

Summary and Conclusions

Benign Prostatic Obstruction

A Systematic Review

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Summary and Conclusions of the SBU Report: Benign Prostatic Obstruction

A Systematic Review

August 2011

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SBU's conclusions

Benign prostate hyperplasia (BPH) is a condition associated with ageing that affects nearly all men. Some of these men have urinary problems, and annually in Sweden around 4 500 receive surgery for an enlarged prostate. Many with mild or moderate bother are treated with medication, or require no treatment at all. If left untreated, obstructed urinary outflow can cause serious retention of urine, which damages the kidneys. Urinary retention can be life threatening.

Approximately 10 diagnostic methods are available to identify the group of men in whom an enlarged prostate causes urinary problems. Several different surgical treatment options are available; some are well established and others are experimental. Also, several drugs were introduced during the 1990s. Hence, SBU determined that a systematic review of the scientific literature addressing these different methods is necessary. The most important conclusions from this project are presented below.

- No single *diagnostic method* can establish that a patient has an enlarged prostate that obstructs urinary outflow. Other diagnoses must be ruled out, prostate size must be estimated, and voiding function must be assessed. A combination of several diagnostic methods can, if findings are consistent, yield a high probability for the presence or absence of obstructed urinary outflow. When findings are uncertain, a more invasive method, bladder pressure measurement, may be needed.

- The report presents reviews of two types of *pharmacotherapy* with different mechanisms of action. The average effect of these drugs is modest, although they might benefit some patients. Since these patients cannot be identified in advance, thorough and systematic follow-up of the outcome of medica-

tion is essential. Several *phytotherapeutic agents* (herbal medicines) are thought to have some effect, but the evidence is limited. Pharmaceuticals are used mainly in patients with moderate problems.

- ❑ *Surgical procedures* are used primarily in patients with severe problems. The most common method is transurethral resection of the prostate (TURP), which involves removing prostate tissue through the urethra. Among the less invasive procedures, transurethral microwave thermotherapy (TUMT) is most common. However, TUMT does not appear to be equally effective in improving symptoms and urinary flow rate. The risk of requiring new treatment is also greater. Various centres have developed new surgical methods intended to achieve the same effects as TURP, but with fewer side effects. It is important to disseminate such methods within the framework of scientific studies.
- ❑ Studies show that men with symptomatic prostate enlargement experience a reduction in *quality of life and sexual function*. Hence, the condition also affects their partner. *Objective information* provided before pharmacotherapy or surgery increases the individual's knowledge and autonomy.
- ❑ *Practices in treating benign prostate hyperplasia* vary by county council and differ as regards the use of medication, number of operations, and choice of surgical procedure. These variations, and the reasons for them, require further analysis.
- ❑ *Health economic analyses* show that surgical treatment is most cost effective in men with more severe problems. Pharmacotherapy appears to be a cost effective *initial* alternative for men with moderate symptoms.

SBU's summary

Purpose and background

Development of new methods for treating benign prostatic obstruction (BPO, benign prostatic hyperplasia with obstruction) has resulted in varying practices within different health service areas. The distribution of responsibility between primary care and specialised urology services varies depending on local resources and traditions. Treatment routines can vary widely. The cost of treating this patient group has gradually decreased, possibly as a result of stricter indications for surgery and increased efficiency, or perhaps because other, more urgent, interventions receive high-priority. Hence, a review of this disease area is justified.

Urology includes several concepts used to describe conditions of the lower urinary tract:

- Lower urinary tract symptoms (LUTS) refer to symptoms that suggest functional disorders in the urinary bladder and/or urethra.
- Benign prostatic obstruction (BPO) refers to obstructed outflow in the urethra due to benign prostatic hyperplasia.
- Benign prostatic hyperplasia (BPH) refers to a diagnosis established by microscopic examination of tissue specimens (histology), but the term is also used in referring to the clinical condition of benign prostatic enlargement.

With BPO, symptoms usually emerge gradually over several years. Patients experience frequent urination and urgency. Symptoms are particularly bothersome at night since they disturb sleep. Emptying symptoms often appear concurrently, but are not particularly disturbing to the patient initially. Symptoms may include: urine stream is weak, difficult to start urination, emptying the bladder takes longer, interruptions in the urine stream, straining to empty the bladder, and a sensation that the bladder is not completely empty.

Assignment to the project group

The project group was assigned to systematically review the scientific literature addressing different diagnostic methods, pharmacotherapy, and surgical interventions for benign prostatic hyperplasia with obstructed urinary outflow. The assignment also included studying current practices in Sweden, health economic aspects, and ethical aspects. The most important questions addressed were:

- What methods should be used to investigate men with urinary problems?
- How can we define the patients that should be treated?
- How should pharmacotherapy be weighed in comparison to surgery?
- Is there reason to increase the utilisation of new surgical methods?
- How should patient preferences be weighed in the selection of treatment?
- What ethical or social problems should receive attention?
- Which treatment methods are the most cost effective?
- What are the treatment practices in Sweden?

Methods: reviewing the literature

The report is based on a systematic review of scientific documentation in the field. The PubMed, Cochrane Library, and EMBASE databases were searched for documents published from January 1975 through November 2008. An updated search was conducted in January 2011. At least two experts reviewed all title and abstract lists generated by the search and the studies that were subsequently retrieved in full text. Inclusion and exclusion criteria were established in advance. Special forms were used in reviewing the quality of the studies. In the section addressing treatment, the GRADE system was used to determine the strength of the evidence for each finding (see Facts 1). To calculate average treatment effects, meta-analyses were used to appraise study results. Findings that addressed diagnostics, ethical and social aspects, and health economics were not graded.

Diagnostics

To identify the group of patients with urinary symptoms due to BPH, certain important diagnoses must be ruled out or deemed improbable. These are urinary tract infection, prostate cancer, bladder cancer, and neurogenic bladder. Even when these diagnoses have been ruled out, other conditions could present similar symptoms. The most common diagnoses in addition to BPO are bladder muscle weakness, overactive bladder muscles (spontaneous and unintentional contraction of the bladder), high production of urine around-the-clock or only at night, and small changes in the nervous system that impair bladder function but otherwise do not give the person any apparent neurological symptoms.

To further investigate causes, clinicians assess the patient's symptoms and bother, estimate prostate size, and measure urine to determine the ability to empty the bladder. In some cases, clinicians also measure urinary bladder pressure to accurately distinguish between a weak bladder and outflow obstruction in the urethra.

Symptoms and bother

Symptoms are measured to determine the severity level of the disease and to register changes. It is important to know how long a patient has been symptomatic and which symptom(s) specifically are most bothersome for him.

Symptoms are assessed by using a questionnaire, the International Prostatic Symptom Score (IPSS), which is filled in by the patient. This questionnaire is used worldwide. Most urologists and many community health centres in Sweden use the questionnaire. Patients answer seven questions about symptoms, each of which receives a score between 0 and 5 points. Hence, total scores vary between 0 and 35. A score of 0 to 7 is classified as *mildly symptomatic*, 8 to 19 points as *moderately symptomatic*, and 20 to 35 points as *severely symptomatic*. A disadvantage of IPSS is that the symptoms do not include incontinence. Although similar symptom scales are also available, the advantage of IPSS is that it is so wide-spread that researchers can compare different groups of patients in studies.

A bother question was added later to the IPSS questionnaire, ie *If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?* The alternatives are rated on a 7-grade scale from 0 (*delighted*) to 6 (*terrible*). In Sweden, the formulation of this question can vary to some extent.

| | Not at all | Less than 1 time in 5 | Less than half the time | About half the time | More than half the time | Almost always |
|---|-------------------|----------------------------------|------------------------------------|--------------------------------|------------------------------------|----------------------|
| 1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating? | 0 | 1 | 2 | 3 | 4 | 5 |
| 2. Over the past month how often have you had to urinate again less than 2 hours after you finished urinating? | 0 | 1 | 2 | 3 | 4 | 5 |
| 3. Over the past month, how often have you found you stopped and started again several times when you urinated? | 0 | 1 | 2 | 3 | 4 | 5 |
| 4. Over the past month, how difficult have you found it to postpone urination? | 0 | 1 | 2 | 3 | 4 | 5 |
| 5. Over the past month, how often have you had a weak urinary stream? | 0 | 1 | 2 | 3 | 4 | 5 |
| 6. Over the past month, how often have you had to push or strain to begin urination? | 0 | 1 | 2 | 3 | 4 | 5 |
| 7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning? | None | 1 time | 2 times | 3 times | 4 times | 5 times or more |
| | 0 | 1 | 2 | 3 | 4 | 5 |

Figure 1 IPSS questionnaire.

Diagnostic methods

Prostate size

The simplest method to estimate prostate size is *digital rectal examination (DRE)*, which is also used to detect prostate cancer. A more exact method is *transrectal ultrasound (TRUS)*, where an ultrasound probe is inserted in the rectum and produces transverse and longitudinal images of the prostate. Prostate volume can be calculated from these images. A third method is to analyse *prostate-specific antigen (PSA)* from a blood specimen. PSA values increase with prostatic hyperplasia and other prostatic disorders.

Voiding function

Urinary flow rate (the volume voided per unit time) and postvoid residual urine (urine remaining in the bladder after urination) are used to measure the voiding function. However, the fact that measurements fall outside of the threshold value provides no information about the cause. Determining whether the probable cause involves obstructed flow or a weak bladder requires more information.

Flow measurement is the most reliable, noninvasive method used in specialised urology clinics. Measurement produces a curve showing the urine outflow rate from start to finish during urination. Maximum urinary flow rate (Q_{\max}) is the value usually measured in assessments. A limitation of flow measurement is that urine flow depends in part on voided volume. Many patients fail to void a sufficiently large volume of urine during the clinical visit, and consequently the flow measurement cannot be evaluated.

A simple type of flow measurement is *timed micturition* (urination). The patient conducts this test at home, measuring the length of time it takes to void 100 ml of urine. The only equipment required is a container with a 100 ml mark and a clock that indicates seconds. An advantage of timed micturition is that one can easily

obtain 10 to 15 measurements for evaluation. The disadvantage is that this method is used only in Sweden. It is not used in international studies and the scientific validation is inadequate.

Another simple method is the *frequency-volume chart*, where a patient records the time of day and volume voided at each micturition, generally over a 48-hour period. The lower the largest voided volumes, the more affected the micturition. The advantage of the frequency-volume chart is that it provides a more reliable profile of urinary function than history does. The disadvantage is that frequency-volume chart is seldom included in studies that assess treatment.

The traditional method to *measure postvoid residual urine* is to use a catheter to empty the bladder of urine remaining after micturition. This method carries the risk of urinary tract infection. Hence, simple ultrasound devices have been developed to measure postvoid residual urine only. These devices are available at specialised clinics and some community health centres. It is important to identify those few patients having large volumes of residual urine. These patients run the risk of developing kidney damage, or bladder muscle damage, and therefore require treatment. The disadvantage of measuring postvoid residual urine is that volumes can vary widely from time to time, thus requiring multiple measurements.

Causes of impaired voiding function

Urodynamic examination (pressure–flow study) is used to determine whether the inability to empty the bladder is due to a weak bladder or urethral obstruction. This study measures bladder pressure and urinary flow concurrently. A catheter with two channels is inserted in the urethra. One channel is used to fill the bladder with fluid, and the other to measure pressure. Since the method is invasive and resource intensive, pressure–flow studies are not used in all patients with LUTS. The results of examination can often, but

not always, provide guidance for further management. If the findings are uncertain, other clinical information must be more thoroughly evaluated.

Diagnose or rule out other diseases

The examination methods mentioned above are used to diagnose or grade benign prostatic obstruction (BPO). Some are used also to find diseases other than BPO. *Digital rectal examination (DRE)* and *PSA* are used in combination with other methods to detect prostate cancer. *Frequency-volume charts* are used to find individuals that urinate often due to large urine volume and those that urinate several times at night due to large nocturnal urine volume. *Pressure-flow measurement* identifies those with a weak urinary bladder or neurogenic bladder disorders.

Other examinations, which provide limited or no information on LUTS suggestive of BPO, can be used in differential diagnoses. These examinations are not assessed here. BPH guidelines usually recommend using *urine dipstick analysis* to identify urinary tract infection. *Serum creatinine* is analysed in blood specimens to assess renal function. It is important to identify the limited group of patients in whom renal function is affected. *Cystoscopy*, inspection of the urethra and bladder, can be used in diagnostics for urethral stricture, bladder cancer, bladder diverticula, and bladder stones. *Cystometry*, urodynamic examination of the bladder's filling phase, can reveal bladder muscles that are overactive as a result of neurogenic bladder disorders.

Radiographic examinations are almost never used to investigate symptoms of the lower urinary tract in adults, but to identify the cause of renal problems, eg stones in the urinary tract and bladder.

Facts 1 Study quality, relevance and evidence grading.

Study quality refers to the scientific quality of an individual study and its capacity to answer a specific question in a reliable way.

Evidence grade refers to the appraised strength of the collective body of scientific evidence and its capacity to answer a specific question in a reliable way. SBU uses an international evidence grading system called GRADE. Study design is the primary factor considered in the overall appraisal of each outcome measure. Secondary factors that can increase or decrease the strength of the evidence include: study quality, relevance, consistency, transferability, effect size, data precision, risk of publication bias, and other aspects, eg, the dose-response relationship.

Evidence grades – four levels

Strong scientific evidence (⊕⊕⊕⊕)

Based on high or moderate quality studies with no factors that weaken the overall assessment.

Moderately strong scientific evidence (⊕⊕⊕○)

Based on high or moderate quality studies with isolated factors that weaken the overall assessment.

Limited scientific evidence (⊕⊕○○)

Based on high or moderate quality studies having factors that weaken the overall assessment.

Insufficient scientific evidence (⊕○○○)

Scientific evidence is deemed insufficient when scientific findings are absent, the quality of available studies is low, or studies of similar quality present conflicting findings.

The stronger the evidence, the lower the likelihood that new research findings would affect the documented results within the foreseeable future.

Conclusions

SBU's conclusions present an overall assessment of benefits, risks, and cost effectiveness.

Facts 2 Diagnostic methods for investigating men with lower urinary tract symptoms (LUTS) suggestive of benign prostatic obstruction (BPO).

| Diagnostic method | Description | Information obtained |
|--|--|--|
| <i>Methods that primarily assess the man's bother</i> | | |
| History | – | Earlier urological disorders. Other diseases. Patient's main problem. Degree of bother |
| Symptom grading | IPSS or other validated scale | No differential diagnostic Correlation to degree of bother |
| Bother grading | SPI, BII or IPSS bother question | Need for treatment |
| <i>Methods that primarily assess prostate size</i> | | |
| Digital rectal examination | – | Prostate size. Suspected prostate cancer |
| TRUS | Transrectal ultrasound examination | Prostate volume |
| <i>Methods that primarily assess voiding function</i> | | |
| Timed micturition | Number of seconds to void 100 ml | Grading bladder voiding function |
| Frequency-volume chart | Time and volume for all micturitions during 24 hours | Grading of bladder voiding function. Large urine volume during 24 hours or during night. Grading of bother. Incontinence |
| Postvoid residual urine | Measurement by ultrasound | Grading of bladder voiding function |

The facts continues on the next page

Facts 2 continued

| Diagnostic method | Description | Information obtained |
|---|--|--|
| <i>Methods that primarily assess voiding function</i> | | |
| Flow measurement | Flow curve for one complete micturition Q_{max} , curve shape | Grading of bladder voiding ability. Suspicion of neurogenic bladder disorder |
| <i>Methods that assess causes of impaired voiding function</i> | | |
| Pressure–flow study | Flow and detrusor pressure during micturition | Grading of outflow obstruction and bladder contractility. Suspected or confirmed neurogenic bladder disorder |
| <i>Methods that primarily diagnose other diseases/conditions</i> | | |
| Urine dipstick analysis | Leukocytes, nitrite | Can show infection |
| PSA | Blood test | Correlation to prostate size. Suspected prostate cancer |
| Creatinine | Blood test | Measure kidney function |
| Cystoscopy | Inspection of urethra and urinary bladder | Prostate size, bladder stones. Can show other diseases |
| Cystometry | Detrusor pressure during bladder filling phase | Can show overactive detrusor. Suspected or confirmed neurogenic bladder disorder |

BII = BPH impact index; IPSS = International prostatic symptom score; PSA = Prostate specific antigen; Q_{max} = Maximum flow rate; SPI = Symptom problem index

Diagnostic-related outcomes

Presented below are the most important conclusions from a review of scientific literature on the diagnostic methods addressed in this report. The terms *high*, *some*, *limited*, and *insufficient* reflect the appraised stability of the scientific evidence.

Pressure–flow study

Pressure in the urinary bladder and resistance in the urethra show high random variation in the same individual.

Pressure–flow studies conducted on different occasions show no systematic difference, but during the same examination the second micturition, and subsequent micturitions, show lower pressure and urethral resistance than the first one.

Pressure–flow studies have some capacity to predict surgical treatment outcomes in men who can urinate and do not have a catheter.

Whether or not pressure–flow studies can predict surgical treatment outcomes in men who cannot urinate and have a catheter could not be determined.

Whether or not pressure–flow measurement can predict treatment outcomes from pharmacotherapy and watchful waiting could not be determined.

Comments

Generally, pressure–flow studies have high value for many patient groups. Pressure–flow studies have good capacity to quantify resistance in the urethra and the strength of bladder contractions, but due to overlap of sick and healthy subjects it is not unusual to obtain a result that offers no clear guidance. Detrusor pressure and urethral resistance vary to the extent that multiple mictur-

itions must be evaluated. Four or five measurements must be conducted to achieve precision of ± 10 cm H₂O.

Pressure–flow studies have some capacity to predict surgical outcomes in patients without a catheter, but only one of the studies quantified this capacity adequately.

Flow measurement

Registration of maximum flow rate shows high random variation in the same individual.

Variation among observers is high. One study investigated how the same observers classified the same flow curve, and even this study showed high variation.

Measurement of maximum flow rate has limited capacity to diagnose flow obstruction. Using the mean value of several measurements improves diagnostic capacity.

Whether or not maximum flow rate can predict treatment outcomes from TURP or TUMT could not be determined. The findings are inconsistent.

Comments

Generally, flow measurement has high value for many patient groups, eg to determine whether or not micturition is normal. Uncertainty in determining maximum flow rate is so high that several measurements are required. Three measurements are needed to achieve precision of ± 2.5 ml/s.

Improving and discussing the criteria for estimating maximum flow rate could possibly reduce some of the inter- and intraobserver variation. The probability of outflow obstruction appears to increase as maximum flow rate decreases.

Timed micturition

The magnitude of random variation in timed micturition in the same individual could not be determined.

Timed micturition has limited capacity to diagnose low flow rate.

No studies could be found that address the capacity of timed micturition to diagnose outflow obstruction.

Whether or not timed micturition can predict the outcome of treatment could not be determined.

Comments

Few scientific studies have assessed timed micturition. The absence of evidence showing benefits of timed micturition should not, however, be considered a reason to stop performing the examination. Clinical experience and theoretical arguments both suggest that timed micturition provides diagnostic information similar to that from flow measurement. When using timed micturition the patient usually performs 10 to 15 measurements.

Frequency-volume chart

The magnitude of random variation in the same individual registering the number of micturitions during the day, the number of micturitions during the night, the number of incontinence episodes, or the volume voided, could not be determined.

Whether or not the volume voided can be used to diagnose outflow obstruction could not be determined.

Comments

Generally, the frequency-volume chart is valuable for most patient groups, eg to determine urine volumes during the day and night and to determine whether or not micturition is normal.

The number of days that a frequency-volume chart should be kept is uncertain, but probably it should be kept for at least 2 days. Experience suggests that it is beneficial to measure urine volume per 24 hours, register the number of micturitions, and measure the volumes voided.

Postvoid residual urine

Random variation is high in measuring postvoid residual urine in the same individual.

Postvoid residual urine has limited capacity to diagnose outflow obstruction.

The capacity to diagnose low flow rate is also limited.

Whether or not postvoid residual urine can predict the treatment outcome of TURP could not be determined; the results of studies are conflicting. Postvoid residual urine has a limited capacity to predict the treatment outcomes of pharmacotherapy and watchful waiting.

Comments

When measuring postvoid residual urine, multiple measurements are needed to increase precision. Postvoid residual urine has limited value in diagnosing outflow obstruction or predicting treatment results in benign prostatic hyperplasia.

Postvoid residual urine is of value primarily in identifying the small group of patients with very high residual urine and bladder decompensation. Measuring postvoid residual urine has greater value in assessing micturition at the group level than in individual patients, where random variation influences the results to a high degree.

TRUS in determining prostate size

Random variation in prostate volume, as determined by TRUS in the same individual, varies with the methodology and the examiner, and it also increases with prostate volume.

Variation is lower in studies with one or more specialised examiners and in studies with 3D ultrasound and planimetry.

The formula used to calculate an ellipsoid underestimates prostate volume by 6 to 15 ml; and this figure can be higher for substantially enlarged prostate glands.

Prostate volume measured by ultrasound has limited capacity to diagnose outflow obstruction.

The capacity to diagnose low flow rate is worse.

The capacity of prostate volume to predict the outcome of surgery could not be determined.

The capacity to predict the outcome of pharmacotherapy is limited.

Comments

Uncertainty in measuring prostate volume is high. To increase precision, volume should be calculated several times, if possible, and by different examiners. Increased training in ultrasonography for urologists may be considered along with the possibility of using 3D ultrasound or planimetry. The probability of outflow obstruction increases with prostate volume.

DRE in determining prostate size

The magnitude of random variation in estimating prostate size by digital rectal examination (DRE) in the same individual could not be determined.

In using DRE to estimate prostate volume, there is a systematic error involving underestimation of the true size. More detailed analysis shows that volumes smaller than approximately 25 ml are slightly overestimated, while volumes larger than approximately 30 ml are underestimated to a relatively high degree.

The level of agreement between DRE by different examiners and TRUS could not be determined. Available data suggest that different examiners estimate prostate volume with varying accuracy in comparison with TRUS.

DRE has limited capacity to diagnose a large prostate. Sensitivity is low, and specificity is high in diagnosing prostate volumes above 50 ml. The results are heterogeneous.

Whether or not prostate size estimated by DRE has the capacity to diagnose outflow obstruction or predict treatment results could not be determined.

Comments

Clinicians at community health centres need to use DRE to estimate prostate size, even if its precision is not particularly good. By being aware of the tendency to estimate that prostate size is close to the mean of 25 to 30 ml, one should be able to compensate somewhat for this systematic error. Precision should improve by performing several independent examinations, preferably by different examiners.

PSA

The magnitude of random variation in PSA in a particular individual could not be determined.

In a patient group that excludes men with PSA above 10 µg/l, and where all those with PSA of 4–10 µg/l have prostate biopsy to rule

out cancer, PSA has some capacity to diagnose a prostate larger than 30 ml and a moderately good capacity to diagnose a prostate larger than 50 ml.

Whether or not PSA has the capacity to diagnose outflow obstruction, low flow rate, and predict treatment outcomes could not be determined.

Comments

Men receiving treatment at community health centres usually do not include those with PSA above 4 µg/l. Studies have not determined the diagnostic capacity of PSA if patients with PSA above 4 µg/l are ruled out. In patients managed by urologists, prostate volume is estimated by TRUS, and it is uncertain whether PSA contributes any additional information. In Swedish patient groups, it remains uncertain whether PSA contributes more than the capacity to suspect prostate cancer – the evidence is insufficient.

The threshold for differentiating between large and small prostate glands is usually around 1.8 µg/l. Since many patients have values close to this threshold, and individual variation is relatively high, several tests are needed to determine whether a patient is above or below the threshold.

Symptom scales

The random variation in IPSS is high in the same individual.

IPSS does not have the capacity to diagnose outflow obstruction, low flow rate, or large prostate.

IPSS with a threshold value of approximately 19 points has some capacity to predict the outcome of TURP.

IPSS does not have the capacity to predict the treatment outcomes of TUMT or medication.

Comments

Symptoms provide little or no diagnostic information except that the patient has a disorder involving the lower urinary tract. Symptom scales are used to monitor changes in the patient's condition rather than establish a diagnosis.

Symptoms differ from bother, and the bother grade must be assessed separately.

There is a problem in using IPSS both as an inclusion criterion in studies, or as an indication for treatment, and as an outcome variable. In surgical treatments where placebo is not an option, the improvement is overestimated due to statistical factors. Evaluation of symptom scales capacity to predict treatment outcomes is not possible when improvement is defined as a major reduction in symptom score. Only those patients with high IPSS scores can show a major reduction, and the symptom scale therefore automatically becomes predictive.

Pharmacotherapy and phytotherapy

Most patients with BPO or LUTS visit primary care as their first contact with health services. An initial examination investigates whether the patient has BPH that causes obstruction, symptoms, and bother. Minor bother usually require no treatment. For moderate bother, medication is often recommended to start with. For more-severe problems, patients are mainly offered invasive methods, eg TUMT and TURP.

Several medications are available to treat patients with bother caused by BPO. The most important are *alpha-blockers* and *5-alpha-reductase inhibitors (5-ARI)*. These have different mechanisms of action: Alpha-blockers reduce outflow obstruction

by relaxing the smooth muscle in the prostate, while 5-ARI acts mainly by reducing prostate size.

In addition to alpha-blockers and 5-ARI, *anticholinergic agents* are also used alone or in combination with alpha-blockers. None of the identified studies involving these drugs met the criteria for inclusion in this review. Hence, the group is not presented under a separate subheading. Other drugs could also affect urinary problems, but are insufficiently studied to be included in this review.

Alpha-blockers are expected to reduce symptoms, but do not have structural effects on the prostate or the lower urinary tract. 5-ARI inhibits prostate growth to such a degree that it shrinks an already enlarged prostate, which can reduce bother. However, the effects on symptoms are minor. The indications for using 5-ARI have expanded into prophylactic treatment to prevent the condition from becoming worse over time. Occasionally 5-ARI is administered together with an alpha-blocker in combination therapy.

The mechanisms of action of the various phytotherapeutic agents for prostate disorders are largely unknown. The plants from which they originate define these agents. This leads to methodological problems in studies since the agents produced by different manufacturers vary in their composition. Also, the manufacturers have less motivation to pursue research since the plants, and hence the agents, cannot be patented.

Generally, it is the patient that initiates phytotherapy. Studies concerning phytotherapeutic agents are available; some are controlled, randomised against placebo, and are sufficiently large to be reviewed in this report. Since the studies are few and relatively small, findings about the effects of phytotherapy are much less certain than those regarding pharmaceuticals.

Evidence-graded results – pharmacotherapy

The following evidence-graded conclusions reflect the results of the systematic literature review of pharmacotherapy for benign prostate hyperplasia. See Facts 1 for a description of the GRADE symbols used in grading the evidence. The certainty of the scientific evidence increases with the number of filled circles.

Alpha-blockers

- Alpha-blockers reduce symptoms slightly more than placebo does. The average difference in IPSS is approximately 2 points (⊕⊕⊕⊕).
- Alpha-blockers improve maximum urinary flow rate slightly more than placebo does. The effect difference is about 1 ml/s, on average (⊕⊕⊕⊕).
- Alpha-blockers have relatively few side effects, but more than placebo does. The most common are dizziness, headache, asthenia, excessively low blood pressure, and erectile dysfunction (⊕⊕⊕○).
- Whether or not alpha-blockers improve the success rate of catheter removal after acute urinary retention could not be determined (⊕○○○).

5-ARI

5-ARI is less effective in small prostate glands (less than 35 ml). Furthermore, the drug reduces PSA levels by about 50%, which must be considered in evaluating the risk of prostate cancer.

- Treatment with 5-ARI reduces symptoms somewhat more than placebo does. The average difference in IPSS is 1 to 2 points for both finasteride (⊕⊕⊕⊕) and dutasteride (⊕⊕⊕○).

- Treatment with 5-ARI improves maximum urinary flow rate somewhat more than placebo does. On average, the effect difference is approximately 1 to 2 ml/s in treatment with finasteride (⊕⊕⊕⊕) or dutasteride (⊕⊕⊕○).
- Patients' bother decrease somewhat more from treatment with finasteride (⊕⊕⊕⊕) or dutasteride (⊕⊕⊕○) compared to placebo.
- Treatment with 5-ARI reduces the risk of larger haemorrhages in urine caused by BPH (⊕⊕○○).
- 5-ARI has relatively few side effects, but more than placebo does (⊕⊕○○). The most common are erectile dysfunction, reduced libido, and ejaculation problems.

Combination therapy

Combination therapy with 5-ARI and alpha-blockers is less effective in small prostate glands (smaller than 35 ml).

- Combination therapy with 5-ARI and alpha-blockers reduces symptoms more than placebo does. The average reduction in IPSS is approximately 3 points (⊕⊕⊕○).
- Combination therapy with 5-ARI and alpha-blockers improves maximum urinary flow rate slightly more than placebo does. Flow rate increases by about 2 ml/s, on average (⊕⊕⊕○).
- Alpha-blockers contribute to the treatment effect in combination therapy to a somewhat greater degree than 5-ARI does (⊕⊕⊕○).

- In the majority of patients, combination therapy for <4 years shows no difference in disease progression compared to 5-ARI alone (⊕⊕⊕○).
- Side effects are more common with combination therapy than with placebo (⊕⊕⊕○).

Phytotherapy

- β -sitosterol (from, eg vegetable oils and grain) and Urtica (from nettles) reduce symptoms. The average reduction in IPSS, compared to placebo, is approximately 5 points (⊕⊕○○).
- Treatment with β -sitosterol and Urtica respectively improves maximum urinary flow rate. On average, the flow rate increases by 3 to 4 ml/s compared to placebo (⊕⊕○○).
- Serenoa repens (American dwarf palm) and Urtica, alone or in combination, reduce symptoms and improve maximum urinary flow rate to the same extent as alpha-blockers (tamsulosin) or 5-ARI (finasteride) do (⊕⊕○○).
- Adding serenoa repens to alpha-blockers does not improve effects compared to alpha-blockers alone (⊕⊕○○).
- The safety and side effects of the agents could not be determined (⊕○○○).

Surgical treatment methods

In the early 1970s, most open procedures for benign prostatic hyperplasia were replaced by surgery via the urethra – transurethral resection of the prostate (TURP). The transition to TURP occurred without any clear scientific evidence and led to increased health care costs. Narrower indications and access to other treat-

ment options are probable reasons why the number of TURP procedures decreased during the 1990s and 2000s. Increased focus on malignant diseases might also have reduced the resources allocated to the patient group with benign prostatic hyperplasia.

The surgeon's skill influences the outcome of all operations, both in terms of outcomes and, primarily, side effects. There is reason to assume that the results achieved in studies are not always achieved in routine practice. Hence, it would be valuable to have a national registry that could report on the outcomes of BPH surgery.

Even though the TURP method has been refined, men with complicated diseases or high age are at risk for complications. A specific complication is TUR syndrome, in which electrolyte-free irrigation fluid enters the veins. The condition can be accompanied by symptoms such as anxiety, confusion, nausea, and could even lead to loss of consciousness.

Several less-invasive methods have gradually become established. The most commonly used is transurethral microwave thermotherapy (TUMT). It might not remove the flow obstruction as effectively as TURP can, but it potentially lowers treatment risks and reduces side effects. Also, since this procedure can be performed as day surgery, it may reduce health care costs.

Several other methods have been developed and are reviewed in the report. However, none of these have been widely disseminated in Sweden. Facts 3 presents an overview of different treatment principles and surgical methods.

The role of TURP as the “gold standard” has not been altered as the numbers of operations have decreased. The traditional indications for prostate surgery have become more predominant among patients treated with TURP. These indications are:

- chronic urinary retention with need for indwelling catheter
- affected kidney function
- bladder stones caused by bladder outlet obstruction
- recurring urinary tract infections
- prostatic bleeding.

Open prostate surgery remains the alternative of first choice in a small group of patients, ie men with a substantially enlarged prostate where TURP requires prolonged operating time, with increased risk of haemorrhage, urethral damage, and TUR syndrome.

Transurethral incision of the prostate (TUIP) is used in patients with problems, but with insignificant or no enlargement of the prostate.

Open surgery, TURP and TUIP clearly play a role in today’s surgical treatment of benign prostatic obstruction, but are targeted at different patient groups. Of the surgical options available, the expert group has chosen to focus on methods already in use, or those currently being introduced, in Sweden. Also, TURP methods have been modified in recent years.

Transurethral vaporisation of the prostate (TUVVP) was introduced in the early 1990s with the aim to reduce bleeding during the procedure and shorten the length of hospital stay. Use of the method has declined for no apparent reason. Possible explanations could be that it provides no tissue specimens for histology, and that the long-term results might be worse.

A bipolar method for vaporisation (B-TUVP) and resection (B-TURP) has become established, and many departments are considering the method when investing in new instrumentation. The method enables operating with saline solution as irrigating fluid, which means that TUR syndrome can be avoided. The risk of overhydration remains, but this complication is more easily treated. It is thought to reduce risks in prolonged operations and can enable transurethral surgery even in large prostates.

The minimally invasive method that is most widely used in Sweden is *transurethral microwave thermotherapy (TUMT)*. The equipment's delivered power has increased, which has improved functional results but also produced more complications. Important technological advancements have been made in Sweden. The literature review has addressed treatment using high-power TUMT.

Several *transurethral laser* methods have been tested in Sweden, but do not appear to have become established as routine methods:

- contact laser ablation of the prostate (CLAP)
- interstitial laser coagulation (ILC)
- visual laser ablation of the prostate (VLAP)
- transurethral ultrasound-guided, laser-induced prostatectomy (TULIP).

A holmium laser can be used to cut tissue. Holmium laser resection of the prostate (HoLRP) has been developed into a method that can remove all newly formed tissue in a way similar to open prostatectomy (HoLEP). This method must be complemented by instrumentation that cuts up the tissue in small pieces so it can be removed from the urinary bladder. Holmium laser enucleation of the prostate (HoLEP) is being tested at a few centres in Sweden, and is considered to be of interest, justifying a literature review.

The literature review also addressed vaporisation with the *KTP laser (green laser)*, which is being used in a few urologic departments. This procedure does not recover any tissue for histology.

Some departments in Sweden use *transurethral needle ablation (TUNA)* involving radio frequency energy, but the use of this method appears to be declining and therefore it has not been targeted for review.

Methods not used in Sweden include *balloon dilatation* of prostatic urethra, *injection of ethanol* to destroy tissue, injection of *botulinum toxin* to influence neuromuscular function, and *high-intensity focused ultrasound (HIFU)*.

Facts 3 Overview of surgical treatment principles and methods.

| Treatment principle | Surgical methods |
|--|---|
| Removal of tissue from inside prostate | <p><i>Methods reviewed:</i> Open surgery (adenoma enucleation), abdominal incision, tissue removed with finger. TURP (transurethral resection of the prostate), tissue cut away by electrical current that is conducted from the prostate to the skin. B-TURP (bipolar TURP), same as above, but electrical current is conducted only through the prostate. HoLEP (holmium laser enucleation of the prostate), tissue cut away by laser</p> |
| Tissue heated to the point that it vaporises and disappears immediately | <p><i>Methods reviewed:</i> TUVP (transurethral vaporisation of the prostate), heating by electric current from prostate to the skin. B-TUVP (bipolar TUVP), same as above but electric current travels only through prostate. KTP laser (green laser), heat by laser</p> <p><i>Methods not reviewed:</i> Contact laser</p> |
| Tissue heated to the point that it dies and is later, dislodged or broken down | <p><i>Methods reviewed:</i> TUMT (transurethral microwave thermotherapy), heat by microwaves from catheter in the urethra</p> <p><i>Methods not reviewed:</i> TUNA (transurethral needle ablation), heat by electric current. VLAP, TULIP, and interstitial laser, heat by laser. HIFU (high intensity focused ultrasound), heat by ultrasound</p> |
| No tissue removed or destroyed | <p><i>Methods reviewed:</i> TUIP (transurethral incision of the prostate), prostate incised longitudinally by electric current</p> |



Evidence-graded results – surgical methods

Presented below are the results of the literature review based on evidence-graded findings. Open surgery and TURP are both reference methods and are often used as comparators in surgical studies. The literature review, in this part, aims to present the outcomes that have been achieved with these methods in recent years. Most data are taken from control groups in randomised trials, but should here be considered as obtained from observational studies. Facts 1 describes the symbols used in grading the evidence. (Strength of the evidence increases with the number of circles filled.)

TURP (transurethral resection of the prostate)

- TURP relieves symptoms markedly. IPSS improves by approximately 16 points, on average, from 21 to 5 points (⊕⊕⊕⊕).
- Maximum urinary flow rate increases strongly following TURP. Improvement is approximately 12 ml/s, on average, from 8 to 20 ml/s (⊕⊕⊕⊕).
- TURP relieves the patients' bother. The bother score decreases by approximately 3 points, on average, from about 4 points to 1 point (⊕⊕⊕⊕).
- Retrograde ejaculation after TURP is common, occurring in 42% to 86% of those receiving the operation (⊕⊕⊕○).
- The risk of TUR syndrome is approximately 1% (⊕⊕○○).
- Perioperative mortality (30 days) in TURP is less than 1% (⊕⊕○○).
- At least 86% of the patients with catheters due to chronic urinary retention and BPO are catheter free after TURP (⊕⊕○○).

- The risk of reoperation due to urethral stricture or bladder neck contracture is less than 3% and 1.5% respectively (⊕⊕○○). The risk of reoperation due to bleeding or residual prostate tissue could not be determined (⊕○○○).
- The risk of permanent urinary leakage due to sphincter damage is less than 0.5% (⊕⊕○○).
- Whether TURP affects erectile function could not be determined (⊕○○○). The frequency of erectile dysfunction appears to be approximately the same before and after surgery.

Open surgery

- Open surgery relieves symptoms markedly. IPSS improves by approximately 16 points, on average, from 21 to 5 points (⊕⊕⊕○).
- Maximum urinary flow rate increases strongly following open surgery. Improvement is approximately 17 ml/s, on average, from approximately 6 to 24 ml/s (⊕⊕⊕○).
- Most studies have not included the bother question in the assessment (⊕○○○).
- Mortality within 30 days of open surgery is less than 1% (⊕⊕○○).
- The percentage of patients with chronic urinary retention that become catheter free could not be determined, nor can the risk for reoperation due to bleeding, urethral stricture, bladder neck contracture, or residual prostate tissue (⊕○○○).

- The risk of permanent urinary leakage is low; no cases were reported in the studies reviewed (⊕⊕○○).
- Whether open surgery affects erectile function and the risk of retrograde ejaculation could not be determined (⊕○○○). However, the risk of affecting erection and ejaculation is probably comparable with that in TURP.

B-TURP (bipolar TURP)

- Bipolar TURP relieves symptoms to the same extent as monopolar TURP. IPSS improves, on average, by approximately 16 points (⊕⊕⊕○).
- Maximum urinary flow rate increases to the same magnitude after bipolar as after monopolar TURP. Average improvement is approximately 12 ml/s (⊕⊕⊕○).
- The patients' bother is relieved to the same extent after bipolar TURP as after monopolar TURP. The bother score decreases, on average, approximately 2 points (⊕⊕○○).
- Use of bipolar TURP avoids the risk of TUR syndrome. The residual risk of overhydration could not be estimated.
- Bipolar TURP shortens catheter time compared to monopolar TURP (⊕⊕○○), but whether the methods differ regarding the length of hospital stay could not be determined given the current evidence (⊕○○○).
- Regarding treatment with bipolar TURP in relation to monopolar TURP, the risk of reoperation due to bleeding, urethral stricture, or bladder neck contracture could not be determined (⊕○○○).

TUVP (transurethral electrovaporisation of the prostate)

- TUVP relieves symptoms to the same extent as TURP. IPSS improves about 15 points, on average (⊕⊕⊕○).
- Maximum urinary flow rate increases to the same magnitude after TUVP as after TURP. Average improvement is approximately 13 ml/s (⊕⊕⊕○).
- The patients' bother is relieved to the same extent after TUVP as after TURP. The bother score decreases about 3 points, on average (⊕⊕⊕○).
- The risk of significant bleeding is lower after TUVP compared to TURP (⊕⊕○○).
- No difference in the risk of urethral stricture has been shown between TUVP and TURP (⊕⊕○○).
- Regarding treatment with TUVP in relation to TURP, the risk of TUR syndrome, bladder neck contracture, or permanent urinary leakage could not be appraised (⊕○○○).

B-TUVP (bipolar transurethral electrovaporisation of the prostate)

- Bipolar TUVP relieves symptoms to the same extent as TURP. IPSS improves about 14 points, on average (⊕⊕○○).
- Maximum urinary flow rate increases to the same extent after bipolar TUVP as after TURP. Average improvement is approximately 11 ml/s (⊕⊕○○).

- Whether bipolar TUVP differs from TURP as regards effects on the patients' bother could not be determined (⊕○○○).
- As regards treatment with bipolar TUVP in relation to TURP, the risk of bleeding, urethral stricture, bladder neck contracture, or permanent urinary leakage could not be determined (⊕○○○).

TUIP (transurethral incision of the prostate)

TUIP can be used as an alternative to TURP in small prostates (less than approximately 30 ml), but the method has been insufficiently evaluated in patients with catheters.

- TUIP relieves symptoms to the same extent as TURP. Improvement on the Madsen-Iversen symptom scale is about 10 points, on average (⊕⊕○○).
- Maximum urinary flow rate increases to the same extent after TUIP as after TURP. Average improvement is approximately 10 ml/s (⊕⊕○○).
- The patient's bother, calculated as the percentage of patients who report that their treatment was successful, is relieved to the same extent after TUIP as after TURP (⊕⊕○○).
- The risk of reoperation due to treatment failure is higher after TUIP in comparison to TURP (⊕⊕○○).
- Regarding treatment with TUIP in relation to TURP, the risk of bleeding, TUR syndrome, urethral stricture, bladder neck contracture, or permanent urinary leakage could not be determined (⊕○○○).

High-power TUMT (transurethral microwave thermotherapy)

TUMT is not appropriate for small prostate glands (less than approximately 30 ml), for distinct lobus tertius, or for patients that have previously undergone TURP.

- TUMT relieves symptoms, but outcomes are somewhat worse compared to TURP. Average improvement is 2 to 4 IPSS points less than with TURP (⊕⊕○○).
- Maximum urinary flow rate increases after TUMT, but outcomes are worse compared to TURP. Average improvement is 5 to 7 ml/s less than with TURP (⊕⊕○○).
- The patients' bother decreases after TUMT, but to a somewhat lesser extent than after TURP. The average difference is approximately 1 point (⊕⊕○○).
- Compared to TURP, TUMT carries greater risk for retreatment within 3 years due to incomplete effects (⊕⊕○○).
- Regarding treatment with TUMT in comparison to TURP; the risk of bleeding, urethral stricture, bladder neck contraction, or permanent urinary leakage could not be determined (⊕○○○). TUR syndrome does not occur after TUMT.

Laser therapy

Holmium laser

HoLEP (holmium laser enucleation of the prostate) has not been fully tested in small prostate glands (less than 40 ml), but appears to be appropriate for very large glands (over 100 ml). The HoLEP method differs substantially from the TURP method, and probably requires a considerable training period.

- HoLEP relieves symptoms to the same extent as TURP. IPSS improves by about 15 points, on average (⊕⊕○○).

- Maximum urinary flow rate increases to the same extent after HoLEP as after TURP. Average improvement is approximately 13 ml/s (⊕⊕⊕○).
- The patients' bother is relieved to the same extent after HoLEP as after TURP. The bother score decreases by about 3 points, on average (⊕⊕○○).
- The risk of urethral stricture is lower after HoLEP compared to TURP (⊕⊕○○).
- Regarding treatment with HoLEP in relation to TURP or open surgery, the risk of reoperation due to bleeding, urethral stricture, bladder neck contracture, or permanent urinary leakage could not be determined (⊕○○○).

KTP laser (potassium titanyl phosphate crystal)

- Treatment with the KTP laser (green laser) in relation to TURP could not be evaluated as regards effects on patient symptoms (IPSS), maximum urinary flow rate, or bother grade (⊕○○○).
- Regarding side effects or complications, the KTP laser in relation to TURP could not be appraised (⊕○○○).

Risk of VTE (venous thromboembolism)

- In open surgery for BPH, the risk of deep venous thrombosis is approximately 2 to 4 times as high as it is with TURP (⊕⊕⊕⊕).
- In open surgery for BPH, pharmacological prophylaxis for thrombosis reduces the risk of thrombosis (⊕⊕⊕○).

- The benefit of thrombosis prophylaxis in TURP could not be appraised (⊕○○○).
- In surgery for BPH, antifibrinolytic treatment does not increase the risk of thrombosis (⊕⊕⊕○).

The following tables summarise the results of the literature review of surgical methods for treating benign prostatic hyperplasia. Table 1 presents the findings on TURP and open surgery. Table 2 presents these methods in comparison to studies of other operative techniques.

Summary of treatment results

Figure 2 presents an overview of the average symptom score before and after treatment in all of the studies included as evidence in this report. Symptoms are measured using the IPSS. The left side illustrates placebo controls and all pharmacotherapy respectively, and the right side illustrates surgical control groups (TURP or open surgery) and all surgical intervention groups in the studies. The figure shows that patients included in the surgical studies have symptoms that are considerably more severe than patients included in the drug trials. The figure also shows that treatment outcomes are substantially better in the surgical groups.

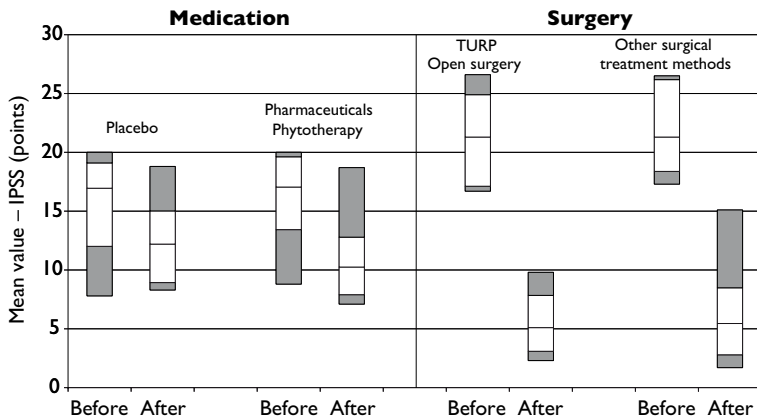


Figure 2 Mean values for IPSS before and after the start of treatment, for all treatment studies included in the review. The different pharmaceutical and surgical treatments have been put together into respective groups, as have all placebo treatments and all reference groups in the surgical studies. The bars show the distribution of the mean values for IPSS in the patient groups studied. The values indicated in the bars are median values, 10th and 90th percentiles, and highest and lowest mean values.



Table 1 Evidence-graded results for TURP and open surgery.

| Outcome | Effect size | Scientific evidence | Side effects and complications (scientific evidence) and other comments |
|------------------------------------|----------------|---------------------|--|
| TURP | | | |
| Symptom relief, IPSS-points | 16 points less | ⊕⊕⊕⊕ | <ul style="list-style-type: none"> • Retrograde ejaculation after TURP is common, and occurs in 42–86% of those receiving surgery (⊕⊕⊕○). • The risk of TUR syndrome is approximately 1% (⊕⊕○○). • Perioperative mortality (30 days) is less than 1% (⊕⊕○○). • At least 86% of patients with a catheter due to chronic urinary stasis and BPO become catheter free (⊕⊕○○). • The risk of reoperation due to urethral stricture or bladder neck sclerosis is less than 3% and 1.5% respectively (⊕⊕○○). • The risk of reoperation due to bleeding or residual prostatic tissue could not be appraised (⊕○○○). • The risk of chronic urinary leakage due to damaged sphincter is less than 0.5% (⊕⊕○○). • Whether or not erectile function is affected could not be determined (⊕○○○). |
| Maximum urine flow, ml/s | 12 ml/s more | ⊕⊕⊕⊕ | |
| Problems, problem question in IPSS | 3 points less | ⊕⊕⊕⊕ | |
| Open surgery | | | |
| Symptom relief, IPSS-points | 16 points less | ⊕⊕⊕⊕ | <ul style="list-style-type: none"> • Mortality within 30 days of open surgery is less than 1% (⊕⊕○○). • The percentage of operated patients with chronic retention that become catheter free could not be appraised (⊕○○○). • The risk of reoperation due to bleeding, urethral stricture, bladder necksclerosis, or residual prostate tissue could not be appraised (⊕○○○). • The risk of chronic urine leakage is low; no cases were reported in the studies reviewed (⊕⊕○○). • The degree to which erectile function is affected, or the risk of retrograde ejaculation, could not be determined (⊕○○○). |
| Maximum urine flow, ml/s | 17 ml/s more | ⊕⊕⊕⊕ | |
| Problems, problem question in IPSS | Not studied | ⊕○○○ | |

BPO = Benign prostatic obstruction; IPSS = International prostatic symptom score; TUR = Transurethral resection; TURP = Transurethral resection of the prostate

Table 2 Evidence-graded results for surgical methods.
TURP is the comparative method.

| | Difference in effect | Scientific evidence | Side effects and complications (scientific evidence) and other comments |
|-----------------------------|----------------------|---------------------|---|
| Bipolar TURP | | | |
| Symptom relief, IPSS-points | No difference | ⊕⊕⊕○ | <ul style="list-style-type: none"> + Risk of TUR syndrome is avoided, but the risk of overhydration could not be appraised (⊕○○○) + Catheter time is shortened (⊕⊕○○) • Risk of reoperation due to bleeding, urethral stricture, bladder neck sclerosis, or chronic urine leakage could not be appraised (⊕○○○) • Differences in length of hospital stay could not be determined (⊕○○○) |
| Maximum urine flow, ml/s | No difference | ⊕⊕⊕○ | |
| Bother question in IPSS | No difference | ⊕⊕○○ | |
| TUVP | | | |
| Symptom relief, IPSS-points | No difference | ⊕⊕⊕○ | <ul style="list-style-type: none"> + Lower risk of significant bleeding (⊕⊕○○) • No difference in risk of urethral stricture (⊕⊕○○) • Risk of TUR syndrome, bladder neck sclerosis, or chronic urine leakage could not be appraised (⊕○○○) |
| Maximum urine flow, ml/s | No difference | ⊕⊕⊕○ | |
| Bother question in IPSS | No difference | ⊕⊕⊕○ | |
| B-TUVP | | | |
| Symptom relief, IPSS-points | No difference | ⊕⊕○○ | <ul style="list-style-type: none"> • Risk of bleeding, urethral stricture, bladder neck sclerosis, or chronic urine leakage could not be appraised (⊕○○○) |
| Maximum urine flow, ml/s | No difference | ⊕⊕○○ | |
| Bother question in IPSS | – | ⊕○○○ | |
| TUIP | | | |
| Symptom relief, IPSS-points | No difference | ⊕⊕○○ | <ul style="list-style-type: none"> – Higher risk of reoperation due to incomplete effects (⊕⊕○○) • Risk of bleeding, TUR syndrome, urethral stricture, bladder neck sclerosis, or chronic urine leakage could not be appraised (⊕○○○) |
| Maximum urine flow, ml/s | No difference | ⊕⊕○○ | |
| Bother question in IPSS | No difference | ⊕⊕○○ | |

The table continues on the next page

Table 2 continued

| | Difference in effect | Scientific evidence | Side effects and complications (scientific evidence) and other comments |
|------------------------------------|----------------------|---------------------|---|
| TUMT | | | |
| Symptom relief, IPSS-points | 2–4 points less | ⊕⊕○○ | <ul style="list-style-type: none"> – Higher risk of retreatment within 3 years due to incomplete effects (⊕⊕○○) • Risk of bleeding, urethral stricture, bladder neck sclerosis, or chronic urine leakage could not be appraised (⊕○○○) + TUR syndrome does not appear after TUMT • TUMT is not appropriate for small prostate glands (less than approximately 30 gram), in obvious lobus tertius, or in patients with previous TURP |
| Maximum urine flow, ml/s | 5–7 ml/s less | ⊕⊕○○ | |
| Bother question in IPSS | 1 point less | ⊕⊕○○ | |
| HoLEP | | | |
| Symptom relief, IPSS-points | No difference | ⊕⊕○○ | <ul style="list-style-type: none"> + Risk of urethral stricture is lower than in TURP (⊕⊕○○) • Differences in the risk of complications could not be appraised (⊕○○○) |
| Maximum urine flow, ml/s | No difference | ⊕⊕⊕○ | |
| Problems, problem question in IPSS | No difference | ⊕⊕○○ | |
| KTP | | | |
| Symptom relief, IPSS-points | – | ⊕○○○ | <ul style="list-style-type: none"> • Differences in effects or risk of complications could not be appraised (⊕○○○) |
| Maximum urine flow, ml/s | – | ⊕○○○ | |
| Bother question in IPSS | – | ⊕○○○ | |

IPSS = International prostatic symptom score; TUIP = Transurethral incision of the prostate; TUR = Transurethral resection; TURP = Transurethral resection of the prostate; TUMT = Transurethral microwave thermotherapy of the prostate; TUVP = Transurethral electrovaporisation of the prostate

Ethical and social aspects

Quality of life

Lower urinary tract symptoms (LUTS) and their effects on quality of life have been assessed primarily through various types of questionnaires answered by the patients. Well-executed studies using qualitative research methodology are lacking in this field.

LUTS related to benign prostatic hyperplasia (BPH) has considerable negative effects on an individual's health-related and disease-specific quality of life. Storage symptoms are more bothersome than emptying and postmicturition symptoms. Urge incontinence is more common than previously thought, and this symptom is important for an individual's quality of life. Quality of life decreases with increasing age as a result of more pronounced symptoms and bother. The treatment goal in LUTS/BPH should focus on reducing the bother a patient experiences rather than mitigating the symptoms. Hence, better models need to be developed and used in controlled trials to assess outcome. These models should also include the symptom of incontinence.

Sexual function

Research findings suggest an association between LUTS/BPH and negative effects on sexual function. This involves both desire and erection. Given the symptoms and bother that individuals experience from LUTS, it is not surprising that sexual function is affected even if BPH per se does not affect erectile function. This is supported by the fact that adequate treatment and reduced bother have positive effects on sexual function.

Partners and family

Partners of men with LUTS/BPH can also be affected by the patient's condition, primarily psychologically and emotionally.

Even sleep, social activity, and sex life can deteriorate. Some of these symptoms would probably decrease if the patient's partner were included in discussing examinations and treatment. Since few qualitative studies focus on the life situation of the partner and family members, this is an important area for research.

Pharmacotherapy

Pharmacotherapy for BPH is justified from ethical and social standpoints. Generally, it has limited effects and can delay the initiation of other effective treatment. Given the knowledge about the negative effects of 5-alpha-reductase inhibitors on sexual function, relevant pretreatment investigation is recommended, as is objective information for patients and their partner.

Surgical treatment

Since changes in sexual functions – both erection and ejaculation disorders – are common in patients with untreated benign prostatic hyperplasia, it is important to assess these functions with validated methods prior to any intervention. Effects of surgical treatment on a partner's quality of life have not been adequately researched. The patient's partner also has a need for objective information about surgical intervention and its consequences.

Information

Information to help patients make decisions, eg brochures, other written material, and video material, increases their knowledge and autonomy. Positive effects are also observed in men with a low level of education and with different ethnic backgrounds. Informational material should be available in the most common immigrant languages. A Swedish population study published in 2004 showed a high rate of LUTS/BPH, with few individuals seeking medical attention. This suggests a need to target the men affected and their partner and family with objective information about examination and treatment opportunities.

Risk of discriminating against groups of men

Older men constitute a patient group that is potentially discriminated against when it comes to evidence-based care for LUTS/BPH. National statistics show that the patient group above 80 years of age has the highest drug prescription rate, but rates vary widely among the county councils. Surgical rates also vary in different parts of Sweden, also in the oldest age group. Further analyses are needed to clarify the causes behind these differences. If the differences were a result of discrimination, this would be an offence against respecting patient autonomy and the principle of justice.

Practice variations

An important ethical aspect is the fairness aspect. National statistics show substantial differences in the prescription of pharmaceuticals and the number of operations performed in different age groups. Nation-wide guidelines, encompassing even the primary care sector, would probably improve the individual patient's opportunities to receive relevant and fair treatment.

Cost and practice

The cost of treating men with symptomatic prostatic hyperplasia in Sweden was estimated to total 412 million Swedish kronor (SEK) in 2008, expressed in 2009 prices. This includes the cost of sick leave. Over the years, the cost curve has changed considerably. The direct costs for outpatient and inpatient care have decreased markedly, while pharmaceutical costs increased until a few years ago when they began to decrease as prices fell.

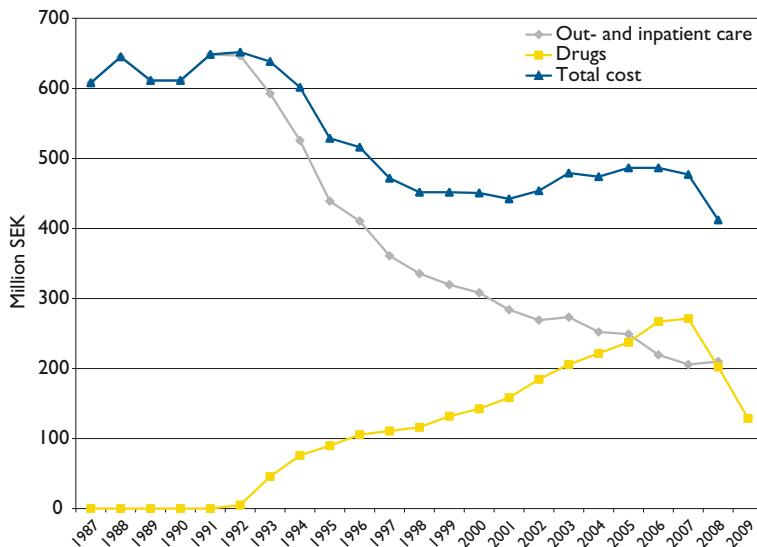


Figure 3 Costs for outpatient and inpatient care, pharmaceuticals, and total direct costs for BPH, 1987–2008. Shown in 2009 prices. Source: National Board of Health and Welfare, Epc Statistics.

The number of operations has gradually decreased, from approximately 12 000 in 1987, to 5 657 in 2005, and 4 556 in 2009. In that year, approximately 270 procedures were performed on outpatients. Approximately 90% of the operations were TURP. Of the operations performed on outpatients, approximately 90% are TUMT.

In 2009, clinicians prescribed 42 million daily doses of pharmaceuticals, which would correspond to one year of pharmacotherapy for BPH symptoms in 115 000 men.

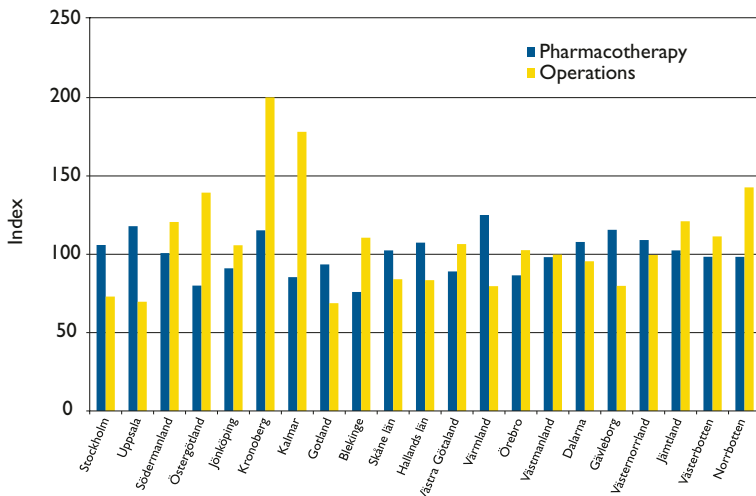


Figure 4 Pharmacotherapy and all BPH surgery for men aged >50 years, by county council. Data from 2009 and 2008 respectively. Index 100 = age-standardised national average.

Figure 4 shows relatively wide variation in treatment among county councils. The index for pharmacotherapy and surgery respectively has been set at 100 = national average for the number of operations and pharmacotherapy in men over 50 years of age in the respective county councils. Consideration was given to the age composition of the respective county councils.

The project included a questionnaire about current surgical practices, which was sent to the surgical units in Sweden. The responses show that monopolar TURP is used routinely and is by far the most common method. Those who used bipolar electrovaporisation indicated that utilisation of the method would increase. Only a few units used TUMT in more than 50 opera-

tions. High-power TUMT is predominant. Other methods were used in a few operations, but in only a single case had the method been introduced as a part of a scientific study.

Health economic aspects

Economic assessment involves comparing the costs and the outcomes of different treatment options. Different types of computer models are often used in economic assessments. Outcome data are then generally taken from well-executed clinical trials and cost data are taken from multiple sources. The models can accommodate different assumptions, enabling researchers to calculate the resulting differences in costs.

Cost effectiveness is a relative concept. When a particular treatment method is designated as cost effective, it is always in relation to some alternative treatment method, or no treatment. There is no generally agreed upon threshold to indicate what constitutes an acceptable cost per quality-adjusted life-year. For practical reasons, different values are often used as a rule of thumb to indicate which treatments should be included in the national health system. International studies often mention a threshold for cost-effectiveness ratios corresponding to SEK 400 000 to SEK 480 000 per quality-adjusted life-year.

This section presents the results of a literature review of cost-effectiveness studies addressing BPH. Only health economic articles published since 1995 were considered relevant for this comparative analysis of different treatment options.

Main findings from health economic studies

Health economic studies that compared different treatment options from a longer perspective have primarily assessed the cost effectiveness of the initial treatment chosen. However, alternative

treatments could be chosen if the outcome of the first option were insufficient. In shorter studies, direct (head-to-head) comparisons between different treatment options were also assessed.

In patients with *severe* BPH symptoms, TURP is more cost effective than pharmacotherapy or watchful waiting.

As initial treatment in patients with moderate symptoms, pharmacotherapy is more cost effective than surgery or watchful waiting. In many patients, drugs have very moderate effects. Careful follow-up and evaluation of the therapy is therefore important from a cost standpoint. As initial treatment, alpha-blocking drugs are probably more cost effective than 5-ARI because they have a somewhat better effect on symptoms. 5-ARI can be cost effective in some patient groups to prevent disease progression, but better methods to identify risk groups are needed.

The scientific evidence is insufficient to assess the health economics of combination therapy.

TURP is the most common surgical method. The cost effectiveness of this method has gradually increased due to fewer side effects and the shorter length of hospital stay. High-power TUMT could potentially be cost effective in comparison to TURP, but the long-term data, particularly concerning the need for additional treatment, is insufficient to reliably assess cost effectiveness.

Several new surgical methods have been introduced, but the scientific evidence is insufficient for a health economic assessment.

Need for future research

More studies need to be conducted to expand the evidence and improve the basis for making decisions in selecting treatment for BPO and LUTS. Also, more studies need to be initiated by independent units with research experience that can design, implement, and evaluate studies for assessing new methods.

Several important issues that require further study are listed below:

- How do patient populations and treatment outcomes in the studies differ from the results in routine clinical practice?
- Regional differences in treatment practices and changes over time need to be analysed.
- Well-executed, comparative (head-to-head) studies using equipotent doses of the compared drugs are lacking.
- Almost no studies use qualitative methods to investigate how men, their partner and family perceive their problems and the improvements that can be achieved.
- How can individuals who could benefit from pharmacotherapy be identified in advance? The low average improvement rate in pharmacotherapy does not rule out that it could relieve symptoms in a smaller group of treated men. If this group could be better characterised, many men could avoid unnecessary medication and side effects.
- More studies need to use outcome measures other than symptom scales in assessing treatment. The prevalence of incontinence, sexual dysfunction, and social consequences are areas that require further study.

- How are the advantages and disadvantages of a treatment best weighed? More knowledge is needed both regarding outcomes in clinical practice and side effects of treatment. Too little is known about the side effect profile of many treatment methods.
- From the patient's perspective, what are the important differences between daily treatment over a prolonged period versus a single episode of treatment (eg drugs versus surgery)?
- How should different treatment methods be prioritised in relation to one another? This includes, eg choosing between active treatment and watchful waiting, the duration of pharmacotherapy, the choice between medication and surgery, and the choice of surgical method.
- What impact have the recent organisational changes in health services had on patients with BPH? Has access decreased? Is this patient group at risk of being pushed aside? Does the decline in surgical rates mean that men with benign prostatic disorders receive lower priority in favour of men with prostate cancer?

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SBU Evaluates Health Care Technology

Below is a brief summary of the mission assigned to SBU by the Swedish Government:

- SBU shall assess healthcare methods by systematically and critically reviewing the underlying scientific evidence.
- SBU shall assess new methods as well as those that are already part of established clinical practice.
- SBU's assessments shall include medical, ethical, social and economic aspects, as well as a description of the potential impact of disseminating the assessed health technologies in clinical practice.
- SBU shall compile, present and disseminate its assessment results such that all parties concerned have the opportunity to take part of them.
- SBU shall conduct informational and educational efforts to promote the application of its assessments to the rational use of available resources in clinical practice, including dental care.
- SBU shall contribute to the development of international co-operation in the field of health technology assessment and serve as a national knowledge centre for the assessment of health technologies.

Benign Prostatic Obstruction

The report on benign prostatic obstruction from the Swedish Council on Health Technology Assessment (SBU) is a systematic review of the scientific literature in the field.

This document presents the summary and conclusions of the full report approved by SBU's Board and Scientific Advisory Committee.

The full report is available at www.sbu.se