Evidence synthesis on the management of benign prostatic hyperplasia

Juan Víctor Ariel Franco

UAB
Universitat Autònoma de Barcelona

Faculty of Medicine

Department Of Pediatrics, Obstetrics And Gynecology, Preventive Medicine And Public Health

PhD programme in Biomedical Research Methodology and Public Health

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Doctoral Thesis

Juan Víctor Ariel Franco

Director

Jae Hung Jung

Tutor

Xavier Bonfill i Cosp

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Unsere Wünsche sind Vorgefühle der Fähigkeiten, die in uns liegen, Vorboten desjenigen, was wir zu leisten imstande sein werden. Was wir können und möchten, stellt sich unserer Einbildungskraft außer uns und in der Zukunft dar; wir fühlen eine Sehnsucht nach dem, was wir schon im Stillen besitzen. So verwandelt ein leidenschaftliches Vorausergreifen das wahrhaft Mögliche in ein erträumtes Wirkliche.[1]

Our wishes are previews of the abilities that lie within us, harbingers of what we will be capable of accomplishing. What we can and desire to do presents itself to our imagination beyond us and in the future; we feel a longing for what we already possess silently. Thus, passionate anticipation transforms the truly possible into a dreamed reality.

Johann Wolfgang von Goethe

[1] Goethe, J. W., Autobiographisches. Aus meinem Leben. Dichtung und Wahrheit, 2. Teil, 1811-1812. 9. Buch

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Conflicts of interests
I declare no conflicts of interest.

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Introducción

La hiperplasia prostática benigna (HPB) es un agrandamiento no maligno de la próstata, que puede causar síntomas obstructivos e irritativos del tracto urinario inferior (STUI). El tratamiento médico incluye el uso de diferentes medicamentos, pero el uso de fitoterapia, incluida la *Serenoa repens*, es común entre los hombres. Para los síntomas que no responden al tratamiento, la resección transuretral de la próstata o RTUP es una opción viable, y ahora hay disponibles nuevos tratamientos mínimamente invasivos (TMI) como alternativa. Cochrane produce revisiones sistemáticas de alta calidad para informar la práctica clínica, y con la participación de partes interesadas externas, han priorizado estos dos temas para la síntesis de evidencia.

Objetivos

Sintetizar los temas prioritarios relacionados con los efectos de los tratamientos para condiciones benignas de la próstata. Los objetivos específicos son:

- Evaluar los efectos de la *Serenoa repens* en el tratamiento de hombres con síntomas del tracto urinario inferior debido a hiperplasia prostática benigna.
- Evaluar la efectividad comparativa de los tratamientos mínimamente invasivos para los síntomas del tracto urinario inferior en hombres con hiperplasia prostática benigna.

Métodos

Realizamos tres revisiones de Cochrane, incluyendo un metaanálisis en red, siguiendo las guías estándar del Manual de Cochrane y las Expectativas Metodológicas para la Realización de Revisiones de Intervenciones (MECIR).

Resultados

Serenoa repens

Para esta actualización, acotamos la pregunta de revisión e incluimos 27 estudios (9 de ellos nuevos) con 4656 participantes, 19 estudios con las siguientes comparaciones:

- *Serenoa repens* versus placebo o ninguna intervención: Según análisis de sensibilidad predefinidos limitados a estudios con bajo riesgo de sesgo, *Serenoa repens* no presenta diferencias significativas en los síntomas urológicos y calidad de vida a corto plazo. *Serenoa repens* probablemente no presenta diferencias significativas en eventos adversos. *Serenoa repens* no presenta diferencias significativas en los síntomas urológicos y calidad de vida a largo plazo. No hubo datos sobre eventos adversos a largo plazo para esta comparación.
- *Serenoa repens* en combinación con otras fitoterapias versus placebo o ninguna intervención: la combinación de agentes con *Serenoa repens*, pueden no presentar diferencias significativas en los síntomas urológicos en comparación con placebo a corto plazo. Hay mucha incertidumbre acerca de los efectos de estos agentes en la calidad de vida. Estos agentes pueden no presentar diferencias significativas en la ocurrencia de

eventos adversos; sin embargo, los intervalos de confianza incluyeron beneficios y daños sustanciales.

Tratamientos mínimamente invasivos

Incluimos 27 ensayos con 3017 participantes aleatorizados, evaluando los efectos de los tratamientos mínimamente invasivos (terapia de vapor de agua con radiofrecuencia convectiva (CRFWVT); embolización arterial prostática (EAP); levantamiento prostático uretral (PUL); dispositivo implantable temporal de nitinol (TIND); y termoterapia transuretral por microondas (TUMT), en comparación con RTUP o tratamiento simulado. Los principales hallazgos de nuestro metaanálisis en red son los siguientes:

- Puntuaciones de síntomas urológicos: A corto plazo, PUL y EAP pueden resultar en poca o ninguna diferencia en las puntuaciones de síntomas urológicos en comparación con RTUP. CRFWVT, TUMT y TIND pueden resultar en puntuaciones de síntomas urológicos peores en comparación con RTUP, pero los intervalos de confianza incluyen poca o ninguna diferencia.
- Calidad de vida: A corto plazo, todas las intervenciones pueden resultar en poca o ninguna diferencia en la calidad de vida en comparación con RTUP.
- Eventos adversos mayores: TUMT probablemente resulte en una reducción importante de eventos adversos mayores en comparación con RTUP, mientras que las otras modalidades de tratamiento (PUL, CRFWVT, TIND y EAP) pueden resultar en una reducción importante de eventos adversos mayores.
- Reintervención: Tenemos una certeza muy baja de los efectos de PUL y EAP en la reintervención en comparación con RTUP. TUMT puede resultar en un aumento sustancial de las tasas de reintervención.
- Función eréctil: Tenemos una certeza muy baja de los efectos de CRFWVT, TIND, PUL y EAP en la función eréctil.
- Función eyaculatoria: Tenemos una certeza muy baja de los efectos de PUL, EAP y TUMT en la disfunción eyaculatoria en comparación con RTUP.
- Eventos adversos menores: TUMT, EAP, CRFWVT y TIND pueden resultar en una mayor incidencia de eventos adversos menores en comparación con RTUP. EAP tuvo una mayor probabilidad de ser la mejor intervención en comparación con las demás.
- Retención urinaria aguda: TUMT, CRFWFT, TIND y EAP pueden resultar en una mayor incidencia de retención urinaria aguda en comparación con RTUP, y PUL puede resultar en poca o ninguna diferencia en este resultado.
- Catéter urinario permanente: No hubo suficiente información para realizar un metaanálisis en red para este resultado.
- La RTUP es el tratamiento de referencia con la mayor probabilidad de ser el más eficaz para los síntomas urinarios, calidad de vida, reintervención, eventos adversos menores y retención urinaria aguda, pero menos favorable en términos de eventos adversos mayores, función eréctil y función eyaculatoria. Entre los procedimientos mínimamente invasivos, PUL y EAP tienen la mayor probabilidad de ser los más eficaces para los síntomas urinarios y la calidad de vida; TUMT para eventos adversos mayores; PUL para reintervención, función eyaculatoria y retención urinaria aguda; CRFWVT y TIND para función eréctil; y EAP para eventos adversos menores.

Conclusiones

Los tratamientos mínimamente invasivos pueden resultar en efectos similares o peores en términos de síntomas urinarios y calidad de vida en comparación con la cirugía tradicional a corto plazo. También pueden resultar en menos eventos adversos mayores. Además, la *Serenoa repens* por sí sola proporciona pocos o ningún beneficio para los hombres.

Resumen (Catalán)

Introducció

La hiperplàsia prostàtica benigna (HPB) és un augment no maligne de la pròstata, que pot causar símptomes obstructius i irritatius del tracte urinari inferior (STUI). El tractament mèdic inclou l'ús de diferents medicaments, però l'ús de fitoteràpia, incloent-hi la *Serenoa repens*, és comú entre els homes. Per als símptomes que no responen al tractament, la resecció transuretral de la pròstata o RTUP és una opció viable, i ara hi ha disponibles nous tractaments mínimament invasius (TMI) com a alternativa. Cochrane produeix revisions sistemàtiques d'alta qualitat per informar la pràctica clínica, i amb la participació de parts interessades externes, han prioritzat aquests dos temes per a la síntesi d'evidència.

Objectius

Sintetitzar els temes prioritaris relacionats amb els efectes dels tractaments per a condicions benignes de la pròstata. Objectius específics:

- Avaluar els efectes de la *Serenoa repens* en el tractament dels homes amb símptomes del tracte urinari inferior causats per hiperplàsia prostàtica benigna.
- Avaluar l'efectivitat comparativa dels tractaments mínimament invasius per als símptomes del tracte urinari inferior en homes amb hiperplàsia prostàtica benigna.

Mètodes

Hem realitzat tres revisions de Cochrane, incloent-hi un metaanàlisi en xarxa, seguint les guies estàndard del Manual de Cochrane i les Expectatives Metodològiques per a la Realització de Revisions d'Intervencions (MECIR).

Resultats

Serenoa repens

Per a aquesta actualització, hem restringit la pregunta de revisió i hem inclòs 27 estudis (9 dels quals eren nous) amb 4656 participants, 19 estudis amb les següents comparacions:

- *Serenoa repens* versus placebo o cap intervenció: Segons els anàlisis de sensibilitat predefinits limitats als estudis amb baix risc de biaix, la *Serenoa repens* no presenta diferències significatives en els símptomes urològics i la qualitat de vida a curt termini. La *Serenoa repens* probablement no presenta diferències significatives en els esdeveniments adversos. La *Serenoa repens* no presenta diferències significatives en els símptomes urològics i la qualitat de vida a llarg termini. No hi havia dades sobre esdeveniments adversos a llarg termini per a aquesta comparació.
- *Serenoa repens* en combinació amb altres fitoteràpies versus placebo o cap intervenció: Agents fitoterapèutics amb diversos agents, incloent-hi la *Serenoa repens*, poden no presentar diferències significatives en els símptomes urològics en comparació amb el placebo a curt termini. Hi ha molta incertesa sobre els efectes d'aquests agents en la qualitat de vida. Aquests agents poden no presentar diferències significatives en la ocurrencia d'esdeveniments adversos, però els intervals de confiança inclouen beneficis i danys substancials.

Tractaments mínimament invasius

Hem inclòs 27 assaigs amb 3017 participants aleatoritzats, avaluant els efectes dels tractaments mínimament invasius (teràpia de vapor d'aigua amb radiofreqüència convectiva (CRFWVT); embolització arterial prostàtica (EAP); aixecament prostàtic uretral (PUL); dispositiu implantable temporal de nitinol (TIND); i termoteràpia transuretral per microones (TUMT)), en comparació amb la RTUP o el tractament simulat. Els principals resultats del nostre metaanàlisi en xarxa són els següents:

- Puntuacions de símptomes urològics: A curt termini, el PUL i l'EAP poden resultar en poca o cap diferència en les puntuacions de símptomes urològics en comparació amb la RTUP a curt termini. La CRFWVT, la TUMT i la TIND poden resultar en puntuacions de símptomes urològics pitjors en comparació amb la RTUP, però els intervals de confiança inclouen poca o cap diferència.
- Qualitat de vida: A curt termini, totes les intervencions poden resultar en poca o cap diferència en la qualitat de vida en comparació amb la RTUP.
- Esdeveniments adversos importants: És probable que la TUMT resulti en una reducció important dels esdeveniments adversos importants en comparació amb la RTUP, mentre que les altres modalitats de tractament (PUL, CRFWVT, TIND i EAP) poden resultar en una reducció important dels esdeveniments adversos importants.
- Reintervenció: Tenim molta incertesa sobre els efectes del PUL i l'EAP en la reintervenció en comparació amb la RTUP. La TUMT pot resultar en un augment substancial de les taxes de reintervenció.
- Funció erèctil: Tenim molta incertesa sobre els efectes de la CRFWVT, la TIND, el PUL i l'EAP en la funció erèctil.
- Funció ejaculatòria: Tenim molta incertesa sobre els efectes del PUL, l'EAP i la TUMT en la disfunció ejaculatòria en comparació amb la RTUP.
- Esdeveniments adversos menors: La TUMT, l'EAP, la CRFWVT i la TIND poden resultar en una major incidència d'esdeveniments adversos menors en comparació amb la RTUP. L'EAP va tenir una probabilitat més alta de ser la millor intervenció en comparaciamb les altres.
- Retenció urinària aguda: La TUMT, la CRFWFT, la TIND i l'EAP poden resultar en una major incidència de retenció urinària aguda en comparació amb la RTUP, i el PUL pot resultar en poca o cap diferència en aquest resultat.
- Catèter urinari permanent: No hi va haver suficient informació per realitzar un metaanàlisi en xarxa per a aquest resultat.
- La RTUP és el tractament de referència amb la major probabilitat de ser el més eficaç per als símptomes urinaris, qualitat de vida, reintervenció, esdeveniments adversos menors i retenció urinària aguda, però menys favorable en termes d'esdeveniments adversos importants, funció erèctil i funció ejaculatòria. Entre els procediments mínimament invasius, el PUL i l'EAP tenen la major probabilitat de ser els més eficaços per als símptomes urinaris i la qualitat de vida; la TUMT per als esdeveniments adversos importants; el PUL per a la reintervenció, la funció ejaculatòria i la retenció urinària aguda; la CRFWVT i la TIND per a la funció erèctil; i l'EAP per als esdeveniments adversos menors.

Conclusions

Els tractaments mínimament invasius poden resultar en efectes similars o pitjors en termes de símptomes urinaris i qualitat de vida en comparació amb la cirurgia tradicional a curt termini. També poden resultar en menys esdeveniments adversos importants. A més, la *Serenoa repens* per si sola proporciona pocs o cap benefici per als homes amb símptomes del tracte urinari inferior causats per l'augment benigna de la pròstata. Hi ha més incertesa sobre el paper de la *Serenoa repens* en combinació amb altres agents fitoterapèutics.

Abstract

Introduction

Benign prostatic hyperplasia (BPH) is a non-malignant enlargement of the prostate, which can lead to obstructive and irritative lower urinary tract symptoms (LUTS). Medical management includes the use of different drugs, but the use of phytotherapy, including Serenoa repens, is common among men. For symptoms unresponsive to treatment, transurethral resection of the prostate or TURP is a viable option, and new minimally invasive treatments (MIT) are now available as an alternative. Cochrane produces high-quality systematic reviews to inform clinical practice, and with the input of external stakeholders, they have prioritized these two topics for evidence synthesis.

Objectives

To synthesise priority topics related to the effects of treatments for benign conditions of the prostate. Specific objectives include:

- To assess the effects of *Serenoa repens* in the treatment of men with lower urinary tract symptoms due to benign prostatic hyperplasia.
- To assess the comparative effectiveness of minimally invasive treatments for lower urinary tract symptoms in men with benign prostatic hyperplasia.

Methods

We conducted three Cochrane reviews, including a network meta-analysis, following standard guidance from the Cochrane Handbook and the Methodological Expectations for the Conduct of Interventions Reviews (MECIR).

Results

Serenoa repens

For this update, we narrowed the review question and included 27 studies (of which 9 were new studies) with 4656 participants, 19 studies with the following comparisons:

- *Serenoa repens* versus placebo or no intervention: Based on predefined sensitivity analyses limited to studies at low risk of bias, *Serenoa repens* results in little to no difference in urologic symptoms and quality of life at short-term follow-up. *Serenoa repens* probably results in little to no difference in adverse events. *Serenoa repens* results in little to no difference in urologic symptoms and quality of life at long-term follow-up. There was no data on long-term adverse events for this comparison.
- *Serenoa repens* in combination with other phytotherapy versus placebo or no intervention: Phytotherapeutic agents with various agents, including *Serenoa repens*, may result in little to no difference in urologic symptoms compared to placebo at short-term follow-up. We are very uncertain about the effects of these agents on quality of life. These agents may result in little to no difference in the occurrence of adverse events; however, the confidence intervals included substantial benefits and harms.

Minimally invasive treatments

We included 27 trials with 3017 randomised participants, assessing the effects of minimally invasive treatments (convective radiofrequency water vapour therapy (CRFWVT); prostatic arterial embolisation (PAE); prostatic urethral lift (PUL); temporary implantable nitinol device (TIND); and transurethral microwave thermotherapy (TUMT), compared to TURP or sham treatment. The main findings of our network meta-analysis are the following:

- Urologic symptoms scores: At short-term follow-up, PUL and PAE may result in little to no difference in urologic symptoms scores compared to TURP at short-term follow-up. CRFWVT, TUMT, and TIND may result in worse urologic symptom scores compared to TURP, but the confidence intervals include little to no difference.

- Quality of life: At short-term follow-up, all interventions may result in little to no difference in the quality of life, compared to TURP.

- Major adverse events: TUMT probably results in a large reduction in major adverse events compared to TURP, whereas the other treatment modalities (PUL, CRFWVT, TIND, and PAE) may result in a large reduction in major adverse events.

- Retreatment: We are very uncertain of the effects of PUL and PAE on retreatment when compared to TURP. TUMT may result in a substantial increase in retreatment rates.

- Erectile function: We are very uncertain of the effects of CRFWVT, TIND, PUL, and PAE on erectile function.

- Ejaculatory function: We are very uncertain of the effects of PUL, PAE, and TUMT on ejaculatory dysfunction compared to TURP.

- Minor adverse events: TUMT, PAE, CRFWVT, and TIND may result in a greater incidence of minor adverse events compared to TURP. PAE had a higher probability of being the best intervention compared to others.

- Acute urinary retention: TUMT, CRFWFT, TIND, and PAE may result in a greater incidence of acute urinary retention compared to TURP, and PUL may result in little to no difference in this outcome.

- Indwelling urinary catheter: There was insufficient information to perform a network meta-analysis for this outcome.

- TURP is the reference treatment with the highest likelihood of being the most efficacious for urinary symptoms, quality of life, retreatment, minor adverse events, and acute urinary retention but the least favourable in terms of major adverse events, erectile function, and ejaculatory function. Among minimally invasive procedures, PUL and PAE have the highest likelihood of being the most efficacious for urinary symptoms and quality of life; TUMT for major adverse events; PUL for retreatment, ejaculatory function, and acute urinary retention; CRFWVT and TIND for erectile function; and PAE for minor adverse events.

Conclusions

Minimally invasive treatments may result in similar or worse effects concerning urinary symptoms and quality of life compared to traditional surgery at short-term follow-up. They may also result in fewer major adverse events. Moreover, *Serenoa repens* alone provides little to no benefits for men with lower urinary tract symptoms due to benign prostatic enlargement. There is more uncertainty about the role of *Serenoa repens* in combination with other phytotherapeutic agents.

Introduction

The prostate gland is an organ about the size of a walnut that lies below the urinary bladder surrounding the male urethra. The prostate can be affected by malignant pathology (cancer) or benign pathology (inflammation or enlargement). Prostate cancer is the second most common cancer and the fifth leading cause of cancer death in men(1). Benign prostate conditions, especially benign prostate enlargement, are the ones with the highest burden of disease (morbidity) in men(2,3). According to the International Classification of Diseases 11 (ICD-11), benign diseases of the prostate are classified into hyperplasia of the prostate (benign prostatic hyperplasia or benign prostatic enlargement) and inflammatory diseases, where the different forms of prostatitis stand out(4). The focus of this thesis is benign prostatic hyperplasia.

Benign prostatic hyperplasia

Benign prostatic hyperplasia (BPH) is a histological diagnosis defined as increased numbers of epithelial and stromal cells in the prostate; this can cause prostate enlargement and subsequent compression of the urethra and obstruction(5). Therefore, BPH can develop with or without lower urinary tract symptoms (LUTS) in men older than 40 years(6). BPH acquires clinical importance when associated with bothersome LUTS(5). The number and severity of symptoms are related to both the deterioration in the quality of life and the search for treatment(7). Self-administered questionnaires such as the International Prostate Symptom Score (IPSS) include a quality of life domain to assess the relative degree of bothersomeness of all LUTS(8). Chapple et al. reported that increasing LUTS severity is associated with worsening general distress in men using a patient's perception of bladder condition, which is a single-item global question (ranging from 1 (causes no problems) to 6 (causes serious problems))(9). Hereafter, BPH will be used as an enlarged prostate with LUTS to define the disease state and the possible need for intervention.

BPH can progress and cause serious consequences, such as acute urinary retention, urinary tract infection, and upper urinary tract impairment. BPH also has a negative impact on public health and a reduction in a person's quality of life (10,11). In Europe, 30% of men over the age of 50, which is equivalent to 26 million men, are affected by bothersome LUTS, including storage symptoms (such as urinary frequency, urgency, and nocturia) or micturition symptoms (such as difficulty to urinate, difficulty urinating). current, straining to urinate, and prolonged voiding), or both. The associated number of prescriptions reported annually is estimated to be around 11.6 million for 74 million people at risk from 2004 to 2008 (12). As shown in **Figure 1**, disability-adjusted life years (DALYs) due to benign enlarged prostate have been increasing in recent decades(13). Population ageing can account for this phenomenon, considering that the incidence of this pathology increases with age: 18%, 29%, 40% and 56% in men aged forty, fifty, sixty and seventy, respectively (14).

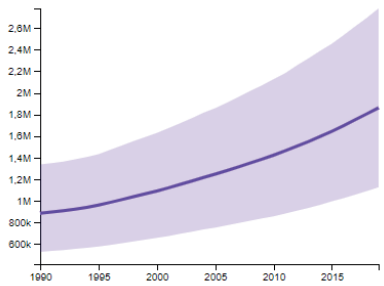

Figure 1. Disability-adjusted life years (DALYs) for benign prostatic enlargement. Source: Global Burden of Disease 2019 (http://ghdx.healthdata.org/)

Initial evaluation for LUTS suggestive of BPH includes patient history, physical examination including digital rectal examination (DRE), urinalysis, prostate-specific antigen (PSA) blood test, voiding diary, and IPSS (15). DRE is performed to assess the size of the prostate and any suspicious lesions for cancer. The prostate gland secretes PSA and is abnormally elevated in conditions such as prostate cancer, BPH, infection or inflammation of the prostate(15). The IPSS is used to assess the severity of urinary symptoms and quality of life. Also used to document subjective responses to treatment (16,17). Measurements of peak flow rate (Qmax) and postvoid residual (PMR) are also often used in diagnostic and treatment decisions (17). A low Qmax and a large RPM predict a higher risk of symptom progression(18). Other tests include radiologic imaging, urodynamic evaluation, and cystoscopy to determine appropriate treatment and predict response to treatment (5,19).

Treatment decisions are based on symptoms and the degree of discomfort reported by the patient. Initial treatment options for BPH include conservative management (watchful waiting and lifestyle modification) and medication (alpha-blockers and 5-alpha reductase inhibitors) (17). If patients have been refractory to medical and conservative treatment, and BPH causes subsequent complications, such as acute urinary retention, recurrent urinary tract infection, bladder stones or diverticula, hematuria, or renal failure, surgical options are considered (17). Until the 1970s, the only option available to treat this condition and alleviate LUTS was open or endoscopic surgery to remove or resected prostate tissue to open the blocked urethra (20). Clinical guidelines recommend monopolar or bipolar transurethral resection of the prostate (TURP) as a standard treatment modality for subjective symptom relief and objective improvements in urinary flow (17), but this procedure is also associated with significant and long-term morbidity complications, including hematuria requiring blood transfusion, urethral stricture, recurrent urinary tract infection, and urinary incontinence. Additionally, men may experience ejaculatory (65%) and erectile (10%) dysfunction related to TURP(21). In addition, BPH is a common disease in older men who are at increased risk of complications from general anaesthesia and the surgery itself (6). Some alternatives to TURP include laser enucleation, vaporisation, and *Aquablation*, but all require spinal anaesthesia (17). In recent years, the number of men undergoing TURP has steadily decreased due to the increase in drug treatments and minimally invasive treatments that are usually performed under local anaesthesia(22), such as convective radiofrequency water vapour therapy(23), prostatic urethral lift(24), prostatic arterial embolisation (25) that are included in current evidence-based guidelines(26). Additionally, a new temporary implantable nitinol device (TIND) technology has recently been developed (27).

Evidence synthesis

Evidence synthesis, particularly through systematic reviews, plays a crucial role in evidence-informed decision making and the development of guidelines. Systematic reviews are comprehensive and rigorous assessments of existing research evidence on a particular topic. By systematically identifying, critically appraising, and synthesising all relevant studies, systematic reviews provide a high level of evidence that can inform healthcare decision making(28). They help to overcome potential biases and limitations of individual studies by combining their findings, resulting in more reliable and robust conclusions. This synthesis of evidence allows policymakers, guideline developers, and healthcare professionals to make informed decisions based on the best available evidence(29).

Meta-analysis is a statistical method commonly used in systematic reviews to combine and analyse data from multiple independent studies on a specific research question or topic. Systematic reviews with meta-analysis offer several advantages that make them indispensable tools in evidence synthesis. Firstly, these methods significantly increase the statistical power of the analysis. By aggregating data from multiple studies, systematic reviews and meta-analysis can uncover small yet significant effects or associations that may remain undetected in individual

studies with limited sample sizes. This enhanced statistical power enhances the reliability and precision of the estimates obtained (28). Secondly, systematic reviews and meta-analysis enable the exploration of heterogeneity across studies. Heterogeneity refers to the variability in results observed among different studies. Through meta-analysis, researchers can identify potential sources of heterogeneity, such as differences in study design, participant characteristics, or interventions. By delving into the reasons behind heterogeneity, researchers can better understand the factors influencing treatment effects or associations, thereby aiding in the development of more tailored and effective interventions(30).

However, despite their numerous advantages, systematic reviews and meta-analysis also have inherent limitations. One significant drawback is the "garbage in, garbage out" phenomenon, which emphasises the importance of including high-quality studies in the analysis(31). If the individual studies included in the review are flawed or biased, the overall conclusions drawn from the meta-analysis may also be compromised. Furthermore, unexplained heterogeneity poses another challenge in systematic reviews and meta-analysis. This can be likened to comparing "apples and oranges," as different studies may vary in their methodologies, populations, or outcome measures(32). The presence of unexplained heterogeneity makes it difficult to draw consistent and generalizable conclusions from the meta-analysis. Lastly, publication bias presents a potential limitation in evidence synthesis(33). Positive or statistically significant findings are more likely to be published than negative or nonsignificant results. This bias towards publishing positive outcomes can skew the overall evidence base and lead to an overestimation of treatment effects.

Most of the current state-of-the art methods for systematic review and meta-analysis were developed by **Cochrane**, an international organisation, present in more than 130 countries, whose mission is to promote evidence-based health decision-making by conducting high-quality, relevant, and accessible systematic reviews, as well as by summarising other scientific evidence. Cochrane publishes its reviews in *The Cochrane Library*. Cochrane guides its actions through the Strategy for Change states its mission as “to produce trusted synthesised evidence, make it accessible to all, and advocate for its use”. Cochrane is a complex organisation composed of:

- **Geographic Groups:** These are local representatives of Cochrane and, depending on their category, they fulfil a wide range of functions, ranging from the production of systematic reviews to dissemination (knowledge translation) and advocacy for evidence.

- **Editorial Groups:** These manage the editorial content of *The Cochrane Library*. They are divided by thematic areas, exceeding 50 worldwide. Each group receives review proposals from independent researchers that they can accept according to their decision-making priority. Among them is the Cochrane Urology Group, of which I am part as Editor.

Cochrane Urology is one of the over 50 editorial groups of Cochrane, an international not-for-profit organisation that aims to promote the use of evidence in healthcare by producing high-quality systematic reviews free from conflict of interest. This group currently holds a portfolio of protocols and reviews dedicated to the diagnosis, prevention, treatment, and rehabilitation of benign and malignant prostate conditions, male sexual dysfunction, benign and malignant renal conditions, and urologic cancers. The group is based at the University of Minneapolis and has a Korean Satellite at Yonsei University in Wonju. Cochrane Urology reviews are not only published in the Cochrane Database of Systematic Reviews, but they are also usually co-published in specialty journals like the BJUI International, Investigative and Clinical Urology and World Journal of Men’s Health for wider dissemination.

Priority setting

A study published in 2017 indicated that certain topics of urological diseases of men with a high disease burden, such as benign diseases of the prostate, were underrepresented in *The Cochrane Library(34)*. The Cochrane Urology group undertook a prioritisation exercise in 2014 that included topics of benign prostate disease, including interventions for chronic nonbacterial prostatitis (now called chronic prostatitis/chronic pelvic pain syndrome). From 2015 to 2019, I developed two large reviews for the group that covered all the pharmacological and non-pharmacological treatments available for this pathology (35,36). In 2020, the Group highlighted the need to update its priorities, including topics on benign conditions of the prostate, especially benign prostatic hyperplasia.

The Cochrane Urology group has a series of systematic reviews addressing the different treatments for BPH. See **Table 2** for a summary of the available evidence.

Table 2. Cochrane Reviews for the treatments of benign prostatic hyperplasia

Type of treatment	**Cochrane Review (year)**
Medical	Silodosin for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (2019)
	Physical activity for lower urinary tract symptoms secondary to benign prostatic obstruction (2019)
	Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia (2018)
	Phosphodiesterase inhibitors for lower urinary tract symptoms consistent with benign prostatic hyperplasia (2018)
	Desmopressin for treating nocturia in men (2017)
	Anticholinergics combined with alpha-blockers for treating lower urinary tract symptoms related to benign prostatic obstruction (2021)
	Serenoa repens for benign prostatic hyperplasia (2012)
	Pygeum africanum for benign prostatic hyperplasia (1998)
	Beta-sitosterols for benign prostatic hyperplasia (1999)

Surgery and procedures	Convective radiofrequency water vapour thermal therapy for lower urinary tract symptoms in men with benign prostatic hyperplasia (2020)*
	Aquablation of the prostate for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (2019)
	Prostatic urethral lift for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (2019)*
	Bipolar versus monopolar transurethral resection of the prostate for lower urinary tract symptoms secondary to benign prostatic obstruction (2019)
	Prostatic arterial embolization for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (2022)*
	Microwave thermotherapy for benign prostatic hyperplasia (2012)*
	Holmium laser enucleation of the prostate for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (protocol stage in 2019)

(*) Minimally invasive treatments

Following the successful experiences of other editorial groups, the Cochrane Urology Group defined the need to establish priorities for the selection of topics for systematic reviews(37–40). Prioritising systematic review topics allows for efficient use of research resources and a greater impact on decision-making, especially if key stakeholders are involved during the prioritisation process.

A common element in the prioritisation exercises is the contact with the key actors, usually researchers and health professionals, and the analysis of the available evidence (41,42). Some main processes during topic prioritisation include a) a development phase where scope definition, literature search, stakeholder engagement and pilot testing are achieved; b) the prioritisation exercise where the initial list of topics is commonly developed with the input of the key actors and an analysis of the literature is carried out to identify gaps in the synthesis of information together with prioritisation of said topics; c) implementation and evaluation of priority topics (41).

In recent years, the methodological group for prioritisation strategies was created by Cochrane(43), who proposed it as a method to generate review topics to which independent researchers apply in work teams in a public place (44).

Currently, the Cochrane Editorial Group has close links with the American Urological Association and the European Urological Association. One of the topics that were preliminarily identified was the evidence supporting minimally invasive treatments, which led to the publication of Cochrane and non-Cochrane reviews to achieve an annual update of the recommendations(26). However, there is a gap in the evaluation of the comparative efficacy of minimally invasive treatments, for which the editorial group prioritises the publication of systematic reviews and updates of existing

ones to achieve a complete collection within *The Cochrane Library* (see reviews with an asterisk in **Table 2**).

Therefore, the editorial Group also found the need to conduct a prioritisation exercise within the scope of benign conditions of the prostate to complete the portfolio of priority reviews on this topic. This exercise included a research project following Cochrane guidance on priority setting (45). We focused on identifying priority topics of interest to our external stakeholders within our editorial scope, specifically related to benign conditions of the prostate. We developed a tiered approach that involved consulting both internal and external stakeholders, including Urological Society members. Through analysing our portfolio and considering factors like feasibility, novelty, and relevance, we narrowed down a list of titles for updates or new reviews. Our editors provided valuable feedback, highlighting gaps in our portfolio, particularly in new treatments for benign prostatic hyperplasia. External stakeholders from 14 countries also provided insights, suggesting additional topics and emphasising the importance of disseminating existing reviews effectively. We identified four priority topics to pursue and two others that require further consideration. By following Cochrane's guidance and conducting a thorough analysis, we were able to identify relevant topics and assess the commissioning process for priority reviews. Among these topics, the first ones prioritised were the following interventions for the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia:

- *Serenoa repens* alone or in combination with other phythotherapy
- Minimally invasive interventions

The full details that led to the prioritisation of the review topics covered in this thesis are described in the publication of **Appendix A**. The description of these interventions and how they may work are described in each of the subsequent published reviews (see **Results**).

Objectives

General objective

To synthesise priority topics related to the effects of treatments for benign conditions of the prostate.

Specific objectives

1) To assess the effects of *Serenoa repens* in the treatment of men with lower urinary tract symptoms due to benign prostatic hyperplasia.

2) To assess the comparative effectiveness of minimally invasive treatments for lower urinary tract symptoms in men with benign prostatic hyperplasia.

Methods

General methods

The general objectives were conducted within the framework of the methods and standards of Cochrane. Cochrane provides the following guidance for the conduct of systematic reviews:

1) The Cochrane Handbook(28)

2) The Methodological Expectations for the Conduct of Intervention Reviews (MECIR)(46)

We followed the MECIR guidance on reporting reviews, which covers the items of the 2020 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)(47). Moreover, the AMSTAR 2 instrument provides guideline on the 16-key elements for trustworthy systematic reviews across their production, which we summarise here:

- All reviews followed a predefined protocol, detailing the background, review question, inclusion criteria, outcomes, search strategy, risk of bias assessment and an analysis plan (AMSTAR 1 and 2). We decided to include randomised controlled trials, as they are the most relevant study design to assess the causal effects of interventions (AMSTAR 3).

- We performed a comprehensive search using multiple databases (the Cochrane Library, MEDLINE, Embase, Scopus, Web of Science, and LILACS), trials registries, and other sources of grey literature, with no restrictions by language or publication status (AMSTAR 4).

- We performed study selection and data extraction in duplicate (AMSTAR 5 and 6) and each published review provides a list of excluded studies (AMSTAR 7).

- We provided a detailed report on the characteristics of each study and a summary of the main characteristics of populations, interventions, comparisons, outcomes and sources of funding (AMSTAR 8 and 10). For the reviews related to minimally invasive interventions we used the Cochrane Risk of Bias tool (ROB 1)(48) and for the latest update of the *Serenoa repens* review we implemented the newest version of the tool (also known as RoB 2)(49) (AMSTAR 9).

- We conducted pairwise random-effects meta-analysis for each outcome when study characteristics were similar across studies, accounting for between-study heterogeneity (AMSTAR 11), exploring heterogeneity through predefined subgroup analysis (AMSTAR 14).

- We assessed the impact of risk of bias through sensitivity analysis, and when sufficient data could be gathered from studies at low risk of bias, we included this analysis in the main findings (*Serenoa repens* review) (AMSTAR 12).

- All reviews assessed the certainty of the evidence following the GRADE approach, which considers study limitations (risk of bias), inconsistency (heterogeneity), imprecision, indirectness and publication bias(50) (AMSTAR 13 and 14).

- Publication bias was assessed through forest plots when sufficient studies were included per comparison/outcome (AMSTAR 15)

- We declared our funding sources and conflicts of interest related to the conduct of these reviews (AMSTAR 16).

In the following section further method specifications will be explained for each review.

Updating Cochrane reviews

Two of the reviews had been previously published using outdated methods and analysing additional surrogate outcomes, less relevant to patients and decision makers (including peak urinary flow or Q_{max}). Following the guidance of the Chapter IV of the Cochrane Handbook(28,51) these reviews followed the criteria for update as they:

a) Addressed a current question (as defined by the priority setting exercise)
b) New methods were available to implement in such reviews.
c) The adoption of new methods would make the reviews more relevant and usable in current clinical practice guidelines and other evidence synthesis projects.

We decided not to write new protocols, as the key elements of the original questions remained unchained, but the re-framing of the analysis could make the results more comparable to current practice.

Since one of the main advances was in the conduct and report of search strategies we followed a "replacement approach", in which only the searches done for the update are described, using the previous review as one source of studies. All studies from the previous reviews were re-assessed for eligibility, data extraction, and risk of bias assessment.

Additional details on each update:

Serenoa repens review update

- We included randomised controlled trials of participants with BPH who were treated with *Serenoa repens* or placebo/no treatment.
- We included trials in two comparisons: *Serenoa repens* versus placebo or *Serenoa repens* in combination with other phytotherapy vs placebo.
- We considered review outcomes measured up to 12 months after randomisation as short-term and beyond 12 months as long-term. Our main outcomes included urologic symptom scores, quality of life, and adverse events.
- We implemented ROB 2 for risk of bias assessment.

Transurethral microwave thermotherapy (TUMT) review update

- We included parallel-group randomised controlled trials of participants with BPH who underwent TUMT.
- We included comparisons to surgery (TURP) or sham (placebo procedure).
- We considered review outcomes measured up to 12 months after randomisation as short-term and beyond 12 months as long-term. Our main outcomes included: urologic symptoms scores, quality of life, major adverse events, retreatment, and ejaculatory and erectile function.
- We decided to use the ROB 1 tool, as it would feed the network-meta-analysis using data from other reviews who had used ROB 1.

Network Meta-Analysis

In order to assess the comparative effectiveness of minimally invasive procedures, we needed to collate the evidence for each of them. The Cochrane Urology Review Group had already published reviews on prostatic urethral lift (PUL), convective radiofrequency water vapour therapy (CRWVT), and prostatic arterial embolisation (PAE) (23–25). However, we needed an up-to-date review on transurethral microwave thermotherapy (TUMT) and temporary implantable nitinol device (TIND). Therefore we needed to produce two research outputs:

1) An update of the review on TUMT from 2012(52) (see previous section).

2) A network meta-analysis (NMA) incorporating the data of the three previous reviews on PUL, CRWVT, PAE, the update of TUMT and a search targeting TIND.

Our primary objective was to assess the comparative effectiveness of minimally invasive treatments for lower urinary tract symptoms in men with BPH through a network meta-analysis. Our secondary objective was to obtain an estimate of the relative ranking of these minimally invasive treatments according to their effects.

We followed the guidance of Chapter 11 of the Cochrane Handbook and the PRISMA extension for NMA(28,53).

We included parallel-group randomised controlled trials assessing the effects of the following minimally invasive treatments, compared to TURP or sham treatment, on men with moderate to severe LUTS due to BPH: convective radiofrequency water vapour therapy (CRFWVT); prostatic arterial embolisation (PAE); prostatic urethral lift (PUL); temporary implantable nitinol device (TIND); and transurethral microwave thermotherapy (TUMT).

We assessed the transitivity, even in the absence of inconsistency, by comparing the characteristics of participants and the distribution of potential effect modifiers, including age, prostate volume, and severity of LUTS.

We performed statistical analyses using a random-effects model for pair-wise comparisons and a frequentist network meta-analysis for combined estimates.

We evaluated the presence of inconsistency both locally and globally(54).

We obtained a treatment hierarchy using P scores for all outcomes of the review(55). P scores allow describing the mean extent of certainty that the underlying treatment effect is larger than that of any other intervention. We used the surface under the cumulative ranking curve (SUCRA) to rank the effectiveness and safety of minimally invasive interventions(56).

Results

Article 1: *Serenoa repens*

(Cochrane review update)[2]

For this update, we narrowed the review question to only comparisons with placebo. We included 27 studies (of which 9 were new) involving a total of 4656 participants, 19 studies comparing *Serenoa repens* with placebo, and 8 studies comparing *Serenoa repens* in combination with other phytotherapeutic agents versus placebo. Most studies included men aged > 50 (mean age range 52 to 68) with moderate urologic symptoms (International Prostate Symptom Score [IPSS] range 8 to 19). Ten studies were funded by the pharmaceutical industry; two studies were funded by government agencies; and the remaining studies did not specify funding sources.

Serenoa repens versus placebo or no intervention

Results for this comparison are based on predefined sensitivity analyses limited to studies at low risk of bias. *Serenoa repens* results in little to no difference in urologic symptoms at short-term follow-up (3 to 6 months; IPSS score range 0 to 35, higher scores indicate worse symptoms; mean difference (MD) -0.90, 95% confidence interval (CI) -1.74 to -0.07; I2 = 68%; 9 studies, 1681 participants; high-certainty evidence). *Serenoa repens* results in little to no difference in the quality of life at short-term follow-up (3 to 6 months; IPSS quality of life domain range 0 to 6, higher scores indicate worse quality of life; MD -0.20, 95% CI -0.40 to -0.00; I2 = 39%; 5 studies, 1001 participants; high-certainty evidence). Serenoa repens probably results in little to no difference in adverse events (1 to 17 months; risk ratio (RR) 1.01, 95% CI 0.77 to 1.31; I2 = 18%; 12 studies, 2399 participants; moderate-certainty evidence). Based on 164 cases per 1000 men in the placebo group, this corresponds to 2 more (38 fewer to 51 more) per 1000 men in the *Serenoa repens* group. *Serenoa repens* results in little to no difference in urologic symptoms at long-term follow-up (12 to 17 months, IPSS score, MD 0.07, 95% CI -0.75 to 0.88; I2 = 34%; 3 studies, 898 participants; high-certainty evidence). *Serenoa repens* results in little to no difference in quality of life at long-term follow-up (12 to 17 months, IPSS quality of life, MD -0.11, 95% CI -0.41 to 0.19; I2 = 65%; 3 studies, 882 participants; high-certainty evidence). There were no data on long-term adverse events for this comparison.

Serenoa repens in combination with other phytotherapy versus placebo or no intervention

Different phytotherapeutic agents that include *Serenoa repens* may result in little to no difference in urologic symptoms compared to placebo at short-term follow-up (12 to 24 weeks, IPSS score, MD -2.41, 95% CI -4.54 to -0.29; I2 = 67%; 4 studies, 460 participants; low-certainty evidence). We are very uncertain about the effects of these agents on quality of life (very low-certainty evidence). These agents may result in little to no difference in the occurrence of adverse events; however, the CIs included substantial benefits and harms (12 to 48 weeks, RR 0.91, 95% CI 0.58 to 1.41; I2 = 0%; 4 studies, 481 participants; low-certainty evidence). Based on 132 cases per 1000 men in the placebo group, this corresponds to 12 fewer (55 fewer to 54 more) per 1000 men in the combined phytotherapeutic agents with *Serenoa repens* group.

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[2] Franco JV, Trivisonno L, Sgarbossa NJ, Alvez GA, Fieiras C, Escobar Liquitay CM, Jung JH. Serenoa repens for the treatment of lower urinary tract symptoms due to benign prostatic enlargement. Cochrane Database Syst Rev. 2023 Jun 22;6(6):CD001423. doi: 10.1002/14651858.CD001423.pub4. PMID: 37345871; PMCID: PMC10286776. *Impact Factor 2023 8.4 - Cited 0 times (07.07.2023)*

Cochrane Library

Cochrane Database of Systematic Reviews

Serenoa repens for the treatment of lower urinary tract symptoms due to benign prostatic enlargement (Review)

Franco JVA, Trivisonno L, Sgarbossa NJ, Alvez GA, Fieiras C, Escobar Liquitay CM, Jung JH

Franco JVA, Trivisonno L, Sgarbossa NJ, Alvez GA, Fieiras C, Escobar Liquitay CM, Jung JH.
Serenoa repens for the treatment of lower urinary tract symptoms due to benign prostatic enlargement.
Cochrane Database of Systematic Reviews 2023, Issue 6. Art. No.: CD001423.
DOI: 10.1002/14651858.CD001423.pub4.

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[Intervention Review]

Serenoa repens for the treatment of lower urinary tract symptoms due to benign prostatic enlargement

Juan VA Franco[1], Leonel Trivisonno[2], Nadia J Sgarbossa[2], Gustavo Ariel Alvez[3], Cecilia Fieiras[3], Camila Micaela Escobar Liquitay[4], Jae Hung Jung[5]

[1]Institute of General Practice, Medical Faculty, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany. [2]Department of Health Science, Universidad Nacional de La Matanza, San Justo, Argentina. [3]Medical School, Instituto Universitario Hospital Italiano de Buenos Aires, Buenos Aires, Argentina. [4]Department of Research, Instituto Universitario Hospital Italiano de Buenos Aires, Buenos Aires, Chile. [5]Department of Urology, Yonsei University Wonju College of Medicine, Wonju, Korea, South

Contact: Juan VA Franco, juan.franco@med.uni-duesseldorf.de.

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ABSTRACT

Background

Benign prostatic hyperplasia (BPH) is a non-malignant enlargement of the prostate, which can lead to obstructive and irritative lower urinary tract symptoms (LUTS). The pharmacologic use of plants and herbs (phytotherapy) for the treatment of LUTS associated with BPH is common. The extract of the berry of the American saw palmetto or dwarf palm plant, *Serenoa repens* (SR), which is also known by its botanical name of *Sabal serrulatum*, is one of several phytotherapeutic agents available for the treatment of BPH.

Objectives

To assess the effects of *Serenoa repens* in the treatment of men with LUTS consistent with BPH.

Search methods

We performed a comprehensive search of multiple databases (the Cochrane Library, MEDLINE, Embase, Scopus, Web of Science, and LILACS), trials registries, other sources of grey literature, and conference proceedings published up to 16 September 2022, with no restrictions on language or publication status.

Selection criteria

We included randomized controlled trials of participants with BPH who were treated with *Serenoa repens* or placebo/no treatment.

Data collection and analysis

Two review authors independently assessed studies for inclusion at each stage and undertook data extraction and risk of bias assessment and GRADE assessment of the certainty of the evidence. We considered review outcomes measured up to 12 months after randomization as short term, and beyond 12 months as long term. Our main outcomes included urologic symptom scores, quality of life, and adverse events.

Main results

For this update, we narrowed the review question to only comparisons with placebo. We included 27 studies (of which 9 were new) involving a total of 4656 participants, 19 studies comparing *Serenoa repens* with placebo, and 8 studies comparing *Serenoa repens* in combination with other phytotherapeutic agents versus placebo. Most studies included men aged > 50 (mean age range 52 to 68) with moderate urologic

symptoms (International Prostate Symptom Score [IPSS] range 8 to 19). Ten studies were funded by the pharmaceutical industry; two studies were funded by government agencies; and the remaining studies did not specify funding sources.

***Serenoa repens* versus placebo or no intervention**

Results for this comparison are based on predefined sensitivity analyses limited to studies at low risk of bias. *Serenoa repens* results in little to no difference in urologic symptoms at short-term follow-up (3 to 6 months; IPSS score range 0 to 35, higher scores indicate worse symptoms; mean difference (MD) −0.90, 95% confidence interval (CI) −1.74 to −0.07; I^2 = 68%; 9 studies, 1681 participants; high-certainty evidence). *Serenoa repens* results in little to no difference in the quality of life at short-term follow-up (3 to 6 months; IPSS quality of life domain range 0 to 6, higher scores indicate worse quality of life; MD −0.20, 95% CI −0.40 to −0.00; I^2 = 39%; 5 studies, 1001 participants; high-certainty evidence). *Serenoa repens* probably results in little to no difference in adverse events (1 to 17 months; risk ratio (RR) 1.01, 95% CI 0.77 to 1.31; I^2 = 18%; 12 studies, 2399 participants; moderate-certainty evidence). Based on 164 cases per 1000 men in the placebo group, this corresponds to 2 more (38 fewer to 51 more) per 1000 men in the *Serenoa repens* group.

Serenoa repens results in little to no difference in urologic symptoms at long-term follow-up (12 to 17 months, IPSS score, MD 0.07, 95% CI −0.75 to 0.88; I^2 = 34%; 3 studies, 898 participants; high-certainty evidence). *Serenoa repens* results in little to no difference in quality of life at long-term follow-up (12 to 17 months, IPSS quality of life, MD −0.11, 95% CI −0.41 to 0.19; I^2 = 65%; 3 studies, 882 participants; high-certainty evidence). There were no data on long-term adverse events for this comparison.

***Serenoa repens* in combination with other phytotherapy versus placebo or no intervention**

Different phytotherapeutic agents that include *Serenoa repens* may result in little to no difference in urologic symptoms compared to placebo at short-term follow-up (12 to 24 weeks, IPSS score, MD −2.41, 95% CI −4.54 to −0.29; I^2 = 67%; 4 studies, 460 participants; low-certainty evidence). We are very uncertain about the effects of these agents on quality of life (very low-certainty evidence). These agents may result in little to no difference in the occurrence of adverse events; however, the CIs included substantial benefits and harms (12 to 48 weeks, RR 0.91, 95% CI 0.58 to 1.41; I^2 = 0%; 4 studies, 481 participants; low-certainty evidence). Based on 132 cases per 1000 men in the placebo group, this corresponds to 12 fewer (55 fewer to 54 more) per 1000 men in the combined phytotherapeutic agents with *Serenoa repens* group.

Authors' conclusions

Serenoa repens alone provides little to no benefits for men with lower urinary tract symptoms due to benign prostatic enlargement. There is more uncertainty about the role of *Serenoa repens* in combination with other phytotherapeutic agents.

PLAIN LANGUAGE SUMMARY

***Serenoa repens* for benign prostatic hyperplasia**

Review question

Does *Serenoa repens* alone or in combination with other phytotherapeutic agents improve symptoms in men with benign prostatic enlargement?

Background

An enlarged prostate may cause bothersome urinary tract symptoms, such as having to urinate often during the day or night, having a weak stream, and the feeling of not completely emptying the bladder. Besides other common drug interventions, using plants and herbs (phytotherapy) is common and has been growing steadily in most Western countries. The extract of the berry of the American saw palmetto, or dwarf palm plant, *Serenoa repens*, which is also known by its botanical name of *Sabal serrulatum*, is one of several phytotherapeutic agents available for the treatment of this condition.

Study characteristics

We found 27 studies with 4656 men comparing *Serenoa repens* alone or in combination with other herbal products to a placebo (participants are made to believe they received treatment when in fact they did not). Most studies included men over 50 with moderate symptoms. Ten studies were funded by pharmaceutical organizations; two studies received government funding; and the remaining studies did not specify funding sources.

Key results

Based on the most trustworthy studies, *Serenoa repens* alone results in little to no difference in urinary tract symptoms or quality of life compared to placebo at three to six months. This treatment is also likely not associated with adverse events. Results were similar at 12 to 17 months.

Serenoa repens in combination with other herbal products may result in little to no difference in urinary tract symptoms, but there is more uncertainty about effects on quality of life and adverse events.

The findings of this review are current to 16 September 2022.

Certainty of the evidence

The certainty of the evidence is primarily high or moderate for *Serenoa repens* alone, but low for *Serenoa repens* in combination with other agents, meaning our confidence in the results is high, moderate, or low.

SUMMARY OF FINDINGS

Summary of findings 1. *Serenoa repens* compared to placebo or no intervention

***Serenoa repens* compared to placebo or no intervention**

Patient or population: lower urinary tract symptoms due to benign prostatic hyperplasia

Setting: outpatient (Australia, Asia, Europe, and the USA)

Intervention: *Serenoa repens*

Comparison: placebo/no treatment

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo/no treatment	Risk difference with *Serenoa repens*
Urologic symptom score Measured by IPSS scores (range 0 to 35) Higher scores indicate worse symptoms. Follow-up: 3 to 6 months MCID: 3 points	1681 (9 RCTs)	⊕⊕⊕⊕ **High**[a]	MD −0.90 (−1.74 to −0.07)	The mean score was 14.33.	**MD 0.90 lower** (1.74 lower to 0.07 lower)
Quality of life Measured by IPSS-QoL score (range 0 to 6) Follow-up: 3 to 6 months MCID: 0.5 points	1001 (5 RCTs)	⊕⊕⊕⊕ **High**[a]	MD −0.20 (−0.40 to 0.00)	The mean score was 3.11.	**MD 0.20 lower** (0.40 lower to 0.00 lower)
Adverse events Cumulative incidence Follow-up: 1 to 17 months MCID: relative risk reduction/increase of 0.25	2399 (12 RCTs)	⊕⊕⊕⊖ **Moderate**[b]	**RR 1.01** (0.77 to 1.31)	164 per 1000	2 more per 1000 (38 fewer to 51 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **IPSS**: International Prostate Symptom Score; **MCID:** minimal clinically important difference; **MD:** mean difference; **QoL**: quality of life; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]We did not downgrade the certainty of the evidence for risk of bias as these results were robust following sensitivity analysis excluding studies at high risk of bias.
[b]We did not downgrade the certainty of the evidence for risk of bias as these results were robust following sensitivity analysis excluding studies at high risk of bias. We downgraded one level due to imprecision as the CI included little to no benefit and also harms (based on a 25% relative risk reduction).

Summary of findings 2. *Serenoa repens* in combination with other phytotherapy versus placebo or no intervention

***Serenoa repens* in combination with other phytotherapy versus placebo or no intervention**

Patient or population: lower urinary tract symptoms due to benign prostatic hyperplasia

Setting: outpatient (Europe/USA)

Intervention: *Serenoa repens* with other phytotherapy

Comparison: placebo/no intervention

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo/no treatment	Risk difference with *Serenoa repens*
Urologic symptom score Measured by IPSS scores (range 0 to 35) Higher scores indicate worse symptoms. Follow-up: 12 to 24 weeks MCID: 3 points	460 (4 RCTs)	⊕⊕⊖⊖ **Low**[a,b]	MD −2.41 (−4.54 to −0.29)	The mean score was 12.	**MD 2.41 lower** (4.54 lower to 0.29 lower)
Quality of life Measured by IPSS-QoL score (range 0 to 6) Follow-up: 2 to 6 months MCID: 0.5 points	265 (2 RCTs)	⊕⊖⊖⊖ **Very low**[c,d,e]	1 study reported improvements (P < 0.05), while the other did not.		
Adverse events Cumulative incidence Follow-up: 12 to 48 weeks MCID: relative risk reduction/increase of 0.25	481 (4 RCTs)	⊕⊕⊖⊖ **Low**[f]	**RR 0.91** (0.58 to 1.41)	132 per 1000	12 fewer per 1000 (55 fewer to 54 more)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **IPSS**: International Prostate Symptom Score; **MCID:** minimal clinically important difference; **MD:** mean difference; **QoL**: quality of life; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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[a]Downgraded one level due to concerns about inconsistency: high statistical inconsistency (I^2 = 67%).
[b]Downgraded one level due to imprecision: wide CI including substantial benefit and little to no effect.
[c]Downgraded one level due to risk of bias: high risk of bias in included studies.
[d]Downgraded one level due to inconsistency: the included studies reported different effects.
[e]Downgraded one level due to imprecision: the included studies reported P values, and we are uncertain about effect sizes.
[f]Downgraded two levels due to imprecision: CI includes substantial benefits and harms.

BACKGROUND

Description of the condition

Description of the condition

The prostate gland is an organ approximately the size of a walnut located below the urinary bladder encircling the urethra (Leissner 1979). Benign prostatic hyperplasia (BPH) is a histological diagnosis defined as an increased number of epithelial and stromal cells in the prostate; this may cause prostatic enlargement and, subsequently, compression of the urethra and obstruction (Roehrborn 2008). BPH may therefore develop with or without lower urinary tract symptoms (LUTS) in men aged over 40 years (Dunphy 2015). BPH acquires clinical significance when associated with bothersome LUTS (Roehrborn 2008). 'Symptom bother' typically correlates with the increased number and severity of symptoms, which relate to both quality of life impairment and treatment seeking (Agarwal 2014). Self-administered questionnaires (e.g. the International Prostate Symptom Score [IPSS]) include the quality of life domain to evaluate the relative degree of bother across all LUTS (Barry 1995). Increased LUTS severity is associated with worsening men's overall distress using the man's perception of bladder condition, which is a single-item global question (ranging from 1 [causes no problems at all] to 6 [causes severe problems]) (Chapple 2017). In this Cochrane Review, we consider the term BPH as prostatic enlargement with LUTS to define the disease condition and potential need for intervention.

BPH can progress and cause serious consequences such as acute urinary retention, infection, and upper urinary tract deterioration. BPH also negatively impacts public health and a reduction in a person's quality of life (Kozminski 2015; Martin 2014). In Europe, 30% of men over 50 years of age, equivalent to 26 million men, are affected by bothersome LUTS, including storage symptoms (such as urinary frequency, urgency, and nocturia) or voiding symptoms (such as urinary hesitancy, weak urinary stream, straining to void, and prolonged voiding), or both. The yearly reported associated number of medical prescriptions is estimated to be around 11.6 million for 74 million people at risk from 2004 to 2008 (Cornu 2010). According to an international study involving 7588 men, the prevalence of LUTS was 18% in 40-year-olds, 29% of men in their 50s, 40% of men in their 60s, and 56% of men in their 70s (Homma 1997). In the USA, an estimated eight million men over 50 years of age have BPH (Roehrborn 2008). More recent data show that the lifetime prevalence of BPH was 26.2% (95% confidence interval 22.8 to 29.6%) (Lee 2017).

Diagnosis

Initial evaluation of LUTS suggestive of BPH includes patient history and physical examination, which may include a digital rectal examination, urinalysis, prostate-specific antigen (PSA), and IPSS (Gravas 2022; Lerner 2021). A digital rectal examination may be performed to assess the prostate for size and any lesions suspicious of cancer. PSA is secreted by the prostate gland and is found to be abnormally elevated in conditions such as prostate cancer, BPH, infection, or inflammation of the prostate (Gravas 2022; Lerner 2021). The IPSS is used to assess urinary symptom severity and quality of life. It is also used to document subjective responses to treatment. Measurements of maximum flow rate (Q_{max}) and postvoid residual (PVR) are also used in diagnosis and treatment decisions (Gravas 2022; Lerner 2021). A low Q_{max} and a large PVR predict an increased risk of symptom progression (Crawford 2006). Further evaluations may be needed for differential diagnosis or pre-surgical assessments (Gravas 2022; Lerner 2021).

Treatment

Treatment decisions are based on symptoms and the degree of bother noted by the patient. Initial treatment options for BPH include conservative management (watchful waiting and lifestyle modification) and medication (alpha-blockers and 5-alpha reductase inhibitors) (Gravas 2022; Lerner 2021). If patients have been refractory to conservative and medical treatment, and BPH causes subsequent complications, such as acute urinary retention, recurrent urinary tract infection, bladder stones or diverticula, hematuria, or renal insufficiency, surgical options are considered (Gravas 2022; Lerner 2021). Currently, guidelines do not recommend the routine use of *Serenoa repens*, but they state that in instances where patients want to avoid adverse side effects of other treatments, these patients should be informed of its modest benefits (Gravas 2022).

Description of the intervention

There are about 30 phytotherapeutic compounds available for the treatment of BPH, and one of the most widely used is an extract from the berry of the American saw palmetto or dwarf palm plant, *Serenoa repens*, which is also known by its botanical name of *Sabal serrulatum*. The extracts can be classified as hexane, ethanolic, and supercritical carbon dioxide. The hexane extract (commercially known as Permixon) is proposed to have a higher biological activity and the lowest variability from batch to batch in free fatty acid content, possibly suggesting a higher efficacy and fewer adverse events (Habib 2004; Scaglione 2008).

Serenoa repens is usually taken in a daily dose of 320 mg, although some studies have investigated higher doses (Barry 2011). The most frequently reported adverse events are minor gastrointestinal symptoms, genitourinary problems, musculoskeletal complaints, and upper respiratory tract infections.

How the intervention might work

The causes of LUTS related to BPH are not entirely known; however, it is theorized that a combination of prostatic cellular proliferation (BPH) and smooth muscle dysfunction are likely reasons (Roehrborn 2020). The purported mechanisms of action for *Serenoa repens* include:

- alteration in cholesterol metabolism (Christensen 1990);
- antiestrogenic and antiandrogenic effects (Dreikorn 1990; Marwick 1995), with *Serenoa repens* (Permixon) acting as a weak surrogate 5-ARI inhibiting the conversion of testosterone to dihydrotestosterone (DHT), Dedhia 2008, and the dependent inhibition of 5-ARI in the stroma and epithelium of the prostate (Weisser 1996);
- anti-inflammatory effects by a decrease in available sex hormone-binding globulin (Di Silverio 1993);
- pro-apoptotic properties and inhibition of cellular proliferation (Vacherot 2000; Vela-Navarrete 2005);
- the relaxation of smooth muscles of the detrusor and the prostate via alpha-1 adrenergic receptors (Roehrborn 2020);
- placebo effect (Roehrborn 2020).

Why it is important to do this review

Phytotherapy is widely used for the relief of lower urinary symptoms attributed to BPH. Since the last update (Tacklind 2012), several new trials have been published. Whereas some newer non-Cochrane reviews have been published, none has included GRADE methods (Novara 2016; Russo 2021; Vela-Navarrete 2018).

OBJECTIVES

To assess the effects of *Serenoa repens* in the treatment of men with LUTS consistent with BPH.

METHODS

Criteria for considering studies for this review

Types of studies

The methods for this update have been extensively modified since its last publication to meet current methodological expectations; please refer to the Differences between protocol and review section. We included parallel-group randomized controlled trials (RCTs). We excluded cluster-RCTs, as these study designs are not relevant in this setting. We included the first phase of cross-over studies. We did not include single-armed studies. We included studies regardless of their publication status or language.

Types of participants

We defined the eligible participant population as men over the age of 40 years with a prostate volume of 20 mL or greater (as assessed by ultrasound or cross-sectional imaging), with lower urinary tract symptoms (LUTS) as determined by International Prostate Symptom Scores (IPSS) of eight or over, and a maximum flow rate (Q_{max}) of less than 15 mL/second, as measured by non-invasive uroflowmetry, invasive pressure flow studies, or both (Dunphy 2015; EAU 2022; McNicholas 2016; McVary 2011). We based the age limit on the fact that the prevalence of BPH increases in middle-aged and older men and is infrequent in younger men (Barry 1997; EAU 2022; Egan 2016). We included studies in which only a subset of participants was relevant to this review (i.e. studies in which more than 75% of participants were relevant to this review) if data were available separately for the relevant subset.

We excluded studies of men with active urinary tract infection, bacterial prostatitis, chronic renal failure, untreated bladder calculi or large diverticula, prostate cancer, and urethral stricture disease, as well as those who had undergone prior prostate, bladder neck, or urethral surgery. We also excluded studies of people with other conditions that affect urologic symptoms, such as neurogenic bladder due to spinal cord injury, multiple sclerosis, or central nervous system disease.

Types of interventions

Experimental intervention

- *Serenoa repens* alone (hexanic and non-hexanic extract)
- *Serenoa repens* in combination with other phytotherapy

Comparator intervention

- Placebo or no intervention

Comparisons

- *Serenoa repens* versus placebo or no intervention
- *Serenoa repens* in combination with other phytotherapy versus placebo or no intervention

To establish fair comparisons, we required that concomitant interventions be the same in the experimental and comparator groups.

Types of outcome measures

We did not use measurement of the outcomes assessed in this review as an eligibility criterion.

Primary outcomes

- Urologic symptom scores (continuous outcome)
- Quality of life (continuous outcome)
- Adverse events

Secondary outcomes

We did not include secondary outcomes.

Method and timing of outcome measurement

We considered the clinically important differences for the review outcome measures to rate the overall certainty of evidence in the summary of findings tables following a minimally contextualized approach (Jaeschke 1989; Johnston 2013). We considered outcomes measured up to and including 12 months after randomization as short term, and later than 12 months as long term. For adverse events, the timing of outcome assessment was not well-defined across studies, and outcome data were not disaggregated by follow-up, so we did not divide them into short and long term.

Urologic symptom scores

Mean change from baseline or final mean value, measured using a validated scale (such as IPSS). We considered the improvement of an IPSS score of three points as the minimal clinically important difference (MCID) to assess the efficacy and comparative effectiveness (Barry 1995). If possible, we used different thresholds of MCID based on the severity of IPSS, with a threshold of three points for men with mild LUTS, five for moderate LUTS, and eight for severe LUTS (Barry 1995).

Quality of life

Mean change from baseline or final mean value measured as a validated scale (such as IPSS-quality of life or BPH Impact Index). No threshold has been established for IPSS quality of life in the literature. However, we used an MCID of 0.5 to assess the efficacy and comparative effectiveness. A BPH Impact Index score of one as an MCID was used to indicate improvement (Barry 2013; Franco 2021; Rees 2015).

Adverse events

The number of participants experiencing at least one adverse event (e.g. gastrointestinal discomfort). There were no reported thresholds in adverse events, thus we considered a clinically important difference a risk ratio reduction or increase of at least 25% (Guyatt 2011).

Search methods for identification of studies

Electronic searches

We searched the following sources from the inception of each database to the date of search with no restrictions on the language of publication:

- the Cochrane Central Register of Controlled Trials (CENTRAL; www.cochranelibrary.com/) (2022, Issue 9) searched 16 September 2022;
- MEDLINE (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to 16 September 2022);
- Embase (www.embase.com/) from 1974 to 16 September 2022;
- Scopus (www.scopus.com/home.uri) from 1966 to 16 September 2022;
- Science Citation Index Expanded (SCI-E) Web of Science Clarivate (www.webofscience.com; from 1970 to 16 September 2022);
- Latin American and Caribbean Literature in Health Sciences (LILACS; lilacs.bvsalud.org/es/; from 1982 to 16 September 2022);
- ClinicalTrials.gov (www.clinicaltrials.gov) (searched 16 September 2022);
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch) (searched 16 September 2022).

Details of the search strategies are provided in Appendix 1.

Searching other resources

We attempted to identify other potentially eligible trials and ancillary publications by searching the reference lists of retrieved included trials, reviews, meta-analyses, and health technology assessment reports. We contacted the study authors of included trials to identify further studies that we may have missed. We contacted drug/device manufacturers for ongoing or unpublished trials. We searched abstract proceedings of relevant meetings of the American Urological Association, the European Association of Urology, and the International Continence Society from 2020 to 2022 for unpublished studies (see Appendix 2).

Data collection and analysis

Selection of studies

We used Covidence to identify and remove potential duplicate records (Covidence). Two review authors (out of LT, NJS, GAA, and CF) scanned abstracts, titles, or both to determine which studies should be assessed further using the same software. Two review authors (out of LT, NJS, GAA, and CF) investigated all potentially relevant records as full text, mapped records to studies, and classified studies as included studies, excluded studies, studies awaiting classification, or ongoing studies following the criteria for each provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022a). Any discrepancies were resolved through consensus or recourse to a third review author (JVAF or JHJ). We documented the reasons for exclusion of excluded studies. We presented a PRISMA flow diagram showing the process of study selection (Page 2021).

Data extraction and management

We developed a dedicated data abstraction form that we pilot-tested ahead of time. For studies that fulfilled our inclusion criteria, two review authors (out of LT, NJS, GAA, and CF) independently abstracted the following information.

- Study design
- Study dates
- Study settings and country
- Participant inclusion and exclusion criteria (e.g. age, baseline IPSS)
- Participant details, baseline demographics (e.g. age, prostate size, IPSS)
- Numbers of participants by study and by study arm
- Details of relevant experimental intervention (e.g. dose, posology, type of *Serenoa repens* extract)
- Definitions of relevant outcomes and methods (e.g. type of instrument, such as IPSS) and timing of outcome measurement (e.g. in months), as well as relevant subgroups (e.g. based on age, prostate volume, and the severity of LUTS)
- Study funding sources
- Declarations of interest by primary investigators

For dichotomous outcomes, we presented numbers of events and totals for populations in a 2 × 2 table and summary statistics with corresponding measures of variance. We obtained the means and standard deviations or data necessary for continuous outcomes to calculate this information. Any disagreements were resolved by discussion or in consultation with a third review author (JVAF or JHJ) if required.

We provided information about potentially relevant studies, including the trial identifiers, in tables. In addition, we contacted the authors of included studies to obtain key missing data as needed.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary study, we maximized the yield of information by mapping all publications to unique studies and collating all available data. We used the most complete data set aggregated across all known publications. In case of doubt, we prioritized the publication reporting the most extended follow-up associated with our primary or secondary outcomes.

Assessment of risk of bias in included studies

Two review authors (out of LT, NJS, GAA, CF) independently assessed the risk of bias for the results of the main outcomes (those included in the summary of findings table, see below) in each included study using the recently developed revision of the Cochrane risk of bias tool, RoB 2 (Flemyng 2023; Higgins 2022b). Any disagreements were resolved by discussion or by involving another review author (JVAF). We assessed the risk of bias according to the following domains, focusing on the effect of assignment to the intervention at baseline:

- the randomization process;
- deviations from intended interventions;
- missing outcome data;

- measurement of the outcome;
- selection of the reported results.

Answers to signaling questions and supporting information collectively lead to a domain-level judgment of 'low risk,' 'some concerns,' or 'high risk' of bias. These domain-level judgments informed an overall risk of bias judgment for the outcome based on the algorithm in the guidance document of RoB 2.

We provided a quote from the study report together with a justification for our judgment in the risk of bias table. We aimed to source published protocols in order to assess selective reporting. Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the risk of bias table. When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome. We made summary assessments of the risk of bias for each important outcome across domains and an overall narrative across studies.

We used a Microsoft Excel spreadsheet tool to manage data supporting the answers to the signaling questions and risk of bias judgments (Microsoft Excel 2023). All of these data are publicly available as supplementary material in the Open Science Framework platform.

Measures of treatment effect

We expressed dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs). We expressed continuous data as mean differences (MDs) with 95% CIs, unless different studies used different measures to assess the same outcome, in which case we re-expressed the data as standardized mean differences (SMDs) with 95% CIs.

Unit of analysis issues

Where multiple trial arms were reported in a single trial, we would include only the treatment arms relevant to the review topic. Had two comparisons from the same trial (e.g. drug A versus placebo and drug B versus placebo) been combined in the same meta-analysis, we would have followed the guidance in Section 6.2 of the *Cochrane Handbook* (Higgins 2022a). Our preferred approach was to combine groups to create a single pair-wise comparison.

Dealing with missing data

We contacted investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data where possible (e.g. when a study was available as an abstract only).

Where numerical outcome data were missing, such as standard deviations or correlation coefficients, and they could not be obtained from the authors, we calculated them from other available statistics such as 95% CI or P values, according to the methods described in the *Cochrane Handbook* (Higgins 2022a). If this was not possible, and the missing data could have introduced serious bias, we planned to explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Assessment of heterogeneity

We identified heterogeneity (inconsistency) through visual inspection of the forest plots to assess the amount of overlap of CIs, and by using the I^2 statistic, which quantifies inconsistency across studies to assess the impact of heterogeneity on the meta-analysis. We interpreted the I^2 statistic as follows (Deeks 2022):

- 0% to 40%: may not be important;
- 30% to 60%: may indicate moderate heterogeneity;
- 50% to 90%: may indicate substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

In the case of heterogeneity, we attempted to identify possible reasons for it by examining individual study and subgroup characteristics.

Assessment of reporting biases

We attempted to obtain study protocols to assess selective outcome reporting. When we included 10 or more studies in a meta-analysis, we used funnel plots to assess small-study effects (Page 2022). Several explanations can be offered for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to study size, poor methodological design (and hence bias of small studies), and publication bias. We therefore used caution in our interpretation of results.

Data synthesis

Unless there was good evidence for homogeneous effects across studies, we summarized data using a random-effects model. We interpreted random-effects meta-analyses with due consideration of the whole distribution of effects. We also performed statistical analyses according to the statistical guidelines contained in the *Cochrane Handbook* (Higgins 2022a). For dichotomous outcomes, we used the Mantel-Haenszel method. For continuous outcomes, we used the inverse variance method. We used Review Manager Web software to perform the analyses (RevMan Web 2022).

Subgroup analysis and investigation of heterogeneity

We expected the following characteristics to potentially introduce clinical heterogeneity, and carried out subgroup analyses to investigate interactions.

- Type of *Serenoa repens* preparation (hexanic versus non-hexanic extract)
- Participant age (less than 65 years versus 65 years or more)
- Severity of LUTS based on IPSS (score less than or equal to 19 [moderately symptomatic] versus greater than 19 [severely symptomatic])

These subgroup analyses are based on the following observations.

- Other reviews highlight that there might be different effects of different *Serenoa repens* extracts (Russo 2021).
- Age is a well-known risk factor for BPH surgery. Older men have a higher rate of postoperative complications compared with younger men (Bhojani 2014; Pariser 2015). The age cut-off is based on the World Health Organization's (WHO) definition of old age (WHO 2002).
- The relationship between changes in IPSS scores and patient global ratings of improvement is influenced by the baseline scores (Barry 1995).

Sensitivity analysis

We performed sensitivity analyses to explore the influence of the following factors (when applicable) on effect size:

- restricting the analysis to RCTs by considering risk of bias, restricting to studies with an overall low risk of bias.

If the sensitivity analyses provided moderate- to high-certainty evidence, we would draw our main conclusions (summary of findings tables) based on this estimate. This is a similar approach to the previous version of this review (Tacklind 2012).

Summary of findings and assessment of the certainty of the evidence

We presented the overall certainty of the evidence for each outcome according to the GRADE approach (Guyatt 2008). For each comparison, two review authors (JVAF and LT) independently rated the certainty of the evidence for each outcome as 'high,' 'moderate,' 'low,' or 'very low,' using GRADEpro GDT software (GRADEpro GDT). Any discrepancies were resolved by consensus or if needed by arbitration from a third review author (JHJ). For each comparison, we presented a summary of the evidence for the main outcomes in the summary of findings table, which provides key information about the best estimate of the magnitude of effect in relative terms and absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of our overall confidence in the effect estimates for each outcome (Schünemann 2022).

We considered five criteria, not only related to internal validity (overall risk of bias, inconsistency, imprecision, and publication bias) but also external validity (directness of results), for downgrading the certainty of the evidence for a specific outcome (Schünemann 2022). We included the following comparisons.

- *Serenoa repens* versus placebo or no intervention
- *Serenoa repens* in combination with other phytotherapy versus placebo or no intervention

Each summary of findings table includes the following outcomes.

- Urologic symptom scores
- Quality of life
- Adverse events

We followed GRADE guidance for detailed footnotes and language to describe the certainty of the evidence (Santesso 2016; Santesso 2020).

RESULTS

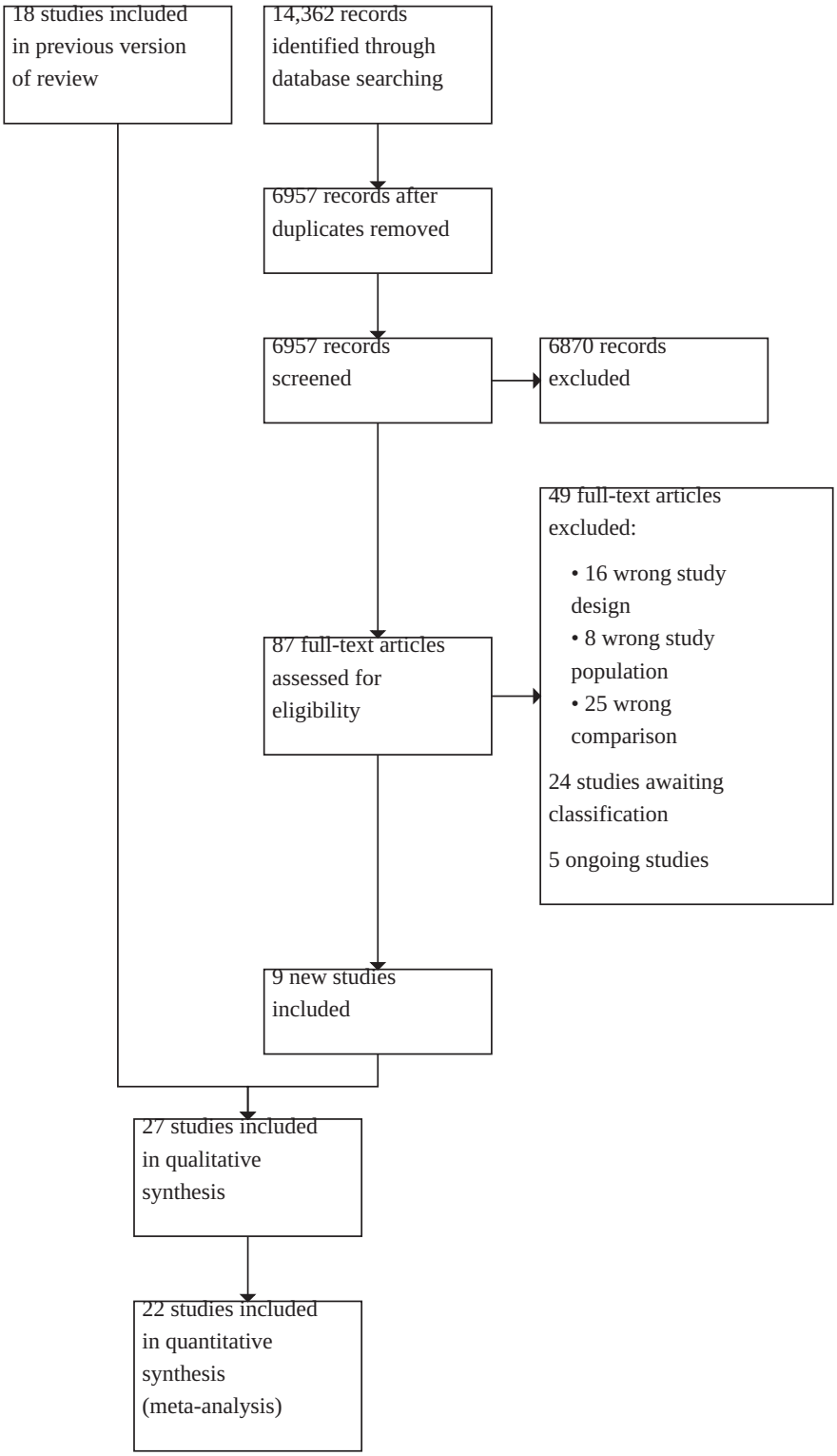
Description of studies

Results of the search

For this update, we narrowed the focus of the review questions, focusing on the effects of *Serenoa repens* versus placebo or in combination with other psychotherapeutic agents versus placebo. As a result, we excluded 7 of 32 studies included in the previous update because they were not included in this focused review question (Braeckman 1997; Carraro 1996; Debruyne 2002; Engelmann 2006; Pannunzio 1986; Roveda 1994; Sökeland 1997), and moved another 7 older studies to awaiting classification because of missing full text (see Characteristics of studies awaiting classification) (Cukier 1985; Emili 1983; Gabric 1987; Löbelenz 1992; Mattei 1990; Mohanty 1999; Tasca 1985). A total of 18 studies from the previous version of this review were relevant to our review question.

We conducted a de novo search and identified 14,362 records from electronic databases. We found no relevant records in additional sources. After removing duplicates, we screened the titles and abstracts of the remaining 6957 records, of which 6870 were excluded. We assessed 87 full-text articles and excluded 49 records for various reasons (see Excluded studies). We identified nine new studies through this search (Argirović 2013; BASTA 2010; Carbin 1990; Coulson 2013; Hong 2009; Iacono 2015; Ryu 2015; Sudeep 2020; Ye 2019). Considering the 18 relevant studies from the previous version of the review, we included 27 studies with 4656 participants in this update. A PRISMA flow diagram illustrating the flow of literature through the assessment process is presented in Figure 1.

Figure 1. Study flow diagram.



Included studies

See Characteristics of included studies and Table 1.

Study design and settings

All studies were RCTs. The median sample size was 100 participants (interquartile range 61 to 212), and the median follow-up was 24 weeks (interquartile range 12 to 52). Studies were conducted in Serbia (Argirović 2013), the USA (Barry 2011; Bent 2006; Gerber 2001; Marks 2000; Preuss 2001), Germany (Bauer 1999; Metzker 1996), Italy (Boccafoschi 1983; Iacono 2015; Mandressi 1983; Morgia 2014), France (Champault 1984; Descotes 1995; Glémain 2002), Turkey (Hizli 2007), Korea (Hong 2009; Ryu 2015), the UK (Reece Smith 1986), China (Shi 2008; Ye 2019), India (Sudeep 2020), Sweden (Carbin 1990), Australia (Coulson 2013; Willetts 2003), and Russia (Lopatkin 2005), and one study was conducted in more than one country (BASTA 2010).

Participants

Most studies included men aged > 50 (mean age range 52 to 68), and a few studies included men with a mean age > 65 (Boccafoschi 1983; Descotes 1995; Glémain 2002; Lopatkin 2005; Marks 2000; Reece Smith 1986). Most studies included men with moderate urologic symptoms (IPSS range 8 to 19), with only three studies including a mean score of 20 or more (Iacono 2015; Morgia 2014; Sudeep 2020). Less than half of the studies reported prostate size, which was mostly small to moderate size (mean size range 26.1 to 58.5 mL) (Argirović 2013; Bauer 1999; Bent 2006; Glémain 2002; Hizli 2007; Hong 2009; Lopatkin 2005; Marks 2000; Morgia 2014; Ryu 2015; Shi 2008; Ye 2019).

Interventions and comparisons

We included 27 studies for the following comparisons.

- *Serenoa repens* versus placebo (19 studies)
  - Nine studies included the hexanic extract of *Serenoa repens* (BASTA 2010; Boccafoschi 1983; Champault 1984; Descotes 1995; Glémain 2002; Hizli 2007; Mandressi 1983; Reece Smith 1986; Ryu 2015).
  - The other studies included other formulations: Prostamol Uno (Argirović 2013, BASTA 2010), Prosta-Urgenin Uno (Barry 2011), Talso Uno (Bauer 1999), carbon dioxide extract (Bent 2006; Willetts 2003), Prostablex (Shi 2008), VISPO/SPO (Sudeep 2020), or other unspecified compounds of *Serenoa repens* (Gerber 2001; Hong 2009; Ye 2019).
- Phytotherapy containing *Serenoa repens* versus placebo (8 studies)
  - Curbicin: pumpkin seed oil and *Serenoa repens* (Carbin 1990)
  - ProstaEZE Max: pumpkin seed oil, *Epilobium*, lycopene, pygeum, and *Serenoa repens* (Coulson 2013)
  - Tradaximina: *Eisenia*, *Tribulus*, chitosan oligosaccharide (Biovis), and *Serenoa repens* (Iacono 2015)
  - PRO 160/120: sabal urtica and *Serenoa repens* (Lopatkin 2005)
  - Lipoidal extract of *Serenoa repens* with other phytotherapeutics (Marks 2000)
  - Prostagutt forte: sabal urtica and *Serenoa repens* (Metzker 1996)
  - Profluss: selenium, lycopene, and *Serenoa repens* (Morgia 2014)
  - Cernitin AF: Cernitin, B-sitoesterol, vitamin E, and *Serenoa repens* (Preuss 2001)

The most commonly used daily dose was 320 mg daily, either as a single dose or 160 mg twice daily. For the comparisons to placebo, one study did not specify the dosing (Shi 2008), and one study used a 200 mg extract twice daily (400 mg daily total; Sudeep 2020). Whereas the doses of *Serenoa repens* in combined treatment with another phototherapy usually ranged from 286 to 320, one study included a higher dose of 480 mg daily (Carbin 1990).

Co-interventions were described in five studies, and in all cases included tamsulosin (Argirović 2013; Glémain 2002; Hizli 2007; Morgia 2014; Ryu 2015).

Outcomes

Twenty-one studies reported data on urologic symptoms (Argirović 2013; Barry 2011; BASTA 2010; Bauer 1999; Bent 2006; Coulson 2013; Gerber 2001; Glémain 2002; Hizli 2007; Hong 2009; Iacono 2015; Lopatkin 2005; Marks 2000; Metzker 1996; Morgia 2014; Preuss 2001; Ryu 2015; Shi 2008; Sudeep 2020; Willetts 2003; Ye 2019), but only a subset of 12 of these studies reported data on quality of life (Argirović 2013; Barry 2011; Bent 2006; Gerber 2001; Glémain 2002; Hizli 2007; Hong 2009; Metzker 1996; Morgia 2014; Ryu 2015; Willetts 2003; Ye 2019). Twenty-four studies reported data on adverse events (Argirović 2013; Barry 2011; BASTA 2010; Bauer 1999; Bent 2006; Boccafoschi 1983; Carbin 1990; Champault 1984; Coulson 2013; Descotes 1995; Gerber 2001; Glémain 2002; Hizli 2007; Lopatkin 2005; Marks 2000; Metzker 1996; Morgia 2014; Preuss 2001; Reece Smith 1986; Ryu 2015; Shi 2008; Sudeep 2020; Willetts 2003; Ye 2019). One study did not report any outcomes relevant to this review (Mandressi 1983).

Funding sources

Ten studies were funded by the pharmaceutical industry (BASTA 2010; Coulson 2013; Gerber 2001; Lopatkin 2005; Marks 2000; Morgia 2014; Preuss 2001; Sudeep 2020; Willetts 2003; Ye 2019); two studies were funded by government agencies (Barry 2011; Bent 2006); and the remaining studies did not specify funding sources.

Excluded studies

See Characteristics of excluded studies.

We excluded 49 studies for the following reasons.

- Sixteen studies were non-randomized studies or had no control group (Al-Shukri 2000; Alcaraz 2022; Authié 1987; Di Maida 2020; Gerber 1998; Giannakopoulos 2002; Giulianelli 2012; Gurzhenko 2020; Ju 2015: Pavone 2010; Popa 2005; Sinescu 2011; Stepanov 1999; Taieb 2010; Vinarov 2010; Zlotta 2005).
- Eight studies included the wrong study population (i.e. men with prostatitis or focus on changes in prostatic tissue) (Aliaev 2009; Di Silverio 1992; Morgia 2013; Pecoraro 2004; Suardi 2014; Vela-Navarrete 2005; Veltri 2002; Weisser 1997).
- Twenty-five studies compared *Serenoa repens* with active components or different doses (Adriazola Semino 1992; Ali 2020; Bartsch 1998; Braeckman 1997; Cai 2013; Carraro 1996; Comar 1986; CTRI/2012/10/003049; CTRI/2020/09/027521; Debruyne 2002; Duborija-Kovacevic 2010; Engelmann 2006; EUCTR2011-005307-33-FR; Grasso 1995; Guzman 2016; Hamdv 1997; Latil 2015; Morgia 2018; NCT00797394; Pannunzio 1986;

Romaniuk 2013; Roveda 1994; Sökeland 1997; Strauch 1994; Yamanishi 2004).

Studies awaiting classification

See Characteristics of studies awaiting classification.

We identified 24 studies (7 from the previous version of the review) with no available full text (Aliaev 2007; Anonymous 2005; Bercovich 2010; Buck 2002; Carreras 1987; Cukier 1985; Dathe 1991; Diehl 2005; Emili 1983; Fabricius 1993; Gabric 1987; Green 2000; Löbelenz 1992; Martínez 1987; Mattei 1990; Mohanty 1999; Neumann 1993; Razumov 2001; Sekikawa 2020; Tasca 1985; Tkachuk 2002; Vahlensieck 1993; Vinarov 2009; Wehr 1995).

Ongoing studies

We also identified five ongoing studies (ISRCTN84633360; JPRN-UMIN000023274; JPRN-UMIN000027902; NCT00497939; NCT02121613). See Characteristics of ongoing studies.

Risk of bias in included studies

The risk of bias assessments for each result in Summary of findings 1 and Summary of findings 2, including all domain judgments and support for judgment, is located in the risk of bias section, at the side of all forest plots. The signaling questions' responses can be found on the Open Science Framework storage (osf.io/65m8e).

The risk of bias of outcomes across all results and domains was mostly 'some concerns' due to a lack of prespecification of outcomes and analysis plans. We assessed three studies as at overall low risk of bias (Barry 2011; Bent 2006; Sudeep 2020). We assessed three studies as at high risk of bias due to missing outcome data or bias in the measurement of the outcome (due to lack of blinding), in addition to some concerns regarding selective reporting (Hizli 2007; Hong 2009; Ryu 2015).

Effects of interventions

See: **Summary of findings 1** *Serenoa repens* compared to placebo or no intervention; **Summary of findings 2** *Serenoa repens* in combination with other phytotherapy versus placebo or no intervention

1. *Serenoa repens* versus placebo or no intervention (short term)

Results for this comparison are based on predefined sensitivity analyses limited to studies at low risk of bias. See Summary of findings 1.

1.1. Urologic symptoms

Serenoa repens results in little to no difference in urologic symptoms at short-term follow-up (3 to 6 months; mean difference (MD) −0.90, 95% confidence interval (CI) −1.74 to −0.07; I^2 = 68%; 9 studies, 1681 participants; high-certainty evidence). All heterogeneity was explained by a single study of 304 participants that compared *Serenoa repens* to placebo and showed a difference in IPSS scores of −2.77 (95% CI −3.71 to −1.83) (Ye 2019), which is statistically significant but clinically unimportant. We did not downgrade the certainty of the evidence for inconsistency, considering a minimally contextualized approach and our predefined MCID. We also did not downgrade for risk of bias, since our main analysis was based on a sensitivity analysis excluding studies at high risk of bias (Analysis 1.1). However, this analysis did not materially differ from the analysis including all studies (Analysis 1.2).

One study with 101 participants found a reduction of urologic symptoms with *Serenoa repens* (P < 0.01) (Bauer 1999). Another study with 1011 participants found a decrease in urologic symptoms with *Serenoa repens* compared to placebo at 12 months follow-up (P = 0.04) (BASTA 2010).

1.2. Quality of life

Serenoa repens results in little to no difference in quality of life at short-term follow-up (3 to 6 months, MD −0.20, 95% CI −0.40 to −0.00; I^2 = 39%; 5 studies, 1001 participants; high-certainty evidence). We did not downgrade the certainty of the evidence for risk of bias since, our main analysis was based on a sensitivity analysis excluding studies at high risk of bias (Analysis 1.3). However, this analysis did not materially differ from the analysis including all studies (Analysis 1.4).

1.3. Adverse events

Serenoa repens probably results in little to no difference in adverse events (1 to 17 months, risk ratio (RR) 1.01, 95% CI 0.77 to 1.31; I^2 = 18%; 12 studies, 2399 participants; moderate-certainty evidence). Based on 164 cases per 1000 men in the placebo group, this corresponds to 2 more (38 fewer to 51 more) per 1000 men in the *Serenoa repens* group. We did not downgrade the certainty of the evidence for risk of bias, since our main analysis was based on a sensitivity analysis excluding studies at high risk of bias (Analysis 1.5). However, this analysis did not materially differ from the analysis including all studies (Analysis 1.6). Nonetheless, we downgraded one level due to imprecision.

We did not incorporate three studies into the meta-analysis because they reported no adverse events in either the treatment or control group (Bauer 1999; Shi 2008; Sudeep 2020).

The most commonly reported adverse events were headache, gastrointestinal disorders (e.g. diarrhea, nausea and vomiting, stomach upset), upper respiratory symptoms (e.g. rhinitis), ejaculation disorders, musculoskeletal symptoms (e.g. arthralgia in the knees and muscular arm pain), and dizziness. Many of these symptoms may be attributable to co-interventions (alpha-blockers).

Few studies in each category precluded subgroup analyses according to age, symptom severity, prostate size, and type of extract (see Included studies).

1.4. Subgroup analysis

1.4.1. Type of *Serenoa repens* preparation

We were unable to detect differences in urologic symptoms when comparing the effects of hexanic versus non-hexanic extract (P = 0.23, see Analysis 1.7).

1.4.2. Other subgroup analyses

Few studies in each category precluded subgroups based on participant age and severity of lower urinary tract symptoms (see Included studies).

1.5. Sensitivity analysis

We conducted a sensitivity analysis excluding studies at overall high risk of bias. Given that these analyses provided moderate- to high-certainty evidence, we incorporated them into the main results and summary of findings table (see above outcomes 1.1, 1.2, and 1.3 and Analysis 1.1; Analysis 1.3; Analysis 1.5).

2. *Serenoa repens* versus placebo or no intervention (long term)

2.1. Urologic symptoms

Serenoa repens results in little to no difference in urologic symptoms at long-term follow-up (12 to 17 months, MD 0.07, 95% CI −0.75 to 0.88; I^2 = 34%; 3 studies, 898 participants; high-certainty evidence). We did not downgrade the certainty of the evidence for risk of bias, since our main analysis was based on a sensitivity analysis excluding studies at high risk of bias (Analysis 1.8). However, this analysis did not materially differ from the analysis including all studies (Analysis 1.9).

2.2. Quality of life

Serenoa repens results in little to no difference in quality of life at long-term follow-up (12 to 17 months, MD −0.11, 95% CI −0.41 to 0.19; I^2 = 65%; 3 studies, 882 participants; high-certainty evidence). We did not downgrade the certainty of the evidence for risk of bias, since our main analysis was based on a sensitivity analysis excluding studies at high risk of bias (Analysis 1.10). However, this analysis did not materially differ from the analysis including all studies (Analysis 1.11).

2.3. Adverse events

None of the included studies reported this outcome.

2.4. Subgroup analysis

Few studies in each category precluded these subgroup analyses (see Included studies).

2.5. Sensitivity analysis

We conducted a sensitivity analysis excluding studies at overall high risk of bias. Given that these analyses provided high-certainty evidence, we incorporated them into the main results and summary of findings table (see above outcomes 2.1 and 2.2 and Analysis 1.8; Analysis 1.10).

3. *Serenoa repens* in combination with other phytotherapy versus placebo or no intervention

See Summary of findings 2.

3.1. Urologic symptoms

Different phytotherapeutic agents that include *Serenoa repens* may result in little to no difference in urologic symptoms compared to placebo at short-term follow-up (12 to 24 weeks, MD −2.41, 95% CI −4.54 to −0.29; I^2 = 67%; 4 studies, 460 participants; low-certainty evidence; Analysis 2.1). The certainty of the evidence is low due to imprecision and inconsistency.

3.1.1. Studies not included in meta-analysis

One study with 60 participants found a 36% reduction in the total IPSS median score in the active group (*Serenoa repens*, lycopene, *Prunus africana*, *Epilobium parviflorum*, and *Cucurbita pepo*) compared to 8% in the placebo group at three months follow-up (P < 0.05) (Coulson 2013). Another study with 225 participants found a greater decrease in IPSS scores for combination therapy (*Serenoa repens*, lycopene, and selenium) compared to control at 12-month follow-up (median change 2.0, range −3 to −1, P < 0.01) (Morgia 2014). One study reported as an abstract did not provide comparative data (only a decrease in IPSS in the intervention group) (Iacono 2015).

3.2. Quality of life

We are very uncertain about the effects of these agents on quality of life (very low-certainty evidence). In one study with 40 participants, 84.2% of participants in the intervention group had improvements in their quality of life after six months of treatment compared to 11.1% of participants in the placebo group (P < 0.001) (Metzker 1996). Another study with 225 participants found little to no difference in quality of life scores (median change 0, range −0.1 to 1) (Morgia 2014). The certainty of the evidence is very low due to risk of bias, inconsistency, and imprecision.

3.3. Adverse events

Different phytotherapeutic agents that include *Serenoa repens* may result in little to no difference in occurrence of adverse events; however, the CIs included substantial benefits and harms (12 to 48 weeks, RR 0.91, 95% CI 0.58 to 1.41; I^2 = 0%; 4 studies, 481 participants; low-certainty evidence; Analysis 2.2). Based on 132 cases per 1000 men in the placebo group, this corresponds to 12 fewer (55 fewer to 54 more) per 1000 men in the combined phytotherapeutic agents with *Serenoa repens* group. We did not incorporate two studies into the meta-analysis because they reported no adverse events in either the treatment or control group (Carbin 1990; Coulson 2013). The certainty of the evidence is low due to severe imprecision.

Another study with 225 participants reported no significant differences in treatment-related adverse events (P = 0.67) (Morgia 2014).

The most commonly reported adverse events were headache, gastrointestinal disorders (e.g. diarrhea, nausea and vomiting, dyspepsia), upper respiratory symptoms (e.g. rhinitis), ejaculation disorders, musculoskeletal symptoms (e.g. arthralgia in the knees and pain), and dizziness. Many of these symptoms may be attributable to co-interventions (alpha-blockers).

3.4. Subgroup analysis

Few studies in each category precluded these subgroup analyses (see Included studies).

3.5. Sensitivity analysis

We were unable to conduct a sensitivity analysis because the meta-analyses did not include studies at overall high risk of bias.

DISCUSSION

Summary of main results

For this update, we narrowed the review question and included 27 studies (of which 9 were new studies) with 4656 participants, 19 studies comparing *Serenoa repens* with placebo and 8

studies comparing *Serenoa repens* in combination with other phytotherapeutic agents versus placebo.

***Serenoa repens* versus placebo or no intervention**

Based on predefined sensitivity analyses limited to studies at low risk of bias, *Serenoa repens* results in little to no difference in urologic symptoms and quality of life at short-term follow-up. *Serenoa repens* probably results in little to no difference in adverse events.

Serenoa repens results in little to no difference in urologic symptoms and quality of life at long-term follow-up. There were no data on long-term adverse events for this comparison.

***Serenoa repens* in combination with other phytotherapy versus placebo or no intervention**

Phytotherapeutic agents with various agents, including *Serenoa repens*, may result in little to no difference in urologic symptoms compared to placebo at short-term follow-up. We are very uncertain about the effects of these agents on quality of life. These agents may result in little to no difference in the occurrence of adverse events; however, the confidence intervals included substantial benefits and harms.

Overall completeness and applicability of evidence

While there has been a growing body of research since the last update of this review, our conclusions remain unchanged. Clinical practice guidelines have since deprioritized *Serenoa repens* in their treatment pathways.

- The 2021 Guideline of the American Urological Association focuses on the treatment of LUTS attributed to BPH using common surgical techniques and minimally invasive surgical therapies, thus the information on the different types of medical interventions is not deepened, much less the use of *Serenoa repens* (Lerner 2021).
- A previous version of this guideline from 2010 mentioned that the available data do not suggest that *Serenoa repens* has a clinically significant effect on LUTS secondary to BPH (McVary 2011). Furthermore, it adds that no dietary supplement, combined herbal medicine, or other unconventional therapy is recommended to manage LUTS secondary to BPH due to the paucity of high-quality published trials (McVary 2011).
- The European Association of Urology guidelines on the management of non-neurogenic male LUTS recommends several therapeutic and surgical interventions in men with BPH (EAU 2022). This guideline recommends offering the hexane extract of *Serenoa repens* to men with LUTS who want to avoid possible adverse events, especially those related to sexual function (weak recommendation), informing the patient that the magnitude of efficacy may be modest (strong recommendation) (EAU 2022). Our review offers a further cautionary note about the use of *Serenoa repens.*
- The Korean Urological Association guidelines for the evidence-based diagnosis and treatment of BPH provide basic information on diagnostic testing, drug therapy, and surgical treatment, but do not mention *Serenoa repens* as a management option (Yeo 2016).

Considering cut-off points of 40 mL and 80 mL for small, medium, and large prostates, all studies included men with small- to average-size prostates and moderate urologic symptoms. We found no studies in men with large prostates, and only a few studies of men with more severe urologic symptoms (see Table 1). This evidence is therefore only be applicable to this population (Franco 2023).

Few studies included co-interventions such as tamsulosin (Argirović 2013; Glémain 2002; Hizli 2007; Morgia 2014; Ryu 2015). However, this did not contribute to statistical heterogeneity when analyzing the outcomes of adverse events. Nonetheless, many of those adverse events described narratively (see footnotes in Analysis 1.5 and Analysis 2.2) include dizziness and ejaculatory disorders, which are typically associated with alpha-blockers (Mansbart 2022).

Quality of the evidence

The overall certainty of the evidence was high for the main comparison, except for adverse events, for which we identified imprecision. We followed a similar approach to previous versions of this review, excluding studies at high risk of bias from our primary analysis. For the second comparison, however, we had additional concerns about precision and inconsistency across outcomes.

Not all studies provided full details of critical outcomes such as urologic symptoms, quality of life, and adverse events, which would be desirable considering men's values and preferences (Dahm 2021).

Potential biases in the review process

We could not locate the full text of seven of the original studies in the review, which could not be re-analyzed using the updated methods (Cukier 1985; Emili 1983; Gabric 1987; Löbelenz 1992; Mattei 1990; Mohanty 1999; Tasca 1985). We contacted the original authors of the review and updates, and they did not hold copies of those studies. In addition to our existing library resources, we also posted a task in Cochrane TaskExchange (currently known as Cochrane Engage) to ask for help on this issue, without success. Based on the characteristics described in the previous version of the review (and available in the Characteristics of studies awaiting classification section), these studies primarily focused on non-validated outcome measures and Q_{max}, which would not have contributed to the main analyses of this review. Moreover, we identified 17 additional references that were also assessed as awaiting classification because we could not retrieve a full text to determine their eligibility. These references were mostly from the 1980s and 1990s, so it is likely that their outcomes would not be able to be incorporated into our main analyses.

Although reporting of the timing of adverse events has improved in recent years, we were unable to identify the timing of their occurrence in the included reports, as required by the CONSORT-Harms statement (Junqueira 2023; Phillips 2019). We therefore did not disaggregate data according to the length of follow-up of the studies, since most of them described adverse events that were related to treatment initiation (gastrointestinal intolerance) or the effect of co-interventions (e.g. dizziness and hypotension due to tamsulosin), which resulted in our assumption that they were all short term.

We could not incorporate the results of five studies in our meta-analyses due to missing data (missing standard deviation or standard error), but we reported these results separately (BASTA 2010; Bauer 1999; Coulson 2013; Iacono 2015; Morgia 2014). Finally, we could not perform many predefined funnel plots and subgroup and sensitivity analyses due to the scarcity of data, low heterogeneity across comparisons, and few trials included in each comparison.

Agreements and disagreements with other studies or reviews

A recent systematic review and network meta-analysis on the same topic included 22 randomized clinical trials with multiple comparisons of hexanic and non-hexanic extracts of *Serenoa repens* with alpha-adrenergic agonists and placebo (Russo 2021). While the authors concluded that there were clinically insignificant improvements in IPSS at 12 weeks, their confidence intervals included little to no difference compared to placebo (MD −0.47, 95% CI −2.69 to 1.74 for hexanic extract; MD −1.69, 95% CI −4.36 to 0.98 for non-hexanic extract). Moreover, the authors reported greater improvements in hexanic extracts than in non-hexanic extracts. Still, the quantitative estimate included little to no difference between subgroups, similar to the findings of our review (MD −2.16, 95% CI −5.64 to 1.30). Finally, this review was limited due to fewer studies comparing *Serenoa repens* with placebo (7 in that review compared to 15 in ours), with a substantial imprecision in their results.

Another systematic review included seven randomized clinical trials comparing hexanic extract (restricted to the Permixon formulation) with placebo for the outcomes of nocturia, Q_{max},and adverse events, but did not assess IPSS (Novara 2016). The authors found a decrease in the episodes of nocturia that may be clinically insignificant (MD −0.31, range −0.59 to −0.03); however, the findings on adverse events were similar to ours.

Finally, a systematic review including 15 randomized clinical trials and 12 observational studies comparing Permixon with placebo assessed nocturia, Q_{max},and adverse events, but did not assess IPSS (Vela-Navarrete 2018). This review also found a small reduction in nocturia that may be clinically insignificant (MD −0.64, range −0.98 to −0.31), and similar results regarding adverse events.

Whereas the dose for almost all studies was 320 mg daily, higher concentrations may result in small but positive improvements in LUTS symptoms, as described in a single study that included doses of 400 mg (Sudeep 2020). The data were insufficient to conduct a subgroup analysis.

AUTHORS' CONCLUSIONS

Implications for practice

Serenoa repens alone provides little to no benefits for men with lower urinary tract symptoms due to benign prostatic enlargement. There is more uncertainty about the role of *Serenoa repens* in combination with other phytotherapeutic agents.

Implications for research

Considering the uncertainties about the effects of *Serenoa repens* in higher doses or combined with other herbal treatments, future high-quality, placebo-controlled randomized controlled trials are needed in this area that focus on patient-important outcomes, including urologic symptoms, quality of life, and adverse events.

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Editorial and peer-reviewer contributions

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The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Philipp Dahm, MD, Urology Section, Minneapolis VA Health Care System, Minneapolis, Minnesota, USA;
- Handling Editor (selected peer reviewers, provided editorial guidance to authors, and made editorial decisions): Muhammad Imran Omar, MD, University of Aberdeen, Aberdeen, UK;
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Jennifer Mariano, Cochrane Urology, USA;
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The authors JVAF and JHJ are contact editors for the Cochrane Urology Group but were excluded from the editorial processing of this article.

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* Indicates the major publication for the study

Article 2: Transurethral Microwave Thermotherapy

(Cochrane review update)[3]

In this update, we identified no new RCTs, but we included data from studies excluded in the previous version of this review. We included 16 trials with 1919 participants, with a median age of 69 and moderate lower urinary tract symptoms. The certainty of the evidence for most comparisons was moderate-to-low due to an overall high risk of bias across studies and imprecision (few participants and events).

TUMT versus TURP

Based on data from four studies with 306 participants, when compared to TURP, TUMT probably results in little to no difference in urologic symptom scores measured by the International Prostatic Symptom Score (IPSS) on a scale from 0 to 35, with higher scores indicating worse symptoms at short-term follow-up (mean difference (MD) 1.00, 95% confidence interval (CI) −0.03 to 2.03; moderate certainty). There is likely to be little to no difference in the quality of life (MD −0.10, 95% CI −0.67 to 0.47; 1 study, 136 participants, moderate certainty). TUMT likely results in fewer major adverse events (RR 0.20, 95% CI 0.09 to 0.43; 6 studies, 525 participants, moderate certainty); based on 168 cases per 1000 men in the TURP group, this corresponds to 135 fewer (153 to 96 fewer) per 1000 men in the TUMT group. TUMT, however, probably results in a large increase in the need for retreatment (risk ratio (RR) 7.07, 95% CI 1.94 to 25.82; 5 studies, 337 participants, moderate certainty) (usually by repeated TUMT or TURP); based on zero cases per 1000 men in the TURP group, this corresponds to 90 more (40 to 150 more) per 1000 men in the TUMT group. There may be little to no difference in erectile function between these interventions (RR 0.63, 95% CI 0.24 to 1.63; 5 studies, 337 participants; low certainty). However, TUMT may result in fewer cases of ejaculatory dysfunction compared to TURP (RR 0.36, 95% CI 0.24 to 0.53; 4 studies, 241 participants; low certainty).

TUMT versus sham

Based on data from four studies with 483 participants we found that, when compared to sham, TUMT probably reduces urologic symptom scores using the IPSS at short-term follow-up (MD −5.40, 95% CI −6.97 to −3.84; moderate certainty). TUMT may cause little to no difference in the quality of life (MD −0.95, 95% CI −1.14 to −0.77; 2 studies, 347 participants; low certainty) as measured by the IPSS quality-of-life question on a scale from 0 to 6, with higher scores indicating a worse quality of life. We are very uncertain about the effects on major adverse events, since most studies reported no events or isolated lesions of the urinary tract. TUMT may also reduce the need for retreatment compared to sham (RR 0.27, 95% CI 0.08 to 0.88; 2 studies, 82 participants, low certainty); based on 194 retreatments per 1000 men in the sham group, this corresponds to 141 fewer (178 to 23 fewer) per 1000 men in the TUMT group. We are very uncertain of the effects on erectile and ejaculatory function (very low certainty), since we found isolated reports of impotence and ejaculatory disorders (anejaculation and hematospermia).

There was no data available for the comparisons of TUMT versus convective radiofrequency water vapour therapy, prostatic urethral lift, prostatic arterial embolisation or temporary implantable nitinol device.

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[3]Franco JV, Garegnani L, Escobar Liquitay CM, Borofsky M, Dahm P. Transurethral microwave thermotherapy for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia. Cochrane Database Syst Rev. 2021 Jun 28;6(6):CD004135. doi: 10.1002/14651858.CD004135.pub4. PMID: 34180047; PMCID: PMC8236484. *Impact Factor 2021 11.874 - Cited 8 times (07.07.2023)*

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Transurethral microwave thermotherapy for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (Review)

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[Intervention Review]

Transurethral microwave thermotherapy for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia

Juan VA Franco[1], Luis Garegnani[2], Camila Micaela Escobar Liquitay[3], Michael Borofsky[4], Philipp Dahm[5]

[1]Associate Cochrane Centre, Instituto Universitario Hospital Italiano de Buenos Aires, Buenos Aires, Argentina. [2]Research Department, Instituto Universitario Hospital Italiano, Buenos Aires, Argentina. [3]Central Library, Instituto Universitario Hospital Italiano, Buenos Aires, Argentina. [4]Department of Urology, University of Minnesota, Minneapolis, Minnesota, USA. [5]Urology Section, Minneapolis VA Health Care System, Minneapolis, Minnesota, USA

Contact: Juan VA Franco, juan.franco@hospitalitaliano.org.ar.

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ABSTRACT

Background

Transurethral resection of the prostate (TURP) has been the gold-standard treatment for alleviating urinary symptoms and improving urinary flow in men with symptomatic benign prostatic hyperplasia (BPH). However, the morbidity of TURP approaches 20%, and less invasive techniques have been developed for treating BPH. Transurethral microwave thermotherapy (TUMT) is an alternative, minimally-invasive treatment that delivers microwave energy to produce coagulation necrosis in prostatic tissue. This is an update of a review last published in 2012.

Objectives

To assess the effects of transurethral microwave thermotherapy for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia.

Search methods

We performed a comprehensive search using multiple databases (the Cochrane Library, MEDLINE, Embase, Scopus, Web of Science, and LILACS), trials registries, other sources of grey literature, and conference proceedings published up to 31 May 2021, with no restrictions by language or publication status.

Selection criteria

We included parallel-group randomized controlled trials (RCTs) and cluster-RCTs of participants with BPH who underwent TUMT.

Data collection and analysis

Two review authors independently assessed studies for inclusion at each stage and undertook data extraction and risk of bias and GRADE assessments of the certainty of the evidence (CoE). We considered review outcomes measured up to 12 months after randomization as short-term and beyond 12 months as long-term. Our main outcomes included: urologic symptoms scores, quality of life, major adverse events, retreatment, and ejaculatory and erectile function.

Main results

In this update, we identified no new RCTs, but we included data from studies excluded in the previous version of this review. We included 16 trials with 1919 participants, with a median age of 69 and moderate lower urinary tract symptoms. The certainty of the evidence for most comparisons was moderate-to-low, due to an overall high risk of bias across studies and imprecision (few participants and events).

TUMT versus TURP

Based on data from four studies with 306 participants, when compared to TURP, TUMT probably results in little to no difference in urologic symptom scores measured by the International Prostatic Symptom Score (IPSS) on a scale from 0 to 35, with higher scores indicating worse symptoms at short-term follow-up (mean difference (MD) 1.00, 95% confidence interval (CI) −0.03 to 2.03; moderate certainty). There is likely to be little to no difference in the quality of life (MD −0.10, 95% CI −0.67 to 0.47; 1 study, 136 participants, moderate certainty). TUMT likely results in fewer major adverse events (RR 0.20, 95% CI 0.09 to 0.43; 6 studies, 525 participants, moderate certainty); based on 168 cases per 1000 men in the TURP group, this corresponds to 135 fewer (153 to 96 fewer) per 1000 men in the TUMT group. TUMT, however, probably results in a large increase in the need for retreatment (risk ratio (RR) 7.07, 95% CI 1.94 to 25.82; 5 studies, 337 participants, moderate certainty) (usually by repeated TUMT or TURP); based on zero cases per 1000 men in the TURP group, this corresponds to 90 more (40 to 150 more) per 1000 men in the TUMT group. There may be little to no difference in erectile function between these interventions (RR 0.63, 95% CI 0.24 to 1.63; 5 studies, 337 participants; low certainty). However, TUMT may result in fewer cases of ejaculatory dysfunction compared to TURP (RR 0.36, 95% CI 0.24 to 0.53; 4 studies, 241 participants; low certainty).

TUMT versus sham

Based on data from four studies with 483 participants we found that, when compared to sham, TUMT probably reduces urologic symptom scores using the IPSS at short-term follow-up (MD −5.40, 95% CI −6.97 to −3.84; moderate certainty). TUMT may cause little to no difference in the quality of life (MD −0.95, 95% CI −1.14 to −0.77; 2 studies, 347 participants; low certainty) as measured by the IPSS quality-of-life question on a scale from 0 to 6, with higher scores indicating a worse quality of life. We are very uncertain about the effects on major adverse events, since most studies reported no events or isolated lesions of the urinary tract. TUMT may also reduce the need for retreatment compared to sham (RR 0.27, 95% CI 0.08 to 0.88; 2 studies, 82 participants, low certainty); based on 194 retreatments per 1000 men in the sham group, this corresponds to 141 fewer (178 to 23 fewer) per 1000 men in the TUMT group. We are very uncertain of the effects on erectile and ejaculatory function (very low certainty), since we found isolated reports of impotence and ejaculatory disorders (anejaculation and hematospermia).

There were no data available for the comparisons of TUMT versus convective radiofrequency water vapor therapy, prostatic urethral lift, prostatic arterial embolization or temporary implantable nitinol device.

Authors' conclusions

TUMT provides a similar reduction in urinary symptoms compared to the standard treatment (TURP), with fewer major adverse events and fewer cases of ejaculatory dysfunction at short-term follow-up. However, TUMT probably results in a large increase in retreatment rates. Study limitations and imprecision reduced the confidence we can place in these results. Furthermore, most studies were performed over 20 years ago. Given the emergence of newer minimally-invasive treatments, high-quality head-to-head trials with longer follow-up are needed to clarify their relative effectiveness. Patients' values and preferences, their comorbidities and the effects of other available minimally-invasive procedures, among other factors, can guide clinicians when choosing the optimal treatment for this condition.

PLAIN LANGUAGE SUMMARY

Transurethral microwave thermotherapy for lower urinary tract symptoms in men with benign prostatic hyperplasia

Review question

Does transurethral microwave thermotherapy (TUMT) improve bothersome urinary symptoms without unwanted side effects in men with an enlarged prostate?

Background

An enlarged prostate may cause bothersome urinary tract symptoms, such as having to urinate often during the day or night, having a weak stream, and the feeling of not completely emptying the bladder. When lifestyle changes (like drinking fewer liquids) or medications do not help, men may choose to have surgery, such as transurethral resection of the prostate. However, this procedure may cause unwanted effects, such as erection and ejaculation problems, or require retreatment. This review looks at the results of transurethral microwave thermotherapy, which is an alternative, less invasive procedure that uses microwave energy to reduce prostatic tissue.

Study characteristics

We found no study comparing transurethral microwave thermotherapy with the other newer and less invasive treatments for this condition.

We found 16 studies with 1919 men that compared transurethral microwave thermotherapy with a simulated procedure (participants are made to believe they received treatment, while in reality, they did not) or with traditional surgery (transurethral resection of the prostate (TURP)). Participants' average age was 69 years, and most had a moderate degree of bothersome urinary symptoms.

Key results

Compared to the traditional surgery (TURP), transurethral microwave thermotherapy probably results in little to no difference in urinary symptoms at short-term follow-up, but we are uncertain about its long-term effects. There may be little to no difference in quality of life or problems with erections between these interventions both short-term and long-term. This procedure likely results in fewer serious side effects and problems with ejaculation compared to surgery. However, it likely results in an increase in the need for retreatment (including surgery).

Compared to a simulated procedure, transurethral microwave thermotherapy probably improves urinary symptoms and the need for retreatment at short-term follow-up (less than 12 months). This treatment may make little to no difference in the quality of life. We are very uncertain whether or not serious unwanted side effects, including problems with erection and ejaculation, are more common.

Findings of this review are up-to-date until 31 May 2021.

Certainty of the evidence

The certainty of the evidence for the outcomes ranged mostly from moderate to low due to shortcomings in how the studies were conducted and small study size. This means that we have either moderate or limited confidence in the results.

SUMMARY OF FINDINGS

Summary of findings 1. Transurethral microwave thermotherapy compared to transurethral resection of the prostate for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia

Transurethral microwave thermotherapy compared to transurethral resection of the prostate for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia

Patient or population: men with lower urinary tract symptoms due to benign prostatic hyperplasia
Setting: outpatient (TUMT) / inpatient (TURP) - UK, Netherlands, Scandinavia, USA
Intervention: Transurethral microwave thermotherapy (TUMT)
Comparison: Transurethral resection of the prostate (TURP)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with transurethral resection of the prostate (TURP)	Risk difference with Transurethral microwave thermotherapy
Urologic symptom scores Assessed with: IPSS Scale from 0 (best: not at all) to 35 (worst: almost always) Follow-up: 6 - 12 months	306 (4 RCTs)	⊕⊕⊕⊖ MODERATE[a]	-	The mean urologic symptoms score (IPSS) was 5.63	MD 1 higher (0.03 lower to 2.03 higher)
Quality of life Assessed with: IPSS-QoL Scale from 0 (best: delighted) to 6 (worst: terrible) Follow-up: 12 months	136 (1 RCT)	⊕⊕⊕⊖ MODERATE[a]	-	The mean quality of life was 1.5	MD 0.10 lower (0.67 lower to 0.47 higher)
Major adverse events Assessed with: Clavien-Dindo classification system (Grade III, IV and V complications) Follow-up: 6 - 12 months	525 (6 RCTs)	⊕⊕⊕⊖ MODERATE[a]	RR 0.20 (0.09 to 0.43)	Study population 168 per 1000	 135 fewer per 1000 (153 fewer to 96 fewer)
Retreatment	463 (5 RCTs)	⊕⊕⊕⊖ MODERATE[a,b]	RR 7.07 (1.94 to 25.82)	Study population	

Participants requiring additional procedures or surgery Follow-up: 6 - 12 months				0 per 1000	90 more per 1000 (40 more to 150 more)
Erectile function (sexually-active men only) Assessed with: issues related to erectile function Follow-up: 6 - 12 months	337 (5 RCTs)	⊕⊕⊖⊖ LOW[a,c]	RR 0.63 (0.24 to 1.63)	Study population 129 per 1000	 48 fewer per 1000 (98 fewer to 82 more)
Ejaculatory function (sexually-active men only) Assessed with: issues related to ejaculatory function Follow-up: 6 - 12 months	241 (4 RCTs)	⊕⊕⊖⊖ LOW[a,c]	RR 0.36 (0.24 to 0.53)	Study population 523 per 1000	 335 fewer per 1000 (397 fewer to 246 fewer)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** mean difference; **RCT:** randomized controlled trial; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level for study limitations: studies at an overall high risk of bias.
[b]We did not downgrade for imprecision since we used a minimally conceptualized approach: although the confidence interval is wide, there are no concerns about whether the effect results in a moderate to a large increase in the retreatment rate.
[c]Downgraded by one level for imprecision: the incidence is mostly reported in a subset of sexually-active participants.

Summary of findings 2. Transurethral microwave thermotherapy compared to sham treatment for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia

Transurethral microwave thermotherapy compared to sham treatment for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia

Patient or population: men with lower urinary tract symptoms due to benign prostatic hyperplasia
Setting: outpatient - France, USA, UK, Sweden, Netherlands
Intervention: Transurethral microwave thermotherapy

Comparison: Sham treatment

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with sham treatment	Risk difference with Transurethral microwave thermotherapy
Urologic symptom scores Assessed with: IPSS Scale from 0 (best: not at all) to 35 (worst: almost always) Follow-up: 3 - 6 months	483 (4 RCTs)	⊕⊕⊕⊖ MODERATE[a]	-	The mean urologic symptom scores was 16.2	MD 5.40 lower (6.97 lower to 3.84 lower)
Quality of life Assessed with: IPSS-QoL Scale from 0 (best: delighted) to 6 (worst: terrible) Follow-up: 6 months	347 (2 RCTs)	⊕⊕⊖⊖ LOW[a,b]	-	The mean quality of life score was 3.05	MD 0.95 lower (1.14 lower to 0.77 lower)
Major adverse events Assessed with: Clavien-Dindo classification system (Grade III, IV and V complications) Follow-up: 6 - 12 months	924 (8 RCTs)	⊕⊖⊖⊖ VERY LOW[a,c]	-	Six studies reported that there were no major adverse events. The two remaining studies reported four isolated cases of lesions of the urinary tract related to the procedure in both groups.	
Retreatment Participants requiring additional procedures or surgery Follow-up: 6 - 12 months	82 (2 RCTs)	⊕⊕⊖⊖ LOW[a,d]	RR 0.27 (0.08 to 0.88)	Study population	
				194 per 1000	141 fewer per 1000 (178 fewer to 23 fewer)
Erectile function (sexually-active men only) Assessed with: issues related to erectile function Follow-up: 6 - 12 months	375 (3 RCTs)	⊕⊖⊖⊖ VERY LOW[a,c]	-	Two studies reported normal erections. One study reported one case of impotence.	

Ejaculatory function (sexually-active men only) Assessed with: issues related to ejaculatory function Follow-up: 6-12 months	727 (5 RCTs)	⊕⊖⊖⊖ VERY LOW[a,c]	-	Three studies reported no issues related to ejaculatory function. The two remaining studies reported isolated cases of loss of ejaculate and hematospermia.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** mean difference; **RCT:** randomized controlled trial; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level for study limitations: studies at an overall high risk of bias.
[b]Downgraded by one level for imprecision: confidence interval crosses assumed threshold of minimal clinically important difference.
[c]Downgraded by two levels for imprecision: very few events (isolated reports).
[d]Downgraded by one level for imprecision: few events.

BACKGROUND

Description of the condition

The prostate gland is an organ approximately the size of a walnut located below the urinary bladder encircling the urethra (Leissner 1979). Benign prostatic hyperplasia (BPH) is a histological diagnosis defined as an increased number of epithelial and stromal cells in the prostate; this may cause prostatic enlargement and subsequently compression of the urethra and obstruction (Roehrborn 2008). BPH may therefore develop with or without lower urinary tract symptoms (LUTS) in men aged over 40 years (Dunphy 2015). BPH acquires clinical significance when associated with bothersome LUTS (Roehrborn 2008). 'Symptom bother' typically correlates with the increased number and severity of symptoms, which relate to both the quality-of-life impairment and treatment-seeking (Agarwal 2014). Self-administered questionnaires, (e.g. the International Prostate Symptom Score (IPSS)), include the quality-of-life domain to evaluate the relative degree of bother across all LUTS (Barry 1995). Chapple 2017 reported that increasing LUTS severity was associated with worsening men's overall distress using the patient perception of bladder condition, which is a single-item global question (ranging from 1 (causes no problems at all) to 6 (causes severe problems)). In this Cochrane Review, we consider the term BPH as prostatic enlargement with LUTS to define the disease condition and potential need for intervention.

BPH can progress and cause serious consequences such as acute urinary retention, urinary tract infection, and upper urinary tract deterioration. BPH also negatively impacts public health and a reduction in a person's quality of life (Kozminski 2015; Martin 2014). In Europe, 30% of men over 50 years of age, equivalent to 26 million men, are affected by bothersome LUTS, including storage symptoms (such as urinary frequency, urgency, and nocturia) or voiding symptoms (such as urinary hesitancy, weak urinary stream, straining to void, and prolonged voiding), or both. The yearly reported associated number of medical prescriptions is estimated to be around 11.6 million for 74 million people at risk from 2004 to 2008 (Cornu 2010). According to an international study involving 7588 men, the prevalence of LUTS was 18% in 40-year-olds, 29% in the 50s, 40% in the 60s, and 56% in the 70s (Homma 1997). In the USA, an estimated eight million men over 50 years of age have BPH (Roehrborn 2008). More recent data show that the lifetime prevalence of BPH was 26.2% (95% confidence interval 22.8 to 29.6%) (Lee 2017).

Diagnosis

Initial evaluation of LUTS suggestive of BPH includes patient history, physical examination including a digital rectal examination, urinalysis, prostate-specific antigen (PSA) blood test, voiding diary, and IPSS (EAU 2021; McVary 2011). A digital rectal examination is performed to assess the prostate for size and any lesions suspicious of cancer. PSA is secreted by the prostate gland and is found to be abnormally elevated in conditions such as prostate cancer, BPH, infection, or inflammation of the prostate (EAU 2021; McVary 2011). The IPSS is used to assess urinary symptom severity and quality of life. It is also used to document subjective responses to treatment (Barry 1992; EAU 2021; McVary 2011). Measurements of maximum flow rate (Q_{max}) and postvoid residual (PVR) are also often used in diagnosis and treatment decisions (EAU 2021; McVary 2011). A low Q_{max} and a large PVR predict an increased risk of symptom progression (Crawford 2006). Other tests include radiological imaging, urodynamic evaluation, and cystoscopy to determine appropriate treatment and predict treatment response (Egan 2016; McVary 2011).

Treatment

Treatment decisions are based on symptoms and the degree of bother noted by the patient. Initial treatment options for BPH include conservative management (watchful waiting and lifestyle modification) and medication (alpha-blockers and 5-alpha reductase inhibitors) (EAU 2021; McVary 2011). If patients have been refractory to conservative and medical treatment, and BPH causes subsequent complications, such as acute urinary retention, recurrent urinary tract infection, bladder stones or diverticula, hematuria, or renal insufficiency, surgical options are considered (EAU 2021; McVary 2011). Until the 1970s, the only option available to treat this condition and relieve LUTS was an open or endoscopic surgery to remove or resect prostatic tissue to open up the blocked urethra (Pariser 2015). Clinical guidelines recommend monopolar or bipolar transurethral resection of the prostate (TURP) as a standard treatment modality for subjective symptom relief and objective improvements in urinary flow (EAU 2021; McVary 2011), but this procedure is also associated with significant morbidity and long-term complications, including hematuria requiring blood transfusion, urethral stricture, recurrent urinary tract infection, and urinary incontinence. Moreover, men may experience ejaculatory (65%) and erectile dysfunction (10%) related to TURP (AUA 2003). Furthermore, BPH is a disease common in elderly men who have an increased risk of complications for general anesthesia and the surgery itself (Dunphy 2015; Yoo 2012). Some alternatives to TURP include laser enucleation, vaporization, and Aquablation, but they all require spinal anesthesia (EAU 2021). In recent years, the number of men undergoing TURP has steadily declined due to increasing pharmacologic treatments (alpha-blockers and 5-alpha-reductase inhibitors) and minimally-invasive treatments that are usually performed under local anesthesia (Dahm 2021), such as convective radiofrequency water vapor therapy (Hwang 2019), prostatic urethral lift (Jung 2019), prostatic arterial embolization (Jung 2020) which are covered in current evidence-based guidelines (Parsons 2020).

Description of the intervention

Transurethral microwave thermotherapy (TUMT) uses microwave-induced heat to ablate prostatic tissue and is designed to have fewer major complications than TURP (Walmsley 2004). The patient is treated in an outpatient setting. Once the patient's bladder is emptied by straight catheterization, a local lidocaine gel is inserted for local anesthesia. The treatment catheter is then placed within the urethra, confirmed by the return of sterile water and transabdominal or transrectal ultrasound, and the balloon is inflated. The catheter is composed of a curved tip, a temperature sensor and a microwave unit. The distal port contains the bladder balloon, allowing for urine drainage and cooling. A rectal probe may be inserted to monitor the rectal temperature (Rubeinstein 2003).

TUMT has evolved over the past decades. Initial systems worked at lower energy or heat settings, and treatment would take around an hour with minimal discomfort, but results were disappointing. Subsequent systems incorporated catheters that provided urethral cooling, thus allowing higher energy delivery. These advances reduced the procedure time to around 30 minutes and improved

outcomes, but the higher energy leads to more significant discomfort during the procedure, in which patients often require sedation and analgesia, with continued risk of urinary retention (Walmsley 2004).

While TUMT was once the most widely-used procedure for minimally-invasive surgical therapies among the USA's Medicare population (Yu 2008), its use has declined since its peak in 2006 (Malaeb 2012). A recent study in Australia highlighted that TUMT currently constitutes only 0.26% of all procedures performed for BPH (Morton 2020).

How the intervention might work

TUMT uses a special transurethral catheter that transmits heat into the prostate using microwaves' electromagnetic radiation, penetrating water-rich tissue. The energy transferred by the microwave to the tissue in the form of heat-induces coagulation necrosis, reducing prostatic volume. This mechanism may also cause denervation of receptors, decreasing smooth muscle tone of the prostatic urethra (Walmsley 2004). Temperatures lower than 45 °C seemed ineffective in producing this effect, so higher-energy devices were developed to reach more than 70 °C, causing thermoablation of the prostatic tissue (Aoun 2015).

Why it is important to do this review

A review was published in 2012 (Hoffman 2012). The Cochrane Urology Review Group commissioned a network meta-analysis of minimally-invasive treatments for lower urinary tract symptoms (Franco 2020) that draws its evidence from individual reviews of these interventions. It therefore became necessary to update the previous version of the review in search of the latest evidence and using the latest Cochrane guidance and methodological standards. This review in its updated format intends to guide clinicians, patients, and guideline developers when assessing the available options for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia, especially considering the critical outcomes of the summary of findings table, which are now comparable with other reviews on this topic published by the Cochrane Urology Group (Hwang 2019; Jung 2019; Jung 2020; Kang 2020).

OBJECTIVES

To assess the effects of transurethral microwave thermotherapy for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia.

METHODS

Criteria for considering studies for this review

Types of studies

The methods for this update have been extensively modified since its last publication to meet current methodological expectations; please refer to the Differences between protocol and review section. We included parallel-group RCTs and cluster-RCTs. We excluded cross-over trials, as these study designs are not relevant in this setting. We did not include single-armed studies. We included studies regardless of their publication status or language.

Types of participants

We defined the eligible participant population as men over the age of 40 years with a prostate volume of 20 mL or greater (as assessed by ultrasound or cross-sectional imaging), with lower urinary tract symptoms (LUTS) as determined by International Prostate Symptom Scores (IPSS) of eight or over, and a maximum flow rate (Q_{max}) of less than 15 mL/second, as measured by non-invasive uroflowmetry, invasive pressure flow studies, or both (Dunphy 2015; EAU 2021; McNicholas 2016; McVary 2011). We based the age limit on the fact that the prevalence of BPH increases in middle-aged and older men and is infrequent in younger men (Barry 1997; EAU 2021; Egan 2016). We included studies in which only a subset of participants was relevant to this review (i.e. studies with more than 75% of participants only as relevant to the review) if data were available separately for the relevant subset.

We excluded studies of men with active urinary tract infection, bacterial prostatitis, chronic renal failure, untreated bladder calculi or large diverticula, prostate cancer, and urethral stricture disease, as well as those who had undergone prior prostate, bladder neck, or urethral surgery. We also excluded studies of people with other conditions that affect urinary symptoms, such as neurogenic bladder due to spinal cord injury, multiple sclerosis, or central nervous system disease.

Types of interventions

Experimental intervention

- Transurethral microwave thermotherapy (TUMT)

Comparator interventions

- Sham control (or no intervention)
- Transurethral resection of the prostate (TURP) (monopolar or bipolar)
- Minimally-invasive therapies: convective radiofrequency water vapor thermal therapy (CRFWVT, also known as Rezum); prostatic urethral lift (PUL), prostatic arterial embolization (PAE), temporary implantable nitinol device (TIND)

We planned to investigate the following comparisons of experimental intervention versus comparator interventions. Concomitant interventions must be the same in the experimental and comparator groups to establish fair comparisons.

Comparisons

- TUMT versus TURP
- TUMT versus sham control (or no intervention)
- TUMT versus CRFWVT
- TUMT versus PUL
- TUMT versus PAE
- TUMT versus TIND

Types of outcome measures

We did not use the measurement of the outcomes assessed in this review as an eligibility criterion.

Primary outcomes

- Urologic symptom scores (continuous outcome)
- Quality of life (continuous outcome)

- Major adverse events (dichotomous outcome)

Secondary outcomes

- Retreatment (dichotomous outcome)
- Erectile function (continuous outcome)
- Ejaculatory function (continuous outcome)
- Minor adverse events (dichotomous outcome)
- Acute urinary retention (dichotomous outcome)
- Indwelling urinary catheter (continuous outcome)

Method and timing of outcome measurement

We considered the clinically important differences for the review outcome measures to rate the overall certainty of evidence in the Summary of findings 1 and Summary of findings 2 (Jaeschke 1989; Johnston 2013).

Urologic symptom scores

- Mean change from baseline or final mean value, measured using a validated scale (such as IPSS)
- We considered the improvement of an IPSS score of three points as the minimal clinically important difference (MCID) to assess the efficacy and comparative effectiveness (Barry 1995). If possible, we used different thresholds of MCID based on the severity of IPSS, with a threshold of three points for men with mild LUTS, five for moderate LUTS, and eight for severe LUTS (Barry 1995).

Quality of life

- Mean change from baseline or final mean value measured as a validated scale (such as IPSS-quality of life or BPH Impact Index)
- A BPH Impact Index score of one as an MCID was used to indicate improvement (Barry 2013; Rees 2015).

Major adverse events

- Example: postoperative hemorrhage requiring admission or intervention
- We used the Clavien-Dindo classification system to assess surgical complications (Dindo 2004), and categorized grade III, IV and V complications as major adverse events. If the study authors of eligible studies did not use the Clavien-Dindo system, we judged the adverse events by severity using the available information described in the studies.

Retreatment

- Events requiring other surgical treatment modalities (e.g. TURP) after the intervention.

Erectile function

- Mean change from baseline or final mean value measured as a total score on the International Index of Erectile Function (IIEF)-5 questionnaire, also known as Sexual Health Inventory for Men (Rosen 1997)
- We considered the MCID an erectile function domain score of four on the IIEF (Rosen 2011). If possible, we used different thresholds of MCID based on the severity of erectile dysfunction, with a threshold of two for men with mild erectile dysfunction, five for moderate erectile dysfunction, and seven for men with severe erectile dysfunction (Rosen 2011). We considered a difference in IIEF-5 score of over five points as the MCID (Spaliviero 2010).

Ejaculatory function

- Mean change from baseline or final mean value measured using the Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EjD) or the four-item version of the MSHQ-EjD (Rosen 2004; Rosen 2007)
- We considered the MCID as an ejaculatory function domain score of two on the MSHQ or a four-item version of the MSHQ-EjD (Rosen 2004; Rosen 2007).

Minor adverse events

- Example: postoperative fever or pain requiring medication
- We used the Clavien-Dindo classification system to assess surgical complications (Dindo 2004) and categorized grade I and II complications as minor adverse events. If the authors of eligible studies did not use the Clavien-Dindo system, we judged the severity of adverse events using the available information described in these studies.

Acute urinary retention

- Events requiring catheterization after the intervention

Indwelling urinary catheter

- Measured in hours from intervention to urinary catheter removal (as a continuous outcome) or the need for urinary catheterization (as a dichotomous outcome)

Hospital stay

- Measured in days from admission to discharge

There were no reported thresholds in adverse events, retreatment, acute urinary retention, indwelling urinary catheter, or hospital stay. We considered a clinically important difference for adverse events, retreatment, acute urinary retention, and indwelling catheter as risk ratio reductions of at least 25% (Guyatt 2011a). We used a MCID of one day (24 hours) to assess the efficacy and comparative effectiveness for indwelling urinary catheter and hospital stay.

We considered outcomes measured up to and including 12 months after randomization as short-term, and later than 12 months as long-term, for urologic symptom scores, quality of life, major adverse events, retreatment, erectile function, ejaculatory function, minor adverse events, and acute urinary retention. We assessed retreatment, indwelling urinary catheter and hospital stay as short-term only.

Search methods for identification of studies

We performed a comprehensive search with no restrictions by date, by language of publication or publication status.

Electronic searches

We searched the following sources from the inception of each database to the date of search, and placed no restrictions on the language of publication:

1. CENTRAL (Cochrane Central Register of Controlled Trials) searched 31 May 2021;

2. MEDLINE (Ovid) searched 31 May 2021;
3. Embase (Elsevier) searched 31 May 2021;
4. LILACS (Bireme) searched 31 May 2021;
5. Scopus searched 31 May 2021;
6. Web of Science (Clarivate analytics) searched 31 May 2021;
7. ClinicalTrials.gov (www.ClinicalTrials.gov) searched 31 May 2021;
8. World Health Organization International Clinical Trials Registry Platform (ICTRP; www.who.int/trialsearch/) searched 31 May 2021.

For detailed search strategies, see Appendix 1.

Searching other resources

We tried to identify other potentially eligible studies or ancillary publications by searching the reference lists of included studies, reviews, meta-analyses, and health technology assessment reports. We also contacted the authors of the included studies to identify any further studies that we may have missed. We contacted drug/device manufacturers for ongoing or unpublished studies. We searched only the published abstract proceedings of relevant meetings of the American Urological Association, European Association of Urology, and International Continence Society for the last three years (2018 to 2020) for unpublished studies (see Appendix 2).

Data collection and analysis

Selection of studies

We used Covidence software to identify and remove potential duplicate records. Two review authors (JVAF, LIG) independently scanned abstracts and titles to determine which studies should be assessed further. Two review authors categorized all potentially relevant records as full-text or mapped records to studies, and classified studies as included studies, excluded studies, studies awaiting classification, or ongoing studies, following the criteria in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). We resolved any disagreements between the two review authors through consensus or by recourse to a third review author (PD). If a resolution was not possible, we designated the corresponding study as 'awaiting classification'. We documented reasons for the exclusion of studies in the Characteristics of excluded studies table. We presented a PRISMA 2020 flow diagram showing the process of study selection (Page 2020).

Data extraction and management

We developed a dedicated data extraction form that we pilot-tested ahead of time.

For studies that fulfilled our inclusion criteria, two review authors (JVAF and LIG) independently abstracted the following information, which we provide in the Characteristics of included studies table.

- Study design
- Study dates (if dates are not available, then this was reported as such)
- Study settings and country
- Participant inclusion and exclusion criteria (e.g. age, baseline IPSS, medical pretreatment)
- Participant details, baseline demographics (e.g. age, prostate size, IPSS)
- The number of participants by study and by study arm
- Details of relevant experimental intervention, such as delivery devices (e.g. size of cystoscope) for the intervention and comparator (e.g. monopolar versus bipolar energy, type of laser)
- Definitions of relevant outcomes, and method (e.g. type of instrument, such as IPSS) and timing of outcome measurement (e.g. in months) as well as any relevant subgroups (e.g. based on age, prostate volume, the severity of LUTS)
- Study funding sources
- Declarations of interest by primary investigators

We extracted outcome data relevant to this Cochrane Review as needed to calculate summary statistics and measures of variance. For dichotomous outcomes, we attempted to obtain numbers of events and totals for the study population in a 2 x 2 table, as well as summary statistics with corresponding measures of variance. We attempted to obtain means and standard deviations or other data necessary to calculate this information for continuous outcomes.

We resolved any disagreements by discussion, or if required by consultation with a third review author (PD).

We have provided information, including study identifiers, about potentially relevant ongoing studies in the Characteristics of ongoing studies table.

We contacted the authors of included studies to obtain key missing data as needed.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents or multiple reports relating to a primary study, we maximized the yield of information by mapping all publications to unique studies and collating all available data. We used the most complete data set aggregated across all known publications. In case of doubt, we gave priority to publications reporting the longest follow-ups associated with our primary or secondary outcomes.

Assessment of risk of bias in included studies

Two review authors (JVAF and LIG) independently assessed the risks of bias of each included study. We resolved disagreements by consensus, or by consultation with a third review author (PD). We have presented a risk of bias summary figure to illustrate these findings. We further summarize the risk of bias across the studies and domains for each outcome in each included study, in accordance with the approach for the summary assessments of the risk of bias presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

We assessed risk of bias using Cochrane's risk of bias assessment tool (Higgins 2021). We assessed the following domains.

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)

- Other potential sources of bias

We judged risk of bias domains as 'low risk', 'high risk' or 'unclear risk' and evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

For selection bias (random sequence generation and allocation concealment), we evaluated risk of bias at study level. For performance bias (blinding of participants and personnel), we considered all outcomes as similarly susceptible to performance bias. For detection bias (blinding of outcome assessment), we grouped outcomes as susceptible to detection bias (subjective) or not susceptible to detection bias (objective).

We defined the following outcomes as subjective outcomes.

- Urologic symptom scores
- Quality of life
- Erectile function
- Ejaculatory function
- Minor adverse events

We defined the following outcomes as objective outcomes.

- Major adverse events
- Retreatment
- Acute urinary retention
- Indwelling urinary catheter

We also assessed attrition bias (incomplete outcome data) on an outcome-specific basis and present the judgment for each outcome separately when reporting our findings in the risk of bias tables.

For reporting bias (selective reporting), we evaluated the risk of bias at the study level.

Measures of treatment effect

We expressed dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs). We expressed continuous data as mean differences (MDs) with 95% CIs, unless different studies used different measures to assess the same outcome, in which case we re-expressed the data as standardized mean differences (SMDs) with 95% CIs.

Unit of analysis issues

The unit of analysis was each individual participant. We planned to take into account the level at which randomization occurred, such as cluster-randomized trials, and multiple observations of the same outcome. If more than one comparison from the same study was eligible for inclusion in the same meta-analysis, we either combined study groups to create a single pairwise comparison or appropriately reduced the sample size so that the same participants did not contribute multiple times (if possible, splitting the 'shared' group into two or more groups). While the latter approach offers some solution to adjust the precision of the comparison, it does not account for correlations arising from the same set of participants being in multiple comparisons (Deeks 2021).

Dealing with missing data

We obtained missing data from corresponding study authors, if feasible, and performed intention-to-treat analyses if data were available. Otherwise, we performed available-case analyses. We investigated attrition rates (e.g. dropouts, losses to follow-up, and withdrawals), and critically appraised issues of missing data. We did not impute missing data.

Assessment of heterogeneity

We planned to assess heterogeneity. We identified heterogeneity (inconsistency) through visual inspection of the forest plots to assess the amount of overlap of CIs, and by using the I^2 statistic, which quantifies inconsistency across studies to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003). We would have interpreted the I^2 statistic as follows (Deeks 2021).

- 0% to 40%: may not be important
- 30% to 60%: may indicate moderate heterogeneity
- 50% to 90%: may indicate substantial heterogeneity
- 75% to 100%: considerable heterogeneity

When we identified heterogeneity, we attempted to determine possible reasons by examining individual study and subgroup characteristics.

Assessment of reporting biases

We tried to obtain study protocols to assess selective outcome reporting.

We could not use funnel plots to assess small-study effects due to the few number of participants in each comparison. If we had included 10 or more studies in a meta-analysis, we would have used funnel plots to assess small-study effects (Page 2021). Several explanations can be offered for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to study size, poor methodological design (and hence bias of small studies), and publication bias. We would therefore have interpreted results cautiously.

Data synthesis

Unless there was good evidence for homogeneous effects across studies, we summarized data using a random-effects model. We interpreted random-effects meta-analyses with due consideration of the whole distribution of effects. We also performed statistical analyses according to the statistical guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). For dichotomous outcomes, we used the Mantel-Haenszel method. For continuous outcomes, we used the inverse variance method. We used Review Manager 5 (RevMan 2020) software to perform analyses.

Subgroup analysis and investigation of heterogeneity

We expected the following characteristics to potentially introduce clinical heterogeneity, and carried out subgroup analyses to investigate interactions.

- Participant age (less than 65 years versus 65 years or more)
- Prostate volume (less than 50 mL versus 50 mL or more)

- Severity of LUTS based on IPSS (score less than or equal to 19 (moderately symptomatic) versus greater than 19 (severely symptomatic))

These subgroup analyses are based on the following observations.

- Age is a well-known risk factor of BPH surgery. Older men have a higher rate of postoperative complications compared with younger men (Bhojani 2014; Pariser 2015). The age cut-off is based on the World Health Organization (WHO) definition of old age (WHO 2012).
- The outcomes and complications of minimally-invasive procedures, such as TURP, correlate with prostate volume (Reich 2008). We adjusted the prostate volume to 50 mL based on the available evidence.
- The relationship between changes in IPSS scores and patient global ratings of improvement is influenced by the baseline scores (Barry 1995).

We planned to limit subgroup analyses to the primary outcomes only.

Sensitivity analysis

We performed sensitivity analyses limited to the primary outcomes to explore the influence of the following factors (when applicable) on effect size.

- Restricting the analysis to RCTs by considering risk of bias, excluding studies with at least one domain at 'high risk' or 'unclear risk' of bias for the analyzed outcome.
- Restricting the analysis to RCTs with adequately-described inclusion criteria (prostate size, age, IPSS value, and Q_{max}).

Summary of findings and assessment of the certainty of the evidence

We presented the overall certainty of the evidence for each outcome according to the GRADE approach (Guyatt 2008). For each comparison, two review authors (JVAF and LIG) independently rated the certainty of the evidence for each outcome as 'high', 'moderate', 'low', or 'very low', using the GRADEpro Guideline Development Tool (GRADEpro GDT). We resolved any discrepancies by consensus or if needed by arbitration from a third review author (PD). For each comparison, we presented a summary of the evidence for the main outcomes in the summary of findings table, which provides key information about the best estimate of the magnitude of effect in relative terms and absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of our overall confidence in the effect estimates for each outcome (Guyatt 2011b; Schünemann 2021). We considered five criteria, not only related to internal validity (risk of bias, inconsistency, imprecision, and publication bias), but also external validity (directness of results), for downgrading the certainty of the evidence for a specific outcome (Schünemann 2021). We included the following outcomes:

- Urologic symptom scores
- Quality of life
- Major adverse events
- Retreatment
- Erectile function
- Ejaculatory function

RESULTS

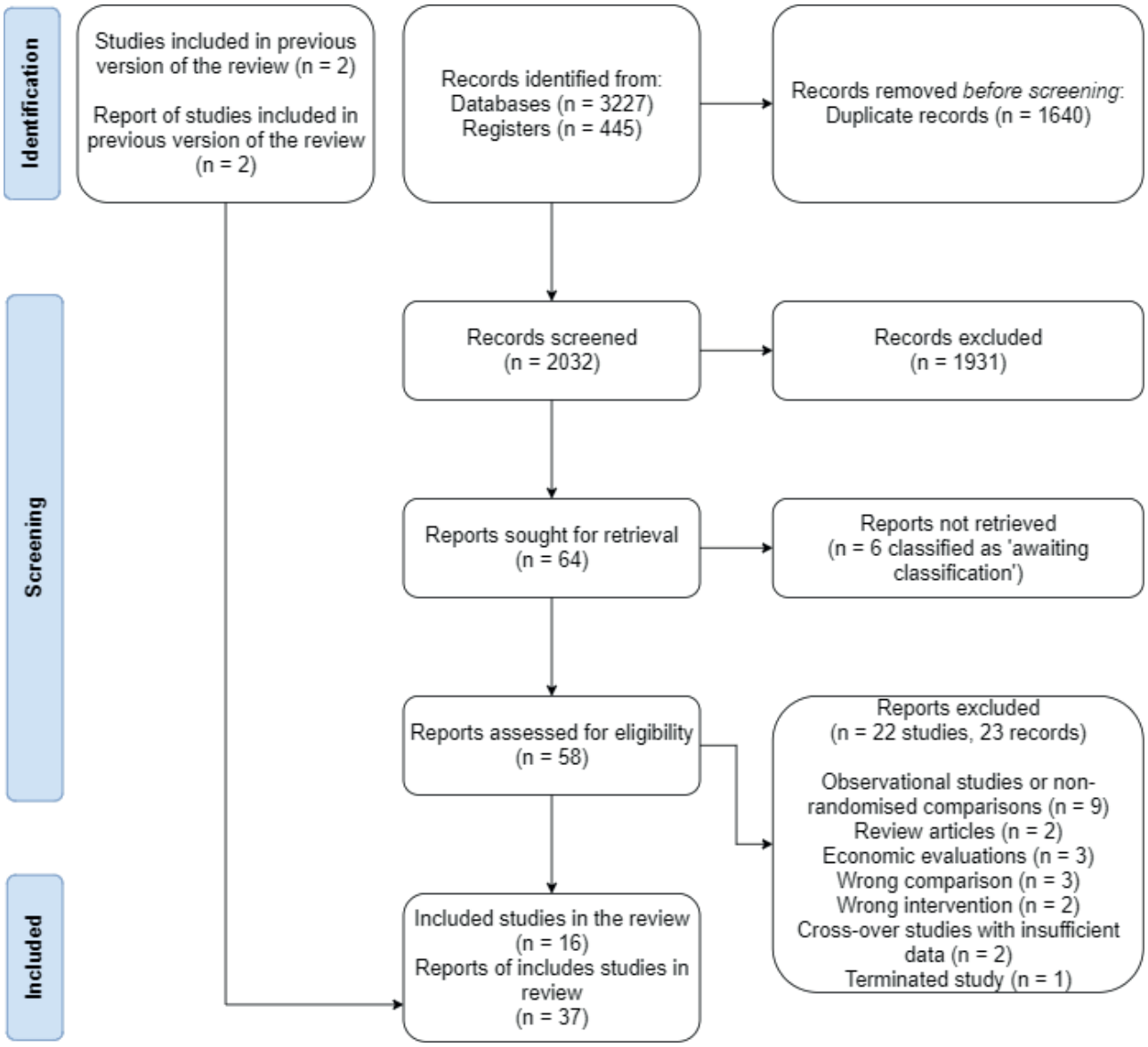
Description of studies

Details of included studies are presented elsewhere (see Table 1 and Characteristics of included studies).

Results of the search

We identified 3635 records from electronic databases, including 445 records from trial registers. We found no relevant records in the grey literature repository. After removing duplicates, we screened the titles and abstracts of the remaining 1995 records, 1935 of which we excluded. We assessed 60 full-text articles: we were unable to find six full-text articles (see Characteristics of studies awaiting classification) and we excluded 22 studies (23 records) for various reasons (see Excluded studies). Finally, we included 16 studies (37 reports) in this review. There were no ongoing studies that met the inclusion criteria or were relevant to the review question. We have shown the flow of literature through the assessment process in the PRISMA 2020 flowchart (Figure 1).

Figure 1. PRISMA 2020 flow diagram.



Included studies

Study design and settings

We included 16 randomized controlled trials. The median sample size was 117 (range 40 to 220). The studies were mostly performed in Europe and the USA: one in France (Abbou 1995), four in the USA (Albala 2002; Blute 1996; Larson 1998; Roehrborn 1998), two in the Netherlands (D'Ancona 1998; Floratos 2001) four in the United Kingdom (Ahmed 1997; Bdesha 1994; Nawrocki 1997; Venn 1995), three in Scandinavian countries (Brehmer 1999; Dahlstrand 1995; Nørby 2002a) and two international studies (De Wildt 1996; Wagrell 2002).

Participants

The included studies randomized 1919 participants with a median age of 69 years. All studies included participants with moderate symptoms, with a median IPSS score of 21 points (range 17 to 29 points); however, four studies did not provide a baseline IPSS score (Abbou 1995; Brehmer 1999; Dahlstrand 1995; De Wildt 1996). The median prostate size was 45 mL (range 33 to 53 mL), but two studies did not provide a baseline prostate size (Bdesha 1994; Brehmer 1999).

Major exclusion criteria relevant to all trials were urethra (e.g. urethral stricture) or bladder disorders (e.g. neurogenic bladder, bladder calculi or diverticula), renal failure, history of prostate, bladder neck, or urethral surgery, and suspected prostate cancer.

Interventions and comparisons

All TUMT procedures were performed in an outpatient setting under local anesthesia. Each device's software and programs varied (most studies used the Prostatron device with the Prostasoft v2.0); however, they delivered a temperature between 45 °C and 55 °C in a 60- to 90-minute session through a urethral catheter. The temperature was monitored through the urethral catheter with a rectal probe that triggered a power cut-off when it reached a certain

temperature (usually 42.5 °C in the rectum). Some studies routinely catheterized participants for two to four days, whereas others only when the participants presented with voiding difficulties or acute urinary retention. Antibiotic prophylaxis across studies was poorly described.

The comparators included:

- Sham: the participants were catheterized with the TUMT system, but a sham procedure took place with activation of the monitors in a simulated program. Furthermore, sometimes heat was externally irradiated to the perineum to maintain blinding of participants.
- TURP: this was poorly described throughout studies; however, most studies reported that senior surgeons performed this surgery under spinal anesthesia. Participants were usually routinely catheterized for some days.

Ten studies with 1287 randomized participants compared TUMT with sham. The devices used to deliver TUMT by these studies included:

- Thermex II (Abbou 1995)
- LEO Microthermer (Bdesha 1994)
- Prostatron (Blute 1996; De Wildt 1996; Nawrocki 1997)
- TherMatrx TMx-2000 (Albala 2002)
- ECP system (Brehmer 1999)
- Targis Microwave (Larson 1998)
- Dornier Urowave (Roehrborn 1998)
- Microwave Engineering Designs (Venn 1995)

Six studies with 632 randomized participants compared TUMT with TURP. The devices used to deliver TUMT by these studies included:

- Prostatron (Ahmed 1997; D'Ancona 1998; Dahlstrand 1995; Floratos 2001; Nørby 2002a)
- ProstaLund Feedback (Wagrell 2002)

Outcomes

Most studies reported urologic symptom scores and quality of life by IPSS and IPSS-quality of life, respectively. Adverse events were poorly reported, and in many cases we had to infer whether they were minor or major according to the Clavien-Dindo classification system. None of the studies reported sexual function as we had predefined, so we extracted data on adverse sexual function instead (i.e. impotence and retrograde ejaculation). Moreover, this information was usually reported in the subset of sexually-active participants. The reporting of indwelling catheter duration was very scarce across studies and influenced by routine versus selective catheterization during the procedure. Data on acute urinary retention were extracted from data on adverse events. Finally, information on the retreatment rates was scattered, and we had to infer it from the sections reporting the flow of participants or accompanying adverse events.

All studies reported short-term follow-up outcomes and only four studies in the TUMT versus TURP comparison reported long-term outcomes (D'Ancona 1998; Dahlstrand 1995; Floratos 2001; Wagrell 2002). In many cases, long-term outcomes were only reported in one arm of the study and without sufficient statistical details.

Funding sources

Most studies did not report their funding sources. Three studies were funded by their manufacturers (Larson 1998; Roehrborn 1998; Wagrell 2002), two by public institutions (Nawrocki 1997; Nørby 2002a) and one by a combination of manufacturers and public funders (Abbou 1995).

Excluded studies

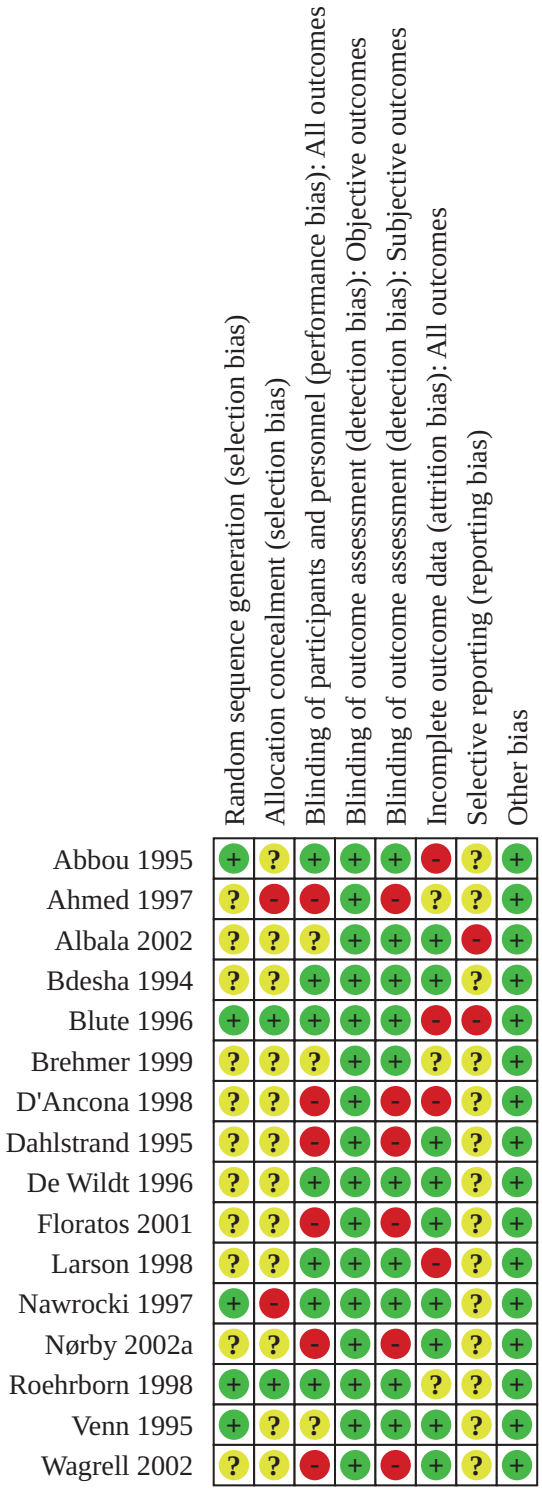
We excluded 22 studies (23 records) for the following reasons:

- Two studies addressed transrectal thermotherapy (Zerbib 1992; Zerbib 1994; Albala 2000)
- Three studies provided economic data on published trials (Kobelt 2004; Norby 2002b; Waldén 1998)
- Cross-over studies with insufficient data (Albala 2000; Tan 2005)
- Observational studies and other non-randomized comparisons (Arai 2000; D'Ancona 1997; Hahn 2000; Hansen 1998; Mulvin 1994; Ohigashi 2007; Servadio 1987; Trock 2004; Vesely 2006)
- Review articles identified through full-text assessment (Dahlstrand 2003; Nørby 2004)
- Ineligible comparison (Djavan 1999; Schelin 2006; Shore 2010)
- Terminated study (ISRCTN23921450)

Risk of bias in included studies

The summary of the risks of bias by study and domain is available in Figure 2.

Figure 2.



Allocation

Random sequence generation

Only five studies reported adequately how the random sequence was generated (Abbou 1995; Blute 1996; Nawrocki 1997; Roehrborn 1998; Venn 1995). The other studies did not provide sufficient information for this domain.

Allocation concealment

Only two studies reported an adequate method for allocation concealment (Blute 1996; Roehrborn 1998). One study used an inadequate method to conceal the allocation (Nawrocki 1997). The other studies did not provide sufficient information for this domain.

Blinding

Blinding of participants and personnel

For the TUMT versus sham comparison, we rated most studies as low risk of bias, since they used an adequate method for blinding (Abbou 1995; Bdesha 1994; Blute 1996; De Wildt 1996; Larson 1998; Nawrocki 1997; Roehrborn 1998). However, three studies did not specify whether personnel were blinded (Albala 2002; Brehmer 1999; Venn 1995), and are rated at unclear risk.

For the TUMT versus TURP comparison, we rated all studies at high risk of bias since blinding was not possible (Ahmed 1997; D'Ancona 1998; Dahlstrand 1995; Floratos 2001; Nørby 2002a; Wagrell 2002).

Blinding of outcome assessment

- Subjective outcomes (urologic symptom scores, quality of life, major adverse events, erectile function, ejaculatory function, and minor adverse events): we judged all unblinded studies for the TUMT versus TURP comparison as high risk of bias.
- Objective outcomes (retreatment, acute urinary retention, and indwelling urinary catheter): we rated all studies as low risk of bias for these outcomes that are not likely to be affected by lack of blinding.

Incomplete outcome data

We rated four studies (Abbou 1995; Blute 1996; D'Ancona 1998; Larson 1998) as high risk of bias due to high and unbalanced attrition affecting all outcomes. Three studies did not provide details on outcome data lost at follow-up (Ahmed 1997; Brehmer 1999; Roehrborn 1998). The rest of the studies were rated as low risk of bias.

Selective reporting

We rated all studies at unclear risk of bias, given the lack of available protocols. Two studies were reported as high risk of bias since they selectively reported outcomes for one of the arms of the study or only graphically (Albala 2002; Blute 1996).

Other potential sources of bias

We rated all studies at low risk of bias; no other sources of bias were identified.

Effects of interventions

See: **Summary of findings 1** Transurethral microwave thermotherapy compared to transurethral resection of the prostate for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia; **Summary of findings 2** Transurethral microwave thermotherapy compared to sham treatment for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia

1. TUMT versus TURP

Six studies (Ahmed 1997; D'Ancona 1998; Dahlstrand 1995; Floratos 2001; Nørby 2002a; Wagrell 2002) with 632 randomized participants were included under this comparison. See Table 1 for a summary of the characteristics of participants, interventions and comparisons. See Summary of findings 1.

1.1. Urologic symptom scores

Based on four studies (Ahmed 1997; D'Ancona 1998; Nørby 2002a; Wagrell 2002) with 306 participants, TUMT probably results in little to no difference in urologic symptom scores measured by IPSS scores when compared to TURP at 6 to 12 months follow-up (mean difference (MD) 1.00, 95% confidence interval (CI) −0.03 to 2.03; Analysis 1.1). In two studies (D'Ancona 1998; Dahlstrand 1995) with 108 participants that assessed this outcome with the Madsen-Iversen score (range 0 to 28) a small difference was found favoring TURP (MD 1.59, 95% CI 0.69 to 2.48; 2 studies, 108 participants; I^2 = 0%, Analysis 1.2). The certainty of the evidence is moderate, due to an overall high risk of bias.

Long-term data

Three studies (D'Ancona 1998; Dahlstrand 1995; Wagrell 2002) with 187 participants reported long-term data. We are uncertain of the effect of TUMT on urologic symptom scores when compared to TURP at 2- to 5-year follow-up (SMD 0.32, 95% CI 0.03 to 0.62; I^2 = 0%; Analysis 1.3). Another study with 155 participants (Floratos 2001) was not incorporated in meta-analysis due to missing data. It reported that the TUMT group had a reduction in IPSS scores from 20 to 12 at three years, whereas the TURP group had a reduction from 20 to 3 in the same period (P < 0.001). The certainty of the evidence is very low due to an overall high risk of bias (severe attrition at long-term follow-up) and imprecision.

Subgroup analysis

Since heterogeneity was extremely low, subgroup analysis by baseline severities found no significant differences across subgroups.

1.2. Quality of life

Based on one study with 136 participants (Wagrell 2002), TUMT likely results in little to no difference in the quality of life when compared to TURP at 12 month follow-up (MD −0.10, 95% CI −0.67 to 0.47; Analysis 1.5). Another study (Nørby 2002a) with 66 participants reported similar scores in quality of life in the TUMT group (median 2, IQR 1 to 3) and in the TURP group (median 1, IQR 1 - 2) at six-month follow-up (P = 0.64 from a three-arm comparison with interstitial laser coagulation). The certainty of the evidence is moderate, due to an overall high risk of bias.

Long-term data

Long-term data from Wagrell 2002 indicated that TUMT may result in little to no difference in the quality of life when compared to TURP at 60-month follow-up (MD 0.00, 95% CI −0.46 to 0.46; Analysis 1.6). Floratos 2001 (155 participants) reported that quality-of-life scores

decreased from 4 to 2 at three years in the TUMT group and from 4 to 1 in the TURP group (P < 0.001).

1.3. Major adverse events

Based on six studies (Ahmed 1997; D'Ancona 1998; Dahlstrand 1995; Floratos 2001; Nørby 2002a; Wagrell 2002) with 525 participants, TUMT probably results in significantly fewer major adverse events when compared to TURP at 6- to 12-month follow-up (RR 0.20, 95% CI 0.09 to 0.43; I^2 = 0%; Analysis 1.7). Based on 168 cases per 1000 men in the TURP group, this corresponds to 135 fewer (153 to 96 fewer) per 1000 men in the TUMT group. These events primarily included: hospitalization due to bleeding, clot retention, serious infection, TURP syndrome, and urethral stricture (requiring another surgical intervention). The certainty of the evidence is moderate, due to an overall high risk of bias.

Subgroup analysis

Since heterogeneity was extremely low, subgroup analysis by baseline severities found no significant differences across subgroups.

1.4. Retreatment

Based on five studies (D'Ancona 1998; Dahlstrand 1995; Floratos 2001; Nørby 2002a; Wagrell 2002) with 463 participants, TUMT probably results in a large increase in the need for retreatment at 6- to 36-month follow-up (RR 7.07, 95% CI 1.94 to 25.82; I^2 = 0%; Analysis 1.9). Retreatment was usually TURP, TUMT, or TUMT and then TURP. Based on no cases per 1000 men in the TURP group, this corresponds to 90 more (40 to 150 more) per 1000 men in the TUMT group. The certainty of the evidence is moderate, due to an overall high risk of bias.

1.5. Erectile function

Based on five studies (Ahmed 1997; Dahlstrand 1995; Floratos 2001; Nørby 2002a; Wagrell 2002) with 337 participants, TUMT may result in little or no difference in erectile function when compared to TURP at 6- to 12-month follow-up (RR 0.63, 95% CI 0.24 to 1.63; I^2 = 35%; Analysis 1.10). The certainty of the evidence is low due to an overall high risk of bias and imprecision (the incidence is mostly reported in a subset of sexually-active participants).

Long-term data

One study (Wagrell 2002) reported five-year data on erectile dysfunction with an incidence of 7.5% in the TUMT group and 15.4% in the TURP group (data were available for 119/154 randomized participants). The certainty of the evidence is very low due to an overall high risk of bias and imprecision (the incidence is mostly reported in a subset of sexually-active participants with high attrition).

1.6. Ejaculatory function

Based on four studies (Ahmed 1997; Dahlstrand 1995; Floratos 2001; Nørby 2002a) with 241 participants, TUMT may result in fewer cases of retrograde ejaculation when compared to TURP at 6- to 12-month follow-up (RR 0.36, 95% CI 0.24 to 0.53; I^2 = 0%, Analysis 1.11). The certainty of the evidence is low, due to an overall high risk of bias and imprecision (the incidence mostly reported in a subset of sexually-active participants).

1.7. Minor adverse events

Based on five studies (Ahmed 1997; D'Ancona 1998; Dahlstrand 1995; Nørby 2002a; Wagrell 2002) with 397 participants, TUMT may result in little to no difference in the incidence of minor adverse events when compared to TURP at 6- to 12-month follow-up (RR 1.27, 95% CI 0.75 to 2.15; I^2 = 0%, Analysis 1.12). These events primarily included urinary tract infection. The certainty of the evidence is low due to an overall high risk of bias and imprecision.

1.8. Acute urinary retention

Based on four studies (Ahmed 1997; D'Ancona 1998; Nørby 2002a; Wagrell 2002) with 343 participants, TUMT may result in an increased incidence of acute urinary retention when compared to TURP at 6- to 12-month follow-up (RR 2.61, 95% CI 1.05 to 6.47; I^2 = 40%; Analysis 1.13). The certainty of the evidence is low due to an overall high risk of bias and imprecision (the incidence mostly reported in a subset of sexually-active participants). In many cases, we highlight that participants undergoing TURP were routinely catheterized after surgery and for shorter periods of time than TUMT (see below).

1.9. Indwelling urinary catheter

The evidence is very uncertain about the effect of TUMT on the duration of catheterization when compared to TURP. This outcome was not adequately reported across the included studies. Furthermore, one study (Floratos 2001) reported that per-protocol all participants were catheterized for 2 to 4 days. Most of the information we found was narrative:

- Ahmed 1997 reported that three participants required an indwelling catheter for 10 days to six weeks in the TUMT group and two participants for four weeks in the TURP group.
- D'Ancona 1998 reported that the mean days of catheterization were 12.7 (range 6 to 35) in the TUMT group and 4.1 (range 4 to 5) in the TURP group.
- Dahlstrand 1995 reported that eight participants required catheterization for less than one week in the TUMT group and two participants in the TURP group required prolonged catheterization.
- Nørby 2002a reported that the median catheterization time in the TUMT group was seven days for those treated with Prostasoft v2.0 and 14 in those with Prostasoft v2.5, whereas the median in the TURP group was two days.
- Wagrell 2002 reported that the mean catheterization time was 14 days (SD 8) after TUMT and 3 days (SD 4) after TURP.

The certainty of the evidence is very low, due to an overall high risk of bias, inconsistency and imprecision.

2. TUMT versus sham

Ten studies with 1287 randomized participants were included under this comparison (Abbou 1995; Albala 2002; Bdesha 1994; Blute 1996; Brehmer 1999; De Wildt 1996; Larson 1998; Nawrocki 1997; Roehrborn 1998; Venn 1995). See Table 1 for a summary of the characteristics of participants, interventions and comparisons. Refer to the Summary of findings 2 for the main outcomes.

2.1. Urologic symptom scores

Based on four studies (Bdesha 1994; Blute 1996; Larson 1998; Roehrborn 1998) with 483 participants, TUMT probably reduces urologic symptom scores measured by IPSS at three to six months when compared to sham (MD −5.40, 95% CI −6.97 to −3.84; I^2 = 45%; Analysis 2.1). Similar results were obtained in two studies (Blute 1996; De Wildt 1996) with 196 participants that used the Madsen-Iversen score (range 0 to 28) (MD −5.10, 95% CI −6.42 to −3.79; I^2 = 0%; Analysis 2.2). The certainty of the evidence is moderate, due to an overall high risk of bias.

Responder rate

Based on four studies (Abbou 1995; Bdesha 1994; De Wildt 1996; Venn 1995) with 322 participants, TUMT may cause little to no difference in the responder rate, defined as a large decrease in symptom scores at three months (RR 2.50, 95% CI 0.57 to 10.86; Analysis 2.4.1), but it may increase the responder rate at 12 months (RR 3.10, 95% CI 1.34 to 7.17, see Analysis 2.4.2). The certainty of the evidence is low, due to imprecision (few events) and overall high risk of bias.

Two studies were not included in the meta-analysis, since they did not report standard deviations or exact P values:

- Albala 2002 with 183 participants reported that the mean AUA score in the active treatment group was 12.4 and 17 in the control group ("statistically significant", P value not available).
- Nawrocki 1997 with 78 participants reported that the mean score in the TUMT group was 9.5 (range 1 to 27) and 9.5 (range 0 to 30) in the sham group (P = 0.81).

2.2. Quality of life

Based on two studies (Larson 1998; Roehrborn 1998) with 347 participants, TUMT may result in little to no difference in quality of life at six months as measured by IPSS subscore (MD −0.95, 95% CI −1.14 to −0.77; I^2 = 25%; Analysis 2.5). The certainty of the evidence is low, due to an overall high risk of bias and imprecision.

2.3. Major adverse events

The evidence is very uncertain about the effect of TUMT on adverse events.

Most studies did not comprehensively report adverse events during their 6- to 12-month follow-up. Six studies (Abbou 1995; Albala 2002; Bdesha 1994; Brehmer 1999; Nawrocki 1997; Roehrborn 1998) with 662 participants reported that all adverse events were minor, but one participant in one study (Bdesha 1994) underwent TURP after persistent acute urinary retention. One multicenter study (De Wildt 1996) with 93 participants did not adequately describe major adverse events, but one of the reports of a single centre of the same study (n = 40) reported that one participant in the TUMT group received TURP due to persistent urinary tract retention and one participant in the sham group received TUMT due to a lesion in the verumontanum. Another study (Larson 1998) with 169 participants reported that two participants were hospitalized after TUMT due to urethral stricture and urinary tract infection. The remaining two studies (Blute 1996; Venn 1995) did not report the incidence of adverse events.

The certainty of the evidence is very low due to an overall high risk of bias and severe imprecision.

2.4. Retreatment

Based on two studies (Bdesha 1994; Brehmer 1999) with 82 participants, TUMT may reduce the incidence of retreatment at 6 to 12 months (RR 0.27, 95% CI 0.08 to 0.88; I^2 = 0%; Analysis 2.6). Based on 194 retreatments per 1000 men in the sham group, this corresponds to 141 fewer (178 to 23 fewer) per 1000 men in the TUMT group. The certainty of the evidence is low, due to an overall high risk of bias and imprecision (few events).

One study (Abbou 1995) reported that 9/66 (14%) in the TUMT group, 6/31 (19%) in the sham group withdrew due to lack of improvement to seek other treatments, but they comprised either medical or surgical treatment. Another study (Larson 1998) reported that 7/42 (17%) participants in the sham group and 2/125 (2%) in the TUMT group required a subsequent therapeutic procedure or medication.

2.5. Erectile function

The evidence is very uncertain about the effect of TUMT on erectile function at 6 to 12 months.

Three studies (Bdesha 1994; Blute 1996; Roehrborn 1998) with 375 participants reported this outcome within the description of adverse events. Bdesha 1994 and Blute 1996 reported that there were normal erections and no report of sexual dysfunction respectively. Roehrborn 1998 reported that 44 (28.9%) participants in the TUMT group and one (1.4%) in the sham group suffered sexual dysfunction, including one case of impotence due to corporeal fibrosis.

The certainty of the evidence is very low, due to an overall high risk of bias and severe imprecision.

2.6. Ejaculatory function

The evidence is very uncertain about the effect of TUMT on ejaculatory function at 6 to 12 months.

Five studies (Albala 2002; Bdesha 1994; Blute 1996; Larson 1998; Roehrborn 1998) with 727 participants reported this outcome within the description of adverse events. Albala 2002, Bdesha 1994, and Blute 1996 reported that there were normal erections and no report of sexual dysfunction. Roehrborn 1998 reported that 44 (28.9%) participants in the TUMT group and one (1.4%) in the sham group suffered sexual dysfunction, including mostly participants with hematospermia and other ejaculatory abnormalities. Larson 1998 reported that five participants (4%) had a loss of ejaculate after TUMT and no cases in the sham group.

The certainty of the evidence is very low, due to an overall high risk of bias and severe imprecision.

2.7. Minor adverse events

Most studies did not comprehensively report adverse events during their 6- to 12-month follow-up. Based on three studies (Abbou 1995; Blute 1996; Larson 1998) with 378 participants, TUMT may increase the incidence of minor adverse events compared to sham (RR 1.42, 95% CI 1.00 to 2.01; I^2 = 31%; Analysis 2.7). The most commonly-described adverse events were: hematuria, urethral bleeding, acute urinary retention and urinary tract infection. Six studies were not included in the meta-analysis, since they did not report the global

incidence of minor adverse events, but the narrative description of the findings are similar to the main analysis of this outcome.

- Albala 2002 (200 participants) reported that both the active treatment arm (6.6%) and the sham arm (4.8%) suffered from dysuria. Gross hematuria (9.1%) and bladder spasm (4.1%) were only reported in the active treatment arm.
- Bdesha 1994 (40 participants) reported that 65% of the active treatment and 60% of the sham-treated participants experienced bladder spasm, while 82% and 83% respectively reported mild or moderate discomfort during treatment. Thirty percent of all participants reported transient dysuria, urgency, frequency or bloodstained urethral discharge lasting up to 48 hours (no disaggregated data).
- Brehmer 1999 (44 participants) reported that two participants contracted bacterial cystitis (no disaggregated data).
- De Wildt 1996 (93 participants) reported that most participants had some hematuria for up to three days. However, one of the reports of a single centre of the same study (n = 40) said that five participants required treatment for urinary tract infection in the TUMT group and one in the sham group.
- Nawrocki 1997(120 participants) reported that all participants treated by standard or simulated TUMT experienced some hematuria and dysuria following treatment, and that these symptoms were self-limiting and none required specific treatment.
- Roehrborn 1998 (220 participants) reported that the main difference in minor adverse events was pain on the day of the treatment (87.8% of the actively treated and 65.8% of sham-treated participants). Others included: bladder spasms, urethral bleeding, and hematuria and other transient adverse events that were distributed similarly across groups.

The remaining study (Venn 1995) did not report the incidence of adverse events. The certainty of the evidence is low, due to an overall high risk of bias and imprecision.

2.8. Acute urinary retention

Based on eight studies (Abbou 1995; Albala 2002; Bdesha 1994; Blute 1996; De Wildt 1996; Larson 1998; Nawrocki 1997; Roehrborn 1998) with 995 participants, TUMT probably results in a large increase in the incidence of acute urinary retention at 6- to 12-month follow-up (RR 9.02, 95% CI 3.31 to 24.63; I^2 = 0%; Analysis 2.8). Based on six cases per 1000 men in the sham group, this corresponds to 54 more (20 to 148 more) per 1000 men in the TUMT group. The certainty of the evidence is moderate, due to high risk of bias.

2.9. Indwelling urinary catheter

This outcome was not adequately reported across the included studies. Four studies reported that participants that suffered from acute urinary retention (see section above) were catheterized for one to six weeks (Abbou 1995; Bdesha 1994; De Wildt 1996; Nawrocki 1997). In some studies (Albala 2002; Larson 1998; Roehrborn 1998), catheterization after each procedure was routinely maintained for two to four days. One study (Brehmer 1999) reported that four participants were catheterized for four days (no disaggregated data by group).

Secondary analyses

Subgroup analysis based on age

We were unable to conduct this analysis due to the lack of data.

Subgroup analysis based on prostate volume

We were unable to conduct this analysis due to the lack of data.

Subgroup analysis based on baseline severity of LUTS

Our predefined subgroup analysis suggests that participants with more severe symptoms (MD −5.07, 95% CI −5.97 to −4.18) may experience less symptom improvement compared to those with moderate symptoms at baseline (MD −9.10, 95% CI −12.83 to −5.37, test for subgroup differences: P = 0.04, I^2 = 76.4%; Analysis 2.3). There were insufficient data to perform these subgroup analyses on other primary outcomes.

3. Other comparisons

We found no trials for the following comparisons:

- TUMT versus CRFWVT
- TUMT versus PUL
- TUMT versus PAE
- TUMT versus TIND

DISCUSSION

Summary of main results

We found evidence for our two main comparisons.

TUMT versus TURP

Based on data from six studies with 414 participants, when compared to TURP, TUMT probably results in little to no difference in urologic symptom scores in the short term, but due to the lack of any eligible study with follow-up longer than 12 months, we are uncertain about the long-term effects. There may be little to no difference in minor adverse events, quality of life or erectile function between these interventions. TUMT likely results in significantly fewer major adverse events and less ejaculatory dysfunction compared to TURP. TUMT, however, likely results in a large increase in the need for retreatment (usually by repeated TUMT or TURP) and acute urinary retention. The duration of indwelling catheterization was not adequately reported across studies.

TUMT versus sham

Based on data from 10 studies with 679 participants, we found that, compared to sham, TUMT probably reduces urologic symptoms scores at short-term follow-up and may result in a higher responder rate at long-term follow-up. TUMT may also reduce the need for retreatment, but it may cause little to no difference in the quality of life. We are very uncertain of the effects on major adverse events, or on erectile and ejaculatory functions. TUMT probably results in a large increase in the incidence of acute urinary retention. The incidence of minor adverse events and the duration of indwelling catheterization was not adequately reported across studies.

Overall completeness and applicability of evidence

The studies did not consistently define or report on adverse events, particularly dysuria, hematuria, and sexual dysfunction, and our estimates for these complications may be unreliable. Few studies evaluated the quality of life. Although studies usually reported the occurrence of urinary retention, they did not consistently or uniformly indicate its duration or the use of catheterization. One important complication that was not reported in the clinical trial literature was thermal injury. On 11 October 2000, the United States Food and Drug Administration (FDA) published a Public Health Notification because they had received 16 reports of severe thermal injury associated with TUMT, including 10 resulting in fistula formation and six resulting in tissue damage to the penis or urethra (Henney 2000). The FDA noted that the injuries could take hours or days to develop. Although the FDA recommended several corrective measures for physicians, they considered TUMT to be safe and effective based on the performance of over 25,000 procedures.

The current American Urological Association guidelines for the management of LUTS considered TUMT to be an appropriate alternative for treating men with lower urinary tract symptoms with small- to average-size prostate (Parsons 2020), with the warning that patients should be advised that surgical retreatment rates are higher compared to TURP, which corresponds with the findings of our review. The Canadian guidelines considered TUMT an optional treatment for men with moderate symptoms, with similar considerations about retreatment (Nickel 2018). The European Association of Urology does not list TUMT as one of their alternatives for managing LUTS (EAU 2021).

Quality of the evidence

The certainty of the evidence was primarily affected by:

- High risk of bias across studies: most studies did not report the randomization process adequately, and for the TUMT versus TURP comparison none of the included studies was blinded.
- Imprecision: details on ejaculatory and erectile function were only reported as binary outcomes in a subset of sexually-active participants.

Furthermore, our interpretation of the retreatment data was cautious, since this was not consistently reported across studies. In some cases, it was described in the initial flow of participants across the studies, in some studies as a comment about follow-up, and in other cases within adverse events. The urinary catheterization data were inconsistently reported, since some studies included them as a standard procedure, and some measured them selectively.

Potential biases in the review process

This update changed the original protocol and replaced it with current methods applied to a suite of other reviews by the Urology Review Group on lower urinary tract symptoms due to benign prostatic hyperplasia (Hwang 2019; Jung 2019; Jung 2020; Kang 2020). This allowed us to secure comparability across interventions and to include the findings of this review in our upcoming network meta-analysis (Franco 2020).

Considering that review methods have improved over time, including the details of the search strategy, we decided to run our searches from inception using the original inclusion criteria but excluding the comparison to alpha-blockers. While our search identified more references for the included studies in the previous review, it failed to identify the included studies Abbou 1995 and Brehmer 1999. Furthermore, we identified the citations of some additional reports of the included studies, including long-term data on one of the studies, but we were unable to retrieve the full text through different means, including the use of Task Exchange (Albala 2000a; Dahlstrand 1994; Dahlstrand 1997; Dahlstrand 1998; Roehrborn 1997). We also identified another randomized study that was cited in the Background of the included studies (Devonec 1994) but again we were unable to retrieve the full text.

Finally, reporting on some of the outcomes was scattered and not thoroughly detailed. For some outcomes, including adverse events, retreatment, acute urinary retention, ejaculatory and erectile function, we had to interpret the data available in the flow of participants and in the section describing "complications." It is unclear whether the studies reported all events or only those they considered relevant, especially with a lack of a prespecified protocol.

Agreements and disagreements with other studies or reviews

The previous version of this Cochrane Review yielded similar results for the global effects of TUMT in relation to sham and TURP (Hoffman 2012). The main difference from the previous version of the review is that we pooled the data for more outcomes in each comparison, with additional critical outcomes in the summary of findings tables. This provided us with a greater understanding of the differences between TURP and TUMT. In this version, we favor an interpretation of similar urinary symptoms scores at short-term follow-up, considering that long-term data from selected studies provided very low-certainty evidence to highlight substantial differences between these interventions. We also found important differences in the incidence of major adverse events and the incidence of retrograde ejaculation between these interventions, favoring TUMT.

We found a few additional systematic reviews on this topic. A health technology assessment from Sweden assessed the average IPSS score, and concluded that TUMT was inferior to TURP in the improvement of symptoms, which does not take into account the confidence interval and minimally important differences (SBU 2011). Furthermore, the authors stated that they could not determine the differences in major adverse events, as we found in our review, which could be explained by the lack of grouping of serious events. Nevertheless, the findings related to retreatment were similar. Another systematic review reported similar results for urinary symptoms and retreatment, but highlighted the lower incidence of serious adverse events with TURP than with TUMT (Barry Delongchamps 2012). They state that the rate of retreatment for TUMT may vary from 20% to 80% (focusing on observational data), but at the same time highlight that the rate of retreatment is lower in long-term randomized trials such as the one included in our review (Wagrell 2002). Finally, two systematic reviews focusing on sexual outcomes reported a lower incidence of sexual adverse events (especially retrograde ejaculation) for men undergoing TUMT compared to TURP, which agrees with our findings (Frieben 2010; Marra 2016). None of these studies followed Cochrane methods for high-quality reviews.

AUTHORS' CONCLUSIONS

Implications for practice

TUMT provides a similar reduction in urinary symptoms compared to the standard treatment (TURP), with fewer major adverse events and fewer cases of ejaculatory dysfunction at short-term follow-up. However, TUMT probably results in a large increase in retreatment rates. Most of the evidence is short-term and from studies with a high risk of bias. Patients' values and preferences, their comorbidities and the effects of other available minimally-invasive procedures, among other factors, can guide clinicians when choosing the optimal treatment for this condition.

Implications for research

Relatively few patients have been studied in controlled clinical trials of TUMT, and there is a paucity of research on this procedure in the last 20 years. Further studies with better reporting, using randomized treatment allocation, larger sample sizes, and comprehensive measures of relevant outcomes, including adverse events, are still needed to better define the role of TUMT techniques for treating lower urinary tract symptoms in men with benign prostatic hyperplasia. With the emergence of newer minimally-invasive treatments, head-to-head comparisons between them could clarify their relative effectiveness.

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* Indicates the major publication for the study

Article 3: Minimally Invasive Procedures

(Cochrane review with network meta-analysis)[4]

We included 27 trials involving 3017 men, mostly over age 50, with severe LUTS due to BPH. The overall certainty of the evidence was low to very low due to concerns regarding bias, imprecision, inconsistency (heterogeneity), and incoherence. Based on the network meta-analysis, the results for our main outcomes were as follows.

- Urologic symptoms (19 studies, 1847 participants): PUL and PAE may result in little to no difference in urologic symptoms scores compared to TURP (3 to 12 months; MD of IPSS range 0 to 35; higher scores indicate worse symptoms; PUL: 1.47, 95% CI -4.00 to 6.93; PAE: 1.55, 95% CI -1.23 to 4.33; low-certainty evidence). CRFWVT, TUMT, and TIND may result in worse urologic symptoms scores compared to TURP at short-term follow-up, but the CIs include little to no difference (CRFWVT: 3.6, 95% CI -4.25 to 11.46; TUMT: 3.98, 95% CI 0.85 to 7.10; TIND: 7.5, 95% CI -0.68 to 15.69; low-certainty evidence).
- Quality of life (QoL) (13 studies, 1459 participants): All interventions may result in little to no difference in the QoL scores, compared to TURP (3 to 12 months; MD of IPSS-QoL score; MD range 0 to 6; higher scores indicate worse symptoms; PUL: 0.06, 95% CI -1.17 to 1.30; PAE: 0.09, 95% CI -0.57 to 0.75; CRFWVT: 0.37, 95% CI -1.45 to 2.20; TUMT: 0.65, 95% CI -0.48 to 1.78; TIND: 0.87, 95% CI -1.04 to 2.79; low-certainty evidence).
- Major adverse events (15 studies, 1573 participants): TUMT probably results in a large reduction of major adverse events compared to TURP (RR 0.20, 95% CI 0.09 to 0.43; moderate-certainty evidence). PUL, CRFWVT, TIND and PAE may also result in a large reduction in major adverse events, but CIs include substantial benefits and harms at three months to 36 months; PUL: RR 0.30, 95% CI 0.04 to 2.22; CRFWVT: RR 0.37, 95% CI 0.01 to 18.62; TIND: RR 0.52, 95% CI 0.01 to 24.46; PAE: RR 0.65, 95% CI 0.25 to 1.68; low-certainty evidence).
- Retreatment (10 studies, 799 participants): We are uncertain about the effects of PAE and PUL on retreatment compared to TURP (12 to 60 months; PUL: RR 2.39, 95% CI 0.51 to 11.1; PAE: RR 4.39, 95% CI 1.25 to 15.44; very low-certainty evidence). TUMT may result in higher retreatment rates (RR 9.71, 95% CI 2.35 to 40.13; low-certainty evidence). There was insufficient data to include data on CRFWVT and TIND in this analysis.
- Erectile function (six studies, 640 participants): We are very uncertain of the effects of minimally invasive treatments on erectile function (MD of International Index of Erectile Function [IIEF-5]; range 5 to 25; higher scores indicates better function; CRFWVT: 6.49, 95% CI -8.13 to 21.12; TIND: 5.19, 95% CI -9.36 to 19.74; PUL: 3.00, 95% CI -5.45 to 11.44; PAE: -0.03, 95% CI -6.38, 6.32; very low-certainty evidence).
- Ejaculatory dysfunction (eight studies, 461 participants): We are uncertain of the effects of PUL, PAE and TUMT on ejaculatory dysfunction compared to TURP (3 to 12 months; PUL: RR 0.05, 95 % CI 0.00 to 1.06; PAE: RR 0.35, 95% CI 0.13 to 0.92; TUMT: RR 0.34, 95% CI 0.17 to 0.68; low-certainty evidence). There was insufficient data to include data on CRFWVT and TIND in this analysis.
- TURP is the reference treatment with the highest likelihood of being the most efficacious for urinary symptoms, QoL and retreatment but the least favourable in terms of major adverse events, erectile function and ejaculatory function. Among minimally invasive procedures with sufficient data for analysis, PUL and PAE have the highest likelihood of

[4] Franco JV, Jung JH, Imamura M, Borofsky M, Omar MI, Escobar Liquitay CM, Young S, Golzarian J, Veroniki AA, Garegnani L, Dahm P. Minimally invasive treatments for lower urinary tract symptoms in men with benign prostatic hyperplasia: a network meta-analysis. Cochrane Database Syst Rev. 2021 Jul 15;7(7):CD013656. doi: 10.1002/14651858.CD013656.pub2. PMID: 34693990; PMCID: PMC8543673. *Impact Factor 2021 11.874 - Cited 13 times (07.07.2023)*

being the most efficacious for urinary symptoms and QoL, TUMT for major adverse events, PUL for retreatment, CRFWVT and TIND for erectile function and PUL for ejaculatory function.

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Minimally invasive treatments for lower urinary tract symptoms in men with benign prostatic hyperplasia: a network meta-analysis (Review)

Franco JVA, Jung JH, Imamura M, Borofsky M, Omar MI, Escobar Liquitay CM, Young S, Golzarian J, Veroniki AA, Garegnani L, Dahm P

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[Intervention Review]

Minimally invasive treatments for lower urinary tract symptoms in men with benign prostatic hyperplasia: a network meta-analysis

Juan VA Franco[1], Jae Hung Jung[2,3], Mari Imamura[4], Michael Borofsky[5], Muhammad Imran Omar[6,7], Camila Micaela Escobar Liquitay[8], Shamar Young[9], Jafar Golzarian[9], Areti Angeliki Veroniki[10], Luis Garegnani[1], Philipp Dahm[5,11]

[1]Associate Cochrane Centre, Instituto Universitario Hospital Italiano de Buenos Aires, Buenos Aires, Argentina. [2]Department of Urology, Yonsei University Wonju College of Medicine, Wonju, Korea, South. [3]Center of Evidence-Based Medicine, Institute of Convergence Science, Yonsei University, Seoul, Korea, South. [4]Health Services Research Unit, University of Aberdeen, Aberdeen, UK. [5]Department of Urology, University of Minnesota, Minneapolis, Minnesota, USA. [6]Guidelines Office, European Association of Urology, Arnhem, Netherlands. [7]Academic Urology Unit, University of Aberdeen, Aberdeen, UK. [8]Central Library, Instituto Universitario Hospital Italiano de Buenos Aires, Buenos Aires, Argentina. [9]Department of Radiology, Division of Interventional Radiology & Vascular Imaging, University of Minnesota, Minneapolis, Minnesota, USA. [10]Department of Primary Education, School of Education, University of Ioannina, Ioannina, Greece. [11]Urology Section, Minneapolis VA Health Care System, Minneapolis, Minnesota, USA

Contact: Juan VA Franco, juan.franco@hospitalitaliano.org.ar.

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ABSTRACT

Background

A variety of minimally invasive treatments are available as an alternative to transurethral resection of the prostate (TURP) for management of lower urinary tract symptoms (LUTS) in men with benign prostatic hyperplasia (BPH). However, it is unclear which treatments provide better results.

Objectives

Our primary objective was to assess the comparative effectiveness of minimally invasive treatments for lower urinary tract symptoms in men with BPH through a network meta-analysis. Our secondary objective was to obtain an estimate of relative ranking of these minimally invasive treatments, according to their effects.

Search methods

We performed a comprehensive search of multiple databases (CENTRAL, MEDLINE, Embase, Scopus, Web of Science and LILACS), trials registries, other sources of grey literature, and conference proceedings, up to 24 February 2021. We had no restrictions on language of publication or publication status.

Selection criteria

We included parallel-group randomized controlled trials assessing the effects of the following minimally invasive treatments, compared to TURP or sham treatment, on men with moderate to severe LUTS due to BPH: convective radiofrequency water vapor therapy (CRFWVT); prostatic arterial embolization (PAE); prostatic urethral lift (PUL); temporary implantable nitinol device (TIND); and transurethral microwave thermotherapy (TUMT).

Data collection and analysis

Two review authors independently screened the literature, extracted data, and assessed risk of bias. We performed statistical analyses using a random-effects model for pair-wise comparisons and a frequentist network meta-analysis for combined estimates. We interpreted them according to Cochrane methods. We considered a minimally important difference of three points for the International Prostate Symptoms Score[IPSS]. We used the GRADE approach to rate the certainty of evidence.

Main results

We included 27 trials involving 3017 men, mostly over age 50, with severe LUTS due to BPH. The overall certainty of evidence was low to very low due to concerns regarding bias, imprecision, inconsistency (heterogeneity), and incoherence. Based on the network meta-analysis, results for our main outcomes were as follows.

Urologic symptoms (19 studies, 1847 participants): PUL and PAE may result in little to no difference in urologic symptoms scores compared to TURP (3 to 12 months; MD of IPSS range 0 to 35; higher scores indicate worse symptoms; PUL: 1.47, 95% CI -4.00 to 6.93; PAE: 1.55, 95% CI -1.23 to 4.33; low-certainty evidence). CRFWVT, TUMT, and TIND may result in worse urologic symptoms scores compared to TURP at short-term follow-up, but the CIs include little to no difference (CRFWVT: 3.6, 95% CI -4.25 to 11.46; TUMT: 3.98, 95% CI 0.85 to 7.10; TIND: 7.5, 95% CI -0.68 to 15.69; low-certainty evidence).

Quality of life (QoL) (13 studies, 1459 participants): All interventions may result in little to no difference in the QoL scores, compared to TURP (3 to 12 months; MD of IPSS-QoL score; MD range 0 to 6; higher scores indicate worse symptoms; PUL: 0.06, 95% CI -1.17 to 1.30; PAE: 0.09, 95% CI -0.57 to 0.75; CRFWVT: 0.37, 95% CI -1.45 to 2.20; TUMT: 0.65, 95% CI -0.48 to 1.78; TIND: 0.87, 95% CI -1.04 to 2.79; low-certainty evidence).

Major adverse events (15 studies, 1573 participants): TUMT probably results in a large reduction of major adverse events compared to TURP (RR 0.20, 95% CI 0.09 to 0.43; moderate-certainty evidence). PUL, CRFWVT, TIND and PAE may also result in a large reduction in major adverse events, but CIs include substantial benefits and harms at three months to 36 months; PUL: RR 0.30, 95% CI 0.04 to 2.22; CRFWVT: RR 0.37, 95% CI 0.01 to 18.62; TIND: RR 0.52, 95% CI 0.01 to 24.46; PAE: RR 0.65, 95% CI 0.25 to 1.68; low-certainty evidence).

Retreatment (10 studies, 799 participants): We are uncertain about the effects of PAE and PUL on retreatment compared to TURP (12 to 60 months; PUL: RR 2.39, 95% CI 0.51 to 11.1; PAE: RR 4.39, 95% CI 1.25 to 15.44; very low-certainty evidence). TUMT may result in higher retreatment rates (RR 9.71, 95% CI 2.35 to 40.13; low-certainty evidence). There was insufficient data to include data on CRFWVT and TIND in this analysis.

Erectile function (six studies, 640 participants): We are very uncertain of the effects of minimally invasive treatments on erectile function (MD of International Index of Erectile Function [IIEF-5]; range 5 to 25; higher scores indicates better function; CRFWVT: 6.49, 95% CI -8.13 to 21.12; TIND: 5.19, 95% CI -9.36 to 19.74; PUL: 3.00, 95% CI -5.45 to 11.44; PAE: -0.03, 95% CI -6.38, 6.32; very low-certainty evidence).

Ejaculatory dysfunction (eight studies, 461 participants): We are uncertain of the effects of PUL, PAE and TUMT on ejaculatory dysfunction compared to TURP (3 to 12 months; PUL: RR 0.05, 95 % CI 0.00 to 1.06; PAE: RR 0.35, 95% CI 0.13 to 0.92; TUMT: RR 0.34, 95% CI 0.17 to 0.68; low-certainty evidence). There was insufficient data to include data on CRFWVT and TIND in this analysis.

TURP is the reference treatment with the highest likelihood of being the most efficacious for urinary symptoms, QoL and retreatment, but the least favorable in terms of major adverse events, erectile function and ejaculatory function. Among minimally invasive procedures with sufficient data for analysis, PUL and PAE have the highest likelihood of being the most efficacious for urinary symptoms and QoL, TUMT for major adverse events, PUL for retreatment, CRFWVT and TIND for erectile function and PUL for ejaculatory function.

Authors' conclusions

Minimally invasive treatments may result in similar or worse effects concerning urinary symptoms and QoL compared to TURP at short-term follow-up. They may also result in fewer major adverse events. PUL and PAE resulted in better rankings for symptoms scores and PUL may result in fewer retreatments, especially compared to TUMT, which had the highest retreatment rates. We are very uncertain about the effects of these interventions on erectile and ejaculatory function. There was limited long-term data, especially for CRFWVT and TIND. Future high-quality studies with more extended follow-up, comparing different, active treatment modalities, and adequately reporting critical outcomes relevant to patients, including those related to sexual function, could provide more information on the relative effectiveness of these interventions.

PLAIN LANGUAGE SUMMARY

How do minimally invasive treatments compare to traditional surgery for treating lower urinary tract symptoms in men?

Background

Older men often suffer from urinary complaints such as frequent urination or a weak urine stream. If these symptoms can be blamed on an enlarged prostate gland and lifestyle changes and medications don't help enough, there are surgical procedures that may help. One such procedure is called transurethral resection of the prostate (traditional surgery). This traditional surgery has been widely used for a

long time, and is known to work well, but it does require anesthesia and has several unwanted effects. Other 'minimally invasive' surgical procedures have become available. These procedures are said to work similarly well, but with fewer unwanted effects. The five minimally invasive procedures are 'prostatic urethral lift', 'convective radiofrequency water vapor therapy', 'transurethral microwave thermotherapy', 'prostatic arterial embolization', and 'temporary implantable nitinol device'.

Review question

We performed this review to compare five newer treatment forms for men with lower urinary tract symptoms to traditional surgery or 'sham surgery'. In sham surgery, men thought they were getting surgery but really did not have anything done.

Methods

We used recommended Cochrane methods and GRADE to rate the certainty of evidence. We also used a special statistical method called network meta-analysis to compare different treatments.

Search date

The findings of our study are up-to-date until February 2021.

Included studies

We included 27 randomized controlled trials. In this type of study, random 'chance' determined whether men were assigned to receive one of the newer surgical procedures, or traditional surgery (or sham surgery). This method of assigning participants to 'intervention' or 'control' groups helps to reduce bias in research studies.

Men were mostly over 50 years of age and had severe urinary symptoms. Most studies (16 studies) used transurethral microwave thermotherapy. Eleven studies followed men for less than one year and nine studies followed men for one year. Only seven studies followed men for two years or longer.

Funding

Most studies did not report their funding sources, while others reported that those who paid for the study received at least some money for the company that made the device that was used.

Key results

We only report the results for what we thought were the three most important outcomes: urinary symptoms, urinary quality of life, and unwanted effects, comparing these treatments to traditional surgery. The review also includes information on several other outcomes and how they compared to sham surgery.

Prostatic urethral lift and arterial embolization may result in little to no difference in men's symptoms than traditional surgery in the short term (up to 12 months). The other minimally invasive interventions may result in worse symptom scores than traditional surgery at short-term follow-up, but there may be no difference. All treatments may result in little to no difference in the quality of life compared to traditional surgery at short-term follow-up. Transurethral microwave thermotherapy probably results in a large reduction in major adverse events compared to traditional surgery, whereas the other minimally invasive treatments may result in a large reduction in major adverse events. Transurethral microwave thermotherapy may result in higher retreatment rates, but we are uncertain about the other minimally invasive procedures. We are also uncertain of the effects of these interventions on erectile function and ejaculation.

Certainty of evidence

Our level of certainty about the evidence was different for each of the outcomes, but was mostly low or very low. This means that we cannot be sure that the results of this review are accurate. A common reason for grading down the certainty of evidence included flaws in the ways the studies were planned and conducted. Also, the results differed a lot among studies, and the results of studies were often imprecise.

SUMMARY OF FINDINGS

Summary of findings 1. Urologic symptoms scores - short term

Minimally invasive treatments versus transurethral resection of the prostate				
Patient or population: men with moderate to severe lower urinary symptoms due to benign prostatic hyperplasia **Interventions:** minimally invasive treatments **Comparator (reference):** transurethral resection of the prostate **Setting:** hospital procedure – outpatient follow-up				
Outcome: urinary symptoms scores **Measured by:** IPSS range 0-35 (lower scores indicate fewer symptoms) **Follow-up:** 3 to 12 months (most of the data is at 3 months follow-up)				
19 studies **1847 participants**	**Anticipated absolute effect (95% CI) ***		**Certainty of the evidence**	**Ranking (SUCRA) ****
	With TURP	**With a minimally invasive procedure**		
PUL (UroLift) (mixed estimate)	Mean score in the included studies: 6.82 (range 5.1 to 12.6)[a]	1.47 higher (4.00 lower to 6.93 higher)	⊕⊕## **LOW** [b c]	2.8 (70.5%)
PAE (mixed estimate)		1.55 higher (1.23 lower to 4.33 higher)	⊕⊕## **LOW** [b d]	2.9 (69.2%)
CRFWVT (Rezūm) (indirect estimate)		3.60 higher (4.25 lower to 11.46 higher)	⊕⊕## **LOW** [b c]	3.9 (52.4%)
TUMT (mixed estimate)		3.98 higher (0.85 higher to 7.10 higher)	⊕⊕## **LOW** [b e]	4.4 (43.0%)
TIND (indirect estimate)		7.50 higher (0.68 lower to 15.69 higher)	⊕⊕## **LOW** [b e]	5.5 (21.5%)

CI: confidence interval; **CRFWVT**: convective radiofrequency water vapor therapy; **IPSS:** International Prostate Symptom Score; **MD**: mean difference; **PAE**: prostatic arterial embolization; **PUL**: prostatic urethral lift; **SUCRA:** surface under the cumulative ranking curve; **TIND**: temporary implantable nitinol device; **TUMT**: transurethral microwave thermotherapy; **TURP:** transurethral resection of prostate.

Network meta-analysis summary of findings table definitions:

* Estimates are reported as mean difference and CI.

** Rank statistics is defined as the probability that a treatment out of n treatments in a network meta-analysis is the best, the second, the third, and so on until the least effective treatment. Between brackets are the surface under the curve (SUCRA) estimates.

GRADE Working Group grades of evidence (or certainty of the evidence).

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]TURP was the highest-ranked intervention for this outcome with a mean rank of 1.7 (SUCRA 88.9%)
[b]Downgraded by one level due to major concerns on within-study bias: nearly all studies contributing to this estimate had an overall high risk of bias.
[c]Downgraded by one level due to major concerns on imprecision: the estimate crosses the threshold for minimally important difference (three points for IPSS) and the line of no effect.
[d]Downgraded by one level due to some concerns on imprecision and inconsistency (heterogeneity): the estimate and prediction interval cross one threshold for minimally important difference (three points for IPSS)
[e]Downgraded by one level due to some concerns regarding inconsistency (heterogeneity): the prediction interval crosses one threshold for minimally important difference (three points for IPSS).

Summary of findings 2. Quality of life - short term

Minimally invasive treatments versus transurethral resection of the prostate
Patient or population: men with moderate to severe lower urinary symptoms due to benign prostatic hyperplasia
Interventions: minimally invasive treatments
Comparator (reference): transurethral resection of the prostate
Setting: hospital procedure – outpatient follow-up
Outcome: Quality of life
Measured by: IPSS QoL range 0-6 (lower scores indicate a fewer impact on the quality of life)

Follow-up: 3 to 12 months

13 studies 1469 participants	Anticipated absolute effect (95% CI) *		Certainty of the evidence	Ranking (SUCRA) **
	With TURP	With a minimally invasive procedure		
PUL (UroLift) (mixed estimate)	Mean score in the included studies: 2.09 (range 0.9 to 3.26)[a]	0.06 higher (1.17 lower to 1.30 higher)	⊕⊕## **LOW** [b c]	2.8 (70.3%)
PAE (mixed estimate)		0.09 higher (0.57 lower to 0.75 higher)	⊕⊕## **LOW** [b d]	2.9 (68.1%)
CRFWVT (Rezūm) (indirect estimate)		0.37 higher (1.45 lower to 2.20 higher)	⊕⊕## **LOW** [b c]	3.6 (56.3%)
TUMT (mixed estimate)		0.65 higher (0.48 lower to 1.78 higher)	⊕⊕## **LOW** [b e]	4.5 (42.2%)
TIND (indirect estimate)		0.87 higher (1.04 lower to 2.79 higher)	⊕⊕## **LOW** [b c]	5.0 (33.4%)

CI: confidence interval; **CRFWVT**: convective radiofrequency water vapor therapy; **IPSS:** International Prostate Symptom Score; **MD**: mean difference; **QoL:** quality of life; **PAE**: prostatic arterial embolization; **PUL**: prostatic urethral lift; **SUCRA:** surface under the cumulative ranking curve; **TIND**: temporary implantable nitinol device; **TUMT**: transurethral microwave thermotherapy; **TURP:** transurethral resection of prostate.

Network meta-analysis summary of findings table definitions:

* Estimates are reported as mean difference and CI.

** Rank statistics is defined as the probability that a treatment out of n treatments in a network meta-analysis is the best, the second, the third, and so on until the least effective treatment. Between brackets are the surface under the curve (SUCRA) estimates.

GRADE Working Group grades of evidence (or certainty of the evidence).

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]TURP was the highest-ranked intervention for this outcome with a mean rank of 2.5 (SUCRA 75.7%)
[b]Downgraded by one level due to major concerns on within-study bias: nearly all studies contributing to this estimate had an overall high risk of bias.
[c]Downgraded by one level due to major concerns on imprecision: the estimate crosses the threshold for minimally important difference (one point for IPSS-QoL) and the line of no effect.
[d]Downgraded by one level due to major concerns on inconsistency (heterogeneity): the prediction interval crosses the threshold for minimally important difference (one point for IPSS-QoL) and the line of no effect.
[e]Downgraded by one level due to some concerns regarding inconsistency (heterogeneity) and imprecision: the estimate and the prediction interval crosses the threshold for minimally important difference (one point for IPSS-QoL)

Summary of findings 3. Major adverse events

Minimally invasive treatments versus transurethral resection of the prostate

Patient or population: men with moderate to severe lower urinary symptoms due to benign prostatic hyperplasia

Interventions: minimally invasive treatments

Comparator (reference): transurethral resection of the prostate

Setting: hospital procedure – outpatient follow-up

Outcome: major adverse events

Defined as: Clavien-Dindo Grade III, IV, and V, including hospitalizations and procedures to treat complications related to the initial intervention.

Follow-up: 3-36 months

15 studies 1573 participants	Anticipated absolute effect (95% CI) *		Relative effect (95% CI)	Certainty of the evidence	Ranking (SUCRA) **
	With TURP	With a minimally invasive procedure			
TUMT (mixed estimate)	Median rate of major adverse events: 130 per 1000[a]	104 fewer per 1000 (118 fewer to 74 fewer)	RR 0.20 (0.09 to 0.43)	⊕⊕⊕# **MODERATE** [b]	2.7 (72.1%)
PUL (UroLift) (mixed estimate)		90 fewer per 1000 (125 fewer to 159 more)	RR 0.30 (0.04 to 2.22)	⊕⊕## **LOW** [b c]	3.6 (56.9%)
CRFWVT (Rezūm) (indirect estimate)		81 fewer per 1000 (129 fewer to 870 more)	RR 0.37 (0.01 to 18.68)	⊕⊕## **LOW** [b c]	4.0 (50.0%)
TIND (indirect estimate)		63 fewer per 1000 (129 fewer to 870 more)	RR 0.52 (0.01 to 24.46)	⊕⊕##	4.3 (44.7%)

				LOW [b c]	
PAE	45 fewer per 1000 (97 to 89 more)	RR 0.65 (0.25 to 1.68)	⊕⊕##	5.0
(mixed estimate)			**LOW** [b c]	(33.6%)

CI: confidence interval; **CRFWVT**: convective radiofrequency water vapor therapy; **IPSS:** International Prostate Symptom Score; **MD**: mean difference; **QoL:** quality of life; **PAE**: prostatic arterial embolization; **PUL**: prostatic urethral lift; **RR:** risk ratio; **SUCRA:** surface under the cumulative ranking curve; **TIND**: temporary implantable nitinol device; **TUMT**: transurethral microwave thermotherapy; **TURP:** transurethral resection of prostate.

Network meta-analysis summary of findings table definitions.

* Estimates are reported as risk difference and confidence interval (CI).

** Rank statistics is defined as the probability that a treatment out of n treatments in a network meta-analysis is the best, the second, the third, and so on until the least effective treatment. Between brackets are the surface under the curve (SUCRA) estimates.

GRADE Working Group grades of evidence (or certainty of the evidence).

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Average rate of retreatment in the control group (13%) or 130 per 1000. TURP was the lowest-ranked intervention for this outcome with a mean rank of 5.9 (SUCRA 17.9%)
[b]Downgraded by one level due to major concerns on within-study bias: nearly all studies contributing to this estimate had an overall high risk of bias.
[c]Downgraded by one level due to major concerns on imprecision: wide confidence interval.

Summary of findings 4. Retreatment - long term

Minimally invasive treatments versus transurethral resection of the prostate

Patient or population: men with moderate to severe lower urinary symptoms due to benign prostatic hyperplasia

Interventions: minimally invasive treatments.

Comparator (reference): transurethral resection of the prostate

Setting: hospital procedure – outpatient follow-up

Outcome: retreatment

Defined as: number of participants requiring a follow-up procedure for lower urinary tract symptoms including another minimally invasive treatment or TURP (this does not include procedures to treat complications - these are included under major adverse events)

Follow-up: 12 - 60 months

10 studies 799 participants	Anticipated absolute effect (95% CI) *		Relative effect (95% CI)	Certainty of the evidence	Ranking (SUCRA) **
	With TURP	With a minimally invasive procedure			
PUL (UroLift) (mixed estimate)	Median rate of retreatment: 12 per 1000[a]	17 more per 1000 (6 fewer to 121 more)	RR 2.39 (0.51 to 11.10)	⊕### **VERY LOW** [b c d]	2.2 (68.8%)
PAE (mixed estimate)		41 more per 1000 (3 more to 173 more)	RR 4.39 (1.25 to 15.44)	⊕### **VERY LOW** [b d e]	3.0 (50.8%)
TUMT (mixed estimate)		104 more per 1000 (16 more to 470 more)	RR 9.71 (2.35 to 40.13)	⊕⊕⊕# **LOW** [b d]	3.7 (32.1%)
CRFWVT (Rezūm) (pairwise)	Based on one study with 197 participants, we are very uncertain about the effects of CRFWVT on retreatment compared to sham at three months follow-up (RR 1.36, 95% CI 0.06 to 32.86).			⊕### **VERY LOW** [f]	Data could not be included in NMA to preserve the transitivity of each network
TIND (pairwise)	Based on one study with 185 participants, we are very uncertain about the effects of TIND on retreatment compared to sham at three-month follow-up (RR 0.67, 95% CI 0.11 to 3.89).			⊕### **VERY LOW** [f]	Data could not be included in NMA to preserve the transitivity of each network

CI: confidence interval; **CRFWVT**: convective radiofrequency water vapor therapy; **IPSS:** International Prostate Symptom Score; **NMA**: network meta-analysis; **QoL:** quality of life; **PAE**: prostatic arterial embolization; **PUL**: prostatic urethral lift; **RR:** risk ratio; **SUCRA:** surface under the cumulative ranking curve; **TIND**: temporary implantable nitinol device; **TUMT**: transurethral microwave thermotherapy; **TURP:** transurethral resection of prostate.

Network meta-analysis summary of findings table definitions.

* Estimates are reported as risk difference and confidence interval (CI).

** Rank statistics is defined as the probability that a treatment out of n treatments in a network meta-analysis is the best, the second, the third, and so on until the least effective treatment. Between brackets are the surface under the curve (SUCRA) estimates.

GRADE Working Group grades of evidence (or certainty of the evidence).

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Average rate of retreatment in the control group (1.15%) or 12 per 1000. TURP was the highest rank intervention for this outcome with a mean rank of 1.1 (SUCRA 96.4%)
[b]Downgraded by one level due to major concerns on within-study bias: nearly all studies contributing to this estimate had an overall high risk of bias.
[c]Downgraded by one level due to major concerns on imprecision: wide confidence interval.
[d]Downgraded by one level due to major concerns on incoherence: the network does not present close loops to assess incoherence.
[e]Downgraded by one level due to some concerns on imprecision and inconsistency (heterogeneity): wide confidence interval and prediction interval.
[f]Downgraded by three levels due to concerns on within-study bias (single study at high risk of bias) and severe imprecision (wide confidence interval).

Summary of findings 5. Erectile function - short term

Minimally invasive treatments versus transurethral resection of the prostate

Patient or population: men with moderate to severe lower urinary symptoms due to benign prostatic hyperplasia

Interventions: minimally invasive treatments.

Comparator (reference): sham procedure or transurethral resection of the prostate

Setting: hospital procedure – outpatient follow-up

Outcome: erectile function

Measured by: IIEF scores range 5-25 (higher scores indicate better function).

Follow-up 3 to 12 months

6 studies 640 participants	Anticipated absolute effect (95% CI) *		Certainty of the evidence	Ranking (SUCRA) **
	With TURP	With a minimally invasive procedure		
CRFWVT (Rezūm) (indirect estimate)	Mean score in the included studies: 15.16 (range 11.67 to 17.70)[a]	6.49 higher (8.13 lower to 21.12 higher)	⊕### **VERY LOW** [b c d]	2.5 (70.7%)
TIND (indirect estimate)		5.19 higher (9.36 lower to 19.74 higher)	⊕### **VERY LOW** [b c d]	2.9 (61.7%)
PUL (UroLift)		3.00 higher (5.45 lower to 11.44 higher)	⊕###	3.5

(mixed estimate)			**VERY LOW** [b c d]	(49.5%)
PAE		0.03 lower (6.38 lower to 6.32 higher)	⊕###	4.4
(mixed estimate)			**VERY LOW** [b c d]	(31.1%)
TUMT	Not reported			

CI: confidence interval; **CRFWVT**: convective radiofrequency water vapor therapy; **IIEF:** International Index of Erectile Function; **IPSS:** International Prostate Symptom Score; **MD**: mean difference; **PAE**: prostatic arterial embolization; **PUL**: prostatic urethral lift; **SUCRA:** surface under the cumulative ranking curve; **TIND**: temporary implantable nitinol device; **TUMT**: transurethral microwave thermotherapy; **TURP:** transurethral resection of prostate.

Network meta-analysis summary of findings table definitions:

* Estimates are reported as mean difference and confidence interval (CI).

** Rank statistics is defined as the probability that a treatment out of n treatments in a network meta-analysis is the best, the second, the third, and so on until the least effective treatment. Between brackets are the surface under the curve (SUCRA) estimates.

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Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]TURP was the lowest-ranked intervention for this outcome with a mean rank of 4.6 (SUCRA 27.2%)
[b]Downgraded by one level due to major concerns on within-study bias: nearly all studies contributing to this estimate had an overall high risk of bias.
[c]Downgraded by one level due to major concerns on imprecision: the estimate crosses the threshold for minimally important difference (five points for IIEF-5) including substantial benefits and harms.
[d]Downgraded by one level due to major concerns on incoherence: the network does not present close loops to assess incoherence.

Summary of findings 6. Ejaculatory function - short term

Minimally invasive treatments versus transurethral resection of the prostate

Patient or population: men with moderate to severe lower urinary symptoms due to benign prostatic hyperplasia

Interventions: minimally invasive treatments

Comparator (reference): transurethral resection of the prostate

Setting: hospital procedure – outpatient follow-up

Outcome: ejaculatory function

Defined as: men with ejaculatory dysfunction - loss or substantial reduction in ejaculation (as an indication of retrograde ejaculation)

Follow-up: 3 to 12 months

8 studies 461 participants	Anticipated absolute effect (95% CI) *		Relative effect (95% CI)	Certainty of the evidence	Ranking (SUCRA) **
	With TURP	With a minimally invasive procedure			
PUL (UroLift) (mixed estimate)	Median rate of ejaculatory dysfunction: 550 per 1000[a]	521 fewer per 1000 (549 fewer to 32 more)	RR 0.05 (0.01 to 1.06)	⊕### **VERY LOW** [b c d]	1.2 (92.1%)
TUMT (mixed estimate)		364 fewer per 1000 (458 fewer to 173 fewer)	RR 0.34 (0.17 to 0.68)	⊕### **VERY LOW** [b c d]	2.3 (55.1%)
PAE (mixed estimate)		356 fewer per 1000 (476 fewer to 42 fewer)	RR 0.35 (0.13 to 0.92)	⊕### **VERY LOW** [b c d]	2.5 (51.1%)
CRFWVT (Rezūm) (pairwise)	Based on one study with 131 participants, CRFWVT may result in little to no difference in events of ejaculatory dysfunction compared to sham at short-term follow-up (RR 4.01, 95% CI 0.22 to 72.78).			⊕### **VERY LOW** [e]	Data could not be included in NMA to preserve the transitivity of each network
TIND (pairwise)	The study assessing TIND compared to sham reported no events of ejaculatory dysfunction.			⊕### **VERY LOW** [e]	Data could not be included in NMA to preserve the transitivity of each network

CI: confidence interval; **CRFWVT**: convective radiofrequency water vapor therapy; **IPSS:** International Prostate Symptom Score; **NMA**: network meta-analysis; **PAE**: prostatic arterial embolization; **PUL**: prostatic urethral lift; **RR:** risk ratio; **SUCRA:** surface under the cumulative ranking curve; **TIND**: temporary implantable nitinol device; **TUMT**: transurethral microwave thermotherapy; **TURP:** transurethral resection of prostate.

Network meta-analysis summary of findings table definitions.

* Estimates are reported as risk difference and confidence interval (CI).

** Rank statistics is defined as the probability that a treatment out of n treatments in a network meta-analysis is the best, the second, the third, and so on until the least effective treatment. Between brackets the surface under the curve (SUCRA) estimates.

GRADE Working Group grades of evidence (or certainty of the evidence).

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Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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[a]Average rate of retreatment in the control group (55%) or 550 per 1000. TURP was the lowest-ranked intervention for this outcome with a mean rank of 4 (SUCRA 1.4%)
[b]Downgraded by one level due to major concerns on within-study bias: nearly all studies contributing to this estimate had an overall high risk of bias.
[c]Downgraded by one level due to concerns on inconsistency (heterogeneity): predictive intervals include substantial benefits and harms.
[d]Downgraded by one level due to major concerns on incoherence: the network does not present close loops to assess incoherence.
[e]Downgraded by two levels due to concerns on within-study bias (single study at high risk of bias) and imprecision (wide confidence interval crossing the minimally importance difference).

BACKGROUND

Description of the condition

The prostate gland is an organ in males. It is approximately the size of a walnut, and is located below the urinary bladder encircling the urethra (Leissner 1979). Benign prostatic obstruction (BPO) is a form of bladder outlet obstruction and may be diagnosed when the cause of outlet obstruction is known to be benign prostatic enlargement (BPE) due to benign prostatic hyperplasia (BPH); however, the latter is restricted to the histological diagnosis, defined as increased numbers of epithelial and stromal cells in the prostate (Abrams 2003). BPH may or may not cause lower urinary tract symptoms (LUTS), characterized by urination frequency, hesitancy, and a weak stream, mainly in men over the age of 40, and receives clinical relevance when associated with perceived bother (Dunphy 2015). Symptom bother typically correlates with increased number and severity of symptoms, which are related to both the impairment in the quality of life and treatment-seeking (Agarwal 2014). Although we understand that LUTS is a functional unit with a multi-factorial etiology of associated symptoms, we considered the term BPH for this Cochrane Review due to its familiarity with the general public (EAU 2021).

The degree of bother across all LUTS can be assessed through self-administered questionnaires, namely, the International Prostate Symptom Score (IPSS; also known as the American Urological Association [AUA] Symptom Index), which includes the quality of life domain (Barry 1995). Chapple 2017 reported that increasing LUTS severity was associated with worsening men's overall distress through the patient perception of the bladder condition, which is a single-item global question (with responses ranging from 1 (causes no problems at all) to 6 (causes severe problems)).

Progression of LUTS has been observed in up to 31% of men with BPH at seven-year follow-up (Emberton 2008). Progression to acute urinary retention is less frequent, and in men with moderate symptoms can range from 3.0 per 1000 person-years in those aged 40 to 49 years to 34.7 per 1000 person-years in those aged 70 to 79 years (Emberton 2008). BPH also has a negative impact on public health and reduces a person's quality of life (Kozminski 2015; Martin 2014). In Europe, 30% of men over 50 years of age, equivalent to 26 million men, are affected by bothersome LUTS, including storage symptoms (such as urinary frequency, urgency, and nocturia) or voiding symptoms (such as urinary hesitancy, weak urinary stream, straining to void, and prolonged voiding), or both. The yearly reported associated number of medical prescriptions was estimated to be around 11.6 million for 74 million people at risk from 2004 to 2008 (Cornu 2010). According to an international study involving 7588 men, the prevalence of LUTS was 18% during their 40s, 29% in their 50s, 40% in their 60s, and 56% in their 70s (Homma 1997). More recent data show the lifetime prevalence of BPH as 26.2% (95% confidence interval (CI) 22.8% to 29.6%) (Lee 2017).

Diagnosis

Initial evaluation of LUTS suggestive of BPH includes patient history, physical examination including a digital rectal examination (DRE), urinalysis, a prostate-specific antigen (PSA) blood test if a diagnosis of prostate cancer changes management, use of a voiding diary, and IPSS (EAU 2021; McVary 2011). A DRE is performed to assess both nodules suspicious for cancer and prostate size; recently, additional imaging studies have been recommended for patients considering surgical intervention (Foster 2019).

PSA is secreted by the prostate gland and is found to be abnormally elevated in conditions such as prostate cancer, BPH, infection, or inflammation of the prostate (EAU 2021; McVary 2011). The IPSS is used to assess urinary symptom severity and quality of life. It is also used to document subjective responses to treatment (Barry 1992; EAU 2021; McVary 2011). Measurement of maximum flow rate (Q_{max}) and postvoid residual (PVR) is often used in diagnosis and treatment decisions (EAU 2021; McVary 2011). A low Q_{max} and a large PVR predict an increased risk of symptom progression (Crawford 2006). Other tests such as radiological imaging, urodynamic evaluation, and cystoscopy can help the clinician determine appropriate treatment and predict treatment response (Egan 2016; McVary 2011).

Treatment

Treatment decisions are based on symptoms, and the degree of symptom bother noted by the patient. Initial treatment options for BPH include conservative management (watchful waiting and lifestyle modification) and the use of medications (alpha-blockers, 5-alpha reductase inhibitors, and, recently, phosphodiesterase inhibitors) (EAU 2021; McVary 2011). When patients have been refractory to conservative and medical treatment, or if BPH causes subsequent complications, such as acute urinary retention, recurrent urinary tract infection, bladder stones, haematuria, or renal insufficiency, surgical options are considered (EAU 2021; McVary 2011).

Until the 1970s, the only option available to treat this condition and relieve LUTS was open simple prostatectomy (in very large prostates) or endoscopic surgery in the form of transurethral prostatectomy, with the aim of removing or resecting prostatic tissue to open up the blocked urethra (Pariser 2015). Clinical guidelines continue to recommend monopolar or bipolar transurethral resection of the prostate (TURP) as a ('gold') reference standard treatment to provide subjective symptom relief while attaining objective improvement in urinary flow (Alexander 2019; EAU 2021; McVary 2011), but this procedure is associated with some morbidity and long-term complications, including hematuria, possibly requiring a blood transfusion, urethral stricture, urinary tract infection, and incontinence, and it usually requires at least overnight hospitalisation. Moreover, men may experience ejaculatory (65%) and erectile dysfunction (10%) related to TURP (Roehrborn 2003). Furthermore, BPH is a disease that is common among elderly men, who have increased preoperative risk for complications of general anesthesia and surgery in general (Dunphy 2015; Yoo 2012).

Recently, several other minimally invasive treatments (MITs) that can be performed in an office setting and do not require general anesthesia have been developed as alternatives to TURP (EAU 2021; McVary 2011) to provide therapeutic alternatives involving lower morbidity. However, most men who consider surgical intervention do so with the expectation that this is a more definitive therapy for LUTS that will preclude the need for additional medical or surgical therapy. Given the relatively high rate of reoperation or continued use of medical therapy after surgical treatment (or both), concern has been raised about the durability of newly launched minimal invasive surgeries (NICE 2015; Strope 2015).

Description of the intervention

Minimally invasive treatments that can be performed in an office setting and do not require general anesthesia include convective radiofrequency water vapor therapy (CRFWVT), prostatic arterial embolization (PAE), prostatic urethral lift (PUL), a temporary implantable nitinol device (TIND), and transurethral microwave thermotherapy (TUMT).

Convective radiofrequency water vapor therapy

The Rezūm system (NxThera Inc., Maple Grove, MN, USA) uses radiofrequency to create thermal energy in the form of water vapor to ablate prostatic tissue (Woo 2017). This system consists of two main components: a radiofrequency power supply generator and a single-use transurethral delivery device that incorporates a standard rigid cystoscope lens, which allows the procedure to be performed under direct visualization. Water vapor thermal energy is generated by applying a radiofrequency current against an inductive coil heater. The handheld control delivers water vapor, providing a consistent energy dose of ~ 208 calories into the prostate tissue through a retractable needle (Woo 2017). CRFWVT is performed with the person in the dorsal lithotomy position, using conscious sedation. A cystoscopic examination is performed to confirm the contours of the prostate and the planned distribution of thermal lesions (Darson 2017; Dixon 2015; Woo 2017). The treatment needle is positioned for starting approximately one centimeter distal from the bladder neck and targeting the transition and central prostate adenoma by eye. Each injection of water vapor lasts approximately nine seconds. Additional injections of vapor are delivered every one centimeter from the initial injection site of the prostatic urethra to the proximal edge of the verumontanum. The total number of injections in each lobe of the prostate is determined by the length of the prostatic urethra and the configuration of the prostate gland (Dixon 2015; Woo 2017). Saline flush irrigation is used to enhance visualization and to cool the urethral surface (Woo 2017). Although most adverse events are transient and are classified as Clavien-Dindo Grade I or II, a non-randomized pilot study has reported 125 adverse events in 45 of 64 participants (69.2%) (Dixon 2015). The most common adverse events are postoperative urinary retention (33.8%), dysuria (21.5%), urinary urgency (20%), and suspected urinary tract infection (20%). Twelve serious adverse events were reported in 10 participants, one of which was suspected to be a procedure- or device-related adverse event (Clavien-Dindo Grade IIIb urinary retention) (Dixon 2015).

Prostatic arterial embolization

Embolization of the prostatic arteries has historically been used to control persistent or massive prostatic bleeding not otherwise amenable for treatment, with typical causes being BPH and locally advanced prostate cancer, or to treat hemorrhage occurring after TURP (Mitchell 1976). DeMeritt 2000 reported a case in which PAE was performed with polyvinyl alcohol particles for BPH-induced hematuria; hematuria was immediately stopped, and the patient reported symptomatic improvement of his BPH symptoms. These researchers also found that prostate size was reduced by 52% and 62% of the initial size at five-month and 12-month follow-up, respectively. Carnevale 2010 reported positive preliminary results of PAE procedures with microspheres as a primary treatment in two patients with acute urinary retention due to BPH. For elderly patients with symptomatic BPH, PAE can be an alternative treatment performed by a femoral or radial artery puncture using conscious sedation instead of general anesthesia. This procedure is typically performed on an outpatient basis and usually does not require catheterization unless the patient is experiencing urinary retention (Wang 2015). In preparation for PAE, preoperative computed tomography or magnetic resonance angiography is typically performed to evaluate the pelvic artery anatomy. Digital subtraction angiography of the right and left internal iliac arteries is performed to assess the prostatic blood supply (Martins Pisco 2012). Super-selective microcatheterization and embolization are then performed on the prostatic arteries. Embolization is typically performed to complete stasis (Carnevale 2010; Martins Pisco 2012; Wang 2015). Cone-beam computed tomography can be used not only to help identify all prostatic arteries but also to identify and avoid embolization of vessels feeding adjacent pelvic structures (Wang 2015). Particle embolics are used almost exclusively, with wide variation in the type and size of particles (Carnevale 2010; DeMeritt 2000). Vasodilators to mitigate vasospasm once the prostatic artery is catheterized are also recommended by some researchers to avoid premature stasis (Martins Pisco 2012). Although the major complication rate is low (less than 1%) (Pisco 2016), perineal pain (9.4%), hematuria (9%), and acute urinary retention (7%) are commonly reported as complications of PAE (Feng 2017). The highest prevalence of acute urinary retention amongst the included studies was 28.4% (Wang 2015). Minor complications, such as hematospermia, rectal bleeding, urinary tract infection, inguinal hematoma, and transient urinary frequency are also reported (Feng 2017; Kuang 2017; Pyo 2017; Shim 2017). However, there is inconsistency in the reporting or classification of adverse events.

Prostatic urethral lift

Prostatic urethral lift (PUL), marketed commercially as UroLift (Teleflex Inc., Pleasanton, CA, USA), has recently become available in several countries and can be performed under local anesthesia with oral or intravenous sedation; it can also be performed in men with blood clotting disorders or in men receiving anticoagulant therapy. It is therefore being proposed and marketed for men at high risk of general anesthesia (Chin 2012; Woo 2012). Typical inclusion criteria for PUL include prostate volume between 20 mL and 70 mL, IPSS of 12 or greater, measured Q_{max} of 15 mL/s or less, and PVR of less than 350 mL (McNicholas 2016). The PUL system consists of two single-use components (a delivery device and an implant). The delivery device consists of a handheld pistol grip to which a needle-shaped probe is attached. Each PUL implant consists of a super-elastic nitinol capsular tab, a polyethylene terephthalate monofilament, and a stainless steel urethral end piece. The surgeon inserts the probe into the urethra until it reaches the widest part of the prostatic urethra; a fine needle at the end of the probe then is deployed to secure an implant in a lobe of the prostate (McNicholas 2016). One end of the implant is anchored in the urethra, and the other is attached to the firm outer surface of the prostatic capsule, thus pulling the prostatic lobe away from the urethra. This is repeated on the other lobe of the prostate. Systematically, four implants for PUL are delivered — two each to the right and left lateral lobes of the prostate (at the 2 o'clock and 10 o'clock positions, distally, from approximately 1.5 cm distal to the bladder neck). PUL generally is not used to treat a hypertrophied median lobe of the prostate, which causes obstructive intravesical protrusion of the prostate (McNicholas 2016); however, a recent small observational study indicated that this might be feasible and effective (Rukstalis 2019). Mild adverse events, such as transient

dysuria and haematuria, are commonly reported with PUL (Chin 2012; Woo 2012). Incontinence may be less prevalent with PUL (5%) than with TURP (11%) (NICE 2015). However, reoperation rates appear to be higher with PUL (8%) than with TURP (6%) (NICE 2015). In one feasibility study, implant encrustation occurred when PUL implants were placed too close to the bladder and were exposed to static urine (Chin 2012; Woo 2012).

Temporary implantable nitinol device

The temporary implantable nitinol device (TIND), commercially marketed as Medi-Tate (Medi-Tate Ltd., Hadera, Israel), is a novel device that aims to provide prostatic patency. This new minimally invasive procedure can be performed in an outpatient setting under light sedation. The device is placed inside the prostatic urethra via cystoscopy and is expanded upon release (Porpiglia 2015), reshaping the bladder neck and the prostatic urethra. No catheterization is required. The 50-mm-long, 33-mm-diameter device comprises three elongated struts and an anchoring leaflet - all made of nitinol, a biocompatible super-elastic shape memory alloy (Porpiglia 2015). The device is removed 5 days after placement in an outpatient setting under local anesthesia (lidocaine gel) with retraction via a cytoscope.

A single-arm multi-center observational study with 32 participants indicated that median IPSS scores decreased from 19 at baseline to 10 at three-week follow-up and to 9 at 12-month follow-up. Four patients suffered short-term complications (urinary incontinence, urinary retention, urinary tract infection, and prostatic abscess) (Porpiglia 2015). A three-year follow-up indicated that IPSS scores reached a median of 12, and no further complications were reported (Porpiglia 2018).

A second-generation TIND device (iTIND) with structural differences is currently available. Only three struts are used, and the upper part of the device allows action exerted on the urethral mucosa at the level of the bladder neck, with potential avoidance of bladder mucosal injury (Bertolo 2018). A single-arm multi-center observational study evaluating iTIND on 81 participants indicated that mean IPSS scores decreased from 22.5 ± 5.6 at baseline to 11.7 ± 8.0 at 1-month follow-up and to 8.8 ± 6.4 at 12-month follow-up. Only mild complications were reported: haematuria (12.3%), micturition urgency (11.1%), pain (9.9%), dysuria (7.4%), urinary tract infection (6.2%), and urinary retention (9.9%). Only one participant required re-intervention in the form of TURP (Porpiglia 2019). At least two ongoing randomized controlled trials are evaluating this treatment (Bertolo 2018). Newer devices, such as the XFLO Expander system, have been tested in pilot studies, with promising results (Woo 2020).

Transurethral microwave thermotherapy

Transurethral microwave thermotherapy (TUMT) uses microwave-induced heat to ablate prostatic tissue and is designed to have fewer major complications than TURP (Walmsley 2004). The patient is treated in an outpatient setting. Once the patient's bladder is emptied by straight catheterization, a local lidocaine gel is inserted for local anesthesia. The treatment catheter is then placed within the urethra, and this is confirmed by return of the sterile water and by transabdominal or transrectal ultrasound; then, the balloon is inflated. The catheter is composed of a curved tip, a temperature sensor, and a microwave unit. The distal port contains the bladder balloon, allowing for urine drainage and cooling. A rectal probe may be inserted and can be used to monitor rectal temperature (Rubeinstein 2003).

TUMT has evolved over the past decades. The first systems worked at lower energy or heat settings, and treatment would take around an hour with minimal discomfort; however, results were disappointing. Subsequent systems incorporated catheters that provided urethral cooling, thus allowing higher energy delivery. These advancements reduced the procedure time to around 30 minutes and improved outcomes. However, higher energy leads to greater discomfort during the procedure, for which patients often require sedation and analgesia and presents a risk for urinary retention (EAU 2021; Walmsley 2004).

How the intervention might work

Convective radiofrequency water vapor therapy

The Rezūm system directly transfers targeted and controlled convective thermal energy doses to the transition zone of the prostate gland to treat BPH by using sterile water vapor through tissue interstitial spaces between cells releases its stored thermal energy to create apoptosis and necrosis when in contact with hyperplastic prostatic tissue (Aoun 2015). Reportedly, no thermal effects are seen beyond the confines of the prostate, thereby leaving the urethra, bladder neck, and external sphincter unaffected (Aoun 2015; Woo 2017). In comparison, conductive ablation therapy can cause necrosis of surrounding tissues as higher temperatures and longer heating periods are required to achieve therapeutic effects (Woo 2017).

Prostatic arterial embolization

The underlying mechanism of PAE is the ischemia or hypoxia that induces apoptosis, necrosis, sclerosis, and prostatic shrinkage with cystic transformation of part, or all, of the gland, resulting in a softer gland with reduced compression of the urethra (DeMeritt 2000; Sun 2008). In addition, PAE may decrease the plasma concentration of free testosterone that enters prostate cells, thereby lowering dihydrotestosterone levels in the prostate. This may result in the secondary inhibition of prostate growth (Sun 2008). Ischemia or hypoxia may induce prostate cell death and necrosis with a decreased number of some receptors, such as alpha-adrenergic receptors. Therefore, the neuromuscular tone may decrease, resulting in improved clinical symptoms associated with the dynamic pathological component of BPH (Zlotta 1997).

Prostatic urethral lift

The fundamental idea of PUL consists of the separation and distraction of enlarged prostatic tissue by a series of implants. The PUL system uses adjustable, permanent implants to hold excess prostatic tissue out of the way, thereby opening the narrowed urethra without cutting or removing enlarged prostatic tissue (McNicholas 2016). These implants are shaped as a double-ended hook and aim to expand the opening of the urethra (McNicholas 2016).

Temporary implantable nitinol device

The fundamental principle of the TIND device involves 'reshaping' the prostatic urethra and bladder neck, thereby reducing urinary flow obstruction (Porpiglia 2015). This may be caused by the radial force of sustained expansion of the TIND device, causing ischemic

necrosis of the tissue and leading to incision to the bladder neck and prostatic urethra.

Transurethral microwave thermotherapy

TUMT uses a special transurethral catheter that transmits heat into the prostate via electromagnetic radiation of microwaves, penetrating water-rich tissue. Energy transferred by the microwave to the tissue in the form of heat induces coagulation necrosis, reducing prostatic volume. This mechanism may also cause denervation of receptors, decreasing the smooth muscle tone of the prostatic urethra (Walmsley 2004). Temperatures lower than 45° C seem ineffective in causing this effect; therefore, higher-energy devices were developed to reach temperatures greater than 70° C, causing thermoablation of the prostatic tissue (Aoun 2015).

Why it is important to do this review

The Cochrane Urology Group has developed four reviews of studies comparing each MIT to TURP and other therapies (Franco 2021; Jung 2017; Jung 2019; Kang 2020); however, these reviews found few head-to-head comparisons. A recent systematic review and network meta-analysis evaluated surgical therapies for BPH, but it covered only invasive therapies such as different forms of TURP and laser ablation (Huang 2019). We found no systematic review and network meta-analysis to date that has used the same rigorous methods used in a Cochrane Review, which includes applying the GRADE approach and focusing on patient-important outcomes (Guyatt 2008). A network meta-analysis could improve the precision of estimates for each pair-wise comparison, create estimates for which no head-to-head trial was found, and provide a ranking of available interventions (Chaimani 2021). In contemporary practice, with the availability of numerous MITs to treat BPH, the findings of this Cochrane Review are expected to be relevant to policymakers, healthcare providers, and patients.

OBJECTIVES

Primary

Our primary objective was to assess the comparative effectiveness of minimally invasive treatments for lower urinary tract symptoms in men with benign prostatic hyperplasia through a network meta-analysis.

Secondary

To obtain an estimate of relative ranking of these minimally invasive treatments according to their effects.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel-group randomized controlled trials (RCTs) only to avoid threatening the transitivity assumption. We excluded cross-over and cluster trials, as these study designs are not relevant in this setting. We excluded single-armed studies, quasi-randomized trials, and observational studies. We included RCTs regardless of their publication status or the language of publication.

Types of participants

We defined the eligible patient population as men over the age of 40 years with a prostate volume of 20 mL or greater (as assessed by DRE, ultrasound, and/or cross-sectional imaging) with LUTS (determined by an IPSS of 8 or over), and a maximal urinary flow rate (Q_{max}) less than 15 mL/s (as measured by non-invasive uroflowmetry, invasive pressure flow studies, or both) (Dunphy 2015; EAU 2021; McNicholas 2016; McVary 2011). The age limitation for this review was based on the observation that the prevalence of BPH is increased in middle-aged and older men and that BPH is infrequent in younger men (Barry 1997; EAU 2021; Egan 2016). If these inclusion criteria had not been fully described, we would have performed a sensitivity analysis (see Sensitivity analysis).

We excluded trials of men with active urinary tract infection; bacterial prostatitis; chronic renal failure; untreated bladder calculi or large diverticula; prostate cancer; urethral stricture disease; or prior prostate, bladder neck, or urethral surgery. We excluded studies of men with other conditions that affect urinary symptoms, such as neurogenic bladder due to spinal cord injury, multiple sclerosis, or central nervous system disease.

We assessed the transitivity assumption by comparing the characteristics of participants and the distribution of potential effect modifiers, including age, prostate volume, and severity of LUTS.

Types of interventions

We included the following interventions.

Experimental interventions (decision set)

- CRFWVT
- PAE
- PUL
- TIND
- TUMT

Comparator interventions (supplementary set)

- Sham control (or no intervention)
- TURP (monopolar or bipolar)

Comparisons

We predefined the structure of the network and its nodes in our protocol (Franco 2020). We included trials comparing experimental interventions versus comparator interventions or performing head-to-head comparisons between experimental interventions (the representation of each network is embedded in the figure accompanying the main outcomes of the review in the section Effects of interventions). We did not include the comparison of TURP versus sham control because our primary interest is the comparative effectiveness of minimally invasive treatments compared to TURP. Participants in the network could in principle be randomized to any of the methods being compared, and we verified this by comparing characteristics of study design, participants, interventions, and comparisons (Salanti 2012) while considering potential sources of clinical heterogeneity and effect modification (see Subgroup analysis and investigation of heterogeneity).

Types of outcome measures

We did not use measurement of the outcomes assessed in this review as an eligibility criterion.

Primary outcomes

- Urological symptom scores
- Quality of life
- Major adverse events

Secondary outcomes

- Retreatment
- Erectile function
- Ejaculatory function
- Minor adverse events
- Acute urinary retention
- Indwelling urinary catheter

Method and timing of outcome measurement

We considered clinically important differences for all outcomes as the basis for rating the certainty of the evidence for imprecision in the 'Summary of findings' tables (Jaeschke 1989; Johnston 2013).

Urological symptom scores

- Mean change measured as IPSS (also known as the AUA Symptom Index) or other validated scores (such as Madsen-Iversen symptom scores). The latter would not be included in a network meta-analysis (see Measures of treatment effect).
- We considered an improvement in IPSS score of 3 points as a minimal clinically important difference (MCID) to assess the efficacy and comparative effectiveness (Barry 1995). If possible, we used different thresholds of MCID based on the severity of IPSS, with a threshold of 3 for mild LUTS, 5 for moderate LUTS, and 8 for severe LUTS (Barry 1995).

Quality of life

- Mean change measured as IPSS-quality of life.
- No formal threshold was established for IPSS-quality of life. We used an MCID of 1 to assess the efficacy and comparative effectiveness (Brasure 2016; Rees 2015).

Major adverse events

- Examples include postoperative hemorrhage requiring admission or intervention.
- We used the Clavien-Dindo classification system to assess surgical complications and categorized Grade III, IV, and V complications as major (Dindo 2004).
- Based on Guyatt 2011a, we considered a 25% relative change as the threshold for a clinically important difference.

Retreatment

- Events requiring other surgical treatment modalities (e.g. TURP) after an intervention. We considered the first retreatment and accounted for repetitive events in a narrative synthesis.
- Based on Guyatt 2011a, we considered a 25% relative change as the threshold for a clinically important difference.

Erectile function

- Mean change, measured as the total score on the International Index of Erectile Function (IIEF)-5 questionnaire (also known as the Sexual Health Inventory for Men) (Rosen 1997).
- We considered a difference in IIEF-5 over 5 points as the MCID (Spaliviero 2010).

Ejaculatory function

- Mean change, measured on the Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EjD) (Rosen 2007).
- We used an MCID of 25% improvement from baseline on the MSHQ-EjD for ejaculatory function (Nickel 2015).

Minor adverse events

- Examples include postoperative fever or pain requiring medication.
- We used the Clavien–Dindo classification system to assess surgical complications and categorized Grade I and II complications as minor (Dindo 2004).
- Based on Guyatt 2011a, we considered a 25% relative change as the threshold for a clinically important difference.

Acute urinary retention

- Events requiring catheterization after intervention.
- Based on Guyatt 2011a, we considered a 25% relative change as the threshold for a clinically important difference.

Indwelling urinary catheter

- Proportion of participants with an indwelling catheter at postoperative 24 hours.
- Based on Guyatt 2011a, we considered a 25% relative change as the threshold for a clinically important difference.

We considered outcomes measured up to 12 months after randomisation as short-term and those later than 12 months as long-term, for urological symptom scores, quality of life, retreatment, erectile function, ejaculatory function, minor adverse events, and acute urinary retention. We assessed major adverse events including short-term and long-term data and indwelling urinary catheter over the short term only.

The selection of patient-important outcomes was based on the input of the clinical authors and their day-to-day practice; we did not formally involve men with BPH symptoms.

Main outcomes for 'Summary of findings' tables

We presented 'Summary of findings' tables reporting the following outcomes listed according to priority.

- Urological symptom scores
- Quality of life
- Major adverse events
- Retreatment
- Erectile function
- Ejaculatory function

Search methods for identification of studies

We performed a comprehensive search with no restrictions on language of publication or publication status.

Electronic searches

We retrieved relevant studies from existing Cochrane Reviews for each individual treatment (Franco 2021; Jung 2017; Jung 2019; Kang 2020). We updated searches for each of the individual Cochrane Reviews assessing each minimally invasive treatment. We performed a comprehensive search for TIND from the inception of each of the following databases (see Appendix 1).

- Cochrane Library via Wiley (from inception until 24 February 2021)
  - *Cochrane Database of Systematic Reviews*
  - Cochrane Central Register of Controlled Trials
  - Database of Abstracts of Reviews of Effects
  - Health Technology Assessment Database
- MEDLINE via Ovid (from 1946 until 24 February 2021)
- Embase via Elsevier (from 1974 until 24 February 2021)
- Scopus (from 1966 until 24 February 2021)
- Web of Science (from 1900 until 24 February 2021)
- Latin American and the Caribbean Health Sciences Literature (LILACS; www.bireme.br/, from 1982 until 24 February 2021)

We also searched the following on 24 February 24 2021.

- ClinicalTrials.gov at the US National Institutes of Health (www.clinicaltrials.gov/)
- World Health Organization (WHO) International Clinical Trials Registry Platform search portal (apps.who.int/trialsearch/)
- Grey literature repository from the current Grey Literature Report (www.greylit.org/)

Searching other resources

We tried to identify other potentially eligible trials and ancillary publications by searching the reference lists of retrieved included trials, reviews, meta-analyses, and health technology assessment reports. We contacted the study authors of included trials to identify further studies that we may have missed. We contacted drug/device manufacturers for ongoing or unpublished trials. We searched abstract proceedings of relevant meetings of the American Urological Association, the European Association of Urology, and the International Continence Society for 2018 to 2020 for unpublished studies (see Appendix 2).

Data collection and analysis

Selection of studies

We used Covidence to identify and remove potential duplicate records. Two review authors (JVAF, LG) scanned abstracts, titles, or both to determine which studies should be assessed further using the same software. Two review authors (JVAF, LG) investigated all potentially relevant records as full text, mapped records to studies, and classified studies as included studies, excluded studies, studies awaiting classification, or ongoing studies following the criteria for each provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). We resolved any discrepancies through consensus or recourse to a third review author (PD). We documented the reasons for exclusion. We presented a PRISMA flow diagram showing the process of study selection (Page 2021).

Data extraction and management

We developed a dedicated data abstraction form that we pilot-tested ahead of time. Because we retrieved relevant studies from existing Cochrane Reviews for each individual treatment for which study characteristics, outcome data, and risk of bias assessments were done by members of our review team (Franco 2021; Jung 2017; Jung 2019; Kang 2020), the following sections apply only to new studies identified by our search methods.

For studies that fulfilled inclusion criteria, two review authors (of JVAF, LG, and JHJ) independently abstracted the following information.

- Study design
- Study dates
- Study settings and country
- Participant inclusion and exclusion criteria (e.g. age, baseline IPSS)
- Participant details, baseline demographics (e.g. age, prostate size, IPSS)
- Numbers of participants by study and by study arm
- Details of relevant experimental intervention (e.g. size of the cystoscope, energy-generating device, embolization agent, delivery device) and comparator intervention (e.g. monopolar versus bipolar energy, specifications of the sham procedure)
- Definitions of relevant outcomes and methods (e.g. type of instrument, such as IPSS) and timing of outcome measurement (e.g. in months), as well as relevant subgroups (e.g. based on age, prostate volume, the severity of LUTS)
- Study funding sources
- Declarations of interest by primary investigators

We extracted outcome data relevant to this Cochrane Review as needed for the calculation of summary statistics and measures of variance. For dichotomous outcomes, we presented numbers of events and totals for populations in a 2×2 table, as well as summary statistics with corresponding measures of variance. For continuous outcomes, we obtained the means and standard deviations or data necessary to calculate this information.

We resolved any disagreements by discussion or, if required, by consultation with a third review author (PD).

In tables, we provided information about potentially relevant studies, including the trial identifiers.

We contacted the authors of included studies to obtain key missing data as needed.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary study, we maximized the yield of information by mapping all publications to unique studies and collating all available data. We used the most complete data set aggregated across all known publications. In case of doubt, we gave priority to the publication reporting the longest follow-up associated with our primary or secondary outcomes.

Assessment of risk of bias in included studies

Two review authors (JVAF and LG) independently assessed the risk of bias of each included study. We resolved disagreements by consensus or by consultation with a third review author (PD). We presented a 'Risk of bias' summary figure to illustrate these findings. We further summarized the risk of bias across domains for each outcome in each included study, as well as across studies and domains, for each outcome in accordance with the approach for summary assessments of risk of bias presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of risk of bias in randomized controlled trials

We assessed the risk of bias using Cochrane's 'Risk of bias' assessment tool (Higgins 2011). We assessed the following domains.

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other sources of bias

We judged the risk of bias domains as 'low risk', 'high risk', or 'unclear risk' and evaluated individual bias items as described in the *Cochrane Handbook* (Higgins 2011).

For selection bias (random sequence generation and allocation concealment), we evaluated the risk of bias at the trial level. For performance bias (blinding of participants and personnel), we considered all outcomes similarly susceptible to performance bias. For detection bias (blinding of outcome assessment), we grouped outcomes as susceptible to detection bias (subjective) or not susceptible to detection bias (objective) outcomes.

We defined the following endpoints as subjective outcomes.

- Urological symptom scores
- Quality of life
- Major adverse events
- Erectile function
- Ejaculatory function
- Minor adverse events

We defined the following endpoints as objective outcomes.

- Retreatment
- Acute urinary retention
- Indwelling urinary catheter

We considered studies that compared MITs to TURP to be unblinded (at high risk of performance bias and detection bias for subjective outcomes). Studies that compared MITs to sham treatments and aimed to blind participants were considered at low risk of detection bias and also performance bias if personnel were also blinded. We assessed attrition bias (incomplete outcome data) on an outcome-specific basis, and we presented the judgement for each outcome separately when reporting our findings in 'Risk of bias' tables.

For reporting bias (selective reporting), we evaluated the risk of bias at a trial level.

Measures of treatment effect

Relative treatment effect

We expressed dichotomous data as risk ratios (RRs) with 95% confidence interval (CIs) to enhance the interpretability of results. We expressed continuous data as mean differences (MDs) with 95% CIs. We prioritized post-intervention over change from baseline measurements. We anticipated that different scales might be used for urological symptom scores (e.g. Madsen symptom score in few older studies), in which case we included outcome data using the preferred scale for this outcome (i.e. IPSS) in order to preserve the transitivity of the network. In the presence of binary and continuous data for the same outcome, we performed analysis for continuous data. If this was not possible due to network geometry, we performed analysis for binary data.

Relative treatment ranking

We obtained a treatment hierarchy using P scores for all outcomes of the review (Rücker 2015). P scores allow describing the mean extent of certainty that the underlying treatment effect is larger than that of any other intervention.

Unit of analysis issues

The unit of analysis was the individual participant. When multiple trial arms are reported in a single trial, we included only the arms with comparisons relevant to prespecified nodes in our network.

Dealing with missing data

We obtained missing data (e.g. missing standard deviations) from study authors and performed intention-to-treat analyses if data were available. We investigated attrition rates (e.g. dropouts, losses to follow-up, withdrawals) and critically appraised issues of missing data. We did not impute missing data.

Assessment of heterogeneity

Network meta-analysis

Assessment of the transitivity assumption

Before conducting a network meta-analysis, we assessed the transitivity assumption. Network meta-analysis rests on the assumption of transitivity, that is, that effect modifiers have a comparable distribution across treatment comparisons in a network (Cipriani 2013; Jansen 2013). To assess the plausibility of this assumption, we visually inspected the comparability of distributions of age, prostate volume, and urological symptom score severity (IPSS), the time point of outcome assessment, and risk of bias (randomization, allocation concealment, and blinding to the risk of bias) as potential treatment effect modifiers across comparisons (Salanti 2014). We assessed the similarity of inclusion and exclusion criteria of all studies, including participants, treatments, and outcomes, to evaluate whether they impacted treatment effects.

Assessment of statistical consistency

Lack of transitivity in a network can threaten the validity of the consistency assumption, that is, the statistical agreement between direct and indirect evidence (Caldwell 2005; Lu 2004).

Results can be misleading in the presence of inconsistency in the network. We evaluated the presence of inconsistency both locally and globally. We evaluated each network locally using the loop-specific method by generating an inconsistency factor along with a 95% CI for each closed-loop (Veroniki 2013). This way, we identified which piece of evidence would be responsible for inconsistency, and we explored this further. We also applied a global assessment for consistency in each network by applying the design-by-treatment interaction model (White 2012a). It has been shown that inconsistency tests have low power to detect true inconsistency (Song 2012; Veroniki 2014). Hence, we assessed transitivity even in the absence of evidence for inconsistency. If inconsistency was found, we followed the guidance provided in the *Cochrane Handbook* (Section 11.4.4.4; Chaimani 2021).

Pair-wise meta-analysis

We identified heterogeneity through visual inspection of forest plots to assess the overlap of CIs and the I^2 statistic, which quantifies between-study variation across studies, to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003). We interpreted the I^2 statistic as follows (Deeks 2021).

- 0% to 40%: may not be important.
- 30% to 60%: may indicate moderate heterogeneity.
- 50% to 90%: may indicate substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

We also used Cochran's Q test to assess for heterogeneity of estimated effect sizes from individual studies. However, we cautiously interpreted these results considering both the low power to detect true heterogeneity when the number of studies is small and the excessive power needed to detect negligible heterogeneity when the number of studies is high (Huedo-Medina 2006; Pereira 2010).

Assessment of reporting biases

We attempted to obtain study protocols to assess for selective outcome reporting.

We used comparison-adjusted funnel plots to assess small-study effects (Chaimani 2013). Several explanations can be offered for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials), and publication bias. We, therefore, interpreted these results carefully.

Data synthesis

Methods for indirect and network comparisons

We fitted a random-effects network meta-analysis model because we anticipated methodological and clinical heterogeneity across studies. We assumed a common within-network heterogeneity estimate across comparisons, and we estimated this using the restricted maximum likelihood (REML) method (Veroniki 2016). This is a reasonable assumption, given that all treatments included in the network are of the same nature. An advantage of this approach is that treatment comparisons informed by a single study can borrow strength from the rest of the studies in the network (Higgins 1996; Salanti 2008). Each network meta-analysis treatment effect estimate was presented along with a 95% CI and a 95% predictive interval (PrI) with reference to the standard treatment (TURP). A PrI is an interval within which the treatment effect estimate of a future study is expected to lie, accounting for both the uncertainty of the treatment effect and between-study variance estimates (Higgins 2009; Riley 2011). We conducted a network meta-analysis using the network suite of commands in Stata (STATA 2019; White 2012; White 2015).

Relative treatment ranking

We estimated the ranking probabilities that all treatments would be at each possible rank for each intervention. We used the surface under the cumulative ranking curve (SUCRA) to rank the effectiveness and safety of minimally invasive interventions (Salanti 2011). SUCRA accounts for both effect size magnitude and uncertainty around the underlying effect size. We displayed results (network plot, SUCRA plots and league table) using the 'network graph package' in Stata (STATA 2019; Chaimani 2015).

Methods for direct treatment comparisons

We performed analyses according to recommendations provided in Chapter 9 of the *Cochrane Handbook* (Deeks 2021), and we used Cochrane's statistical software, Review Manager 5 (Review Manager 2014), for analysis. When possible, we performed these standard pair-wise meta-analyses using a random-effects model because we anticipated methodological and clinical heterogeneity across studies. We calculated corresponding 95% CIs for all analyses, and we graphically presented the results using forest plots. When trials were clinically too heterogeneous to be combined, we performed only subgroup analyses without calculating an overall estimate. In order to avoid duplication with the supporting reviews of this network meta-analysis, we described only the pairwise comparisons for the data that could not be included in the network due to concerns about transitivity.

Subgroup analysis and investigation of heterogeneity

When we find important heterogeneity and/or inconsistency, we explored possible sources for primary outcomes. When sufficient studies are available, we performed subgroup analysis by using the following potential effect modifiers as possible sources of inconsistency and/or heterogeneity.

- Patient age (younger than 65 years versus 65 years and older).
- Prostate volume (≤ 40 mL or > 40 mL).
- Severity of LUTS based on IPSS (score ≤ 19 (moderately symptomatic) versus > 19 (severely symptomatic)).

These subgroup analyses are based on the following observations.

- Age is a well-known risk factor for BPH surgery. Older people have a higher rate of postoperative complications compared with younger people (Bhojani 2014; Pariser 2015). The age cut-off is based on the WHO definition of old age (WHO 2002).
- Outcomes and complications of minimally invasive procedures, such as TURP, correlate with prostate volume (Reich 2008). Prostate volume cut-off greater than 40 mL is based on this being the most commonly used threshold to distinguish 'small' from 'large' for the indication of treatment with a 5-alpha reductase inhibitor (EAU 2021).
- The relationship between changes in IPSS scores and patient global ratings of improvement is influenced by baseline scores (Barry 1995).

We planned to perform subgroup analyses limited to the primary outcomes.

Sensitivity analysis

We planned to perform sensitivity analyses limited to the primary outcomes to explore the influence of the following factors (when applicable) on effect size.

- Restricting the analysis in RCTs by taking into account risk of bias, by excluding studies at 'high risk' or 'unclear risk' (studies with at least one domain at 'high risk' or 'unclear risk' of bias for the analyzed outcome).
- Restricting the analysis to RCTs with adequately described inclusion criteria (prostate size, age, IPSS value, and Q_{max}).

Summary of findings and assessment of the certainty of the evidence

We used 'Summary of findings' tables to summarize key results of the review, using the Confidence in Network Meta-analysis (CINeMA) framework and software (Chaimani 2021; CINeMA 2017; Salanti 2014). We included the following outcomes.

- Urological symptom scores
- Quality of life
- Major adverse events
- Retreatment
- Erectile function
- Ejaculatory function

Our reference for the network meta-analysis was TURP, considering that it is the reference treatment for all minimally invasive procedures. We used the five GRADE criteria (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to evaluate the quality of the body of evidence as it relates to studies that contributed data to the meta-analysis for each pre-specified outcome (Guyatt 2008). Two review authors (JVAF and LG) independently made judgments about the certainty of the evidence (high, moderate, low, or very low) and resolved disagreements by discussion or consultation with a third review author (PD). We created a 'Summary of findings' table for each outcome, using the approach presented by Yepes-Nuñez 2019.

RESULTS

Description of studies

Details of the included studies are presented in Characteristics of included studies and Table 1.

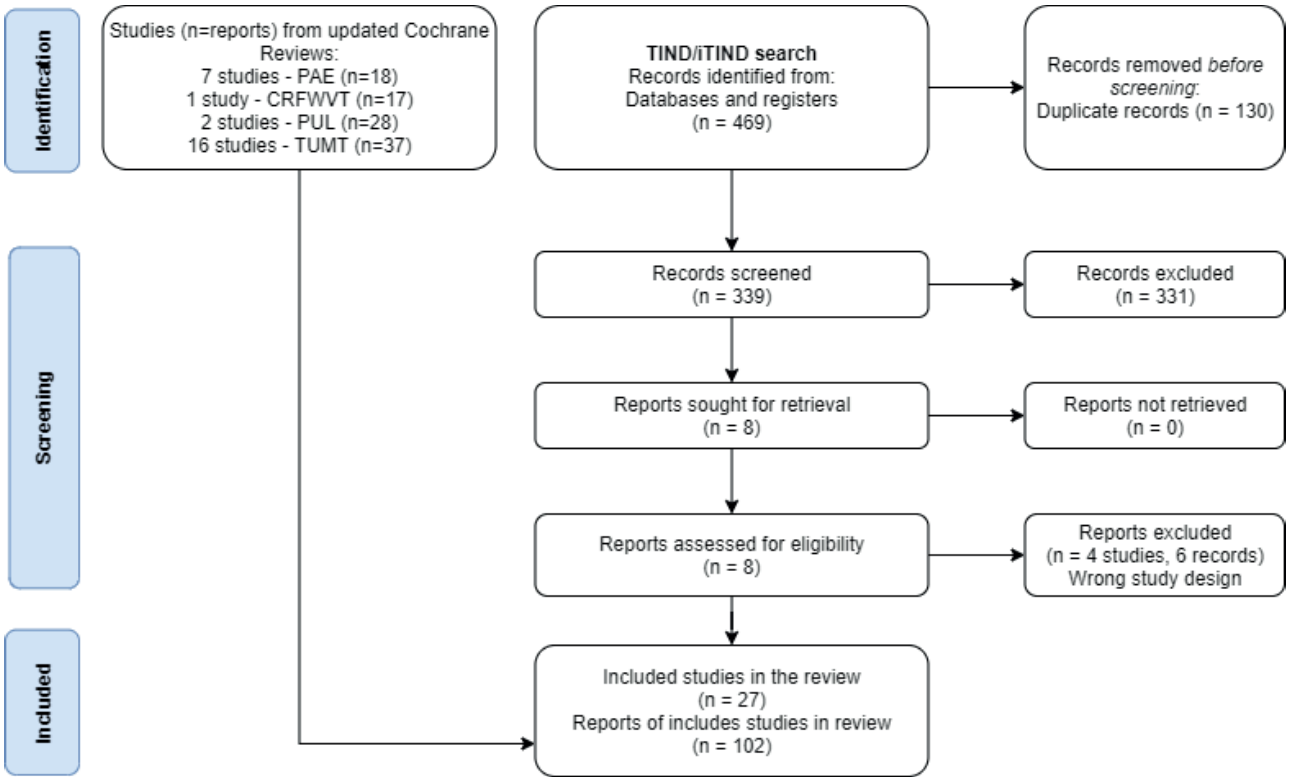
Results of the search

We retrieved 26 studies from the previous Cochrane reviews.

- Seven studies (18 reports) from the PAE review (Jung 2020) — last updated on 28 September 2020
- One study (17 reports) from the CRFWVT (Rezūm) review (Kang 2020) — last updated on 30 October 2020
- Two studies (28 reports) from the PUL (UroLift) review (Jung 2019) — last updated on 28 October 2020
- 16 studies (37 reports) from the TUMT review (Franco 2021) — last updated on 31 May 2021

For the TIND search, we identified 469 records from electronic databases. We found no relevant records in the grey literature repository. After removing duplicates, we screened the titles and abstracts of the remaining 339 records, 331 of which we excluded. We assessed eight full-text articles, and we excluded six records for various reasons. Finally, we included one study (two reports) in this review for this intervention. There were no ongoing studies for this intervention that met the inclusion criteria or were relevant to the review question. We have shown the flow of literature through the assessment process in the PRISMA flowchart (Figure 1).

Figure 1. PRISMA 2020 flow diagram



Included studies

Study design and sample size

We included 27 trials with 3017 randomized participants. Their median sample size was 103 (interquartile range 61-155).

Setting

The studies were conducted usually in tertiary hospitals, mostly in Europe, the USA and Canada, except for four PAE trials in China, Brazil, and Egypt. Most of the TUMT trials were conducted between 1991 and 1999, whereas the other interventions (CRFWVT, PUL, PAE, and TIND) took place between 2007 and 2018.

Participants

Most studies included men over 45 to 50 years old with moderate LUTS refractory to medical treatment; with a Q_{max} < 12/15 mL/s, a voided volume ≥ 125 mL and a prostate volume between 30/100 g to 60/100 g. Participants were usually screened for prostate cancer and infection, among other comorbidities, before inclusion.

Interventions and comparisons

We included trials with the following interventions and comparisons.

- CRFWVT versus sham treatment (McVary 2016)
- PAE versus sham treatment (Pisco 2020)
- PAE versus TURP (Abt 2018; Carnevale 2016; Gao 2014; Insausti 2020; Radwan 2020; Zhu 2018)
- PUL versus sham treatment (Gratzke 2017)
- PUL versus TURP (Roehrborn 2013)
- TIND versus sham treatment (Chughtai 2020)
- TUMT versus sham treatment (Abbou 1995; Albala 2002; Bdesha 1994; Blute 1996; Brehmer 1999; De Wildt 1996; Larson 1998; Nawrocki 1997; Roehrborn 1998; Venn 1995)
- TUMT versus TURP (Ahmed 1997; D'Ancona 1998; Dahlstrand 1995; Floratos 2001; Norby 2002; Wagrell 2002)

Outcomes

Most trials reported the primary outcomes of our review: urologic symptoms scores and quality of life (measured by IPSS and IPSS-QoL) and major adverse events. Older trials assessing TUMT included other scales such as the Madsen-Iversen symptom score, which is thoroughly described in one of our supporting reviews (Franco 2021). Retreatment rates were mostly reported narratively, and we had to analyze which ones constituted retreatment as defined in our review or retreatment as a major adverse event (i.e. retreatment due to a complication). Ejaculatory function and erectile function were usually reported in a subset of sexually active participants, contributing to the risk of bias due to attrition. We extracted both the IIEF-5/IIEF scale and the MSHQ-EjD scale, but since they were not consistently reported across studies, we also extracted data on the incidence of sexual dysfunction (i.e. erectile dysfunction and ejaculatory problems), for which we present the analysis using the continuous and dichotomous data. Other outcomes such as minor adverse events and acute urinary retention were also poorly reported across studies. The duration of indwelling urinary catheterization was only reported in two studies and described narratively as subsidiary to acute urinary retention.

Funding

Fourteen studies did not state their funding sources (Ahmed 1997; Albala 2002; Bdesha 1994; Blute 1996; Brehmer 1999; Carnevale 2016; D'Ancona 1998; Dahlstrand 1995; De Wildt 1996; Floratos 2001; Gao 2014; Radwan 2020; Venn 1995; Zhu 2018), nine studies were funded by the manufacturers or sponsors of the procedure (Chughtai 2020; Gratzke 2017; Insausti 2020; Larson 1998; McVary 2016; Pisco 2020; Roehrborn 1998; Roehrborn 2013; Wagrell 2002) and four studies were funded by public institutions or hospitals (Nawrocki 1997; Norby 2002; Abbou 1995; Abt 2018).

Excluded studies

For TIND we excluded two single-arm studies (Porpiglia 2015; Porpiglia 2019), one case series (Lim 2011), and one study assessing the wrong intervention (Yachia 1996). For PUL we excluded a single-arm study (Gratzke 2018). For PAE we excluded five studies due to a wrong study design (Bagla 2017; Brown 2018; NCT01835860; Pereira 2018; Qiu 2017). Another study was excluded due to wrong comparison (PAE versus simple prostatectomy, Russo 2015). Another report was a letter to the editor (Bilhim 2015). For CRFWVT we excluded one educational lecture from a conference (Woo 2018). For TUMT, we excluded 22 studies for the following reasons: two studies addressed transrectal thermotherapy (Zerbib 1992; Zerbib 1994; Albala 2000), three studies provided economic data on published trials (Kobelt 2004; Norby 2002b; Waldén 1998), two were cross-over studies with insufficient data (Albala 2000; Tan 2005), nine were observational studies and other non-randomized comparisons (Arai 2000; D'Ancona 1997; Hahn 2000; Hansen 1998; Mulvin 1994; Ohigashi 2007; Servadio 1987; Trock 2004; Vesely 2006), two were review articles identified through full-text assessment (Dahlstrand 2003; Nørby 2004), three had an ineligible comparison (Djavan 1999; Schelin 2006; Shore 2010) and one was a terminated study (ISRCTN23921450).

Ongoing trials

We have identified six ongoing trials assessing the effects of PAE (ACTRN12617001235392; NCT02006303; NCT02566551; NCT04236687) and PUL (NCT04178811; NCT04338776).

Risk of bias in included studies

See Characteristics of included studies for a full description of the risk of bias assessment by study and outcome.

Allocation

Random sequence generation

We identified 14 studies that adequately described the random sequence generation (mostly using electronic systems, random numbers tables, random permuted blocks) and were rated as having a low risk of bias (Abbou 1995; Abt 2018; Blute 1996; Chughtai 2020; Gao 2014; Gratzke 2017; Insausti 2020; McVary 2016; Nawrocki 1997; Pisco 2020; Roehrborn 1998; Roehrborn 2013; Venn 1995; Zhu 2018). The remaining studies were rated as unclear risk of bias as they did not provide sufficient information for judgement.

Allocation concealment

We rated eight studies as having a low risk of bias, mostly by using a centralized allocation using software (Abt 2018; Blute 1996; Chughtai 2020; Gratzke 2017; McVary 2016; Pisco 2020; Roehrborn 1998; Roehrborn 2013). Two studies used inadequate methods to conceal allocation or had evidence of possible tampering of the process (Ahmed 1997; Nawrocki 1997). The remaining studies were rated as having an unclear risk of bias due to a lack of information on the allocation method.

Blinding

Blinding of participants and personnel

Minimally invasive treatments versus sham treatment

While the eight studies were rated as low risk of bias due to blinding of participants and personnel (Blute 1996; Nawrocki 1997; Roehrborn 1998; Abbou 1995; Bdesha 1994; Chughtai 2020; De Wildt 1996; Larson 1998), three studies were rated as high risk of bias due to lack of blinding of study personnel (McVary 2016; Pisco 2020; Roehrborn 2013). Three studies did not adequately describe blinding methods (Albala 2002; Brehmer 1999; Venn 1995).

Minimally invasive treatments versus TURP

All 13 studies were judged as having a high risk of bias given lack of assurance of appropriate methods of blinding of participants and personnel considering the nature of the comparison (Abt 2018; Ahmed 1997; Carnevale 2016; D'Ancona 1998; Dahlstrand 1995; Floratos 2001; Gao 2014; Gratzke 2017; Insausti 2020; Norby 2002; Radwan 2020; Wagrell 2002; Zhu 2018).

Blinding of outcome assessment

Minimally invasive treatments versus sham treatment

- Subjective outcomes (urologic symptom scores, quality of life, major adverse events, erectile function, ejaculatory disorders, and minor adverse events): All 14 studies were considered to be at low risk of bias since participants were blinded (Abbou 1995; Albala 2002; Bdesha 1994; Blute 1996; Brehmer 1999; Chughtai 2020; De Wildt 1996; Larson 1998; McVary 2016; Nawrocki 1997; Pisco 2020; Roehrborn 1998; Roehrborn 2013; Venn 1995)
- Objective outcomes (re-treatment, acute urinary retention, indwelling urinary catheter, and hospital stay): we rated all studies as having a low risk of bias for these outcomes as they were unlikely to be affected by lack of blinding (ascertaining this does not involve judgement)

Minimally invasive treatments versus TURP

- Subjective outcomes (urologic symptom scores, quality of life, major adverse events, erectile function, ejaculatory disorders, and minor adverse events): we judged all 13 studies as having a high risk of bias given lack of assurance of appropriate methods of blinding considering the nature of the comparison (Abt 2018; Ahmed 1997; Carnevale 2016; D'Ancona 1998; Dahlstrand 1995; Floratos 2001; Gao 2014; Gratzke 2017; Insausti 2020; Norby 2002; Radwan 2020; Wagrell 2002; Zhu 2018).
- Objective outcomes (retreatment, acute urinary retention, indwelling urinary catheter, and hospital stay): we rated all studies as having a low risk of bias for these outcomes as they were unlikely to be affected by lack of blinding (ascertaining this does not involve judgement).

Incomplete outcome data

Urologic symptoms score/quality of life

- Short-term follow-up: Six studies were rated as having a high risk of bias due to substantial or unbalanced attrition (Abbou

1995; Blute 1996; Chughtai 2020; D'Ancona 1998; Insausti 2020; Larson 1998), four studies were rated as unclear risk of bias due to insufficient information or moderate attrition (Ahmed 1997; Gao 2014; Gratzke 2017; Roehrborn 1998) and the rest of the studies were rated as low risk of bias.

- Long-term follow-up: three studies with a low risk of bias at short-term follow-up suffered important attrition in the long term and were rated as high risk of bias (Abt 2018; Dahlstrand 1995; Wagrell 2002).

Major/minor adverse events

Four studies were rated as having a high risk of bias due to substantial or unbalanced attrition (Abbou 1995; Chughtai 2020; D'Ancona 1998; Larson 1998), five studies were rated as unclear risk of bias due to insufficient information or moderate attrition (Ahmed 1997; Blute 1996; Brehmer 1999; Radwan 2020; Roehrborn 1998), and the rest of the studies were rated as low risk of bias.

Retreatment

Six studies were rated as having a high risk of bias (Abbou 1995; Chughtai 2020; Dahlstrand 1995; D'Ancona 1998; Larson 1998; Wagrell 2002), and one study was rated as having an unclear risk of bias (Brehmer 1999), and the rest of the studies were rated as low risk of bias.

Erectile function

We rated four studies as having a high risk of bias (Chughtai 2020; Floratos 2001; Gratzke 2017; McVary 2016) primarily due to the measurement of the outcome in a subgroup of sexually active participants. Three studies were rated as unclear risk of bias (Ahmed 1997; Blute 1996; Roehrborn 1998) and the rest as unclear risk of bias.

Ejaculatory function

We rated six studies as having a high risk of bias (Chughtai 2020; Floratos 2001; Gratzke 2017; Larson 1998; McVary 2016; Roehrborn 2013) primarily due to the measurement of the outcome in a subgroup of sexually active participants. Three studies were rated as unclear risk of bias (Ahmed 1997; Blute 1996; Roehrborn 1998) and the rest as unclear risk of bias.

Acute urinary retention

We rated three studies as having a high risk of bias (Abbou 1995; Chughtai 2020; Larson 1998), three studies with an unclear risk of bias (Albala 2002; Blute 1996; Roehrborn 1998) the rest of the studies as low risk of bias.

Indwelling urinary catheter

We rated one study as having a high risk of bias (Abbou 1995). Except for three studies that adequately reported this outcome for nearly all participants (Abt 2018; Gao 2014; McVary 2016), the rest of the studies only included a narrative statement, not fully reporting this outcome.

Selective reporting

Three studies were rated as high risk of bias due to the selective presentation of data for a single group (active treatment) or for only certain time points, and the definitions of outcomes that did not match the protocol (Albala 2002; Blute 1996; Insausti 2020). Four studies reported their results according to a pre-specified plan and were rated as having a low risk of bias (Gratzke 2017; McVary 2016; Pisco 2020; Roehrborn 2013). The rest of the studies did not provide sufficient information for judgement, mostly due to the lack of a pre-registered or published protocol.

Other potential sources of bias

We rated all studies as having low risk of bias as we identified no other sources of bias.

Effects of interventions

See: **Summary of findings 1** Urologic symptoms scores - short term; **Summary of findings 2** Quality of life - short term; **Summary of findings 3** Major adverse events; **Summary of findings 4** Retreatment - long term; **Summary of findings 5** Erectile function - short term; **Summary of findings 6** Ejaculatory function - short term

1. Network meta-analysis: Minimally invasive treatments versus TURP

The geometry of the networks is presented in each of the figures (Figure 2; Figure 3; Figure 4; Figure 5; Figure 6; Figure 7). Considering that the majority of trials assessed the effect of TUMT and PAE, the networks were not densely connected, and in some cases, they were star-shaped with no closed loops (this is discussed in the section Quality of the evidence). The following analyses present data from networks with no concerns on transitivity or global consistency (except in those networks in which it was not possible to assess it due to the lack of closed loops).

Figure 2. Urologic symptoms scores (IPSS). Top left: visual representation of the network. Bottom left: comparison-adjusted funnel plot for the detection of publication bias. We found no important asymmetry in this plot; therefore publication bias is not strongly suspected.Top right panel: forest plot representing the estimates from the network meta-analysis. Bottom right: The surface under the curve (SUCRA) of each of these plots defines the probability that a treatment out of n treatments in a network meta-analysis is the best, the second, the third, and so on until the least effective treatment. CRFWVT: convective radiofrequency water vapor therapy; PAE: prostatic arterial embolization; PUL: prostatic urethral lift; TIND: temporary implantable nitinol device; TUMT: transurethral microwave thermotherapy; TURP: transurethral resection of the prostate.

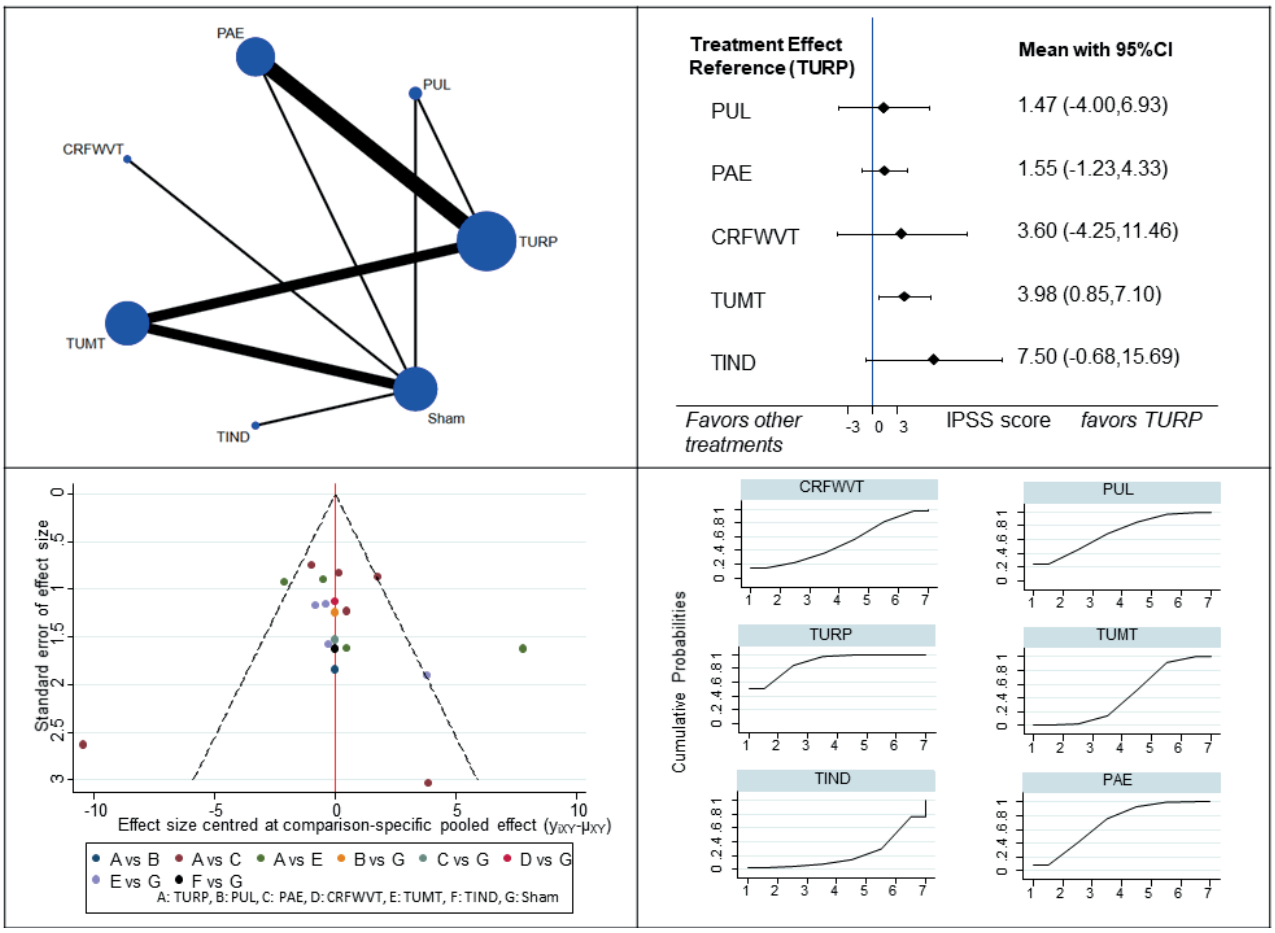


Figure 3. Quality of life (IPSS-QoL). Top left: visual representation of the network. Bottom left: comparison-adjusted funnel plot for the detection of publication bias. We found no important asymmetry in this plot, therefore publication bias is not strongly suspected.Top right panel: forest plot representing the estimates from the network meta-analysis. Bottom right: The surface under the curve (SUCRA) of each of these plots defines the probability that a treatment out of n treatments in a network meta-analysis is the best, the second, the third, and so on until the least effective treatment. CRFWVT: convective radiofrequency water vapor therapy; PAE: prostatic arterial embolization; PUL: prostatic urethral lift; TIND: temporary implantable nitinol device; TUMT: transurethral microwave thermotherapy; TURP: transurethral resection of the prostate.

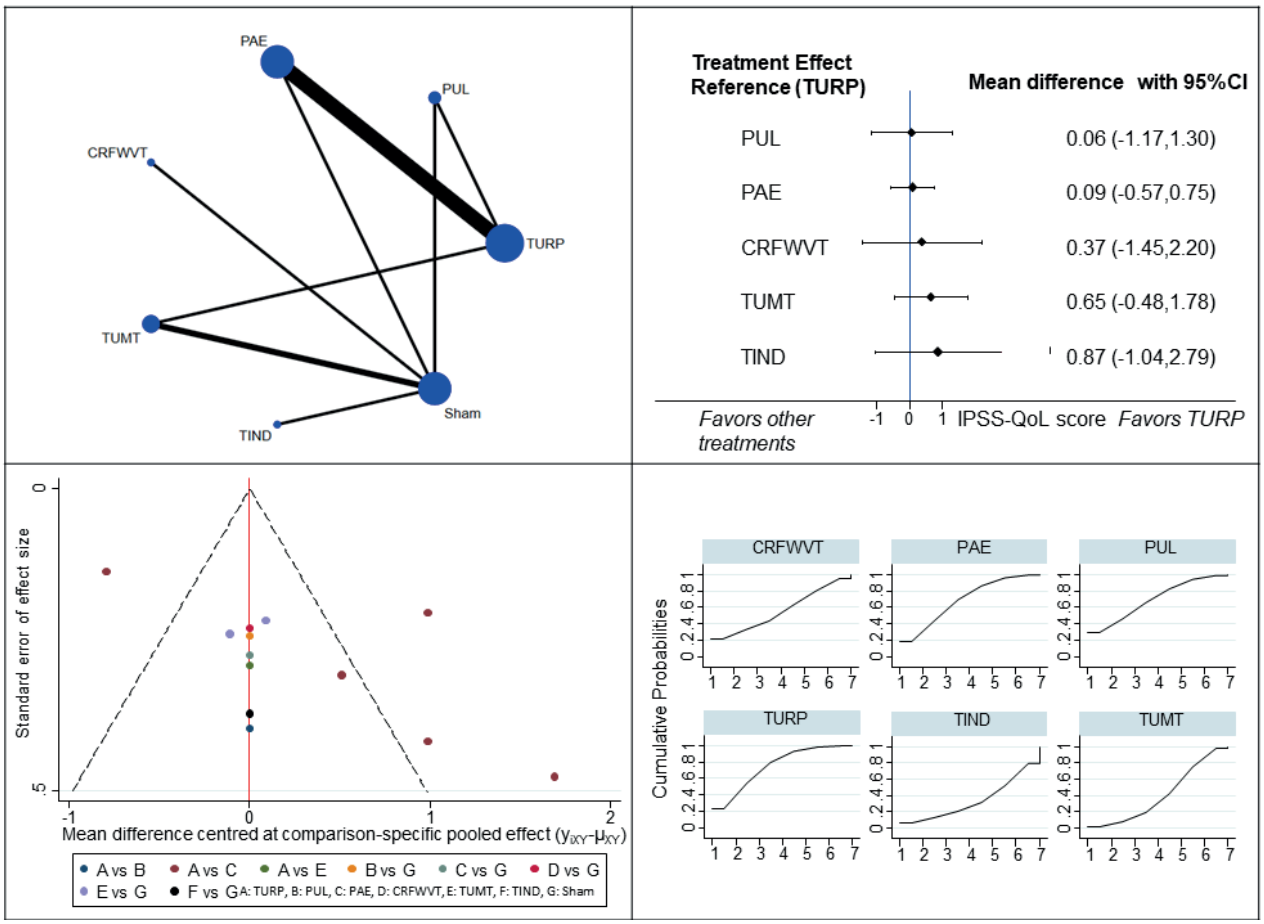


Figure 4. Major adverse events. Top left: visual representation of the network. Bottom left: comparison-adjusted funnel plot for the detection of publication bias. We found no important asymmetry in this plot, therefore publication bias is not strongly suspected.Top right panel: forest plot representing the estimates from the network meta-analysis, log scale. Bottom right: The surface under the curve (SUCRA) of each of these plots defines the probability that a treatment out of n treatments in a network meta-analysis is the best, the second, the third, and so on until the least effective treatment. CRFWVT: convective radiofrequency water vapor therapy; PAE: prostatic arterial embolization; PUL: prostatic urethral lift; TIND: temporary implantable nitinol device; TUMT: transurethral microwave thermotherapy; TURP: transurethral resection of the prostate.

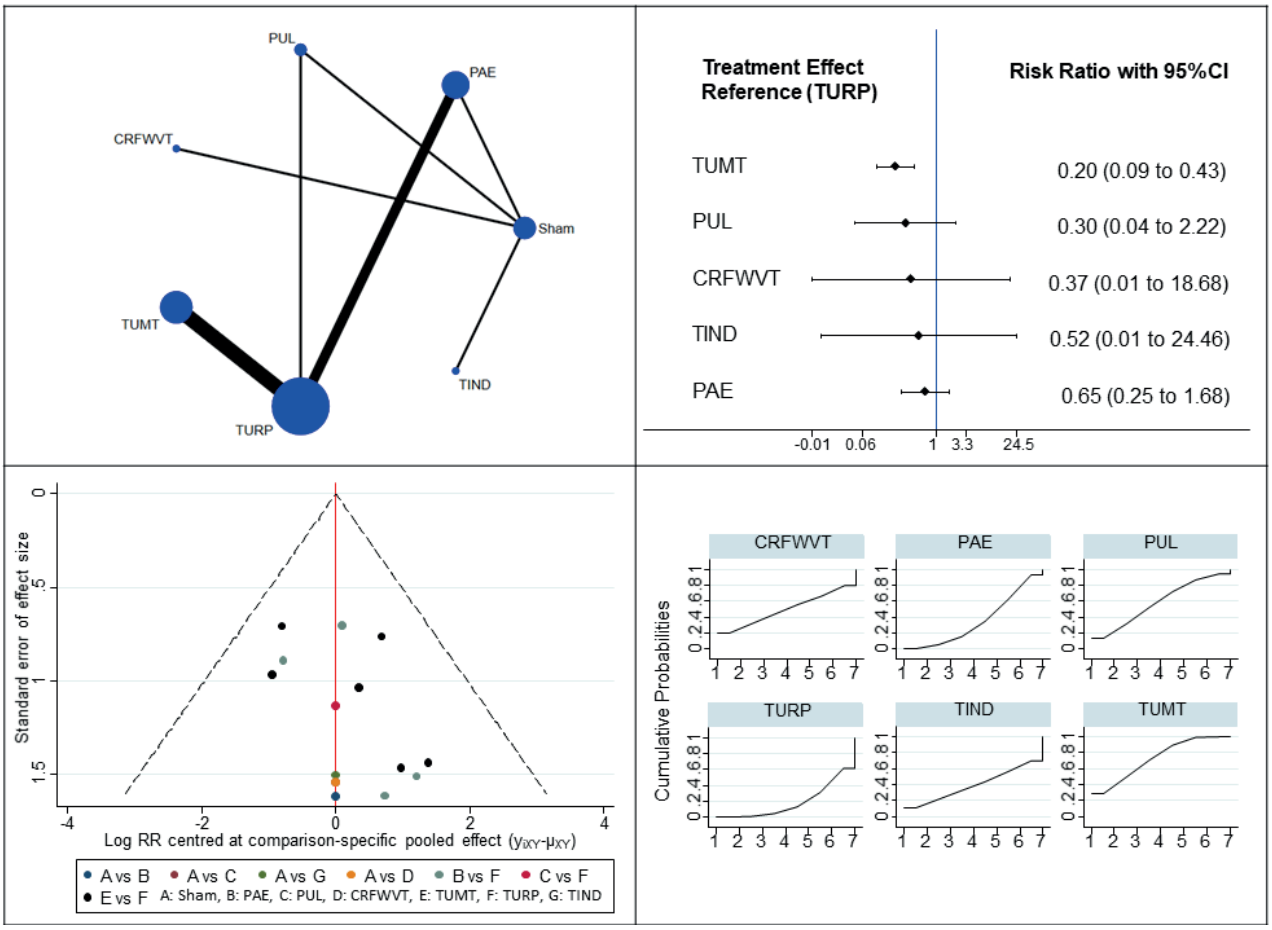


Figure 5. Retreatment. Top left: visual representation of the network. Bottom left: comparison-adjusted funnel plot for the detection of publication bias. We found no important asymmetry in this plot, therefore publication bias is not strongly suspected. Top right panel: forest plot representing the estimates from the network meta-analysis, log scale. Bottom right: The surface under the curve (SUCRA) of each of these plots defines the probability that a treatment out of n treatments in a network meta-analysis is the best, the second, the third, and so on until the least effective treatment. PAE: prostatic arterial embolization; PUL: prostatic urethral lift; TUMT: transurethral microwave thermotherapy; TURP: transurethral resection of the prostate.

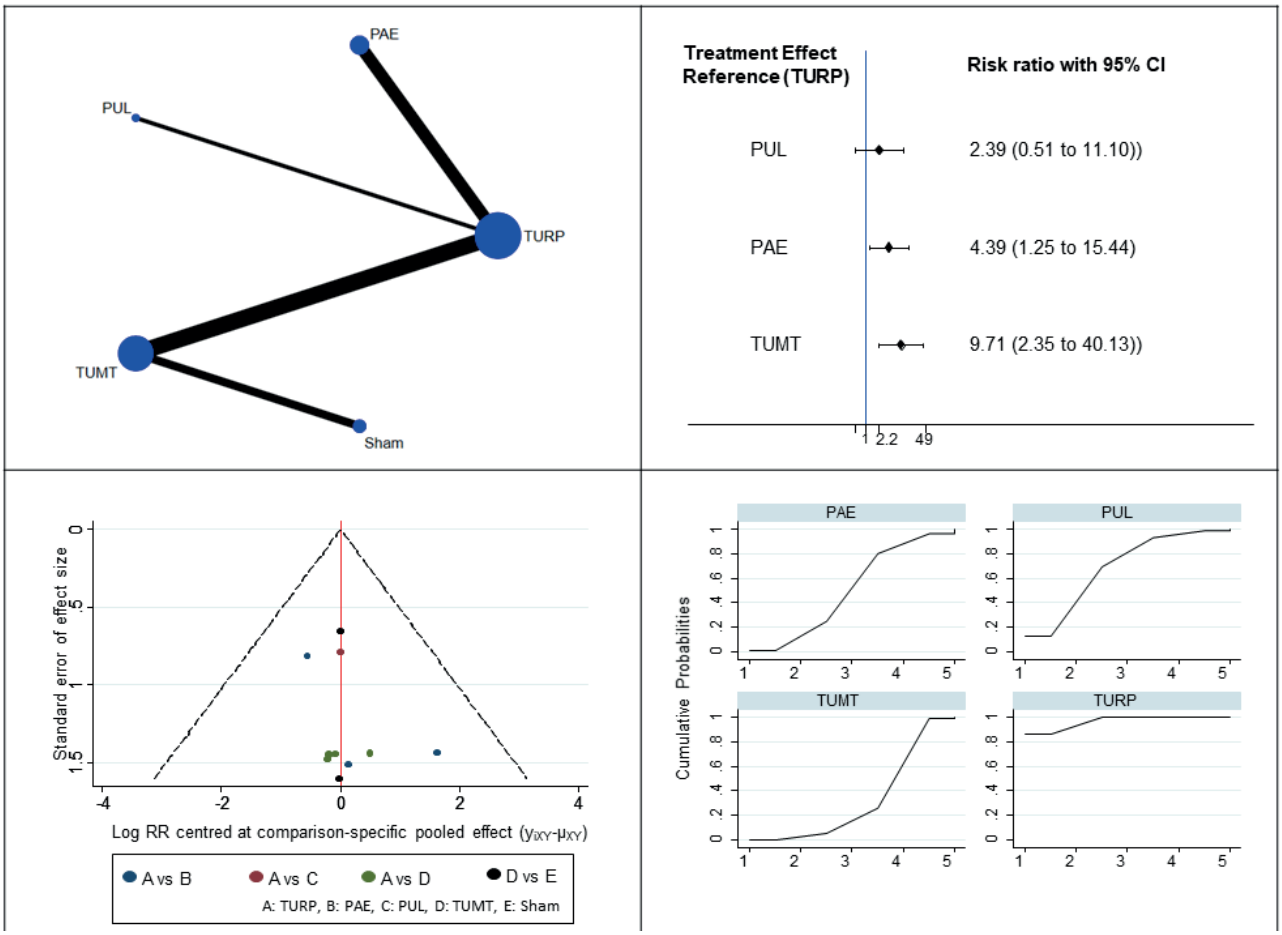


Figure 6. Erectile function (IIEF-5). Top left: visual representation of the network.Top right panel: forest plot representing the estimates from the network meta-analysis. Bottom: The surface under the curve (SUCRA) of each of these plots defines the probability that a treatment out of n treatments in a network meta-analysis is the best, the second, the third, and so on until the least effective treatment. A funnel plot is not available (few trials). CRFWVT: convective radiofrequency water vapor therapy; PAE: prostatic arterial embolization; PUL: prostatic urethral lift; TIND: temporary implantable nitinol device; TUMT: transurethral microwave thermotherapy; TURP: transurethral resection of the prostate.

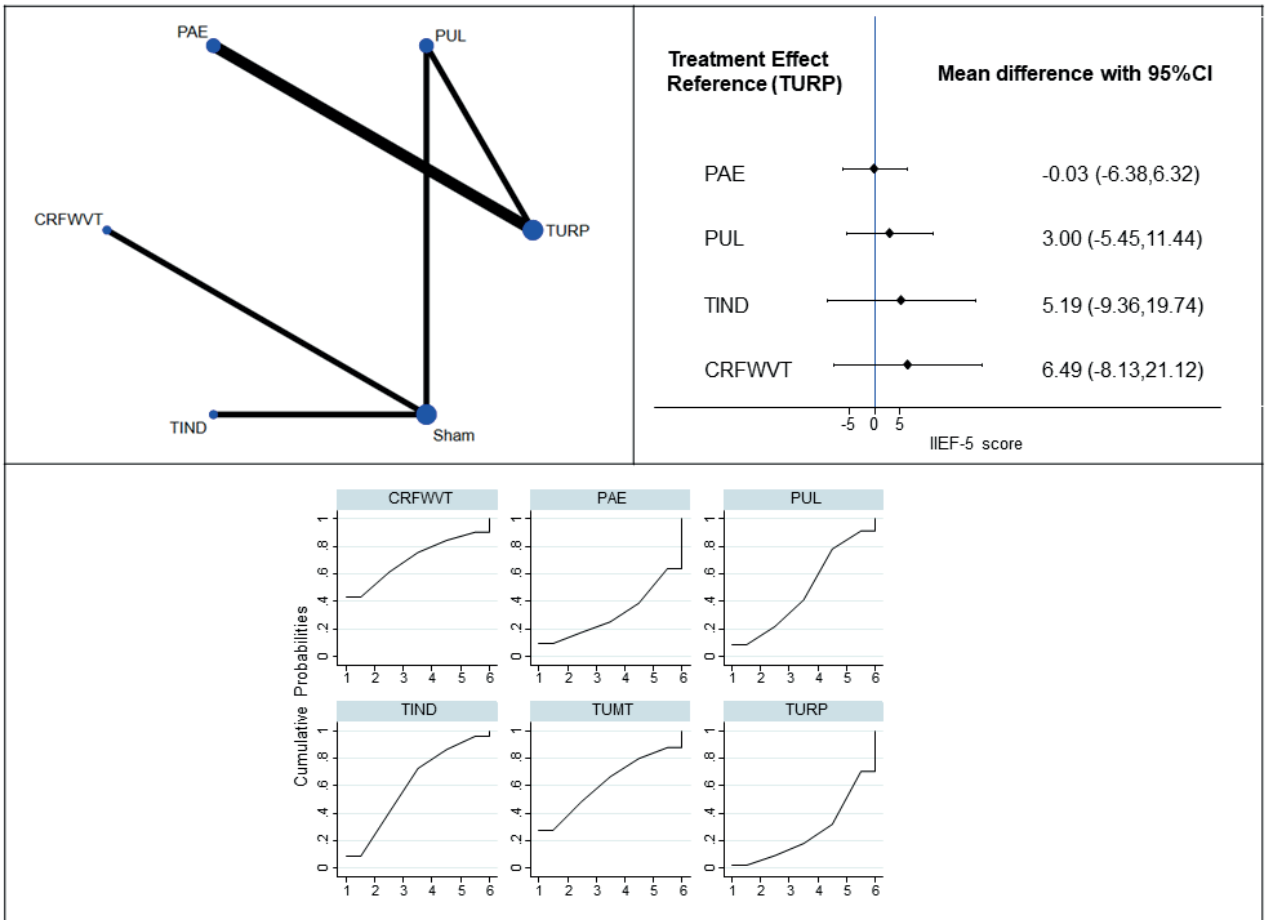
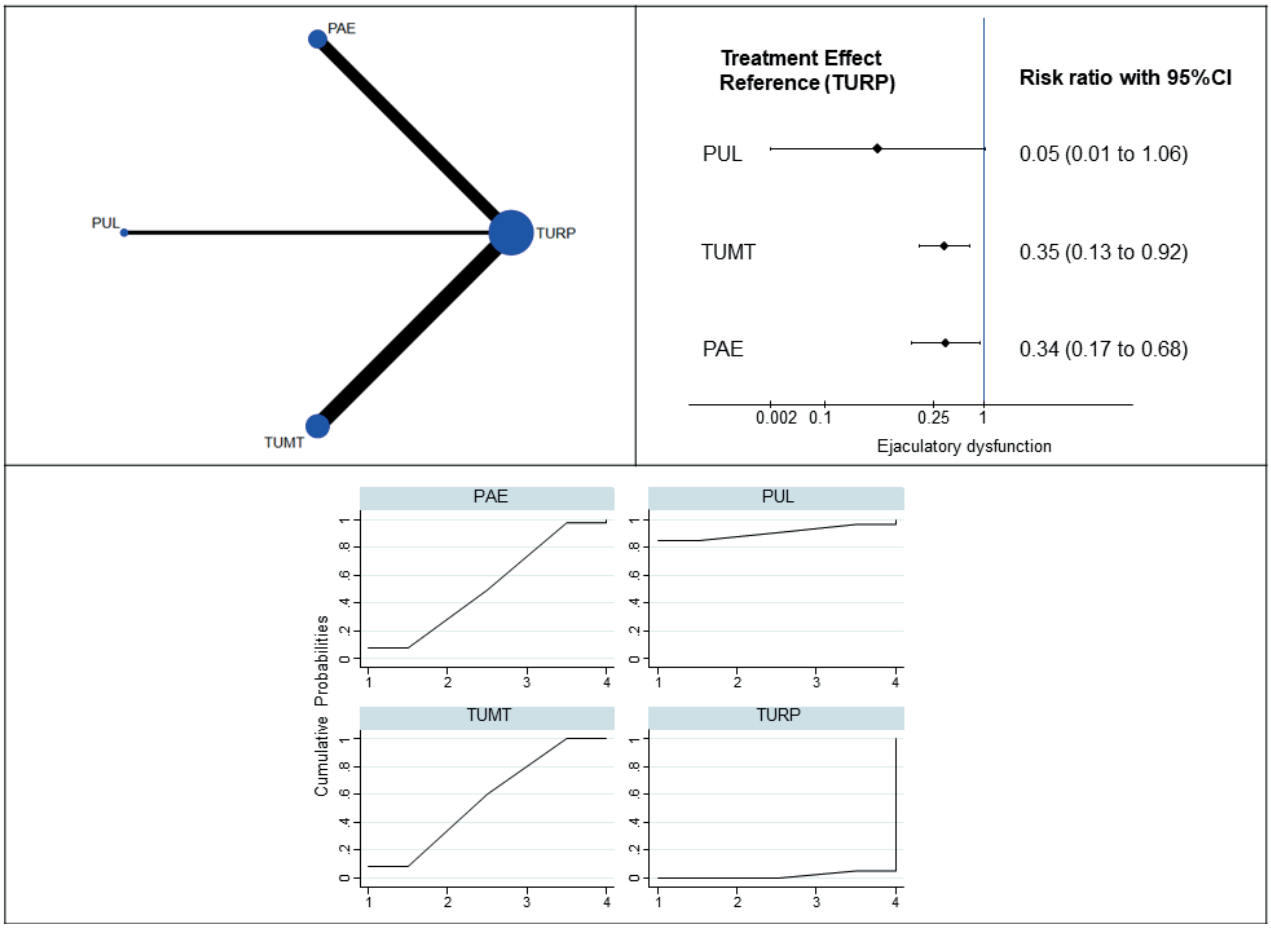


Figure 7. Erectile function (IIEF-5). Top left: visual representation of the network.Top right panel: forest plot representing the estimates from the network meta-analysis, log scale. Bottom: The surface under the curve (SUCRA) of each of these plots defines the probability that a treatment out of n treatments in a network meta-analysis is the best, the second, the third, and so on until the least effective treatment. A funnel plot is not available (few trials). PAE: prostatic arterial embolization; PUL: prostatic urethral lift; TUMT: transurethral microwave thermotherapy; TURP: transurethral resection of the prostate.



1.1. Urologic symptoms scores

See Summary of findings 1, Table 2 (league table with the effect estimates) and Figure 2 (forest plot and SUCRA).

Based on 19 studies with 1847 participants (Abt 2018; Ahmed 1997; Bdesha 1994; Blute 1996; Carnevale 2016; Chughtai 2020; D'Ancona 1998; Gao 2014; Gratzke 2017; Insausti 2020; Larson 1998; McVary 2016; Norby 2002; Pisco 2020; Radwan 2020; Roehrborn 1998; Roehrborn 2013; Wagrell 2002; Zhu 2018) PUL and PAE may result in little to no difference in urologic symptoms scores compared to TURP at short-term follow-up (3 to 12 months, MD of IPSS score, range 0 to 35, higher scores indicate worse symptoms; PUL: 1.47, 95% CI -4.00 to 6.93; PAE: 1.55, 95% CI -1.23 to 4.33). CRFWVT, TUMT, and TIND may result in worse urologic symptoms scores compared to TURP at short-term follow-up, but the confidence intervals include little to no difference (CRFWVT: 3.6, 95% CI -4.25 to 11.46; TUMT: 3.98, 95% CI 0.85 to 7.10; TIND: 7.5, 95% CI -0.68 to 15.69). TURP had the highest likelihood of being the most efficacious for this outcome, however, among minimally invasive procedures PUL and PAE were the highest-ranked interventions (See SUCRA plot in Figure 2). The certainty of the evidence is low due to major concerns about within-study bias, imprecision and inconsistency (heterogeneity, see Table 3).

1.2. Quality of life

See Summary of findings 2, Table 2 (league table with the effect estimates) and Figure 3 (forest plot and SUCRA).

Based on 13 studies with 1469 participants (Abt 2018; Carnevale 2016; Chughtai 2020; Gao 2014; Gratzke 2017; Insausti 2020; Larson 1998; McVary 2016; Pisco 2020; Roehrborn 1998; Roehrborn 2013; Wagrell 2002; Zhu 2018), all interventions (PUL, PAE, CRFWVT, TUMT, TIND) may result in little to no difference in the quality of life scores compared to TURP at short-term follow-up (3 to 12 months; MD of IPSS-QoL score, range 0-6, higher scores indicate worse symptoms; PUL: 0.06, 95% CI -1.17 to 1.30; PAE: 0.09, 95% CI -0.57 to 0.75; CRFWVT: 0.37, 95% CI -1.45 to 2.20; TUMT: 0.65, 95% CI -0.48 to 1.78; TIND: 0.87, 95% CI -1.04 to 2.79). TURP had the highest likelihood of being the most efficacious for this outcome, however, among minimally invasive procedures PUL and PAE were the highest-ranked interventions (See SUCRA plot in Figure 3). The certainty of the evidence is low due to major concerns on within-

study bias, imprecision and inconsistency (heterogeneity, see Table 3).

1.3. Major adverse events

See Summary of findings 3, Table 2 (league table with the effect estimates) and Figure 4 (forest plot and SUCRA).

Based on 15 studies with 1573 participants (Abt 2018; Ahmed 1997; Carnevale 2016; Chughtai 2020; D'Ancona 1998; Dahlstrand 1995; Floratos 2001; Gao 2014; Gratzke 2017; Insausti 2020; McVary 2016; Norby 2002; Pisco 2020; Roehrborn 2013; Wagrell 2002) TUMT probably results in a large reduction in major adverse events compared to TURP (RR 0.20, 95% CI 0.09 to 0.43). PUL, CRFWVT, TIND, and PAE may also result in a large reduction in major adverse events, but the confidence interval includes substantial benefits and harms (at 3 to 36 months; PUL: RR 0.30, 95% CI 0.04 to 2.22; CRFWVT: RR 0.37, 95% CI 0.01 to 18.62; TIND: 0.52, 95% CI 0.01 to 24.46; PAE: 0.65, 95% CI 0.25 to 1.68). Furthermore, TUMT has the highest likelihood of being the most efficacious for this outcome while TURP was the lowest-ranked intervention (See SUCRA plot in Figure 4). The certainty of the evidence is low for CRFWVT, TIND, PUL, and PAE due to major concerns on the within-study bias and severe imprecision. The certainty of the evidence for TUMT is moderate due to major concerns on the within-study bias.

The most commonly reported major adverse events included hematuria with blood clots requiring evacuation or transfusion and severe infection. Less frequently and with a delayed presentation, some patients developed meatal/urethral stenosis, which usually required additional procedures for resolution (bladder neck incision/urethrotomy).

1.4. Retreatment

See Summary of findings 4, Table 2 (league table with the effect estimates) and Figure 5 (forest plot and SUCRA).

Based on 10 studies with 799 participants (Abt 2018; Bdesha 1994; Brehmer 1999; Carnevale 2016; D'Ancona 1998; Dahlstrand 1995; Floratos 2001; Gao 2014; Gratzke 2017; Wagrell 2002), we are uncertain about the effects of PAE and PUL on retreatment compared to TURP at long-term follow-up (12 to 60 months; PUL: RR 2.39, 95% CI 0.51 to 11.1; PAE: RR 4.39, 95% CI 1.25 to 15.44). TUMT may result in a higher increase in retreatment rates (RR 9.71, 95% CI 2.35 to 40.13). TURP had the highest likelihood of being the most efficacious for this outcome; however, among minimally invasive procedures, PUL was the highest-ranked intervention (See SUCRA plot in Figure 5). The certainty of the evidence is very low for PUL and PAE due to major concerns about the within-study bias, imprecision, inconsistency (heterogeneity, see Table 3) and incoherence. The certainty of the evidence for TUMT is low due to major concerns about within-study bias and incoherence.

These results do not include CRFWVT or TIND because of short-term follow-up (these results are displayed separately below, under pairwise comparisons).

1.5. Erectile function

See Summary of findings 5, Table 2 (league table with the effect estimates) and Figure 6 (forest plot and SUCRA).

Based on six studies with 640 participants (Abt 2018; Carnevale 2016; Chughtai 2020; Gratzke 2017; McVary 2016; Roehrborn 2013), we are very uncertain of the effects of minimally invasive treatments on erectile function (MD of IIEF-5, range 5 to 25, higher scores indicates better function; CRFWVT: 6.49, 95% CI -8.13 to 21.12; TIND: 5.19, 95% CI -9.36 to 19.74; PUL: 3.00, 95% CI -5.45 to 11.44; PAE: -0.03, 95% CI -6.38, 6.32). CRFWVT and TIND have the highest likelihood of being the most efficacious for this outcome, while TURP was the lowest-ranked intervention (See SUCRA plot in Figure 6); the certainty of the evidence is very low due to major concerns about the within-study bias, incoherence and severe imprecision.

Studies related to TUMT did not report this outcome as defined in this analysis (these results are displayed separately below in pairwise comparisons).

1.6. Ejaculatory function

See Summary of findings 6, Table 2 (league table with the effect estimates) and Figure 7 (forest plot and SUCRA).

Based on eight studies with 461 participants (Abt 2018; Ahmed 1997; Carnevale 2016; Dahlstrand 1995; Floratos 2001; Gratzke 2017; Insausti 2020; Norby 2002), we are uncertain of the effects of PUL, PAE, and TUMT on ejaculatory dysfunction compared to TURP (at 3 to 12 months; PUL: RR 0.05, 95 % CI 0.00 to 1.06; PAE: RR 0.35, 95% CI 0.13 to 0.92; TUMT: RR 0.34, 95% CI 0.17 to 0.68). PUL has the highest likelihood of being the most efficacious for this outcome, while TURP was the lowest-ranked intervention (See SUCRA plot in Figure 7). The certainty of the evidence is very low due to major concerns about the within-study bias, inconsistency (heterogeneity, see Table 3), and incoherence.

CRFWVT was not included in this section because these studies were disconnected from the network (see description below). The study assessing TIND reported no events of ejaculatory dysfunction.

1.7. Minor adverse events

Based on 13 studies with 1374 participants (Abbou 1995; Blute 1996; Carnevale 2016; Chughtai 2020; D'Ancona 1998; Dahlstrand 1995; Gao 2014; Larson 1998; McVary 2016; Norby 2002; Pisco 2020; Radwan 2020; Wagrell 2002), TUMT, PAE, CRFWVT, and TIND may result in a greater incidence of minor adverse events compared to TURP, but the confidence interval includes substantial benefits and harms (TUMT: RR 1.43, 95% CI 0.74 to 2.75; CRFWVT: RR 1.78, 95% CI 0.51 to 6.21; TIND: RR 3.35, 95% CI 0.74 to 15.26; PAE: RR 1.06, 95% CI 0.57 to 1.99). TURP had the highest likelihood of being the most efficacious for this outcome; however, among minimally invasive procedures PAE was the highest-ranked intervention (see data in Table 2). The certainty of the evidence is low due to major concerns about within-study bias and severe imprecision.

The most commonly reported minor adverse events included: urinary tract infection, hematuria, dysuria, hematospermia, and pain. For PAE, a “post-embolization syndrome” was described, consisting primarily of pain, malaise, and frequent urination.

PUL was not included in this analysis since the contributing studies reported minor adverse events in greater detail and incidence, which contributed to significant incoherence in the network (these results are displayed separately below in pairwise comparisons).

1.8. Acute urinary retention

Based on 19 studies with 2235 participants (Abt 2018; Ahmed 1997; Albala 2002; Blute 1996; Chughtai 2020; Dahlstrand 1995; De Wildt 1996; Gao 2014; Gratzke 2017; Insausti 2020; Larson 1998; McVary 2016; Nawrocki 1997; Norby 2002; Radwan 2020; Roehrborn 1998; Roehrborn 2013; Wagrell 2002; Zhu 2018), CRFWFT, TIND, and PAE may result in a greater incidence of acute urinary retention compared to TURP, but the confidence interval includes substantial benefits and harms (CRFWVT: RR 2.02, 95% CI 0.07 to 55.79; TIND: RR 2.73, 95% CI 0.1 73.42; PAE: RR 1.82, 95% CI 0.75 to 4.41). PUL may result in little to no difference in the incidence of acute urinary retention compared to TURP, but the confidence interval includes substantial benefits and harms (RR 1.09, 95% CI 0.12 to 10.03). The certainty of the evidence for these estimates is low due to major concerns about within-study bias and imprecision. TUMT may result in a greater incidence of acute urinary retention compared to TURP (RR 2.93, 95% CI 1.19 to 7.22). The certainty of the evidence is low due to major concerns on within-study bias and inconsistency (heterogeneity, see Table 3). Furthermore, TURP and PUL had the highest likelihood of being the most efficacious for this outcome (see data in Table 2).

1.9. Indwelling urinary catheter

Most of the included studies did not adequately report this outcome since they usually only mention catheterization as an event related to acute urinary retention. Therefore, there was insufficient information to perform a network meta-analysis.

2. Pairwise comparisons

The supporting data from the pairwise comparisons are available in the analyses Analysis 1.1; Analysis 1.2; Analysis 1.3; Analysis 1.4; Analysis 1.5; Analysis 1.6; Analysis 1.7; Analysis 1.8; Analysis 1.9; Analysis 1.10; Analysis 1.11; Analysis 1.12; Analysis 1.13; Analysis 1.14; Analysis 1.15; Analysis 1.16; Analysis 1.17; Analysis 1.18; Analysis 1.19; Analysis 2.1; Analysis 2.2; Analysis 2.3; Analysis 2.4; Analysis 2.5; Analysis 2.6; Analysis 2.7; Analysis 2.8; Analysis 2.9; Analysis 2.10; Analysis 2.11; Analysis 2.12; Analysis 2.13; Analysis 2.14. The full descriptions of these results are available in our supporting reviews (Franco 2021; Jung 2017; Jung 2019; Kang 2020). We describe here some key information that we were unable to include in our network meta-analysis, to preserve the transitivity of each network.

2.1. Retreatment: CRFWVT and TIND

Based on one study with 197 participants (McVary 2016), we are very uncertain about the effects of CRFWVT on retreatment compared to sham treatment at three months follow-up (RR 1.36, 95% CI 0.06 to 32.86; Analysis 2.4). Based on another study with 185 participants (Chughtai 2020), we are very uncertain about the effects of TIND on retreatment compared to sham treatment at three-month follow-up (RR 0.67, 95% CI 0.11 to 3.89; Analysis 2.4). The certainty of the evidence is very low due to concerns about the risk of bias and severe imprecision. These results could not be included in the network due to their short-term follow-up.

2.2. Erectile function: TUMT

Based on four studies with 278 participants (Ahmed 1997; Floratos 2001; Norby 2002; Wagrell 2002), TUMT may result in little to no difference in erectile function (defined as an event of erectile dysfunction) compared to TURP at short-term follow-up (RR 0.79, 95% CI 0.40 to 1.55; I^2 = 0%, Analysis 1.10). One study (Wagrell 2002) found a similar result at long-term follow-up (RR 0.49, 95% CI 0.17 to 1.41, Analysis 1.11). The certainty of the evidence is low due to concerns about the risk of bias and imprecision. These results could not be included in the network because they were assessed as binary data and not IIEF scores.

2.3. Ejaculatory function: CRFWVT

Based on one study with 131 participants (McVary 2016), CRFWVT may result in little to no difference in events of ejaculatory dysfunction compared to sham treatment at short-term follow-up (RR 4.01, 95% CI 0.22 to 72.78, Analysis 2.9). The certainty of the evidence is low due to concerns about the risk of bias and imprecision. These results could not be included in the network because they were disconnected from all nodes.

2.4. Minor adverse events: PUL

Based on one study with 79 participants (Gratzke 2017), PUL may result in little to no difference on minor adverse events compared to TURP (RR 0.88, 95% CI 0.70 to 1.09; Analysis 1.15). The certainty of the evidence is low due to concerns about the risk of bias and imprecision. These results could not be included in the network because they introduced incoherence, probably related to a different pattern in the report of adverse events (they reported a higher incidence, and reported in greater detail).

3. Subgroup analysis

We investigated the sources of heterogeneity for urologic symptoms scores and quality of life. We did not identify heterogeneity for major adverse events. Some of the subgroup analyses were not possible to perform due to the scarcity of data (see Differences between protocol and review).

3.1. Urologic symptoms scores

We were unable to identify subgroup differences due to age or symptom severity for the comparisons to TURP (Test for subgroup differences: Chi^2 = 0.01, degrees of freedom [df] = 1 [P = 0.93], I^2 = 0%, see Analysis 1.18; Test for subgroup differences: Chi^2 = 0.31, df = 1 [P = 0.58], I^2 = 0%, see Analysis 1.19) or due to age for the comparisons to sham treatment (test for subgroup differences: Chi^2 = 0.99, df = 1 [P = 0.32], I^2 = 0%, see Analysis 2.13).

3.2. Quality of life

We were unable to find subgroup differences due to age for the comparisons to sham treatment (Analysis 2.14).

DISCUSSION

Summary of main results

We included 27 trials with 3017 randomized participants, assessing the effects of minimally invasive treatments, compared to TURP or sham treatment. The main findings of our network meta-analysis are the following.

Urologic symptoms scores: At short-term follow-up, PUL and PAE may result in little to no difference in urologic symptoms scores compared to TURP at short-term follow-up. CRFWVT, TUMT, and TIND may result in worse urologic symptoms scores compared to TURP, but the confidence intervals include little to no difference.

Quality of life: At short-term follow-up, all interventions may result in little to no difference in the quality of life, compared to TURP.

Major adverse events: TUMT probably results in a large reduction in major adverse events compared to TURP, whereas the other treatment modalities (PUL, CRFWVT, TIND, and PAE) may result in a large reduction in major adverse events.

Retreatment: We are very uncertain of the effects of PUL and PAE on retreatment when compared to TURP. TUMT may result in a substantial increase in retreatment rates.

Erectile function: We are very uncertain of the effects of CRFWVT, TIND, PUL, and PAE on erectile function.

Ejaculatory function: We are very uncertain of the effects of PUL, PAE, and TUMT on ejaculatory dysfunction compared to TURP.

Minor adverse events: TUMT, PAE, CRFWVT, and TIND may result in a greater incidence of minor adverse events compared to TURP. PAE had a higher probability of being the best intervention, compared to others.

Acute urinary retention: TUMT, CRFWFT, TIND, and PAE may result in a greater incidence of acute urinary retention compared to TURP, and PUL may result in little to no difference in this outcome.

Indwelling urinary catheter: There was insufficient information to perform a network meta-analysis for this outcome.

TURP is the reference treatment with the highest likelihood of being the most efficacious for urinary symptoms, quality of life, retreatment, minor adverse events, and acute urinary retention, but the least favorable in terms of major adverse events, erectile function, and ejaculatory function. Among minimally invasive procedures, PUL and PAE have the highest likelihood of being the most efficacious for urinary symptoms and quality of life; TUMT for major adverse events; PUL for retreatment, ejaculatory function, and acute urinary retention; CRFWVT and TIND for erectile function; and PAE for minor adverse events.

Overall completeness and applicability of evidence

The largest limitation of this study relates to issues related to the underlying body of evidence (see below), in particular, the lack of head-to-head trials for MITs against TURP. For example, RCTs for CRFWVT (McVary 2016) and TIND (Chughtai 2020) were limited to comparisons against sham treatment that were unblinded after three months and in many cases had short-term follow-up. The latter issues are underscored by the fact that the AUA guideline panel on the surgical management of LUTS had determined it required a minimum follow-up of greater than 12 months to supports its recommendations (Foster 2019, Parsons 2020), as reflected in the underlying systematic review (Dahm 2021a). Since longer-term RCT data is so limited, observational data may provide complementary information. For example, a systematic review of such studies found that the rate of retreatment may be higher for PUL than assessed here, close to 6% per year (Miller 2020a). Meanwhile, another systematic review has suggested that the long-term effects of CRFWVT may be sustained with a relatively low retreatment rate (Miller 2020b).

The reporting of adverse events was not uniform across studies, especially those that might be different across procedures, such as the 'post-embolization syndrome' in PAE. This was also highlighted in a recent review of observational data in which over a quarter of patients suffered this syndrome, but it was not uniformly characterized (Svarc 2020). Whereas the Clavien-Dindo (Dindo 2004) system provides a well-established system to grade the severity of surgical complications, it may be less than ideal to characterize, for example, the adverse event profile for such different MITs as PUL and PAE.

A recent systematic review on men's values and preferences highlighted that they expect a high success rate with low remission and complication rates, which minimally invasive treatments may provide compared to TURP (Malde 2021). However, men also value the preservation of their sexual function, for which we have greater uncertainties. It is therefore important that clinicians engage in shared-decision making with their patients when discussing the available options (Dahm 2021b).

Quality of the evidence

The certainty of the evidence was mostly low to very low due to the following considerations:

- Within-study bias: All of the included studies were rated as having a high or unclear risk of bias across outcomes. While in the comparisons to TURP it was mostly due to the lack of blinding of participants and personnel, there were also significant problems related to missing outcome data and an inadequate report of randomisation and allocation methods.
- Imprecision: Most of our combined estimates in the network meta-analysis and many in our pairwise analysis had substantial imprecision, including substantial benefits and harms. This was primarily due to a low number of participants in each comparison and, for dichotomous outcomes, few events.
- Inconsistency (heterogeneity): we found substantial unexplained heterogeneity in our estimates, although it was not a major concern in most cases.
- Incoherence: We drew our networks and compiled our data with careful consideration of transitivity by inspecting the distribution of effect modifiers to reduce the probability of finding global and local incoherence (see below). Nevertheless, some of our networks were loosely connected. Due to the lack of closed loops, we were unable to assess incoherence adequately. Therefore, following the current guidance, we rated down the certainty of the evidence.

There is also the possibility of novelty bias, which refers to the mere appearance that a new treatment is better when it is new (Salanti 2010; Salanti 2014). This type of bias can be assessed by the visual inspection of funnel plots (see Figure 3) where newer treatments such as PAE produce asymmetries with relation to older treatments in the distribution of effect sizes, related to the quality of life.

Potential biases in the review process

We made minor modifications from our protocol regarding the reporting of additional data available in each supporting review (especially pairwise comparisons), and the display of the ranking results both graphically and in the 'Summary of findings' tables. These changes were documented in Differences between protocol and review.

Due to the adjustment in the outcome data that was required for our network meta-analysis (see above), there are minor differences with the estimates presented in the supporting reviews (Franco 2021; Jung 2017; Jung 2019; Kang 2020), with no substantial changes in direction and magnitude of effects.

The most important specification that we made throughout the conduct of our review was to restrict our network meta-analysis to the comparison of minimally invasive treatments versus TURP. This limited the presentation of multiple head-to-head comparisons between minimally invasive treatments. Therefore, we prioritized this main comparison, which would be most relevant to clinicians deciding between alternatives to TURP. Furthermore, considering the scarcity of data, we would have had an extremely low certainty of the evidence for these indirect estimates.

For our main analysis (Urologic symptoms scores - short-term), we found substantial incoherence based on the data of our supporting reviews. We then identified as a possible cause the different time points in which the outcomes were assessed (12, 24, and 52 weeks). Therefore, we extracted the data, when possible, for nearly all our results to the time point of 12 weeks, and incoherence was not subsequently identified. Additionally, we reclassified some of the events extracted as 'retreatment' within 'major adverse events', considering that our definition of retreatment was restricted to other interventions aimed at treating lower urinary tract symptoms and not including complications of the first procedure (which would be a major adverse event). Due to this, the pairwise comparisons do not exactly match those of our supporting reviews, although, in general, they present similar estimates. We had defined at the protocol stage the timing of each outcome as short-term and long-term, but for adverse events, this was not clear from the report; therefore, we conducted a single analysis considering that most of these events (hematuria and clotting) were in the short term.

We were unable to include all available trials and interventions in all networks, primarily due to the lack of reporting of the outcomes in the desired format or definition. For the outcome 'retreatment', we were unable to include CRFWVT or TIND because of short-term follow-up; for erectile function, ejaculatory function, CRFWVT was not included because the study was disconnected from the network, and the study related to TIND reported no events. For minor adverse events, PUL was not included in this analysis since the contributing studies reported minor adverse events in greater detail and incidence, which contributed to significant incoherence in the network. Moreover, long-term data was insufficient to build networks for some critical outcomes. Nevertheless, we included all available data in pairwise comparisons.

Finally, we were unable to perform subgroup and sensibility analysis due to the limited representation of subgroups in trials. Moreover, sensitivity analyses were not possible, considering that most of the studies were at a high or unclear risk of bias.

Agreements and disagreements with other studies or reviews

We identified several systematic reviews focusing on minimally invasive treatments, reporting similar findings with regard to the efficacy of TIND, PUL, PAE, and CRFWVT, and highlighting that these are relatively effective treatments, with a lower incidence of adverse events and sexual dysfunction, compared to TURP (Amparore 2019; Jing 2020; Knight 2021; Tallman 2021; Tzeng 2021; Xiang 2021). While some of these findings are similar to our review, we highlight the uncertainty surrounding some of these outcomes, especially those related to sexual function, in which the data are sparse and usually available for only a subset of participants in each study, as was highlighted by one review (Lokeshwar 2020). Furthermore, many of these reviews included evidence from non-randomized studies and had an overall low quality (Malling 2019; Tanneru 2020). In some cases, the evidence was synthesized by the authors of the primary studies (Amparore 2019; Zumstein 2019). There is a paucity of reviews focusing on TUMT in the last few years, considering that no trials are available since the previous version of the Cochrane Review (Hoffman 2012).

AUTHORS' CONCLUSIONS

Implications for practice

Minimally invasive treatments may result in similar or worse effects concerning urinary symptoms and quality of life, compared to the standard treatment (transurethral resection of the prostate) at short-term follow-up. They may result in a large reduction of major adverse events, especially in the use of prostatic urethral lift and prostatic arterial embolization, which resulted in better rankings for symptomatic symptoms scores. Prostatic urethral lift may result in fewer retreatments compared to other interventions, especially transurethral microwave thermotherapy, which has the highest retreatment rates at long-term follow-up. We are very uncertain about the effects of these interventions on erectile function; however, these treatments may result in fewer cases of ejaculatory dysfunction. Considering that patients value the effects of these treatments on urinary symptoms, retreatment rates, and adverse events, including sexual function, it becomes necessary to engage in shared decision-making when discussing their different treatment options, highlighting the existing uncertainties and eliciting their preferences.

Implications for research

There needs to be a better reporting of basic trial methodology, such as methods of randomisation and allocation concealment, as well as a greater emphasis on patient-reported outcomes, especially those related to sexual function. These were usually described poorly in the included studies. Many studies broke the blinding period after three months, and patients crossed to the active treatment group, which prevented us from knowing the long-term effects of these interventions. This is particularly relevant for convective radiofrequency water vapor therapy and temporary implantable nitinol device, both of which are supported only by single trials that compared the new therapeutic approach to a sham control, with a three-month time horizon. Given the existence of a well-established and effective standard of care, and the availability of multiple other active treatment modalities, sham-controlled trials provide only limited and indirect evidence to inform decision-making (Dahm 2021a). Future research should be conducted in accordance with the 'Idea, Development, Exploration, Assessment, Long-term study' (IDEAL) principles, with the 'Assessment Stage' (corresponding to Phase III trials in drug development) centered around an active comparison of active treatment and a focus on patient-important outcomes (Tradewell 2019). Also, as reflected in a priori determinations by the American Urological Association guideline panel (Foster 2019; Parsons 2020), decision-making about surgical treatment options should be based

on follow-up data of greater than 12 months. A core outcome set, as it is available for a few other urological disease entities (Duffy 2021; Foust-Wright 2017; MacLennan 2017), should establish which outcomes should be collected, and how and when they should be collected.

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Juan Víctor Ariel Franco is a PhD candidate in the Programme of Methodology of Biomedical Research and Public Health, Universitat Autònoma de Barcelona (Spain).

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* Indicates the major publication for the study

Discussion

Main results

Serenoa repens

For this update, we narrowed the review question to two comparisons: *Serenoa repens* vs placebo and *Serenoa repens* in combination with other phytotherapeutic agents versus placebo(57). The main results of this update, including new evidence, indicated that *Serenoa repens* results in little to no difference in urologic symptoms and quality of life at long-term follow-up compared to placebo. In contrast, phytotherapeutic agents with various agents, including *Serenoa repens*, may result in little to no difference in urologic symptoms compared to placebo at short-term follow-up. These agents may result in little to no difference in the occurrence of adverse events; however, the confidence intervals included substantial benefits and harms.

Minimally invasive treatments

Our updated Cochrane review on transurethral microwave thermotherapy (TUMT) found no new studies but re-analysed the results of the previous review in light of the current information needs and methods(58). Whereas the previous version of the TUMT Cochrane review yielded similar results for its global effects in relation to sham and TURP(52), this review provided a greater understanding of the differences between TURP and TUMT. In this version, we favour an interpretation of similar urinary symptom scores at short-term follow-up, considering that long-term data from selected studies provided very low-certainty evidence to highlight substantial differences between these interventions. We also found important differences in the incidence of major adverse events and the incidence of retrograde ejaculation between these interventions, favouring TUMT.Based on moderate certainty of the evidence, TUMT probably reduces urinary symptoms compared to a sham intervention, but low certainty evidence indicates there might be little to no difference when compared to transurethral resection of the prostate (TURP). TUMT may cause fewer major adverse events compared to TURP.

When these results from TUMT were incorporated into the network meta-analysis alongside the evidence from the other minimally invasive interventions (Convective Radiofrequency Water Vapour Therapy, CRWVT; Prostatic Arterial Embolisation, PAE; Temporary Implantable Nitinol Device, TIND and Prostatic Urethral Lift, PUL) and traditional surgery (TURP) we were able to obtain estimates of the relative effectiveness of these interventions(59). TURP was the reference treatment with the highest likelihood of being the most efficacious for urinary symptoms, quality of life, retreatment, minor adverse events, and acute urinary retention but the least favourable in terms of major adverse events, erectile function, and ejaculatory function. Among minimally invasive procedures, PUL and PAE have the highest likelihood of being the most efficacious for urinary symptoms and quality of life; TUMT for major adverse events; PUL for retreatment, ejaculatory function, and acute urinary retention; CRFWVT and TIND for erectile function; and PAE for minor adverse events.

Results in the context of previous research

Serenoa repens

A recent systematic review and network meta-analysis on the same topic included 22 randomised clinical trials with multiple comparisons of hexanic and non-hexanic extracts of *Serenoa repens* with alpha-adrenergic agonists and placebo(60). While the authors concluded that there were clinically insignificant improvements in IPSS at 12 weeks, their confidence intervals included little to no difference compared to placebo (MD −0.47, 95% CI −2.69 to 1.74 for hexanic extract; MD −1.69, 95% CI −4.36 to 0.98 for non-hexanic extract). Moreover, the authors reported greater improvements in hexanic extracts than in non-hexanic extracts. Still, the quantitative estimate included little to no difference between subgroups, similar to the findings of our review (MD −2.16, 95% CI −5.64 to 1.30). Finally, this review was limited due to fewer studies comparing *Serenoa repens* with placebo (7 in that review compared to 15 in ours), with a substantial imprecision in their results. This highlights common problems when interpreting subgroup analysis and the importance of formally testing these differences (Section 10.11.2 of the Handbook (28) and MECIR conduct standard 67 (46).

Minimally invasive treatments

Due to a paucity in research in this area, we found few comparable studies from the last few years for TUMT. A health technology assessment from Sweden assessed the average IPSS score, and concluded that TUMT was inferior to TURP in the improvement of symptoms, which does not take into account the confidence interval and minimally important differences (61). Furthermore, the authors stated that they could not determine the differences in major adverse events, as we found in our review, which could be explained by the lack of grouping of serious events. Nevertheless, the findings related to retreatment were similar. Another systematic review reported similar results for urinary symptoms and retreatment, but highlighted the lower incidence of serious adverse events with TURP than with TUMT (62). They state that the rate of retreatment for TUMT may vary from 20% to 80% (focusing on observational data), but at the same time, highlight that the rate of retreatment is lower in long-term randomised trials such as the one included in our review (63).

In contrast, we found a growing number of systematic reviews on newer minimally invasive procedures reporting similar findings with regard to the efficacy of TIND, PUL, PAE, and CRFWVT, and highlighting that these are relatively effective treatments, with a lower incidence of adverse events and sexual dysfunction, compared to TURP (64–69). While some of these findings are similar to our review, we highlight the uncertainty surrounding some of these outcomes, especially those related to sexual function, in which the data are sparse and usually available for only a subset of participants in each study, as was highlighted by one review(70). Furthermore, many of these reviews included evidence from non-randomised studies and had an overall low quality (71,72). In some cases, the evidence was synthesised by the authors of the primary studies (64,73), which compromises the independence of evaluations.

Limitations in the body of evidence

Serenoa repens

The overall certainty of the evidence was high for the main comparison, except for adverse events, for which we identified imprecision since we restricted the main findings to the studies of the highest quality. For the second comparison, however, we had additional concerns about precision and inconsistency across outcomes.

Minimally invasive treatments

The certainty of this body of evidence was primarily affected by:

- Risk of bias: All of the included studies were rated as having a high or unclear risk of bias across outcomes. While in the comparisons to TURP it was mostly due to the lack of blinding of participants and personnel, there were also significant problems related to missing outcome data and an inadequate report of randomisation and allocation methods.

- Imprecision: Most of our combined estimates in the network meta-analysis and many in our pairwise analysis had substantial imprecision, including substantial benefits and harms. This was primarily due to a low number of participants in each comparison and, for dichotomous outcomes, few events.

- Inconsistency (heterogeneity): we found substantial unexplained heterogeneity in our estimates, although it was not a major concern in most cases.

- Incoherence: We drew our networks and compiled our data with careful consideration of transitivity by inspecting the distribution of effect modifiers to reduce the probability of finding global and local incoherence. Nevertheless, some of our networks were loosely connected. Due to the lack of closed loops, we were unable to assess incoherence adequately. Therefore, following the current guidance, we rated down the certainty of the evidence.

The reporting of retreatment rates was not consistent across studies and various interpretations had to be made to infer their incidence. The description of adverse events, especially sexual adverse events and sexual function, was usually reported irregularly and for a subset (of sexually active) participants, which increased the risk of bias as they were considered conditional outcomes (patients were not stratified for sexually active status).

Limitations of the review process

Serenoa repens

We could not locate the full text of seven of the original studies in the review, which could not be re-analyzed using the updated methods, even after exhausting the methods mentioned above. Based on the characteristics described in the previous version of the review, these studies primarily focused on non-validated outcome measures and Q_{max}, which would not have contributed to the main analyses of this review. Moreover, we identified 17 additional references that were also assessed as awaiting classification because we could not retrieve a full text to determine their eligibility. These references were mostly from the 1980s and 1990s, so it is likely that their outcomes would not be able to be incorporated into our main analyses.

Minimally invasive treatments

The update of the TUMT Cochrane Review required substantial re-structuring of the methods and core outcomes which could have introduced biases, considering the existing analyses of the previous version of the review. Nonetheless, we included the core methods of other reviews of the Cochrane Urology Review Group (23–25,74). This allowed us to secure comparability across interventions and to include the findings of this review for the network meta-analysis. Nonetheless, we were unable to retrieve the full text of older studies using different resources (contact with previous authors, library resources and TaskExchange). These studies, based on the description of the previous review, may not have affected the main findings since they did not report the main outcomes of this version of the review.

For our network meta-analysis, we strictly followed our protocol with minor deviations and only post-hoc specifications. The most important specification that we made throughout the conduct of our review was to restrict our network meta-analysis to the comparison of minimally invasive treatments versus TURP. This limited the presentation of multiple head-to-head comparisons between minimally invasive treatments. Therefore, we prioritised this main comparison, which would be most relevant to clinicians deciding between alternatives to TURP. Furthermore, considering the scarcity of data, we would have had an extremely low certainty of the evidence for these indirect estimates.

For our main analysis (Urologic symptoms scores - short-term), we found substantial incoherence based on the data of our supporting reviews. We then identified as a possible cause the different time points in which the outcomes were assessed (12, 24, and 52 weeks). Therefore, we extracted the data, when possible, for nearly all our results to the time point of 12 weeks, and incoherence was not subsequently identified. Additionally, we reclassified some of the events extracted as 'retreatment' within 'major adverse events', considering that our definition of retreatment was restricted to other interventions aimed at treating lower urinary tract symptoms and not including complications of the first procedure (which would be a major adverse event). Due to this, the pairwise comparisons do not exactly match those of our supporting reviews, although, in general, they present similar estimates. We had defined at the protocol stage the timing of each outcome as short-term and long-term, but for adverse events, this was not clear from the report; therefore, we conducted a single analysis considering that most of these events (hematuria and clotting) were in the short term.

As mentioned in the previous section, reporting on some of the outcomes across all studies was scattered and not thoroughly detailed. For some outcomes, including adverse events, retreatment, acute urinary retention, ejaculatory and erectile function, we had to interpret the data available in the flow of participants and in the section describing “complications.” It is unclear whether the

studies reported all events or only those they considered relevant, especially with a lack of a prespecified protocol. This is particularly true for adverse events, especially those that might be different across procedures, such as the 'post-embolisation syndrome' in PAE. This was also highlighted in a recent review of observational data in which over a quarter of patients suffered from this syndrome, but it was not uniformly characterised (75). Whereas the Clavien-Dindo (Dindo 2004) system provides a well-established system to grade the severity of surgical complications(76), it may be less than ideal to characterise, for example, the adverse event profile for such different MITs as PUL and PAE.

Reporting the right outcomes at the right follow-up time impacted some of our analyses. For the outcome 'retreatment', we were unable to include CRFWVT or TIND because of short-term follow-up; for erectile function, ejaculatory function, CRFWVT was not included because the study was disconnected from the network, and the study related to TIND reported no events. For minor adverse events, PUL was not included in this analysis since the contributing studies reported minor adverse events in greater detail and incidence, which contributed to significant incoherence in the network. Moreover, long-term data was insufficient to build networks for some critical outcomes. Nevertheless, we included all available data in pairwise comparisons.

Finally, we were unable to perform most subgroup and sensibility analyses in the three reviews due to the limited representation of subgroups in trials. Moreover, sensitivity analyses were not possible, considering that most of the studies were at a high or unclear risk of bias.

Implications for practice

The reviews included in this thesis provide evidence to guide the management of lower urinary tract symptoms in men with benign prostatic enlargement. We have disseminated the findings of our research, reflecting on the implications for practice through various educational reviews (see **Appendix B** and **Appendix C**) and co-publication of abridged versions of the Cochrane reviews (articles 2 and 3 - see **Appendix D**)(77,78). Here we summarise the main implications for practice in the context of the wider management of LUTS due to BPH.

Medical management

Current guidelines indicate that for men with moderate symptoms, alpha-blockers are the first treatment option, reducing symptoms by 30–40% and improving urinary flow by 20–25%(15). Moreover, 5-alpha reductase inhibitors (5-ARI) can cause a moderate reduction in symptoms (15–30%) and prostate size, reducing the risk of AUR and the need for surgery, but there is a latency for this improvement (3–6 months), and they are most effective in patients with larger prostates (>30 cc.) that will be treated on a long-term basis(15). In highly symptomatic patients with large prostates, the combined use of alpha-blockers and 5-ARI can result in faster symptomatic improvement and a reduction in the incidence of long-term complications.

Other drugs can be considered in the presence of specific symptoms. The results of clinical trials of phosphodiesterase inhibitors (PDE-Is) such as tadalafil indicate that they may be marginally beneficial over placebo in reducing LUTS(79). Moreover, LUTS due to BPH may coexist with symptoms of urgency, frequency, and incontinence due to detrusor overactivity (i.e. overactive bladder). In these cases, beta-3 adrenergic agonists, such as mirabegron and vibegron, stimulate detrusor relaxation without compromising bladder contractility. According to the available clinical trials, they would be effective in reducing irritative symptoms (80). They can be used alone or in combination with anticholinergics.

Phytotherapeutic agents, such as *Serenoa repens*, which was thoroughly assessed in our Cochrane review, have failed to demonstrate symptomatic relief in multiple clinical trials against placebo(57). Based on this evidence, clinical practice guidelines have since deprioritised *Serenoa repens* in their treatment pathways.

- The 2021 Guideline of the American Urological Association focuses on the treatment of LUTS attributed to BPH using common surgical techniques and minimally invasive surgical therapies; thus, the information on the different types of medical interventions is not deepened, much less the use of *Serenoa repens* (81). However, a previous version of this guideline from 2010 mentioned that the available data do not suggest that *Serenoa repens* has a clinically significant effect on LUTS secondary to BPH (5). Furthermore, it adds that no dietary supplement, combined herbal medicine, or other unconventional therapy is recommended to manage LUTS secondary to BPH due to the paucity of high-quality published trials.

- The European Association of Urology guidelines recommends offering the hexane extract of *Serenoa repens* to men with LUTS who want to avoid possible adverse events, especially those related to sexual function (weak recommendation), informing the patient that the magnitude of efficacy may be modest (strong recommendation)(15). Our review offers a further cautionary note about the use of *Serenoa repens.*

Other phytotherapeutic agents, including pumpkin seeds (*Cucurbita pepo*) and African plum (*Pygeum africanum*) in some small clinical trials, have moderate efficacy in reducing symptoms(82).

These drugs have fewer adverse events, but considering their limited effectiveness, their role in treating LUTS is limited.

Surgery and minimally invasive procedures

Transurethral resection of the prostate (TURP) is one of the most widely used techniques, and the probability of symptomatic improvement with this treatment is between 75% and 96%, and it is considered the "gold standard" treatment (83). The morbidity associated with TUR varies between 5% and 30%. Intraoperative complications include uncontrollable bleeding and capsular perforation with the consequent massive absorption of irrigation fluid ("post-TURP syndrome") and its consequences of dilutional hyponatremia, acute renal failure due to hemolysis, cerebral edema, and even death (84). Early postoperative complications include hematuria, which may persist for up to six weeks, and infection, whereas late complications include urethral stricture (<10%), bladder neck fibrosis, and urinary incontinence (~1%)(85,86). The most frequent late adverse effect of TURP is retrograde ejaculation (66% to 86% of operated patients); it can produce sterility but is not accompanied by alterations when achieving orgasm. Between 10% and 15% of patients present with psychogenic erectile dysfunction after TUR, and up to 2% to 5% with surgery-derived erectile dysfunction(87,88). The reoperation rate is close to 3.3%, mostly related to the aforementioned late complications(59,89). Improvements in the TURP technique, including the use of bipolar energy, have reduced the risk of post-TUR syndrome and bleeding (89).

Alternatives to TURP with spinal anaesthesia

There are currently several surgical procedures with laser devices for the treatment of BPH, which allow the use of saline solution as an irrigation medium (with the same advantages as bipolar TURP) and are performed on an outpatient basis under spinal anaesthesia with a requirement bladder catheter that averages 24 to 48 hours(90). Laser enucleation uses a technique that, similar to open surgery, consists of resecting the middle and lateral lobes from the verumontanum to the bladder neck and then grinding the surgical material in the bladder for pathological study using Holmium (HoLEP) or Thulium (ThuLEP) lasers. This procedure offers results comparable to TURP with less morbidity and hospital stay(90,91).

Laser ablation, on the other hand, is a technique that uses lasers to cauterise glandular tissue until an adequately patent prostatic canal is achieved. Similarly, photo-selective vaporisation of the prostate (PVP) uses green light for this purpose(92). The disadvantages of ablation and vaporisation procedures include the impossibility of obtaining material for biopsy and a time of dysuria that is usually longer than with TURP, whereas the advantages over the latter are a shorter hospital stay, subsequent bleeding, and the need for a bladder catheter, with similar results in terms of symptom improvement(91,92).

Finally, water ablation therapy (also known as Aquablation®) is a recently developed surgical procedure that, using real-time visualisation and ultrasound, uses a high-velocity, non-heated, sterile saline water jet to ablate prostate tissue. This procedure is probably as effective as TUR, with a lower incidence of ejaculation problems but no little difference in erectile function(74).

Alternatives to TURP using local anaesthesia or sedation: minimally invasive procedures

Many patients with moderate or severe symptoms are older adults with a high surgical risk, which led to the emergence of minimally invasive alternatives that, unlike the aforementioned procedures, can be performed with local anaesthesia, on an outpatient basis, and selective post-procedure catheterisation. These procedures, with the exception of arterial embolisation, in

principle, are not designed for large prostates. These procedures include the main interventions included in our Cochrane reviews: TUMT, PAE, CRFWVT, TIND and PUL.

Most of these procedures have a low rate of major complications compared to TURP (see below). Pain, dysuria, urinary retention, and urinary tract infection are common side effects(93–98). In the case of PAE, some of these local and systemic adverse events (dysuria, pain, fever, and nausea) are clustered in a poorly defined "post-PAE syndrome."(75).

Based on our Cochrane reviews and Network Meta-analysis, PUL and PAE are likely to be more effective in reducing urinary symptoms, among other minimally invasive procedures(23,24,58,99). The evidence is limited and of low to very low certainty and of short-term follow-up (<12 months)(59,77). Major adverse events across procedures may also be less frequent than TURP. The evidence is insufficient on the effects of minimally invasive procedures on sexual outcomes, including erectile and ejaculatory function. This brings into question the labelling of 'ejaculation-preserving' procedures as they have not been able to demonstrate better sexual outcomes.(100) This is due to the fact that most studies did not systematically evaluate these outcomes using validated outcome measures or only assessed them in a subset of participants, breaking the principle of randomisation. The rate of retreatments is very uncertain for some procedures for which the trials were unblinded, and participants crossed over at three months (CRFWVT and TIND). Nevertheless, at long-term follow-up, retreatment rates were higher than TURP for PAE and PUL, but especially for TUMT, which was nearly ten times more than TURP (59,77). Following the numerous trials on TUMT in the 1990s and 2000s, prostatic arterial embolisation has the largest evidence based on randomised controlled trials, counting seven studies with 488 participants, some with 2-year follow-up, in contrast to other technologies with smaller trials with short-term follow-up (23,24,58,99).

The recommendations regarding the role of these procedures vary substantially across influential guidelines such as those from the National Institute for Health and Care Excellence (NICE) (101), the European Association of Urology (EAU) (102), and the American Urological Association (AUA) (81). Recommendations by NICE and the AUA are based on a systematic review of the evidence; however, the interpretation of the panels issuing the recommendations varies substantially (see **Table 3**). This highlights the uncertainties on the role of minimally invasive treatments as valid alternatives to TURP and whether which of these might be the best.

Table 3. Main recommendations from influential guidelines

<table>
<tr><th></th><th>NICE</th><th>EAU</th><th>AUA</th></tr>
<tr><td>Prostatic urethral lift</td><td rowspan="3">Alternative to TURP</td><td rowspan="2">Alternative to TURP with lower effectiveness</td><td>Conditional recommendation</td></tr>
<tr><td>Prostatic arterial embolisation</td><td>Only use in research</td></tr>
<tr><td>Water vapour thermal therapy</td><td>Insufficient evidence</td><td>Moderate recommendation</td></tr>
<tr><td>Transurethral microwave</td><td>Avoid using</td><td>Not mentioned</td><td>Conditional</td></tr>
</table>

thermotherapy			recommendation
Temporary implantable nitinol device	Only use in research	Insufficient evidence	Not mentioned

TURP: transurethral resection of the prostate (standard surgery), NICE: National Institute for Health and Care Excellence (NICE), EAU: European Association of Urology, AUA: American Urological Association.

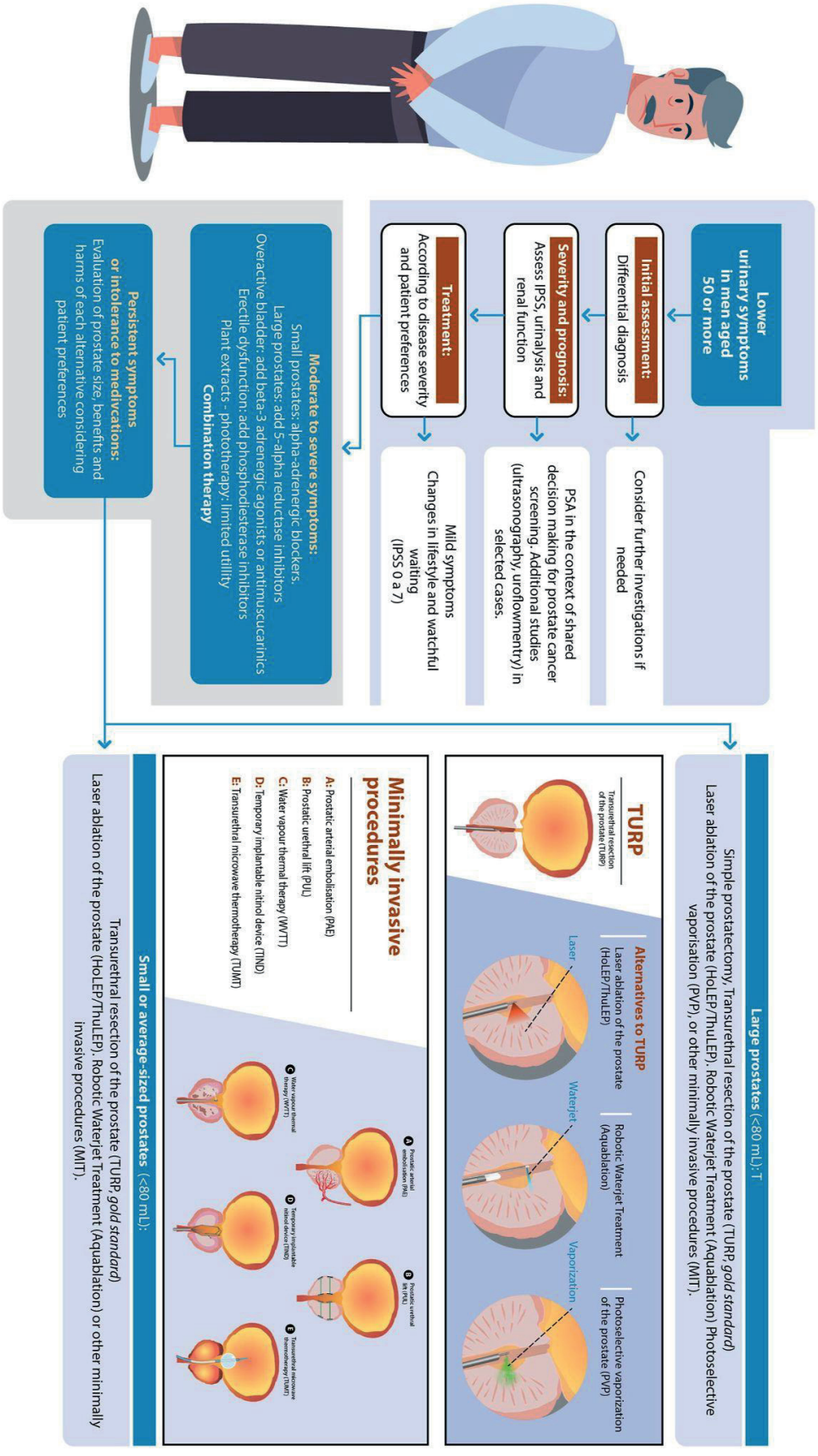
The current uncertainties about the effects of these interventions, together with the inconsistent recommendations across guidelines, put patients and doctors in an awkward position. Guidance on how to make decisions in this context is urgently needed. For instance, based on a recent systematic review on men's values and preferences highlighted that they expect a high success rate with low remission and complication rates, which minimally invasive treatments may provide compared to TURP (103). However, men also value the preservation of their sexual function, for which we have greater uncertainties. It is, therefore, important that clinicians engage in shared-decision making with their patients when discussing the available options (104). Evidence-based decision aids are needed to help clinicians throughout these conversations(105). We provide some pointers in **Table 4** and a summary of the management of LUTS due to BPH in **Figure 2** so patients can engage in meaningful conversations with their health providers about these treatments.

Table 4. Guidance for engaging in conversations about minimally invasive treatments

Steps in shared-decision making	**Example of triggers for conversations with the patient**
Invite the patient to shared decision-making (choice-talk)	I would like to discuss what is the best treatment option for you. Would you be interested in talking about it? The decision about having surgery can be complex, and we might need to discuss the alternatives and your thoughts about it. Would you like me to discuss the available options?
Help explore and compare treatment options (option-talk)	An option may be to continue taking the medication, in your case, and because you are stable in relation to your symptoms, surgical treatment may not have additional improvements; however, in the case of not opting for surgical treatment, it is important to know that there is a risk of acute urinary retention in the coming years (the probability of this will depend on the size of the prostate and how much urine you retain). On the other hand, if you choose surgical treatment, the risk of acute urinary retention will be lower; however, it is important to consider the risks of postoperative complications of the different procedures, which include: ejaculatory problems (66% to 86%), erectile dysfunction (up to 5%), blood in urine and in some rare cases urinary

	incontinence All of these could occur less frequently with some minimally invasive procedures, although it is important to consider that these have a high rate of need for long-term retreatment (that means, again for surgery).
Inquire into the patient's values and preferences (option-talk)	Looking at the alternatives, benefits and harms, what is most important to you? How important are the benefits? What do you think about the side effects?
Evaluate the decision (decision-talk)	Do you need additional information or consult someone else before making a decision? Do you want to make a decision now or later? How comfortable are you with the decision we made?”

Figure 2. Infographic



(Credits to Cristián Baulán - graphic designer)

Implication for research

Relatively few patients have been studied in controlled clinical trials of TUMT, and there is a paucity of research on this procedure in the last 20 years. However, with the emergence of newer minimally-invasive treatments, head-to-head comparisons between them, including TUMT, could clarify their relative effectiveness. Similarly, fewer studies were found on the effectiveness of *Serenoa repens* alone; however, more trials can be expected in combination with other herbal treatments.

The largest area of research in which further trials are expected is in the field of newer minimally invasive procedures (see **Table 4**); however, improvements are needed in basic trial methodology, such as methods of randomisation and allocation concealment, as well as a greater emphasis on patient-reported outcomes, especially those related to sexual function. These were usually described poorly in the included studies.

Many studies broke the blinding period after three months, and patients crossed to the active treatment group, which prevented us from knowing the long-term effects of these interventions. This is particularly relevant for convective radiofrequency water vapour therapy and temporary implantable nitinol device, both of which are supported only by single trials that compared the new therapeutic approach to sham control, with a three-month time horizon. Given the existence of a well-established and effective standard of care, and the availability of multiple other active treatment modalities, sham-controlled trials provide only limited and indirect evidence to inform decision-making (22). Future research should be conducted in accordance with the 'Idea, Development, Exploration, Assessment, Long-term study' (IDEAL) principles, with the 'Assessment Stage' (corresponding to Phase III trials in drug development) centred around an active comparison of active treatment and a focus on patient-important outcomes (106). Also, as reflected in a priori determinations by the American Urological Association guideline panel, decision-making about surgical treatment options should be based on follow-up data of greater than 12 months(26). A core outcome set, as it is available for a few other urological disease entities (Duffy 2021; Foust-Wright 2017; MacLennan 2017), should establish which outcomes should be collected and how and when they should be collected(107–109).

Table 5. Example of ongoing studies on minimally invasive procedures

Trial identification	Intervention	Comparison	Sample size / Follow-up	Status
Comparisons between procedures				
ACTRN12617001235392	PAE	TURP	44 / 60 months	Unknown
NCT02006303	PAE	Green Light Photo-Selective Vaporisation	73 / 12 months	Unknown
NCT04084938	PAE	TURP	140 / 5 years	Recruiting

NCT04236687	PAE	Holmium laser enucleation	100 / 6 months	Not yet recruiting
NCT04757116	TIND	TURP	140 / 12 months	Not yet recruiting
NCT04178811	PUL	Holmium laser enucleation	64 / 12 months	Not yet recruiting
NCT04338776	PUL	WVTT	120 / 12 months	Recruiting
NCT04987138	Zenflow*	Sham	279 / 3 months**	Recruiting
NCT04807010	PAE	Sham	108 / 6 months**	Not yet recruiting
Minimally invasive treatments versus medical treatment				
NCT04245566	PAE	5-alpha reductase inhibitors + Alpha-blockers	425 / 5 years	Not yet recruiting
NCT02869971	PAE	Dutasteride + Tamsulosin	90 / 24 months	Active, not recruiting
NCT04838769	WVTT	5-alpha reductase inhibitors + Alpha-blockers	394 / 24 months	Recruiting
NCT04987892	PUL	Tamsulosin	250 / 3 months	Not yet recruiting

Footnotes: PAE: prostatic arterial embolisation, WVTT: Water vapour thermal therapy; PUL: Prostatic urethral lift; TIND: temporary implantable nitinol device; TUMT: transurethral microwave thermotherapy; TURP: transurethral resection of the prostate. Status in November 2021. (*) Zenflow is an implantable device similar to TIND. (**) Follow-up before cross-over.

Conclusions

This thesis provides evidence from high-quality systematic reviews to inform clinical practice guidelines on the management of lower urinary tract symptoms due to benign prostatic enlargement.

Serenoa repens alone provides little to no benefits for men with lower urinary tract symptoms due to benign prostatic enlargement. There is more uncertainty about the role of *Serenoa repens* in combination with other phytotherapeutic agents. (Article 1)

Minimally invasive treatments may result in similar or worse effects concerning urinary symptoms and quality of life compared to traditional surgery at short-term follow-up. They may also result in fewer major adverse events. Prostatic urethral lift and prostatic arterial embolisation resulted in better rankings for symptom scores, and prostatic urethral lift may result in fewer retreatments, especially compared to transurethral microwave thermotherapy, which had the highest retreatment rates. We are very uncertain about the effects of these interventions on erectile and ejaculatory function. There was limited long-term data, especially for convective radiofrequency water vapour therapy and temporary implantable nitinol device. (Articles 2 and 3)

Future high-quality studies with more extended follow-up, comparing different, active treatment modalities and adequately reporting critical outcomes relevant to patients, including those related to sexual function, could provide more information on the relative effectiveness of these interventions. Given the current uncertainties, the development of patient decision aids and the strengthening of shared-decision making are key to providing high-quality patient care.

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Appendices

Appendix A - Prioritisation project

Publication in the new Cochrane Journal

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RESEARCH ARTICLE

Cochrane Evidence Synthesis and Methods

Quick prioritization of Cochrane reviews on benign conditions of the prostate

Juan V. A. Franco[1] | Jae H. Jung[2,3] | Philipp Dahm[4]

[1]Institute of General Practice, Medical Faculty of the Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany

[2]Department of Urology, Yonsei University Wonju College of Medicine, Wonju, South Korea

[3]Centre of Evidence-Based Medicine, Institute of Convergence Science, Yonsei University, Seoul, South Korea

[4]Minneapolis VAMC, Urology Section and Department of Urology, University of Minnesota, Minneapolis, Minnesota, USA

Correspondence

Juan V. A. Franco, Moorenstraße 5, 40225 Düsseldorf, Germany.
Email: juan.franco@med.uni-duesseldorf.de

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Abstract

Introduction: Benign conditions of the prostate include benign prostatic enlargement and prostatitis, which constitute an important cause of morbidity in men.

Objective: We aimed to generate a list of priority topics of interest to our external stakeholders within our editorial scope.

Methods: Following Cochrane's guidance, we developed a tiered approach for consulting internal and external stakeholders, including members from Urological societies. First, we analyzed our portfolio, including different impact measurements, to assess the need for updates. Then, following criteria related to the feasibility, novelty and relevance of prospective topics for evidence synthesis, we narrowed the list to a suite of titles for updates or new reviews.

Results: Twelve editors provided initial feedback as to what the priorities were for updating existing reviews and for new reviews in our portfolio. The editors identified gaps in our portfolio, mainly covering new treatments for benign prostatic hyperplasia. Then we consulted external stakeholders obtaining 30 responses from 14 countries. These stakeholders provided additional information about the relative importance of existing topics and suggested new ones. We identified that many of the latter were already covered in our portfolio, highlighting gaps in their dissemination. Finally, we narrowed down four priority topics that the editorial group will take forward and two additional topics that might need other considerations before being commissioned.

Conclusions: Following Cochrane's guidance on priority setting, we identified topics relevant to our editors and external stakeholders by analysing our portfolio and two rounds of surveys. Moreover, we identified opportunities for disseminating existing reviews. Further evaluation is needed of the following up commissioning process for priority reviews.

KEYWORDS

benign prostatic hyperplasia, Cochrane, prostatitis and prioritization/priority setting, systematic reviews

1 | INTRODUCTION

Cochrane Urology is one of the over 50 editorial groups of Cochrane, an international not-for-profit organization that aims to promote the use of evidence in healthcare by producing high-quality systematic reviews free from conflict of interest. This group currently holds a portfolio of protocols and reviews dedicated to the diagnosis, prevention, treatment, and rehabilitation of benign and malignant prostate conditions, male sexual dysfunction, benign and malignant renal conditions, and urologic cancers. The group is based at the University of Minneapolis and has a Korean Satellite at Yonsei University in Wonju. Cochrane Urology reviews are not only published in the *Cochrane Database of Systematic Reviews*, but they are also usually co-published in specialty journals like the *BJUI International*, *Investigative and Clinical Urology* and *World Journal of Men's Health* for wider dissemination.

Since 2014, the group has not conducted a formal process for the prioritization of review topics. The editorial team relies on the submission of proposals by author teams and the input of the content expertise of the editors. Prioritizing topics for evidence synthesis can increase the relevancy of reviews, reduce research waste, and, by engaging with stakeholders, increase their uptake for decision-making [1–4].

One of the main topics covered by our group is diseases of the prostate. The prostate gland is an organ about the size of a walnut that lies below the urinary bladder that surrounds the male urethra. The prostate can be affected by malignant conditions (cancer) or benign conditions (inflammation or enlargement). Prostate cancer is the second most common cancer and the fifth leading cause of cancer death in men [5], and benign prostate conditions, especially benign prostate enlargement, have the highest burden of disease in men [6, 7]. According to the International Classification of Diseases 11 (ICD-11), benign diseases of the prostate are classified into hyperplasia of the prostate (benign prostatic hyperplasia or benign prostatic enlargement) and inflammatory diseases, where the different forms of prostatitis stand out [8].

A recent systematic review identified a wide variety of steps to prioritize evidence synthesis, which can be grouped into three phases: a) a pre-prioritization phase aimed at collecting data, planning and selection of topics, b) a prioritization phase aimed at analysing evidence gaps, establishing criteria and draw rankings, and c) a postprioritization phase aimed at effectively implementing the priorities, with subsequent monitoring and evaluation [9]. In this manuscript, we described the activities of our group aimed at generating a list of priority topics of interest to our stakeholders within our editorial scope and a special focus on benign conditions of the prostate. We report the findings of this process following the Reporting guideline for priority setting of health research (REPRISE) [10].

2 | METHODS

2.1 | Context and scope of prioritization

Geographical scope: Cochrane is a global organization; therefore, we aimed to provide evidence of global relevance. We sampled a wide variety of stakeholders for this purpose (see below).

Health topic and intended beneficiaries: Due to the broad scope of the Group's review portfolio and limited resources for conducting prioritization activities, the first part of this project focused on men with benign conditions of the prostate, including prostatitis and lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH). Previous research has highlighted that the number of Cochrane reviews underrepresented the burden of these conditions [11].

Target audience of the priorities: Our group focused on healthcare professionals providing care for men with benign conditions of the prostate with a focus on urologists and professional organizations developing clinical practice guidelines.

Research area and type of research questions: Clinical research with a focus on diagnostic, prognostic and intervention reviews.

2.2 | Governance and team

Our steering group was composed of the Coordinating Editors from the (PD from the USA, JHJ from Korea), a contact editor and project lead (JVAF in Argentina/Germany) with support from the managing editors (Robert Lane and Jennifer Mariano in the USA). PD and JHJ are urologists and JVAF is a family physician. We received methodological support from the Cochrane's Editorial & Methods Department (see Acknowledgments).

2.3 | Framework for priority setting

The full protocol for this process was published on Cochrane's websites and in Open Science Framework, and we followed the framework of Cochrane's Priority Setting Guidance Note [12, 13]. This Guidance outlines five different scenarios that Cochrane Review Groups may choose to

follow with regard to priority setting depending on the breadth of the project, and the availability of resources. This project was aligned with the scenario of a "quick update and prioritization" based on our limited resources and included an analysis of our current portfolio and two rounds of feedback from editors and external stakeholders in the field of urology. This approach was chosen based on the previous experience of other Cochrane Groups [14–17].

2.4 | Stakeholders or participants

We aligned our inclusion criteria with our target audience of the priorities, but we also considered the wider participation of policymakers and patients, although our snowball sampling strategy was not aimed at these groups. We gathered contact information (email addresses) from three sources: a) A map of stakeholders provided by the Cochrane Cancer Network, which included patient organizations, funders and others (while the focus was on cancer, some stakeholders focused on problems of the prostate more broadly, including benign conditions), b) The list of 99 urological associations worldwide available at the American Urological Association website (https://www.auanet.org/education/global-academic-exchanges/international-societies/, last access October 2021, now not available), c) Personal contact through snowball sampling through our editors and mailing lists (mostly guideline developers). Our surveys (see below) were also disseminated through Twitter and our websites. We did not provide compensation for participation in this project, but we offered acknowledgment. Participants were asked to provide their email addresses if they wanted the final published report of the prioritization project. This project was approved by the institutional review board of Instituto Universitario Hospital Italiano de Buenos Aires (Approval number 0038-2020).

2.5 | Identification and collection of research priorities

Collecting initial priorities: We collated all reviews and protocols registered in our Cochrane Group within the scope of benign conditions of the prostate alongside metrics of impact (citations, Altmetrics scores, and citations in guidelines). Then we sent a survey to our editors, asking them to rate the topics' importance for update and suggestions for new topics. After collating and summarizing the responses, we sent a second survey to the stakeholders described in the first section. In this survey we asked them to rate the importance of topics in our portfolio and those suggested by our editors. We also asked them to propose new topics. The surveys were created and distributed with SurveyMonkey (Momentive Inc.)
Collating, categorizing and modifying priorities: New topics following the PICO format were worded according to the guidance of the Cochrane Handbook for naming reviews and reviewed by the steering group. We deduplicated topics and mapped those that overlapped and we also identified questions in which larger or smaller reviews could be framed.
Identifying overlapping reviews: We consulted our editors and ran exploratory searches for non-Cochrane systematic reviews indexed in MEDLINE in the last 5 years.

2.6 | Prioritization of topics

We held an online editorial meeting where we presented the data summarized in the previous section, and we identified the main topics we prioritized for updates or the commission of new reviews by discussion and consensus. We created a PowerPoint presentation with the data available in Appendix, and we discussed the status of ongoing reviews and teams.

Our main criteria for prioritization included some of the FINER criteria for primary research [18] (*Feasible, Interesting, Novel, Ethical and Relevant*):

- **Feasibility**: considering the methodological challenges, the potential size of the review, the availability of primary studies and existing high-quality systematic reviews on this topic.
- **Relevance and novelty**: for patients, clinicians and guideline developers, including areas of ongoing controversies or where new technologies, drugs or procedures are being implemented.

We did not include the criterion 'interesting' since we worked under the assumption that the priorities would be picked up by groups of review authors who would be highly interested in those topics. Conversely, small research groups could have strong interests in topics with little relevance for practice. Moreover, the criteria 'Ethical' from this framework would not be applicable for systematic reviews.

Based on these criteria, the priorities of our editors and external stakeholders were consolidated. We did not use a formal ranking system at this stage, reaching consensus was the priority, and no areas of conflict or dissent arose during this process; however, if present, we had planned it to be handled by our Co-ordinating editor. We did not seek further feedback from external stakeholders at this stage.

3 | RESULTS

3.1 | Results from the surveys

For the first round of surveys, 12 out of 14 editors replied (80% response rate). The remaining two editors because their methodological or clinical expertise fell outside the scope of this project. The topics that they prioritized for update or completion were:

- Antimicrobial therapy for chronic bacterial prostatitis—review from 2013 (67%).
- Anticholinergics combined with alpha-blockers for LUTS—protocol from 2016 (50%).
- Microwave thermotherapy for LUTS—review from 2012 (42%).
- 5-alpha-reductase inhibitors for LUTS due to BPH—protocol from 2015 (42%).
- *Serenoa repens* for BPH—review from 2012 (25%).
- *Pygeum africanum* for BPH—review from 1998 (17%).
- Beta-sitosterols for BPH—review from 1999 (8%).
- Desmopressin for treating nocturia in men—protocol from 2016 (8%).

The editors provided feedback as to how the review questions could be revised (merging phytotherapy or focusing on combination therapy for 5-ARI). Moreover, two of the top-rated topics (anticholinergics had already been identified for prioritization and the publication was scheduled in 2021 [19, 20]. The editors also suggested the following new topics:

- β3 adrenoceptor agonists (Mirabegron) for lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH).
- High-intensity focused ultrasound (HIFU) for LUTS due to BPH.
- Urodynamic studies for the management of BPH.
- Photovaporisation for the treatment of BPH.
- Thulium enucleation for the treatment of BPH.
- Prognostic factors for the progression of LUTS.
- Diagnostic test accuracy of investigations for bladder outlet obstruction in men.

For our second round of the survey, we received 30 responses from external stakeholders, of which 27 (90%) identified as physicians, seven as researchers, six as members of a scientific organization, five as guideline developers, three as carers of someone affected by prostatic diseases, four as systematic reviewers, two as policymakers, and one as someone affected by a prostatic disease. We cannot calculate a precise response rate due to the sampling method (snowball). The geographical distribution was diverse (see Figure 1).

The topics prioritized for update by these stakeholders were:

- Antimicrobial therapy for chronic bacterial prostatitis (70%).
- 5-alpha-reductase inhibitors for LUTS due to BPH (50%).
- Desmopressin for treating nocturia in men (33%).
- *Serenoa repens* for BPH (27%).
- *Pygeum africanum* for BPH (7%).
- Beta-sitosterols for benign prostatic hyperplasia (0%).

Many external stakeholders listed new review topics already covered in our portfolio, which may indicate a need to disseminate our work further. Nonetheless, removing these overlapping topics, we identified the following new topics:

- Surgical management comparison
  - Efficacy of robotic simple prostatectomy compared to HoLEP.
  - Robot simple prostatectomy for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia.
  - Photoselective vaporization (PVP).
  - Anatomical endoscopic enucleation of the prostate (AEEP).
- Other medical therapies for LUTS:
  - Early surgery (relative indications) versus medical treatment of BPH.
  - Doxazosin for treatment of lower tract symptoms in men with BPH.
  - Use of *Serenoa repens* for the treatment of Luts in men with dysmetabolic diseases.

FIGURE 1 Geographical distribution of respondents (blue-gradient scale). Argentina 3, Brazil 1, Germany 1, Iceland 1, Italy 1, Japan 1, Malaysia 1, Netherlands 1, Panama 3, South Africa 2, South Korea 2, Switzerland 1, United Kingdom 10, United States 2.

- o B3 receptor agonist for the treatment in men with BPH.
- o Role of Imipramine in the treatment of severe voiding symptoms.

- Diagnosis and LUTS:
  - o Accuracy of digital rectal examination in the diagnosis of benign prostatic hyperplasia in general practitioners.
  - o Accuracy of cut-off of uroflow for detecting obstruction.
  - o Accuracy of prostate ultrasonography in the diagnosis of benign prostatic hyperplasia/Role of digital rectal examination.

Finally, external stakeholders rated the importance of new topics suggested by our editors (in brackets weighted average, range 1–5, ordered by decreasing importance):

- Prognostic factors for the progression of LUTS (4.33).
- Diagnostic test accuracy of investigations for bladder outlet obstruction in men (4.27).
- Urodynamic studies for the management of BPH (3.73).
- β3 adrenoceptor agonists (Mirabegron) for lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) (3.67).
- Thulium enucleation for the treatment of BPH (3.37).
- Photo vaporization for the treatment of BPH (3.1).
- High-intensity focused ultrasound (HIFU) for LUTS due to BPH (2.67).

3.2 | Final editorial prioritization

Considering the input from our editors and external stakeholders, we held an editorial meeting in February 2022. We identified two topics that needed updating and two new topics that may be covered in Cochrane reviews:

- 5-alpha-reductase inhibitors for lower urinary tract symptoms secondary to benign prostatic obstruction (update of the 2018 review).
- *Serenoa repens* for the treatment of LUTS (update of the 2012 review).
- Robotic simple prostatectomy for LUTS (new review).
- Early procedures vs medical treatment of BPH (new review).

Additionally, going through the list of topics, we identified that there is an opportunity to invite authors that produce high-quality systematic reviews outside of Cochrane to create new and up-to-date Cochrane reviews on the following topics, but there were some additional considerations:

- Diagnostic test accuracy of investigations for bladder outlet obstruction in men/Prognostic factors for the progression of lower urinary tract symptoms: these reviews require special expertise in Cochrane reviews on diagnostic and prognosis.

- β3 adrenoceptor agonists (Mirabegron) for lower urinary tract symptoms due to benign prostatic hyperplasia: this review overlaps with the scope of the Cochrane Incontinence Group (which covers overactive bladder syndrome).

Unlike other topics in which we identified a clear PICO question, the focus on the diagnostic accuracy of investigations and prognostic factors for the progression of symptoms was not well defined. The type of diagnostic investigations may include a wide array of possibilities, including digital rectal examination and prostatic ultrasonography. Moreover, some prognostic factors, including age, are well known to predict the onset and progression of symptoms, so it would be important to know what is the knowledge gap that needs to be covered.

4 | DISCUSSION

4.1 | Postprioritization: Monitoring, evaluation, and feedback

Of the four prioritized topics, two are either advanced in their development (5-alpha-reductase inhibitors for lower urinary tract symptoms secondary to benign prostatic obstruction) or have already been submitted for publication (*Serenoa repens* for the treatment of lower urinary tract symptoms). Our CRG is yet to define the scope and coverage of the other two new reviews, considering that the evidence from RCTs might be lacking and observational studies might shape the reviews (robotic simple prostatectomy for LUTS) or the evidence base depends on ongoing studies (early procedures vs medical treatment of BPH). For the former, a scoping review of existing evidence may better inform the conduct of subsequent reviews. For the latter, our group receives weekly updates from Pubmed/MEDLINE to survey published trials. Our CRG will also assess funding opportunities and the possibility of recruiting and providing support to new authors to increase capacity in systematic review development.

Our project suffered several delays due to the lack of specific funding and a low response rate from external stakeholders. We intended to repeat this project 6 months after its completion within another topic of our scope, but we have been unable to do so due to a lack of capacity. We also decided not to use ranking or scoring in all stages of the process, which could have resulted in a quantitative output for prioritization since we believed that meaningful discussions from our editorial board would be more productive in prioritizing and re-shaping review questions. We found this was a preferred approach even in larger and funded priority-setting exercises such as those conducted by the Cochrane Consumers and Communications Group [21]. Additionally, the prioritization criteria (feasibility, relevance and novelty) could have been defined alternatively and heavily relied on subjective judgements. For instance, feasibility may depend on access to funding or greater collaboration; however, certain aspects, such as the availability of ongoing or published primary studies, are key when defining priorities. We are confident in our assessment of the relevance, considering the history of the group and its international board, which frequently engages key stakeholders, including guideline developers. Novelty may also have important equity considerations since the availability of technology and drugs for benign conditions of the prostate vary widely across settings. Our low response rate limits the representativity of the views and perspectives of external stakeholders. For instance, we contacted 14 Asian associations of urology, where there is a high incidence of this condition, but we received few responses, mostly from South Korea, where one of the editorial bases of the Group sits. This highlights the need to develop and grow meaningful and engaging links with stakeholders before consultation.

External stakeholders highlighted the need for reviews on minimally invasive treatments and desmopressin for lower urinary tract symptoms, for which there is a suite of Cochrane reviews [20, 22–26]. The CRG strategy for dissemination was co-publication of those reviews [22, 27–29], which has been shown to improve the impact of Cochrane reviews by reaching a highly specialized readership [30]. Moreover, both reviews have been cited in clinical practice guidelines. Nonetheless, additional actions may be taken to increase the visibility of our reviews. The Cochrane Framework for Knowledge Translation describes many activities beyond prioritization, including the engagement of stakeholders, push-and-pull strategies and translations, some of which cover the work of our Review Group [31]. The Group has ongoing communications with the main guideline developers from the American Urological Association and the European Society of Urology. Moreover, we engaged in small-scale projects to package and push our reviews, including the Cochrane-Wikipedia Initiative. Finally, Cochrane has partners across their geographic centers that provide translations of our reviews in multiple languages.

Finally, considering that a swift publication of reviews has not followed other prioritization projects, we will also have to monitor the production and editorial processing of priority topics [32]. Considering that the reviews from our Cochrane Review Group are above the Cochrane average in their use in guidelines, we will also have to monitor the uptake and feedback by our key stakeholders [33].

5 | CONCLUSIONS

Through an analysis of our portfolio and two rounds of internal and external feedback, we identified high-priority topics for our key stakeholders, including clinicians and guidelines developers. Additional evaluations of the impact of this process is needed, including the output of prioritized reviews and their use in clinical practice guidelines.

AUTHOR CONTRIBUTIONS

Juan V. A. Franco: Conceptualisation, data curation, formal analysis, investigation, methodology, project administration. **Jae H. Jung**: Conceptualisation, formal analysis, investigation. **Philipp Dahm**: Conceptualisation, formal analysis, investigation.

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CONFLICT OF INTEREST STATEMENT

Philipp Dahm and Jae Hung Jung are Co-ordinating editors, and Juan Franco is the contact editor for the Cochrane Urology Group. Juan Franco is also Managing Editor for the Cochrane Metabolic and Endocrine Disorders Group, elected member of Cochrane's Governing Board and Editor-in-Chief of BMJ Evidence-Based Medicine, and Clinical Editor of the BMJ.

DATA AVAILABILITY STATEMENT

All anonymized survey data is available upon request.

ETHICS STATEMENT

This project was approved by the institutional review board of Instituto Universitario Hospital Italiano de Buenos Aires (Approval number 0038-2020).

ORCID

Juan V. A. Franco https://orcid.org/0000-0003-0411-899X

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Appendix B - Uncertainties on minimally invasive procedures

Educational review

1 Institute of General Practice, Medical Faculty of the Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany

2 Research Department, Instituto Universitario Hospital Italiano de Buenos Aires, Argentina

3 Department of Urology, Yonsei University Wonju College of Medicine, Wonju, South Korea

4 Central Library, Instituto Universitario Hospital Italiano de Buenos Aires, Argentina

5 Minneapolis VAMC, Urology Section and Department of Urology, University of Minnesota, Minneapolis, USA

Correspondence to JVA Franco
juan.franco@med.uni-duesseldorf.de

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UNCERTAINTIES

What is the role of minimally invasive surgical treatments for benign prostatic enlargement?

Juan Victor Ariel Franco, [1,2] Jae Hung Jung, [3] Camila Micaela Escobar Liquitay, [4] Philipp Dahm[5]

What you need to know

- New minimally invasive surgical treatments for benign prostatic enlargement that do not use spinal or general anaesthesia are available for patients experiencing lower urinary tract symptoms
- Some of these procedures may offer similar improvement in symptoms as traditional surgery, with fewer adverse events, but the evidence is of low to very low quality, short term, and insufficient
- Refer patients whose condition does not improve with conservative measures and medications to a urologist to discuss surgical options, considering benefits and possible complications, effect on sexual function, and need for retreatment

Benign prostatic enlargement (BPE), also called benign prostatic hyperplasia, is a common cause of lower urinary tract symptoms in men over 50. Increased frequency or urgency of urination, nocturia, difficulty starting urination, or dribbling at the end of urination, are common symptoms.[1] BPE is characterised by growth of glands and smooth muscle parts of the prostate and is separate from prostate cancer. In later stages, it can result in bladder outlet obstruction with complications including urinary retention, infection, and possibly impaired renal function.

Initially, if no complications are evident, patients are advised conservative measures such as reducing the amount of fluid intake in the evening, and medications, including α blockers and 5-α reductase inhibitors.[2] Surgical ablation to reduce the physical obstruction caused by BPE is an option if symptoms do not improve, patients experience side effects (for example, orthostatic hypotension, which can occur with α blockers, or sexual adverse events with 5-α reductase inhibitors) or do not prefer to take medications long term.

Transurethral resection of the prostate (TURP) is the mainstay of surgical treatment.[2] This involves shaving off inner sections of the prostate with an electric loop under direct vision of a cystoscope (fig 1a). TURP requires general (or spinal) anaesthesia and usually catheterisation and admission to hospital at least overnight. It can result in complications such as blood loss which requires transfusion (5%), dilutional hyponatraemia (TUR syndrome) (2%), urinary tract infection, and problems with erections (up to 10%) and retrograde ejaculation (65-75%).[2,3] Technical advances such as improved visualisation and the use of bipolar rather than monopolar electrocautery have reduced these complications.[3]

This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. You can read more about how to prepare and submit an Education article on our Instructions for Authors pages:https://www.bmj.com/about-bmj/resources-authors/article-types

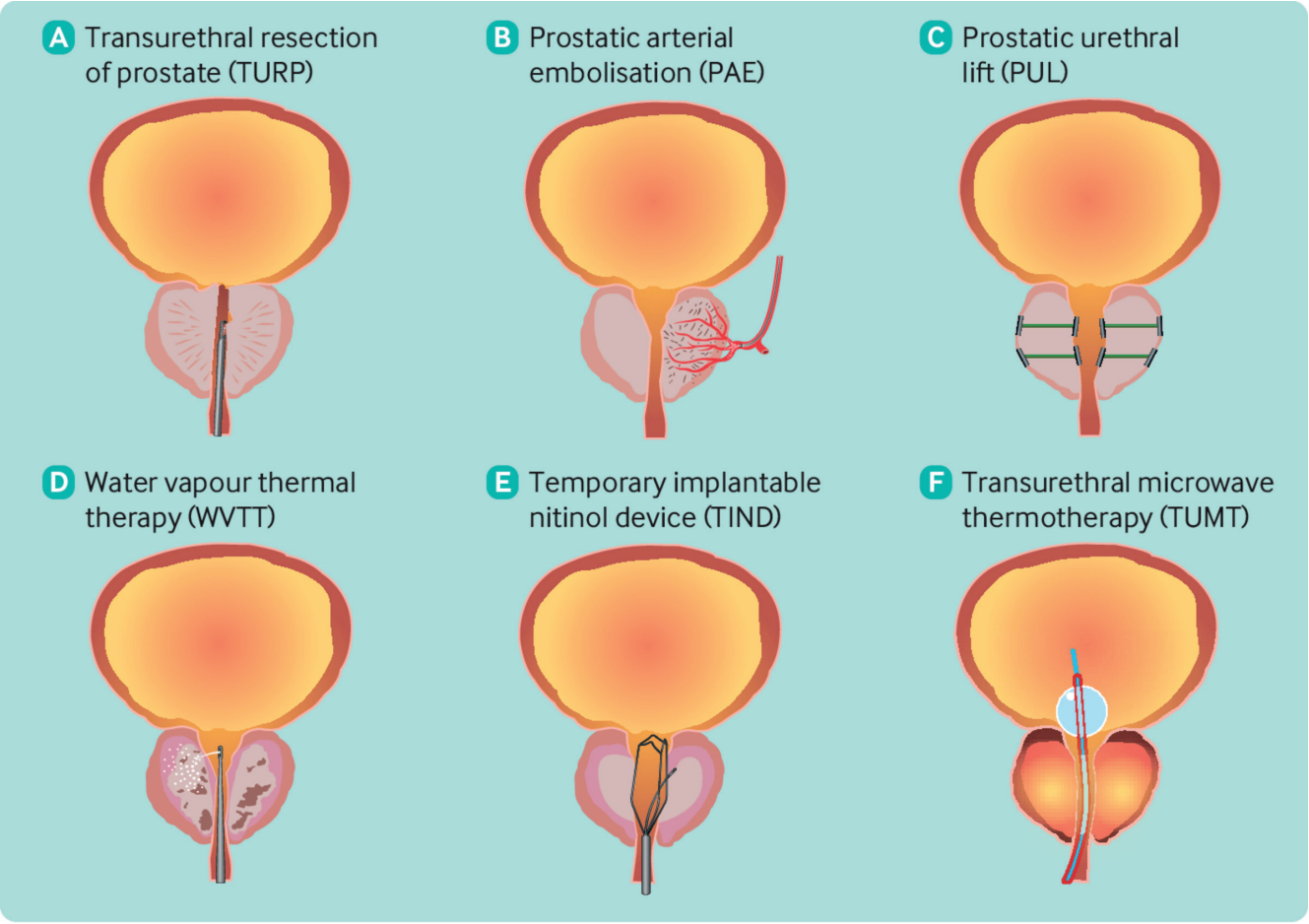

Fig 1 | Main treatment modalities used in minimally invasive procedures and traditional surgery. a) Transurethral resection of the prostate (traditional surgery)—a resectoscope is inserted through the urethra to remove prostatic tissue using a wire loop. b) Prostatic arterial embolisation—microspheres are released into the prostatic artery causing tissue ischaemia. c) Prostatic urethral lift—hooks are placed that pull the urethral wall, expanding on the inner lumen. d) Water vapour thermotherapy: a jet of water vapour triggers prostatic necrosis. e) Temporary implantable device—a cage-like device expands the lumen of the urethra, causing necrosis to the adjacent prostatic tissue. f) Transurethral microwave thermotherapy—a transurethral probe irradiates heat to the prostatic tissue causing necrosis

Minimally invasive surgical therapies have been developed that use intravenous sedation and avoid having to admit patients to hospital. Figure 1 depicts these procedures. Guidelines differ in their recommendations for these procedures[4-6] (table 1). Other procedures, such as aquablation, are sometimes labelled as "minimally invasive" owing to their surgical approach, but they typically require general or spinal anaesthesia, and are not covered in this article.

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Table 1 | Guideline recommendations on minimally invasive surgical treatments for benign prostatic enlargement

	National Institute for Health and Care Excellence (NICE)[4] 2014-2019	European Association of Urology (EAU)[5] 2022	American Urological Association (AUA)[6] 2021
Prostatic urethral lift	Consider as an alternative to TURP (2014-2018)	Offer to men interested in preserving ejaculatory function, with prostate volume < 70 mL and no middle lobe	Considered as a treatment option provided prostate volume 30–80 cc and verified absence of an obstructive middle lobe
Prostatic arterial embolisation		Offer to men who wish to consider minimally invasive treatment options and accept less optimal outcomes compared with TURP	Not supported by current data, and benefit over risk remains unclear; therefore, it is not recommended outside the context of clinical trials
Water vapour thermal therapy		No recommendation (techniques under investigation)	Consider as a treatment option provided prostate volume 30-80 cc.
Transurethral microwave thermotherapy	Do not offer this procedure (2015)	Not mentioned	May be offered as a treatment option
Temporary implantable nitinol device	This procedure should only be used in the context of research (2019)	No recommendation (techniques under investigation)	Not mentioned

TURP=transurethral resection of the prostate (standard surgery)

TURP remains the most frequently used procedure, but use of minimally invasive treatments, predominantly prostatic urethral lift (PUL), has nearly doubled over the past decade according to studies in the US and Australia.[7 8] The array of options to choose from can be confusing for clinicians and patients. It is uncertain if minimally invasive treatments are safe and effective compared with TURP, and which of these might be the best.

What is the evidence of uncertainty?

Minimally invasive treatments result in broadly similar or less improvement in urinary symptoms and quality of life compared with TURP in men with BPE having moderate to severe symptoms as per a Cochrane network meta-analysis published in 2021 (27 randomised controlled trials, 3017 patients)[9 10] (fig 2). Among minimally invasive procedures, PUL and prostatic artery embolisation (PAE) are likely to be more effective in reducing urinary symptoms. The evidence is limited and of low to very low certainty.[11]

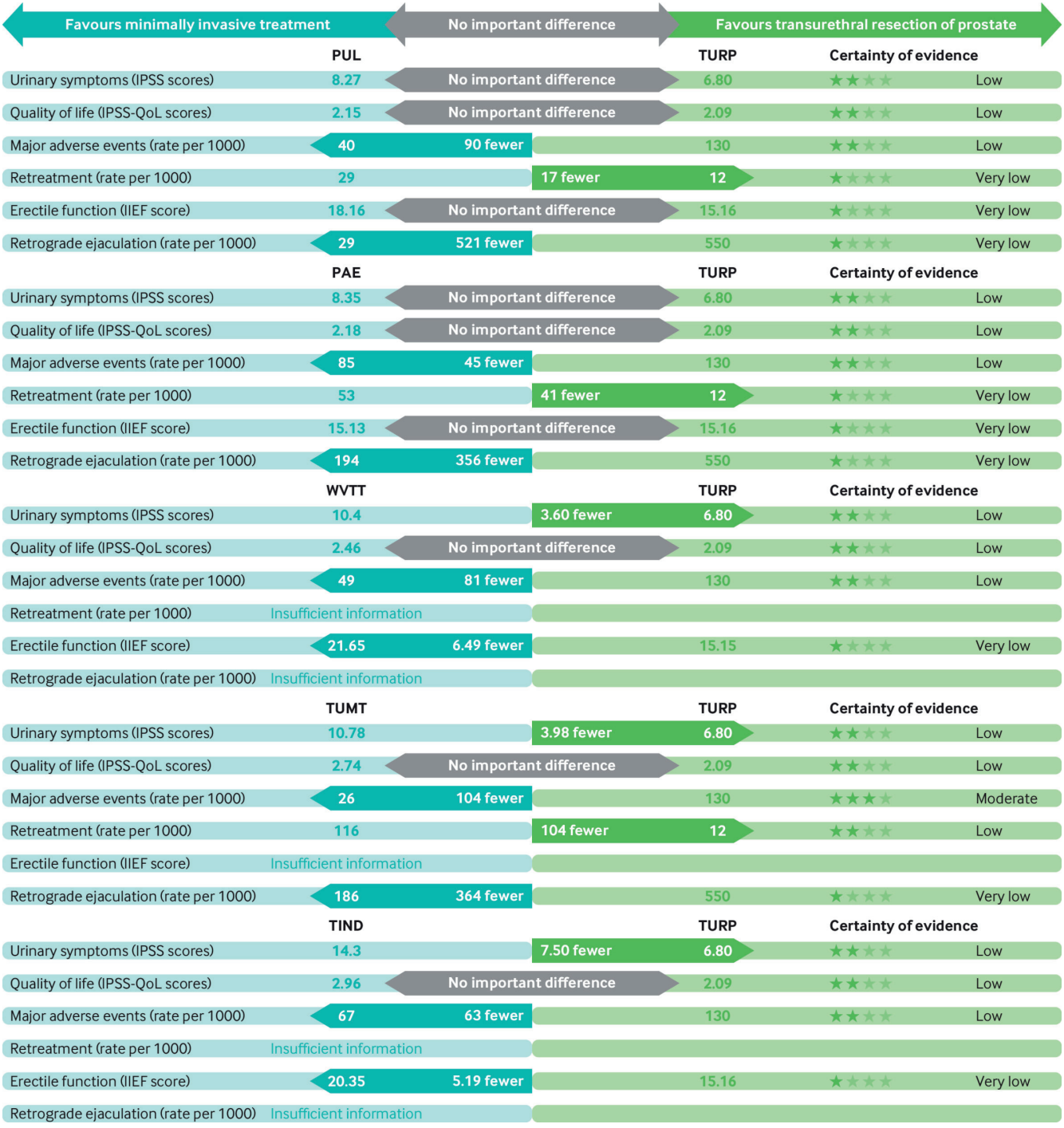

Fig 2 | Summary of the main evidence from a systematic review with network meta-analysis on minimally invasive treatments in patients with lower urinary symptoms attributable to benign prostatic enlargement compared to transurethral resection of the prostate. RCT=randomised controlled trials; PAE=prostatic arterial embolisation; WVTT=water vapour thermal therapy; PUL=prostatic urethral lift; TIND=temporary implantable nitinol device; TUMT=transurethral microwave thermotherapy; TURP=transurethral resection of the prostate. IPSS=International Prostate Symptom Score. IPSS-QoL: IPSS scoring on quality of life. Insufficient information: the trials for TIND and WVTT were very short-term and did not provide adequate data for comparison with other interventions. We considered a threshold of 3 points for IPSS, 1 point for IPSS-QoL, and 5 points for IIEF-5 based on the literature

Major adverse events may be fewer (45-100 fewer events per 1000) compared with TURP (130 events per 1000). Evidence is insufficient on the effects of minimally invasive procedures on sexual outcomes including erectile and ejaculatory function. These have not been systematically assessed, for example, in a well defined group of sexually active patients to be randomised. Reporting was limited to a subset of sexually active patients, which raises concerns about selection bias and comparability. Retreatment rates with TURP tend to be lower overall (12 per 1000) compared with minimally invasive therapies. Higher retreatment rates were reported with transurethral microwave therapy (TUMT).[9 10]

Most studies have important methodological limitations and were rated at high risk of bias. A fairly large number of trials have assessed TUMT (n=16) and PAE (n=7), but much less evidence is available on the latest additions, namely PUL (n=2), water vapour thermal therapy (WVTT) (n=1), and temporarily implanted nitinol devices (TIND) (n=1). Trials of WVTT and TIND compare these interventions with a sham procedure (a form of surgical placebo) rather than any active treatment. Most of the data is short term. Follow-up data of the trials on WVTT and TIND is limited to three months, leaving it uncertain how patients fared long term, and, if and when they were retreated in some form.

We also identified three trials assessing the effects of intraprostatic botulinum A toxin injections, another minimally invasive procedure, as an alternative to oral medications. This treatment seems to provide little to no symptomatic relief based on the limited evidence available.[12 -14]

These procedures may have lower costs related to anaesthesia and inpatient care, but data are insufficient to suggest if they are more cost effective than TURP.[15 16]

Sources and selection criteria

As part of the Cochrane Urology group, we published a network meta-analysis in 2021 on effectiveness of minimally invasive treatments compared with TURP in men with BPE. This included trials in Cochrane reviews on these individual treatments over the past two years.[11 12 15 16] For this article, we have drawn largely from the network meta-analysis. In addition, we searched Cochrane Central Register of Controlled Trials, Medline, and Embase from their inception to October 2021 for additional studies. We did not place restrictions on the language of publication.

GRADE Working Group grades of evidence

- High certainty—we are very confident that the true effect lies close to that of the estimate of the effect
- Moderate certainty—we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- Low certainty—our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
- Very low certainty—we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Is ongoing research likely to provide relevant evidence?

We searched ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (ICTRP) in October 2021 for ongoing trials assessing minimally invasive treatments. We identified 14 ongoing randomised trials (table 2). Ten studies compare these surgical treatments among each other; most of them (n=6) focus on PAE, and one investigates a new device (Zenflow). Four trials compare minimally invasive surgical therapies with medications, thereby exploring their use as first line treatment offered upfront instead of at least a trial of medications.

Table 2 | Ongoing trials assessing minimally invasive surgical therapies for BPE (as of November 2021)

Trial identification	Intervention	Comparison	Sample size	Follow-up	Status
Comparisons between procedures					
ACTRN12617001235392	PAE	TURP	44	60 months	Unknown
NCT02006303	PAE	Green light photo-selective vaporisation	73	12 months	Unknown
NCT04084938	PAE	TURP	140	5 years	Recruiting
NCT04236687	PAE	Holmium laser enucleation	100	6 months	Not yet recruiting
NCT02054013	PAE	TURP	101	24 months	Active, not recruiting
NCT04757116	TIND	TURP	140	12 months	Not yet recruiting
NCT04178811	PUL	Holmium laser enucleation	64	12 months	Not yet recruiting
NCT04338776	PUL	WVTT	120	12 months	Recruiting
NCT04987138	Zenflow*	Sham	279	3 months**	Recruiting
NCT04807010	PAE	Sham	108	6 months**	Not yet recruiting
Minimally invasive treatments versus medical treatment					
NCT04245566	PAE	5-α reductase inhibitors + α-blockers	425	5 years	Not yet recruiting
NCT02869971	PAE	Dutasteride + Tamsulosin	90	24 months	Active, not recruiting
NCT04838769	WVTT	5-α reductase inhibitors + α-blockers	394	24 months	Recruiting
		NCT04987892	PUL	3 months	Not yet recruiting

PAE=prostatic arterial embolisation; WVTT=water vapour thermal therapy; PUL=prostatic urethral lift; TIND=temporary implantable nitinol device; TUMT=transurethral microwave thermotherapy; TURP=transurethral resection of the prostate. *Zenflow is an implantable device similar to TIND.**Follow-up before cross-over

Most of these trials are at an early stage of recruitment, or their status is unclear. Based on details provided in their protocol registration, we are unsure if these studies will provide conclusive results. A couple of trials employ sham as a comparator. There is insufficient focus on outcomes that matter to patients, including retreatment rates and sexual function, and short follow-up (less than the two years recommended by the AUA guideline panel).[6]

Newer treatments are being assessed in trials, including various implantable devices (ClearRing, Butterfly, XFLO Expander, among

others) similar to TIND. The current evidence is limited to small, uncontrolled, observational studies.[17]

What should we do in light of the uncertainty?

Firstly, consider conservative measures such as a reduction of fluids with diuretic effect (caffeinated and alcoholic beverages), reduced fluid intake prior to the period of greatest symptoms (night time or working hours), and medications. The onset of action of different treatments varies. We suggest monitoring treatment response and patient satisfaction over subsequent months. If these options fail to provide relief of symptoms or patients experience side effects, offer referral to a urologist to discuss surgical procedures.

TURP is the mainstay of surgical treatment. Minimally invasive therapies are usually performed by a urologist or, in the case of PAE, by an interventional radiologist. These can be office based procedures or completed in an ambulatory surgical theatre. These procedures require specialised equipment, expertise, and training.

When discussing surgery, assess the patient's perceived burden of symptoms, his understanding of the success rate of a given procedure and potential complications, as well as his willingness to accept other surgical interventions at a later date (ie, retreatment) if the first is unsuccessful.[18] Discuss their concerns, for example, with regard to the preservation of sexual function after the procedure. Inform patients of benefits and harms of each procedure compared with TURP, highlighting the lack of evidence and important uncertainties surrounding claims of lower incidence of sexual adverse events with some of these procedures (see box 'What patients need to know').

Education into practice

- How would you communicate the benefits and harms of each minimally invasive intervention to a patient with BPE?
- How would you elicit the patient's values and preferences on the available options to ensure shared decision making?

Recommendations for further research

- Defining a core outcome set incorporating patient reported outcome measures for future trials in patients with lower urinary tract symptoms secondary to BPE
- Future trials that include an active comparator rather than sham
- Active comparators should include established therapies (ie, TURP), but they may also include other minimally invasive procedures, which would provide direct evidence of their relative effectiveness
- Trial follow-up of sufficient duration, specifically two years or greater, to establish the rate of retreatment
- Cost-effectiveness analyses for different interventions
- Formal decision aids to serve as an evidence based information source, and assist decision making

What patients need to know

- If you experience bothersome urinary symptoms and are diagnosed with benign enlargement of the prostate, your doctor will suggest measures to reduce symptoms and may advise medications
- If symptoms persist, different surgical treatments are available. Your doctor may offer you referral to a urologist for these
- Traditional surgery, called *transurethral resection of the prostate*, requires general or spinal anaesthesia and hospital admission for at least one night. It may have risks such as blood loss, infection, and can affect sexual function
- Other treatments are being offered that can be done without using spinal or general anaesthesia and without hospital admission, and they are called *minimally invasive procedures*
- These procedures act through different mechanisms to improve the flow of urine and alleviate symptoms
- Since these procedures are relatively new, it is uncertain how good they are compared with traditional surgery. Each procedure may have a different profile of benefits and harms
- You may find information claiming that these procedures produce similar results with fewer sexual adverse events (problems with erection and ejaculation), but the evidence on this is still uncertain. These treatments may need to be repeated. Not enough long term data are available on this.
- Discuss with your doctor the available options and what is more important to you so you can make an informed decision

How patients were involved in the creation of this article

Two male patients with lower urinary tract symptoms resulting from benign prostatic enlargement (one of them considering surgery) reviewed this manuscript prior to submission. They provided input that helped to improve the presentation of data and reduce medical jargon. They also provided feedback on how the treatments, and their benefits and harms, can be better presented. Two patient reviewers also reviewed this article for *The BMJ*. We gratefully acknowledge the contribution of patients to this article.

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JVAF conceived the article; JVAF, PD, and JHJ planned the structure of the article, analysed the evidence, and wrote the clinical sections of the article; CMEL designed the search strategy, coordinated the selection of articles and wrote the search methods; JVAF is the guarantor of the paper.

Provenance and peer review: Commissioned, based on an idea from the author; externally peer reviewed.

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Appendix C - Update on minimally invasive procedures

Clinical review

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Review Article

Update on the management of benign prostatic hyperplasia and the role of minimally invasive procedures

Juan V.A. Franco [a, *], Pablo Tesolin [b], Jae Hung Jung [c, d]

[a] Institute of General Practice, Medical Faculty of the Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany
[b] Family and Community Division, Hospital Italiano de Buenos Aires, Argentina
[c] Department of Urology, Yonsei University Wonju College of Medicine, Wonju, Korea
[d] Center of Evidence-Based Medicine, Institute of Convergence Science, Yonsei University, Korea

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ABSTRACT

Lower urinary tract symptoms due to benign prostatic hyperplasia constitute a substantial burden, affecting the quality of life of those affected by this condition. While watchful waiting and medical management using a wide array of pharmaceuticals can be effective, surgery has been one of the most definite solutions for those highly affected by this condition. Transurethral resection of the prostate (TURP) is the gold standard surgical procedure, but other alternatives using laser (HoLEP and ThuLEP) and robotic water jets (Aquablation) are emerging treatments aimed at reducing postoperative morbidity. Minimally invasive procedures conducted in outpatient settings and under local anesthesia or sedation are increasingly being used, especially in those patients with high surgical risk due to comorbidities. These procedures include prostatic arterial embolization, water vapor thermal therapy (Rezum), prostatic urethral lift (Urolift), temporary implantable nitinol device (TIND/iTIND), and transurethral microwave thermotherapy (TUMT). The evidence supporting these treatments is growing, but some uncertainties remain as to what is the magnitude of their advantages and disadvantages compared to TURP. Innovations in the technologies involved in these new procedures may improve their profile for effectiveness and safety. Moreover, new devices are being investigated for marketing approval. Issues around costs and patients' preferences are also yet to be elucidated, thus their evolving role needs to be weighed against the aforementioned considerations.

1. Introduction

Benign prostatic hyperplasia (BPH) is a noncancerous enlargement of the prostate gland due to androgenic stimulus exerted by dihydrotestosterone, a metabolite derived from testosterone by the action of the enzyme 5-alpha reductase.[1] The most important risk factors for developing BPH include age and the presence of functioning testicles (due to their hormonal influence); a family history of this condition and obesity.[2] A total of 50% of 60-year-old men and 90% of 85-year-olds have microscopic BPH; however, only 50% of patients with this histological finding will have a macroscopic enlargement of the gland, and about 50% of these will develop symptoms.[3] Therefore, the most appropriate name for this entity is "lower urinary tract symptoms" (LUTS), considering that prostate enlargement is only one of the factors related to the presence of symptoms. The prevalence of LUTS is between 10% and 30% for men in their 60–70s and 30% in their 80s.[4]

Patients may present with obstructive or irritative symptoms.[1] Diagnosis is based on clinical history, and complementary studies are very useful to evaluate the degree of obstruction, rule out complications, and exclude other differential diagnoses.[1] Disease severity can be assessed using valid questionnaires, including the International Prostate Symptom Score (IPSS), which consist of seven questions rated on a 0–5 Likert scale, and the total score ranges from 0 to 35.[5] Based on the sum score, symptoms can be classified as mild (0–7), moderate,[8–19] or severe.[20–35] An additional question rates from 0 to 6 the overall impact in the quality of life (IPSS-QoL).[5] Long-term complications of BPH include acute urinary retention (AUR), recurrent urinary tract infections, bladder stones, and post-obstructive kidney failure. AUR is one of the most frequent complications, and the risk is up to 14% in 10 years in patients with large prostates and moderate to severe symptoms.[6].

* Corresponding author. Moorenstraße 5, 40225, Düsseldorf, Germany.
E-mail address: juan.franco@med.uni-duesseldorf.de (J.V.A. Franco).

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2. Medical management

The natural history of BPH shows that the progression of symptoms is very slow, and serious complications are infrequent. Watchful waiting and lifestyle modifications may be warranted in those with mild symptoms. Physical activity could reduce the symptoms of prostatism, so the recommendation to exercise regularly could be part of this management strategy.[7] Clinicians frequently advise avoiding irritants, such as coffee, spicy foods, and alcohol, although there is little to no evidence to support these recommendations.[8]

For those with moderate symptoms, alpha-blockers are the first treatment option, reducing symptoms by 30–40% and improving urinary flow by 20–25%.[9] Common side effects include hypotension and ejaculatory dysfunction. However, 5-alpha reductase inhibitors (5-ARI) can cause a moderate reduction in symptoms (15–30%) and prostate size, reducing the risk of AUR and the need for surgery, but there is a latency for this improvement (3–6 months), and they are most effective in patients with larger prostates (>30 cc) that will be treated on a long-term basis.[9,10] Patients should be warned that side effects include sexual dysfunction (e.g. erectile and ejaculatory disorder). In highly symptomatic patients with large prostates, the combined use of alpha-blockers and 5-ARI can result in faster symptomatic improvement and a reduction in the incidence of long-term complications.

Other drugs can be considered in the presence of specific symptoms. The result of clinical trials of phosphodiesterase inhibitors (PDE-Is) such as tadalafil indicate that they may be marginally beneficial over placebo in reducing LUTS.[11] While there is a potential risk of hypotension in combination with alpha-adrenergic blockers, a recent meta-analysis reported that a concomitant treatment with α-blockers and PDE-Is does not increase the rate of adverse events due to hypotension.[12] Tadalafil may be considered in patients with persistent symptoms in the context of concomitant erectile sexual dysfunction, although it requires close monitoring of adverse events. Moreover, LUTS due to BPH may coexist with symptoms of urgency, frequency, and incontinence due to detrusor overactivity (i.e. overactive bladder). In these cases, beta-3 adrenergic agonists, such as mirabegron and vibegron, stimulate detrusor relaxation without compromising bladder contractility. According to the available clinical trials, they would be effective in reducing irritative symptoms.[13] They can be used alone or in combination with anticholinergics. Common side effects include an increase in blood pressure.

Phytotherapeutic agents, such as *Serenoa repens*, also called *Sabal serrulatum* or Saw palmetto, have failed to demonstrate symptomatic relief in multiple clinical trials against placebo.[14] Pumpkin seeds (*Cucurbita pepo*) and African plum (*Pygeum africanum*) in some small clinical trials have moderate efficacy in reducing symptoms.[15] These drugs have fewer adverse events, but considering their limited effectiveness, their role in treating LUTS is limited.

3. Surgery and minimally invasive procedures

Transurethral resection of the prostate (TURP) is one of the most widely used techniques, and the probability of symptomatic improvement with this treatment is between 75% and 96%, and it is considered the “gold standard” treatment. The intervention is brief (usually within 60 minutes) and requires general or spinal anesthesia. The tissue is removed through the urethra using a resectoscope, and the patient remains with a bladder catheter for approximately a couple of days, and after this period, he is discharged from hospital.[16] The morbidity associated with TUR varies between 5% and 30%. Intraoperative complications include uncontrollable bleeding and capsular perforation with the consequent massive absorption of irrigation fluid (“post-TURP syndrome”) and its consequences dilutional hyponatremia, acute renal failure due to hemolysis, cerebral edema, and even death.[17] Early postoperative complications include hematuria, which may persist for up to six weeks, and infection; whereas, late complications include urethral stricture (<10%), bladder neck fibrosis, and urinary incontinence (~1%).[18,19] The most frequent late adverse effect of TURP is retrograde ejaculation (66% to 86% of operated patients); it can produce sterility but be not accompanied by alterations when achieving orgasm. Between 10% and 15% of patients present with psychogenic erectile dysfunction after TUR, and up to 2% to 5% with surgery-derived erectile dysfunction.[20,21] The reoperation rate is close to 3.3%, mostly related to the aforementioned late complications.[22,23] Improvements in TURP technique, including the use of bipolar energy, have reduced the risk of post-TUR syndrome and bleeding.[23]

4. Alternatives to TURP with spinal anesthesia

There are currently several surgical procedures with laser devices for the treatment of BPH, which allow the use of saline solution as an irrigation medium (with the same advantages as bipolar TURP) and are performed on an outpatient basis under spinal anesthesia with a requirement bladder catheter that averages 24 to 48 hours.[24] Laser *enucleation* uses a technique that, similar to open surgery, consists of resecting the middle and lateral lobes from the verumontanum to the bladder neck and then grinding the surgical material in the bladder for pathological study using Holmium (HoLEP) or Thulium (ThuLEP) lasers. This procedure offers results comparable to TURP with less morbidity and hospital stay.[24,25]

Laser *ablation*, on the other hand, is a technique that uses lasers to cauterize glandular tissue until an adequately patent prostatic canal is achieved. Similarly, photo-selective vaporization of the prostate (PVP) uses green light for this purpose.[26] The disadvantages of ablation and vaporization procedures include the impossibility of obtaining material for biopsy and a time of dysuria that is usually longer than with TURP; whereas, the advantages over the latter are a shorter hospital stay, subsequent bleeding, and the need for a bladder catheter, with similar results in terms of symptom improvement.[25,26]

Finally, water ablation therapy (also known as Aquablation®) is a recently developed surgical procedure that, using real-time visualization and ultrasound, uses a high-velocity, non-heated, sterile saline water jet to ablate prostate tissue. This procedure is probably as effective as TUR with a lower incidence of ejaculation problems, but no little difference in erectile function.[27]

5. Alternatives to TURP using local anesthesia or sedation: minimally invasive procedures

Many patients with moderate or severe symptoms are older adults with a high surgical risk, which led to the emergence of minimally invasive alternatives that, unlike the aforementioned procedures, can be performed with local anesthesia, on an outpatient basis, and selective post-procedure catheterization. These procedures, with the exception of arterial embolization, in principle, are not designed for large prostates. These procedures include as follows:

Prostatic arterial embolization (PAE): using femoral or radial artery puncture and guided by a preoperative assessment (using CT or MRI) of the pelvic artery anatomy, super-selective microcatheterization and embolization is then performed on the prostatic arteries to induce tissue necrosis.[28] Particle emboli are used

almost exclusively, with wide variation in the type and size of particles.[29]

Prostatic urethral lift (PUL, Urolift®, Teleflex Inc., Pleasanton, CA, USA): using a handheld pistol grip to which a needle-shaped probe is attached, four hook-shaped implants are placed to pull the urethral wall to expand the inner lumen, and two in each one of the lateral lobes of the prostate. This procedure is generally not used to treat a hypertrophied median lobe of the prostate, which causes obstructive intravesical protrusion of the prostate.[30]

Temporary implantable nitinol device (TIND®, Medi-Tate Ltd., Hadera, Israel): a cage-like device expands the lumen of the urethra causing necrosis to the adjacent prostatic tissue. This device was modified in its original 4-strout to a 3-intertwined strout to reduce the risk of mucosal damage into a second generation (iTIND®).[31]

Water vapor thermal therapy (WVTT, Rezum®, NxThera Inc., Maple Grove, MN, USA): it uses radiofrequency to create thermal energy through a jet of water vapor that triggers prostatic necrosis. This procedure is performed with the person in the dorsal

Table 1
Summary of the main trials and systematic reviews for minimally invasive procedures.

Study name (trial period)	Country	n	Follow-up	Main characteristics
Convective radiofrequency water vapor therapy (Rezum)				
McVary 2016 (2013-2014)	USA	197	3 months	• **Pivotal study** – sham comparison • Lower IPSS scores (MD -6.70, 95% CI -8.90 to −4.50), similar erectile function, and minor adverse events compared to sham. • Uncertainties about retreatment rate (cross-over at 3 months) • Low certainty of evidence.
Prostatic arterial embolization (PAE)				
Jung 2022 (Cochrane review of trials)	Europe and China	217	24 months	• **Two main long-term follow-up trials** • PAE may result in little to no difference in urologic symptom scores (MD 2.58 points, 95% CI −1.54 to 6.71; meta-analysis of 2 trials with 176 participants; $I^2 = 73\%$), adverse events, and sexual adverse events (low certainty evidence) • PAE likely increases retreatments (RR 3.80, 95% CI 1.32 to 10.93; one trial with 81 participants; moderate-certainty evidence)
Pisco 2020 (2014–2018)	Portugal	80	6 months	• Sham comparison • Lower IPSS scores (MD -12.70, 95% CI -15.69 to −9.71), similar erectile function, and minor adverse events compared to sham (low certainty evidence) • Uncertainties about retreatment rate (short-term follow-up)
Prostatic urethral lift (PUL)				
Gratzke 2017 (2012–2013)	Europe	91	24 months	• **First longer-term comparison with TURP.** • Higher IPSS scores (MD 4.80, 95% CI 1.11 to 8.49), but similar erectile function, retreatment rates and adverse events compared to TURP (moderate to low certainty evidence)
Roehrborn 2013 (2011)	North America and Australia	206	3 months	• **Pivotal study** – sham comparison. • Lower IPSS scores (MD -7.30, 95% CI -9.73 to −4.87), similar erectile function, and minor adverse events compared to sham (moderate certainty evidence). • Uncertainties about retreatment rate (cross-over at 3 months)
Temporary implantable nitinol device (TIND)				
Chughtai 2020 (2015–2018)	USA/Canada	185	3 months	• **Pivotal study** – sham comparison • Lower IPSS scores (MD -7.30, 95% CI -9.73 to −4.87), similar erectile function, and minor adverse events compared to sham (before cross-over). • Uncertainties about retreatment rate (cross-over at 3 months)
Transurethral microwave thermotherapy (TUMT)				
Franco 2021 (Cochrane Review of studies between 1994–2002)	Europe and the US	1919	6 months–5 years	• Ten studies compared TUMT with sham and **six studies compared TUMT with TURP**, mostly studies at a high-risk of bias and short-term follow-up. • TUMT probably results in little to no difference in IPSS scores compared to TURP (MD 1.00, 95% CI −0.03 to 2.03; meta-analysis of 4 studies with 306 participants) and fewer adverse events (RR 0.20, 95% CI 0.09 to 0.43; meta-analysis of 6 studies with 525 participants). Moderate to low certainty of the evidence. • Studies with long-term follow-up (24 months to 5 years) indicated a high rate of conversion to TURP (RR for retreatment 7.07, 95% CI 1.94 to 25.82; meta-analysis of 5 studies with 337 participants). • There are uncertainties about differences in the rate of sexual adverse events.

Footnote: certainty ratings were extracted from corresponding Cochrane reviews. IPSS: International Prostate Symptom Score; RR: risk ratio; MD: mean difference.

Table 2
Guidance to engage in conversations about minimally invasive treatments

Steps in shared decision-making	Example of triggers for conversations with the patient
Invite the patient to shared decision-making *(choice-talk)*	I would like to discuss what is the best treatment option for you, would you be interested in talking about it? The decision about having surgery can be complex and we might need to discuss the alternatives and your thoughts about it. Would you like me to discuss the available options?
Help explore and compare treatment option *(option-talk)*	An option may be to continue taking the medication, in your case and because you are stable in relation to your symptoms, surgical treatment may not have additional improvements, however, in the case of not opting for surgical treatment it is important to know that there is a risk of acute urinary retention in the coming years (the probability of this will depend on the size of the prostate and how much urine you retain). On the other hand, if you choose surgical treatment, the risk of acute urinary retention will be lower; however, it is important to consider the risks of postoperative complications of the different procedures, which include: ejaculatory problems (66% to 86%), erectile dysfunction (up to 5%), blood in urine and in some rare cases urinary incontinence All of these could occur less frequently with some minimally invasive procedures, although it is important to consider that these have a high rate of need for long-term retreatment (that means, again for surgery).
Inquire into the patient's values and preferences *(option-talk)*	Looking at the alternatives, benefits, and harms, what is most important to you? How important are the benefits? What do you think about the side effects?
Evaluate the decision *(decision-talk)*	Do you need additional information or consult someone else before making a decision? Do you want to make a decision now or later? How comfortable are you with the decision we made?"

lithotomy position, and using a cystoscopy, a treatment needle delivers injections of water vapor lasting approximately 9 seconds.[32]

Transurethral microwave thermotherapy (TUMT): this is one of the first procedures developed in this category. TUMT uses a transurethral probe to radiate heat to the prostatic tissue causing necrosis.[33] A rectal probe may be inserted and can be used to monitor rectal temperature.[34] There are different types of devices and manufacturers, including those using high-energy to reduce the time of the procedure and urethral cooling to reduce damage.[33]

Most of these procedures have a low rate of major complications compared to TURP (see below). Pain, dysuria, urinary retention, and urinary tract infection are common side effects.[32,35–39] In the case of PAE, some of these local and systemic adverse events (dysuria, pain, fever, and nausea) are clustered in a poorly defined "post-PAE-syndrome."[40]

5.1. Benefits and harms of minimally invasive procedures

Based on a Cochrane review with network meta-analysis, PUL and PAE are likely to be more effective in reducing urinary

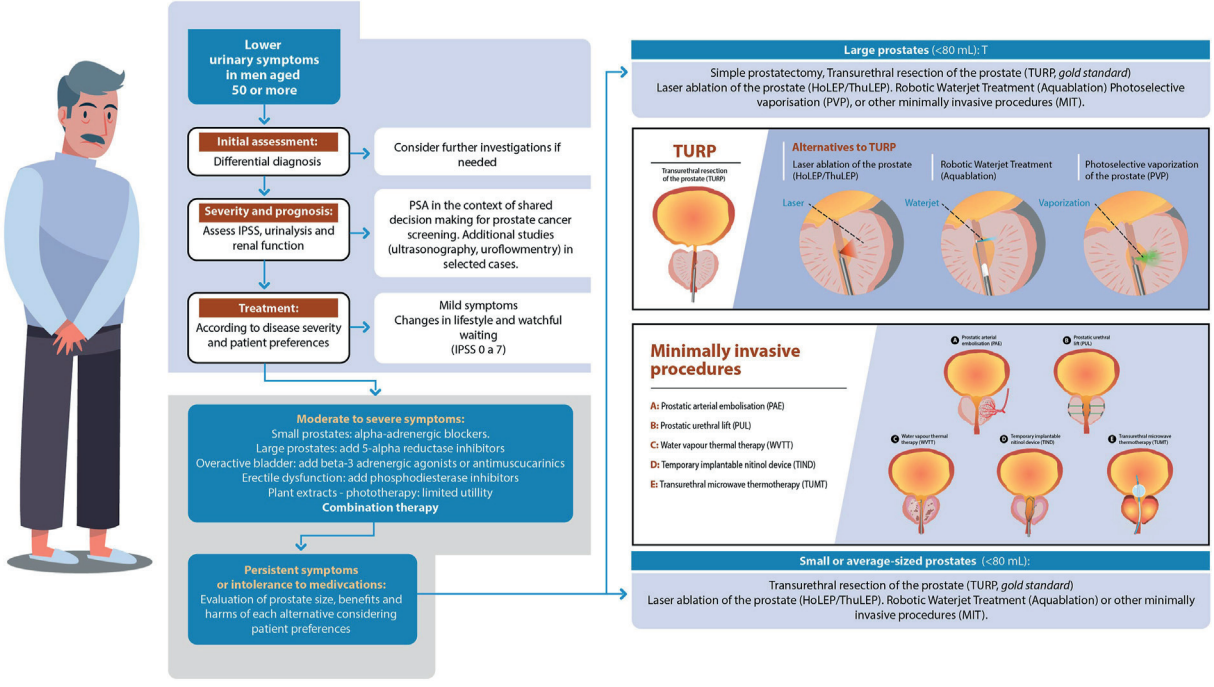

Fig. 1. Summary of the current management of lower urinary tract symptoms due to benign prostatic hyperplasia in men.

symptoms, among other minimally invasive procedures. See Table 1 for a summary of key trials[41–45] and systematic reviews[46–49] for each of these procedures. The evidence is limited and of low to very low certainty and short-term follow-up (<12 months).[22,50] Major adverse events across procedures may also be less frequent than TURP. The evidence is insufficient on the effects of minimally invasive procedures on sexual outcomes, including erectile and ejaculatory function. This brings into question the labeling of "ejaculation-preserving" procedures as they have not been able to demonstrate better sexual outcomes.[51] This is due to the fact that most studies did not systematically evaluate these outcomes using validated outcome measures or only assessed them in a subset of participants, breaking the principle of randomization. The rate of retreatments is very uncertain for some procedures for which the trials were unblinded and participants crossed over at three months (WVTT and TIND). Nevertheless, at long-term follow-up, retreatment rates were higher than TURP for PAE and PUL, but specially for TUMT, which was nearly ten times more than TURP.[22,50] Following the numerous trials on TUMT in the 1990s and 2000s, prostatic arterial embolization has the largest evidence based on randomized controlled trials, counting seven studies with 488 participants, some with two-year follow-up, in contrast to other technologies with smaller trials with short-term follow-up.[46–49]

5.2. Finding the right spot for new treatments – what comes next?

Currently, TURP remains the most frequently used procedure, but minimally invasive treatments are on the rise, particularly prostatic urethral lift in the US and Australia.[52,53] Insurers, third-party authorization, and the incorporation in guidelines are important factors for their implementation. For instance, while PUL is recommended as an alternative for TURP by the American Urological Association (AUA), the National Institute for Care and Excellence (NICE) in the UK, and the European Association of Urology (EAU), TIND and TUMT are either not mentioned or discouraged due to high retreatment rates.[9,54,55] Moreover, the NICE and the AUA have conflicting recommendations regarding the use of PAE and the AUA and EAU on the use of WVTT.[56] Moreover, considerations about cost-effectiveness are paramount, but determinations may be challenging. For instance, one cost-effectiveness analysis found that PUL and WVTT may not be cost-effective compared to TURP or PVP (green light).[57] Other head-to-head economic evaluations found that WVTT was cost-effective compared to PUL at a four-year horizon; however, the effectiveness data for WVTT was extrapolated from the trial that was unblinded and allowed cross-over at three months.[58] The results of these analyses should be interpreted with caution due to the emergent data on effectiveness and safety and the evolving changes in the cost base for these procedures.

Technical innovations may also modulate the benefits and harms of each procedure. However, there have not been new models for TUMT and WVTT (Rezum®), and a new generation of PUL (marketed as Urolift®) was launched in March 2022 (UroLift 2®), using the same implant with improved features in the delivery system.[59] Moreover, the elements of PAE, including particle type and size, can also provide a better effectiveness profile. Procedures using smaller particle size (<300 μm) may be associated with a greater reduction of IPSS scores[60] but a greater incidence of adverse events.[61] Promising results have been reported in single-arm trials using newer embolic particles (e.g. polyethylene glycol microspheres also called HydroPearl®) with a tighter calibration of size[62]. More investigation is needed as to how to better perform this procedure to reduce the dose of radiation and avoid collateral damage to anastomotic pudendal arteries[63]. Finally, a growing area of development includes newer temporary implantable devices similar to iTIND, including ClearRing®, ZenFlow Spring®, and Butterfly®.[64] Small single-arm trials for ClearRing® and Butterfly® indicate a 53% and 40% reduction in IPSS scores, respectively.[65,66]

The decision to undergo traditional surgery or a minimally invasive procedure can be led by the balance of benefits and harms based on patients' values and preferences. Men prefer a quick relief, ideally obtaining stable results, but at the same time, they are mindful of the risks and they prefer avoiding sexual side effects and AUR.[67] Sexual effects may be less important in those sexually inactive, such as elderly adults, but at the same time, the elderly may also be less prone to choosing surgical options.[67] Nevertheless, these studies on values have limitations in their internal validity and generalizability, and an individualized approach eliciting a patient's preferences through shared decision-making is still warranted.[68] Evidence-based decision aids are needed to help clinicians throughout these conversations.[69] We provide some pointers in Table 2 and a summary of the management of LUTS due to BPH in Fig. 1 so patients can engage in meaningful conversations with their health providers about these treatments.

In a recent analysis of the uncertainties of the evidence surrounding these new procedures, we found ten ongoing trials

Table 3
Ongoing studies involving minimally invasive procedures

Trial identification	Intervention	Comparison
Comparisons between procedures		
ACTRN12617001235392	PAE	TURP
NCT02006303	PAE	Green light photo-selective vaporization
NCT04084938	PAE	TURP
NCT04236687	PAE	Holmium laser enucleation
NCT02054013	PAE	TURP
NCT04757116	TIND	TURP
NCT04178811	PUL	Holmium laser enucleation
NCT04338776	PUL	WVTT
NCT04987138	ZenFlow*	Sham
NCT04807010	PAE	Sham
Minimally invasive treatments versus medical treatment		
NCT04245566	PAE	5-alpha reductase inhibitors + Alpha-blockers
NCT02869971	PAE	Dutasteride + Tamsulosin
NCT04838769	WVTT	5-alpha reductase inhibitors + Alpha-blockers
NCT04987892	PUL	Tamsulosin

Footnotes: PAE: prostatic arterial embolization, WVTT: water vapor thermal therapy (Rezum); PUL: prostatic urethral lift (Urolift); TIND: temporary implantable nitinol device; TURP: transurethral resection of the prostate. Status in November 2021. (*) ZenFlow is an implantable device similar to TIND. (**) Follow-up before cross-over.

comparing them to TURP or alternatives to TURP, which would further clarify their role in the treatment of LUTS due to BPH.56 Interestingly, we have identified four trials comparing these procedures with medical management (NCT04245566, NCT02869971, NCT0483876, and NCT04987892), which highlights the emerging role as initial treatment of this condition.[56] More recently, it has been proposed that WVTT can be a cost-effective first-line therapy, but this is reliant in the previously described weak evidence base.[70] More trials will shed more light into the role of these treatments (see Table 3).

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Appendix D - Co-publication of Cochrane Reviews

Original Article
Prostate diseases and male voiding dysfunctions

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Transurethral Microwave Thermotherapy for Benign Prostatic Hyperplasia: An Updated Cochrane Review

Juan Victor Ariel Franco[1], Luis Garegnani[1], Camila Micaela Escobar Liquitay[2], Michael Borofsky[3], Philipp Dahm[4]

[1]*Associate Cochrane Centre, Instituto Universitario Hospital Italiano de Buenos Aires,* [2]*Central Library, Instituto Universitario Hospital Italiano de Buenos Aires, Buenos Aires, Argentina,* [3]*Department of Urology, University of Minnesota,* [4]*Urology Section, Minneapolis VA Health Care System, Minneapolis, MN, USA*

Purpose: To assess the effects of transurethral microwave thermotherapy (TUMT) for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (BPH).
Materials and Methods: We performed a comprehensive search using multiple databases up to May 2021, with no language or publication status restrictions. We included parallel-group randomized controlled trials of participants with BPH who underwent TUMT. We used standard Cochrane methods, including a GRADE assessment of the certainty of the evidence (CoE).
Results: In this update of a previous Cochrane review, we included 16 trials with 1,919 participants. TUMT probably results in little to no difference in urologic symptom scores at short-term follow-up compared to transurethral resection of the prostate (TURP). There is likely to be little to no difference in the quality of life. TUMT likely results in fewer major adverse events. TUMT, however, probably results in a large increase in the need for retreatment. There may be little to no difference in erectile function between these interventions. However, TUMT may result in fewer cases of ejaculatory dysfunction compared to TURP. The overall CoE was moderate to low.
Conclusions: TUMT provides a similar reduction in urinary symptoms compared to TURP, with fewer major adverse events and fewer cases of ejaculatory dysfunction at short-term follow-up. However, TUMT probably results in a large increase in retreatment rates. Study limitations and imprecision reduced the confidence we can place in these results.

Keywords: Lower urinary tract symptoms; Microwaves; Minimally invasive surgical procedures; Prostatic hyperplasia

INTRODUCTION

Benign prostatic hyperplasia (BPH) may cause prostatic enlargement and subsequently compression of the urethra and obstruction. BPH acquires clinical significance when associated with bothersome lower urinary tract symptoms (LUTS) [1]. BPH can progress and cause serious consequences such as acute urinary retention, urinary tract infection, and upper urinary tract deterioration. Initial evaluation of LUTS sugges-

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Correspondence to: Juan Victor Ariel Franco https://orcid.org/0000-0003-0411-899X
Associate Cochrane Centre, Instituto Universitario Hospital Italiano de Buenos Aires, Potosí 4234 C1199ACL Buenos Aires, Argentina.
Tel: +54-91162938136, **Fax:** +54-1149590200, **E-mail:** juan.franco@hospitalitaliano.org.ar

tive of BPH includes patient history, physical examination including a digital rectal examination, urinalysis, prostate-specific antigen (PSA) blood test, voiding diary, and International Prostate Symptom Score (IPSS) [2,3]. Measurements of maximum flow rate (Qmax) and postvoid residual are also often used in diagnosis and treatment decisions [2].

Treatment decisions are based on symptoms and the degree of bother noted by the patient. Initial treatment options for BPH include conservative management (watchful waiting and lifestyle modification) and medication (alpha-blockers and 5-alpha reductase inhibitors) [2]. If patients have been refractory to conservative and medical treatment and BPH causes subsequent complications, such as acute urinary retention, recurrent urinary tract infection, bladder stones or diverticula, hematuria, or renal insufficiency, surgical options are considered [2]. Clinical guidelines recommend monopolar or bipolar transurethral resection of the prostate (TURP) as a standard treatment modality for subjective symptom relief and objective improvements in urinary flow, but this procedure is also associated with significant morbidity and long-term complications, including hematuria requiring blood transfusion, urethral stricture, recurrent urinary tract infection, and urinary incontinence [2]. Moreover, men may experience ejaculatory (65%) and erectile dysfunction (10%) related to TURP [4]. Furthermore, BPH is a disease common in older men who have an increased risk of complications for general anaesthesia and the surgery itself [5]. Some alternatives to TURP include laser enucleation, vaporisation, and Aquablation, but they all require spinal anaesthesia [2]. In recent years, the number of men undergoing TURP has steadily declined due to increasing pharmacologic treatments (alpha-blockers and 5-alpha-reductase inhibitors) and minimally-invasive treatments that are usually performed under local anaesthesia [6], such as convective radiofrequency water vapour therapy [7], prostatic urethral lift [8], prostatic arterial embolisation [9] which are covered in current evidence-based guidelines [10].

Transurethral microwave thermotherapy (TUMT) uses microwave-induced heat to ablate prostatic tissue and is designed to have fewer major complications than TURP [11]. The patient is treated in an outpatient setting under local anaesthesia. The treatment catheter is then placed within the urethra, confirmed by the return of sterile water and transabdominal or transrectal ultrasound, and the balloon is inflated. The catheter is composed of a curved tip, a temperature sensor and a microwave unit. The distal port contains the bladder balloon, allowing for urine drainage and cooling. A rectal probe may be inserted to monitor the rectal temperature [12]. TUMT has evolved over the past decades, incorporating urethral cooling, thus allowing higher energy delivery and reducing the procedure time to around 30 minutes and improved outcomes, but the higher energy leads to more significant discomfort during the procedure, in which patients often require sedation and analgesia, with a continued risk of urinary retention [11].

While TUMT was once the most widely-used procedure for minimally-invasive surgical therapies among the USA's Medicare population [13], its use has declined since its peak in 2006 [14]. A recent study in Australia highlighted that TUMT currently constitutes only 0.26% of all procedures performed for BPH [15].

This is an abridged version of an updated Cochrane review focusing on comparing TUMT *versus* TURP. This review aimed to assess the effects of TUMT to treat LUTS in men with BPH. The full review details the methods and additional results and analyses [16].

MATERIALS AND METHODS

1. Inclusion criteria

We updated the methods of this review based on the protocol of a suite of reviews on minimally invasive treatments for LUTS [7-9]. We included parallel-group RCTs regardless of their publication status or language. We included men over the age of 40 with a prostate volume of 20 mL or greater with LUTS as determined by IPSS of eight or over, and a Qmax <15 mL/s, as measured by non-invasive uroflowmetry, invasive pressure flow studies, or both. We excluded studies of men with active urinary tract infection, bacterial prostatitis, chronic renal failure, untreated bladder calculi or large diverticula, prostate cancer, and urethral stricture disease, as well as those who had undergone prior prostate, bladder neck, or urethral surgery. We also exclude studies of people with other conditions that affect urinary symptoms, such as neurogenic bladder due to spinal cord injury, multiple sclerosis, or central nervous system disease.

Our comparison included TUMT *versus* TURP, other minimally invasive treatments, or sham. We did not

use the measurement of the outcomes assessed in this review as an eligibility criterion. Our primary outcomes included urologic symptom scores, quality of life, and major adverse events. Our secondary outcomes were retreatment, erectile function, ejaculatory function, minor adverse events, acute urinary retention, and indwelling urinary catheter. We considered the clinically important differences for the review outcome measures to rate the overall certainty of evidence [17]. We considered outcomes measured up to and including 12 months after randomisation as short-term and later than 12 months as long-term for urologic symptom scores, quality of life, major adverse events, retreatment, erectile function, ejaculatory function, minor adverse events, and acute urinary retention. We assessed retreatment, indwelling urinary catheter and hospital stay as short-term only.

2. Search methods

We performed a comprehensive search with no restrictions by date, by the language of publication or publication status. We searched the following sources on May 31st 2021: CENTRAL (Cochrane Central Register of Controlled Trials); MEDLINE (Ovid); Embase (Elsevier); LILACS (Bireme); CINAHL; Scopus; Web of Science (Clarivate analytics); ClinicalTrials.gov; World Health Organization International Clinical Trials Registry Platform. We also performed searches in additional resources.

3. Data collection and analysis

We used Covidence software (Veritas Health Innovation, Melbourne, Australia) to identify and remove potential duplicate records. Two review authors (JVAF, LG) independently screened articles for eligibility and independently extracted data [18]. We presented a PRISMA 2020 flow diagram showing the process of

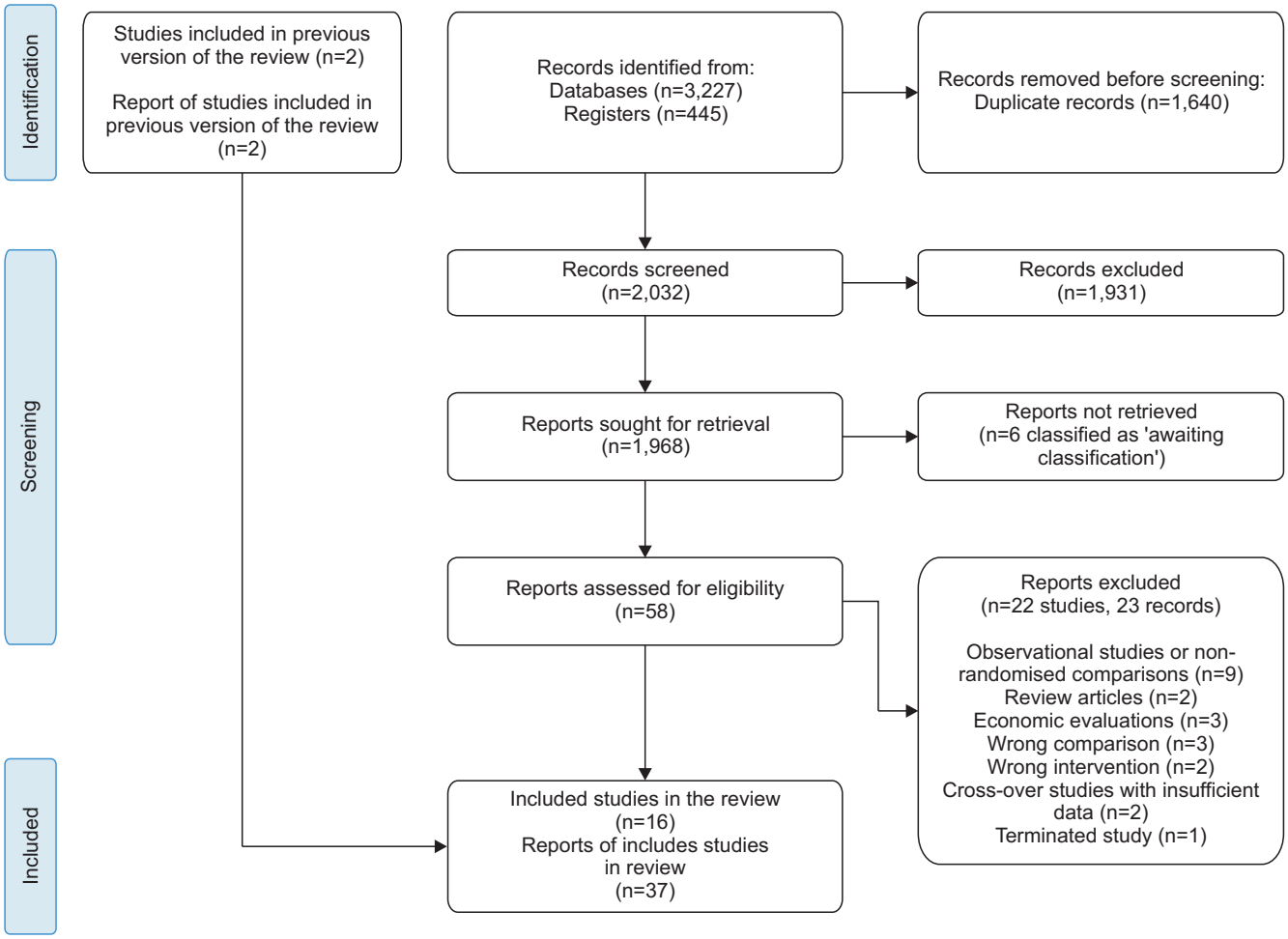

Fig. 1. PRISMA flow diagram.

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Table 1. Characteristics of the included studies

Study name	Trial period	Setting/country	Description of participants	Duration of follow-up (mo)	Intervention and comparator	Age (y)	IPSS	Prostate volume (mL)
Abbou et al, 1995 [21]	N/A	France	Men ≥50 years with symptoms >3 months, prostate 30–80 g, PFR <15 mL/s, PVR <300 mL	12	TUMT (Thermex II, Prostcare, BSD-50)	65±8	N/A	45±15 g
					Sham	66±7	N/A	44±11 g
Ahmed et al, 1997 [22]	N/A	UK	Men ≥55 years with AUA score >12, >1 year, prostate 25–100 mL, PFR <15 mL/s, and a PVR <300 mL	6	TUMT (Prostatron)	69.36	18.5	36.6
					TURP	69.45	18.4	46.1
Albala et al, 2002 [23]	N/A	USA	Men 50–80 years, AUA index >13 and a bother score >11, PFR <12 mL/s, and PVR >125 mL; prostate 30–100 mL without a significant intravesical middle lobe	12	TUMT (TMx-2000)	65.2±7.3	22.2±5.0	50.5±18.6
					Sham	64.6±7.1	22.7±5.7	47.1±17.9
Bdesha et al, 1994 [24]	N/A	UK	Men with prostatism (WHO score >14), PVR >50 mL, and PFR <15 mL/s	3	TUMT (LEO Microthermer)	63.7	19.2	N/A
					Sham	62.6	18.8	N/A
Blute et al, 1996 [25]	N/A	USA	Men suffering from urinary symptoms (Madsen Symptom score >8), PVR 10,000 mL, PFR <10 mL/s, and prostate length 30–50 mm	12	TUMT (Prostatron)	66.9±7.8	19.9±7.2	37.4±14.2
					Sham	66.9±7.1	20.8±6.7	36.1±13.4
Brehmer et al, 1999 [26]	N/A	Sweden	Men suffering from lower urinary tract symptoms and with an enlarged prostate	12	TUMT (30' - 60' - ECP system)	70.4	N/A	N/A
					Sham			
D'Ancona et al, 1998 [28]	1994–1995	Netherlands	Men ≥45 years with Madsen score >8 months, prostate 2.5–5 cm/30–100 mL, PFR <15 mL/s, and PRV <350 mL	24	TUMT (Prostatron)	69.6±8.5	16.7±5.6	45±15
					TURP	69.3±5.9	18.3±6.3	43±12
Dahlstrand et al, 1995 [27]	N/A	Sweden	Men ≥45 years with Madsen score >8 months, prostate 3.5–5 cm, PFR <15 mL/s, and PRV >150 mL	24	TUMT (Prostatron)	68	N/A	33
					TURP	79	N/A	37
De Wildt et al, 1996 [29]	1991–1992	Netherlands/UK	Men ≥45 years with Madsen score >8 months, PFR <15 mL/s, and PRV >150 mL	12	TUMT (Prostatron)	63.3±8.1	N/A	48.6±16.6
					Sham	66.9±6.0	N/A	49.0±20.0
Floratos et al, 2001 [30]	1996–1997	Netherlands	Men ≥45 years, prostate ≥30 cm3, prostatic urethral length ≥25 mm, a Madsen symptom score ≥8, PFR ≤15 mL/s, and PVR ≤350 mL	36	TUMT (Prostatron)	68	21	42
					TURP	66	20	48
Larson et al, 1998 [31]	1994–1996	USA	Men ≥45 years with AUA score >9, enlarged prostate (3–5 cm TRUS), and PFR <12 mL/s without a significantly enlarged middle lobe	12	TUMT (Targis)	66	20.8	38.1
					Sham	65.9	21.3	44.7
Nawrocki et al, 1997 [32]	N/A	UK	Men with a Madsen symptom score ≥8, PFR ≤15 mL/s, PVR >150 mL, and detrusor pressure >70 cmH2O	6	TUMT (Prostatron)	70	19	41.2±14.6
					Sham		17.5	46.7±16.8
Nørby et al, 2002 [33]	1996–1997	Denmark	Men ≥50 years, IPSS ≥7, and PFR ≤12 mL/s	6	TUMT (Prostatron)	66±7	20.5±5.7	43
					TURP/TUIP	68±7	21.3±6.6	44
Roehrborn et al, 1998 [34]	N/A	USA	Men ≥55 years, AUA-SI ≥13, PFR ≤12 mL/s, and prostate volume 25–100 mL	6	TUMT (Dornier)	66.3±6.5	23.6±5.6	48.1±16.2
					Sham	66.0±5.8	23.9±5.6	50.5±18.1

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Table 1. Continued

Study name	Trial period	Setting/country	Description of participants	Duration of follow-up (mo)	Intervention and comparator	Age (y)	IPSS	Prostate volume (mL)
Venn et al, 1995 [35]	N/A	UK	Men with a Madsen symptom score ≥8 and PVR <250 mL	6	TUMT (Microwave Engineering Designs)	70.5	19.2	40.4
					Sham	68	20.1	40.6
Wagrell et al, 2002 [36]	1998–1999	Scandinavia/USA	Men IPSS ≥13, PFR ≤13 mL/s, and prostate volume 30–100 mL	5 years	TUMT (ProstaLund Feedback)	67±8	21.0±5.4	48.9±15.8
					TURP	69±8	20.4±5.9	52.7±17.3

Values are presented as mean±standard deviation or mean only.
IPSS: International Prostate Symptom Score, N/A: not available, PFR: peak flow rate, PVR: postvoid residual, TUMT: transurethral microwave thermotherapy, AUA: American Urological Association, TURP: transurethral resection of the prostate, WHO: World Health Organization, LEO: laser electro optics, TUIP: transurethral incision of the prostate, AUA-SI: American Urological Association Symptom Index.

study selection [19]. Two review authors (JVAF, LG) authors independently extracted data and assessed the risk of bias of the included studies using the Cochrane risk-of-bias tool for randomized trials [20]. We summarized data using a random-effects model. We planned to assess heterogeneity statistically with the I^2 statistic >50% were considered to indicate substantial heterogeneity. We planned to test for publication bias by assessing funnel plot asymmetry, but the number of trials per comparison was insufficient. We used Review Manager 5 software (Cochrane Collaboration, Copenhagen, Denmark) to perform the statistical analyses. When possible, we explored the effect of bias in the effect estimates and performed pre-defined subgroup analysis. We intended to explore the effect of bias in the results, but all studies were at a high or unclear risk of bias. We included a 'Summary of findings' table reporting the primary outcomes using the GRADE approach.

RESULTS

We identified 3,227 records from electronic databases, including 445 records from trial registers. After removing duplicates, we screened the titles and abstracts and then full texts, finally including 16 randomized controlled trials (37 reports) in this review (see Fig. 1 for PRISMA flow chart and Table 1 for a summary of the study's characteristics) [21-36]. The list of excluded studies is available in the full version of the review [16]. All studies were at an overall high or unclear risk of bias (see Fig. 2). In this abridged version of the review, we summarize the findings of the six studies with 632 randomized participants in the main comparison of TUMT *versus* TURP [22,27,28,30,33,36]. Most studies did not report their funding sources; three studies were funded by their manufacturers [31,34,36], two by public institutions [32,33], and one by a combination of manufacturers and public funders [21]. See Table 2 for a summary of the main results.

1. Urologic symptom scores

Based on four studies with 306 participants, TUMT probably results in little to no difference in urologic symptom scores measured by IPSS scores when compared to TURP at 6 to 12 months follow-up (mean difference [MD], 1.00; 95% confidence interval [CI], -0.03 to 2.03) [22,28,33,36]. In two studies with 108 participants

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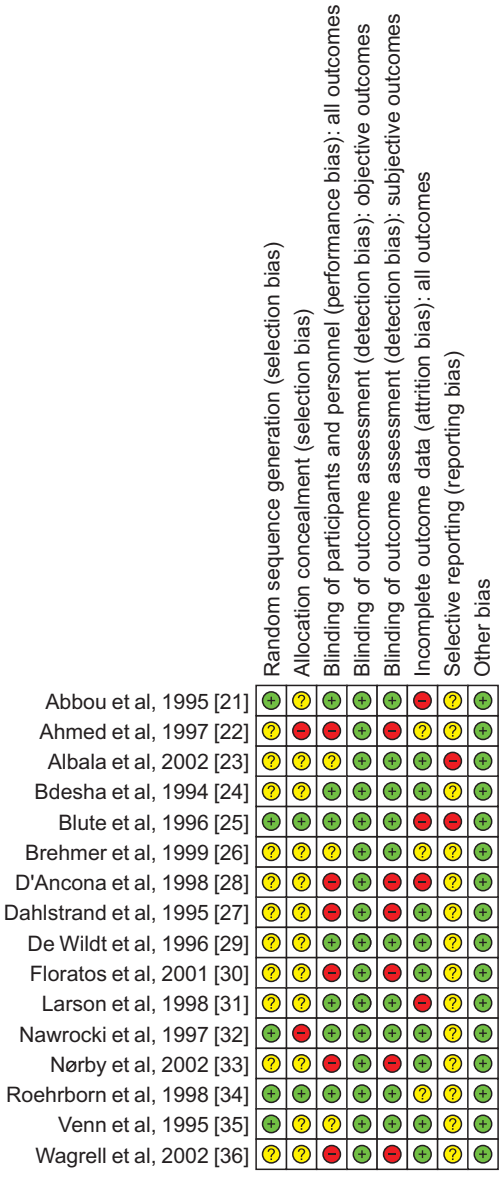

Fig. 2. Risk of bias of the included studies.

that assessed this outcome with the Madsen-Iversen score (range 0 to 28), a small difference was found favouring TURP (MD, 1.59; 95% CI, 0.69–2.48; 2 studies, 108 participants; I^2=0%) [27,28]. The certainty of the evidence is moderate due to an overall high risk of bias. As for long-term data, three studies with 187 participants reported long-term data, and we are uncertain of the effect of TUMT on urologic symptom scores when compared to TURP at 2- to 5-year follow-up (standardized MD, 0.32; 95% CI, 0.03–0.62; I^2=0%) [27,28,36]. Another study with 155 participants was not incorporated in meta-analysis due to missing data and reported that the TUMT group had a reduction in IPSS scores from 20 to 12 at three years, whereas the TURP group had a reduction from 20 to 3 in the same period (p<0.001) [30]. The certainty of the evidence is very low due to an overall high risk of bias (severe attrition at long-term follow-up) and imprecision.

2. Quality of life

Based on one study with 136 participants, TUMT likely results in little to no difference in the quality of life compared to TURP at 12-month follow-up (MD, -0.10; 95% CI -0.67 to 0.47) [36]. Another study with 66 participants reported similar scores in quality of life in the TUMT group (median, 2; interquartile range [IQR] 1–3) and in the TURP group (median, 1; IQR, 1–2) at six-month follow-up (p=0.64 from a three-arm comparison with interstitial laser coagulation) [33]. The certainty of the evidence is moderate due to an overall high risk of bias. As for long-term data, TUMT may result in little to no difference in the quality of life compared to TURP at 60-month follow-up (MD, 0.00; 95% CI, -0.46 to 0.46) [36]. Another study with 155 participants reported that quality-of-life scores decreased from 4 to 2 at three years in the TUMT group and from 4 to 1 in the TURP group (p<0.001) [30].

3. Major adverse events

Based on six studies with 525 participants, TUMT probably results in significantly fewer major adverse events when compared to TURP at 6- to 12-month follow-up (risk ratio [RR], 0.20; 95% CI, 0.09–0.43; I^2=0%) [22,27,28,30,33,36]. Based on 168 cases per 1,000 men in the TURP group, this corresponds to 135 fewer (153 to 96 fewer) per 1,000 men in the TUMT group. These events primarily included: hospitalization due to bleeding, clot retention, serious infection, TURP syndrome, urethral stricture (requiring another surgical intervention). The certainty of the evidence is moderate due to an overall high risk of bias.

4. Retreatment

Based on five studies with 463 participants, TUMT probably results in a large increase in the need for retreatment at 6- to 36-month follow-up (RR, 7.07; 95% CI, 1.94–25.82; I^2=0%) [27,28,30,33,36]. Retreatment was usually TURP, TUMT, or TUMT and then TURP. Based on no cases per 1,000 men in the TURP group, this corresponds to 90 more (40 to 150 more) per 1,000 men in the TUMT group. The certainty of the evidence is

Table 2. TUMT compared to TURP for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia

Outcome	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE[b])	Relative effect (95% CI)	Anticipated absolute effects[a] (95% CI)	
				Risk with TURP	Risk difference with TUMT
Urologic symptom scores Assessed with: IPSS Scale from 0 (best: not at all) to 35 (worst: almost always) Follow-up: 6–12 months	306 (4 RCTs)	⨁⨁⨁⊖ MODERATE[c]	-	The mean urologic symptoms score (IPSS) was 5.63	Mean differences 1.00 higher (0.03 lower to 2.03 higher)
Quality of life Assessed with: IPSS-QoL Scale from 0 (best: delighted) to 6 (worst: terrible) Follow-up: 12 months	136 (1 RCT)	⨁⨁⨁⊖ MODERATE[c]	-	The mean quality of life was 1.5	Mean differences 0.10 lower (0.67 lower to 0.47 higher)
Major adverse events Assessed with: Clavien–Dindo classification system (Grade III, IV, and V complications) Follow-up: 6–12 months	525 (6 RCTs)	⨁⨁⨁⊖ MODERATE[c]	RR 0.20 (0.09–0.43)	168 per 1,000	Study population 135 fewer per 1,000 (153 fewer to 96 fewer)
Retreatment Participants requiring additional procedures or surgery Follow-up: 6–12 months	463 (5 RCTs)	⨁⨁⨁⊖ MODERATE[c,d]	RR 7.07 (1.94–25.82)	0 per 1,000	Study population 90 more per 1,000 (40 more to 150 more)
Erectile function (sexually active men only) Assessed with: issues related to erectile function Follow-up: 6–12 months	337 (5 RCTs)	⨁⨁⊖⊖ LOW[c,e]	RR 0.63 (0.24–1.63)	129 per 1,000	Study population 48 fewer per 1,000 (98 fewer to 82 more)
Ejaculatory function (sexually-active men only) Assessed with: issues related to ejaculatory function Follow-up: 6–12 months	241 (4 RCTs)	⨁⨁⊖⊖ LOW[c,e]	RR 0.36 (0.24–0.53)	523 per 1,000	Study population 335 fewer per 1,000 (397 fewer to 246 fewer)

Patient or population: men with lower urinary tract symptoms due to benign prostatic hyperplasia. Setting: outpatient (TUMT)/inpatient (TURP)-UK, Netherlands, Scandinavia, USA. Intervention: TUMT. Comparison: TURP.

TUMT: transurethral microwave thermotherapy, TURP: transurethral resection of the prostate, CI: confidence interval, RCT: randomized controlled trial, IPSS: International Prostate Symptom Score, IPSS-QoL: IPSS-quality of life, RR: risk ratio.

[a]The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]GRADE Working Group grades of evidence: (1) High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. (2) Moderate certainty: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. (3) Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. (4) Very low certainty: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

[c]Downgraded by one level for study limitations: studies at an overall high risk of bias.

[d]We did not downgrade for imprecision since we used a minimally conceptualized approach: although the confidence interval is wide, there are no concerns about whether the effect results in a moderate to a large increase in the retreatment rate.

[e]Downgraded by one level for imprecision: the incidence is mostly reported in a subset of sexually active participants.

moderate due to an overall high risk of bias.

5. Erectile function

Based on five studies with 337 participants, TUMT may result in little or no difference in erectile function when compared to TURP at 6- to 12-month follow-up (RR, 0.63; 95% CI, 0.24–1.63; I^2=35%) [22,27,30,33,36]. The certainty of the evidence is low due to an overall high risk of bias and imprecision (the incidence is mostly reported in a subset of sexually active participants). As for long-term data, one study reported five-year data on erectile dysfunction with an incidence of 7.5% in the TUMT group and 15.4% in the TURP group (data were available for 119/154 randomized participants) [36]. The certainty of the evidence is very low due to an overall high risk of bias and imprecision (the incidence is mostly reported in a subset of sexually active participants with high attrition).

6. Ejaculatory function

Based on four studies with 241 participants, TUMT may result in fewer cases of retrograde ejaculation when compared to TURP at 6- to 12-month follow-up (RR, 0.36; 95% CI, 0.24–0.53; I^2=0%) [22,27,30,33]. The certainty of the evidence is low due to an overall high risk of bias and imprecision (the incidence mostly reported in a subset of sexually active participants).

7. Minor adverse events

Based on five studies with 397 participants, TUMT may result in little to no difference in the incidence of minor adverse events when compared to TURP at 6- to 12-month follow-up (RR, 1.27; 95% CI, 0.75–2.15; I^2=0%) [22,27,28,33,36]. These events primarily included urinary tract infections. The certainty of the evidence is low due to an overall high risk of bias and imprecision.

8. Acute urinary retention

Based on four studies with 343 participants, TUMT may result in an increased incidence of acute urinary retention when compared to TURP at 6- to 12-month follow-up (RR, 2.61; 95% CI, 1.05–6.47; I^2=40%) [22,28,33,36]. The certainty of the evidence is low due to an overall high risk of bias and imprecision (the incidence mostly reported in a subset of sexually active participants). In many cases, we highlight that participants undergoing TURP were routinely catheterised after surgery and for shorter periods than TUMT (see below).

9. Indwelling urinary catheter

The evidence is very uncertain about the effect of TUMT on the duration of catheterisation compared to TURP. This outcome was not adequately reported across the included studies.

DISCUSSION

Based on data from six studies with 414 participants, when compared to TURP, TUMT probably results in little to no difference in urologic symptom scores in the short term, but due to the lack of any eligible study with follow-up longer than 12 months, we are uncertain about the long-term effects. There may be little to no difference in minor adverse events, quality of life or erectile function between these interventions. TUMT likely results in significantly fewer major adverse events and less ejaculatory dysfunction compared to TURP. TUMT, however, likely results in a large increase in the need for retreatment (usually by repeated TUMT or TURP) and acute urinary retention. The duration of indwelling catheterization was not adequately reported across studies.

The studies did not consistently define or report on adverse events, particularly dysuria, hematuria, and sexual dysfunction, and our estimates for these complications may be unreliable. In addition, few studies evaluated the quality of life. Although studies usually reported the occurrence of urinary retention, they did not consistently or uniformly indicate its duration or the use of catheterization. One important complication that was not reported in the clinical trial literature was thermal injury. On 11 October 2000, the U. S. Food and Drug Administration (FDA) published a Public Health Notification because they had received 16 reports of severe thermal injury associated with TUMT, including ten resulting in fistula formation and six resulting in tissue damage to the penis or urethra [37]. The FDA noted that the injuries could take hours or days to develop. Although the FDA recommended several corrective measures for physicians, they considered TUMT to be safe and effective based on the performance of over 25,000 procedures.

The current American Urological Association guidelines for the management of LUTS considered TUMT to be an appropriate alternative for treating men with

LUTS with small- to average-size prostate [10], with the warning that patients should be advised that surgical retreatment rates are higher compared to TURP, which corresponds with the findings of our review. The Canadian guidelines considered TUMT an optional treatment for men with moderate symptoms, with similar considerations about retreatment [38]. The European Association of Urology does not list TUMT as one of their alternatives for managing LUTS [2].

The certainty of the evidence was primarily affected by: (1) high risk of bias across studies: most studies did not report the randomization process adequately, and for the TUMT *versus* TURP comparison, none of the included studies was blinded; (2) imprecision: details on ejaculatory and erectile function were only reported as binary outcomes in a subset of sexually-active participants; (3) our interpretation of the retreatment data was cautious since this was not consistently reported across studies; in some cases, it was described in the initial flow of participants across the studies, in some studies as a comment about follow-up, and in other cases within adverse events.

Considering that review methods have improved over time, including the details of the search strategy, we decided to run our searches from inception using the original inclusion criteria of the previous version of the review but excluding the comparison to alpha-blockers. We identified the citations of some additional reports of the included studies, including long-term data on one of the studies, but we were unable to retrieve some of the full text through different means. Finally, reporting on some of the outcomes was scattered and not thoroughly detailed. For some outcomes, including adverse events, retreatment, acute urinary retention, ejaculatory and erectile function, we had to interpret the data available in the flow of participants and the section describing "complications". It is unclear whether the studies reported all events or only those they considered relevant, especially with a lack of a prespecified protocol.

The previous version of this Cochrane Review yielded similar results for the global effects of TUMT in relation to sham and TURP [39]. The main difference from the previous version of the review is that we pooled the data for more outcomes in each comparison, with additional critical outcomes in the summary of findings tables. This provided us with a greater understanding of the differences between TURP and TUMT. In this version, we favour an interpretation of similar urinary symptoms scores at short-term follow-up, considering that long-term data from selected studies provided very low-certainty evidence to highlight substantial differences between these interventions. We also found important differences in the incidence of major adverse events and the incidence of retrograde ejaculation between these interventions, favouring TUMT.

We found a few additional systematic reviews on this topic. A health technology assessment from Sweden assessed the average IPSS score and concluded that TUMT was inferior to TURP in improving symptoms, which does not consider the confidence interval and minimally important differences [40]. Furthermore, the authors stated that they could not determine the differences in major adverse events, as we found in our review, which could be explained by the lack of grouping of serious events. Nevertheless, the findings related to retreatment were similar. Another systematic review reported similar results for urinary symptoms and retreatment but highlighted the lower incidence of serious adverse events with TURP than TUMT [41]. They state that the retreatment rate for TUMT may vary from 20% to 80% (focusing on observational data) but simultaneously highlight that the rate of retreatment is lower in long-term randomised trials such as the one included in our review [36]. Finally, two systematic reviews focusing on sexual outcomes reported a lower incidence of sexual adverse events (especially retrograde ejaculation) for men undergoing TUMT compared to TURP, which agrees with our findings [42,43]. None of these studies followed Cochrane methods for high-quality reviews.

CONCLUSIONS

TUMT provides a similar reduction in urinary symptoms compared to the standard treatment (TURP), with fewer major adverse events and fewer cases of ejaculatory dysfunction at short-term follow-up. However, TUMT probably results in a large increase in retreatment rates. Most of the evidence is short-term and from studies with a high risk of bias. Patients' values and preferences, their comorbidities and the effects of other available minimally-invasive procedures, among other factors, can guide clinicians when choosing the optimal treatment for this condition.

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Conflict of Interest

JVAF: none declared. LG: none declared. CMEL: none declared. MB: Boston Scientific (consultant for endourology and stone management), Auris Health (consultant for robotic surgery and endourology). PD: none declared.

Author Contribution

JVAF: conceived, designed, and wrote the protocol and full review, and performed all aspects of the data abstraction, analysis, risk of bias assessment and certainty of evidence ratings. LG: performed all aspects of the data abstraction, analysis, risk of bias assessment and certainty of evidence ratings, and drafted the review. CMEL: designed and ran the electronic searches, drafting the full review. MB: reviewed critical content, and gave final approval for the draft of the review. PD: conceived, designed and wrote the protocol for the update, reviewed the methods and the critical content, and gave final approval for the draft of the review.

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Review

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Minimally invasive treatments for benign prostatic hyperplasia: a Cochrane network meta-analysis

Juan Victor Ariel Franco[1], Jae Hung Jung[2,3], Mari Imamura[4], Michael Borofsky[5], Muhammad Imran Omar[6,7], Camila Micaela Escobar Liquitay[8], Shamar Young[9], Jafar Golzarian[9], Areti Angeliki Veroniki[10], Luis Garegnani[1] and Philipp Dahm[11]

[1]*Associate Cochrane Centre, Instituto Universitario Hospital Italiano de Buenos Aires, Buenos Aires, Argentina,* [2]*Department of Urology, Yonsei University Wonju College of Medicine, Wonju,* [3]*Center of Evidence-Based Medicine, Institute of Convergence Science, Yonsei University, Seoul, South Korea,* [4]*Health Services Research Unit, University of Aberdeen, Aberdeen, UK,* [5]*Department of Urology, University of Minnesota, Minneapolis, MN, USA,* [6]*Guidelines Office, European Association of Urology, Arnhem, The Netherlands,* [7]*Academic Urology Unit, University of Aberdeen, Aberdeen, UK,* [8]*Central Library, Instituto Universitario Hospital Italiano de Buenos Aires, Buenos Aires, Argentina,* [9]*Department of Radiology, Division of Interventional Radiology & Vascular Imaging, University of Minnesota, Minneapolis, MN, USA,* [10]*Department of Primary Education, School of Education, University of Ioannina, Ioannina, Greece, and* [11]*Urology Section, Minneapolis VA Health Care System, Minneapolis, MN, USA*

Objective

To assess the comparative effectiveness and ranking of minimally invasive treatments (MITs) for lower urinary tract symptoms (LUTS) in men with benign prostatic hyperplasia (BPH).

Materials and Methods

We searched multiple databases up to 24 February 2021. We included randomized controlled trials assessing the following treatments: convective radiofrequency water vapour thermal therapy (WVTT; or Rezūm); prostatic arterial embolization (PAE); prostatic urethral lift (PUL; or Urolift); temporary implantable nitinol device (TIND); and transurethral microwave thermotherapy (TUMT) compared to transurethral resection of the prostate (TURP) or sham surgery. We performed a frequentist network meta-analysis.

Results

We included 27 trials involving 3017 men. The overall certainty of the evidence of most outcomes according to GRADE was low to very low. Compared to TURP, we found that PUL and PAE may result in little to no difference in urological symptoms, while WVTT, TUMT and TIND may result in worse urological symptoms. MITs may result in little to no difference in quality of life, compared to TURP. MITs may result in a large reduction in major adverse events compared to TURP. We were uncertain about the effects of PAE and PUL on retreatment compared to TURP, however, TUMT may result in higher retreatment rates. We were very uncertain of the effects of MITs on erectile function and ejaculatory function. Among MITs, PUL and PAE had the highest likelihood of being the most efficacious for urinary symptoms and quality of life, TUMT for major adverse events, WVTT and TIND for erectile function and PUL for ejaculatory function. Excluding WVTT and TIND, for which there were only studies with short-term (3-month) follow-up, PUL had the highest likelihood of being the most efficacious for retreatment.

Conclusions

Minimally invasive treatments may result in similar or worse effects concerning urinary symptoms and quality of life compared to TURP at short-term follow-up.

Keywords

benign prostatic hyperplasia, lower urinary tract symptoms, minimally invasive treatments, network meta-analysis, transurethral microwave thermotherapy, prostatic urethral lift, temporary implantable nitinol device, prostatic arterial embolization, #Urology, #UroBPH, #UroUTI

Introduction

Benign prostatic obstruction is a form of BOO and may be diagnosed when the cause of outlet obstruction is known to be BPH [1]. BPH may or may not cause LUTS, which are characterized by urination frequency, hesitancy and a weak stream, mainly in men over the age of 40 years, and has clinical relevance when associated with perceived bother [2]. Symptom bother typically correlates with increased number and severity of symptoms, which are related to impairment in quality of life and treatment-seeking [3]. Although we understand that LUTS comprise a functional unit with a multi-factorial aetiology of associated symptoms, we considered the term BPH for this Cochrane Review because of its familiarity among the general public [4]. The degree of bother across all LUTS can be assessed through self-administered questionnaires, namely, the IPSS (also known as the AUA Symptom Index), which includes a quality-of-life domain [5]. According to an international study involving 7588 men, the prevalence of LUTS was 18% during men's 40s, 29% in their 50s, 40% in their 60s, and 56% in their 70s [6].

Initial treatment options for BPH include conservative management (watchful waiting and lifestyle modification) and the use of medications (alpha-blockers, 5-alpha reductase inhibitors, and, recently, phosphodiesterase inhibitors) [4]. Surgical options are considered when patients have been refractory to conservative and medical treatment or if BPH causes subsequent complications, such as acute urinary retention, recurrent UTI, bladder stones, haematuria, or renal insufficiency [4]. Clinical guidelines continue to recommend monopolar or bipolar TURP as a ('gold') reference standard treatment to provide subjective symptom relief while attaining objective improvement in urinary flow [4,7], but this procedure is associated with some morbidity and long-term complications, including haematuria that may require a blood transfusion, urethral stricture, UTI and incontinence, and it usually requires at least overnight hospitalization. In addition, men may experience ejaculatory (65%) and erectile dysfunction (10%) related to TURP [8]. Furthermore, BPH is a common disease among elderly men, who have increased preoperative risk for complications of general anaesthesia and surgery in general [2]. Recently, several other minimally invasive treatments (MITs) that can be performed in an office setting and do not require general anaesthesia have been developed as alternatives to TURP to provide therapeutic options involving lower morbidity [4]. However, given the relatively high rate of reoperation or continued use of medical therapy after surgical treatment (or both), concern has been raised about the durability of newly launched MITs [9].

Minimally invasive treatments that can be performed in an office setting and do not require general anaesthesia include: a) convective radiofrequency water vapour thermal therapy (WVTT; or Rezūm), which uses thermal energy in the form of water vapour to ablate prostatic tissue [10]; b) prostatic arterial embolization (PAE), which uses super-selective microcatheterization with microspheres to promote tissue necrosis [11]; c) prostatic urethral lift (PUL; or Urolift), which consists of separating and distracting enlarged prostatic tissue by a series of implants to hold excess prostatic tissue out of the way, thereby opening the narrowed urethra without cutting or removing enlarged prostatic tissue [12]; d) temporary implantable nitinol device (TIND), which involves 'reshaping' the prostatic urethra and bladder neck with an implantable device, thereby reducing urinary flow obstruction [13]; and e) transurethral microwave thermotherapy (TUMT), which uses heat into the prostate via electromagnetic radiation of microwaves, inducing coagulation necrosis, reducing prostatic volume [14].

This review aims to assess the comparative effectiveness of MITs for LUTS in men with BPH and obtain an estimate of relative ranking. This is an abridged report of the full Cochrane review [15].

Materials and Methods

Inclusion Criteria

We followed standard Cochrane methods based on a published protocol [16]. We included parallel-group randomized controlled trials (RCTs) including men aged > 40 years with a prostate volume of 20 mL or greater (as assessed by DRE, ultrasonography or cross-sectional imaging) with LUTS (determined by an IPSS of ≥8), and a maximum urinary flow rate (Q_{max}) less than 15 mL/s (as measured by non-invasive uroflowmetry, invasive pressure flow studies, or both) [4]. We excluded trials of men with other conditions that affect urinary symptoms. We included the following MITs, defined as those that do not require general anaesthesia, compared to TURP or sham: WVTT, PAE, PUL, TIND and TUMT. We would also have included head-to-head comparisons between MITs, but none were found. We predefined the structure of the network and its nodes in our protocol [16]. Participants in the network could, in principle, be randomized to any of the methods being compared, and we verified this by comparing characteristics of study design, participants, interventions, and comparisons while considering potential sources of clinical heterogeneity and effect modification (see subgroup analysis and investigation of heterogeneity) [17].

Our main outcomes included urinary symptoms, quality of life, major adverse events, retreatment, erectile function and ejaculatory function. We considered clinically important differences for all outcomes as the basis for rating the certainty of the evidence for imprecision in a 'summary of

findings' table [18]. We considered outcomes measured up to 12 months after randomization as short-term and those measured after 12 months as long-term, except for major adverse events (merging short and long-term data).

Search Methods

We performed a comprehensive search with no restrictions on the language of publication or publication status. We retrieved relevant studies from existing Cochrane Reviews for each treatment [19–22]. We updated searches for each of the individual Cochrane Reviews assessing each MIT. We performed a comprehensive search for TIND from the inception of each of the following databases until 24 February 2021: Cochrane Library via Wiley; MEDLINE via Ovid; Embase via Elsevier; Scopus; Web of Science; Latin American and the Caribbean Health Sciences Literature (LILACS) via Bireme; ClinicalTrials.gov at the US National Institutes of Health (www.clinicaltrials.gov/); and the WHO International Clinical Trials Registry Platform search portal (https://trialsearch.who.int/). We searched the reference lists of included studies, contacted experts, searched the grey literature and screened the abstract proceedings of relevant meetings.

Selection of Studies

We used Covidence software to identify and remove potential duplicate records [23]. Two review authors (J.V.A.F., L.G.) scanned abstracts, titles, or both to determine which studies should be assessed further using the same software, investigating all potentially relevant records as full text, and classified the studies as included studies, excluded studies, studies awaiting classification, or ongoing studies according to the Cochrane Handbook criteria [24]. We resolved any discrepancies through consensus or recourse to a third review author (P.D.). We presented a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram showing the process of study selection [25].

Data Extraction and Risk-of-Bias Assessment

Because we retrieved relevant studies from existing Cochrane Reviews for each treatment for which study characteristics and outcome data were collected and risk-of-bias assessments were performed by members of our review team [19–22], the following sections apply only to new studies identified by our search methods. For studies that fulfilled the inclusion criteria, two review authors (two of J.V.A.F., L.G. and J.H.J.) independently abstracted the characteristics of the participants, the interventions, comparisons and outcomes, funding sources and conflict of interests. We resolved any disagreements by discussion or, if required, by consultation with a third review author (P.D.). In addition, we contacted the authors of included studies to obtain key missing data as needed. Two review authors (J.V.A.F. and L.G.) independently assessed the risk of bias of each included study using the Cochrane tool for RCTs [26]. We resolved disagreements by consensus or by consultation with a third review author (P.D.).

Statistical Analysis and Certainty of the Evidence

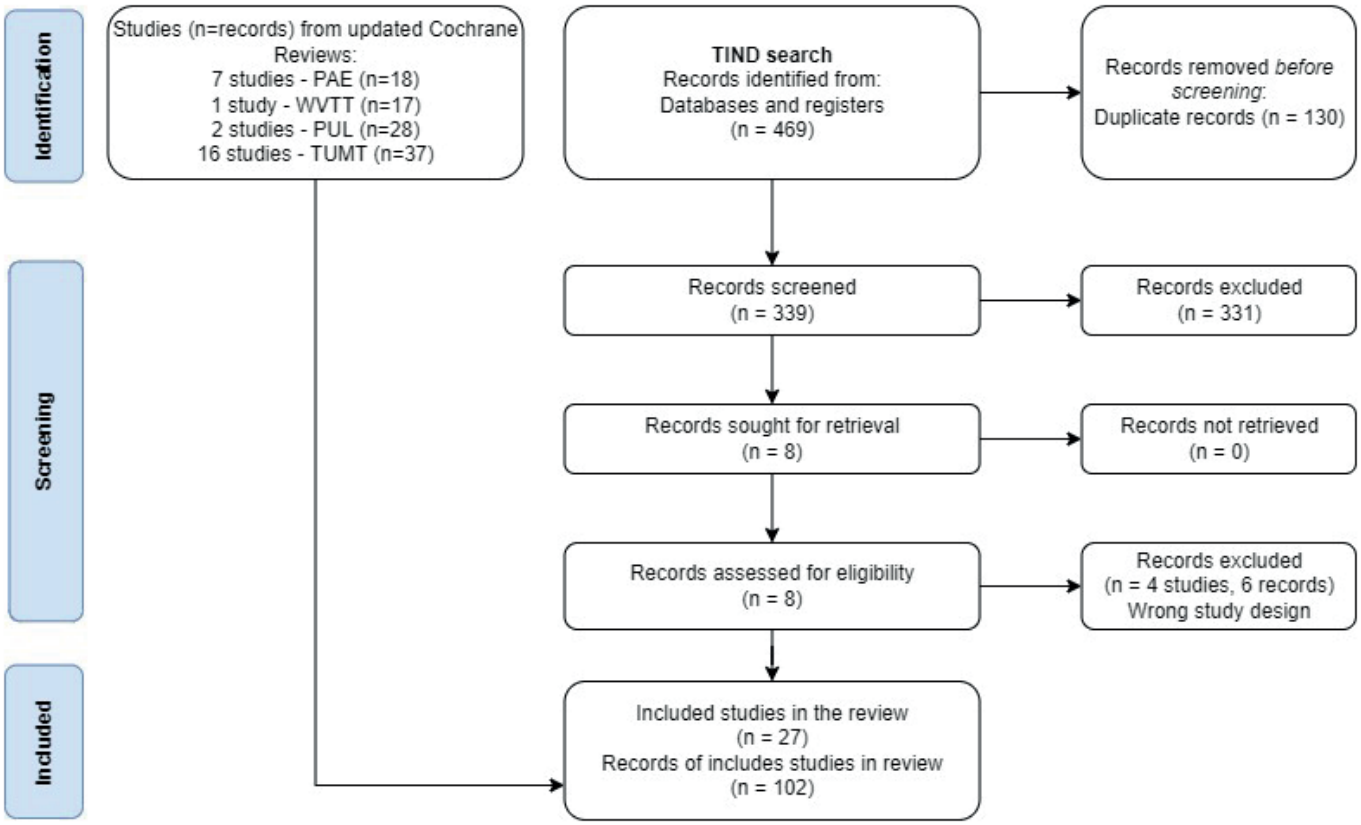
We expressed dichotomous data as risk ratios (RRs) with 95% CIs to enhance the interpretability of results. We expressed continuous data as mean differences (MDs) with 95% CIs. Before conducting a network meta-analysis, we assessed the transitivity assumption by visually inspecting the characteristics of the potential effect modifiers of the included studies across intervention comparisons [27]. We evaluated the presence of inconsistency both locally by loop-specific method and globally by the design-by-treatment interaction model [28,29]. We used comparison-adjusted funnel plots to assess small-study effects indicative of publication bias [30]. We fitted a random-effects network meta-analysis model because we anticipated methodological and clinical heterogeneity across studies. We assumed a common within-network heterogeneity estimate across comparisons, and we estimated this using the restricted maximum likelihood method [31]. We conducted a network meta-analysis using the network suite of commands in Stata (StataCorp. 2019) [29,32,33]. We used the surface under the cumulative ranking curve to rank the effectiveness and safety of MITs [34]. When sufficient studies were available, we intended to perform subgroup analysis by age and severity of symptoms. We also planned to perform sensitivity analyses limited to the primary outcomes to explore the influence of risk of bias by excluding studies at 'high risk' or 'unclear risk'. We used 'summary of findings' tables to summarize key results of the review, using the Confidence in Network Meta-analysis (CINeMA) framework and software [35,36]. We presented an adapted single 'Summary of findings' table for all outcomes, using a modified approach based on the existent guidance [37].

Results

Search Results

We retrieved 26 studies from the previous Cochrane reviews. For the TIND search, we identified 469 records from electronic databases. After removing duplicates, we screened the titles and abstracts of the remaining 339 records, 331 of which we excluded. We assessed eight full-text articles, and we excluded six records for various reasons. Finally, we included one study (two reports) in this review for this intervention. The flow of literature through the assessment process is shown in a PRISMA flowchart (Fig. 1).

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram. PAE, prostatic arterial embolization; PUL, prostatic urethral lift; TIND, temporary implantable nitinol device; TUMT, transurethral microwave thermotherapy; WVTT, water vapour thermal therapy.



Characteristics of the Studies Included

We included 27 trials with 3017 randomized participants. Details of the included studies are presented in Table 1. Most studies included men aged > 45–50 years with moderate LUTS refractory to medical treatment, and with a Q_{max} <12/15 mL/s, a voided volume ≥ 125 mL and a prostate volume between 30/100 g and 60/100 g. Participants were usually screened for prostate cancer and infection, among other comorbidities, before inclusion. We included trials with the following interventions and comparisons: WVTT vs sham treatment [38], PAE vs sham treatment [39], PAE vs TURP [40–45], and PUL vs sham treatment [46], PUL vs TURP [47], TIND vs sham treatment [48], TUMT vs sham treatment [49–58], and TUMT vs TURP [59–64]. Half of the studies did not state their funding sources, nine studies were funded by the manufacturers or sponsors of the procedure [38,39,43,46–48,55,57,64], and four were funded by public institutions or hospitals [40,49,56,63]. All studies were considered to have a high or unclear risk of bias, mainly due to lack of blinding in most comparisons, missing outcome data and poor reporting of the characteristics of the included studies. The details for the risk of bias and the characteristics of the excluded and ongoing studies can be found in the full version of the review [15].

Network Meta-Analysis: Minimally Invasive Treatments vs TURP

Considering that most trials assessed the effect of TUMT and PAE, the networks were not densely connected, and in some cases, they were star-shaped with no closed loops. The following analyses present data from networks with no concerns regarding transitivity or global consistency (except in those networks in which it was not possible to assess it due to the lack of closed loops). Table 2 shows a summary of the main findings and Fig. 2 shows a representation of the networks and their corresponding forest plot for each outcome.

Urological symptoms scores

Based on 19 studies with 1847 participants, PUL and PAE may result in little to no difference in urological symptom scores compared to TURP at short-term follow-up

Table 1 Characteristics of the included studies.

Study, year	Trial period	Country	Description of participants	Intervention and comparator	Duration of follow-up	Age, years*	IPSS*	Prostate volume, mL*
Convective radiofrequency WVTT								
McVary et al., 2016 [18]	2013-2014	USA	Men aged ≥ 50 years, symptomatic BPH with IPSS ≥ 13, Q_{max} 5–15 mL/s voided volume ≥ 125 mL, prostate volume 30–80 g	WVTT	3 months	63 ± 7.1	22 ± 4.8	45.8 ± 13.0
				Sham		62.9 ± 7.0	21.9 ± 4.7	44.5 ± 13.3
PAE								
Abt et al., 2018 [40]	2014-2017	Switzerland	Men aged ≥ 40 years, refractory symptoms, prostate 25–80 mL, with IPSS ≥ 8, IPSS-QoL ≥ 3, with Q_{max} < 12 mL/s or urinary retention	PAE	24 months	65.7 ± 9.3	19.38 ± 6.37	52.8 ± 32.0
				TURP		66.1 ± 9.8	17.59 ± 6.17	56.5 ± 31.1
Carnevale et al., 2016 [41]	2010-2012	Brazil	Men aged > 45 years, IPSS > 19, refractory symptoms > 6 months, prostate 30–90 mL, BOO (urodynamic examination)	PAE	12 months	63.5 ± 8.7	25.3 ± 3.6	63.0 ± 17.8
				TURP		66.4 ± 5.6	27.6 ± 3.2	56.6 ± 21.5
Gao et al., 2014 [42]	2007-2012	China	Men with IPSS > 7 after failed medical therapy, prostate volume 20–100 mL, Q_{max} < 15 mL/s	PAE	24 months	67.7 ± 8.7	22.8 ± 5.9	64.7 ± 19.7
				TURP		66.4 ± 7.8	23.1 ± 5.8	63.5 ± 18.6
Insausti et al., 2020 [43]	2014-2017	Spain	Men aged > 60 years, LUTS refractory to medical treatment >6 months, IPSS ≥ 8, IPSS-QoL ≥ 3, Q_{max} ≤ 10 mL/s or urinary retention	PAE	12 months	72.4 ± 6.2	25.8 ± 4.64	60.0 ± 21.6
				TURP		71.8 ± 5.5	26.0 ± 7.29	62.8 ± 23.8
Pisco et al., 2020 [39]	2014-2018	Portugal	Men aged > 45 years; severe LUTS; IPSS ≥ 20 and IPSS-QoL ≥ 3 > 6 months' treatment with alpha-blockers; Q_{max} < 12 mL/s; prostate volume 40 mL	PAE	6 months	64	25.5	63.5
				Sham		64	27.5	66
Radwan et al., 2020 [44]	2016-2018	Egypt	Men with LUTS with an IPSS 8–35, Q_{max} ≤ 10 mL/s; prostate volume < 100 mL	PAE	6 months	63.0 ± 7.2	27.0 ± 5.0	58.7 ± 23.4
				TURP		62.0 ± 9.0	26.5 ± 4.0	60.1 ± 21.5
Zhu et al., 2018 [45]	2016	China	Men with a comprehensive diagnosis of BPH through ultrasound prostate examination, DRE, IPSS, etc.; no absolute contraindication for surgery; no previous history of surgery; not taking 5-alpha reductase inhibitors	PAE	12 months	61.1 ± 4.4	25.63 ± 4.28	81.21 ± 6.34
				TURP		62.4 ± 4.9	26.22 ± 4.35	82.09 ± 6.47

Table 1 (continued)

Study, year	Trial period	Country	Description of participants	Intervention and comparator	Duration of follow-up	Age, years*	IPSS*	Prostate volume, mL*
PUL								
Gratzke et al., 2017 [46]	2012-2013	Europe	Men aged ≥ 50 years with IPSS > 12, Q_{max} ≤ 15 mL/s for 125 mL voided volume, PRV < 350 mL, prostate volume ≤ 60 mL, sexually active, Incontinence Severity Index score ≤ 4	PUL	24 months	63 ± 6.8	22 ± 5.7	38 ± 12
				TURP		65 ± 6.4	23 ± 5.9	41 ± 13
Roehrborn et al., 2013 [47]	2011	19 centres/US, Canada, and Australia	Men aged ≥ 50 years, AUA-SI ≥ 13, Q_{max} ≤ 12 mL/s with a 125 mL voided volume and a 30–80 mL prostate volume	PUL	3 months	67 ± 8.6	22.2 ± 5.48	44.5 ± 12.4
				Sham		65 ± 8.0	24.4 ± 5.75	40.9 ± 10.8
TIND								
Chughtai et al. 2021 [48]	2015-2018	USA/Canada	Men aged ≥ 50 years, symptomatic BPH, IPSS ≥ 10, Q_{max} < 12 mL/s, voided volume > 125 mL, prostate volume 25–75 mL	TIND	3 months	61.5 ± 6.5	22.1 ± 6.8	43.4 ± 15.5
				Sham		60.1 ± 6.3	22.8 ± 6.2	43.8 ± 13.3
TUMT								
Abbou et al., 1995 [49]	N/A	France	Men aged ≥ 50 years with symptoms > 3 months, prostate 30–80 g, Q_{max} < 15 mL/s, PVR < 300 mL	TUMT	12 months	65 ± 8	N/A	45 ± 15
				Sham		66 ± 7	N/A	44 ± 11
Ahmed et al., 1997 [59]	N/A	UK	Men aged ≥ 55 years with AUA score >12 > 1 year, prostate 25–100 mL, Q_{max} < 15 mL/s and a PVR < 300 mL	TUMT	6 months	69.36	18.5	36.6
				TURP		69.45	18.4	46.1
Albala et al., 2002 [50]	N/A	USA	Men aged 50–80 years, AUA-SI index > 13 and a bother score >11, Q_{max} < 12 mL/sec and PVR > 125 mL; prostate 30-100 mL without a significant intravesical middle lobe	TUMT	12 months	65.2 ± 7.3	22.2 ± 5.0	50.5 ± 18.6
				Sham		64.6 ± 7.1	22.7 ± 5.7	47.1 ± 17.9
Bdesha et al., 1994 [51]	N/A	UK	Men with prostatism (WHO score > 14), PVR > 50 mL, Qmax <15 mL/s	TUMT	3 months	63.7	19.2	N/A
				Sham		62.6	18.8	N/A
Blute et al., 1996 [52]	N/A	USA	Men suffering from urinary symptoms (Madsen symptom score >8), PVR 10000 mL, Q_{max} < 10 mL/s, prostate length 30–50 mm	TUMT	12 months	66.9 ± 7.8	19.9 ± 7.2	37.4 ± 14.2
				Sham		66.9 ± 7.1	20.8 ± 6.7	36.1 ± 13.4
Brehmer et al., 1999 [53]	N/A	Sweden	Men experiencing LUTS and with an enlarged prostate	TUMT	12 months	70.4	N/A	N/A
				Sham				

Table 1 (continued)

Study, year	Trial period	Country	Description of participants	Intervention and comparator	Duration of follow-up	Age, years*	IPSS*	Prostate volume, mL*
D'Ancona et al., 1998 [60]	1994-1995	Netherlands	Men ≥ 45 years with Madsen score > 8 months, prostate 2.5-5 cm/30–100 mL, Q_{max} < 15 mL/s PVR < 350 mL	TUMT	24 months	69.6 ± 8.5	16.7 ± 5.6	45 ± 15
				TURP		69.3 ± 5.9	18.3 ± 6.3	43 ± 12
Dahlstrand et al., 1995 [61]	N/A	Sweden	Men ≥ 45 years with Madsen score > 8 months, prostate 3.5–5 cm, Q_{max} < 15 mL/s, PVR > 150 mL	TUMT	24 months	68	N/A	33
				TURP		79	N/A	37
De Wildt et al., 1996 [54]	1991-1992	Netherlands/UK	Men ≥ 45 years with Madsen score > 8 months, Q_{max} < 15 mL/s PVR > 150 mL	TUMT	12 months	63.3 ± 8.1	N/A	48.6 ± 16.6
				Sham		66.9 ± 6.0	N/A	49.0 ± 20.0
Floratos et al., 2001 [62]	1996-1997	Netherlands	Men ≥ 45 years, prostate ≥ 30 cm^3, prostatic urethral length ≥ 25 mm, Madsen symptom score ≥ 8, Q_{max} ≤ 15 mL/s, PVR ≤ 350 mL	TUMT	36 months	68	21	42
				TURP		66	20	48
Larson et al., 1998 [55]	1994-1996	USA	Men aged ≥ 45 years with AUA score > 9, enlarged prostate (3–5 cm TRUS), Q_{max} < 12 mL/s without a significantly enlarged middle lobe	TUMT	12 months	66	20.8	38.1
				Sham		65.9	21.3	44.7
Nawrocki et al., 1997 [56]	N/A	UK	Men with a Madsen symptom score ≥ 8, Q_{max} ≤ 15 mL/s, PVR > 150 mL, detrusor pressure > 70 cm H_2O	TUMT	6 months	70	19	41.2 ± 14.6
				Sham			17.5	46.7 ± 16.8
Norby et al., 2002 [63]	1996-1997	Denmark	Men aged ≥ 50 years, IPSS ≥ 7, Q_{max} ≤ 12 mL/s	TUMT	6 months	66 ± 7	20.5 ± 5.7	43
				TURP/TUIP		68 ± 7	21.3 ± 6.6	44
Roehrborn et al., 1998 [57]	N/A	United States	Men aged ≥ 55 years, AUA-SI ≥ 13, Q_{max} ≤ 12 mL/s, prostate volume 25–100 mL	TUMT	6 months	66.3 ± 6.5	23.6 ± 5.6	48.1 ± 16.2
				Sham		66.0 ± 5.8	23.9 ± 5.6	50.5 ± 18.1
Venn et al., 1995 [58]	N/A	UK	Men with a Madsen symptom score ≥ 8, PVR < 250 mL	TUMT	6 months	70.5	19.2	40.4
				Sham		68	20.1	40.6
Wagrell et al., 2002 [64]	1998-1999	Scandinavia/USA	Men IPSS ≥ 13, Q_{max} ≤ 13 mL/s, prostate volume 30–100 mL	TUMT	5 years	67 ± 8	21.0 ± 5.4	48.9 ± 15.8
				TURP		69 ± 8	20.4 ± 5.9	52.7 ± 17.3

*AUA-SI, AUA Symptom Index; PAE, prostatic arterial embolization; PUL, prostatic urethral lift; PVR, postvoid residual urine volume; Q_{max}, maximum urinary flow rate; TIND, temporary implantable nitinol device; TUMT, transurethral microwave thermotherapy; WVTT, water vapour thermal therapy. *Mean/median, ± SD when available.*

(3−12 months; MD of IPSS [range 0 to 35, higher scores indicate worse symptoms] for PUL: 1.47, 95% CI −4.00 to 6.93; for PAE: 1.55, 95% CI −1.23 to 4.33). WVTT, TUMT and TIND may result in worse urological symptoms scores compared to TURP at short-term follow-up, but the CIs include little to no difference (WVTT: 3.6, 95% CI −4.25 to 11.46; TUMT: 3.98, 95% CI 0.85 to 7.10; TIND: 7.5, 95% CI −0.68 to 15.69). TURP had the highest likelihood of being the most efficacious for this outcome; however, among minimally invasive procedures, PUL and PAE were the highest-ranked interventions. The certainty of the evidence was low because of major concerns about within-study bias, imprecision and inconsistency.

Quality of life

Based on 13 studies with 1469 participants, all interventions (PUL, PAE, WVTT, TUMT, TIND) may result in little to no difference in quality-of-life scores compared to TURP at short-term follow-up (3−12 months; MD of IPSS-Quality-of-Life score [range 0–6, higher scores indicate worse symptoms] for PUL: 0.06, 95% CI −1.17 to 1.30; for PAE: 0.09, 95% CI −0.57 to 0.75; for WVTT: 0.37, 95% CI −1.45 to 2.20; for TUMT: 0.65, 95% CI −0.48 to 1.78; for TIND: 0.87, 95% CI −1.04 to 2.79). TURP had the highest likelihood of being the most efficacious for this outcome; however, among MITs, PUL and PAE were the highest-ranked interventions. The certainty of the evidence was low because of major concerns regarding within-study bias, imprecision and inconsistency.

Major adverse events

Based on 15 studies with 1573 participants, TUMT probably results in a large reduction in major adverse events compared to TURP (RR 0.20, 95% CI 0.09 to 0.43). PUL, WVTT, TIND and PAE may also result in a large reduction in major adverse events, but the CI includes substantial benefits and harms (at 3−36 months, PUL: RR 0.30, 95% CI 0.04 to 2.22; WVTT: RR 0.37, 95% CI 0.01 to 18.62; TIND: 0.52, 95% CI 0.01 to 24.46; PAE: 0.65, 95% CI 0.25 to 1.68). Furthermore, TUMT had the highest likelihood of being the most efficacious for this outcome, while TURP was the lowest-ranked intervention. The certainty of the evidence was low for WVTT, TIND, PUL and PAE because of major concerns regarding within-study bias and severe imprecision. The certainty of the evidence for TUMT was moderate because of major concerns regarding within-study bias.

The most commonly reported major adverse events included haematuria with blood clots requiring evacuation or transfusion and severe infection. Less frequently and with a delayed presentation, some patients developed meatal/urethral stenosis, which usually required additional procedures for resolution (bladder neck incision/urethrotomy).

Retreatment

Based on 10 studies with 799 participants, we were uncertain about the effects of PAE and PUL on retreatment compared to TURP at long-term follow-up (12−60 months; PUL: RR 2.39, 95% CI 0.51 to 11.1; PAE: RR 4.39, 95% CI 1.25 to 15.44). TUMT may result in a higher increase in retreatment rates (RR 9.71, 95% CI 2.35 to 40.13). TURP had the highest likelihood of being the most efficacious for this outcome; however, PUL was the highest-ranked intervention among MITs. The certainty of the evidence was very low for PUL and PAE due to major concerns about the within-study bias, imprecision, inconsistency and incoherence. The certainty of the evidence for TUMT was low due to major concerns about within-study bias and incoherence.

These results do not include WVTT or TIND because of short-term follow-up (these results are displayed separately below, under pairwise comparisons).

Erectile function

Based on six studies with 640 participants (Abt et al. 2018; Carnevale 2016; Chughtai 2020; Gratzke 2017; McVary 2016; Roehrborn 2013), we are very uncertain of the effects of MITs on erectile function (MD of IIEF-5 [range 5 to 25, higher scores indicate better function]: WVTT: 6.49, 95% CI −8.13 to 21.12; TIND: 5.19, 95% CI −9.36 to 19.74; PUL: 3.00, 95% CI −5.45 to 11.44; PAE: −0.03, 95% CI −6.38 to 6.32). WVTT and TIND had the highest likelihood of being the most efficacious for this outcome, while TURP was the lowest-ranked intervention; the certainty of the evidence was very low due to major concerns about the within-study bias, incoherence and severe imprecision.

Studies related to TUMT did not report this outcome as defined in this analysis (these results are displayed separately below in pairwise comparisons).

Ejaculatory function

Based on eight studies with 461 participants, we are uncertain of the effects of PUL, PAE and TUMT on ejaculatory dysfunction compared to TURP (at 3−12 months, PUL: RR 0.05, 95% CI 0.00 to 1.06; PAE: RR 0.35, 95% CI 0.13 to 0.92; TUMT: RR 0.34, 95% CI 0.17 to 0.68). PUL has the highest likelihood of being the most efficacious for this outcome, while TURP was the lowest-ranked intervention. The certainty of the evidence was very low due to major concerns about within-study bias, inconsistency, and incoherence. WVTT was not included in this section because these studies were disconnected from the network (see description below). In addition, the study assessing TIND reported no events of ejaculatory dysfunction.

Table 2 Summary of findings table.

Patient or population: men with moderate to severe LUTS due to BPH Interventions: minimally invasive treatments Comparator (reference): TURP Setting: hospital procedure, outpatient follow-up					
Outcome: urinary symptom scores, measured by: IPSS range 0–35 (lower scores indicate fewer symptoms); follow-up: 3–12 months (most of the data are from 3-month follow-up)					
19 studies 1847 participants	**Anticipated absolute effect (95% CI)***		**Certainty of the evidence**	**Ranking (SUCRA)†**	
	With TURP	**With a minimally invasive procedure**			
PUL (UroLift; mixed estimate)	Mean score in the included studies: 6.82 (range 5.1 to 12.6)[a]	1.47 higher (4.00 lower to 6.93 higher)	⊕⊕⊖⊖ Low	2.8 (70.5%)	
PAE (mixed estimate)		1.55 higher (1.23 lower to 4.33 higher)	⊕⊕⊖⊖ Low	2.9 (69.2%)	
WVTT (Rezūm; indirect estimate)		3.60 higher (4.25 lower to 11.46 higher)	⊕⊕⊖⊖ Low	3.9 (52.4%)	
TUMT (mixed estimate)		3.98 higher (0.85 higher to 7.10 higher)	⊕⊕⊖⊖ Low	4.4 (43.0%)	
TIND (indirect estimate)		7.50 higher (0.68 lower to 15.69 higher)	⊕⊕⊖⊖ Low	5.5 (21.5%)	
Outcome: quality of life, measured by: IPSS-QoL range 0–6 (lower scores indicate a lesser impact on quality of life); follow-up: 3–12 months					
13 studies 1469 participants	**Anticipated absolute effect (95% CI)***		**Certainty of the evidence**	**Ranking (SUCRA)†**	
	With TURP	**With MIT**			
PUL (UroLift; mixed estimate)	Mean score in the included studies: 2.09 (range 0.9–3.26)[a]	0.06 higher (1.17 lower to 1.30 higher)	⊕⊕⊖⊖ Low	2.8 (70.3%)	
PAE (mixed estimate)		0.09 higher (0.57 lower to 0.75 higher)	⊕⊕⊖⊖ Low	2.9 (68.1%)	
WVTT (Rezūm; indirect estimate)		0.37 higher (1.45 lower to 2.20 higher)	⊕⊕⊖⊖ Low	3.6 (56.3%)	
TUMT (mixed estimate)		0.65 higher (0.48 lower to 1.78 higher)	⊕⊕⊖⊖ Low	4.5 (42.2%)	
TIND (indirect estimate)		0.87 higher (1.04 lower to 2.79 higher)	⊕⊕⊖⊖ Low	5.0 (33.4%)	
Outcome: major adverse events, defined as Clavien–Dindo Grade III, IV and V, including hospitalizations and procedures to treat complications related to the initial intervention; follow-up: 3–36 months					
15 studies 1573 participants	**Anticipated absolute effect (95% CI)***		**Relative effect (95% CI)**	**Certainty of the evidence**	**Ranking (SUCRA)†**
	With TURP	**With MIT**			
TUMT (mixed estimate)	Median rate of major adverse events: 130 per 1000[a]	104 fewer per 1000 (118 fewer to 74 fewer)	RR 0.20 (0.09 to 0.43)	⊕⊕⊕⊖ Moderate	2.7 (72.1%)
PUL (UroLift; mixed estimate)		90 fewer per 1000 (125 fewer to 159 more)	RR 0.30 (0.04 to 2.22)	⊕⊕⊖⊖ Low	3.6 (56.9%)
WVTT (Rezūm; indirect estimate)		81 fewer per 1000 (129 fewer to 870 more)	RR 0.37 (0.01 to 18.68)	⊕⊕⊖⊖ Low	4.0 (50.0%)
TIND (indirect estimate)		63 fewer per 1000 (129 fewer to 870 more)	RR 0.52 (0.01 to 24.46)	⊕⊕⊖⊖ Low	4.3 (44.7%)
PAE (mixed estimate)		45 fewer per 1000 (97 to 89 more)	RR 0.65 (0.25 to 1.68)	⊕⊕⊖⊖ Low	5.0 (33.6%)
Outcome: retreatment, defined as number of participants requiring a follow-up procedure for LUTS including another MIT or TURP (this does not include procedures to treat complications; these are included under major adverse events); follow-up: 12–60 months					
10 studies 799 participants	**Anticipated absolute effect (95% CI)***		**Relative effect (95% CI)**	**Certainty of the evidence**	**Ranking (SUCRA)†**
	With TURP	**With MIT**			
PUL (UroLift; mixed estimate)	Median rate of retreatment: 12 per 1000[a]	17 more per 1000 (6 fewer to 121 more)	RR 2.39 (0.51 to 11.10)	⊕⊖⊖⊖ Very low	2.2 (68.8%)
PAE (mixed estimate)		41 more per 1000 (3 more to 173 more)	RR 4.39 (1.25 to 15.44)	⊕⊖⊖⊖ Very low	3.0 (50.8%)
TUMT (mixed estimate)		104 more per 1000 (16 more to 470 more)	RR 9.71 (2.35 to 40.13)	⊕⊕⊕⊖ Low	3.7 (32.1%)

Table 2 (continued)

Outcome: retreatment, defined as number of participants requiring a follow-up procedure for LUTS including another MIT or TURP (this does not include procedures to treat complications; these are included under major adverse events); follow-up: 12–60 months					
10 studies 799 participants	**Anticipated absolute effect (95% CI)***		**Relative effect (95% CI)**	**Certainty of the evidence**	**Ranking (SUCRA)†**
	With TURP	**With MIT**			
WVTT (Rezūm; pairwise)	We are very uncertain about the effects of WVTT on retreatment compared to sham at 3 months follow-up (RR 1.36, 95% CI 0.06 to 32.86, 1 study, 197 participants).			⊕⊖⊖⊖ Very low	Not in NMA
TIND (pairwise)	We are very uncertain about the effects of TIND on retreatment compared to sham at 3-month follow-up (RR 0.67, 95% CI 0.11 to 3.89, 1 study, 185 participants).			⊕⊖⊖⊖ Very low	Not in NMA
Outcome: erectile function, measured by IIEF score (range 5–25; higher scores indicate better function); follow-up 3–12 months					
6 studies 640 participants	**Anticipated absolute effect (95% CI) ***			**Certainty of the evidence**	**Ranking (SUCRA)†**
	With TURP	**With MIT**			
WVTT (Rezūm; indirect estimate)	Mean score in the included studies: 15.16 (range 11.67 to 17.70)[a]	6.49 higher (8.13 lower to 21.12 higher)		⊕⊖⊖⊖ Very low	2.5 (70.7%)
TIND (indirect estimate)		5.19 higher (9.36 lower to 19.74 higher)		⊕⊖⊖⊖ Very low	2.9 (61.7%)
PUL (UroLift; mixed estimate)		3.00 higher (5.45 lower to 11.44 higher)		⊕⊖⊖⊖ Very low	3.5 (49.5%)
PAE (mixed estimate)		0.03 lower (6.38 lower to 6.32 higher)		⊕⊖⊖⊖ Very low	4.4 (31.1%)
TUMT	Not reported				
Outcome: ejaculatory function, defined as men with ejaculatory dysfunction, loss or substantial reduction in ejaculation (as an indication of retrograde ejaculation); follow-up: 3–12 months					
8 studies 461 participants	**Anticipated absolute effect (95% CI)***		**Relative effect (95% CI)**	**Certainty of the evidence**	**Ranking (SUCRA)†**
	With TURP	**With MIT**			
PUL (UroLift; mixed estimate)	Median rate of ejaculatory dysfunction: 550 per 1000	521 fewer per 1000 (549 fewer to 32 more)	RR 0.05 (0.01 to 1.06)	⊕⊖⊖⊖ Very low	1.2 (92.1%)
TUMT (mixed estimate)		364 fewer per 1000 (458 fewer to 173 fewer)	RR 0.34 (0.17 to 0.68)	⊕⊖⊖⊖ Very low	2.3 (55.1%)
PAE (mixed estimate)		356 fewer per 1000 (476 fewer to 42 fewer)	RR 0.35 (0.13 to 0.92)	⊕⊖⊖⊖ Very low	2.5 (51.1%)
WVTT (Rezūm; pairwise)	Based on one study with 131 participants, WVTT may result in little to no difference in events of ejaculatory dysfunction compared to sham at short-term follow-up (RR 4.01, 95% CI 0.22 to 72.78).			⊕⊖⊖⊖ Very low	Not in NMA
TIND (pairwise)	The study assessing TIND compared to sham reported no events of ejaculatory dysfunction.			⊕⊖⊖⊖ Very low	Not in NMA

*GRADE Working Group grades of evidence (or certainty of the evidence); MIT, minimally invasive treatment; NMA, network meta-analysis; PAE, prostatic arterial embolization; PUL, prostatic urethral lift; RR, risk ratio; SUCRA, surface under the cumulative ranking curve; TIND, temporary implantable nitinol device; TUMT, transurethral microwave thermotherapy; WVTT, water vapour thermal therapy. High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the effect estimate. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. *Estimates are reported as risk difference and CI. †Rank statistics are defined as the probability that a treatment out of n treatments in a network meta-analysis is the best, the second, the third, and so on until the least effective treatment. SUCRA estimates are in brackets.*

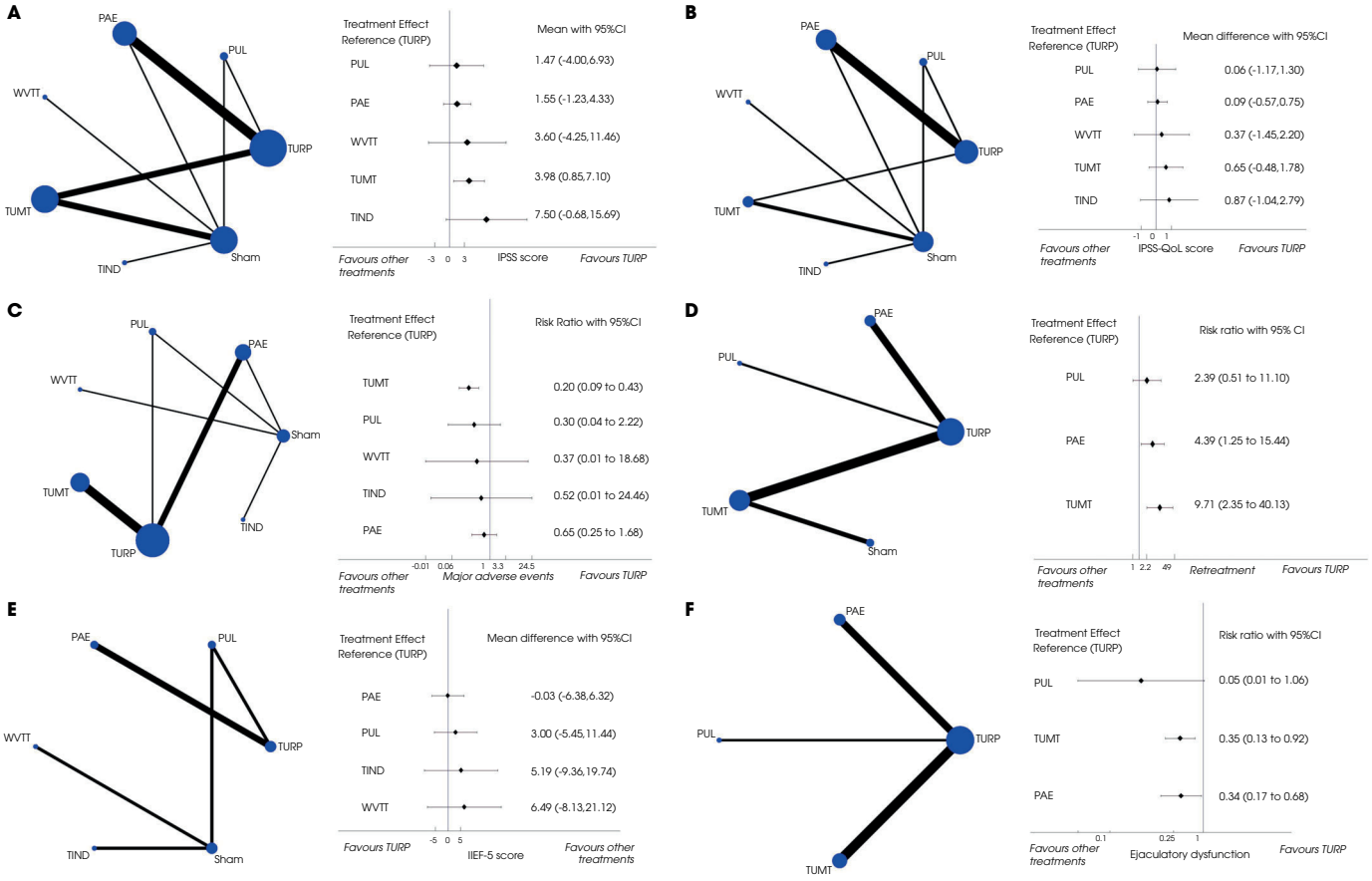


Fig. 2 Network maps and forest plots. IIEF, International Index of Erectile Function; PAE, prostatic arterial embolization; PUL, prostatic urethral lift; TIND, temporary implantable nitinol device; TUMT, transurethral microwave thermotherapy; WVTT, water vapour thermal therapy.

Pairwise Comparisons

We describe here some key information that we were unable to include in our network meta-analysis to preserve the transitivity of each network.

Retreatment: water vapour thermal therapy and temporary implantable nitinol device

Based on one study with 197 participants, we are uncertain about the effects of WVTT on retreatment compared to sham treatment at 3 months follow-up (RR 1.36, 95% CI 0.06 to 32.86) [38]. Based on another study with 185 participants, we are very uncertain about the effects of TIND on retreatment compared to sham treatment at 3-month follow-up (RR 0.67, 95% CI 0.11 to 3.89) [48]. The certainty of the evidence was very low due to concerns about risk of bias and severe imprecision. These results could not be included in the network due to their short-term follow-up.

Erectile function: transurethral microwave thermotherapy

Based on four studies with 278 participants, TUMT may result in little to no difference in erectile function (defined as an event of erectile dysfunction) compared to TURP at short-term follow-up (RR 0.79, 95% CI 0.40 to 1.55; $I^2 = 0\%$). One study found a similar result at long-term follow-up (RR 0.49, 95% CI 0.17 to 1.41) [64]. However, the certainty of the evidence was low due to concerns about risk of bias and imprecision. These results could not be included in the network because they were assessed as binary data and not IIEF scores.

Ejaculatory function: water vapour thermal therapy

Based on one study with 131 participants, WVTT may result in little to no difference in events of ejaculatory dysfunction compared to sham treatment at short-term follow-up (RR 4.01, 95% CI 0.22 to 72.78) [38]. The certainty of the

evidence was low due to concerns about risk of bias and imprecision. These results could not be included in the network because they were disconnected from all nodes.

Subgroup analysis

We found no subgroup differences in urological symptom scores according to age or symptom severity. We found no subgroup differences in quality of life according to age. Most of the prespecified subgroup analyses were not possible to perform due to the scarcity of data.

Discussion

We included 27 trials with 3017 randomized participants, assessing the effects of MITs compared to TURP or sham treatment. TURP is the reference treatment and was found to have the highest likelihood of being the most efficacious for urinary symptoms, quality of life, retreatment, minor adverse events, and acute urinary retention, but the least favourable in terms of major adverse events, erectile function and ejaculatory function. Among MITs, PUL and PAE had the highest likelihood of being the most efficacious for urinary symptoms and quality of life, and TUMT for major adverse events, PUL for retreatment, ejaculatory function and acute urinary retention, WVTT and TIND for erectile function, and PAE for minor adverse events.

The largest limitation of this study relates to issues related to the underlying body of evidence (see below), particularly the lack of head-to-head trials for MITs against TURP. For example, RCTs for WVTT and TIND were limited to comparisons against sham treatment that were unblinded after 3 months and had a short-term follow-up in many cases. The latter issues are underscored by the fact that the AUA guideline panel on the surgical management of LUTS had determined it required a minimum follow-up of longer than 12 months to support its recommendations [65,66]. Since longer-term RCT data are so limited, observational data may provide complementary information. For example, a systematic review of such studies found that the retreatment rate may be higher for PUL than assessed in the present review, at close to 6% per year [67]. Meanwhile, another systematic review has suggested that the long-term effects of WVTT may be sustained with a relatively low retreatment rate [68].

The reporting of adverse events was not uniform across studies, especially of those that differ across procedures, such as 'post-embolization syndrome' in PAE. This was also highlighted in a recent review of observational data in which over a quarter of patients experienced this syndrome, but it was not uniformly characterized [69]. Although the Clavien–Dindo system provides a well-established system to grade the severity of surgical complications, it may be less than ideal to characterize, for example, the adverse event profile for such different MITs as PUL and PAE.

A recent systematic review on men's values and preferences highlighted that men expect a high success rate with low remission and complication rates, which MITs may provide compared to TURP [70]. However, men also value the preservation of their sexual function, for which there are greater uncertainties. Therefore, clinicians must engage in shared decision-making with their patients when discussing the available options [71].

The certainty of the evidence was mostly low to very low owing to risk of bias, imprecision, inconsistency and the inability to assess incoherence in loosely connected networks. There is also the possibility of novelty bias, which refers to the mere appearance that a new treatment is better when it is new [27,72]. We made minor modifications from our protocol regarding the reporting of additional data available in each supporting review and the display of the ranking results both graphically and in the 'Summary of findings' tables. All these changes were duly documented in the full version of the review [15]. We could not include all available trials and interventions in all networks, primarily because of the lack of reporting of the outcomes in the desired format or definition. Finally, we could not perform subgroup and sensibility analyses due to the limited representation of subgroups in trials. Moreover, sensitivity analyses were not possible, considering that most of the studies were at a high or unclear risk of bias.

We identified several systematic reviews focusing on MITs, reporting similar findings concerning the efficacy of TIND, PUL, PAE and WVTT, and highlighting that these are relatively effective treatments, with a lower incidence of adverse events and sexual dysfunction, compared to TURP [73–78]. While some of these findings are similar to those of the present review, we highlight the uncertainty surrounding some of these outcomes, especially those related to sexual function, in which the data are sparse and usually available for only a subset of participants in each study, as was highlighted by one review [79]. Furthermore, many of these reviews included evidence from non-randomized studies and had an overall low quality [80,81]. In some cases, the evidence was synthesized by the authors of the primary studies [73]. Finally, there is a paucity of reviews focusing on TUMT in the last few years as no trials have been reported since the previous version of the Cochrane Review [82].

In conclusion, MITs may result in similar or worse effects concerning urinary symptoms and quality of life, compared to the standard treatment (TURP) at short-term follow-up. They may result in a large reduction of major adverse events, especially in the use of PUL and PAE, which resulted in better rankings for symptom scores. PUL may result in fewer

retreatments than other interventions, especially TUMT, which has the highest retreatment rates at long-term follow-up. We are very uncertain about the effects of these interventions on erectile function; however, these treatments may result in fewer cases of ejaculatory dysfunction. Considering that patients value the effects of these treatments on urinary symptoms, retreatment rates, and adverse events, including sexual function, it becomes necessary to engage in shared decision-making when discussing patients' different treatment options, highlighting the existing uncertainties and eliciting their preferences.

There needs to be better reporting of basic trial methodology and a greater emphasis on patient-reported outcomes, especially those related to sexual function. Many studies broke the blinding period after 3 months and patients crossed to the active treatment group, which prevented us from knowing the long-term effects of these interventions. This is particularly relevant for WVTT and TIND, both of which are supported only by single trials that compared the new therapeutic approach to sham control, with a 3-month time horizon. Sham-controlled trials provide only limited and indirect evidence to inform decision-making, and future research could focus on active comparisons and patient-important outcomes with a follow-up longer than 12 months [65,66,83]. A core outcome set should establish which outcomes should be collected and how and when they should be collected.

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Conflict of Interest

Juan V. A. Franco, Jae Hung Jung, Mari Imamura, Jafar Golzarian, Muhammad Imran Omar, Camila Micaela Escobar Liquitay, Areti Angeliki Veroniki, Luis Garegnani and Philip Dahm: none declared. Shamar Young: Boston Scientific (speaker), Galvanize (consultant). Michael Borofsky: Boston Scientific (Consultant for Endourology and Stone Management), Auris Health (Consultant for Robotic Surgery and Endourology), Urotronic (Disease Monitoring and Safety Board).

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Correspondence: Juan Victor Ariel Franco, Associate Cochrane Centre, Instituto Universitario Hospital Italiano de Buenos Aires, Potosí 4234C1199ACL, Buenos Aires, Argentina.

e-mail: juan.franco@hospitalitaliano.org.ar

Abbreviations: MD, mean difference; MIT, minimally invasive treatment; PAE, prostatic arterial embolization; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; PUL, prostatic urethral lift; Q_{max}, maximum urinary flow rate; RCT, randomized controlled trial; RR, risk ratio; TIND, temporary implantable nitinol device; TUMT, transurethral microwave thermotherapy; WVTT, water vapour thermal therapy.