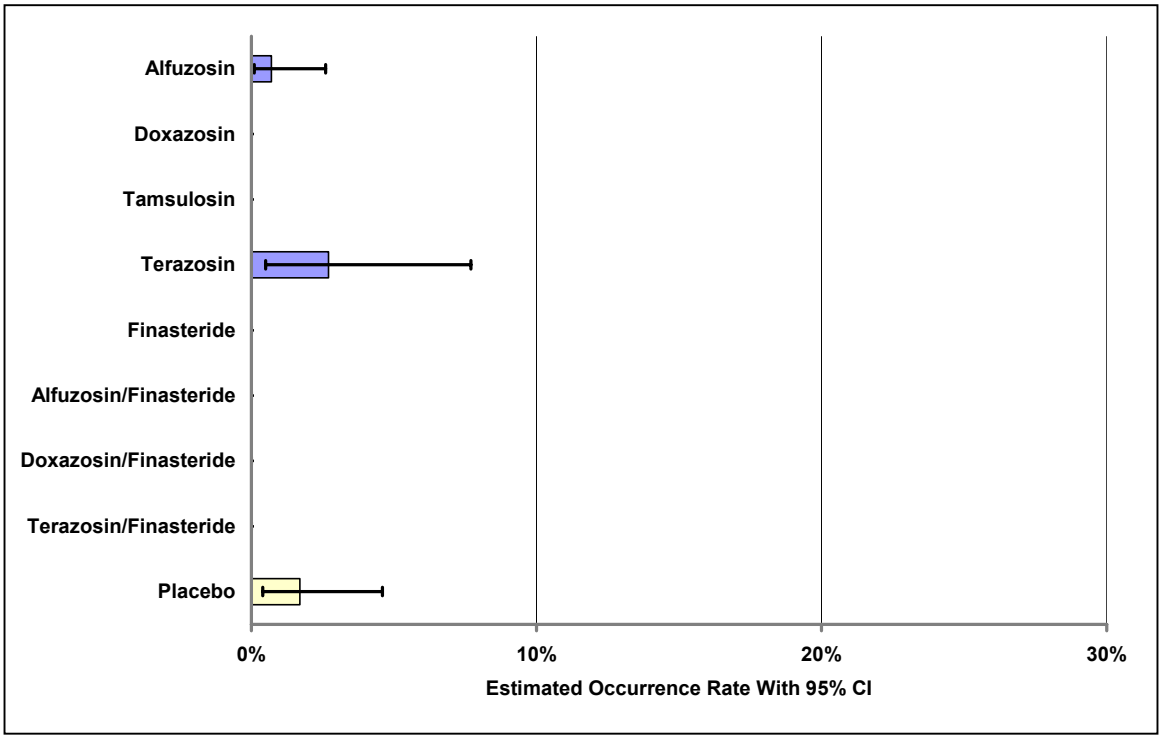
Figure 3.18. Asymptomatic hypotension rates for medical therapies (based on single-arm meta-analysis). Missing bars indicate that data were not available.



Symptomatic hypotension

Symptomatic hypotension has been reported in few studies of alpha blockers (Figure 3.19). This is primarily an artifact of the way data were analyzed for this project. Most of the symptomatic hypotension data were reported and analyzed as occurrences of symptomatic postural hypotension.

Figure 3.19. Symptomatic hypotension rates for medical therapies (based on single-arm meta-analysis). The missing bar indicates that data were not available.

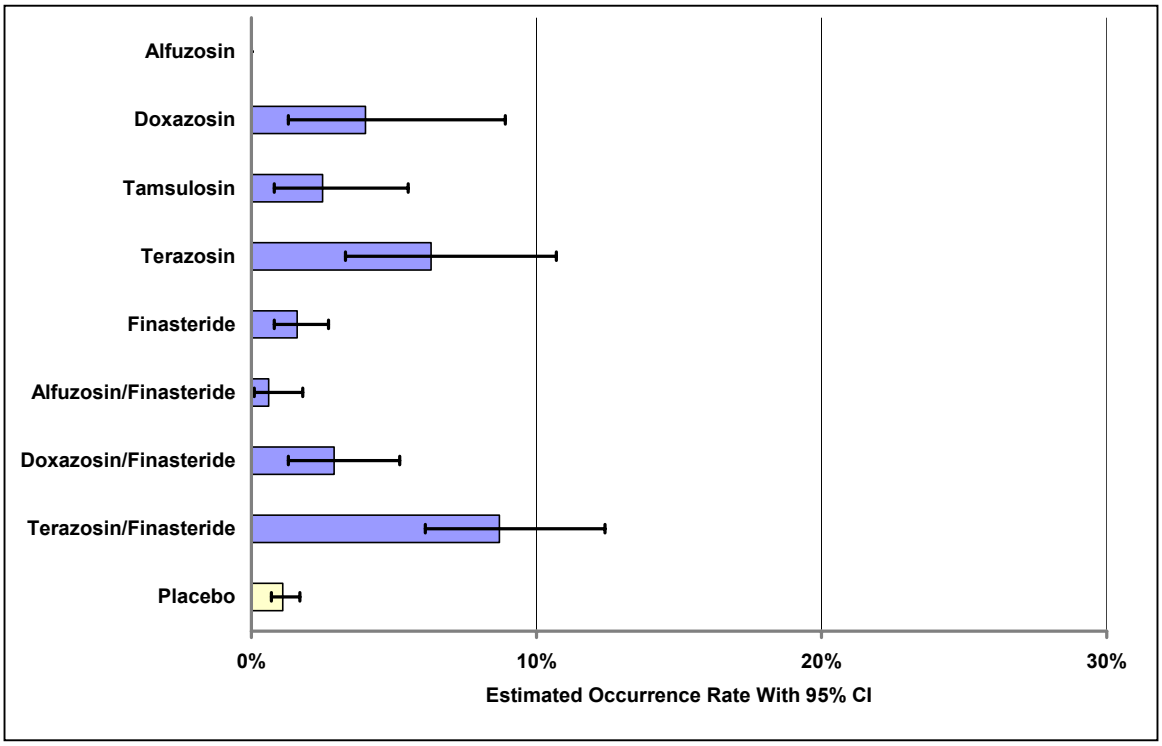


Symptomatic postural hypotension

Based on meta-analyses of RCTs, rates of symptomatic postural hypotension were similar to placebo for tamsulosin-treated patients but were statistically significantly higher in those treated with terazosin. A single RCT found the rate for doxazosin to be statistically significantly higher than that for placebo. Single-arm meta-analyses found the rate for patients treated with tamsulosin to be lower than rates for patients receiving either doxazosin or terazosin (3%, 4%, and 6%, respectively; Figure 3.20). Pairwise comparisons based on meta-analytic results of RCT data revealed that the rate of postural hypotension was significantly ($p < .05$) lower in those receiving tamsulosin than in patients treated with either doxazosin or terazosin. (No studies were found for alfuzosin that reported on symptomatic postural hypotension.)

Meta-analyses of RCT data found that treatment with finasteride was not associated with an increased rate of symptomatic postural hypotension compared with placebo. The combination of terazosin/finasteride but not of doxazosin/finasteride was associated with a statistically significantly increased risk of the condition; in each case, however, these results were based on data from single studies and therefore should be viewed as preliminary. (No RCTs reported on this outcome for alfuzosin/finasteride.)

Figure 3.20. Symptomatic postural hypotension rates for medical therapies (based on single-arm meta-analysis). The missing bar indicates that data were not available.



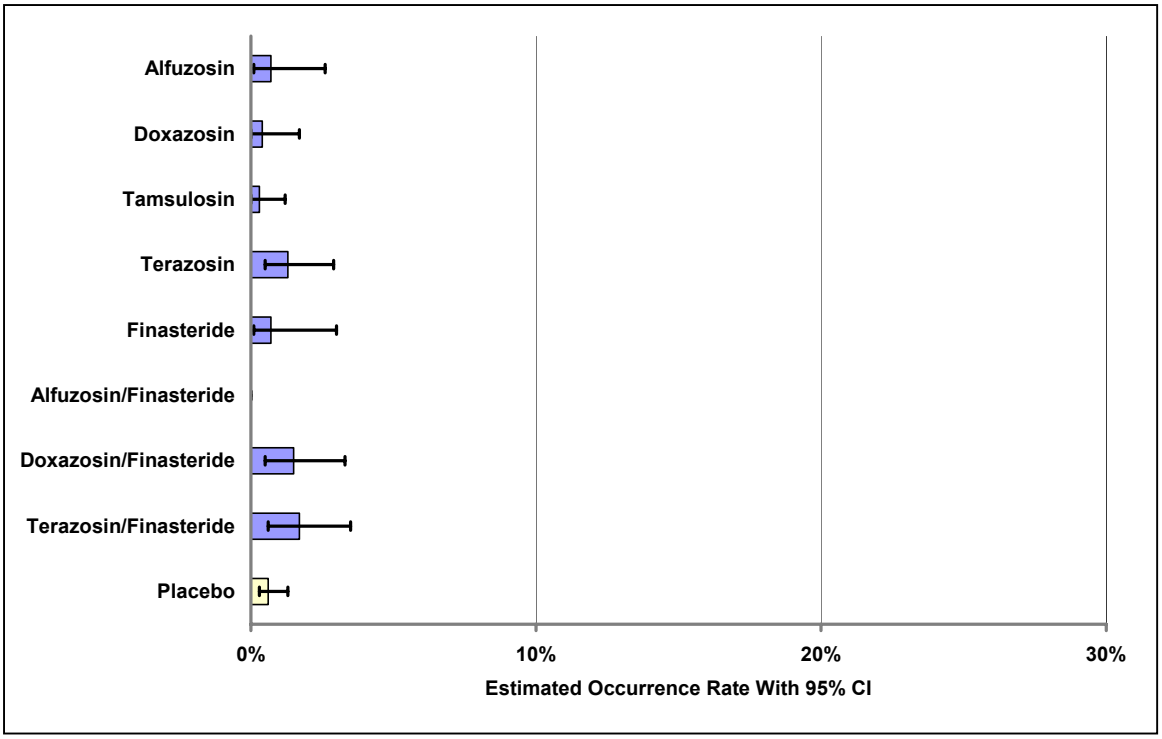
Syncope

Meta-analyses of RCTs for terazosin and single RCTs for the other three alpha blockers revealed no statistically significant differences between rates of syncope in patients treated with any of the four drugs compared with placebo. Syncope is a rare side effect of all alpha blockers with estimated rates of occurrence ≤ 1% for each therapy (Figure 3.21). Pairwise comparisons

based on meta-analyses of RCT data revealed no statistically significant differences between alpha-blocker treatment groups.

Analysis of the outcomes of the combination therapy trials found that, in one RCT, patients receiving terazosin/finasteride had a statistically significant increase in the occurrence of syncope, but this 1% increase was probably not of clinical significance. Single-arm analyses showed a similar 1% increase in the rate of occurrence for terazosin monotherapy and doxazosin/finasteride combination therapy; nevertheless, these results did not reach statistical significance. (No studies reported syncope associated with alfuzosin/finasteride.)

Figure 3.21. Syncope rates for medical therapies (based on single-arm meta-analysis). The missing bar indicates that data were not available.



Summary of hypotensive adverse events: The Panel's review of the combined analysis demonstrates no clear advantage of one alpha blocker over another with respect to hypotension-related adverse events. However, in one double-blind RCT of 50 normotensive patients with

LUTS, a daily tamsulosin dose of 0.4 mg produced a significantly lower frequency of symptomatic hypotensive episodes than did terazosin titrated from a dose of 1 to 5 mg within a 3-week period. Tamsulosin, therefore, may be associated with a slightly lower incidence of adverse blood pressure effects than terazosin[97].

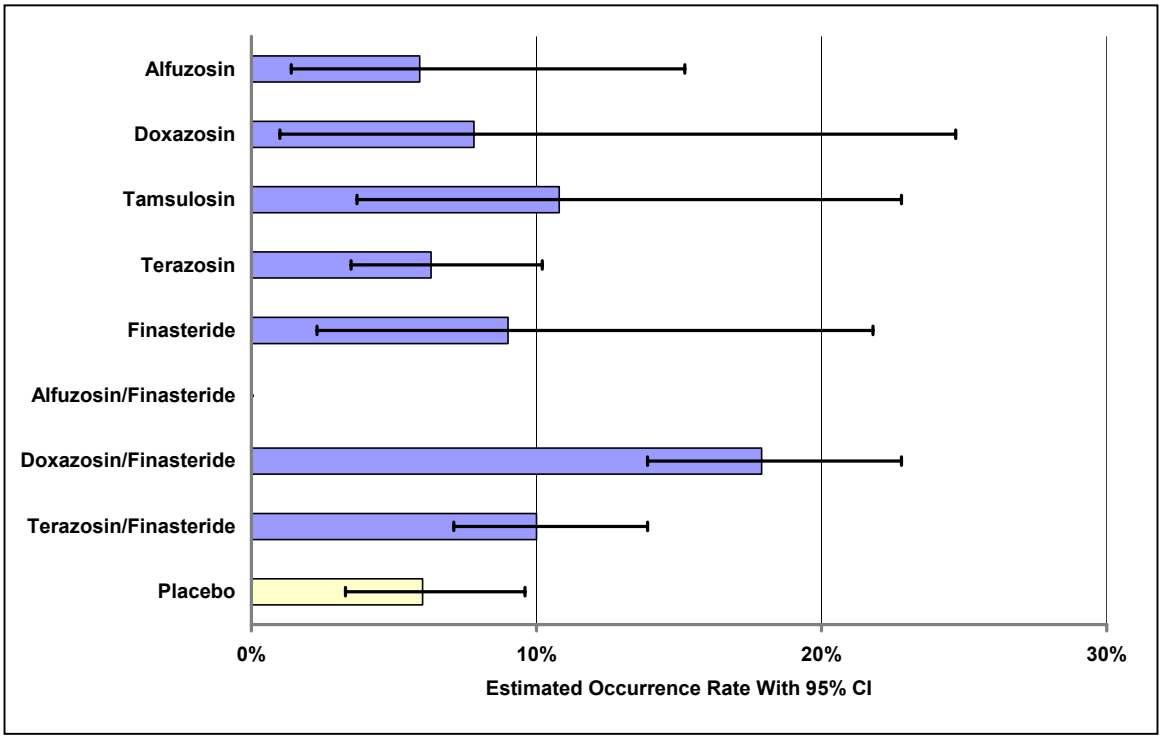
Respiratory/Nasal Congestion

This category encompasses a large variety of respiratory tract-related adverse events, the most common and significant being a feeling of "stuffiness" and nasal congestion commonly seen with certain alpha-adrenergic receptor blockers. The feeling of a stuffy nose, nasal congestion, and respiratory adverse events are commonly reported in alpha-blocker trials for BPH. The estimated frequency based on a SAMA of all placebo arms of 10 RCTs was 6%.

Meta-analyses of data from RCTs revealed no statistically significant difference from placebo in rates of respiratory/nasal congestion for alfuzosin or terazosin; the rate in patients treated with tamsulosin was significantly greater than that for patients receiving placebo. A single RCT found the rate for doxazosin to be similar to that for placebo. Single-arm meta-analyses of alpha-blocker study arms revealed rates were highest in patients receiving tamsulosin (11%) compared with alfuzosin (6%), doxazosin (8%), or terazosin (6%) (Figure 3.22). Pair-wise comparative analyses of meta-analytic results of RCTs showed significant differences in rates of respiratory/nasal congestion between patients receiving tamsulosin versus alfuzosin ($p < .05$), but only trends toward significance were observed in differences between patients treated with tamsulosin versus doxazosin or terazosin ($p < .10$).

Patients treated with finasteride or with combinations of finasteride and either terazosin or doxazosin did not experience statistically significantly increased rates of respiratory side effects compared with placebo-treated patients. (No studies were found reporting these side effects for alfuzosin/finasteride.)

Figure 3.22. Respiratory/nasal adverse-event rates for medical therapies (based on single-arm meta-analysis). The missing bar indicates that data were not available.



Sexually Related Adverse Events

The category of sexually related adverse events is further subdivided into erectile dysfunction, ejaculatory dysfunction, and libido problems.

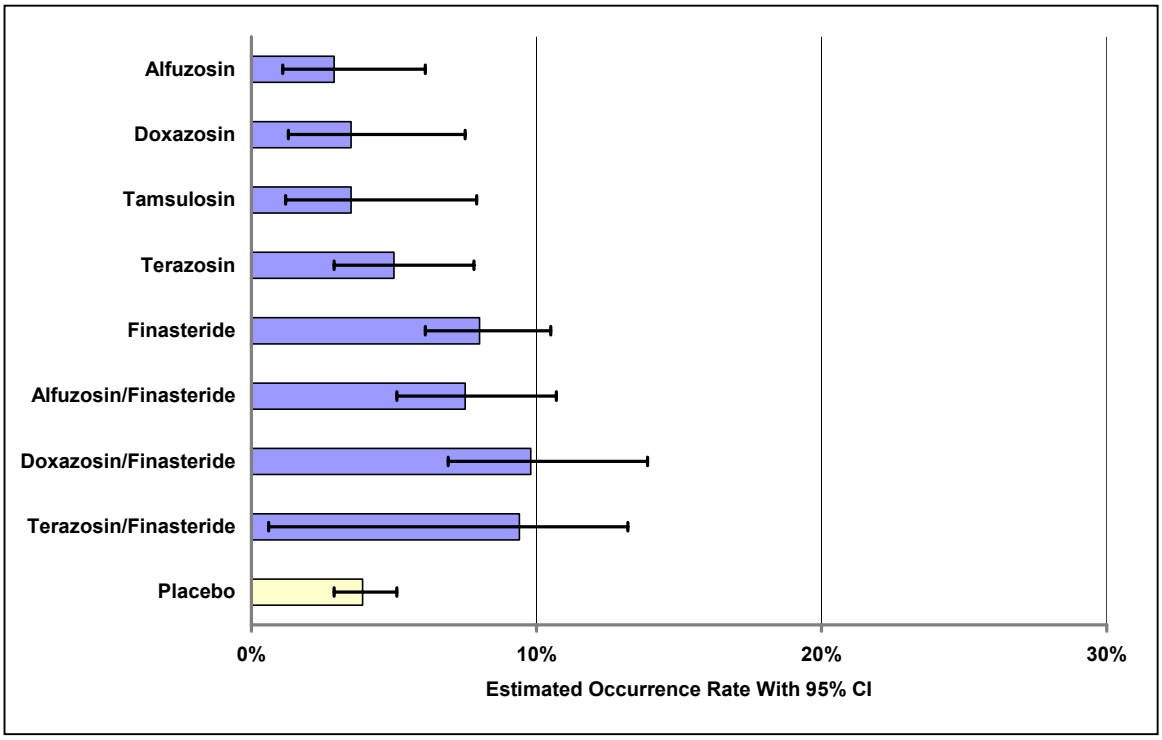
Erectile dysfunction

Randomized, controlled trials found rates of erectile dysfunction to be similar in patients treated with placebo and in those treated with alpha blockers. The range of such dysfunction in patients treated with alpha blockers (3% to 5%) was similar to the percent reported by patients treated with placebo (4%; Figure 3.23).

Finasteride alone or in combination with terazosin or doxazosin resulted in statistically significantly increased levels of erectile dysfunction (range based on a SAMA for finasteride

alone or single studies for combination therapies: 8% to 10%) when compared to treatment with placebo (Figure 3.23). (No RCTs reported on erectile dysfunction for alfuzosin/finasteride.)

Figure 3.23. Erectile dysfunction rates for medical therapies (based on single-arm meta-analysis).



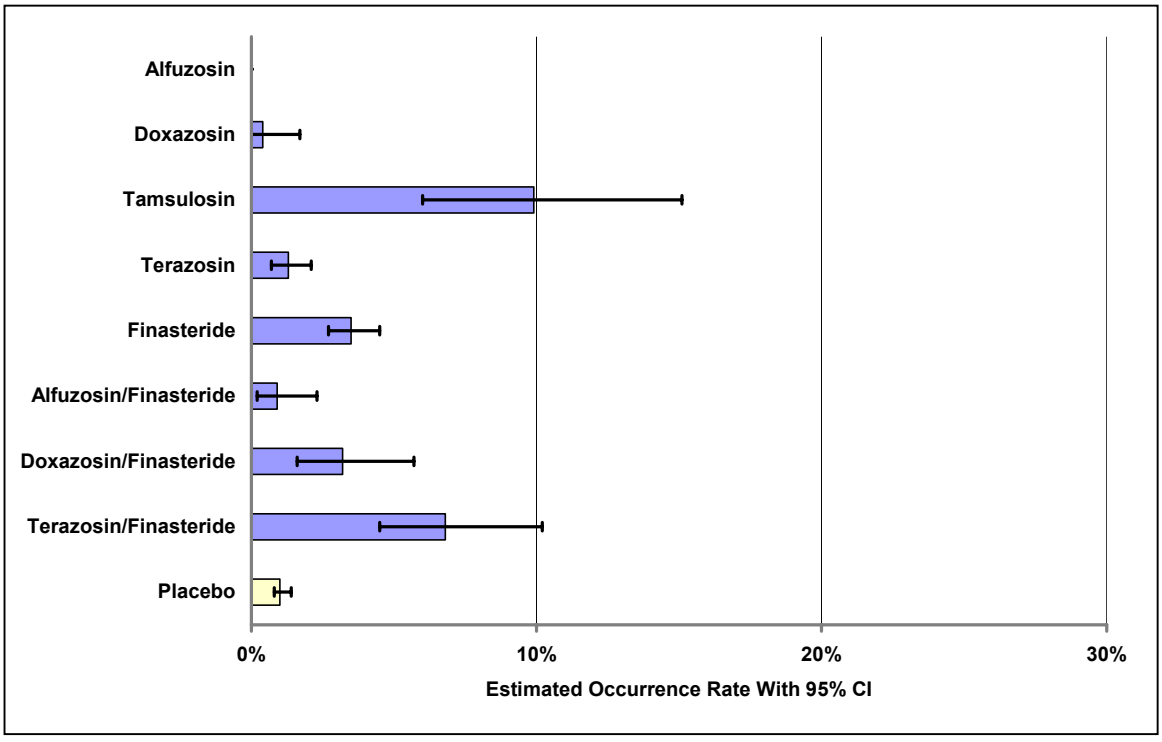
Ejaculatory dysfunction

Ejaculatory disorders encompass absence of ejaculation, decreased amount of ejaculation, and retrograde ejaculation. For the patient, all reported events have the same implication: no or significantly reduced expulsion of semen during climax. Mechanistically, alpha blockers affect the transport/expulsion of the ejaculate while finasteride decreases the production of seminal fluid. Therefore, retrograde ejaculation more commonly occurs with certain alpha adrenergic-receptor blockers while reduced volume of ejaculate is a more common adverse event of the 5 alpha-reductase inhibitor finasteride.

Meta-analyses of RCTs revealed rates of ejaculatory dysfunction to be similar in patients treated with placebo and in those receiving terazosin; the rate was statistically significantly higher in patients receiving tamsulosin than in those receiving placebo. A single RCT found the rate for doxazosin to be similar to that for placebo. Rates ranged from approximately 1% in placebo-, doxazosin- and terazosin-treated patients to 10% in those treated with tamsulosin (based on SAMAs for tamsulosin and terazosin or a single-arm study for doxazosin; Figure 3.24).

Using RCT data, treatments with finasteride or with terazosin/finasteride but not with doxazosin/finasteride were associated with statistically significantly higher rates of ejaculatory dysfunction than placebo therapy. (No study reported on ejaculatory outcomes for alfuzosin alone or in combination with finasteride or tamsulosin in combination with finasteride.)

Figure 3.24. Ejaculatory dysfunction rates for medical therapies (based on single-arm meta-analysis). The missing bar indicates that data were not available.

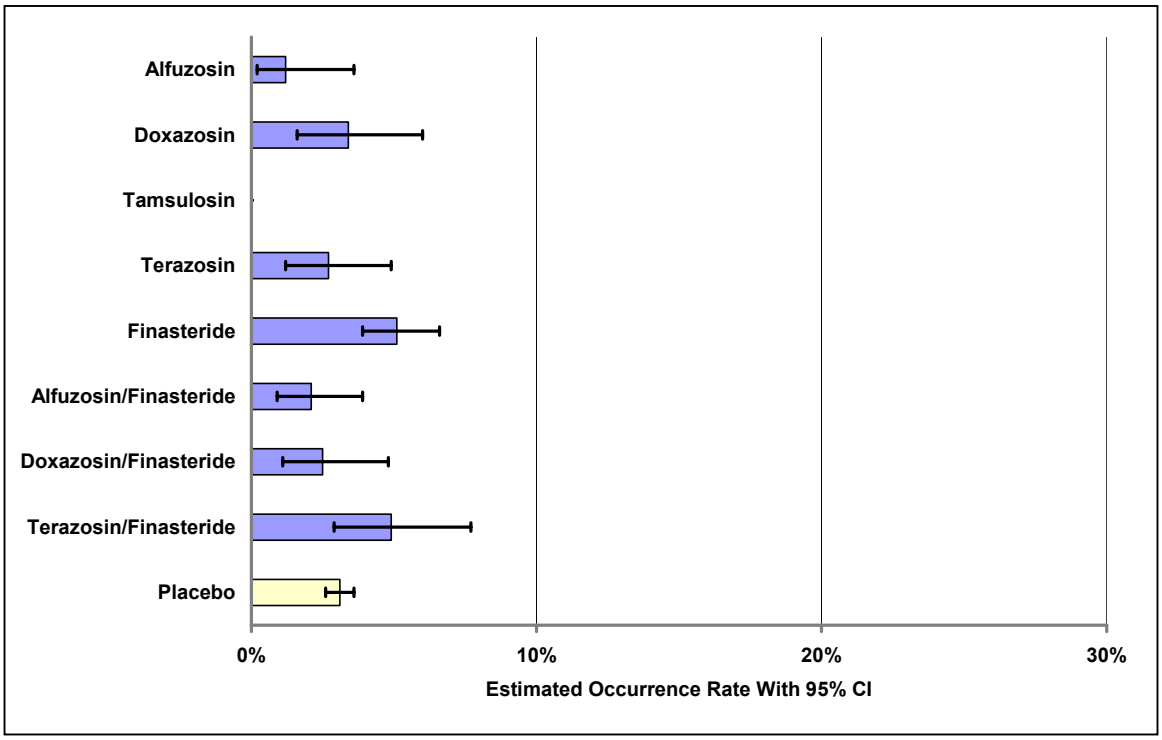


Libido problems

Based on RCT data, rates of libido problems in patients treated with alfuzosin, doxazosin, or terazosin were similar to those in patients receiving placebo. (No RCT or single-arm study reports were found for tamsulosin.) Just 3% of placebo-treated patients reported libido problems; data from single-arm studies revealed rates of ≤ 3% in patients receiving therapy with the three alpha blockers evaluated (Figure 3.25).

A meta-analysis of RCTs of finasteride and an RCT of terazosin/finasteride therapy found statistically significantly increased rates of libido problems compared with placebo; rates of approximately 5% were estimated for both therapies (Figure 3.25). Doxazosin/finasteride use did not result in an increased rate of libido problems. (No RCT reports were found detailing libido changes for alfuzosin/finasteride.)

Figure 3.25. Libido problem rates for medical therapies (based on single-arm meta-analysis). The missing bar indicates that data were not available.



Other

Cardiovascular adverse events

No statistically significant increase in the risk of cardiovascular adverse events was found among patients treated with any of the four alpha blockers compared with placebo. Likewise, neither finasteride nor the doxazosin/finasteride combination was associated with an increase in such events. (No RCT or single-arm study reports were found for alfuzosin/finasteride or for terazosin/finasteride.) Similarly, peripheral edema as reported in RCTs was no more common with alfuzosin or terazosin than with placebo, although in the single-arm analyses terazosin was associated with a risk of peripheral edema of about 4% compared to about 1% for placebo; the confidence intervals about these two point estimates do not overlap.

The low risk of cardiovascular adverse events with the alpha blockers, with no clear attributable risk, is reassuring in the wake of a preliminary publication from the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a randomized study of antihypertensive drugs from four different classes for the treatment of hypertension in high-risk patients 55 years of age or older[47]. In this study, the risk of the primary outcome, fatal coronary heart disease or nonfatal myocardial infarction, was similar among subjects in the chlorthalidone and doxazosin arms. However, the risk of stroke was about 20% higher with doxazosin, and the risk of combined cardiovascular disease outcomes was about 25% higher with doxazosin. The risk of congestive heart failure in particular was about twice as high with doxazosin.

Overall, these results do not prove that doxazosin (or other alpha blockers) *causes* strokes or cardiovascular events such as congestive heart failure in older individuals but rather that in the setting of hypertension, thiazide diuretics are more effective at *preventing* these events. Doxazosin-related adverse sequelae are most likely due to ineffectiveness in preventing cardiovascular disease and not because they are a causal influence, especially since the trial did

not contain a placebo arm. The major clinical implication of the ALLHAT results concerns the theoretically attractive possibility of treating both BPH and hypertension with an alpha blocker because these conditions commonly coexist among older men. Unfortunately, the ALLHAT results strongly suggest that alpha-blocker monotherapy is not optimal therapy for hypertension and that treatment of these two conditions in the same patient should be approached separately.

Breast adverse events

Meta-analyses of RCTs revealed no significant difference from placebo in the rate of breast adverse events is new for finasteride. (No RCT or single-arm study reports were found for any of the four alpha blockers or the combinations of alfuzosin/finasteride, doxazosin/finasteride, or terazosin/finasteride with regard to adverse events related to the male breast.)

The occurrence of breast cancer in men completed and ongoing studies of finasteride recently has been compiled by the National Institutes of Health (NIH) (written communication, July 2002). As of June 2002, in their sponsored MTOPS trial, four cases of breast cancer (56.5 per 100,000 patient-years) were reported in finasteride-treated patients whereas none occurred in the doxazosin and placebo treatment arms. These data appear to be at odds with those reported from other large finasteride-treatment trials. In PLESS, two male patients receiving placebo developed breast cancer (44.8 per 100,000 patient-years)[108] and one patient in both the finasteride- and placebo-treatment groups developed breast cancer in the Prostate Cancer Prevention Trial, a study of approximately 18,000 patients with an average follow-up of approximately 5 years. The 95% confidence intervals for he rate of breast cancer per 100,000 patient-years is 1.1 to 111.8 for finasteride and -17.3 to 106.9 for placebo. While the difference between PLESS and MTOPS cannot readily be explained, it may be due to chance alone. After reviewing these data, the FDA has not recommended a special alert regarding the issue of breast cancer in finasteride-treated patients.

Short-term Adverse Events Reported With Minimally Invasive and Invasive Therapies

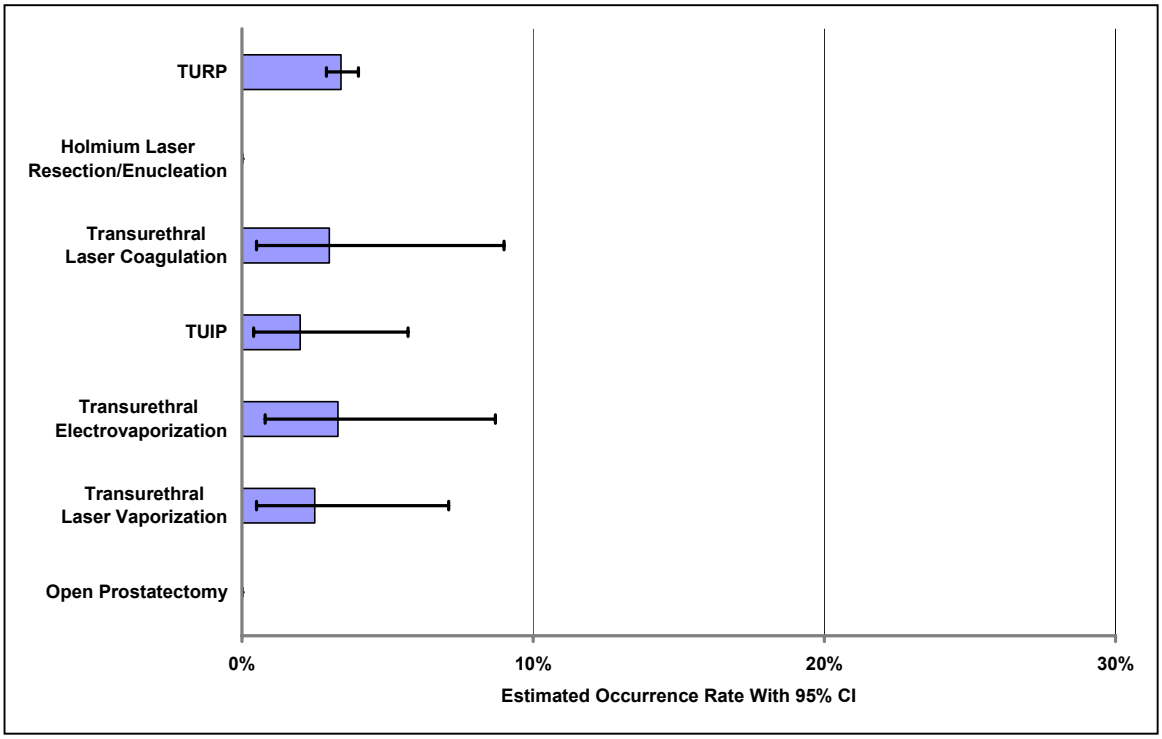
Intraoperative Complications

The category of intraoperative complications includes a broad spectrum of complications that occur during surgical procedures. (See Appendix 2-E-b for a comprehensive list of categorized complications under this heading.)

Results of meta-analyses of RCTs using TURP as the control showed that transurethral electrovaporization was not associated with an increased rate of intraoperative complications; a lone RCT of TUIP versus TURP also found intraoperative complication rates to be similar. Single-arm meta-analyses revealed intraoperative complication rates of ≤ 3% in patients treated with TURP, transurethral laser coagulation, transurethral electrovaporization, or transurethral laser vaporization (Figure 3.26); single-arm studies reported similar rates for TUIP and Targis TUMT (Appendix 3e). One small single-arm study of TUNA reported intraoperative complications in 1 in 10 patients. (No studies reported on these complications for the Prostatron Versions 2.0 or 2.5 TUMT, the UroLume stent, holmium laser resection/enucleation prostatectomy, or open prostatectomy. No RCT reports versus TURP were found for the Targis TUMT, TUNA, transurethral laser coagulation, or transurethral laser vaporization.)

The single RCT that compared Targis TUMT with sham found intraoperative complication rates to be similar. (No studies evaluating other minimally invasive therapies found intraoperative complications.)

Figure 3.26. Intraoperative complication rates for surgical therapies (based on single-arm meta-analysis). Missing bars indicate that data were not available.



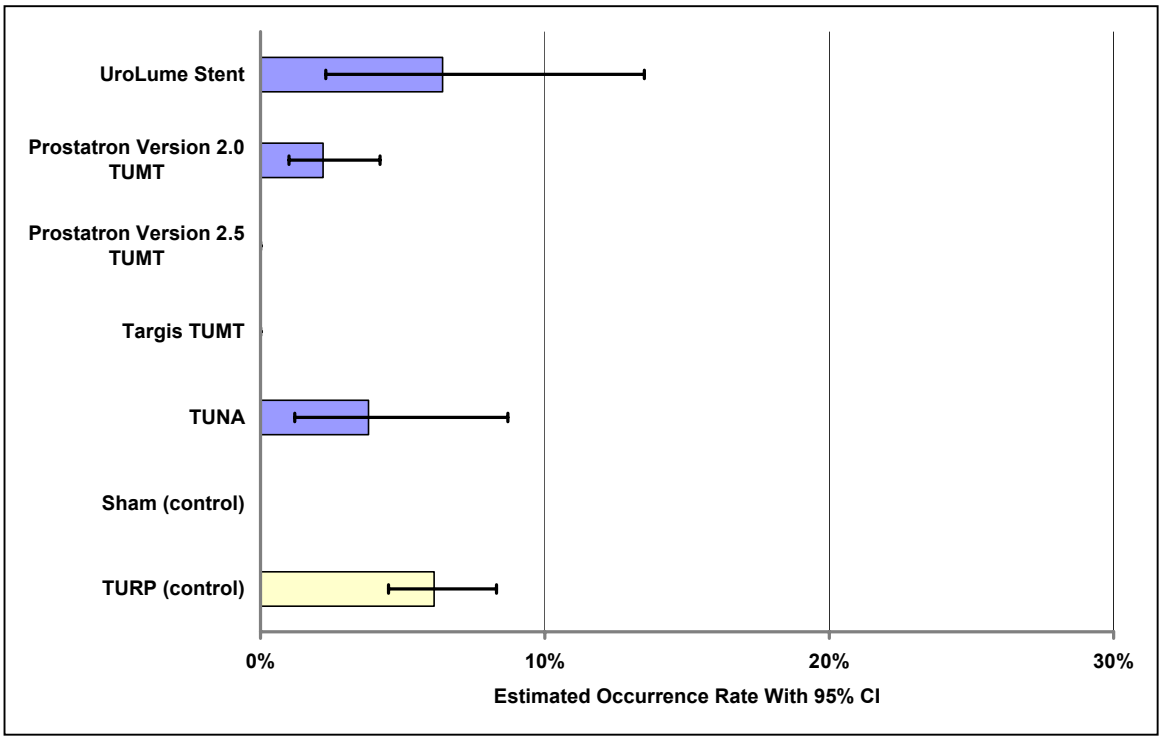
Hematuria

An effort was made to catalogue all significant bleeding adverse events except for transfusions under the term "significant hematuria," including intraoperative and postoperative bleeding, return to the operating room for hemostasis, clot retention, and need for clot evaluation. Transfusion requirements were recorded separately.

Overall, significant hematuria rarely was reported following minimally invasive therapies. The SAMA of 15 studies reporting hematuria data for TURP (n=1015) yielded an estimated frequency of 6% for this adverse event (Figure 3.27). Significant hematuria was reported in SAMAs of the UroLume stent (6% of patients), TUNA (4% of patients), and Prostatron Version 2.0 TUMT (2% of patients). The higher rate observed with the UroLume stent presumably is due to the trauma of stent insertion. The single RCT that compared rates of hematuria for the

Prostatron Version 2.0 TUMT versus TURP found no statistically significant difference between therapies. (No RCTs with TURP controls reported hematuria data for the Prostatron Version 2.5 TUMT, Targis TUMT, TUNA or the UroLume stent. No single-arm studies reported hematuria data for any TUMT except Prostatron Version 2.0. No RCT comparing any minimally invasive therapy to sham reported hematuria data.)

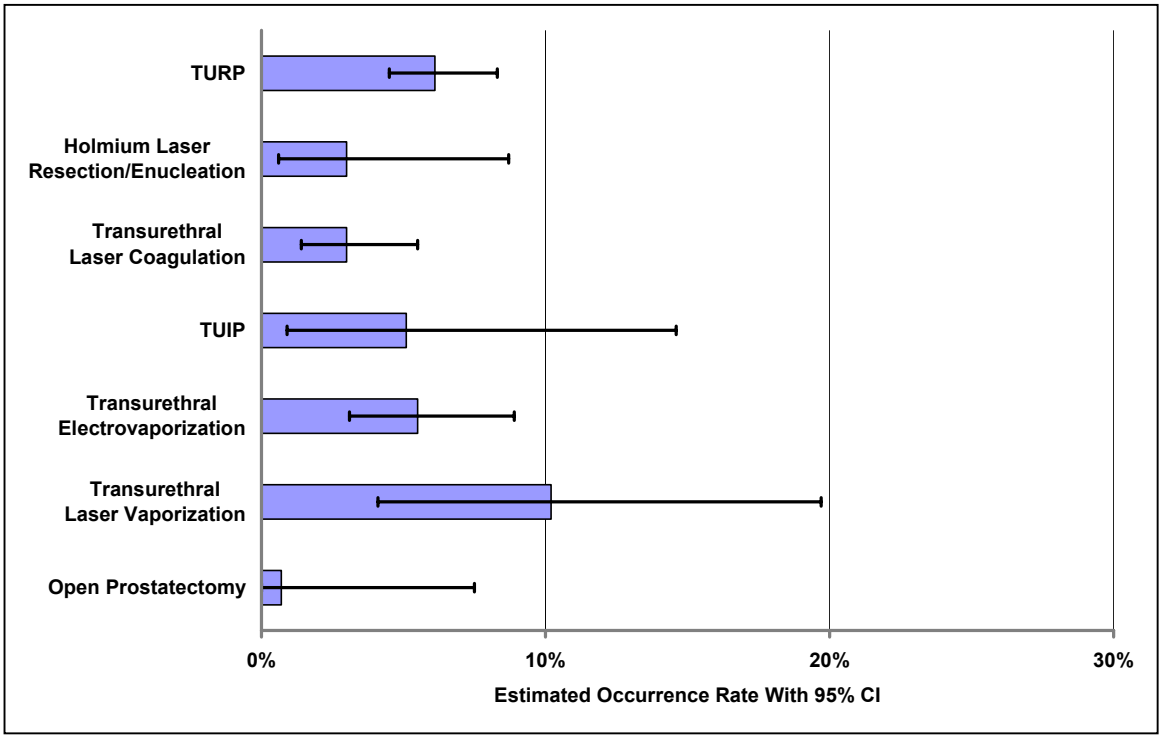
Figure 3.27. Significant hematuria rates for minimally invasive therapies (based on single-arm meta-analysis). Missing bars indicate that data were not available.



Using TURP as the control, meta-analyses of RCTs showed rates of significant hematuria were similar in patients treated with transurethral laser coagulation, transurethral electrovaporization, or transurethral laser vaporization; single RCTs found no statistically significant differences between significant hematuria rates for either TUIP or open prostatectomy versus TURP. Estimated rates based on SAMAs for invasive surgical therapies ranged from 3% for holmium laser resection/enucleation prostatectomy and transurethral laser coagulation to

approximately 10% for transurethral laser vaporization; one single-arm study reported a rate of 1% for open prostatectomy (Figure 3.28). Possible reporting differences across studies or, in the case of open prostatectomy, differences in local operative techniques probably account for these anomalous data. (No RCT reported hematuria data for holmium laser resection/enucleation.)

Figure 3.28. Significant hematuria rates for surgical therapies (based on single-arm meta-analysis).



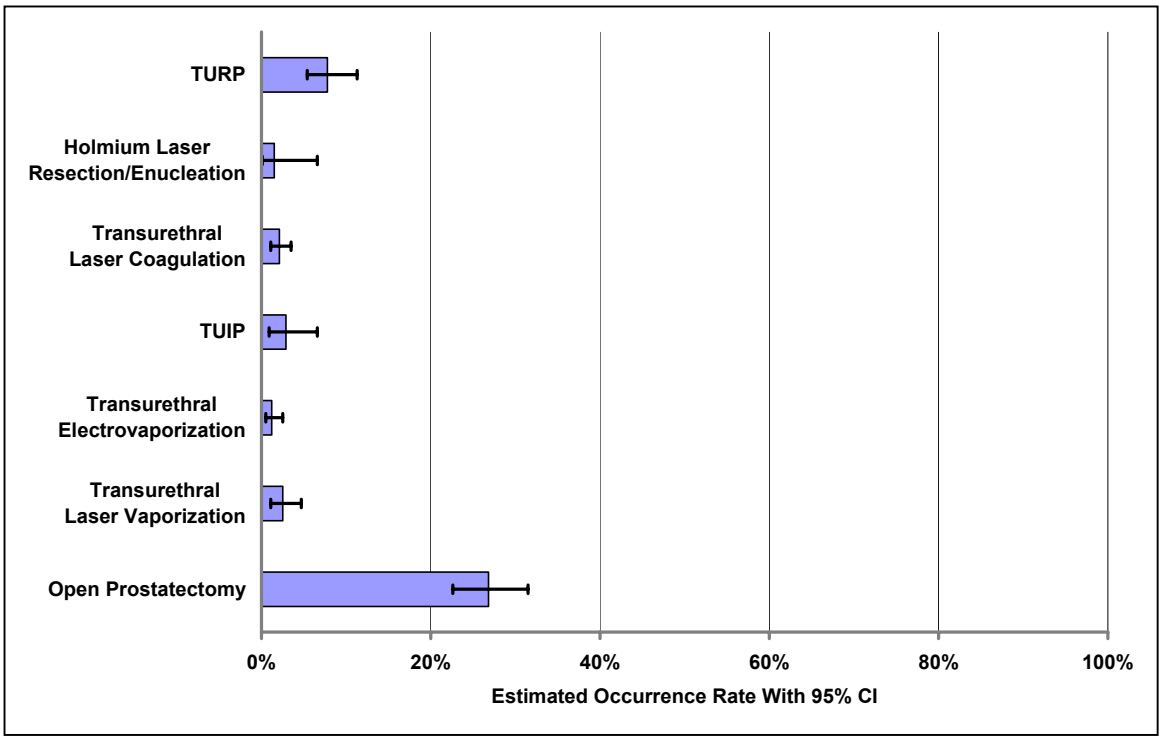
Transfusion

Although direct negative effects on health are small, patients have a general aversion to receiving a blood transfusion, making this outcome important. Results of the present analysis should be interpreted with some caution, however, because the Panel believes that the transfusion rate reported in the TURP-control arms may overestimate the actual rate found in current practice due to the inclusion of older case-series data reported when threshold standards for transfusion were lower. The estimated frequency of 8% in the present analysis was calculated

from reports of TURP-treated patients in 23 trials that included 6375 patients (Figure 3.29). The Veterans Affairs Cooperative Study, the single best TURP trial conducted to date, reported a transfusion rate of 4% to 5% — a rate the Panel believes better reflects current practice[30].

Results of meta-analyses of RCTs revealed that the frequency of transfusion was significantly ($p < .05$) lower in those treated with transurethral laser coagulation than with TURP while transfusion rates were similar in those treated with TUIP or transurethral electrovaporization versus TURP; a single RCT found the transfusion rate for transurethral laser vaporization to be statistically significantly lower than for TURP. (No RCTs reported transfusion data for holmium laser resection/enucleation or open prostatectomy.) Transfusion rates based on SAMAs were <3% for transurethral laser coagulation, TUIP, holmium laser resection/enucleation prostatectomy, transurethral electrovaporization, and transurethral laser vaporization (Figure 3.29). On the basis of one single-arm study (n=380), the transfusion rate following open prostatectomy was estimated to be nearly 27%; the Panel does not believe this rate reflects current practice and is of the opinion that the current transfusion rate for open prostatectomy is less than the rate reflected in this study. Transfusion is not a risk for minimally invasive, heat-based therapy such as TUMT or TUNA.

Figure 3.29. Transfusion rates for surgical therapies (based on single-arm meta-analysis).



Infections/Urinary Tract Infections

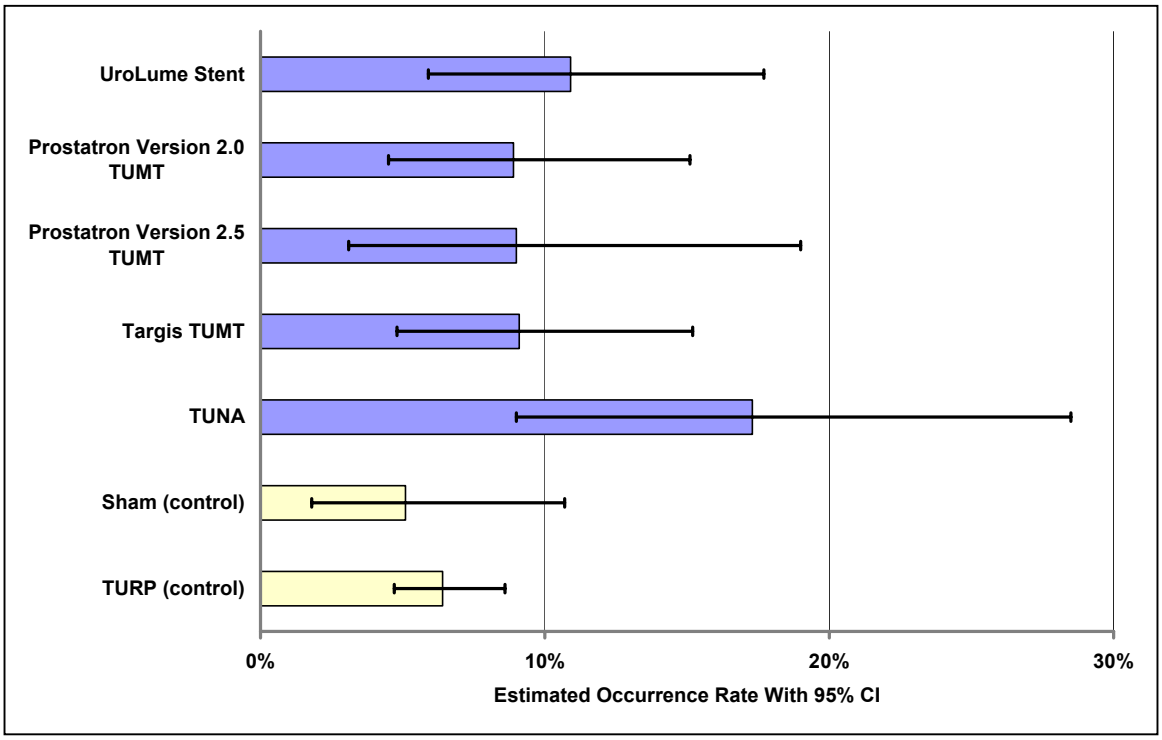
The category of infections or UTIs includes a wide variety of infectious diseases, such as wound infections, epididymitis, orchitis, and bacterial UTI reported at any time after an intervention.

Results of meta-analyses of RCTs revealed that the frequency of infections/UTIs was similar in those treated with either Prostatron Versions 2.0 or 2.5 TUMT as compared to TURP (6% rate). A single RCT found patients treated with TUNA experienced a statistically significantly higher rate of infections/UTIs compared with TURP (Figure 3.30). Single-arm analysis also showed higher rates with TUNA than TURP. It is not clear why this is the case, and the finding may be the result of reporting variation. Rates based on SAMAs were ≤ 10% for the Prostatron

Versions 2.0 and 2.5 TUMT and Targis TUMT. (No RCTs with TURP controls reported on UTI rates for the Targis TUMT or the UroLume stent.)

With the rate of infections/UTIs associated with sham therapy (5% rate) as the comparator, RCTs showed that the frequency of occurrence of these conditions was similar in patients treated with Targis TUMT. The rate was found in one RCT to be statistically significantly higher in those treated with the Prostatron Version 2.0 TUMT than in sham-treated patients. (No RCTs with sham controls that reported UTI rates were found for the Prostatron Version 2.5 TUMT.)

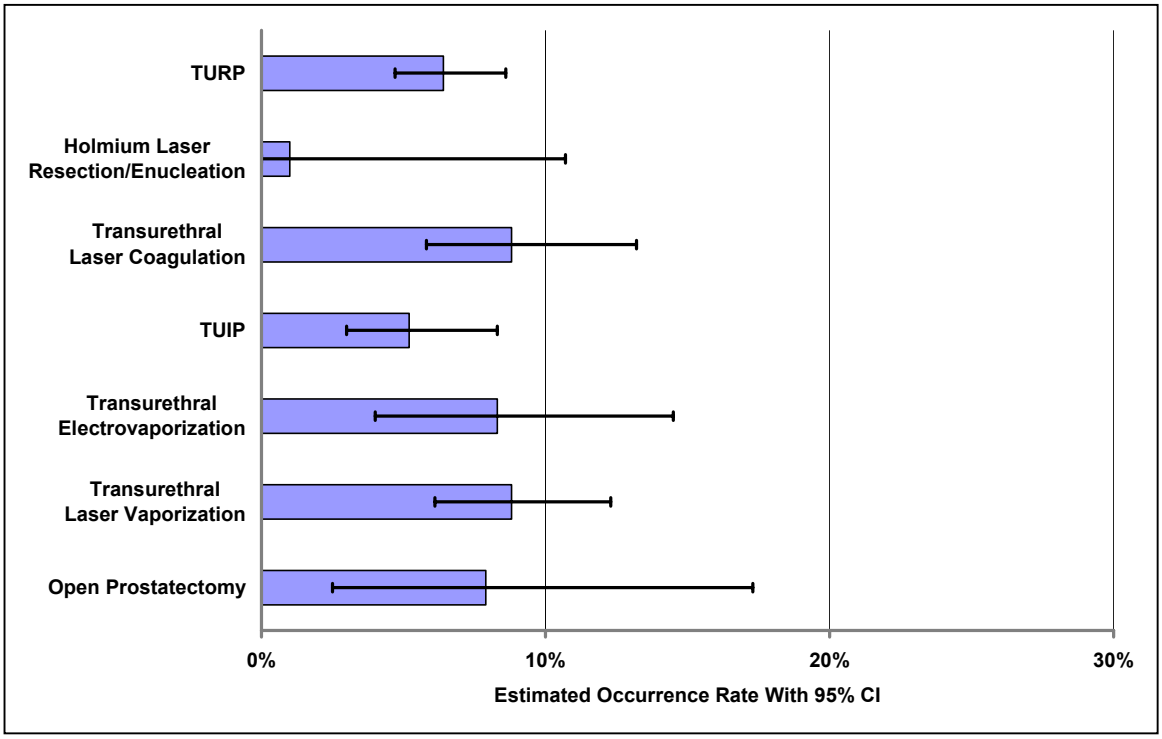
Figure 3.30. Infection/UTI rates for minimally invasive therapies (based on single-arm meta-analysis).



Meta-analyses of RCTs showed rates of infection/UTI in patients treated with transurethral laser coagulation, TUIP, or transurethral electrovaporization were not statistically significantly different from those for TURP-treated patients; single RCTs also found similar results for either transurethral laser vaporization or open prostatectomy compared to TURP. Results of SAMAs

revealed rates ranging from 5% for TUIP to 9% for transurethral laser coagulation and transurethral laser vaporization (Figure 3.31); one small single-arm study reported a 1% rate in patients treated with holmium laser resection/enucleation. (No RCTs reported UTI rates for holmium laser resection/enucleation.)

Figure 3.31. Infection/UTI rates for surgical therapies (based on single-arm meta-analysis).



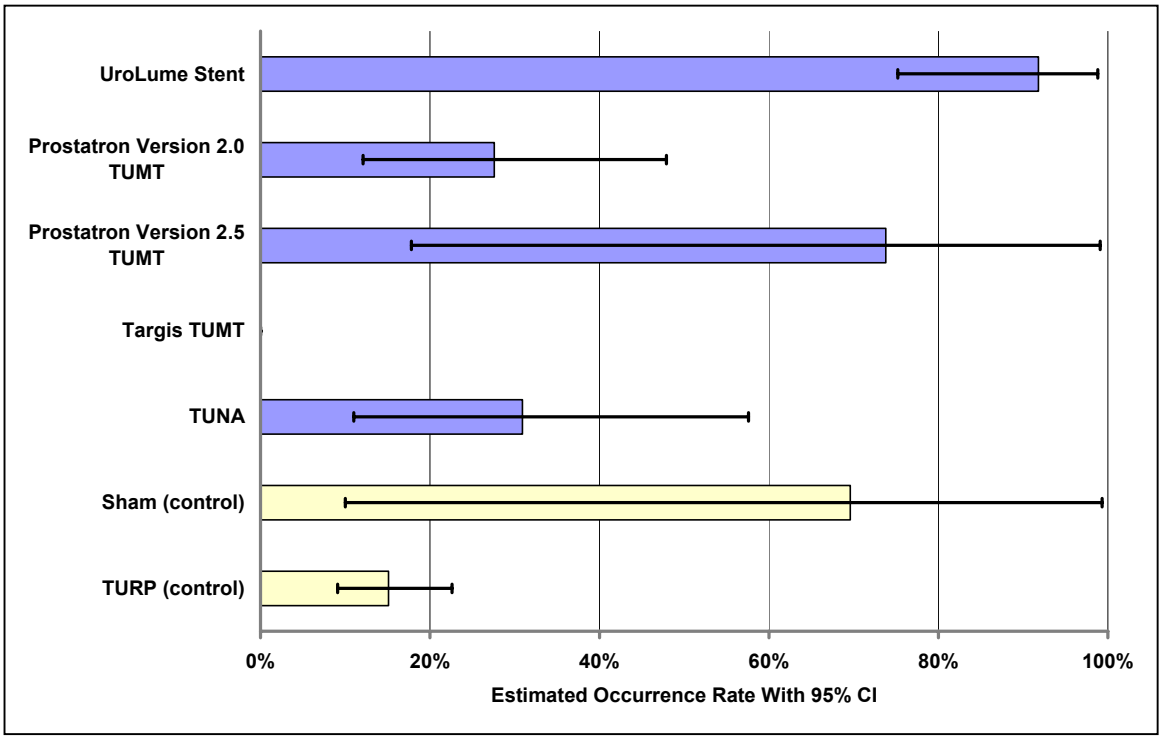
Irritative Voiding Symptoms

Minimally invasive and surgical procedures induce irritative voiding symptoms immediately after and for some time subsequent to the procedure. Periprocedure and postprocedure adverse events associated with voiding symptoms include frequency, urgency, and urge incontinence and are categorized as postprocedure irritative adverse events. Such events are reported more often following heat-based therapies than following tissue-ablative surgical procedures. Because they impact quality of life, irritative events are important and warrant documentation in outcomes

tables. Unfortunately, all patients will have some symptoms immediately following the procedure during the healing process. Because there is no standard for reporting this outcome, some studies reported these early symptoms while others did not.

Results of single RCTs show no statistically significant differences in rates of irritative voiding symptoms between patients treated with TURP (15% rate) versus those treated with Prostatron Versions 2.0 or 2.5 TUMT or TUNA. Findings from SAMAs showed that large percentages of patients undergoing minimally invasive treatments for BPH with the UroLume stent or the Prostatron Version 2.5 TUMT experienced irritative voiding symptoms (92% and 74%, respectively; Figure 3.32). (No RCT comparisons with TURP were found for the UroLume stent; no RCT comparisons with TURP or single-arm study reports were found for Targis TUMT.)

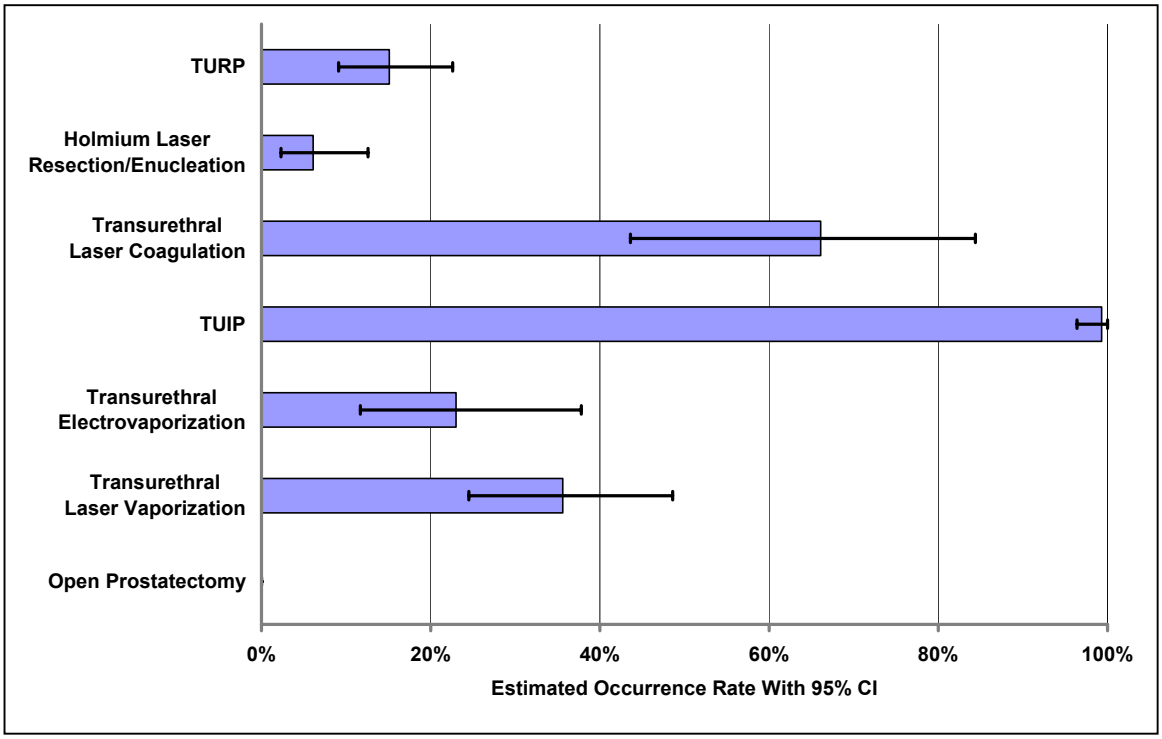
Figure 3.32. Postprocedure irritative voiding symptom rates for minimally invasive therapies (based on single-arm meta-analysis). The missing bar indicates that data were not available.



Two RCTs using sham as control reported on irritative voiding symptoms. One study reported that 100% of patients in both the sham and treatment (Prostatron Version 2.0) arms had irritative voiding symptoms immediately following the procedure. Meta-analysis resulted in very high (70%) rates for sham and virtually 100% for Prostatron Version 2.0. These rates are probably inaccurate and reflect the early irritative voiding symptoms as discussed above. A single study comparing microwave heat treatment to sham showed a 16% rate for sham-treated patients and a 42% rate for those treated with the Urowave TUMT (Dornier MedTech, Sana'a, Yemen) ($p < .05$).

No statistically significant differences between irritative voiding symptom rates for transurethral laser coagulation or transurethral electrovaporization versus TURP were found in meta-analysis of RCTs; a single RCT found rates to be similar for transurethral laser vaporization and TURP. Rates of occurrence of this adverse event varied widely across therapies. For example, a single-arm study of holmium laser resection/enucleation prostatectomy found such symptoms in 5/84 (6%) of patients while another such study of TUIP found that 100/100 patients reported postprocedure irritative voiding symptoms (Figure 3.33). Single-arm meta-analyses of transurethral laser coagulation, transurethral electrovaporization, and transurethral laser vaporization revealed irritative voiding symptom rates of 66%, 23%, and 36%, respectively. (No RCTs reported irritative voiding symptom rates for TUIP or the holmium laser resection/enucleation; no studies reporting irritative voiding symptoms were found for open prostatectomy.)

Figure 3.33. Postprocedure irritative voiding symptom rates for surgical therapies (based on single-arm meta-analysis). The missing bar indicates that data were not available.



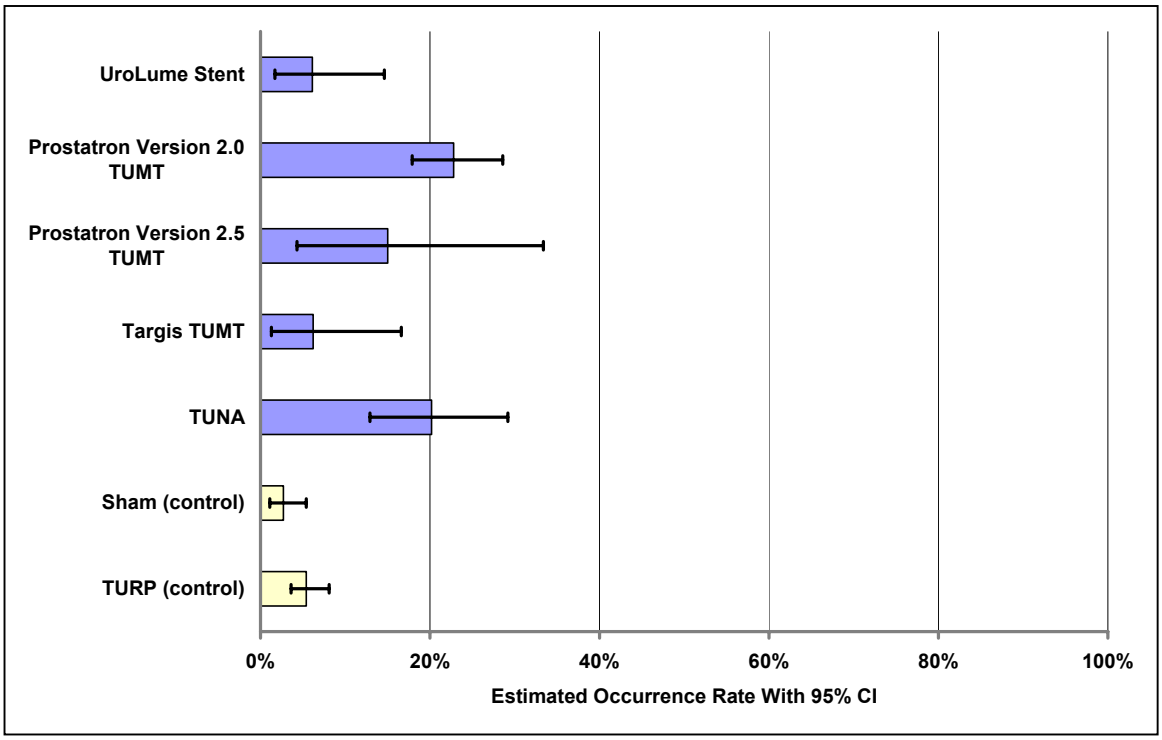
Acute Urinary Retention

The category of acute urinary retention reflects the number of patients requiring recatheterization after a protocol-defined postprocedure period of catheterization. Unfortunately, some studies report "protocol required" or "investigator option" episodes of postprocedure catheterization while others report only catheterization performed for inability to urinate. Such differences in reporting are reflected in the wide confidence intervals for frequency estimates.

Meta-analyses of RCTs showed acute urinary retention was statistically significantly more common in patients treated with the Prostatron Version 2.0 TUMT than in those treated with TURP (where acute urinary retention occurs in approximately 5% of patients); the single RCT comparing the Prostatron Version 2.5 TUMT with TURP found similar rates of acute urinary retention for these therapies. Rates based on SAMAs revealed a range of 23% for the Prostatron

Version 2.0 TUMT and 20% for TUNA to 6% for Targis and the UroLume stent (Figure 3.34). (No RCTs with TURP controls reported on acute urinary retention for Targis TUMT, TUNA, or the UroLume stent.)

Figure 3.34. Acute urinary retention rates for minimally invasive procedures (based on single-arm meta-analysis).

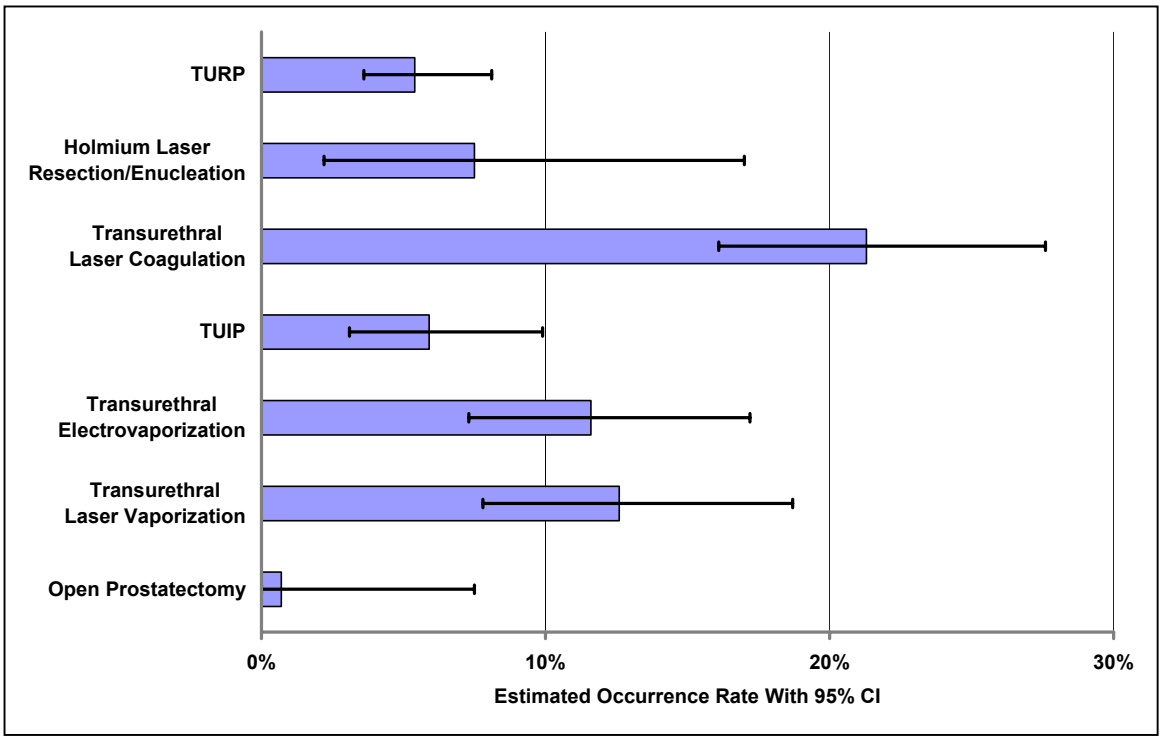


With the rate of acute urinary retention associated with sham therapy (3% rate) as the comparator, meta-analyses of RCTs showed that the frequency of occurrence was statistically significantly higher in patients treated with the Prostatron Version 2.0 TUMT. A single RCT did not find a statistically significantly higher rate for the Targis TUMT versus sham. (No sham-controlled RCTs have reported complications for the Prostatron Version 2.5 TUMT.)

Based on meta-analyses of RCTs with TURP controls, acute urinary retention was statistically significantly more common with transurethral vaporization (either electrocautery or laser) but not with TUIP; single RCTs using TURP as the comparator found a statistically

significant higher rate of acute urinary retention in those treated with transurethral laser coagulation but not in patients undergoing open prostatectomy. Single-arm meta-analyses revealed rates of ≥ 10% for transurethral electrovaporization and transurethral laser vaporization and >20% for laser coagulation (Figure 3.35). (No RCTs reported on acute urinary retention for holmium laser resection/enucleation.)

Figure 3.35. Acute urinary retention rates for surgical therapies (based on single-arm meta-analysis).



Long-term Adverse Events Reported With Minimally Invasive and Invasive Therapies

Urinary Incontinence

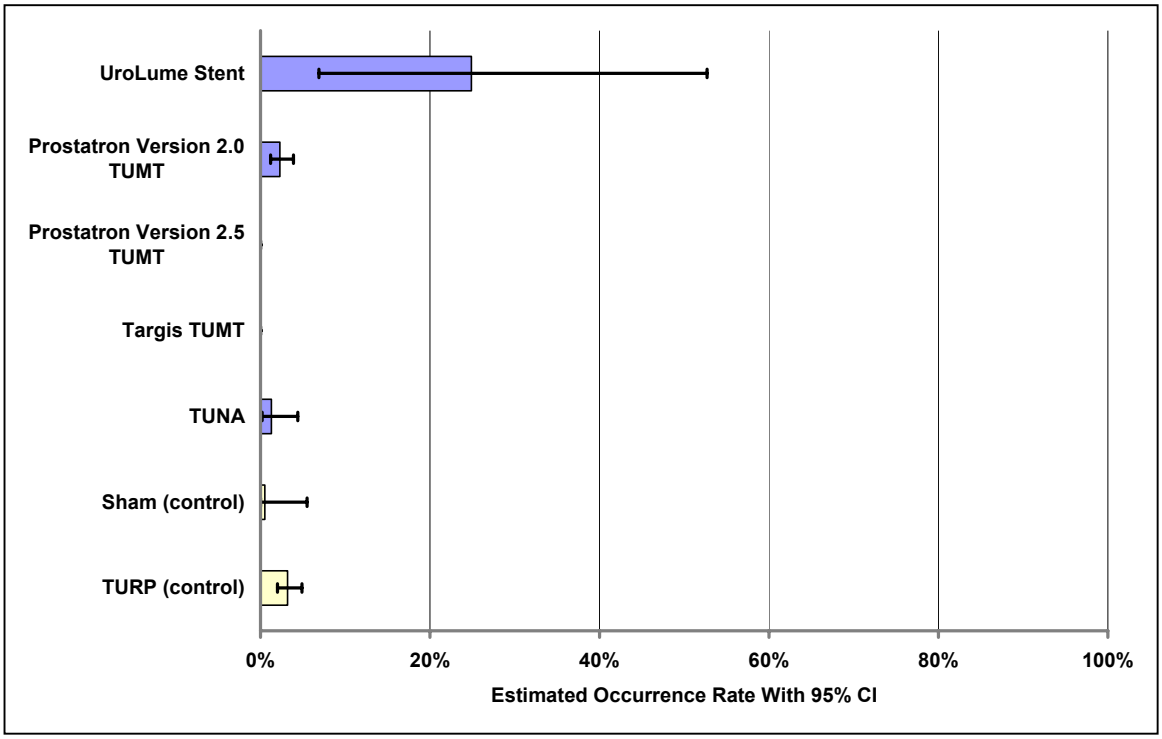
The category urinary incontinence represents a heterogeneous group of adverse events, including total and partial urinary incontinence, temporary or persistent incontinence, and stress or urge incontinence. The estimated frequency of 3% for TURP was calculated from 19 trials that included 5005 TURP-treated patients (Figure 3.36). However, the Veterans Affairs Cooperative Study, the single best TURP trial conducted to date, reported an incontinence rate of

1% in both the TURP and watchful waiting arms[30]. Results of the present analysis showed considerable variability in rates of occurrence between minimally invasive and surgical interventions.

A meta-analysis of RCTs comparing Prostatron Version 2.0 TUMT to TURP and a single RCT of TUNA versus TURP revealed no statistically significant differences in rates of incontinence between therapies. Results of SAMAs yielded rates ranging from <3% for the Prostatron Version 2.0 TUMT and TUNA to 25% for the UroLume stent (Figure 3.36). The higher rates for the UroLume stent may be the result of selection bias because this treatment is usually reserved for more infirm patients. (No studies reported on incontinence for the Prostatron Version 2.5 TUMT or Targis TUMT. No RCTs reporting incontinence data were found for the UroLume stent.)

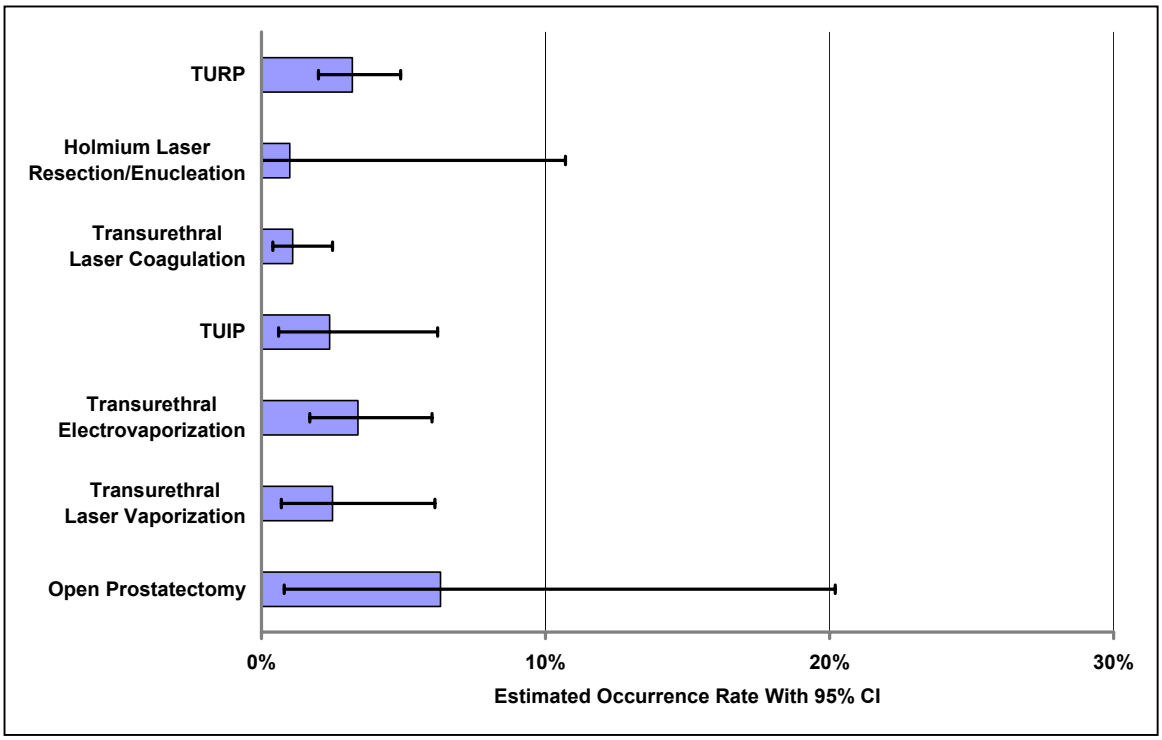
The incontinence rate for the Prostatron Version 2.0 TUMT was not found to be significantly different from sham in one RCT.

Figure 3.36. Urinary incontinence rates for minimally invasive therapies (based on single-arm meta-analysis). Missing bars indicate that data were not available.



Results of meta-analyses of RCTs revealed no statistically significant differences between rates of incontinence in those treated with TURP compared with transurethral laser coagulation, TUIP, or transurethral electrovaporization. Similarly, single RCTs showed no statistically significant differences between such rates for patients treated with TURP versus holmium laser resection/enucleation prostatectomy, transurethral laser vaporization, or open prostatectomy. Incontinence rates based on SAMAs were <5% for transurethral laser coagulation, TUIP, transurethral electrovaporization, holmium laser resection/enucleation prostatectomy and transurethral laser vaporization (Figure 3.37). The probability of occurrence with open prostatectomy was found to be 6%, although the Panel believes this rate does not reflect current practice.

Figure 3.37. Urinary incontinence rates for surgical therapies (based on single-arm meta-analysis).



Secondary Procedures

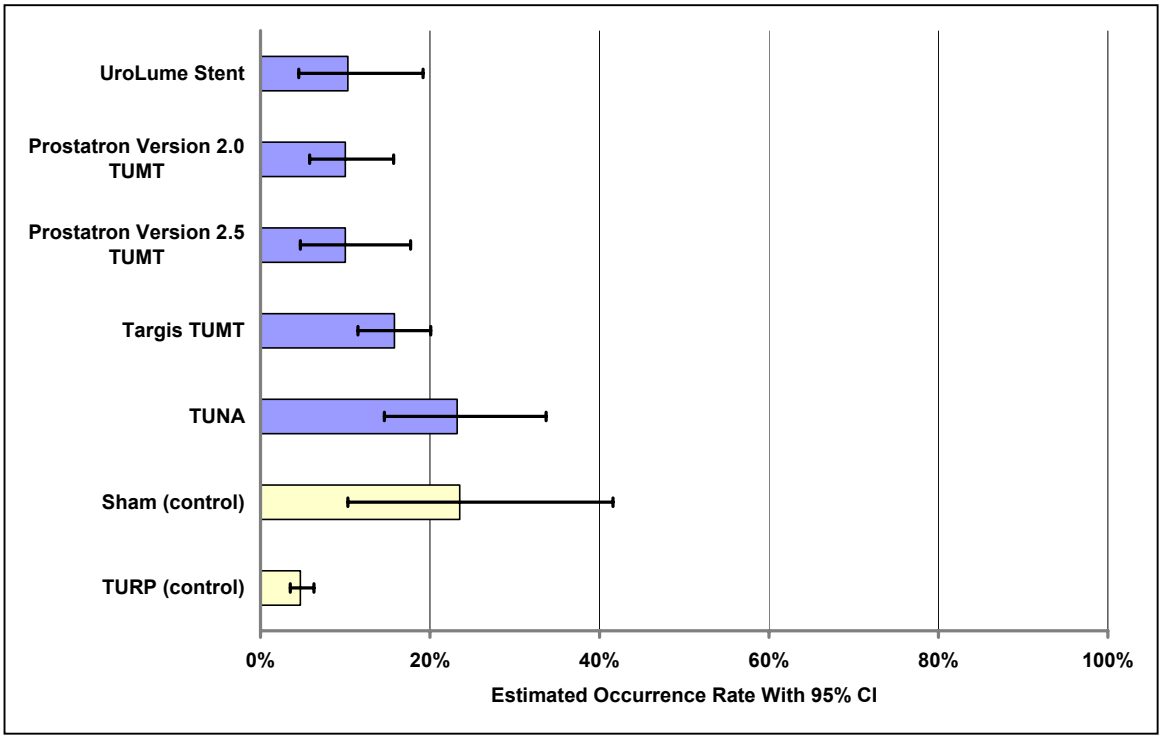
Secondary procedures, defined as interventions rendered by the treating physician for the same underlying condition as the first intervention, are challenging to classify. Examples of such procedures include initiation of medical therapy following a minimally invasive or surgical treatment, minimally invasive treatment following surgical intervention, or surgical intervention following a minimally invasive treatment.

Enumerating secondary procedures from published reports is difficult. First, the threshold for initiating a secondary procedure varies by patient, physician, and the patient-physician interaction. In the absence of clearly defined thresholds for the success or failure of an initial intervention, secondary procedures are initiated on the basis of subjective perceptions on the part of either patients or treating physicians, which may not be reproducible or comparable between

investigators, trials, or interventions. In many cases, patients involved in treatment trials feel a sense of responsibility toward the physician; given this commitment, patients may abstain from having a secondary procedure even through they may feel inadequately treated. Conversely, patients involved in treatment trials are more closely scrutinized in terms of their subjective and objective improvements; therefore, failures may be recognized more readily and patients may be referred more quickly for additional treatment. Moreover, the duration of trials and follow-up periods both affect rates at which secondary procedures are performed. Thus, although patients receiving long-term follow-up are at greater risk for treatment failure than those followed for short periods, it is virtually impossible to construct Kaplan-Meier curves or perform survival analyses for secondary procedure rates. In short, while it is quite clear that secondary procedures and treatment failures cause major health expenditures for the treatment of patients with BPH, it is also clear that the current literature does not allow a meaningful comparison of secondary procedures across therapies. As a result, the estimates for secondary procedure rates in the tables and graphs should be viewed with caution.

The estimated frequency of 5% used in the present analysis of secondary procedures was calculated from reports of TURP-treated patients in 21 trials (Figure 3.38). Findings of meta-analyses of RCTs showed that secondary procedure rates were statistically significantly higher than for TURP for the Prostatron Version 2.0 TUMT but not for the Prostatron Version 2.5 TUMT. Single-arm meta-analyses revealed that approximately 10% of patients treated with the Prostatron Versions 2.0 or 2.5 TUMT or with the UroLume stent required secondary procedures. Although rates were slightly higher for Targis TUMT and TUNA, these data may be anomalous because information for only limited numbers of trials and patients was available. (No RCT comparisons to TURP were found for Targis TUMT, TUNA, or the UroLume stent.)

Figure 3.38. Secondary procedure rates for minimally invasive therapies (based on single-arm meta-analysis).

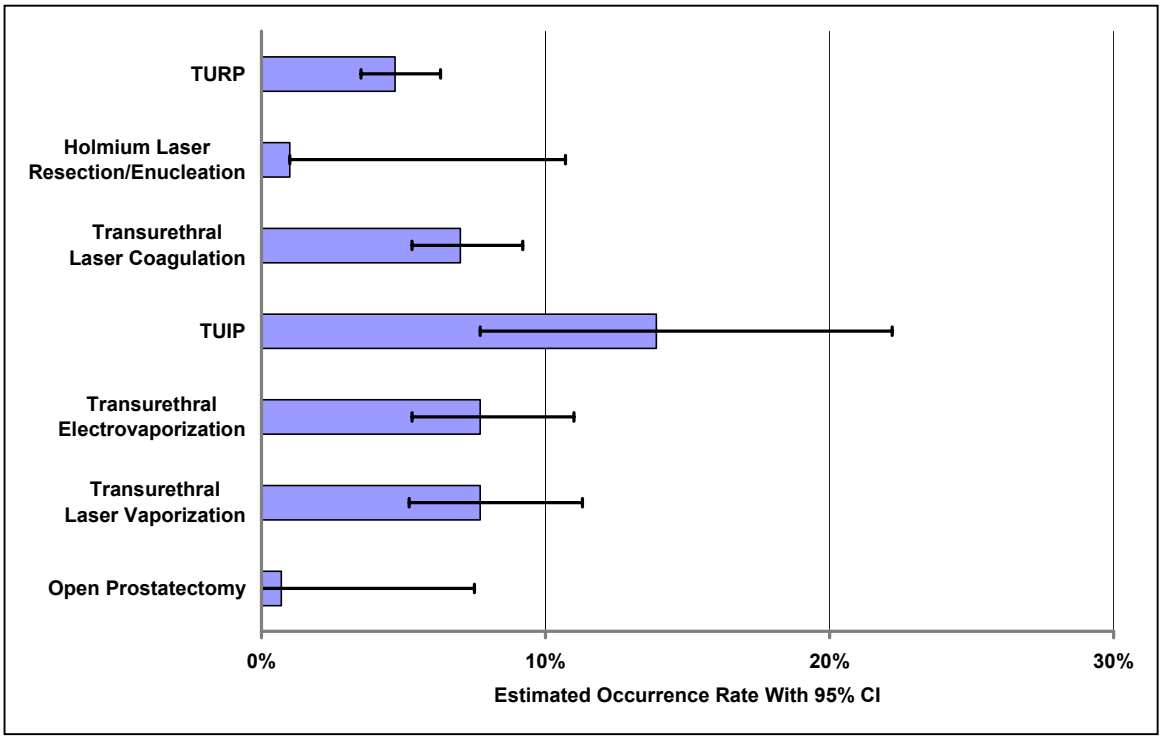


No statistically significant difference was found between the secondary procedure rates for sham (24% rate) and the Prostatron Version 2.0 TUMT in meta-analyses of RCTs. (No RCTs with sham controls were found for the Prostatron Version 2.5 or Targis TUMT.)

Results of meta-analyses of RCTs found secondary procedure rates for TUIP and transurethral laser vaporization to be statistically significantly higher than for TURP but rates for transurethral laser coagulation and transurethral electrovaporization to be similar to those for TURP. The single RCT comparing open prostatectomy with TURP found no significant difference between therapies in secondary procedure rates. Single-arm meta-analyses found secondary procedure rates of approximately 7% for transurethral laser coagulation, transurethral electrovaporization, and transurethral laser vaporization while the rate for TUIP was 14% (Figure 3.39). The lone single-arm study of open prostatectomy reported a secondary procedure

rate of <1%. (No RCTs reported on secondary procedures for holmium laser resection/enucleation.)

Figure 3.39. Secondary procedure rates for surgical therapies (based on single-arm meta-analysis).



Bladder Neck Contracture/Urethral Stricture

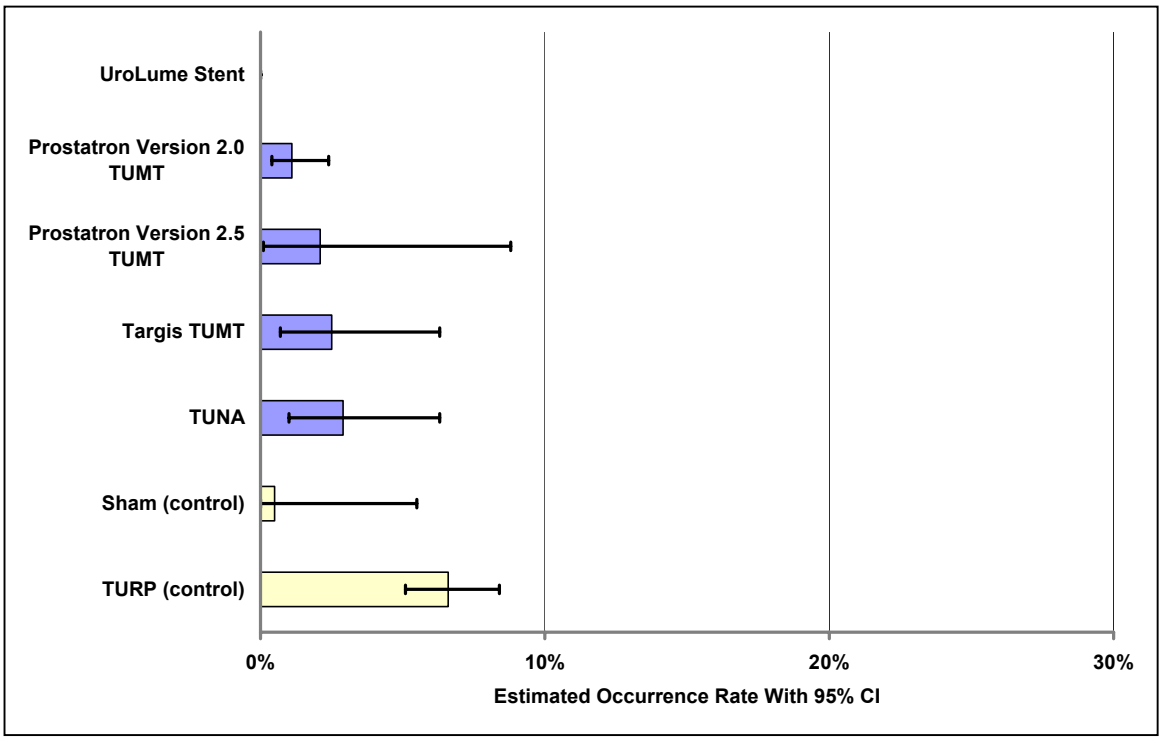
Minimally invasive and surgical interventions for BPH have the potential of inducing scarring around the bladder neck or in the urethra. These outcomes are far less common with minimally invasive treatments than with procedures that ablate tissue.

Meta-analyses of RCTs revealed no statistically significant differences between rates of bladder neck contracture and urethral stricture in patients treated with the Prostatron Versions 2.0 or 2.5 TUMT versus TURP (7% rate); a single RCT of TUNA versus TURP also found rates of this adverse event to be similar between therapies. For these procedures, SAMAs yielded estimated rates less than half the rate estimated for TURP (Figure 3.40). The rarity of this

outcome may account for the lack of statistical significance in the RCT data; very large studies would be needed to show statistical significance. Also there is a question of ascertainment bias because not all investigators may look closely for small strictures. (No RCTs with TURP controls reporting these outcomes were found for Targis TUMT; no RCT comparisons with TURP or single-arm study reports were found for the UroLume stent.)

The estimated frequency of bladder neck contracture and urethral stricture in sham-treated patients was <1%, not appreciably different from the <3% rates for the Prostatron Versions 2.0 and 2.5 TUMT and for Targis TUMT based on SAMAs and single-arm studies (Figure 3.40). (No RCT reports with sham controls were found for the Prostatron Versions 2.0 or 2.5 TUMT.)

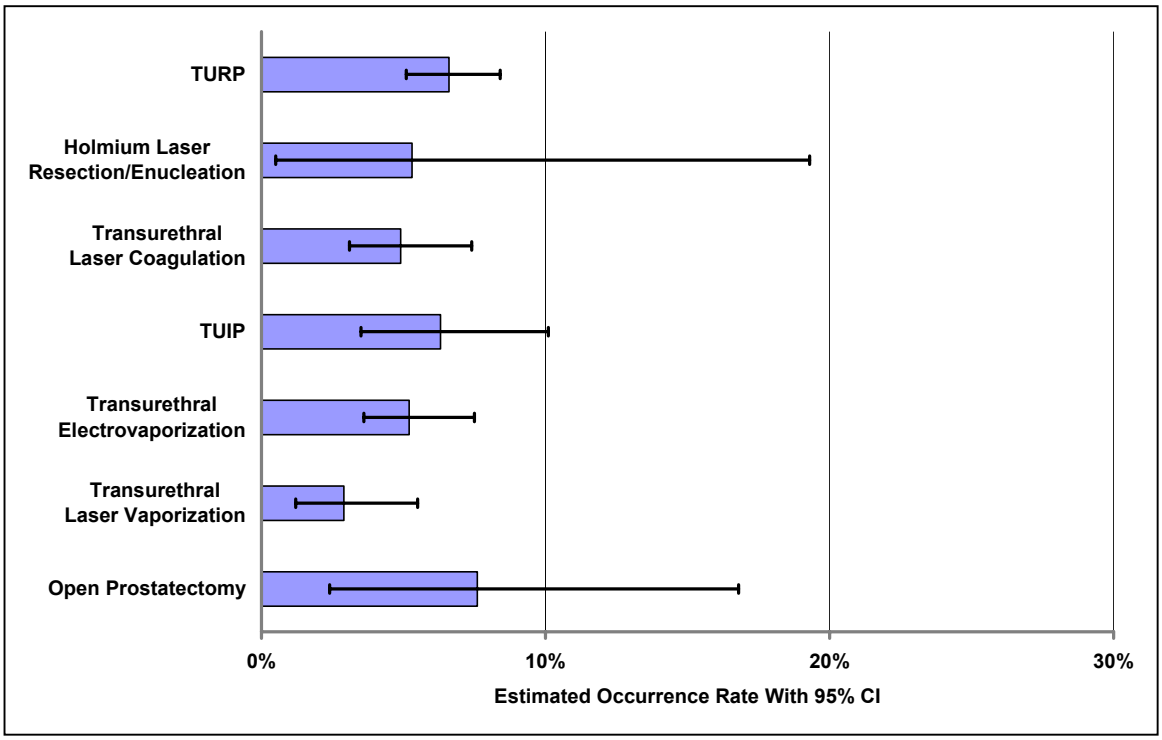
Figure 3.40. Bladder neck contracture and urethral stricture rates for minimally invasive therapies (based on single-arm meta-analysis). The missing bar indicates that data were not available.



Results of meta-analyses of RCTs showed no statistically significant differences between rates of bladder neck contracture and urethral stricture for transurethral laser coagulation, TUIP,

transurethral electrovaporization, or transurethral laser vaporization versus TURP. The one RCT comparing open prostatectomy with TURP also found no statistically significant difference in rates between procedures. Single-arm studies or SAMAs revealed rates of <8% for all procedures (Figure 3.41). (No RCTs reported on bladder neck contracture and urethral stricture for holmium laser resection/enucleation.)

Figure 3.41. Bladder neck contracture and urethral stricture rates for surgical therapies (based on single-arm meta-analysis).

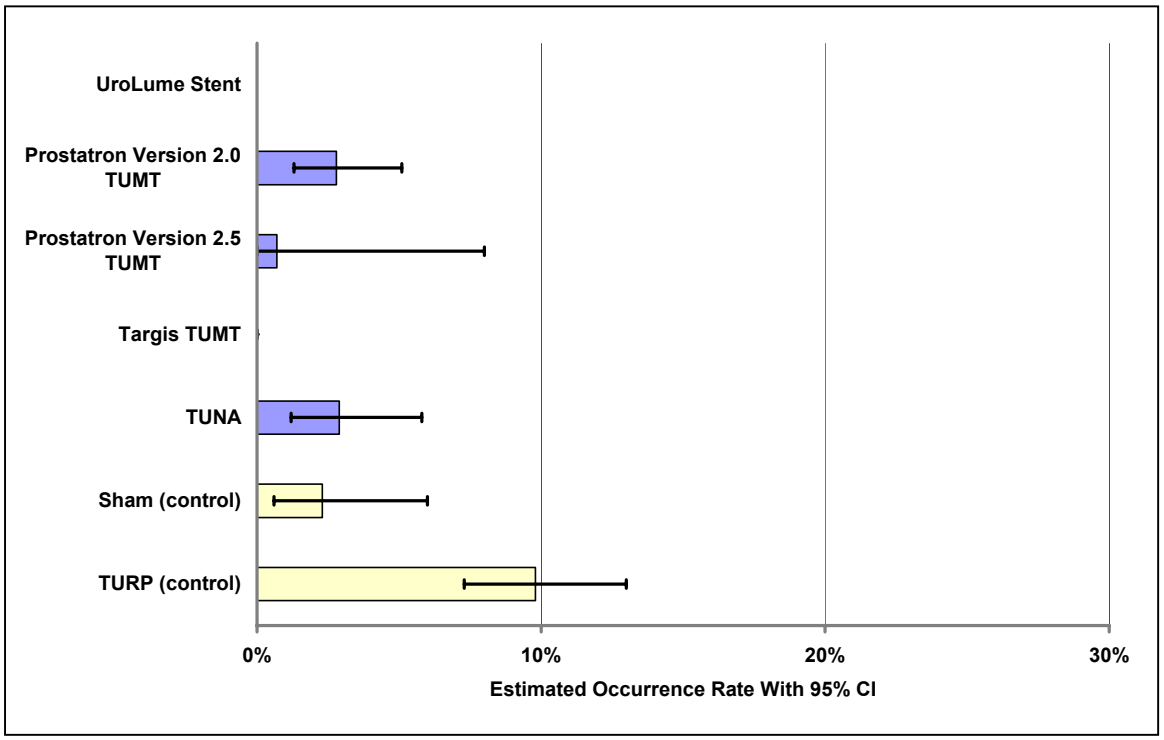


Sexual Dysfunction

Minimally invasive and surgical interventions have the capacity to induce sexual dysfunction in the form of erectile dysfunction or in the form of retrograde or absent ejaculation. These adverse events were classified as either erectile dysfunction or ejaculatory dysfunction. The estimated frequencies for erectile dysfunction were calculated as 10% based on 15 trials that included TURP-control arms and as 2% based on four trials that included sham controls (Figure

3.42). In the Veterans Affairs Cooperative Study, the incidence of erectile dysfunction was actually lower in the TURP arm than in the watchful waiting arm[30]. The estimated rate for ejaculatory dysfunction for TURP was calculated as 65% based on 19 trials (including TURP-control arms), and the rate for sham was 2% based on the control arms from three trials.

Figure 3.42. Erectile dysfunction rates for minimally invasive therapies (based on single-arm meta-analysis). Missing bars indicate that data were not available.



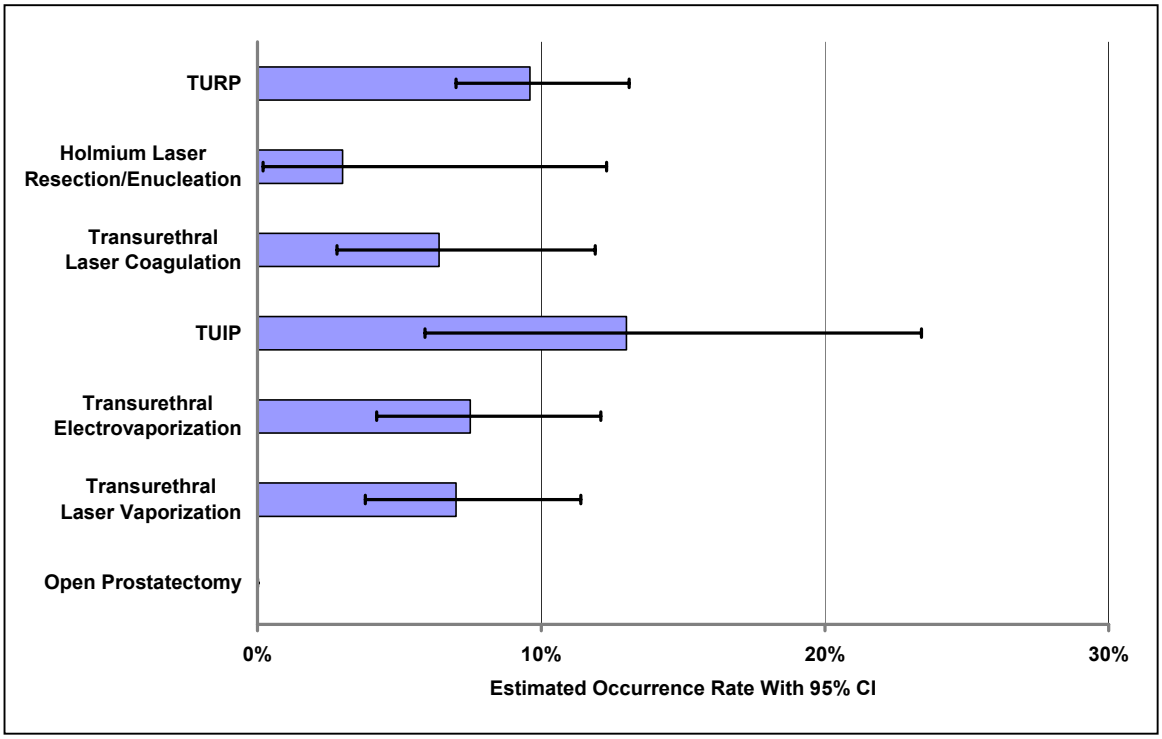
Results of meta-analyses of RCTs revealed that erectile dysfunction rates were similar in patients treated with the Prostatron Version 2.0 TUMT and TURP. Randomized controlled trials of the Prostatron Version 2.5 TUMT versus TURP found no statistically significant difference between therapies but a statistically significantly lower rate for TUNA versus TURP. The clinical relevance of the statistical significance is questionable given the low rates involved. Single-arm studies and SAMAs for the Prostatron Versions 2.0 and 2.5 TUMT and TUNA

showed erectile dysfunction rates of <3% (Figure 3.42). (No studies reporting on erectile dysfunction were found for the Targis TUMT or UroLume stent.)

A single RCT of the Prostatron Version 2.0 TUMT versus sham found no statistically significant difference in erectile dysfunction rates. (No sham-controlled RCTs reporting on erectile dysfunction were found for the Prostatron Version 2.5 TUMT; no studies reported on erectile dysfunction for the Targis TUMT.)

Meta-analyses of RCTs found no statistically significant differences between rates of erectile dysfunction between TUIP or transurethral electrovaporization versus TURP. Randomized controlled trials also found no statistically significant differences between rates of erectile dysfunction for transurethral laser coagulation or transurethral laser vaporization versus TURP. Single-arm meta-analyses revealed erectile dysfunction rates of <15% for transurethral laser coagulation, TUIP, holmium laser resection/enucleation prostatectomy, transurethral electrovaporization, and transurethral laser vaporization (Figure 3.43). (No RCT data were found for erectile dysfunction rates for holmium laser resection/enucleation prostatectomy, and no data were found for open prostatectomy.)

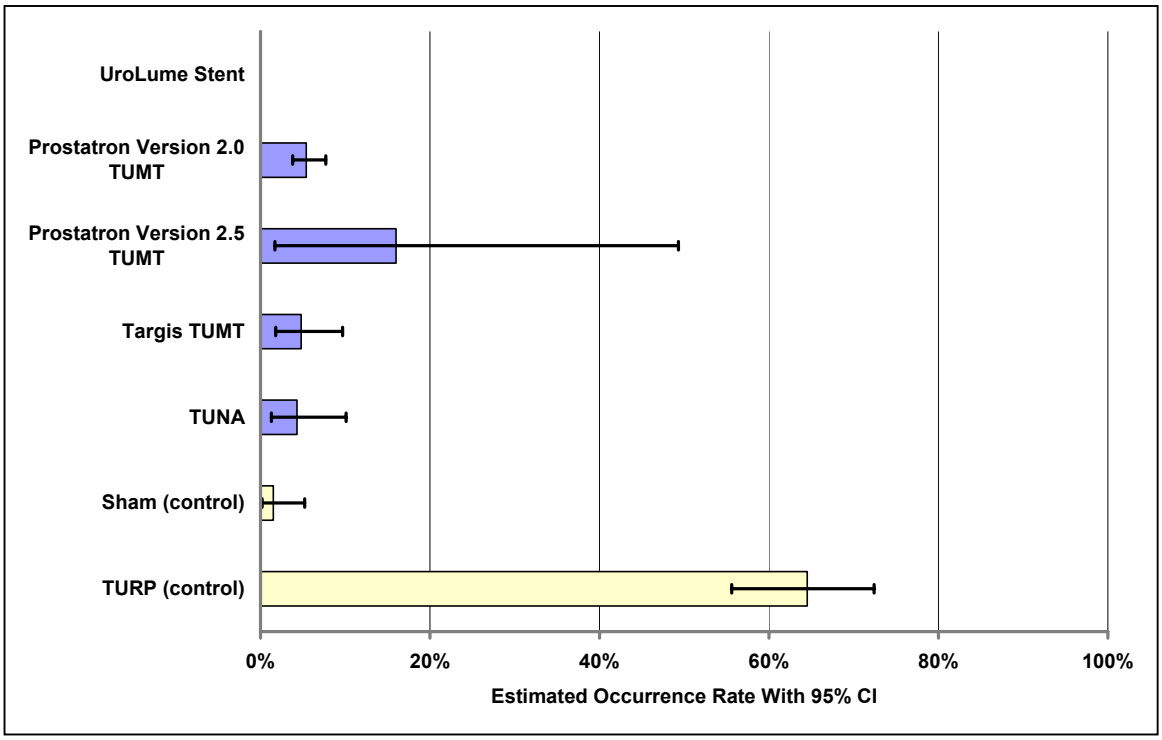
Figure 3.43. Erectile dysfunction rates for surgical therapies (based on single-arm meta-analysis). The missing bar indicates that data were not available.



Results of meta-analyses of RCTs revealed that ejaculatory dysfunction rates were statistically significantly lower in patients treated with the Prostatron Version 2.0 TUMT versus TURP; single RCTs found parallel results for the Prostatron Version 2.5 TUMT and for TUNA. Results of SAMAs revealed rates of 5%, 16%, and 4%, respectively, for these therapeutic alternatives to TURP (Figure 3.44). A SAMA of data for Targis TUMT revealed an ejaculatory dysfunction rate of 5%. This is most likely due to the fact that all patients had intraprostatic wires placed for temperature monitoring that resulted in hemospermia. (No RCTs reporting ejaculatory dysfunction versus TURP were found for the Targis TUMT; no studies reported ejaculatory data for the UroLume stent.)

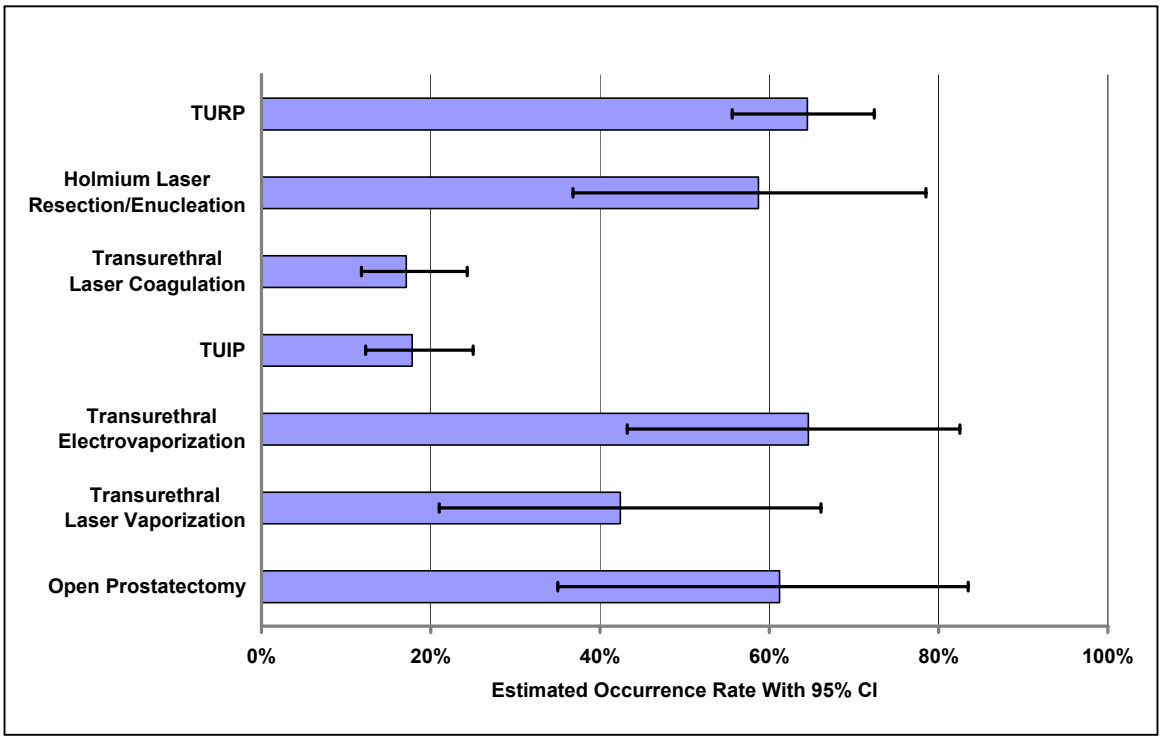
A single RCT comparing sham and the Targis TUMT revealed no statistically significant difference between therapies. (No RCTs reporting ejaculatory dysfunction versus sham were found for the Prostatron Versions 2.0 or 2.5 TUMT.)

Figure 3.44. Ejaculatory dysfunction rates for minimally invasive therapies (based on single-arm meta-analysis). The missing bar indicates that data were not available.



Meta-analyses of RCTs found rates of ejaculatory dysfunction to be statistically significantly lower with either transurethral laser coagulation or TUIP versus TURP; differences between transurethral electrovaporization and transurethral laser vaporization versus TURP were not statistically significant. The single RCT comparing open prostatectomy and TURP found no significant difference between therapies in rates of this adverse event. As would be expected, SAMAs revealed the lowest rates of ejaculatory dysfunction with transurethral laser coagulation and TUIP (17% and 18%, respectively; Figure 3.45). (No RCT data on ejaculatory dysfunction were found for holmium laser resection/enucleation.)

Figure 3.45. Ejaculatory dysfunction rates for surgical therapies (based on single-arm meta-analysis).



Appendix 3: Detailed Outcomes Tables

Summary. Analysis Approach and Explanation of Layouts of Detailed Benign Prostatic Hyperplasia Outcomes Table Layouts

Analysis Approach

Analysis was performed in two ways because the available evidence includes both randomized controlled trials and clinical series. In what is called "single-arm analysis" (see discussion below), all patient groups from all studies that evaluate a particular treatment are combined and meta-analyzed to estimate the frequency of each outcome. Obviously, only patient groups reporting a particular outcome were used in estimating the frequency of that outcome. An exception was made where a zero occurrence of an adverse event could reasonably be inferred; inferred zeros were included. Due to lack of variance data, single-arm analyses for symptom scores, peak flow, and quality of life measures were performed using weighted averages instead of meta-analyses.

Randomized controlled trials (RCTs) evaluate two or more different interventions. Analysis of RCT data allows for control of various confounding factors, of which patient selection is primary. Because of differences in baseline symptom score and/or flow rate, the Panel has elected to use the absolute change from baseline in score or flow rate as the basis for analysis. The absolute change was used rather than the percentage change because a large majority of studies reported results as the absolute change. Because information on the spread change values within a study is necessary for meta-analysis, only studies that reported change data and a measure of spread (variance, standard deviation, or standard error) of that change have been used in symptom score or peak flow RCT analysis. Studies that reported both initial and follow-up values (or for which follow-up values could be computed) have been used in the single-arm analysis. Naturally, studies that were used in the RCT analysis were used in the single-arm analysis. For the analysis of adverse events, the actual rates of adverse events in the two arms were needed. Because the outcomes are binary (either occur or not), no spread data were needed or appropriate.

The analysis of the RCT data determines the absolute difference between two arms of the study. In the case of adverse events, this difference is interpreted in a straightforward manner. If the adverse event occurred in 3 percent of patients in arm 1 and 4 percent of patients in arm 2, the difference is 1 percent; i.e., the adverse event occurred in 1 percent more of patients in group 2 than patients in group 1. In the case of symptom scores, it is a bit more complex. The basis of analysis is a change in score. The difference in score change between two arms is the result of the analysis. Thus if in arm 1 there is a baseline score of 20 and a follow-up score of 15, the change is –5 (15 – 20). In arm 2, if the baseline is 21 and the follow-up is 16.5, the change is –4.5. The difference is .5 (-4.5 – -5.0). Arm 2 received .5 less of a symptom score reduction than arm 1.

The principal advantage of using RCT data is the fact that RCTs control for a number of potential biases. One disadvantage is that not all RCTs compare the same treatments. For the purpose of this analysis, we have concentrated on RCTs that compare treatments to standard comparison treatments. For medical treatments, the standard comparison treatment is placebo.

Appendix 3: Detailed Outcomes Tables

For minimally invasive treatments, two standard comparison treatments have been used, sham and TURP. For surgical studies, TURP is the standard comparison treatment. Studies that randomize treatments to therapies other than the standard comparisons were not included in the RCT analyses on these tables, although they were included in the single-arm analyses.

Because the meta-analysis was performed using two methods, the results of the two analyses were adjusted to a similar scale. The single-arm analysis estimated either the rate (for a adverse event) or the change (for symptom scores or flow rates). RCT analyses yielded the difference in rate or change compared to a standard comparator. Adding a value for the comparator to the RCT difference yields an estimate for the treatment that should be comparable to the single-arm analysis. The value that has been used for the comparator is the value resulting from the single-arm analysis. This will become clear in the examples below.

Layouts of Outcomes Tables

Detailed Benign Prostatic Hyperplasia (BPH) Outcomes Tables are included in this appendix. Three types of tables summarize data concerning:

1. Estimates of change in efficacy scores/rates
2. Estimates of rates of occurrence of adverse events
3. Comparison of analyses of rates of occurrence of adverse events

Information is summarized separately for medical therapies, minimally invasive therapies, surgical therapies, and phytotherapies. Outcomes for medical and phytotherapies are compared with outcomes reported for placebo. Outcomes for minimally invasive therapies are compared with both sham and TURP, while those for surgical therapies are compared only with TURP.

The following describes each type of table, provides an example of the layout of each using medical therapy with alpha blockers versus placebo as the example, and describes the contents of each cell within the table. These latter cell-specific descriptions apply to all tables of the given type regardless of the specific therapy being evaluated.

Note that in all tables, only data for single arm or single-arm meta-analyses are included for the comparator category (placebo, sham, or TURP); comparing a comparator category against itself is meaningless.

Abbreviations used throughout:

AE = adverse event
RCT = randomized controlled trial
SA = single arm
SAMA = single-arm meta-analysis

Appendix 3: Detailed Outcomes Tables

1. Tables Summarizing Estimates of Change in Efficacy Scores/Rates

These tables summarize results of analyses for four outcomes.

1. Symptom score as converted to American Urological Association (AUA)/International Prostate Symptom Score (IPSS) scale (0-35)
2. Peak urinary flow rate
3. The Disease Specific Quality of Life Question score from the IPSS (range 0 – 6)
4. The BPH Impact Index (BII)

Three different time points were analyzed for each outcome and each therapy.

1. 3 to 9 months—Preference was given for 6-month data or as close to 6 months as possible for studies that reported multiple time points within the range.
2. 10 to 16 months—Preference was given for 12-month data.
3. > 16 months—Preference was given for 24-month data.

The example below compares estimates of changes in AUA/IPSS in patients treated with alpha blockers versus those treated with placebo at 3 to 9 months.

Estimates of change in efficacy scores/rates

			Alpha Blockers			
		Placebo	Alfuzosin	Doxazosin	Tamsulosin	Terazosin
AUA / IPSS						
At 3-9 Months						
RCT diff. + SA control:	Estimated change		-4.44	-5.10	-4.63	-6.22
RCT:	Difference in change from control		-2.00	-2.66	-2.19	-3.78
	Confidence interval		-3.03, -.97	-3.56, -1.76	-2.98, -1.39	-5.52, -2.05
	# of studies		2	4	5	2
SA:	Estimated change	-2.44	-5.07	-7.36	-5.99	-6.91
	# of groups / # of patients	30/5960	2/307	4/335	8/1939	10/1319

Cell Descriptions:

RCT diff. + SA control: Estimated change — Estimate of the change in score for this treatment, computed as the sum of the estimate of change in score from control (from the cell labeled *RCT: Difference in change from control* for the given therapy) and the SA estimate of change in score for the control group (from the cell labeled *SA: Estimated change* in the control group). In this case, the sum of -2.00 and -2.44 = -4.44 for alfuzosin.

RCT: *Difference in change from control* — Estimate of the difference in change in score between therapy and control based on the meta-analysis of RCT data.

Appendix 3: Detailed Outcomes Tables

RCT: Confidence interval — 95% confidence interval for the difference reported in the cell above; if the confidence interval does not cross zero, the difference is significant at the 0.05 level.

RCT: # of studies — Number of studies included in the meta-analysis of RCTs.

SA: Estimated change — Estimated change in score based on a weighted average of results of SA studies.

SA: # groups / # patients — Number of patient groups included in the weighted average estimate / total number of patients included in the weighted average estimate.

2. Tables Summarizing Estimates of Rates of Occurrence of Adverse Events

These tables summarize results of analyses of rates of occurrence of 17 adverse events associated with medical therapies, 15 such events associated with minimally invasive or surgical therapies, and 9 adverse events associated with phytotherapies.

The example below compares estimates of rates of occurrence of acute urinary retention in patients treated with alpha blockers versus those treated with placebo.

Estimates of rates of occurrence of adverse events

Adverse Event		Placebo	Alpha Blockers			
			Alfuzosin	Doxazosin	Tamsulosin	Terazosin
Acute Urinary Retention						
RCT:	Difference in rate from control			-0.015	0.28	-0.001
	Confidence interval			-.031, .001	-.008, .064	-.054, .052
	# of studies			1	1	2
SAMA:	Estimated rate	0.031		0.001	0.035	0.035
	Confidence interval	.021, .045		.000, .009	.012, .079	.012, .076
	# of groups	12		1	1	4
	# of AEs / # of patients	172/4613		0/272	4/118	4/199

Cell Descriptions:

RCT: Difference in rate from control — Estimate of the difference in the rate of occurrence of the AE between the therapy and control based on the meta-analysis of RCT data.

RCT: Confidence interval — 95% confidence interval for the difference reported in the cell above; if the confidence interval does not cross zero, the difference is significant at the 0.05 level.

Appendix 3: Detailed Outcomes Tables

RCT: # of studies — Number of studies included in the meta-analysis of RCTs.

SAMA: Estimated rate — Estimate of the rate of occurrence of the AE for this treatment based on a SAMA of all groups receiving the treatment regardless of study type.

SAMA: Confidence interval — 95% confidence interval for the SAMA estimate reported in the cell above; this confidence interval will never cross zero and is used only to indicate the amount of variability in the estimate.

SAMA: # groups — Number of patient groups included in the SAMA.

SAMA: # of AEs / # of patients — Total number of occurrences of AEs in this category in all groups included in the SAMA estimate / total number of patients in all groups included in the SAMA estimate.

3. Tables Summarizing Comparison of Analyses of Rates of Occurrence of Adverse Events

These tables compare results of three types of analyses of rates of occurrence of adverse events for medical, minimally invasive, and surgical therapies.

The example below compares analyses of rates of occurrence of acute urinary retention in patients treated with alpha blockers versus those treated with placebo.

Comparison of analyses of rates of occurrence of adverse events

Adverse Event		Placebo	Alpha Blockers			
			Alfuzosin	Doxazosin	Tamsulosin	Terazosin
Acute Urinary Retention						
Bayesian:	Estimated rate			0.017	0.06	0.031
	Confidence interval			-.003, .036	.022, .098	-.024, .085
SAMA:	Estimated rate	0.031		0.001	0.035	0.035
	Confidence interval	.021, .045		.000, .009	.012, .079	.012, .076
RCT diff. + SA control:	Estimated rate			0.016	0.311	0.03

Cell Descriptions:

Bayesian: Estimated rate — Bayesian estimate of the rate of occurrence of the AE for this treatment, computed by finding the distribution for the random variable that is the sum of the SAMA control and the RCT meta-analysis of the difference from the control.

Appendix 3: Detailed Outcomes Tables

Bayesian: Confidence interval — 95% confidence interval for the Bayesian estimate reported in the cell above; if the confidence interval does not cross zero, the difference is significant at the 0.05 level.

SAMA: Estimated rate — Estimate of the rate of occurrence of the AE for this treatment based on a SAMA of all groups receiving the treatment regardless of study type.

SAMA: Confidence interval — 95% confidence interval for the SAMA estimate reported in the cell above; this confidence interval will never cross zero and is used only to indicate the amount of variability in the estimate.

RCT diff. + SA control: Estimated rate — Estimate of the rate of occurrence of the AE for this treatment, computed as the sum of the estimate of the difference in the rate from control (from the cell labeled *RCT: Difference in rate from control* for any given therapy in the corresponding "Estimate of Rates of Occurrence of Adverse Events" table) and the single-arm estimate of the rate for the control group (from the cell labeled *SAMA: Estimated rate* in the control group in the corresponding "Estimate of Rates of Occurrence of Adverse Events" table). In this case, the sum of -0.015 and +0.031 = 0.017 for doxazosin.

Summary

These Detailed Outcomes Tables provide estimates of the various outcomes for each intervention, where data are available. RCT data are analyzed in a manner that takes advantage of the structure of such studies, but additional SA analyses have been performed to allow all available data to be used. Unfortunately, the results of the different analyses are not always consistent, and the reader needs to recognize this difficulty.

The 9 tables of the appendix are organized as follows:

	Type of Table		
Type of Therapy	Estimates of change in efficacy scores/ rates	Estimates of rates of occurrence of adverse events	Comparison of analyses of rates of occurrence of adverse events
Medical	3-a	3-b	3-g
Minimally Invasive	3-c	3-d	3-g
Surgical	3-e	3-f	3-g
Phytotherapies	3-h	3-i	n/a

Table 3-a. Medical therapies: Estimates of change in efficacy scores/rates

			Alpha Blockers				Hormonal	Combinations		
		Placebo	Alfuzosin	Doxazosin	Tamsulosin	Terazosin	Finasteride	Alfuzosin/ Finasteride	Doxazosin/ Finasteride	Terazosin/ Finasteride
AUA / IPSS										
At 3-9 Months										
RCT diff. + SA control:	Estimated change		-4.44	-5.10	-4.63	-6.22	-3.44		-5.64	
RCT:	Difference in change from control		-2.00	-2.66	-2.19	-3.78	-1.00		-3.20	
	Confidence interval		-3.03, -.97	-3.56, -1.76	-2.98, -1.39	-5.52, -2.05	-1.92, -.07		-4.20, -2.20	
	# of studies		2	4	5	2	5		1	
SA:	Estimated change	-2.44	-5.07	-7.36	-5.99	-6.91	-3.29	-6.10	-9.10	-5.90
	# of groups / # of patients	30/5960	2/307	4/335	8/1939	10/1319	21/8525	1/338	1/217	1/288
At 12 Months										
RCT diff. + SA control:	Estimated change			-5.63		-5.99	-3.40		-6.53	
RCT:	Difference in change from control			-3.30		-3.66	-1.07		-4.20	
	Confidence interval			-4.50, -2.10		-4.48, -2.83	-1.73, -.42		-5.37, -3.03	
	# of studies			1		2	6		1	
SA:	Estimated change	-2.33		-9.50	-7.53	-7.03	-3.40		-10.40	-6.21
	# of groups / # of patients	18/6679		1/188	3/442	6/1621	19/8313		1/188	1/278
> 16 Months										
RCT diff. + SA control:	Estimated change						-2.37			
RCT:	Difference in change from control						-1.34			
	Confidence interval						-1.71, -.97			
	# of studies						4			
SA:	Estimated change	-1.03					-2.41			
	# of groups / # of patients	7/3253					8/3462			

Table 3-a. Medical therapies: Estimates of change in efficacy scores/rates

			Alpha Blockers				Hormonal	Combinations		
		Placebo	Alfuzosin	Doxazosin	Tamsulosin	Terazosin	Finasteride	Alfuzosin/ Finasteride	Doxazosin/ Finasteride	Terazosin/ Finasteride
Peak Flow Rate (Qmax)										
At 3-9 Months										
RCT diff. + SA control:	Estimated change		2.05	3.11	1.85	2.51	2.11		3.96	
RCT:	Difference in change from control		1.19	2.25	0.99	1.65	1.25		3.10	
	Confidence interval		.38, 2.01	1.38, 3.12	.69, 1.32	.52, 2.78	-.37, 2.86		2.30, 3.90	
	# of studies		2	3	5	2	3		1	
SA:	Estimated change	0.86	1.97	2.66	1.60	2.79	1.43	2.30	4.30	3.50
	# of groups / # of patients	33/4687	2/306	4/711	7/1685	10/1299	17/4140	1/338	1/204	1/284
At 12 Months										
RCT diff. + SA control:	Estimated change			2.98		1.94	1.66		3.38	2.63
RCT:	Difference in change from control			2.50		1.46	1.18		2.90	2.15
	Confidence interval			1.48, 3.52		.55, 2.37	.50, 1.87		1.99, 3.81	1.20, 3.09
	# of studies			1		2	7		1	1
SA:	Estimated change	0.48		2.54	1.86	2.36	1.41		4.30	3.25
	# of groups / # of patients	16/3992		2/519	3/286	7/846	18/4016		1/179	1/277
> 16 Months										
RCT diff. + SA control:	Estimated change						1.95			
RCT:	Difference in change from control						1.47			
	Confidence interval						.88, 2.06			
	# of studies						2			
SA:	Estimated change	0.48		1.90		2.61	1.59			
	# of groups / # of patients	4/2444		1/297		2/254	10/2775			

Table 3-a. Medical therapies: Estimates of change in efficacy scores/rates

			Alpha Blockers				Hormonal	Combinations		
		Placebo	Alfuzosin	Doxazosin	Tamsulosin	Terazosin	Finasteride	Alfuzosin/ Finasteride	Doxazosin/ Finasteride	Terazosin/ Finasteride
QOL Score										
At 3-9 Months										
RCT diff. + SA control:	Estimated change		-1.10	-1.25	-1.43		-0.75		-1.15	
RCT:	Difference in change from control		-0.45	-0.60	-0.78		-0.10		-0.50	
	Confidence interval		-.67, -.22	-.86, -.34	-1.07, -.49		-.34, .14		-0.76, -0.24	
	# of studies		2	1	4		1		1	
SA:	Estimated change	-0.65	-0.88	-1.60	-1.53	-1.70	-1.40		-1.50	
	# of groups / # of patients	8/1383	2/307	1/214	4/960	2/300	2/670		1/217	
At 12 Months										
RCT diff. + SA control:	Estimated change			-1.47		-1.37	-0.87		-1.57	
RCT:	Difference in change from control			-0.80		-0.70	-0.20		-0.90	
	Confidence interval			-1.08, -.52		-.81, -.59	-.48, .08		-1.18, -0.62	
	# of studies			1		1	1		1	
SA:	Estimated change	-0.67		-1.80		-1.30	-1.20		-1.90	
	# of groups / # of patients	2/1127		1/189		1/943	1/183		1/190	
BPH Impact Index										
At 3-9 Months										
RCT diff. + SA control:	Estimated change			-2.00			-1.50		-2.20	
RCT:	Difference in change from control			-1.00			-0.50		-1.20	
	Confidence interval			-1.47, -.53			-.98, -.02		-1.68, -0.72	
	# of studies			1			1		1	
SA:	Estimated change	-1.00		-2.60		-1.45	-1.11		-2.80	-1.55
	# of groups / # of patients	2/482		1/212		1/288	2/481		1/218	1/288
At 12 Months										
RCT diff. + SA control:	Estimated change			-2.47		-2.09	-1.21		-2.57	-2.03
RCT:	Difference in change from control			-1.50		-1.12	-0.24		-1.60	-1.06
	Confidence interval			-2.06, -.94		-1.36, -.87	-.55, .07		-2.17, -1.04	-1.49, -0.63
	# of studies			1		2	3		1	1
SA:	Estimated change	-0.97		-3.20		-2.15	-1.19		-3.30	-1.57
	# of groups / # of patients	4/2361		1/189		4/1209	6/3356		1/190	1/279

Table 3-b. Medical therapies: Estimates of rates of occurrence of adverse events

Adverse Event		Placebo	Alpha Blockers				Hormonal	Combinations		
			Alfuzosin	Doxazosin	Tamsulosin	Terazosin	Finasteride	Alfuzosin/ Finasteride	Doxazosin/ Finasteride	Terazosin/ Finasteride
Acute Urinary Retention										
RCT:	Difference in rate from control			-0.015	0.028	-0.001	-0.016		-0.015	
	Confidence interval			-.031, .001	-.008, .064	-.054, .052	-.024, .010		-.031, .001	
	# of studies			1	1	2	7		1	
SAMA:	Estimated rate	0.031		0.001	0.035	0.035	0.015	0.003	0.001	
	Confidence interval	.021, .045		.000, .009	.012, .079	.012, .076	.010, .022	.000, .013	.000, .009	
	# of groups	12		1	1	4	9	1	1	
	# of AEs / # of patients	172/4613		0/272	4/118	4/199	73/4836	1/349	0/285	
Asthenia										
RCT:	Difference in rate from control		0.019	0.095	0.033	0.055	-0.006		0.063	0.070
	Confidence interval		-.018, .056	.041, .148	.011, .055	.031, .078	-.013, .001		.015, .111	.022, .118
	# of studies		2	3	5	7	4		1	1
SAMA:	Estimated rate	0.037	0.043	0.150	0.066	0.115	0.023	0.009	0.126	0.139
	Confidence interval	.027, .051	.014, .097	.126, .177	.033, .116	.103, .128	.010, .044	.002, .023	.093, .170	.105, .182
	# of groups	23	2	9	7	13	6	1	1	1
	# of AEs / # of patients	180/5713	13/319	151/1048	119/1463	304/2772	61/2946	3/349	36/285	43/309
Breast										
RCT:	Difference in rate from control						0.005			
	Confidence interval						-.001, .012			
	# of studies						2			
SAMA:	Estimated rate	0.015					0.009			
	Confidence interval	.003, .045					.004, .017			
	# of groups	4					2			
	# of AEs / # of patients	9/1871					15/1810			
Cardiovascular										
RCT:	Difference in rate from control		-0.017	-0.033	-0.048	0.000	-0.003		-0.034	
	Confidence interval		-.048, .014	-.065, .002	-.109, .013	-.052, .052	-.019, .013		-.065, .003	
	# of studies		1	1	1	2	4		1	
SAMA:	Estimated rate	0.039	0.012	0.019	0.078	0.022	0.053		0.018	
	Confidence interval	.020, .065	.002, .036	.007, .040	.023, .180	.013, .034	.023, .101		.007, .038	
	# of groups	14	1	1	3	4	5		1	
	# of AEs / # of patients	196/4361	2/176	5/272	45/659	23/1248	162/2779		5/285	

Table 3-b. Medical therapies: Estimates of rates of occurrence of adverse events

Adverse Event		Placebo	Alpha Blockers				Hormonal	Combinations		
			Alfuzosin	Doxazosin	Tamsulosin	Terazosin	Finasteride	Alfuzosin/ Finasteride	Doxazosin/ Finasteride	Terazosin/ Finasteride
Cardiovascular - Peripheral Edema										
RCT:	Difference in rate from control		-0.011			0.034				
	Confidence interval		-.035, .013			-.040, .108				
	# of studies		1			2				
SAMA:	Estimated rate	0.011	0.001	0.014		0.041				
	Confidence interval	.005, .020	.000, .014	.006, .027		.024, .063				
	# of groups	3	1	1		4				
	# of AEs / # of patients	11/1226	0/176	6/450		43/1119				
Cardiovascular - Serious										
RCT:	Difference in rate from control					-0.009	0.010			
	Confidence interval					-.015, .002	.003, .017			
	# of studies					1	1			
SAMA:	Estimated rate	0.008				0.001	0.011	0.003		
	Confidence interval	.005, .013				.000, .004	.002, .030	.000, .013		
	# of groups	3				1	2	1		
	# of AEs / # of patients	19/2724				1/1053	24/1921	1/349		
Dizziness										
RCT:	Difference in rate from control		0.024	0.089	0.039	0.088	-0.004		0.062	0.141
	Confidence interval		-.023, .070	.024, .152	.013, .064	.038, .138	-.019, .010		.011, .114	.087, .195
	# of studies		2	5	6	6	4		1	1
SAMA:	Estimated rate	0.053	0.051	0.133	0.115	0.154	0.047	0.023	0.140	0.214
	Confidence interval	.040, .070	.014, .121	.093, .187	. 077, .169	.119, .198	.017, .099	.011, .043	.105, .186	.171, .263
	# of groups	24	2	11	8	13	5	1	1	1
	# of AEs / # of patients	241/4421	16/319	138/1217	197/1655	426/2779	52/1229	8/349	40/285	66/309
GI Systems										
RCT:	Difference in rate from control		0.011	0.035	-0.016	0.006	-0.018		-0.020	
	Confidence interval		-.050, .071	-.086, .155	-.044, .012	-.021, .033	-.056, .020		-.068, .029	
	# of studies		1	2	6	4	5		1	
SAMA:	Estimated rate	0.059	0.097	0.101	0.106	0.054	0.059		0.084	
	Confidence interval	.040, .086	.060, .147	.063, .151	.055, .179	.028, .092	.032, .098		.057, .123	
	# of groups	20	1	2	7	10	7		1	
	# of AEs / # of patients	324/5201	17/176	30/311	152/1298	61/1858	202/3169		24/285	

Table 3-b. Medical therapies: Estimates of rates of occurrence of adverse events

Adverse Event		Placebo	Alpha Blockers				Hormonal	Combinations		
			Alfuzosin	Doxazosin	Tamsulosin	Terazosin	Finasteride	Alfuzosin/ Finasteride	Doxazosin/ Finasteride	Terazosin/ Finasteride
Headache										
RCT:	Difference in rate from control		0.028	0.003	0.017	-0.005	0.001		-0.016	0.019
	Confidence interval		-.012, .069	-.056, .061	-.010, .043	-.047, .036	-.009, .010		-.065, .033	-.013, .051
	# of studies		1	4	6	5	6		1	1
SAMA:	Estimated rate	0.051	0.052	0.077	0.115	0.072	0.035	0.015	0.088	0.052
	Confidence interval	.036, .072	.026, .091	.044, .123	.060, .192	.052, .100	.020, .058	.005, .031	.060, .127	.031, .081
	# of groups	24	1	7	7	12	10	1	1	1
	# of AEs / # of patients	250/4903	9/176	66/1100	223/1640	124/1762	97/3578	5/349	25/285	16/309
Hypotension - Asymptomatic										
RCT:	Difference in rate from control			0.036	0.066	0.009	-0.007		0.013	
	Confidence interval			-.008, .080	.032, .100	.001, .017	-.026 , .012		-.012, .038	
	# of studies			3	2	1	1		1	
SAMA:	Estimated rate	0.019		0.054	0.067	0.075	0.037	0.080	0.029	
	Confidence interval	.013, .027		.026, .097	.021, .152	.020, .181	.005, .122	.056, .114	.013, .052	
	# of groups	10		3	5	5	2	1	1	
	# of AEs / # of patients	25/2241		23/510	54/1092	36/1232	30/606	28/349	8/285	
Hypotension - Symptomatic										
RCT:	Difference in rate from control		0.006			0.008				
	Confidence interval		-.010, .021			-.043, .060				
	# of studies		1			1				
SAMA:	Estimated rate	0.017	0.007			0.027				
	Confidence interval	.004, .046	.001, .026			.005, .077				
	# of groups	3	1			1				
	# of AEs / # of patients	5/437	1/176			2/81				
Hypotension - Symptomatic - Postural										
RCT:	Difference in rate from control			0.048	0.004	0.042	0.002		0.013	0.077
	Confidence interval			.015, .080	-.006, .014	.010, .073	-.022, .027		-.012, .038	.043, .111
	# of studies			1	4	5	2		1	1
SAMA:	Estimated rate	0.011		0.040	0.025	0.063	0.016	0.006	0.029	0.087
	Confidence interval	.007, .017		.013, .089	.008, .055	.033, .107	.008, .027	.001, .018	.013, .052	.061, .124
	# of groups	9		2	4	8	3	1	1	1
	# of AEs / # of patients	20/2574		26/722	9/645	81/2132	12/916	2/349	8/285	27/309

Table 3-b. Medical therapies: Estimates of rates of occurrence of adverse events

Adverse Event		Placebo	Alpha Blockers				Hormonal	Combinations		
			Alfuzosin	Doxazosin	Tamsulosin	Terazosin	Finasteride	Alfuzosin/ Finasteride	Doxazosin/ Finasteride	Terazosin/ Finasteride
Hypotension - Symptomatic - Syncope										
RCT:	Difference in rate from control		0.006	0.006	-0.008	0.006	0.002		0.010	0.016
	Confidence interval		-.010, .021	-.012, .012	-.034, .010	-.007, .020	-.013, .018		-.007, .027	.001, .031
	# of studies		1	1	1	4	2		1	1
SAMA:	Estimated rate	0.006	0.007	0.004	0.003	0.013	0.007		0.015	0.017
	Confidence interval	.003, .013	.001, .026	.000, .017	.000, .012	.005, .029	.001, .030		.005, .033	.006, .035
	# of groups	8	1	1	1	4	2		1	1
	# of AEs / # of patients	3/1379	1/176	1/272	1/381	4/508	3/572		4/285	5/309
Respiratory - Nasal Congestion										
RCT:	Difference in rate from control		0.011	0.010	0.079	0.023	-0.023		-0.014	0.041
	Confidence interval		-.025, .046	-.057, .076	.044, .115	-.025, .071	-.061, .016		-.078, .051	-.002, .084
	# of studies		2	1	4	2	2		1	1
SAMA:	Estimated rate	0.060	0.059	0.078	0.108	0.063	0.090		0.179	0.100
	Confidence interval	.033, .096	.014, .152	.010, .247	.037, .228	.035, .102	.023, .218		.139, .228	.071, .139
	# of groups	10	2	2	6	5	2		1	1
	# of AEs / # of patients	126/1655	20/319	64/722	179/1345	48/954	55/572		51/285	31/309
Sexual - Ejaculation										
RCT:	Difference in rate from control			-0.011	0.095	0.003	0.021		0.017	0.055
	Confidence interval			-.029, .006	.024, .165	-.021, .026	.013, .028		-.009, .042	.023, .086
	# of studies			1	5	2	8		1	1
SAMA:	Estimated rate	0.010		0.004	0.099	0.013	0.035	0.009	0.032	0.068
	Confidence interval	.008, .014		.000, .017	.060, .151	.007, .021	.027, .045	.002, .023	.016, .057	.045, .102
	# of groups	13		1	6	3	11	1	1	1
	# of AEs / # of patients	54/6933		1/272	152/1395	16/1410	273/8623	3/349	9/285	21/309
Sexual - Erectile Problems										
RCT:	Difference in rate from control		0.017	0.018	0.009	0.031	0.037		0.065	0.048
	Confidence interval		-.014, .048	-.016, .052	-.031, .048	-.031, .093	.027, .047		.024, .105	.007, .088
	# of studies		1	1	1	2	13		1	1
SAMA:	Estimated rate	0.039	0.029	0.035	0.035	0.050	0.080	0.075	0.098	0.094
	Confidence interval	.029, .051	.011, .061	.013, .075	.012, .079	.029, .078	.061, .105	.051, .107	.069, .139	.006, .132
	# of groups	24	1	2	1	4	18	1	1	1
	# of AEs / # of patients	277/7169	5/176	23/722	4/118	37/925	810/9891	26/349	28/285	29/309

Table 3-b. Medical therapies: Estimates of rates of occurrence of adverse events

Adverse Event		Placebo	Alpha Blockers				Hormonal	Combinations		
			Alfuzosin	Doxazosin	Tamsulosin	Terazosin	Finasteride	Alfuzosin/ Finasteride	Doxazosin/ Finasteride	Terazosin/ Finasteride
Sexual - Libido										
RCT:	Difference in rate from control		0.006	0.015		0.013	0.020		0.006	0.035
	Confidence interval		-.016, .028	-.013, .042		-.010, .036	.014, .027		-.019, .031	.008, .063
	# of studies		1	1		1	10		1	1
SAMA:	Estimated rate	0.031	0.012	0.034		0.027	0.051	0.021	0.025	0.049
	Confidence interval	.026, .036	.002, .036	.016, .060		.012, .049	.039, .066	.009, .039	.011, .048	.029, .077
	# of groups	15	1	1		1	14	1	1	1
	# of AEs / # of patients	150/5824	2/176	9/272		8/305	435/9283	7/349	7/285	15/309

Table 3-c. Minimally invasive therapies: Estimates of change in efficacy scores/rates

		Sham	Sham-Based Comparisons: Prostatron Version 2.0 TUMT	Prostatron Version 2.5 TUMT	Targis TUMT	TUNA
AUA / IPSS						
At 3-9 Months						
RCT diff. + SA control:	Estimated change				-10.14	-9.17
RCT:	Difference in change from control				-3.77	5.48
	Confidence interval				-6.81, -.73	2.28, 8.68
	# of studies				1	1
SA:	Estimated change	-6.37	-10.93	-8.83	-11.76	-12.63
	# of groups / # of patients	9/342	15/990	7/553	8/713	7/312
At 12 Months						
RCT diff. + SA control:	Estimated change					
RCT:	Difference in change from control					
	Confidence interval					
	# of studies					
SA:	Estimated change		-10.47	-10.72	-11.78	-12.36
	# of groups / # of patients		9/712	3/248	5/546	6/241
> 16 Months						
RCT diff. + SA control:	Estimated change					
RCT:	Difference in change from control					
	Confidence interval					
	# of studies					
SA:	Estimated change		-9.27	-10.73	-10.76	-11.38
	# of groups / # of patients		5/239	2/91	4/264	3/116

Table 3-c. Minimally invasive therapies: Estimates of change in efficacy scores/rates

			TURP-Based Comparisons				
		TURP	Prostatron Version 2.0 TUMT	Prostatron Version 2.5 TUMT	Targis TUMT	TUNA	UroLume Stent
AUA / IPSS							
At 3-9 Months							
RCT diff. + SA control:	Estimated change				-10.88	-11.48	
RCT:	Difference in change from control				3.77	3.17	
	Confidence interval				-.50, 8.04	-.01, 6.35	
	# of studies				1	1	
SA:	Estimated change	-14.65	-10.93	-8.83	-11.76	-12.63	-11.15
	# of groups / # of patients	25/894	15/990	7/553	8/713	7/312	1/113
At 12 Months							
RCT diff. + SA control:	Estimated change				-9.44	-9.32	
RCT:	Difference in change from control				5.36	5.48	
	Confidence interval				.19, 10.53	2.28, 8.68	
	# of studies				1	1	
SA:	Estimated change	-14.80	-10.47	-10.72	-11.78	-12.36	-12.44
	# of groups / # of patients	19/689	9/712	3/248	5/546	6/241	1/117
> 16 Months							
RCT diff. + SA control:	Estimated change					-8.10	
RCT:	Difference in change from control					5.44	
	Confidence interval					1.48, 9.40	
	# of studies					1	
SA:	Estimated change	-13.54	-9.27	-10.73	-10.76	-11.38	-13.22
	# of groups / # of patients	12/552	5/239	2/91	4/264	3/116	1/28

Table 3-c. Minimally invasive therapies: Estimates of change in efficacy scores/rates

		Sham-Based Comparisons			
	Sham	Prostatron Version 2.0 TUMT	Prostatron Version 2.5 TUMT	Targis TUMT	TUNA
Peak Flow Rate (Qmax)					
At 3-9 Months					
RCT diff. + SA control: Estimated change				2.64	
RCT: Difference in change from control				1.61	
Confidence interval				-.52, 3.74	
# of studies				1	
SA: Estimated change	1.03	3.39	4.51	3.94	5.31
# of groups / # of patients	10/305	15/978	7/549	9/791	8/327
At 12 Months					
RCT diff. + SA control: Estimated change					
RCT: Difference in change from control					
Confidence interval					
# of studies					
SA: Estimated change		2.81	4.54	3.57	5.55
# of groups / # of patients		9/688	3/221	5/519	6/235
> 16 Months					
RCT diff. + SA control: Estimated change					
RCT: Difference in change from control					
Confidence interval					
# of studies					
SA: Estimated change		2.26	4.42	3.28	4.81
# of groups / # of patients		5/303	2/91	2/190	3/104

Table 3-c. Minimally invasive therapies: Estimates of change in efficacy scores/rates

			TURP-Based Comparisons				
		TURP	Prostatron Version 2.0 TUMT	Prostatron Version 2.5 TUMT	Targis TUMT	TUNA	UroLume Stent
Peak Flow Rate (Qmax)							
At 3-9 Months							
RCT diff. + SA control:	Estimated change				5.68	3.01	
RCT:	Difference in change from control				-4.86	-7.53	
	Confidence interval				-7.76, -1.96	-10.31, -4.75	
	# of studies				1	1	
SA:	Estimated change	10.54	3.39	4.51	3.94	5.31	7.37
	# of groups / # of patients	29/1045	15/978	7/549	9/791	8/327	2/134
At 12 Months							
RCT diff. + SA control:	Estimated change				5.29	4.25	
RCT:	Difference in change from control				-5.48	-6.52	
	Confidence interval				-9.57, -1.39	-9.86, -3.18	
	# of studies				1	1	
SA:	Estimated change	10.77	2.81	4.54	3.57	5.55	7.80
	# of groups / # of patients	20/734	9/688	3/221	5/519	6/235	1/66
> 16 Months							
RCT diff. + SA control:	Estimated change					-0.93	
RCT:	Difference in change from control					-8.99	
	Confidence interval					-12.06, -5.92	
	# of studies					1	
SA:	Estimated change	8.06	2.26	4.42	3.28	4.81	
	# of groups / # of patients	15/642	5/303	2/91	2/190	3/104	

Table 3-c. Minimally invasive therapies: Estimates of change in efficacy scores/rates

		Sham-Based Comparisons			
	Sham	Prostatron Version 2.0 TUMT	Prostatron Version 2.5 TUMT	Targis TUMT	TUNA
QOL Score					
At 3-9 Months					
RCT diff. + SA control: Estimated change				-2.20	
RCT: Difference in change from control				-1.16	
Confidence interval				-1.76, -.56	
# of studies				1	
SA: Estimated change	-1.04	-1.95	-1.25	-2.33	-2.49
# of groups / # of patients	3/138	3/127	1/28	7/784	7/327
At 12 Months					
RCT diff. + SA control: Estimated change					
RCT: Difference in change from control					
Confidence interval					
# of studies					
SA: Estimated change		-1.75		-1.30	-2.56
# of groups / # of patients		2/88		5/546	6/239
> 16 Months					
RCT diff. + SA control: Estimated change					
RCT: Difference in change from control					
Confidence interval					
# of studies					
SA: Estimated change		-1.70		-2.31	-2.36
# of groups / # of patients		1/43		4/265	3/114

Table 3-c. Minimally invasive therapies: Estimates of change in efficacy scores/rates

			TURP-Based Comparisons				
		TURP	Prostatron Version 2.0 TUMT	Prostatron Version 2.5 TUMT	Targis TUMT	TUNA	UroLume Stent
QOL Score							
At 3-9 Months							
RCT diff. + SA control:	Estimated change				-2.43	-3.06	
RCT:	Difference in change from control				1.01	0.38	
	Confidence interval				.08, 1.94	-.28, 1.04	
	# of studies				1	1	
SA:	Estimated change	-3.44	-1.95	-1.25	-2.33	-2.49	
	# of groups / # of patients	4/136	3/127	1/28	7/784	7/327	
At 12 Months							
RCT diff. + SA control:	Estimated change				-2.44	-2.70	
RCT:	Difference in change from control				0.90	0.64	
	Confidence interval				-.05, 1.85	-.02, 1.30	
	# of studies				1	1	
SA:	Estimated change	-3.34	-1.75		-1.30	-2.56	
	# of groups / # of patients	3/112	2/88		5/546	6/239	
> 16 Months							
RCT diff. + SA control:	Estimated change					-2.44	
RCT:	Difference in change from control					0.59	
	Confidence interval					-.29, 1.47	
	# of studies					1	
SA:	Estimated change	-3.03	-1.70		-2.31	-2.36	
	# of groups / # of patients	2/35	1/43		4/265	3/114	

Table 3-c. Minimally invasive therapies: Estimates of change in efficacy scores/rates

		Sham	Sham-Based Comparisons: Prostatron Version 2.0 TUMT	Prostatron Version 2.5 TUMT	Targis TUMT	TUNA
BPH Impact Index						
At 3-9 Months						
RCT diff. + SA control:	Estimated change					
RCT:	Difference in change from control					
	Confidence interval					
	# of studies					
SA:	Estimated change	-2.30				-5.20
	# of groups / # of patients	1/66				1/113
At 12 Months						
RCT diff. + SA control:	Estimated change					
RCT:	Difference in change from control					
	Confidence interval					
	# of studies					
SA:	Estimated change					-5.00
	# of groups / # of patients					1/91

Table 3-c. Minimally invasive therapies: Estimates of change in efficacy scores/rates

			TURP-Based Comparisons				
		TURP	Prostatron Version 2.0 TUMT	Prostatron Version 2.5 TUMT	Targis TUMT	TUNA	UroLume Stent
BPH Impact Index							
At 3-9 Months							
RCT diff. + SA control:	Estimated change						
RCT:	Difference in change from control						
	Confidence interval						
	# of studies						
SA:	Estimated change					-5.20	
	# of groups / # of patients					1/113	
At 12 Months							
RCT diff. + SA control:	Estimated change						
RCT:	Difference in change from control						
	Confidence interval						
	# of studies						
SA:	Estimated change					-5.00	
	# of groups / # of patients					1/91	

Table 3-d. Minimally invasive therapies compared to sham and TURP: Estimates of rates of occurrence of adverse events

Adverse Event		Sham	Sham-Based Comparisons: Prostatron Version 2.0 TUMT	Prostatron Version 2.5 TUMT	Targis TUMT
Aborted Procedure/Device Failure					
RCT:	Difference in rate from control				0.001
	Confidence interval				-.035, .036
	# of studies				1
SAMA:	Estimated rate	0.005	0.007		0.009
	Confidence interval	.000, .055	.000, .029		.001, .037
	# of groups	1	1		1
	# of AEs / # of patients	0/44	1/158		1/125
Acute Urinary Retention					
RCT:	Difference in rate from control		0.305		0.050
	Confidence interval		.047, .525		-.021, .121
	# of studies		4		1
SAMA:	Estimated rate	0.027	0.228	0.150	0.062
	Confidence interval	.011, .054	.179, .286	.043, .334	.013, .166
	# of groups	9	17	4	2
	# of AEs / # of patients	2/295	398/1728	60/502	11/176
BNC/Stricture					
RCT:	Difference in rate from control				0.016
	Confidence interval				-.026, .059
	# of studies				1
SAMA:	Estimated rate	0.005	0.011	0.021	0.025
	Confidence interval	.000, .055	.004, 024	.001, .088	.007, .063
	# of groups	1	5	2	1
	# of AEs / # of patients	0/44	4/727	0/61	3/125
Cardiovascular					
RCT:	Difference in rate from control				
	Confidence interval				
	# of studies				
SAMA:	Estimated rate	0.003			
	Confidence interval	.000, .034			
	# of groups	1			
	# of AEs / # of patients	0/73			

Table 3-d. Minimally invasive therapies compared to sham and TURP: Estimates of rates of occurrence of adverse events

Adverse Event		TURP	TURP-Based Comparisons: Prostatron Version 2.0 TUMT	Prostatron Version 2.5 TUMT	Targis TUMT	TUNA	UroLume Stent
Aborted Procedure/Device Failure							
RCT:	Difference in rate from control						
	Confidence interval						
	# of studies						
SAMA:	Estimated rate		0.007		0.009	0.035	0.342
	Confidence interval		.000, .029		.001, .037	.008, .091	.113, .641
	# of groups		1		1	2	4
	# of AEs / # of patients		1/158		1/125	4/167	61/198
Acute Urinary Retention							
RCT:	Difference in rate from control		0.138	0.032			
	Confidence interval		.051, .222	-.113, .176			
	# of studies		3	1			
SAMA:	Estimated rate	0.054	0.228	0.150	0.062	0.202	0.061
	Confidence interval	.036, .081	.179, .286	.043, .334	.013, .166	.129, .292	.017, .146
	# of groups	19	17	4	2	7	2
	# of AEs / # of patients	73/1399	398/1728	60/502	11/176	103/439	4/88
BNC/Stricture							
RCT:	Difference in rate from control		-0.088	-0.059		-0.056	
	Confidence interval		-.183, .008	-.153, .036		-.134, .022	
	# of studies		2	2		1	
SAMA:	Estimated rate	0.066	0.011	0.021	0.025	0.029	
	Confidence interval	.051, .084	.004, .024	.001, .088	.007, .063	.010, .063	
	# of groups	32	5	2	1	4	
	# of AEs / # of patients	205/5766	4/727	0/61	3/125	4/241	
Cardiovascular							
RCT:	Difference in rate from control						
	Confidence interval						
	# of studies						
SAMA:	Estimated rate	0.005					
	Confidence interval	.001, .016					
	# of groups	2					
	# of AEs / # of patients	4/325					

Table 3-d. Minimally invasive therapies compared to sham and TURP: Estimates of rates of occurrence of adverse events

Adverse Event		Sham	Sham-Based Comparisons: Prostatron Version 2.0 TUMT	Sham-Based Comparisons: Prostatron Version 2.5 TUMT	Sham-Based Comparisons: Targis TUMT
Cardiovascular, Serious					
RCT:	Difference in rate from control				
	Confidence interval				
	# of studies				
SAMA:	Estimated rate				
	Confidence interval				
	# of groups				
	# of AEs / # of patients				
Cardiovascular, Thrombo-embolic					
RCT:	Difference in rate from control				
	Confidence interval				
	# of studies				
SAMA:	Estimated rate				
	Confidence interval				
	# of groups				
	# of AEs / # of patients				
Hematuria, Significant					
RCT:	Difference in rate from control				
	Confidence interval				
	# of studies				
SAMA:	Estimated rate		0.022		
	Confidence interval		.010, .042		
	# of groups		3		
	# of AEs / # of patients		9/488		
Incontinence					
RCT:	Difference in rate from control		0.032		
	Confidence interval		-.015, .079		
	# of studies		1		
SAMA:	Estimated rate	0.005	0.023		
	Confidence interval	.000, .055	.012, .039		
	# of groups	1	5		
	# of AEs / # of patients	0/44	9/617		

Table 3-d. Minimally invasive therapies compared to sham and TURP: Estimates of rates of occurrence of adverse events

Adverse Event		TURP	TURP-Based Comparisons				
			Prostatron Version 2.0 TUMT	Prostatron Version 2.5 TUMT	Targis TUMT	TUNA	UroLume Stent
Cardiovascular, Serious							
RCT:	Difference in rate from control						
	Confidence interval						
	# of studies						
SAMA:	Estimated rate	0.016					
	Confidence interval	.001, .061					
	# of groups	1					
	# of AEs / # of patients	1/75					
Cardiovascular, Thrombo-embolic							
RCT:	Difference in rate from control						
	Confidence interval						
	# of studies						
SAMA:	Estimated rate	0.021				0.017	
	Confidence interval	.002, .075				.002, .064	
	# of groups	2				1	
	# of AEs / # of patients	12/3986				1/71	
Hematuria, Significant							
RCT:	Difference in rate from control		-0.065				
	Confidence interval		-.149, .020				
	# of studies		1				
SAMA:	Estimated rate	0.061	0.022			0.038	0.064
	Confidence interval	.045, .083	.010, .042			.012, .087	.023, .135
	# of groups	15	3			3	3
	# of AEs / # of patients	44/1015	9/488			4/156	5/108
Incontinence							
RCT:	Difference in rate from control		-0.011			-0.036	
	Confidence interval		-.064, .041			-.093, .022	
	# of studies		2			1	
SAMA:	Estimated rate	0.032	0.023			0.013	0.249
	Confidence interval	.020, .049	.012, .039			.002, .044	.069, .527
	# of groups	19	5			3	3
	# of AEs / # of patients	50/5005	9/617			0/172	22/98

Table 3-d. Minimally invasive therapies compared to sham and TURP: Estimates of rates of occurrence of adverse events

Adverse Event		Sham	Sham-Based Comparisons: Prostatron Version 2.0 TUMT	Sham-Based Comparisons: Prostatron Version 2.5 TUMT	Sham-Based Comparisons: Targis TUMT
Infection / UTI					
RCT:	Difference in rate from control		0.173		0.033
	Confidence interval		.033, .365		-.052, .118
	# of studies		1		1
SAMA:	Estimated rate	0.051	0.089	0.090	0.091
	Confidence interval	.018, .107	.045, .151	.031, .190	.048, .152
	# of groups	3	10	3	2
	# of AEs / # of patients	5/138	119/1246	7/103	15/176
Intraoperative					
RCT:	Difference in rate from control				0.017
	Confidence interval				-.025, .058
	# of studies				1
SAMA:	Estimated rate	0.005			0.025
	Confidence interval	.000, .055			.007, .063
	# of groups	1			1
	# of AEs / # of patients	0/44			3/125
Post Procedure, Irritative					
RCT:	Difference in rate from control		-0.388		
	Confidence interval		-.532, .222		
	# of studies		1		
SAMA:	Estimated rate	0.696	0.276	0.738	
	Confidence interval	.100, .993	.121, .479	.178, .991	
	# of groups	2	4	2	
	# of AEs / # of patients	52/113	96/359	39/61	
Secondary Procedure					
RCT:	Difference in rate from control		-0.060		
	Confidence interval		-.210, .093		
	# of studies		3		
SAMA:	Estimated rate	0.235	0.100	0.100	0.158
	Confidence interval	.103, .416	.058, .157	.047, .177	.115, .201
	# of groups	4	16	3	1
	# of AEs / # of patients	23/110	328/1864	29/363	33/204

Table 3-d. Minimally invasive therapies compared to sham and TURP: Estimates of rates of occurrence of adverse events

Adverse Event		TURP	TURP-Based Comparisons: Prostatron Version 2.0 TUMT	Prostatron Version 2.5 TUMT	Targis TUMT	TUNA	UroLume Stent
Infection / UTI							
RCT:	Difference in rate from control		0.053	0.012		0.195	
	Confidence interval		-.061, .165	-.183, .207		.049, .333	
	# of studies		2	2		1	
SAMA:	Estimated rate	0.064	0.089	0.090	0.091	0.173	0.109
	Confidence interval	.047, .086	.045, .151	.031, .190	.048, .152	.090, .285	.059, .177
	# of groups	25	10	3	2	7	4
	# of AEs / # of patients	245/6801	119/1246	7/103	15/176	58/454	18/198
Intraoperative							
RCT:	Difference in rate from control						
	Confidence interval						
	# of studies						
SAMA:	Estimated rate	0.034			0.025	0.114	
	Confidence interval	.029, .040			.007, .063	.011, .381	
	# of groups	5			1	1	
	# of AEs / # of patients	144/4337			3/125	1/10	
Post Procedure, Irritative							
RCT:	Difference in rate from control		0.088	0.094		-0.036	
	Confidence interval		-.061, .233	-.137, .315		-.093, .020	
	# of studies		1	1		1	
SAMA:	Estimated rate	0.151	0.276	0.738		0.309	0.918
	Confidence interval	.091, .226	.121, .479	.178, .991		.110, .576	.752, .988
	# of groups	10	4	2		7	4
	# of AEs / # of patients	73/449	96/359	39/61		146/521	172/198
Secondary Procedure							
RCT:	Difference in rate from control		0.103	0.091			
	Confidence interval		.010, .194	-.089, .264			
	# of studies		2	2			
SAMA:	Estimated rate	0.047	0.100	0.100	0.158	0.232	0.103
	Confidence interval	.035, .063	.058, .157	.047, .177	.115, .201	.146, .337	.045, .192
	# of groups	21	16	3	1	5	3
	# of AEs / # of patients	35/1237	328/1864	29/363	33/204	40/186	9/108

Table 3-d. Minimally invasive therapies compared to sham and TURP: Estimates of rates of occurrence of adverse events

Adverse Event		Sham	Sham-Based Comparisons: Prostatron Version 2.0 TUMT	Sham-Based Comparisons: Prostatron Version 2.5 TUMT	Sham-Based Comparisons: Targis TUMT
Sexual, Ejaculation					
RCT:	Difference in rate from control				0.034
	Confidence interval				-.014, .082
	# of studies				1
SAMA:	Estimated rate	0.015	0.054	0.160	0.048
	Confidence interval	.002, .052	.038, .077	.017, .493	.018, .097
	# of groups	3	7	2	2
	# of AEs / # of patients	0/137	25/712	4/28	7/176
Sexual, Erectile Problems					
RCT:	Difference in rate from control		-0.007		
	Confidence interval		-.047, .033		
	# of studies		1		
SAMA:	Estimated rate	0.023	0.029	0.007	
	Confidence interval	.006, .060	.013, .053	.000, .080	
	# of groups	4	10	1	
	# of AEs / # of patients	1/148	42/1105	0/30	
Transfusion					
RCT:	Difference in rate from control				-0.007
	Confidence interval				-.039, .025
	# of studies				1
SAMA:	Estimated rate	0.005	0.009	0.021	0.002
	Confidence interval	.000, .055	.001, .040	.001, .088	.000, .020
	# of groups	1	2	2	1
	# of AEs / # of patients	0/44	0/181	0/61	0/125

Table 3-d. Minimally invasive therapies compared to sham and TURP: Estimates of rates of occurrence of adverse events

Adverse Event		TURP	TURP-Based Comparisons: Prostatron Version 2.0 TUMT	Prostatron Version 2.5 TUMT	Targis TUMT	TUNA	UroLume Stent
Sexual, Ejaculation							
RCT:	Difference in rate from control		-0.373	-0.395		-0.779	
	Confidence interval		-.609, .100	-.647, .094		-.873, .653	
	# of studies		2	1		1	
SAMA:	Estimated rate	0.645	0.054	0.160	0.048	0.043	
	Confidence interval	.556, .724	.038, .077	.017, .493	.018, .097	.013, .101	
	# of groups	19	7	2	2	4	
	# of AEs / # of patients	283/445	25/712	4/28	7/176	10/295	
Sexual, Erectile Problems							
RCT:	Difference in rate from control		0.000	-0.130		-0.124	
	Confidence interval		-.047, .046	-.257, .002		-.213, .034	
	# of studies		2	1		1	
SAMA:	Estimated rate	0.098	0.029	0.007		0.029	
	Confidence interval	.073, .130	.013, .053	.000, .080		.012, .058	
	# of groups	15	10	1		4	
	# of AEs / # of patients	46/636	42/1105	0/30		5/295	
Transfusion							
RCT:	Difference in rate from control		-0.051	-0.007			
	Confidence interval		-.194, .094	-.081, .067			
	# of studies		2	1			
SAMA:	Estimated rate	0.078	0.009	0.021	0.002	0.028	
	Confidence interval	.054, .113	.001, .040	.001, .088	.000, .020	.005, .084	
	# of groups	23	2	2	1	3	
	# of AEs / # of patients	635/6375	0/181	0/61	0/125	1/105	

Table 3-e. Surgical therapies: Estimates of change in efficacy scores/rates

			Transurethral						
		TURP	Holmium Laser R/E *	Laser Coagulation	Incision of the Prostate	Electro-vaporization	Laser Vaporization	Open Prostatectomy	Watchful Waiting
AUA / IPSS									
At 3-9 Months									
RCT diff. + SA control:	Estimated change			-16.96					
RCT:	Difference in change from control			-2.31					
	Confidence interval			-6.61, 1.99					
	# of studies			2					
SA:	Estimated change	-14.65	-17.77	-14.76	-11.86	-11.49	-13.43		-1.00
	# of groups / # of patients	25/894	2/67	19/1065	3/148	17/640	8/299		1/42
At 12 Months									
RCT diff. + SA control:	Estimated change			-20.20	-15.19				
RCT:	Difference in change from control			-5.40	-0.39				
	Confidence interval			-11.37, .57	-5.29, 4.51				
	# of studies			1	1				
SA:	Estimated change	-14.80	-17.90	-13.73	-13.45	-15.75	-14.10		-0.50
	# of groups / # of patients	19/689	1/11	11/532	4/178	10/407	4/160		1/1064
> 16 Months									
RCT diff. + SA control:	Estimated change			-18.44					
RCT:	Difference in change from control			-4.90					
	Confidence interval			-12.61, 2.81					
	# of studies			1					
SA:	Estimated change	-13.54		-13.69	-10.79	-19.34	-14.20	-10.11	
	# of groups / # of patients	12/552		4/130	5/185	3/89	1/33	1/27	

* Transurethral Holmium Laser Resection/Enucleation

Table 3-e. Surgical therapies: Estimates of change in efficacy scores/rates

			Transurethral						
		TURP	Holmium Laser R/E *	Laser Coagulation	Incision of the Prostate	Electro-vaporization	Laser Vaporization	Open Prostatectomy	Watchful Waiting
Peak Flow Rate (Qmax)									
At 3-9 Months									
RCT diff. + SA control:	Estimated change			8.49			6.64		
RCT:	Difference in change from control			-2.05			-3.90		
	Confidence interval			-5.90, 1.80			-8.29, .489		
	# of studies			2			1		
SA:	Estimated change	10.54	12.16	7.94	8.66	10.51	9.46	15.50	-0.03
	# of groups / # of patients	29/1045	2/58	23/754	5/226	13/541	14/457	1/27	1/42
At 12 Months									
RCT diff. + SA control:	Estimated change			10.97	2.24				
RCT:	Difference in change from control			0.20	-8.53				
	Confidence interval			-13.60, 13.99	-14.24, -2.83				
	# of studies			1	1				
SA:	Estimated change	10.77	10.96	8.68	7.65	12.52	11.10	11.50	
	# of groups / # of patients	20/734	2/95	11/510	7/315	9/387	6/189	1/7.5	
> 16 Months									
RCT diff. + SA control:	Estimated change			3.26					2.16
RCT:	Difference in change from control			-4.80					-5.90
	Confidence interval			-12.51, 2.91					-7.48, -4.32
	# of studies			1					1
SA:	Estimated change	8.06		9.19	6.31	12.46	9.00	14.01	0.40
	# of groups / # of patients	15/642		4/114	8/298	3/89	1/33	2/53	1/276

* Transurethral Holmium Laser Resection/Enucleation

Table 3-e. Surgical therapies: Estimates of change in efficacy scores/rates

			Transurethral						
		TURP	Holmium Laser R/E *	Laser Coagulation	Incision of the Prostate	Electro-vaporization	Laser Vaporization	Open Prostatectomy	Watchful Waiting
QOL Score									
At 3-9 Months									
RCT diff. + SA control:	Estimated change								
RCT:	Difference in change from control								
	Confidence interval								
	# of studies								
SA:	Estimated change	-3.44		-3.22		-3.60	-4.02		
	# of groups / # of patients	4/136		3/54		1/52	2/44		
At 12 Months									
RCT diff. + SA control:	Estimated change								
RCT:	Difference in change from control								
	Confidence interval								
	# of studies								
SA:	Estimated change	-3.34			-3.67	-3.70	-1.70		
	# of groups / # of patients	3/112			1/96	1/51	1/7		
> 16 Months									
RCT diff. + SA control:	Estimated change								
RCT:	Difference in change from control								
	Confidence interval								
	# of studies								
SA:	Estimated change	-3.03			-3.73				
	# of groups / # of patients	2/35			1/92				

* Transurethral Holmium Laser Resection/Enucleation

Table 3-e. Surgical therapies: Estimates of change in efficacy scores/rates

			Transurethral						
		TURP	Holmium Laser R/E *	Laser Coagulation	Incision of the Prostate	Electro-vaporization	Laser Vaporization	Open Prostatectomy	Watchful Waiting
BPH Impact Index									
At 3-9 Months									
RCT diff. + SA control:	Estimated change								
RCT:	Difference in change from control								
	Confidence interval								
	# of studies								
SA:	Estimated change								
	# of groups / # of patients								
At 12 Months									
RCT diff. + SA control:	Estimated change								
RCT:	Difference in change from control								
	Confidence interval								
	# of studies								
SA:	Estimated change								
	# of groups / # of patients								

* Transurethral Holmium Laser Resection/Enucleation

Table 3-f. Surgical therapies: Estimates of rates of occurrence of adverse events

Adverse Event		TURP	Transurethral: Holmium Laser R/E *	Transurethral: Laser Coagulation	Transurethral: Incision of the Prostate	Transurethral: Electro-vaporization	Transurethral: Laser Vaporization	Open Prostatectomy	Watchful Waiting
Aborted Procedure/Device Failure									
RCT:	Difference in rate from control								
	Confidence interval								
	# of studies								
SAMA:	Estimated rate								
	Confidence interval								
	# of groups								
	# of AEs / # of patients								
Acute Urinary Retention									
RCT:	Difference in rate from control			0.252	0.025	0.092	0.102	0.019	-0.007
	Confidence interval			.141, .356	-.036, .086	.037, .146	.002, .200	-.048, .086	-.037, .023
	# of studies			1	2	5	3	1	1
SAMA:	Estimated rate	0.054	0.075	0.213	0.059	0.116	0.126	0.007	0.033
	Confidence interval	.036, .081	.022, .170	.161, .276	.031, .099	.073, .172	.078, .187	.000, .075	.016, .059
	# of groups	19	2	10	4	13	12	1	1
	# of AEs / # of patients	73/1399	6/106	101/505	13/267	85/701	57/543	0/32	9/276
BNC/Stricture									
RCT:	Difference in rate from control			0.006	-0.045	-0.01	-0.055	0.103	
	Confidence interval			-.023, .035	-.111, .021	-.051, .031	-.300, .196	-.070, .271	
	# of studies			5	6	7	2	1	
SAMA:	Estimated rate	0.066	0.053	0.049	0.063	0.052	0.029	0.076	
	Confidence interval	.051, .084	.005, .193	.031, .074	.035, .101	.036, .075	.012, .055	.024, .168	
	# of groups	32	1	16	9	13	8	3	
	# of AEs / # of patients	205/5766	1/22	27/910	10/310	23/628	3/334	20/418	
Cardiovascular									
RCT:	Difference in rate from control								
	Confidence interval								
	# of studies								
SAMA:	Estimated rate	0.005							
	Confidence interval	.001, .016							
	# of groups	2							
	# of AEs / # of patients	4/325							

* Transurethral Holmium Laser Resection/Enucleation

Table 3-f. Surgical therapies: Estimates of rates of occurrence of adverse events

Adverse Event		TURP	Transurethral						
			Holmium Laser R/E *	Laser Coagulation	Incision of the Prostate	Electro-vaporization	Laser Vaporization	Open Prostatectomy	Watchful Waiting
Cardiovascular, Serious									
RCT:	Difference in rate from control			0.000					
	Confidence interval			-.044, .043					
	# of studies			1					
SAMA:	Estimated rate	0.016		0.015					
	Confidence interval	.001, .061		.001, .060					
	# of groups	1		1					
	# of AEs / # of patients	1/75		1/76					
Cardiovascular, Thrombo-embolic									
RCT:	Difference in rate from control			-0.027					
	Confidence interval			-.082, .029					
	# of studies			1					
SAMA:	Estimated rate	0.021		0.015				0.011	0.001
	Confidence interval	.002, .075		.001, .060				.004, .025	.000, .009
	# of groups	2		1				1	1
	# of AEs / # of patients	12/3986		1/76				4/380	0/276
Hematuria, Significant									
RCT:	Difference in rate from control			-0.021	-0.212	-0.034	-0.016	-0.065	
	Confidence interval			-.104, .061	-.442, .045	-.167, .100	-.105, .074	-.153, .025	
	# of studies			2	1	2	2	1	
SAMA:	Estimated rate	0.061	0.030	0.030	0.051	0.055	0.102	0.007	
	Confidence interval	.045, .083	.006, .087	.014, .055	.009, .146	.031, .089	.041, .197	.000, .075	
	# of groups	15	2	7	3	8	4	1	
	# of AEs / # of patients	44/1015	2/106	5/514	2/93	21/522	12/148	0/32	
Incontinence									
RCT:	Difference in rate from control		0.027	0.008	-0.083	0.005	-0.015	0.110	
	Confidence interval		-.107, .160	-.025, .040	-.271, .111	-.029, .038	-.059, .030	-.034, .250	
	# of studies		1	2	2	4	1	1	
SAMA:	Estimated rate	0.032	0.010	0.011	0.024	0.034	0.025	0.063	0.015
	Confidence interval	.020, .049	.000, .107	.004, .025	.006, .062	.017, .060	.007, .061	.008, .202	.005, .034
	# of groups	19	1	9	3	8	5	2	1
	# of AEs / # of patients	50/5005	0/22	0/682	2/158	6/350	1/255	11/374	4/276

* Transurethral Holmium Laser Resection/Enucleation

Table 3-f. Surgical therapies: Estimates of rates of occurrence of adverse events

Adverse Event		TURP	Transurethral: Holmium Laser R/E *	Transurethral: Laser Coagulation	Transurethral: Incision of the Prostate	Transurethral: Electro-vaporization	Transurethral: Laser Vaporization	Open Prostatectomy	Watchful Waiting
Infection / UTI									
RCT:	Difference in rate from control			0.052	-0.018	0.017	0.002	0.057	
	Confidence interval			-.097, .199	-.138, .103	-.022, .057	-.065, .070	-.084, .196	
	# of studies			3	3	5	1	1	
SAMA:	Estimated rate	0.064	0.010	0.088	0.052	0.083	0.088	0.079	0.001
	Confidence interval	.047, .086	.000, .107	.058, .132	.030, .083	.040, .145	.061, .123	.025, .173	.000, .009
	# of groups	25	1	19	6	9	9	2	1
	# of AEs / # of patients	245/6801	0/22	94/1202	16/378	54/598	34/487	23/412	0/276
Intraoperative									
RCT:	Difference in rate from control				-0.009	0.020			
	Confidence interval				-.051, .033	-.026, .066			
	# of studies				1	2			
SAMA:	Estimated rate	0.034		0.030	0.020	0.033	0.025		0.001
	Confidence interval	.029, .040		.005, .090	.004, .057	.008, .087	.005, .071		.000, .009
	# of groups	5		3	1	3	3		1
	# of AEs / # of patients	144/4337		1/95	2/110	2/120	2/220		0/276
Post Procedure, Irritative									
RCT:	Difference in rate from control			0.059		0.054	0.195		
	Confidence interval			-.183, .293		-.133, .238	-.001, .377		
	# of studies			2		3	1		
SAMA:	Estimated rate	0.151	0.061	0.661	0.993	0.230	0.356		
	Confidence interval	.091, .226	.023, .126	.436, .844	.964, 1.000	.117, .378	.245, .486		
	# of groups	10	1	12	1	8	7		
	# of AEs / # of patients	73/449	5/84	435/599	100/100	178/488	106/352		
Secondary Procedure									
RCT:	Difference in rate from control			0.030	0.193	0.013	0.080	-0.065	0.206
	Confidence interval			-.002, .062	.094, .288	-.022, .048	.000, .158	-.153, .025	.152, .260
	# of studies			4	3	4	2	1	1
SAMA:	Estimated rate	0.047	0.010	0.070	0.139	0.077	0.077	0.007	0.551
	Confidence interval	.035, .063	.010, .107	.053, .092	.077, .222	.053, .110	.052, .113	.000, .075	.492, .608
	# of groups	21	1	16	6	8	9	1	1
	# of AEs / # of patients	35/1237	0/22	61/1139	44/361	25/446	26/466	0/32	152/276

* Transurethral Holmium Laser Resection/Enucleation

Table 3-f. Surgical therapies: Estimates of rates of occurrence of adverse events

Adverse Event		TURP	Transurethral: Holmium Laser R/E *	Transurethral: Laser Coagulation	Transurethral: Incision of the Prostate	Transurethral: Electro-vaporization	Transurethral: Laser Vaporization	Open Prostatectomy	Watchful Waiting
Sexual, Ejaculation									
RCT:	Difference in rate from control			-0.578	-0.457	-0.052	-0.146	0.088	
	Confidence interval			-.786, .303	-.623, .253	-.328, .233	-.833, .673	-.232, .395	
	# of studies			3	6	2	2	1	
SAMA:	Estimated rate	0.645	0.587	0.171	0.178	0.646	0.424	0.612	
	Confidence interval	.556, .724	.368, .785	.118, .243	.123, .250	.432, .825	.210, .661	.350, .835	
	# of groups	19	2	17	11	6	5	1	
	# of AEs / # of patients	283/445	25/42	116/731	70/409	140/225	40/92	8/13	
Sexual, Erectile Problems									
RCT:	Difference in rate from control			-0.027	0.013	0.043	-0.015		0.142
	Confidence interval			-.142, .088	-.100, .125	-.074, .159	-.124, .094		.085, .198
	# of studies			1	5	3	1		1
SAMA:	Estimated rate	0.098	0.030	0.064	0.130	0.075	0.070		0.210
	Confidence interval	.073, .130	.002, .123	.028, .119	.059, .234	.042, .121	.038, .114		.166, .262
	# of groups	15	2	12	10	10	9		1
	# of AEs / # of patients	46/636	0/42	29/444	45/368	8/293	9/298		58/276
Transfusion									
RCT:	Difference in rate from control			-0.082	-0.099	-0.011	-0.169		-0.012
	Confidence interval			-.133, .031	-.219, .023	-.034, .012	-.254, .081		-.027, .003
	# of studies			4	5	6	1		1
SAMA:	Estimated rate	0.078	0.015	0.021	0.029	0.012	0.025	0.268	0.001
	Confidence interval	.054, .113	.001, .066	.011, .035	.009, .066	.005, .025	.011, .047	.226, .315	.000, .009
	# of groups	23	2	12	6	10	10	1	1
	# of AEs / # of patients	635/6375	0/106	4/840	1/234	0/598	2/493	102/380	0/276

* Transurethral Holmium Laser Resection/Enucleation

Table 3-g. Comparison of analyses of rates of occurrence of adverse events: Medical therapies

Adverse Event		Placebo	Alpha Blockers				Hormonal	Combinations		
			Alfuzosin	Doxazosin	Tamsulosin	Terazosin	Finasteride	Alfuzosin/ Finasteride	Doxazosin/ Finasteride	Terazosin/ Finasteride
Acute Urinary Retention										
Bayesian:	Estimated rate			0.017	0.060	0.031	0.015		0.017	
	Confidence interval			-.003, .036	.022, .098	-.024, .085	.001, .029		.-.003, .036	
SAMA:	Estimated rate	0.031		0.001	0.035	0.035	0.015	0.003	0.001	
	Confidence interval	.021, .045		.000, .009	.012, .079	.012, .076	.010, .022	.000, .013	.000, .009	
RCT diff. + SA control:	Estimated rate			0.016	0.059	0.030	0.015		0.016	
Asthenia										
Bayesian:	Estimated rate		0.057	0.133	0.071	0.093	0.032		0.101	0.108
	Confidence interval		.018, .096	.078, .187	.046, .097	.067, .119	.018, .046		.051, .151	.059, .158
SAMA:	Estimated rate	0.037	0.043	0.150	0.066	0.115	0.023	0.009	0.126	0.139
	Confidence interval	.027, .051	.014, .097	.126, .177	.033, .116	.103, .128	.010, .044	.002, .023	.093, .170	.105, .182
RCT diff. + SA control:	Estimated rate		0.056	0.132	0.070	0.092	0.031		0.100	0.107
Breast										
Bayesian:	Estimated rate						0.023			
	Confidence interval						0, .046			
SAMA:	Estimated rate	0.015					0.009			
	Confidence interval	.003, .045					.004, .017			
RCT diff. + SA control:	Estimated rate						0.020			
Cardiovascular										
Bayesian:	Estimated rate		0.026	0.009	-0.005	0.043	0.040		0.008	
	Confidence interval		-.006, .064	-.029, .048	-.070, .060	-.014, .099	.012, .067		-.030, .047	
SAMA:	Estimated rate	0.039	0.012	0.019	0.078	0.022	0.053		0.018	
	Confidence interval	.020, .065	.002, .036	.007, .040	.023, .180	.013, .034	.023, .101		.007, .038	
RCT diff. + SA control:	Estimated rate		0.022	0.006	-0.009	0.039	0.036		0.005	
Cardiovascular - Peripheral Edema										
Bayesian:	Estimated rate		0.000			0.046				
	Confidence interval		-.020, .021			-.028, .120				
SAMA:	Estimated rate	0.011	0.001	0.014		0.041				
	Confidence interval	.005, .020	.000, .014	.006, .027		.024, .063				
RCT diff. + SA control:	Estimated rate		0.000			0.045				
Cardiovascular - Serious										
Bayesian:	Estimated rate					0.000	0.018			
	Confidence interval					-.007, .007	.010, .026			
SAMA:	Estimated rate	0.008				0.001	0.011	0.003		
	Confidence interval	.005, .013				.000, .004	.002, .030	.000, .013		
RCT diff. + SA control:	Estimated rate					-0.001	0.018			

Table 3-g. Comparison of analyses of rates of occurrence of adverse events: Medical therapies

Adverse Event		Placebo	Alpha Blockers				Hormonal	Combinations		
			Alfuzosin	Doxazosin	Tamsulosin	Terazosin	Finasteride	Alfuzosin/ Finasteride	Doxazosin/ Finasteride	Terazosin/ Finasteride
Dizziness										
Bayesian:	Estimated rate		0.076	0.141	0.091	0.141	0.047		0.115	0.194
	Confidence interval		.027, .125	.075, .207	.062, .121	.088, .193	.029, .065		.061, .168	.137, .250
SAMA:	Estimated rate	0.053	0.051	0.133	0.115	0.154	0.047	0.023	0.140	0.214
	Confidence interval	.040, .070	.014, .121	.093, .187	. 077, .169	.119, .198	.017, .099	.011, .043	.105, .186	.171, .263
RCT diff. + SA control:	Estimated rate		0.077	0.142	0.092	0.141	0.049		0.115	0.194
GI Systems										
Bayesian:	Estimated rate		0.071	0.095	0.044	0.066	0.042		0.040	
	Confidence interval		.006, .135	-.028, .217	.008, .079	.031, .101	-.002, .086		-.013, .094	
SAMA:	Estimated rate	0.059	0.097	0.101	0.106	0.054	0.059		0.084	
	Confidence interval	.040, .086	.060, .147	.063, .151	.055, .179	.028, .092	.032, .098		.057, .123	
RCT diff. + SA control:	Estimated rate		0.070	0.094	0.043	0.065	0.041		0.039	
Headache										
Bayesian:	Estimated rate		0.079	0.053	0.067	0.045	0.051		0.035	0.069
	Confidence interval		.035, .123	-.008, .114	.036, .099	.001, .090	.032, .071		-.017, .087	.033, .106
SAMA:	Estimated rate	0.051	0.052	0.077	0.115	0.072	0.035	0.015	0.088	0.052
	Confidence interval	.036, .072	.026, .091	.044, .123	.060, .192	.052, .100	.020, .058	.005, .031	.060, .127	.031, .081
RCT diff. + SA control:	Estimated rate		0.079	0.054	0.068	0.046	0.052		0.035	0.070
Hypotension - Asymptomatic										
Bayesian:	Estimated rate			0.055	0.085	0.029	0.012		0.032	
	Confidence interval			.010, .100	.050, .120	.018, .039	-.008, .032		.006, .058	
SAMA:	Estimated rate	0.019		0.054	0.067	0.075	0.037	0.080	0.029	
	Confidence interval	.013, .027		.026, .097	.021, .152	.020, .181	.005, .122	.056, .114	.013, .052	
RCT diff. + SA control:	Estimated rate			0.055	0.085	0.028	0.012		0.032	
Hypotension - Symptomatic										
Bayesian:	Estimated rate		0.025			0.027				
	Confidence interval		-.002, .051			-.028, .083				
SAMA:	Estimated rate	0.017	0.007			0.027				
	Confidence interval	.004, .046	.001, .026			.005, .077				
RCT diff. + SA control:	Estimated rate		0.023			0.025				
Hypotension - Symptomatic - Postural										
Bayesian:	Estimated rate			0.059	0.016	0.053	0.014		0.025	0.089
	Confidence interval			.026, .092	.005, .026	.021, .085	-.011, .039		.000, .050	.055, .123
SAMA:	Estimated rate	0.011		0.040	0.025	0.063	0.016	0.006	0.029	0.087
	Confidence interval	.007, .017		.013, .089	.008, .055	.033, .107	.008, .027	.001, .018	.013, .052	.061, .124
RCT diff. + SA control:	Estimated rate			0.059	0.015	0.053	0.013		0.024	0.088

Table 3-g. Comparison of analyses of rates of occurrence of adverse events: Medical therapies

Adverse Event		Placebo	Alpha Blockers				Hormonal	Combinations		
			Alfuzosin	Doxazosin	Tamsulosin	Terazosin	Finasteride	Alfuzosin/ Finasteride	Doxazosin/ Finasteride	Terazosin/ Finasteride
Hypotension - Symptomatic - Syncope										
Bayesian:	Estimated rate		0.013	0.008	0.000	0.014	0.010		0.018	0.024
	Confidence interval		-.003, .030	-.006, .021	-.027, .028	.000, .028	-.006, .027		.000, .036	.008, .040
SAMA:	Estimated rate	0.006	0.007	0.004	0.003	0.013	0.007		0.015	0.017
	Confidence interval	.003, .013	.001, .026	.000, .017	.000, .012	.005, .029	.001, .030		.005, .033	.006, .035
RCT diff. + SA control:	Estimated rate		0.012	0.012	-0.002	0.012	0.008		0.016	0.022
Respiratory - Nasal Congestion										
Bayesian:	Estimated rate		0.072	0.071	0.141	0.085	0.039		0.048	0.103
	Confidence interval		.024, .120	-.002, .145	.093, .188	.027, .142	-.011, .089		-.024, .120	.049, .156
SAMA:	Estimated rate	0.060	0.059	0.078	0.108	0.063	0.090		0.179	0.100
	Confidence interval	.033, .096	.014, .152	.010, .247	.037, .228	.035, .102	.023, .218		.139, .228	.071, .139
RCT diff. + SA control:	Estimated rate		0.071	0.070	0.139	0.083	0.037		0.046	0.101
Sexual - Ejaculation										
Bayesian:	Estimated rate			-0.001	0.105	0.013	0.031		0.027	0.065
	Confidence interval			-.018, .017	.035, .176	-.010, .037	.023, .040		.001, .053	.034, .097
SAMA:	Estimated rate	0.010		0.004	0.099	0.013	0.035	0.009	0.032	0.068
	Confidence interval	.008, .014		.000, .017	.060, .151	.007, .021	.027, .045	.002, .023	.016, .057	.045, .102
RCT diff. + SA control:	Estimated rate			-0.001	0.105	0.013	0.031		0.027	0.065
Sexual - Erectile Problems										
Bayesian:	Estimated rate		0.056	0.057	0.047	0.07	0.076		0.103	0.087
	Confidence interval		.023, .089	.021, .093	.006, .089	.007, .133	.061, .091		.061, .146	.045, .128
SAMA:	Estimated rate	0.039	0.029	0.035	0.035	0.050	0.080	0.075	0.098	0.094
	Confidence interval	.029, .051	.011, .061	.013, .075	.012, .079	.029, .078	.061, .105	.051, .107	.069, .139	.006, .132
RCT diff. + SA control:	Estimated rate		0.056	0.057	0.048	0.070	0.076		0.104	0.087
Sexual - Libido										
Bayesian:	Estimated rate		0.036	0.045		0.044	0.051		0.037	0.066
	Confidence interval		.014, .059	.017, .073		.020, .067	.043, .059		.011, .062	.038, .094
SAMA:	Estimated rate	0.031	0.012	0.034		0.027	0.051	0.021	0.025	0.049
	Confidence interval	.026, .036	.002, .036	.016, .060		.012, .049	.039, .066	.009, .039	.011, .048	.029, .077
RCT diff. + SA control:	Estimated rate		0.037	0.046		0.044	0.051		0.037	0.066

Table 3-g. Comparison of analyses of rates of occurrence of adverse events: Minimally invasive therapies

Adverse Event		Sham	Sham-Based Comparisons: Prostatron Version 2.0 TUMT	Prostatron Version 2.5 TUMT	Targis TUMT
Aborted Procedure/Device Failure					
Bayesian:	Estimated rate				0.012
	Confidence interval				-.035, .059
SAMA:	Estimated rate	0.005	0.007		0.009
	Confidence interval	.000, .055	.000, .029		.001, .037
RCT diff. + SA control:	Estimated rate				0.006
Acute Urinary Retention					
Bayesian:	Estimated rate		0.328		0.078
	Confidence interval		.088, .569		.005, .152
SAMA:	Estimated rate	0.027	0.228	0.150	0.062
	Confidence interval	.011, .054	.179, .286	.043, .334	.013, .166
RCT diff. + SA control:	Estimated rate		0.332		0.077
BNC/Stricture					
Bayesian:	Estimated rate				0.028
	Confidence interval				-.024, .079
SAMA:	Estimated rate	0.005	0.011	0.021	0.025
	Confidence interval	.000, .055	.004, 024	.001, .088	.007, .063
RCT diff. + SA control:	Estimated rate				0.021
Cardiovascular					
Bayesian:	Estimated rate				
	Confidence interval				
SAMA:	Estimated rate	0.003			
	Confidence interval	.000, .034			
RCT diff. + SA control:	Estimated rate				
Cardiovascular, Serious					
Bayesian:	Estimated rate				
	Confidence interval				
SAMA:	Estimated rate				
	Confidence interval				
RCT diff. + SA control:	Estimated rate				

Table 3-g. Comparison of analyses of rates of occurrence of adverse events: Minimally invasive therapies

Adverse Event		TURP	TURP-Based Comparisons: Prostatron Version 2.0 TUMT	Prostatron Version 2.5 TUMT	Targis TUMT	TUNA	UroLume Stent
Aborted Procedure/Device Failure							
Bayesian:	Estimated rate						
	Confidence interval						
SAMA:	Estimated rate		0.007		0.009	0.035	0.342
	Confidence interval		.000, .029		.001, .037	.008, .091	.113, .641
RCT diff. + SA control:	Estimated rate						
Acute Urinary Retention							
Bayesian:	Estimated rate		0.193	0.088			
	Confidence interval		.104, .281	-.059, .234			
SAMA:	Estimated rate	0.054	0.228	0.150	0.062	0.202	0.061
	Confidence interval	.036, .081	.179, .286	.043, .334	.013, .166	.129, .292	.017, .146
RCT diff. + SA control:	Estimated rate		0.192	0.086			
BNC/Stricture							
Bayesian:	Estimated rate		-0.022	0.007		0.010	
	Confidence interval		-.118, .075	-.088, .104		-.070, .090	
SAMA:	Estimated rate	0.066	0.011	0.021	0.025	0.029	
	Confidence interval	.051, .084	.004, .024	.001, .088	.007, .063	.010, .063	
RCT diff. + SA control:	Estimated rate		-0.022	0.007		0.010	
Cardiovascular							
Bayesian:	Estimated rate						
	Confidence interval						
SAMA:	Estimated rate	0.005					
	Confidence interval	.001, .016					
RCT diff. + SA control:	Estimated rate						
Cardiovascular, Serious							
Bayesian:	Estimated rate						
	Confidence interval						
SAMA:	Estimated rate	0.016					
	Confidence interval	.001, .061					
RCT diff. + SA control:	Estimated rate						

Table 3-g. Comparison of analyses of rates of occurrence of adverse events: Minimally invasive therapies

Adverse Event		Sham	Sham-Based Comparisons: Prostatron Version 2.0 TUMT	Prostatron Version 2.5 TUMT	Targis TUMT
Cardiovascular, Thrombo-embolic					
Bayesian:	Estimated rate				
	Confidence interval				
SAMA:	Estimated rate				
	Confidence interval				
RCT diff. + SA control:	Estimated rate				
Hematuria, Significant					
Bayesian:	Estimated rate				
	Confidence interval				
SAMA:	Estimated rate		0.022		
	Confidence interval		.010, .042		
RCT diff. + SA control:	Estimated rate				
Incontinence					
Bayesian:	Estimated rate		0.043		
	Confidence interval		-.012, .010		
SAMA:	Estimated rate	0.005	0.023		
	Confidence interval	.000, .055	.012, .039		
RCT diff. + SA control:	Estimated rate		0.037		
Infection / UTI					
Bayesian:	Estimated rate		0.225		0.087
	Confidence interval		.020, .429		-.010, .184
SAMA:	Estimated rate	0.051	0.089	0.090	0.091
	Confidence interval	.018, .107	.045, .151	.031, .190	.048, .152
RCT diff. + SA control:	Estimated rate		0.224		0.084
Intraoperative					
Bayesian:	Estimated rate				0.028
	Confidence interval				-.024, .079
SAMA:	Estimated rate	0.005			0.025
	Confidence interval	.000, .055			.007, .063
RCT diff. + SA control:	Estimated rate				0.022

Table 3-g. Comparison of analyses of rates of occurrence of adverse events: Minimally invasive therapies

Adverse Event		TURP	TURP-Based Comparisons: Prostatron Version 2.0 TUMT	Prostatron Version 2.5 TUMT	Targis TUMT	TUNA	UroLume Stent
Cardiovascular, Thrombo-embolic							
Bayesian:	Estimated rate						
	Confidence interval						
SAMA:	Estimated rate	0.021				0.017	
	Confidence interval	.002, .075				.002, .064	
RCT diff. + SA control:	Estimated rate						
Hematuria, Significant							
Bayesian:	Estimated rate		-0.003				
	Confidence interval		-.090, .083				
SAMA:	Estimated rate	0.061	0.022			0.038	0.064
	Confidence interval	.045, .083	.010, .042			.012, .087	.023, .135
RCT diff. + SA control:	Estimated rate		-0.004				
Incontinence							
Bayesian:	Estimated rate		0.021			-0.003	
	Confidence interval		-.033, .076			-.062, .056	
SAMA:	Estimated rate	0.032	0.023			0.013	0.249
	Confidence interval	.020, .049	.012, .039			.002, .044	.069, .527
RCT diff. + SA control:	Estimated rate		0.021			-0.004	
Infection / UTI							
Bayesian:	Estimated rate		0.117	0.077		0.259	
	Confidence interval		.002, .232	-.120, .273		.115, .402	
SAMA:	Estimated rate	0.064	0.089	0.090	0.091	0.173	0.109
	Confidence interval	.047, .086	.045, .151	.031, .190	.048, .152	.090, .285	.059, .177
RCT diff. + SA control:	Estimated rate		0.117	0.076		0.259	
Intraoperative							
Bayesian:	Estimated rate						
	Confidence interval						
SAMA:	Estimated rate	0.034			0.025	0.114	
	Confidence interval	.029, .040			.007, .063	.011, .381	
RCT diff. + SA control:	Estimated rate						

Table 3-g. Comparison of analyses of rates of occurrence of adverse events: Minimally invasive therapies

Adverse Event		Sham	Sham-Based Comparisons: Prostatron Version 2.0 TUMT	Prostatron Version 2.5 TUMT	Targis TUMT
Post Procedure, Irritative					
Bayesian:	Estimated rate		0.263		
	Confidence interval		-.275, .801		
SAMA:	Estimated rate	0.696	0.276	0.738	
	Confidence interval	.100, .993	.121, .479	.178, .991	
RCT diff. + SA control:	Estimated rate		0.308		
Secondary Procedure					
Bayesian:	Estimated rate		0.182		
	Confidence interval		-.037, .401		
SAMA:	Estimated rate	0.235	0.100	0.100	0.158
	Confidence interval	.103, .416	.058, .157	.047, .177	.115, .201
RCT diff. + SA control:	Estimated rate		0.175		
Sexual, Ejaculation					
Bayesian:	Estimated rate				0.052
	Confidence interval				-.003, .107
SAMA:	Estimated rate	0.015	0.054	0.160	0.048
	Confidence interval	.002, .052	.038, .077	.017, .493	.018, .097
RCT diff. + SA control:	Estimated rate				0.049
Sexual, Erectile Problems					
Bayesian:	Estimated rate		0.019		
	Confidence interval		-.030, .067		
SAMA:	Estimated rate	0.023	0.029	0.007	
	Confidence interval	.006, .060	.013, .053	.000, .080	
RCT diff. + SA control:	Estimated rate		0.016		
Transfusion					
Bayesian:	Estimated rate				0.004
	Confidence interval				-.040, .048
SAMA:	Estimated rate	0.005	0.009	0.021	0.002
	Confidence interval	.000, .055	.001, .040	.001, .088	.000, .020
RCT diff. + SA control:	Estimated rate				-0.002

Table 3-g. Comparison of analyses of rates of occurrence of adverse events: Minimally invasive therapies

Adverse Event		TURP	TURP-Based Comparisons: Prostatron Version 2.0 TUMT	Prostatron Version 2.5 TUMT	Targis TUMT	TUNA	UroLume Stent
Post Procedure, Irritative							
Bayesian:	Estimated rate		0.240	0.245		0.116	
	Confidence interval		.078, .403	.008, .482		.028, .205	
SAMA:	Estimated rate	0.151	0.276	0.738		0.309	0.918
	Confidence interval	.091, .226	.121, .479	.178, .991		.110, .576	.752, .988
RCT diff. + SA control:	Estimated rate		0.239	0.245		0.115	
Secondary Procedure							
Bayesian:	Estimated rate		0.150	0.138			
	Confidence interval		.057, .244	-.040, .315			
SAMA:	Estimated rate	0.047	0.100	0.100	0.158	0.232	0.103
	Confidence interval	.035, .063	.058, .157	.047, .177	.115, .201	.146, .337	.045, .192
RCT diff. + SA control:	Estimated rate		0.150	0.138			
Sexual, Ejaculation							
Bayesian:	Estimated rate		0.275	0.255		-0.131	
	Confidence interval		.005, .545	-.036, .546		-.270, .007	
SAMA:	Estimated rate	0.645	0.054	0.160	0.048	0.043	
	Confidence interval	.556, .724	.038, .077	.017, .493	.018, .097	.013, .101	
RCT diff. + SA control:	Estimated rate		0.272	0.250		-0.134	
Sexual, Erectile Problems							
Bayesian:	Estimated rate		0.097	-0.032		-0.027	
	Confidence interval		.042, .153	-.165, .102		-.121, .068	
SAMA:	Estimated rate	0.098	0.029	0.007		0.029	
	Confidence interval	.073, .130	.013, .053	.000, .080		.012, .058	
RCT diff. + SA control:	Estimated rate		0.098	-0.032		-0.026	
Transfusion							
Bayesian:	Estimated rate		0.029	0.072			
	Confidence interval		-.095, .176	-.007, .152			
SAMA:	Estimated rate	0.078	0.009	0.021	0.002	0.028	
	Confidence interval	.054, .113	.001, .040	.001, .088	.000, .020	.005, .084	
RCT diff. + SA control:	Estimated rate		0.027	0.071			

Table 3-g. Comparison of analyses of rates of occurrence of adverse events: Surgical therapies

Adverse Event		TURP	Transurethral: Holmium Laser R/E *	Transurethral: Laser Coagulation	Transurethral: Incision of the Prostate	Transurethral: Electro-vaporization	Transurethral: Laser Vaporization	Open Prostatectomy	Watchful Waiting
Aborted Procedure/Device Failure									
Bayesian:	Estimated rate								
	Confidence interval								
SAMA:	Estimated rate								
	Confidence interval								
RCT diff. + SA control:	Estimated rate								
Acute Urinary Retention									
Bayesian:	Estimated rate			0.306	0.081	0.147	0.157	0.074	
	Confidence interval			.197, .416	.016, .146	.089, .206	.056, .259	.004, .145	
SAMA:	Estimated rate	0.054	0.075	0.213	0.059	0.116	0.126	0.007	0.033
	Confidence interval	.036, .081	.022, .170	.161, .276	.031, .099	.073, .172	.078, .187	.000, .075	.016, .059
RCT diff. + SA control:	Estimated rate			0.306	0.079	0.146	0.156	0.073	0.047
BNC/Stricture									
Bayesian:	Estimated rate			0.072	0.021	0.056	0.012	0.168	
	Confidence interval			.039, .105	-.047, .089	.012, .100	-.238, .262	-.003, .340	
SAMA:	Estimated rate	0.066	0.053	0.049	0.063	0.052	0.029	0.076	
	Confidence interval	.051, .084	.005, .193	.031, .074	.035, .101	.036, .075	.012, .055	.024, .168	
RCT diff. + SA control:	Estimated rate			0.072	0.021	0.056	0.011	0.169	
Cardiovascular									
Bayesian:	Estimated rate								
	Confidence interval								
SAMA:	Estimated rate	0.005							
	Confidence interval	.001, .016							
RCT diff. + SA control:	Estimated rate								
Cardiovascular, Serious									
Bayesian:	Estimated rate			0.019					
	Confidence interval			-.034, .073					
SAMA:	Estimated rate	0.016		0.015					
	Confidence interval	.001, .061		.001, .060					
RCT diff. + SA control:	Estimated rate			0.016					

* Transurethral Holmium Laser Resection/Enucleation

Table 3-g. Comparison of analyses of rates of occurrence of adverse events: Surgical therapies

Adverse Event		TURP	Transurethral: Holmium Laser R/E *	Transurethral: Laser Coagulation	Transurethral: Incision of the Prostate	Transurethral: Electro-vaporization	Transurethral: Laser Vaporization	Open Prostatectomy	Watchful Waiting
Cardiovascular, Thrombo-embolic									
Bayesian:	Estimated rate			-0.001					
	Confidence interval			-.068, .067					
SAMA:	Estimated rate	0.021		0.015				0.011	0.001
	Confidence interval	.002, .075		.001, .060				.004, .025	.000, .009
RCT diff. + SA control:	Estimated rate			-0.006					
Hematuria, Significant									
Bayesian:	Estimated rate			0.041	-0.146	0.028	0.046	-0.002	
	Confidence interval			-.044, .125	-.392, ..099	-.107, .163	-.045, .138	-.093, .089	
SAMA:	Estimated rate	0.061	0.030	0.030	0.051	0.055	0.102	0.007	
	Confidence interval	.045, .083	.006, .087	.014, .055	.009, .146	.031, .089	.041, .197	.000, .075	
RCT diff. + SA control:	Estimated rate			0.040	-0.151	0.027	0.045	-0.004	
Incontinence									
Bayesian:	Estimated rate		0.043	0.040	-0.049	0.037	0.018	0.142	
	Confidence interval		.011, .075	.005, .076	-.241, .143	.001, .074	-.029, .065	0, .286	
SAMA:	Estimated rate	0.032	0.010	0.011	0.024	0.034	0.025	0.063	0.015
	Confidence interval	.020, .049	.000, .107	.004, .025	.006, .062	.017, .060	.007, .061	.008, .202	.005, .034
RCT diff. + SA control:	Estimated rate		0.059	0.040	-0.051	0.037	0.017	0.142	
Infection / UTI									
Bayesian:	Estimated rate			0.116	0.047	0.082	0.069	0.121	
	Confidence interval			-.033, .266	-.075, .168	.037, .126	-.003, .137	-.020, .262	
SAMA:	Estimated rate	0.064	0.010	0.088	0.052	0.083	0.088	0.079	0.001
	Confidence interval	.047, .086	.000, .107	.058, .132	.030, .083	.040, .145	.061, .123	.025, .173	.000, .009
RCT diff. + SA control:	Estimated rate			0.116	0.046	0.081	0.066	0.121	
Intraoperative									
Bayesian:	Estimated rate				0.025	0.054			
	Confidence interval				-.017, .068	.008, .100			
SAMA:	Estimated rate	0.034		0.030	0.020	0.033	0.025		0.001
	Confidence interval	.029, .040		.005, .090	.004, .057	.008, .087	.005, .071		.000, .009
RCT diff. + SA control:	Estimated rate				0.025	0.054			

* Transurethral Holmium Laser Resection/Enucleation

Table 3-g. Comparison of analyses of rates of occurrence of adverse events: Surgical therapies

Adverse Event		TURP	Transurethral: Holmium Laser R/E *	Transurethral: Laser Coagulation	Transurethral: Incision of the Prostate	Transurethral: Electro-vaporization	Transurethral: Laser Vaporization	Open Prostatectomy	Watchful Waiting
Post Procedure, Irritative									
Bayesian:	Estimated rate			0.210		0.207	0.346		
	Confidence interval			-.038, .459		.009, .404	.145, .548		
SAMA:	Estimated rate	0.151	0.061	0.661	0.993	0.230	0.356		
	Confidence interval	.091, .226	.023, .126	.436, .844	.964, 1.000	.117, .378	.245, .486		
RCT diff. + SA control:	Estimated rate			0.210		0.205	0.346		
Secondary Procedure									
Bayesian:	Estimated rate			0.078	0.240	0.061	0.127	-0.016	
	Confidence interval			.044, .113	.142, .338	.024, .098	.047, .207	-.092, .074	
SAMA:	Estimated rate	0.047	0.010	0.070	0.139	0.077	0.077	0.007	0.551
	Confidence interval	.035, .063	.010, .107	.053, .092	.077, .222	.053, .110	.052, .113	.000, .075	.492, .608
RCT diff. + SA control:	Estimated rate			0.077	0.240	0.060	0.127	-0.018	0.253
Sexual, Ejaculation									
Bayesian:	Estimated rate			0.074	0.191	0.593	0.516	0.730	
	Confidence interval			-.184, .332	-.012, .394	.298, .887	-.289, 1.32	.403, 1.06	
SAMA:	Estimated rate	0.645	0.587	0.171	0.178	0.646	0.424	0.612	
	Confidence interval	.556, .724	.368, .785	.118, .243	.123, .250	.432, .825	.210, .661	.350, .835	
RCT diff. + SA control:	Estimated rate			0.067	0.188	0.593	0.499	0.733	
Sexual, Erectile Problems									
Bayesian:	Estimated rate			0.070	0.110	0.140	0.083		
	Confidence interval			-.049, .189	-.006, .226	.019, .261	-.031, .196		
SAMA:	Estimated rate	0.098	0.030	0.064	0.130	0.075	0.070		0.210
	Confidence interval	.073, .130	.002, .123	.028, .119	.059, .234	.042, .121	.038, .114		.166, .262
RCT diff. + SA control:	Estimated rate			0.071	0.111	0.141	0.083		0.240
Transfusion									
Bayesian:	Estimated rate			-0.002	-0.019	0.069	-0.089		
	Confidence interval			-.061, .056	-.144, .105	.031, .106	-.180, .002		
SAMA:	Estimated rate	0.078	0.015	0.021	0.029	0.012	0.025	0.268	0.001
	Confidence interval	.054, .113	.001, .066	.011, .035	.009, .066	.005, .025	.011, .047	.226, .315	.000, .009
RCT diff. + SA control:	Estimated rate			-0.004	-0.021	0.067	-0.091		0.066

* Transurethral Holmium Laser Resection/Enucleation

Table 3-h. Phytotherapy: Estimates of change in efficacy scores/rates

			Phytotherapy					
		Placebo	Beta-sitosterol 20 mg tid	Beta-sitosterol 130 mg qd	Cerniton Pollen Extract	Pygeum Africanum 50 mg bid	Serenoa Repens 50 mg bid	Sabal Urtica
AUA / IPSS								
At 3-9 Months								
RCT diff. + SA control:	Estimated change							
RCT:	Difference in change from control							
	Confidence interval							
	# of studies							
SA:	Estimated change	-2.64	-7.10	-8.20	-6.13	-6.00	-5.80	-7.50
	# of groups / # of patients	31/6058	1/96	1/88	1/179	1/84	1/467	1/19
At 12 Months								
RCT diff. + SA control:	Estimated change							
RCT:	Difference in change from control							
	Confidence interval							
	# of studies							
SA:	Estimated change	-2.33						
	# of groups / # of patients	18/6679						
Long Term								
RCT diff. + SA control:	Estimated change							
RCT:	Difference in change from control							
	Confidence interval							
	# of studies							
SA:	Estimated change	-1.03						
	# of groups / # of patients	7/3253						

Table 3-h. Phytotherapy: Estimates of change in efficacy scores/rates

Peak Flow Rate (Qmax)		Placebo	Phytotherapy: Beta-sitosterol 20 mg tid	Beta-sitosterol 130 mg qd	Cerniton Pollen Extract	Pygeum Africanum 50 mg bid	Serenoa Repens 50 mg bid	Sabal Urtica
At 3-9 Months								
RCT diff. + SA control:	Estimated change							3.60
RCT:	Difference in change from control							2.75
	Confidence interval							1.54, 3.96
	# of studies							1
SA:	Estimated change	0.85	6.25		2.07	2.23	2.67	3.30
	# of groups / # of patients	34/4781	3/208		2/77	2/122	1/464	1/19
At 12 Months								
RCT diff. + SA control:	Estimated change							
RCT:	Difference in change from control							
	Confidence interval							
	# of studies							
SA:	Estimated change	0.48						
	# of groups / # of patients	16/3992						
Long Term								
RCT diff. + SA control:	Estimated change							
RCT:	Difference in change from control							
	Confidence interval							
	# of studies							
SA:	Estimated change	0.48						
	# of groups / # of patients	4/2444						

Table 3-h. Phytotherapy: Estimates of change in efficacy scores/rates

			Phytotherapy					
		Placebo	Beta-sitosterol 20 mg tid	Beta-sitosterol 130 mg qd	Cerniton Pollen Extract	Pygeum Africanum 50 mg bid	Serenoa Repens 50 mg bid	Sabal Urtica
QOL Score								
At 3-9 Months								
RCT diff. + SA control:	Estimated change							
RCT:	Difference in change from control							
	Confidence interval							
	# of studies							
SA:	Estimated change	-0.65	-1.59			-1.32	-1.40	
	# of groups / # of patients	8/1383	2/184			1/85	1/467	
At 12 Months								
RCT diff. + SA control:	Estimated change							
RCT:	Difference in change from control							
	Confidence interval							
	# of studies							
SA:	Estimated change	-0.67						
	# of groups / # of patients	2/1127						
BPH Impact Index								
At 3-9 Months								
RCT diff. + SA control:	Estimated change							
RCT:	Difference in change from control							
	Confidence interval							
	# of studies							
SA:	Estimated change	-1.00						
	# of groups / # of patients	2/482						
At 12 Months								
RCT diff. + SA control:	Estimated change							
RCT:	Difference in change from control							
	Confidence interval							
	# of studies							
SA:	Estimated change	-0.97						
	# of groups / # of patients	16/8560						

Table 3-i. Phytotherapy: Estimates of rates of occurence of adverse events

Adverse Event		Placebo	Phytotherapy: Serenoa Repens* 50 mg bid	Pygeum Africanum 50 mg bid	Urtica Dioica 300 mg / Pygeum Africanum 25 mg bid	Urtica Dioica 150 mg / Pygeum Africanum 12.5 mg bid	Betasitosteryl Glucoside 0.3 mg qd	B-Sitosterol 20 mg tid	Cernitin Pollen Extract 126 mg bid
Acute Urinary Retention									
RCT:	Difference in rate from control		-0.009	0.002			-0.033		
	Confidence interval		-.023, .004	-.009, .014			-.127, .062		
	# of studies		1	1			1		
SAMA:	Estimated rate	0.031	0.013	0.002			0.009		
	Confidence interval	.021, .045	.006, .025	.000, .019			.000, .095		
	# of groups	12	1	1			1		
	# of AEs / # of patients	172/4613	7/551	0/131			0/25		
Asthenia									
RCT:	Difference in rate from control		-0.001						
	Confidence interval		-.030, .028						
	# of studies		1						
SAMA:	Estimated rate	0.038	0.01		0.018				
	Confidence interval	.027, .051	.001, .038		.002, .068				
	# of groups	23	1		1				
	# of AEs / # of patients	180/5698	1/120		1/67				
Cardiovascular									
RCT:	Difference in rate from control		0.006						
	Confidence interval		-.019, .031						
	# of studies		1						
SAMA:	Estimated rate	0.042	0.029						
	Confidence interval	.023, .068	.012, .056						
	# of groups	15	2						
	# of AEs / # of patients	204/4444	19/671						

* Highlighted Serenoa Repens RCT data are from a study comparing Serenoa Repens to Finasteride. These were combined with finasteride/placebo data to yield the results in the table.

Table 3-i. Phytotherapy: Estimates of rates of occurence of adverse events

Adverse Event		Placebo	Phytotherapy: Serenoa Repens* 50 mg bid	Pygeum Africanum 50 mg bid	Urtica Dioica 300 mg / Pygeum Africanum 25 mg bid	Urtica Dioica 150 mg / Pygeum Africanum 12.5 mg bid	Betasitosteryl Glucoside 0.3 mg qd	B-Sitosterol 20 mg tid	Cernitin Pollen Extract 126 mg bid
Dizziness									
RCT:	Difference in rate from control							-0.010	
	Confidence interval							-.037, .017	
	# of studies							1	
SAMA:	Estimated rate	0.052						0.002	
	Confidence interval	.039, .068						.000, .025	
	# of groups	25						1	
	# of AEs / # of patients	243/4504						0/100	
GI Systems									
RCT:	Difference in rate from control		-0.028	0.023				0.010	
	Confidence interval		-.062, .007	-.006, .052				-.028, .048	
	# of studies		1	1				1	
SAMA:	Estimated rate	0.059	0.022	0.024				0.022	
	Confidence interval	.040, .085	.002, .087	.006, .060				.004, .063	
	# of groups	21	2	1				1	
	# of AEs / # of patients	329/5299	20/671	3/131				2/100	
Headache									
RCT:	Difference in rate from control		-0.001						
	Confidence interval		-.030, .028						
	# of studies		1						
SAMA:	Estimated rate	0.050	0.014			0.018			
	Confidence interval	.035, .070	.005, .028			.002, .068			
	# of groups	25	2			1			
	# of AEs / # of patients	251/4986	8/671			1/67			
Sexual - Ejaculation									
RCT:	Difference in rate from control						0.041		
	Confidence interval						-.059, .140		
	# of studies						1		
SAMA:	Estimated rate	0.010					0.047		
	Confidence interval	.008, .014					.004, .172		
	# of groups	14					1		
	# of AEs / # of patients	55/7016					1/25		

Table 3-i. Phytotherapy: Estimates of rates of occurence of adverse events

Adverse Event		Placebo	Phytotherapy: Serenoa Repens* 50 mg bid	Pygeum Africanum 50 mg bid	Urtica Dioica 300 mg / Pygeum Africanum 25 mg bid	Urtica Dioica 150 mg / Pygeum Africanum 12.5 mg bid	Betasitosteryl Glucoside 0.3 mg qd	B-Sitosterol 20 mg tid	Cernitin Pollen Extract 126 mg bid
Sexual - Erectile Problems									
RCT:	Difference in rate from control		-0.019				0.274	0.020	
	Confidence interval		-.057, .019				.088, .441	-.013, .053	
	# of studies		1				1	1	
SAMA:	Estimated rate	0.039	0.015	0.037			0.283	0.022	0.008
	Confidence interval	.029, .051	.006, .030	.010, .091			.135, .473	.004, .063	.000, .085
	# of groups	24	2	1			1	1	1
	# of AEs / # of patients	277/7169	9/671	3/85			7/25	2/100	0/28
Sexual - Libido									
RCT:	Difference in rate from control		0.012				0.041	0.020	
	Confidence interval		-.008, .033				-.059, .140	-.013, .053	
	# of studies		1				1	1	
SAMA:	Estimated rate	0.031	0.022				0.047	0.022	
	Confidence interval	.026, .036	.012, .037				.004, .172	.004, .063	
	# of groups	15	1				1	1	
	# of AEs / # of patients	150/5824	12/551				1/25	2/100	

* Highlighted Serenoa Repens RCT data are from a study comparing Serenoa Repens to Finasteride. These were combined with finasteride/placebo data to yield the results in the table.