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Health Technology Review

Extracorporeal Shockwave Therapy for Erectile Dysfunction

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Rapid Review with Expert Input

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Abbreviations

ED	Erectile dysfunction
EHS	Erectile Hardness Scale
ESWT	Extracorporeal shockwave therapy
HTA	Health Technology Assessment
IIEF-EF	International Index of Erectile Function-Erectile Function
Li-SWT	Low intensity shockwave therapy
Li-ESWT	Low intensity extracorporeal shockwave therapy
PDE5	Phosphodiesterase-5
SEP	Sexual encounter profile
SR	Systematic Review
SWT	Shockwave therapy

Key Messages

What Is the Issue?

- Male sexual dysfunction, including erectile dysfunction is a common problem for men starting in their early 40s and increases with age.
- Erectile dysfunction may be caused by one or more reasons, including organic (e.g., vasculogenic, hormonal), psychogenic, or mixed psychogenic and organic reasons. Erectile dysfunction is also common after pelvic trauma and penile fracture, surgery (e.g., prostatectomy), and radiation therapy (e.g., prostate cancer).
- There are many non-surgical treatment options for erectile dysfunction, including oral phosphodiesterase-5 inhibitors, penile self-injections with vasoactive drugs, and extracorporeal shockwave therapy. A review of the clinical effectiveness of extracorporeal shockwave therapy could help clarify the potential role in clinical practice, in which populations and with which treatment protocols.

What Did We Do?

- To inform decisions regarding the use of extracorporeal shockwave therapy, we conducted a rapid review to identify and summarize evidence that compared the clinical effectiveness of extracorporeal shockwave therapy to any comparators (e.g., sham or no treatment, pharmacological therapy, platelet-rich plasma). We identified evidence-based guidelines that provided recommendations related to extracorporeal shockwave therapy in men with erectile dysfunction.
- We searched key resources, including journal citation databases, and conducted a focused internet search for relevant evidence published since 2014. One reviewer screened articles for inclusion based on predefined criteria, critically appraised the included studies, and narratively summarized the findings.

What Did We Find?

- We found 1 health technology assessment (HTA), 1 overview of systematic reviews, 7 systematic reviews (SRs) that evaluated the clinical effectiveness of extracorporeal shockwave therapy for erectile dysfunction. We found 4 evidence-based guidelines that provided recommendations on the use of extracorporeal shockwave therapy for erectile dysfunction.
- Comparing extracorporeal shockwave therapy to sham or no treatment, shockwave therapy increases the mean International Index of Erectile Function Erectile Function subscale (IIEF-EF) score and the proportion of men achieving a minimally clinical important difference (MCID) when compared to sham or no treatment. This differed when looking at subpopulations. Similarly, extracorporeal shockwave therapy increases the mean Erectile Hardness Scale (EHS) score and the proportion of men with an improvement of ≥3 when compared to sham or no treatment. This differed when looking at subpopulations.
- Comparing extracorporeal shockwave therapy to pharmacological therapy, there was no statistical difference between groups for International Index of Erectile Function Erectile Function subscale (IIEF-EF) (when reported) and Erectile Hardness Score (EHS). One observational study in a systematic review reported a statistically significant difference in the number of men who had an improved EHS score to ≥3 after treatment.
- Comparing extracorporeal shockwave therapy to platelet-rich plasma, there was no difference in any outcomes, however, this was poorly reported.
- Comparing extracorporeal shockwave therapy protocols, there was no difference in any outcomes, however, this was poorly reported.
- One systematic review reported on treatment-related adverse effects, with few adverse effected reported. Two systematic reviews reported on discontinuation from treatment, with no discontinuations.
- International guidelines varied on recommending extracorporeal shockwave therapy for erectile dysfunction, with 2 recommending it in specific populations, 1 not recommending it, and 1 guideline (published in 2019) stating there was insufficient evidence to make a recommendation.

What Does This Mean?

- Extracorporeal shockwave therapy may improve clinical outcomes for men with erectile dysfunction when compared to sham or no treatment.

- There may be differences in the effectiveness of extracorporeal shockwave therapy treatment for subpopulations.
- Data on the clinical effectiveness of different protocols of extracorporeal shockwave therapy is limited.
- Extracorporeal shockwave therapy is safe, with few treatment-related adverse events.

Research Questions

1. What is the clinical effectiveness of extracorporeal shockwave therapy for erectile dysfunction?
2. What are the evidence-based guidelines regarding the use of extracorporeal shockwave therapy for erectile dysfunction?

Context and Policy Issues

What Is Erectile Dysfunction?

Normal male sexual function requires an interaction between vascular, neurologic, hormonal, and psychological systems.[1] Male sexual dysfunction, which includes erectile dysfunction (ED), diminished libido, and ejaculatory disorders, is a problem that becomes more common with increasing age.[1] In a cross-sectional study of men aged 40 to 88 years old, visiting primary care physicians' offices from July 2001 to November 2002, 49.4% reported some degree of ED during the past 4 weeks or were taking oral medication for ED, with overall prevalence and severity of ED increasing with age.[2] More recently, in a 2015 Canadian survey of 1162 men between the ages of 40 and 59 years, 23.8% reported having erection problems, a significant contributor to their overall sexual happiness.[3]

ED is defined as "the consistent or recurrent inability to acquire or sustain an erection of sufficient rigidity and duration for sexual intercourse."[1] ED is classified as organic (i.e., vasculogenic, neurogenic, local penile [cavernous] factors, hormonal, drug-induced), psychogenic, or mixed psychogenic and organic.[1] In addition to age, risk factors for erectile dysfunction are cardiovascular disease, diabetes mellitus, hypertension, obesity, dyslipidemia, hypogonadism, smoking, depression, and medication use.[1] ED is also common after trauma (pelvic trauma and penile fracture), surgery (pelvic, penile, urethral, prostatectomy), and radiation therapy.[5]

What is the Current Practice?

There are several treatment options for ED, including non-surgical and surgical treatment. Non-surgical treatment options for ED include oral phosphodiesterase-5 (PDE5) inhibitors, penile self-injections with vasoactive drugs, intraurethral suppositories, vacuum erection devices, stem cell therapy, hyperbaric oxygen therapy, platelet-rich plasma injections, and extracorporeal shockwave therapy (ESWT), also referred to as low intensity shockwave therapy (Li-SWT) or low intensity extracorporeal shockwave therapy (Li-ESWT). Surgical options include penile prostheses and penile revascularization.[6]

What is Extracorporeal Shockwave Therapy?

Shockwave therapy, specifically extracorporeal shockwave lithotripsy, has been utilized by urologists since the 1980s for the non-invasive fragmentation of kidney stones. Within the realm of sexual medicine, Li-ESWT has been investigated for the treatment of ED. There are three types of Li-ESWT energy source generators available, electrohydraulic, electromagnetic, and piezoelectric, with similar mechanistic actions which produce acoustic waves that transfer energy to tissue, leading to potential improvement in microcirculation and vasodilation, a decrease in fibrosis, and nerve regeneration.[7] Waves may be focused or radial, with differing tissue penetrance depth and energy. Li-ESWT uses focused shockwaves which have a tissue penetrance depth of 10-12 cm, compared to <3 cm depth from radial waves. Additionally, Li-ESWT has an energy of 0.09 to 1.5 mJ/mm^2 compared to 0.02 to 0.06 mJ/mm^2 of radial waves. For these reasons, it is said that radial therapy is not comparable to Li-ESWT for management of ED.[8]

Why Is It Important to Do This Review?

There are many non-surgical treatment options for erectile dysfunction, including oral phosphodiesterase-5 inhibitors, penile self-injections with vasoactive drugs, and extracorporeal shockwave therapy. A review of the clinical effectiveness of extracorporeal shockwave therapy could help clarify the potential role in clinical practice, in which populations (e.g., mild erectile dysfunction, Peyronie's disease) and with which treatment protocols.

Objective

The objectives of the report are to summarize the evidence regarding the clinical effectiveness of extracorporeal shockwave therapy for the treatment of erectile dysfunction and to report on recommendations found in guidelines.

Methods

Literature Search Methods

An information specialist conducted a literature search on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were erectile dysfunction and shock wave. The search was completed on December 4, 2024 and limited to English-language documents published since January 1, 2014.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Criteria	Description
Population	Adults (≥ 18 years) who experience erectile dysfunction
Intervention	Extracorporeal shockwave therapy
Comparator	Q1: Medication, placebo, no comparator (i.e., treatment as usual). Q2: NA
Outcomes	Q1: Benefits (e.g., improvement in erectile function, patient reported satisfaction) and harms (e.g., adverse events, visits to the emergency room). Q2: Recommendations regarding best practices (e.g., whether to use, frequency of treatment)
Study designs	Health technology assessments, systematic reviews, evidence-based guidelines.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications or were published prior to 2014. Systematic reviews in which all relevant studies were captured in other more recent or more comprehensive systematic reviews were excluded. Guidelines with unclear methodology or that were published before 2019 were also excluded. Due to the volume of included Health Technology Assessments (HTAs), systematic reviews (SRs) and guidelines, primary studies were excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[9] for systematic reviews, the Downs and Black checklist[10] for randomized and non-randomized studies, and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument[11] for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

- This report includes 1 HTA, 1 overview of systematic reviews, 7 SRs, and 4 evidence-based guidelines. 1. Rosen RC, Khera M. Epidemiology and etiologies of male sexual dysfunction. UpToDate; 2024.

2. Grover SA, Lowensteyn I, Kaouache M, et al. The Prevalence of Erectile Dysfunction in the Primary Care Setting. Importance of Risk Factors for Diabetes and Vascular Disease. *Arch Intern Med*. 2006;166:213-219.
3. Quinn-Nilas C, Milhausen RR, McKay A, Holzapfel S. Prevalence and Predictors of Sexual Problems Among Midlife Canadian Adults: Results from a National Survey. *Journal of Sexual Medicine*. 2018;15:873-879.
4. Johannes C, Araujo A, Feldman H, Derby C, Kleinman K, McKinlay J. Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts male aging study. *J Urol*. 2000;163(2):460.
5. Domes T, Najafabadi BT, Roberts M, et al. Canadian Urological Association guideline: Erectile dysfunction. *Can Urol Assoc*. 2021;15(10):310-322.
6. Khera M. Treatment of male sexual dysfunction. UpToDate; 2024.
7. Katz JE, Clavijo RI, Rizk P, Ramasamy R. The Basic Physics of Waves, Soundwaves, and Shockwaves for Erectile Dysfunction. Research Support, Non-U.S. Gov't Review. *Sex Med Rev*. 01 2020;8(1):100-105. doi:https://dx.doi.org/10.1016/j.sxmr.2019.09.004
8. Liu JL, Chu KY, Gabrielson AT, et al. Restorative Therapies for Erectile Dysfunction: Position Statement From the Sexual Medicine Society of North America (SMSNA). Review. *Sex*. Jun 2021;9(3):100343. doi:https://dx.doi.org/10.1016/j.esxm.2021.100343
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12. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of Clinical Epidemiology*. 2009;62(10):e1-e34.
13. Syful Azlie M, Izzuna M. *Extracorporeal shockwave therapy for the treatment of erectile dysfunction. Technology Review*. 2023. 005-2023.
14. Medrano-Sanchez EM, Pena-Cantonero B, Candon-Ballester P, Blanco-Diaz M, Diaz-Mohedo E. Effectiveness of Low-Intensity Extracorporeal Shock Wave Therapy in Erectile Dysfunction: An Analysis of Sexual Function and Penile Hardness at Erection: An Umbrella Review. Review. *J*. Feb 04 2024;14(2):04. doi:https://dx.doi.org/10.3390/jpm14020177
15. Panunzio A, Labate C, Zacheo F, et al. Platelet-rich plasma intracavernosal injections for the treatment of primary organic erectile dysfunction: a systematic review and meta-analysis of contemporary controlled studies. Systematic Review Meta-Analysis Review. *Int J Impot Res*. Sep 2024;36(6):562-571. doi:https://dx.doi.org/10.1038/s41443-023-00798-y
16. Bocchino AC, Pezzoli M, Martinez-Salamanca JI, Russo GI, Lo Giudice A, Cocci A. Low-intensity extracorporeal shock wave therapy for erectile dysfunction: Myths and realities. Review. *Investig Clin Urol*. 03 2023;64(2):118-125. doi:https://dx.doi.org/10.4111/icu.20220327
17. Rosenberg JE, Ergun O, Hwang EC, et al. Non-surgical therapies for Peyronie's disease. Systematic Review Review Research Support, Non-U.S. Gov't. *Cochrane Database Syst Rev*. 07 17 2023;7:CD012206. doi:https://dx.doi.org/10.1002/14651858.CD012206.pub2
18. Sighinolfi MC, Eissa A, Bellorofonte C, et al. Low-intensity Extracorporeal Shockwave Therapy for the Management of Postprostatectomy Erectile Dysfunction: A Systematic Review of the Literature. Review. *Eur Urol Open Sci*. Sep 2022;43:45-53. doi:https://dx.doi.org/10.1016/j.euros.2022.07.003
19. Yao H, Wang X, Liu H, et al. Systematic Review and Meta-Analysis of 16 Randomized Controlled Trials of Clinical Outcomes of Low-Intensity Extracorporeal Shock Wave Therapy in Treating Erectile Dysfunction. Meta-Analysis Research Support, Non-U.S. Gov't Systematic Review. *Am j*. Mar-Apr 2022;16(2):15579883221087532. doi:https://dx.doi.org/10.1177/15579883221087532
20. Marchioni M, De Francesco P, Castellucci R, et al. Management of erectile dysfunction following robot-assisted radical prostatectomy: a systematic review. Systematic Review. *Minerva Urol Nefrol*. Oct 2020;72(5):543-554. doi:https://dx.doi.org/10.23736/S0393-2249.20.03780-7
21. Sokolakis I, Hatzichristodoulou G. Clinical studies on low intensity extracorporeal shockwave therapy for erectile dysfunction: a systematic review and meta-analysis of randomised controlled trials. Meta-Analysis Systematic Review. *Int J Impot Res*. May 2019;31(3):177-194. doi:https://dx.doi.org/10.1038/s41443-019-0117-z
22. Salonia A, Bettocchi C, Capogrosso P, et al. EAU Guidelines on Sexual and Reproductive Health. European Association of Urology; 2024.
23. Chung E, Lee J, Liu CC, Taniguchi H, Zhou HL, Park HJ. Clinical Practice Guideline Recommendation on the Use of Low Intensity Extracorporeal Shock Wave Therapy and Low Intensity Pulsed Ultrasound Shock Wave Therapy to Treat Erectile

Dysfunction: The Asia-Pacific Society for Sexual Medicine Position Statement. Review. *World j*. Jan 2021;39(1):1-8. doi:https://dx.doi.org/10.5534/wjmh.200077

24. Capogrosso P, Frey A, Jensen CFS, et al. Low-Intensity Shock Wave Therapy in Sexual Medicine-Clinical Recommendations from the European Society of Sexual Medicine (ESSM). Review. *J Sex Med*. 10 2019;16(10):1490-1505. doi:https://dx.doi.org/10.1016/j.jsxm.2019.07.016

Appendix 1 presents the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[12] flowchart of the study selection. Appendix 6 provides additional references of potential interest that did not meet our inclusion criteria.

Summary of Study Characteristics

Summaries of study characteristics are organized by research question. Appendix 2 provides detailed characteristics of the included publications.

Included Studies for Question 1: Clinical effectiveness of extracorporeal shockwave therapy for erectile dysfunction

We identified 1 HTA,[13] published in 2023, which included men 18 years and older with vasculogenic, general, or diverse pathogeneses of ED. Six SRs, 3 randomized controlled trials, and 2 non-randomized studies in the HTA are relevant to this review. There was significant overlap of SRs and primary studies, with overlap addressed in Appendix 5. Therefore, only the 2 randomized controlled trials and 2 non-randomized studies not reported in any other SRs, are reported in this review. The HTA compared Li-ESWT to several comparators including pharmacology therapy, medical devices, combination therapy, and placebo (sham).

We identified 1 overview of systematic reviews,[14] published in 2024, which included men with vascular-origin ED. This overview included 5 SRs, all of which were identified in the current review and were evaluated for primary study overlap. As the overview of systematic reviews only included studies that compared Li-ESWT to placebo specific to men with vascular-origin ED, not all primary studies were used in the reporting of the results. For this reason, we have not reported any of the results from this overview of systematic reviews in this review, as they will be included in the systematic review section.

We identified 7 SRs, published between 2019 and 2024,[15-21] of which 4 included meta-analyses.[15,17,19,21] All SRs included men 18 years and older with ED.

Two SRs do not provide any outcomes for the current review.[16,20] Marchioni (2020)[20] review summarized evidence about the efficacy of available treatment for ED after robotic assisted radical prostatectomy, and included conservative (e.g., pharmacological therapy, vacuum pump erectile devices, ESWT) and surgical interventions. Eleven studies were included, with 1 primary study evaluating Li-ESWT, However, it is a non-comparative study and is therefore not relevant to the current review. Bocchino (2023)[16] included men with ED according to the European Guidelines diagnostic criteria, had a search date of August 2022, and identified 52 studies, 28 relevant to this review, evaluating Li-ESWT. However, they only reported the outcomes for the intervention group. As no data is extracted for this review, we did not assess overlapping primary studies.

Among the 5 SRs that provide data for the current review, 2 had broader inclusion criteria than the current review. Panunzio (2024)[15] included randomized and non-randomized comparative studies published up to July 2023 (including in meeting abstract format) that evaluated platelet-rich plasma intracavernosal injections compared to other therapies (e.g., pharmacological, EDWT, placebo) for the treatment of primary organic ED. One observational study, published in 2021, is relevant to the current review. Sokolakis (2019)[21] included men with ED, not otherwise described, and had broader inclusion in terms of study design, as they included RCTs and single-arm studies. Search dates were from January 2010 to September 2018. A total of 28 studies were included, 14 single-arm studies and 14 RCTs. Their meta-analyses included 10 RCTs that compared Li-ESWT to sham therapy.

Two SRs included specific populations. Rosenberg (2023)[17] had narrower inclusion criteria related to the types of therapies evaluated because they included men with Peyronie's disease. Although men with Peyronie's disease may experience ED, the presence of ED was not an inclusion criterion. All non-surgical therapies were included (e.g., ESWT, injections, penile traction therapy). Two primary studies, published in 2009 and 2010 are relevant to the current review. Sighinolfi (2022)[18] included randomized and non-randomized comparative studies published between 2015 and 2022 (search date not reported), in postprostatectomy patients. Three RCTs, 3 non-randomized studies, and one conference abstract were included that compared Li-ESWT to delayed Li-ESWT, pharmacological therapy alone, sham or no treatment. The 3 RCTs were also included in the meta-analysis in Yao (2022),[19] so only the data from the non-randomized studies are reported in this review.

Yao (2022)[19] had similar inclusion criteria to the current review, included men with ED not otherwise described, and compared Li-EWST with or without pharmacological therapy to pharmacological therapy alone, sham or no treatment. Sixteen RCTs published between 2010 and 2021 were included, all relevant to the current review.

Across the primary studies in the SRs, the protocols for Li-ESWT varied in terms of energy density (e.g., 0.09, 0.15, 0.16 mJ/mm^2), frequency (e.g., 2, 5 Hz), pulses per treatment (e.g., 600, 3000, 4000), machine (e.g., RENOVA electromagnetic device, Omnispec ED1000, MT 2000H, Duolith SDI, Richard Wolf GmbH, Swiss Dolorclast, Dornier Aries device), number of treatments per week (e.g., 1, 2), number of treatment weeks (e.g., 3 weeks on, 3 weeks break, 3 weeks on or consecutive 4, 5, 8 weeks).

Erection related outcomes were patient-reported outcomes using the International Index of Erectile Function (IIEF) Erectile Function subscale (EF) (also called the IIEF-5) and the Erectile Hardness Scale (EHS). The IIEF-EF was reported as a mean (SD)[13,15,18,19,21] as a proportion of those who reached a minimal clinically important difference (MCID),[13,21] or as an increase since baseline.[21] The IIEF-EF score determines the severity of ED, with a score of 26-30 as no ED, 22-25 as mild ED, 17-21 as mild to moderate ED, 11-16 as moderate ED, and 6-10 as severe ED. Achieving a MCID differs based on the baseline ED severity (e.g., an increase of 2 points for mild, 4 or 5 points for moderate, and 7 points for severe ED). The EHS score was reported as mean (SD)[13,15,19] and as an improvement of ≥3 points.[18,21] The EHS is a scale with 5 options ranging from 0 penis does not enlarge to 4 penis is completely hard and fully rigid. Other outcomes were sparsely reported including self-esteem and relationship (SEAR),[13,15] sexual encounter profile (SEP),[19] the sexual bother score and sexual function score from the Expanded Prostate Cancer Index Composite,[18] quality of life,[17] treatment-related adverse effects,[17] and discontinuation from treatment.[15,17]

Included Studies for Question 2: Evidence-based guidelines regarding the use of extracorporeal shockwave therapy for erectile dysfunction

Four guidelines, published between 2019 and 2024 were identified. These guideline were developed by the European Association of Urology,[22] the Canadian Urological Association,[5] the Asia-Pacific Society for Sexual Medicine,[23] and the European Society of Sexual Medicine.[24] Recommendations from 2 guidelines were specific for men with ED.[5,23] Two guidelines provided recommendations for ED and other conditions, however, only recommendations related to ED were relevant to the current report. The guideline by the European Association of Urology[22] provided recommendations for male sexual dysfunction, male infertility, and male hypogonadism. The European Society of Sexual Medicine provided recommendations for ED, Peyronie's disease, and chronic prostatitis/chronic pelvic pain syndrome.[24] The guidelines looked at a variety of options for diagnosis and treatment, including pharmacological therapies, Li-ESWT, vacuum and pump devices, and surgery (e.g., prosthesis).

Guideline groups used different methods to identify their evidence base. The European Association of Urology guideline[22] did not state the exact method; however, their guideline handbook states that they use a staged approach, first searching for systematic reviews, then conducting a new systematic review, if required. The Canadian Urological Association[5] did not state their method to identify the evidence base, however, they use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the certainty of the evidence, which should be based on a systematic review. The Asia-Pacific Society for Sexual Medicine guideline[23] was based on a literature review, analyzed and summarized the evidence, and presented it at a scientific meeting. The European Society of Sexual Medicine[24] performed a review which could be considered systematic based on their methodology description. Groups used consensus to develop recommendations, with some using a formal approach to evaluate the strength of the recommendations. The European Association of Urology guideline[22] used a recommendations worksheet based on a modified GRADE approach, with strong recommendations typically indicating a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference and weak recommendations typically indicating availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference. The Canadian Urological Association[5] used the GRADE Evidence to Decision framework. The 2 other guidelines did not describe their process.

Two guidelines stated that the outcomes the considered included items such as benefits and harms, patient values and preferences, costs and resource utilization, equity, feasibility and acceptability.[5,22] One guideline looked at the treatment template and patient selection, clinical outcomes, and safety and tolerabilty[23] and one looked at the treatment efficacy, treatment protocol, clinical indications, and safety.[24]

Summary of Critical Appraisal

Health Technology Assessment and Overview of Systematic Reviews

The HTA[13] and the overview of systematic reviews[14] were assessed using AMSTAR 2[9] with additional questions specifically related to overview of systematic reviews (e.g., evaluating overlap of primary studies included in the SRs). Several strengths were identified. Both searched multiple electronic databases, sufficiently described the inclusion criteria, provided a PRISMA flow diagram, performed critical appraisal of the included studies, reported the source of funding, and declared conflicts of interest. The overview of systematic reviews[14] requested registration in PROSPERO (an open-access international prospective register of systematic reviews) and reported on the overlap of the primary studies in the included SRs. Several limitations were identified. The HTA[13] did not provide any details around a protocol. The HTA[13] had 1 reviewer perform study selection and the overview of systematic reviews[14] did not adequately describe how study selection was performed. Neither the HTA or the overview of systematic reviews sufficiently described the process for data extraction and critical appraisal, provided a list of excluded studies, or reported on the source of funding on the included studies. These limitations can reduce the level of confidence that all relevant studies were identified and included, that all relevant data was extracted, and that critical appraisal was correctly and consistently performed.

Systematic Reviews

The 7 SRs were assessed using AMSTAR 2.[9] All SRs provided a PRISMA flow diagram, which is a flow chart mapping the number of records identified, included and excluded, and the reasons for exclusion during the different levels of study selection, which increases the transparency of the SR process and may increase the reproducibility of the SR. All SRs also reported on conflicts of interest, which can help identify real or perceived author bias. There were several strengths identified in SRs, however, not across all reviews. Two SRs[15,17] reported on a protocol developed prior to undertaking the review, which can reduce selection (of studies) and reporting (e.g., outcomes) bias. Four SRs[15,17,20,21] provided sufficient details around inclusion criteria, with exclusion criteria much less explicitly defined, mainly reported for years of publication, study designs, and language. Six SRs searched multiple electronic databases, with Bocchino (2023)[16] searching only PubMed. Three SRs[15,17,21] conducted supplemental searching (e.g., looking at the reference lists of included studies), which can identify studies not captured in the search of electronic databases. Three SRs[17,19,21] did not limit language of publication. The methodological conduct of study selection, data extraction, and risk of bias assessment varied across reviews, with dual-independent selection, extraction, and critical appraisal increasing the likelihood that all studies, relevant data, and limitations were identified. Four[15,17,20,21] SRs reported that two independent reviewers performed study selection, 4 SRs[15-17,21] reported that two independent reviewers performed data extraction, and 5 SRs[15,17-19,21] reported that two independent reviewers performed risk of bias assessment. Three SRs[15,17,18] provided sufficient details around the included studies, which helped in identifying which were relevant to the current review. Four SRs[16-19] reported the source of funding. Four SRs performed meta-analyses,[15,17,19,21] often resulting in high levels of heterogeneity, which can influence our trust in the generalizability of the results. Two SRs[19,21] performed subgroup analyses (e.g., timing of outcome, severity of baseline ED), which may or may not have affected the levels of heterogeneity. Rosenberg (2023)[17] is a Cochrane review and followed rigorous methodological conduct and reporting of SRs. It was the only SR that provided a list of excluded studies and funding details of the included primary studies. However, it included studies in men with Peyronie's disease, with only 2 studies relevant to the current review.

Guidelines

The guidelines were assessed using the AGREE-II tool.[11] All guidelines provided a description of the scope and purpose of the guideline, clearly described the methods used for formulating the recommendations, considered the health benefits, side effects, and risks when formulating the recommendations, provided an explicit link between the recommendations the supporting evidence, clearly presented recommendations that were specific, and provided a statement around the competing interests of the members of the guideline development group.

One guideline group[22] refer to a Guideline development handbook and SR handbook, which provides additional details around incorporating views and preferences of the target population, searching for evidence, methods for formulating recommendations, etc. There were inconsistencies in reporting around if the guideline was externally reviewed, a procedure for updating the guideline, description of facilitators and barriers to guideline application, and resource implications across the guidelines.

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

Appendix 4 presents the main study findings.

There was some overlap in the primary studies that were included in the SRs; therefore, to avoid duplication of results, outcome data from an individual primary study are reported for most SRs. Yao (2022)[19] and Sokolakis (2019)[21] present meta-analyzed results, so there is overlap in these results. A citation matrix illustrating the degree of overlap is presented in Appendix 5.

Clinical Effectiveness of Extracorporeal Shockwave Therapy vs Sham or No Treatment

International Index of Erectile Function Erectile Function subscale (IIEF-EF)

Mean score. One RCT in the HTA by Syful (2023)[13] reported a statistically significant difference between those who received ESWT and the sham group at 1-, 3-, and 6-months follow-up, with those in the ESWT reporting higher IIEF-EF scores (i.e., less ED). All meta-analyses in Yao (2022)[19] reported statistically significant differences in the mean difference, favouring the group who received ESWT. This was reported at 1-, 3-, and 6-months follow-up when combining studies of all severities of ED and when subgroup analysis was performed based on severity of ED at baseline (i.e., mild, moderate, severe). Sokolakis (2019)[21] reported a statistically significant difference, favouring the group who received ESWT, when all populations were combined. However, when looking at the subgroups of PDE5i-responders and kidney transplant recipients, there was no longer a statistically significant difference between those who received ESWT or sham. The difference remained statistically significant in PDE5i-non-responders and in men with post radical cystectomy.

Proportion achieving MCID. When combining all populations, Sokolakis (2019)[21] reported a statistically significant difference in those who achieved a MCID in the IIEF-EF score in those who received ESWT compared to those who received sham. In subgroup analysis, this statistical difference remained in the PDE5i-responders, PDE5i-non-reponders, and in kidney transplant recipients, but not in men who had undergone post-radical cystectomy.

Erectile Hardness Scale (EHS)

Mean score. One RCT in the HTA by Syful (2023)[13] reported a statistically significant difference with those in the ESWT reporting higher EHS means scores compared to the sham group at 1-, 3-, and 6-months follow-up.

Improvement in score to ≥3. In a meta-analysis of 8 RCTs, Yao (2022)[19] reported that men in the ESWT group were more likely to go from an EHS score of ≤2 at baseline to a score of ≥3 after treatment when compared to those who received control. Sokolakis (2019)[21] also reported a statistically significant difference, with those receiving ESWT more likely to have improvement in EHS scores. This significant difference held in subgroups analysis for PDE5i-resonders, PDE5i-non-responsders, but not in kidney transplant recipients and men with post radical cystectomy.

Sexual encounter profile (SEP)

Three RCTs in Yao (2022)[19] reported on those who answered yes to question 2 and question 3 on the SEP. Question 2 on the SEP asks “Were you able to insert your penis into your partner’s vagina?” and question 3 asks “Did your erection last long enough for you to have successful intercourse?”.There was no statistical difference in the number of those who answered yes to either question.

Expanded Prostate Cancer Index Composite

Sexual bother score. One observational study from Sighinolfi (2022)[18] reported sexual bother scores, but did not provide a measure of statistical significance to determine if there was a difference between groups.

Sexual function score. One observational study from Sighinolfi (2022)[18] reported sexual bother scores, but did not provide a measure of statistical significance to determine if there was a difference between groups.

Quality of life

Rosenberg (2023)[17] reported a statistically significant difference in the mean difference in quality of life, with those who received ESWT having higher scores.

Treatment-related adverse effects

Two RCTs in the SR by Rosenberg (2023)[17] reported few treatment-related adverse events in both groups. The meta-analysis in the SR included studies not relevant to this review, so a measure of statistical significance was not provided for these 2 studies alone.

Discontinuation from treatment

Two RCTs in the SR by Rosenberg (2023)[17] reported that no participants discontinued from treatment.

Clinical Effectiveness of Extracorporeal Shockwave Therapy vs Pharmacological therapy

International Index of Erectile Function Erectile Function subscale (IIEF-EF)

Mean score. One RCT in the HTA by Syful (2023)[13] reported a higher mean IIEF-EF score in the ESWT group compared to pharmacological therapy group at 12 weeks follow-up but does not provide a measure of statistical significance. The two observational studies in this HTA[13] reported no statistically significant difference between the two groups. One observational study in the SR by Sighinolfi (2022)[18] reported similar scores at 3 months follow-up, with higher scores in the ESWT group at 6- and 12-months follow-up, but no measure of statistical significance provided.

Proportion achieving MCID. One observational study in the HTA by Syful (2023)[13] reported no difference in those who achieved a MCID in the IIEF-EF score between groups.

Erectile Hardness Scale (EHS)

Mean score. One RCT in the HTA by Syful (2023)[13] reported similar mean EHS scores in the ESWT and pharmacological therapy group at 12 weeks follow-up. One observational study in this HTA[13] reports no statistically significant difference between the two groups.

Improvement in score to ≥3. One observational study in the SR by Sighinolfi (2022)[18] reported no statistical difference in those who had an improvement in the EHS score to ≥3 between the ESWT and pharmacological therapy groups at 3 weeks, 1-month and 3 -months follow-up. However, at 6-months follow-up, those who received ESWT were more likely to have improved their EHS score to ≥3.

Self-esteem and relationship (SEAR)

One observational study in Syful (2023)[13] reported no statistical difference in SEAR score between those who received ESWT and those who received pharmacological therapy.

Clinical Effectiveness of Extracorporeal Shockwave Therapy vs Platelet-Rich Plasma

International Index of Erectile Function Erectile Function subscale (IIEF-EF)

Mean score. One observational study in the SR by Panunzio (2023)[15] reported that both groups had improvement in the mean IIEF score, “with no statistically significant difference” (p. 567). However, it is not clear if it was no significant difference improvement from baseline or between groups at follow-up.

Erectile Hardness Scale (EHS)

Mean score. Mean EHS scores were provided in Panunzio (2023),[15] 3.04 vs 3.89, however no statistical test was provided to measure if there was a statistical difference between the two groups.

Self-esteem and relationship (SEAR)

One observational study in the SR by Panunzio (2023)[15] reported mean SEAR scores in ESWT and PRP groups, 45.25 and 48.33, respectively, but did not provide a measure of statistical significance.

Discontinuation from treatment

One observational study in the SR by Panunzio (2023)[15] reported that no participants discontinued from treatment.

Clinical Effectiveness of Extracorporeal Shockwave Therapy vs Different Protocol of Extracorporeal Shockwave Therapy

International Index of Erectile Function Erectile Function subscale (IIEF-EF)

Increase in IIEF-EF score or proportion achieving MCID. The SR by Sokolakis (2019)[21] included 3 RCTs that evaluated different Li-ESWT treatment protocols. These RCTs were included only in Sokolakis (i.e., no overlap with other SRs). One RCT had no statically significant difference in those who had an IIEF-EF score increase by >5 when comparing 5 sessions vs 10 sessions. The other RCT reported that 62% of men who received 6 treatments (1 per week for 6 weeks) achieved MCID in the IIEF-EF score

compared to 71% who received 12 treatments (2 per week for 6 weeks). Sokolakis (2019)[21] reported the increase of IIEF-EF scores since baseline, but did not report if these differences were statistically significant between groups.

Erectile Hardness Scale (EHS)

Improvement in score to ≥3. One RCT in Sokolakis (2019)[21] compared different ESWT protocols, 10 sessions vs 5 sessions. There was not a statistically significant difference between protocols in the number of men who improved to a EHS score of ≥3.

Sexual encounter profile (SEP)

Two RCTs in Sokolakis (2019)[21] reported on the proportion of men who answered yes to Question 3 in the SEP, but no statistical test was provided to measure if there was a statistical difference between the two groups.

Guidelines Regarding the Use of Extracorporeal Shockwave Therapy

Four evidence-based guidelines[5,22-24] were identified providing recommendations for ESWT for the treatment of ED.

Recommendations for the use of Li-EWST vary across the guidelines. The European Association of Urology guideline (2024)[22] recommends the use of Li-SWT for ED in specific patients, including those with mild vasculogenic ED, as an alternative therapy in well-informed patients who do not wish to have or are not suitable for oral vasoactive therapy, and in patients with vasculogenic ED who are poor responders to PDE5is (quality of evidence: not reported; strength rating: weak). The Asia-Pacific Society for Sexual Medicine guideline (2021)[23] has similar recommendations, stating that clinical adoption of Li-ESWT should be restricted to men with mild-moderate vasculogenic ED, either responder or non-responders to PDE5is, and should ideally be performed in high specialized centres with documented experience with Li-ESWT (based on SRs of RCTs or non-randomized studies). Contrarily, the Canadian Urological Association guideline (2021)[5] suggests against the use of Li-SWT for patients with ED (quality of evidence: low; strength rating: conditional). Last, the European Society of Sexual Medicine guideline (2019)[24] does not provide a recommendation as the current evidence is still controversial and more high-quality studies are needed.

The Asia-Pacific Society for Sexual Medicine guideline (2021)[23] recommends that there is a need to define which subgroup of ED population is best suited and which Li-EWST protocols to use (based on SRs of RCTs or non-randomized studies). The European Society of Sexual Medicine guideline (2019)[24] also states that there are only a few studies comparing different treatment protocol with the same SW generator, therefore a specific protocol cannot be suggested. Further, the European Society of Sexual Medicine guideline (2019)[24] states that there are no studies that compared linear to focused SW therapy, so research is needed. Both the Asia-Pacific Society for Sexual Medicine guideline (2021)[23] and the European Society of Sexual Medicine guideline (2019)[24] states that Li-ESWT is a safe and well-tolerated procedure (based on SRs of RCTs).

Limitations

One HTA,[13] 1 overview of systematic reviews,[14] and 7 SRs[15-21] were identified with primary studies that evaluated ESWT for ED. Overall, the quality of conduct and reporting for these reviews was mixed (e.g., no supplemental searching, lack of details around the methods of study selection, lack of details around the participants in the primary studies, no list of excluded studies), making it difficult to determine if all relevant primary studies were captured by the HTA, overview of systematic reviews, and SRs. Additionally, SRs did not always report on the comorbid risk factors of the participants in the primary studies (e.g., diabetes, cardiovascular disease, medication use), which may impact the reason for experiencing ED and the efficacy of ESWT in treating ED. One SR[16] identified 28 relevant studies, which would be the most comprehensive SR, however, there were several limitations to the conduct and reporting of this SR. Only 1 electronic database was searched, there are no details around how study selection was performed, critical appraisal of the primary studies was not performed, there are no descriptors of the comparators, and they only report the results in the active treatment group. We have included this review, however, have not reported the results, due to their significant limitations. There were 9 primary studies in this SR that were not captured by the other included SRs. References for these studies have been provided in Appendix 6.

Some SRs were conducted in specific populations, for example, in men with Peyronie's disease, in men with chronic pelvic pain, and in men who had undergone prostatectomy. In these SRs, the men were included for these reasons, and it is difficult to

determine if the participants also had ED, as it is not always described in the inclusion criteria of the study or provided in the population characteristics in the SR. Therefore, it is possible that some primary study results in the included SRs were missed for these populations. Additionally, ESWT therapy for chronic pelvic pain syndrome can be applied using a perineal approach, and therefore may not be comparable to ESWT delivered on the penis.

There is variation in the ESWT protocols across primary studies in the SRs, in terms of the number of treatments, the number of weeks in which the treatments are given, the energy density of the treatment, the shockwave frequency (Hz), the number of pulses per treatment and overall, and the different types of shockwaves (e.g., linear, focused). Sokolakis (2019)[21] is the only SR that included studies (n=3) that compared some of these protocols, with variation of the protocols compared.

There are several limitations in the outcomes and reporting of these outcomes in the SRs. First, reported outcomes are subjective and may be influenced by the knowledge of intervention received. RCTs with blinded participants would not be impacted, but outcomes from RCTs where blinding was not possible (e.g., ESWT vs PRP) and in observational studies where the participant knew they were receiving active treatment may be influenced by this knowledge. Second, adverse effects of treatment were poorly reported. One SR reported adverse effects of treatment[17] and 2 SRs reported on discontinuation from treatment.[15,17] It is unclear if this is because they are not reported in the primary studies included in the SRs or if the SR authors did not extract these outcomes. Two international guidelines state that ESWT is safe and well-tolerated, with 1 of the guidelines providing 12 references of single-arm and sham-controlled trials[24] and 1 guideline providing 8 references to clinical trials and SRs[23] to support statements around safety and tolerability. Last, SRs did not always report on the variance (e.g., standard deviation) or on the measure of difference between the groups (e.g., p-value), making it difficult to determine if results were statistically significant or not.

The primary studies included in the SRs have a small number of participants. For example, in the 16 RCTs included in Yao (2022),[19] the range of participants in the primary studies is 20 to 118, with a median of 63 participants. Meta-analysis offers additional precision by increasing the number of participants contributing to the pooled estimate, however, in the meta-analyses in the SRs had high heterogeneity. This was sometimes explained by conducting subgroup analyses (e.g., mild baseline severity of ED[19]), but heterogeneity in most subgroup analyses remained high. No SRs conducted a subgroup meta-analysis based on type of ED (e.g., vasculogenic, men who had undergone prostatectomy).

Follow-up for most primary studies are 1, 3, and 6 months, with few reporting at 12 months, and none of the relevant primary studies within the SRs reporting after 12 months. Guidelines have also highlighted this limitation and have stated the uncertainty of the clinical long-term significance of the improvement offered from treatment.[23]

Results from the primary studies included in the SRs may be generalizable to Canadian clinical practice, as they included men with vasculogenic ED and men with ED with complications (e.g., prostatectomy), however, results from the primary studies included in the SRs in men with vasculogenic ED may not be generalizable to men with Peyronie's disease, who had received radiotherapy for prostate cancer, or who had received prostatectomy, and vice versa. Guidelines provide recommendations on specific populations who should receive ESWT for ED (e.g., men with mild vasculogenic ED, poor responders to PDE5is), but also highlight the need to define which subgroup of ED population is best suited to received ESWT.[23] The Canadian Urology Association guideline (2021)[5] suggested against the use of ESWT in men with ED, however, this was based on 4 RCTs (after removing 3 RCTs that were rated as high risk of bias) with low levels of certainty.

Conclusions and Implications for Decision- or Policy-Making

One HTA,[13] 1 overview of systematic reviews,[14] and 7 SRs[15-21] were identified with primary studies that evaluated ESWT for ED. Four guidelines[5,22-24] were identified that provided recommendations for the use of ESWT in men with ED. Overall, treatment with ESWT for ED increases the mean score of the IIEF-EF scale, when compared to sham or no treatment. However, ESWT when compared to sham or no treatment, may not be beneficial in all men, for example, in kidney transplant recipients.[21] Further, SRs report a clinically meaningful improvement in the IIEF-EF score (i.e., those achieving a MCID) in most men who received ESWT compared to sham treatment.[21] Poor reporting of patient populations and high heterogeneity leads to uncertainty in what population is best suited for ESWT. Most men also see an improvement (i.e., ≥3) on the EHS score,[19,21] with the exception of kidney transplant recipients and men with post radical cystectomy,[21] however, there are few studies that report on these populations. There was little difference in other outcomes (e.g., self-esteem and relationship score,[13,15] sexual encounter profile,[19,21] sexual bother and sexual function score[18]), however, this was sparsely reported in the SRs and only in 1 to 3 primary studies in the SRs. There were few

statistically significant differences in outcomes when comparing ESWT to pharmacological therapy, when compared to platelet-rich plasma, or when comparing different ESWT treatment protocols. Results should be interpreted with caution, as there were several limitations identified in the conduct and reporting of the HTA, overview of reviews, and SRs that were included. Limitations in conduct reduces our confidence that all relevant studies were captured, all relevant data was extracted, studies were properly critically appraised, and data was appropriately meta-analyzed. Limitations in reporting reduces transparency and confidence in the quality of conduct. Last, several included studies did not report a measure of statistical significance between groups, which limits interpretation if there were differences between the two groups.

Twenty-five SRs were identified and evaluated for overlap, with 7 SRs included in the current review, showing significant overlap in the SRs that have been published. However, the quality of conduct and reporting of most of the included SRs highlights the need for a well-conducted and well-reported comprehensive review on the efficacy of ESWT for the treatment of ED. A new systematic review should be done to address the limitations identified in the existing HTA, overview of reviews, and SRs included here, with the goal of increasing transparency, and improving on the quality of conduct and reporting. It should include comparative studies (i.e., randomized and comparative observational studies) in all populations, which may allow for subgroup analysis and further evaluation of heterogeneity of the included studies, recognizing that the ability to conduct these subgroup analyses would be dependent on the quality of the conduct and reporting of the primary studies. The SR by Rosenberg (2023),[17] specific to men with Peyronie's disease, was the only SR to provide summary of findings tables. This additional step should be taken in the new SR to determine the certainty of the evidence.

There is variation in recommending ESWT in the included guidelines. Two guidelines recommend ESWT in men with mild[22] or mild-moderate[23] vasculogenic ED, and in men who do not wish or are not suitable for vasoactive therapy,[22] and in vasculogenic ED patients who are poor responders to PDE5is.[22] The Canadian Urology Association[5] suggests against the use of ESWT in men with ED, however, this is based on 4 RCTs and low levels of certainty in the evidence. The fourth guideline[24] does not provide a recommendation, as "current evidence is promising but controversial". It is important to highlight that this guideline was published in 2019 and does not include studies published since December 2018.

Transparency in conduct and reporting across SRs and guidelines may help identify differences in included studies, risk of bias assessments, conclusions and recommendations. Lack of transparency leads to the inability to determine why differences occur. For example, although risk of bias assessment was undertaken in most SRs, there is a lack of transparency on how judgments were made (i.e., no explanatory statement) and there is variation in how primary studies were assessed between reviews and guidelines. The Canadian Urology Association guideline (2021)[5] rated three primary studies as high risk and excluded them from the analysis that was used to provide the final recommendation (i.e., suggest against the use of Li-ESWT). However, in Yao (2022),[19] two of these primary studies were rated as low risk for all domains with the third study rated as low risk in 5 domains and unclear in 2 domains. With no explanatory statements on why these judgments were made, the reader how no context to the judgment. Future SRs should aim to be more transparent in their reporting.

For primary studies, clinical trials with longer term follow-up should be performed to determine how long the effects of ESWT last and if and when retreatment with ESWT might be necessary.

Other implications to consider are the accessibility of the technology and the health care resources to administer the ESWT. This is highlighted in the Asia-Pacific Society for Sexual Medicine guideline (2021)[23] that states ESWT should be administered in specialized centres with experience in administering the therapy. It is not mentioned in the included SRs who administered the ESWT and the length of time (e.g., in minutes) of treatment. Human resources and time allocated for treatment should be considered for decision and policy-making.

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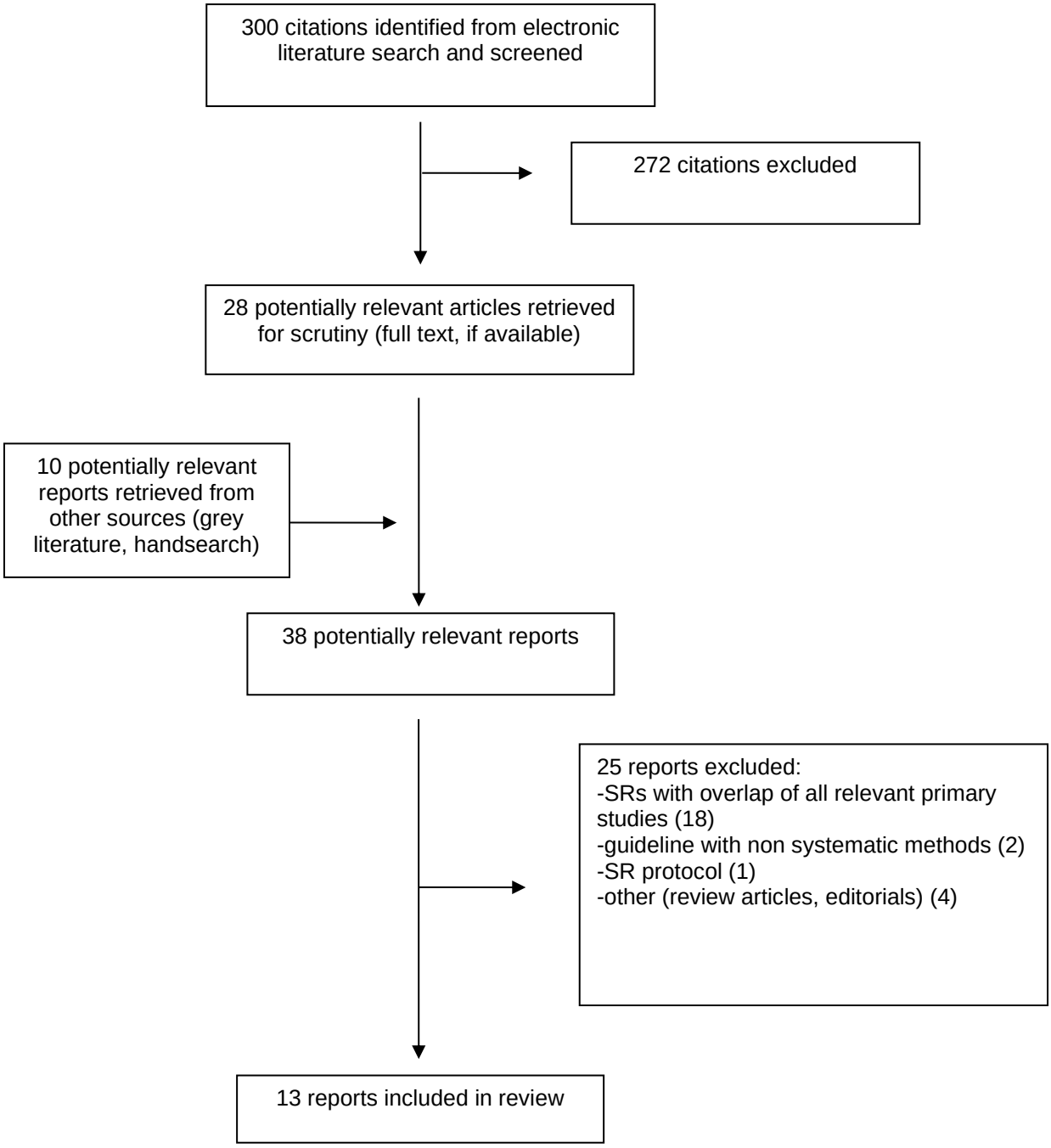
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies

Alt text: 300 citations were identified, 272 were excluded, while 28 electronic literature and 10 grey literature potentially relevant full text reports were retrieved for scrutiny. In total 13 reports are included in the review.



Appendix 2: Characteristics of Included Publications

Table 1: Characteristics of Included HTAs, Overview of Systematic Reviews, and Systematic Reviews

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
HEALTH TECHNOLOGY ASSESSMENT				
Syful et al. (2023)[13] Malaysia **Funding source:** Ministry of Health Malaysia	13 studies in total published up to April 2023; 6 SRs, 3 RCTs and 2 non-randomized studies relevant to the present review. To reduce overlap, 2 RCTs and 2 non-randomized studies are reported in this review	Men, 18 years and older with vasculogenic, general, or diverse pathogeneses (psychogenic, organic and mixed) ED N in relevant studies = 251	**Intervention:** Li-ESWT **Comparator**: pharmacologic therapy, medication refractory patients or in those with intolerable side effects, medical devices, combination therapy, placebo (sham)	Outcomes: Effectiveness (e.g., IIEF-EF score, EHS, Treatment satisfaction), Safety, Organizational issues (e.g., procedural time), Economic implications Follow-up: up to 6 months
OVERVIEW OF SYSTEMATIC REVIEWS				
Medrano-Sanchez (2024)[14] Spain **Funding source:** None	5 systematic reviews published up to June 2023; 5 relevant to the present review. All SRs have been evaluated for overlap of the SR and have either been excluded due to primary study overlap or have been reported separately in the current review.	Men with vascular-origin ED	**Intervention:** Li-ESWT **Comparator**: Placebo	Outcomes: Sexual function (i.e., IIEF-EF), Penile hardness at erection (EHS) Follow-up: NR
SYSTEMATIC REVIEWS				
Panunzio et al. (2024)[15] Italy **Funding source:** NR	7 studies in total published up to July 2023; 1 non-randomized study relevant to the present review	Men 18 years and older with primary organic ED N in relevant study = 60	**Intervention:** Platelet-rich plasma intracavernosal injections alone or in combination with other therapies **Comparator**: Pharma, ESWT, Placebo	Outcomes: IIEF-5, EHS, Self-esteem and relationship (SEAR), Adverse events Follow-up: 3 months
Bocchino et al. (2023)[16] Italy **Funding source:** None	52 studies in total published between 2012 and August 2022; 22 RCTs and 6 non-randomized studies relevant to the present review. No outcome data presented for comparator group, so	Men with ED (according to European Guideline diagnostic criteria)	**Intervention:** Li-ESWT **Comparator**: NR	Outcomes: Efficacy (e.g., IIEF-5, EHS, peak systolic velocity), Safety (adverse events) Follow-up: up to 12 months

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
	no outcome data has been presented in the current review.			
Rosenberg et al. (2023)[17] USA Funding source: Internal salary support for members of investigator team, Minneapolis Veterans' Administration Healthcare System, Urology Section. External support: None	14 RCTs in total published up to September 23, 2022; 2 RCTs relevant to the present review	Men 18 years and older with a clinical diagnosis of Peyronie's disease N in relevant studies = 136	**Intervention:** Oral therapies, injection therapies, mechanical therapies **Relevant Intervention**: Mechanical therapy (i.e., ESWT) **Comparator:** Placebo, no treatment	Outcomes: Patient-reported ability to have intercourse, Quality of life, Treatment-related adverse effects, Penile curvature, Discontinuation of treatment, Subjective patient-reported change in penile curvature, Improvement in penile pain Follow-up: up to 26 weeks after end of treatment
Sighinolfi et al. (2022)[18] Italy Funding source: None	9 studies in total up to April 2022; 3 RCTs, 3 non-randomized studies relevant to present review	Patients with postprostatectomy ED N in relevant studies = 583	**Intervention:** Li-ESWT with or without pharmacological therapy **Comparator:** Delayed Li-ESWT, Pharmacological therapy, Sham, No treatment	Outcomes: IIEF-5 score, EHS, Sexual bother score from Expanded Prostate Cander Index Composite, Sexual function score from Expanded Prostate Cander Index Composite, Sexual Health Inventory for Men (not reported in relevant studies) Follow-up: up to 12 months
Yao et al. (2022)[19] China Funding source: National Nature Science Foundation of China and Taishan Scholars Program of Shandong Province	16 studies in total published between July 2011 to June 2021; 16 RCTs relevant to present review	Men with ED, with or without complications, any severity of ED, PDE5i responders and non-responders	**Intervention:** Li-ESWT with or without pharmacological therapy **Comparator:** Sham, pharmacological therapy, no treatment	Outcomes: IIEF, EHS, Sexual Encounter Profile (SEP) Follow-up: up to 6 months
Marchioni et al. (2020)[20] Italy	11 studies in total published up to November 2019; 0	Patients with ED after robot-assisted radical prostatectomy	**Intervention:** conservative (e.g. pharma, topical alprostadil, vacuum	Outcomes: Erectile function recovery after conservative treatment,

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Funding source: NR	relevant to the present review		device, hyperbaric therapy, Li-ESWT) and surgical treatments (e.g., penile prosthesis) **Relevant intervention**: Li-ESWT **Comparator:** NR	Sexual function after prosthesis implant Follow-up: up to 24 months
Sokolakis et al. (2019)[21] Germany Funding source: NR	28 studies in total published between January 2010 to September 2018; 14 RCTs relevant to the present review (however, 1 RCT was retracted for plagiarized data).	Men with ED, including vasculogenic ED, men with ED after nerve sparing radical cystectomy, and kidney transplant recipients. Responders and non-responders to PDE5i	**Intervention:** Li-ESWT **Comparator:** Sham, different protocol of Li-ESWT	Outcomes: IIEF, EHS, Sexual Encounter Profile Follow-up: up to 12 months

ED = erectile dysfunction; EHS = Erection Hardness Score IIEF-EF = International Index of Erectile Function-Erectile Function; Li-ESWT = low-intensity extracorporeal shockwave therapy; NR = not reported; PDE5i = phosphodiesterase-5 inhibitors; RCT = randomized controlled trial

Table 2: Characteristics of Included Guidelines

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
Salonia 2024[22]						
Intended Users: NR **Target Population**: Male sexual dysfunction, male infertility, and male hypogonadism	Screening, diagnosis, treatment, and/or management for late-onset hypogonadism, male sexual dysfunction (e.g., erectile dysfunction, premature ejaculation, other ejaculatory disorders), sexual desire, penile curvature, penile size abnormalities and dysmorphophobia, priapism, male infertility.	There are no details within this guideline around what outcomes were considered.	The European Association of Urology uses a staged approach to evidence review. First searching for existing systematic reviews, then conducting a new systematic review, if required, using gold standard methods.	Dependent on the study design, for example, the Cochrane risk of bias tool version 1 for randomized controlled trials	Consensus, using a recommendations worksheet considering the overall certainty of the evidence, the balance of benefits and harms, differences in patient values and preferences, or uncertainty about them, and uncertainty about costs and resource utilization	External review (no information on who provided this review)
Domes 2021[5]						
Intended Users: learners and practitioners **Target Population**: males with erectile dysfunction	Patient assessment including testing (e.g., laboratory) and treatment options (e.g., Li-SWT, pharmacological, vacuum and pump device)	Improvements in erectile function (measured by the International Index of Erectile Function [IIEF]-EF score), Quality of life, and Adverse events	No description provided.	GRADE approach was used to evaluate the certainty in the evidence.	GRADE Evidence to Decision framework, considering the desirable effects, undesirable effects, balance of the effects (net benefit), certainty in estimates of effect, patients' values and preferences, resources required, cost-effectiveness, equity, feasibility, and acceptability	NR
Chung 2021[23]						
Intended Users: NR **Target Population**: Men	Li-ESWT and LIPUS (low intensity pulsed ultrasound)	Effectiveness, Treatment protocols, Patient selection, Safety	Available literature identified in Medline and Embase. Literature review, analyzed and	"The quality of evidence was graded on the Oxford Centre for Evidence-Based	Clinical findings were internally discussed, and the quality of evidence was graded. "Any disagreements were resolved by consensus	NR

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
with erectile dysfunction			summarizes, and then presented at a scientific meeting.	Medicine recommendations." (p. 2)	and the clinical principle was given when available data was insufficient or not suitable to draw conclusions." (p. 2)	
Capogrosso 2019[24]						
Intended users: NR **Target population**: Men with erectile dysfunction, Peyronie's disease, and chronic prostatitis/chronic pelvic pain syndrome	LISWT for erectile dysfunction, Peyronie's disease, and chronic prostatitis/chronic pelvic pain syndrome	Treatment efficacy (e.g., International Index of Erectile Function, Erection Hardness Scale), Treatment protocol, Clinical indications, Safety	Abstracts reviewed, then full text for those relevant. Relevant studies were analyzed and summarized after an interactive peer-review process of the panel. When the evidence from RCTs was not enough to draw conclusions for clinical practice, data from nonrandomized cohort studies were assessed.	Cochrane Risk of Bias tool was used to evaluate randomized controlled trials. The quality of evidence was graded by applying the Oxford Centre for Evidence-Based Medicine recommendation.	The level of evidence was according to the Oxford 2011 criteria and graded using the Oxford Centre for Evidence-Based Medicine recommendations. No recommendations were given when the available data were insufficient to draw conclusions. Disagreements were resolved by consensus.	NR

GRADE = Grading of Recommendations Assessment, Development, and Evaluation; Li-ESWT = low-intensity extracorporeal shockwave therapy; LISWT = low-intensity shockwave therapy

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of HTA, Overview of Systematic Reviews, and Systematic Reviews Using AMSTAR 2[9]

Strengths	Limitations
Health Technology Assessment	
Syful et al. (2023)[13]	
▪ Nine electronic databases were searched. Supplemental searching performed by reviewing the bibliographies of retrieved articles ▪ Elements of PICO were sufficiently described ▪ A PRISMA flow diagram was provided ▪ Risk of bias assessments are provided ▪ Elements of primary studies sufficiently described ▪ Source of funding for the review was reported ▪ Author declared competing interest (i.e., none)	▪ There was no statement that the review methods were established before the review conduct and no mention of a protocol ▪ One reviewer screening the titles and abstracts ▪ Only articles published in English were included ▪ Unclear how many reviewers extracted the data and performed critical appraisal of the included studies ▪ A list of excluded studies was not provided, but high-level reasons were provided in the PRISMA flow diagram ▪ Publication bias was not assessed ▪ Source of funding of the included primary studies not provided
Overview of Systematic Reviews	
Medrano-Sanchez (2024)[14]	
▪ Registration requested in PROSPERO ▪ Five electronic databases were searched ▪ Elements of inclusion were sufficiently described ▪ A PRISMA flow diagram was provided ▪ Two independent evaluators performed critical appraisal performed using AMSTAR. A third evaluator was available to resolve potential discrepancies ▪ Overlap of the primary studies in the systematic reviews is presented ▪ Elements of the included systematic reviews described ▪ Source of funding for the review was reported (i.e., none) ▪ Author declared conflicts of interest (i.e., none)	▪ Unclear how study selection was performed. They state “through the consensus of three evaluators” (p. 4) ▪ Two authors performed data extraction, however, there are no details on the exact process (e.g., dual independent) ▪ A list of excluded studies was not provided, but high-level reasons were provided in the PRISMA flow diagram ▪ Source of funding of the included systematic reviews not provided
Systematic Reviews	
Panunzio (2024)[15]	
▪ *A priori* published protocol available in PROSPERO	▪ Only English language publications included ▪ A list of excluded studies was not provided, but high-level reasons were provided in the PRISMA flow diagram

▪ Four electronic databases were searched. Additional searching of clinical trials registry and reference lists of relevant and recent systematic reviews ▪ Elements of PICO were sufficiently described ▪ Two independent reviewers screened titles, abstracts, and full text publications. Disagreements were resolved by discussion until consensus was reached ▪ Two reviewers extracted data, with discrepancies resolved by discussion until consensus was reached ▪ Risk of bias independently assessed by two reviewers ▪ A PRISMA flow diagram was provided ▪ Elements of primary studies sufficiently described ▪ Author declared conflicts of interest (i.e., none)	▪ Source of funding of the included primary studies not provided ▪ Source of funding of review not provided
Bocchino (2023)[16]	
▪ A PRISMA flow diagram was provided ▪ Two independent authors evaluated and extracted data. Disagreements in data extraction were resolved through discussions with a third investigator ▪ Elements of primary studies sufficiently described ▪ Source of funding for the review was reported (i.e., none) ▪ Author declared conflicts of interest (i.e., none)	▪ *A priori* exclusion of non-English literature is mentioned, however, there is no mention of a protocol or any other established methods for conduct ▪ Elements of PICO were not clearly reported, mostly around where restrictions were not placed ▪ Only PubMed was searched ▪ Only articles published in English were included ▪ No details around how study selection was performed ▪ A list of excluded studies was not provided, but high-level reasons were provided in the PRISMA flow diagram ▪ Risk of bias was not assessed ▪ Publication bias was not assessed ▪ Although the supplemental file reports on a per study basis which outcomes it reports, it is not presented in a user-friendly way to determine which studies contribute to the pooled analysis ▪ There are no descriptions of the comparators ▪ Etiologies of ED are combined in pooled results, with no subgroup analysis provided ▪ Peak velocity is reported as an outcome in the methods section, but there are no results. Adverse events are only reported narratively in the discussion section, with no reference to the studies ▪ Source of funding of the included primary studies not provided
Rosenberg (2023)[17]	
▪ *A priori* published protocol, with deviations from protocol reported	None

▪ Six electronic databases were searched. Supplemental searching of two trial registries, annual meeting proceedings, reference lists of retrieved included studies, contacted authors of included trials, contacted device manufacturers ▪ No restrictions on language ▪ Elements of PICO were sufficiently described ▪ A PRISMA flow diagram was provided ▪ Two reviewers independently screened records for inclusion (title and abstract screening and full text screening). Discrepancies resolved through consensus or 3rd reviewer ▪ Two reviewers independently performed data extraction. Discrepancies resolved through consensus or 3rd reviewer ▪ Risk of bias was performed independently by four reviewers (4 reviewers working in pairs) ▪ Elements of primary studies sufficiently described ▪ A list of excluded studies is provided ▪ Source of funding of the included primary studies provided ▪ Source of funding for the review was reported ▪ Publication bias would have been conducted, however, no analyses included 10 or more studies ▪ Author declared competing interest	
Sighinolfi (2022)[18]	
▪ Two databases searched, no other details around supplemental searching ▪ A PRISMA flow diagram was provided ▪ Elements of primary studies sufficiently described ▪ Risk of bias was performed independently by two authors ▪ Source of funding for the review was reported ▪ Author declared competing interest (i.e., none)	▪ There was no statement that the review methods were established before the review conduct and no mention of a protocol ▪ Elements of PICO not well described ▪ Only English language publications included ▪ Methodology of study selection not described ▪ Methodology of data extraction not described, just states that two authors extracted data ▪ A list of excluded studies was not provided, but high-level reasons were provided in the PRISMA flow diagram ▪ Source of funding of the included primary studies not provided
Marchioni (2020)[20]	
▪ Three databases searched (described as “such as”, so there may have been more) ▪ Elements of PICO were sufficiently described	▪ There was no statement that the review methods were established before the review conduct and no mention of a protocol ▪ Only English language publications included

▪ Two reviewers independently screened records for inclusion ▪ No description of full-text screening, however, they state "Discrepancies were solved by a third author" (p. 545) implying screening was done independently, in duplicate ▪ A PRISMA flow diagram was provided ▪ Elements of primary studies described ▪ Author declared competing interest (i.e., none)	▪ A list of excluded studies was not provided, but high-level reasons were provided in the PRISMA flow diagram ▪ Methodology of data extraction not described ▪ Risk of bias performed, however, there are no details on how this was done (e.g., dual independent) ▪ Source of funding of the included primary studies not provided ▪ Source of funding of review not provided
Yao (2020)[19]	
▪ Three databases searched. No details around supplemental searching ▪ No restriction on language of inclusion ▪ A PRISMA flow diagram was provided ▪ "All authors independently participated in the evaluation of each RCT and exchanged results." (p. 2). Conflicts resolved through discussion ▪ Author declared competing interest (i.e., none) ▪ Source of funding for the review was reported	▪ There was no statement that the review methods were established before the review conduct and no mention of a protocol ▪ Elements of PICO not well described ▪ Two reviewers independently read each article, although it is unclear if this was full text only and how title and abstract screening was performed ▪ "Two authors extracted data" (p. 2), no additional details ▪ A list of excluded studies was not provided, but high-level reasons were provided in the PRISMA flow diagram ▪ Elements of primary studies described (e.g., no details on participants comorbidities such as prostatectomy, no details on co-interventions such as pharmacotherapy) ▪ Risk of bias performed, however, there are no details on how this was done (e.g., dual independent) ▪ Source of funding of the included primary studies not provided
Sokolakis (2019)[21]	
▪ Five databases searched. Supplemental searching by looking at reference lists and at related citations in PubMed ▪ No restriction on language of inclusion ▪ Elements of PICO sufficiently described ▪ Reviewers independently screened titles/abstract and full text articles. Any discrepancies were discussed and consensus reached ▪ A PRISMA flow diagram was provided ▪ Reviewers independently extracted data using a data collection form that was developed *a priori* ▪ Reviewers independently assessed the risk of bias. Any discrepancies were discussed and consensus reached ▪ Author declared competing interest (i.e., none)	▪ There was no statement that the review methods were established before the review conduct and no mention of a protocol ▪ A list of excluded studies was not provided, but high-level reasons were provided in the PRISMA flow diagram ▪ Active treatment well described, however, participants and comparator (i.e., sham) not well described ▪ Source of funding of the included primary studies not provided ▪ Source of funding of review not provided

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; PICO = Participants, Intervention, Comparator, Outcomes

Table 4: Strengths and Limitations of Guidelines Using AGREE II[11]

Item	Salonia (2024)[22]	Domes (2021)[5]	Chung (2021)[23]	Capogrosso (2019)[24]
Domain 1: scope and purpose				
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes	Yes	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes	Yes	Yes
Domain 2: stakeholder involvement				
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes	Yes, based on author affiliations	Yes, based on author affiliations
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes, in Development handbook[a]	Unclear, not reported	Unclear, not reported	Unclear, not reported
6. The target users of the guideline are clearly defined.	No, no explicit statement	Yes	No, no explicit statement	Yes, those in clinical practice
Domain 3: rigour of development				
7. Systematic methods were used to search for evidence.	Yes, in SR handbook[b]	Unclear, not well reported	Unclear, not well reported	Yes
8. The criteria for selecting the evidence are clearly described.	No	Unclear, not reported	Unclear, not well reported	Yes
9. The strengths and limitations of the body of evidence are clearly described.	No	Yes (Appendix)	No	Yes
10. The methods for formulating the recommendations are clearly described.	Yes, in SR handbook[b]	Yes	Yes	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes, in Development handbook[a]	Yes	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes	Yes	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	Yes, in Development handbook[a]	Unclear, not reported	Unclear, not reported	Unclear, not reported
14. A procedure for updating the guideline is provided.	Yes, in Development handbook[a]	No	No	No
Domain 4: clarity of presentation				

Item	Salonia (2024)[22]	Domes (2021)[5]	Chung (2021)[23]	Capogrosso (2019)[24]
15. The recommendations are specific and unambiguous.	Yes	Yes	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes	Yes	Yes
Domain 5: applicability				
18. The guideline describes facilitators and barriers to its application.	Yes	Yes (Appendix)	No	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes	No	No	No
20. The potential resource implications of applying the recommendations have been considered.	Yes, in Development handbook[a]	Yes	Yes, lack of published data on cost-effectiveness highlighted	No
21. The guideline presents monitoring and/or auditing criteria.	Yes, in Development handbook[a]	No	No	No
Domain 6: editorial independence				
22. The views of the funding body have not influenced the content of the guideline.	Yes	Unclear, not reported	Unclear, not reported	Yes, no funding was received
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes	Yes	Yes

AGREE II = Appraisal of Guidelines for Research and Evaluation II; SR = systematic review

[a] The European Association of Urology have a Guidelines Development Handbook which provides a detailed approach to how their guidelines are developed (uroweb.org/eau-guidelines/methodology-policies)

[b] The European Association of Urology have a Systematic Review Handbook which provides a detailed methodological approach to how the evidence base is identified (uroweb.org/eau-guidelines/methodology-policies).

Appendix 4: Main Study Findings

Table 5: Summary of Findings by Outcome — International Index of Erectile Function-Erectile Function (also called IIEF-5): Mean (SD) score

Study	Details (e.g., timepoint, population)	Intervention	Comparator	Difference between groups
ESWT vs Sham				
Syful (2023)[13]				
Ong 2022, RCT	1 month follow-up	14.1 (NR)	9.3 (NR)	p < 0.001
Ong 202, RCT	3 months follow-up	14.9 (NR)	8.6 (NR)	p < 0.001
Ong 202, RCT	6 months follow-up	14.2 (NR)	7.9 (NR)	p < 0.001
Yao (2022)[19]	1-month follow-up, all ED severities, 13 RCTs	Li-ESWT vs control: MD = 3.18 (95% CI 1.38 to 4.98), p = 0.0005, I^2 = 94%		
Yao (2022)[19]	3-month follow-up, all ED severities, 8 RCTs	Li-ESWT vs control: MD = 3.01 (95% CI 2.04 to 3.98), p < 0.00001, I^2 = 57%		
Yao (2022)[19]	6-month follow-up, all ED severities, 4 RCTs	Li-ESWT vs control: MD = 3.20 (95% CI 2.49 to 3.92), p < 0.00001, I^2 = 8%		
Yao (2022)[19]	any follow-up, all severities (baseline), 15 RCTs	Li-ESWT vs control: MD = 4.02 (95%CI 2.74 to 5.30), p < 0.00001, I^2 = 87%		
Yao (2022)[19]	any follow-up, severe ED at baseline, 6 RCTs	Li-ESWT vs control: MD = 4.07 (95%CI 0.49 to 7.64), p = 0.03, I^2 = 95%		
Yao (2022)[19]	any follow-up, moderate ED at baseline, 6 RCTs	Li-ESWT vs control: MD = 4.24 (95%CI 2.88 to 5.59), p < 0.00001, I^2 = 47%		
Yao (2022)[19]	any follow-up, mild ED at baseline, 3 RCTs	Li-ESWT vs control: MD = 3.87 (95%CI 3.37 to 4.36), p < 0.00001, I^2 = 0%		
Sokolakis (2019)[21]	last follow-up, all populations, 8 RCTs	Li-ESWT vs sham: MD = 3.71 (95%CI 0.29 to 7.14), p = 0.03, I^2 = 98%		
Sokolakis (2019)[21]	last follow-up, PDE5i-Responders, 5 RCTs	Li-ESWT vs sham: MD = 4.33 (95%CI -0.90 to 9.55), p = 0.10, I^2 = 98%		
Sokolakis (2019)[21]	last follow-up, PDE5i-non-Responders, 1 RCT	Li-ESWT vs sham: MD = 5.00 (95%CI 4.01 to 5.99), p < 0.00001		
Sokolakis (2019)[21]	last follow-up, PDE5i-Responders, kidney transplant recipients, 1 RCT	Li-ESWT vs sham: MD = 0.69 (95%CI -4.01 to 5.39), p = 0.77		
Sokolakis (2019)[21]	last follow-up, post radical cystectomy (with bilateral nerve-sparing) ED, 1 RCT	Li-ESWT vs sham: MD = 1.80 (95%CI 1.06 to 2.54), p < 0.00001		
ESWT vs Pharmacological therapy				
Syful (2023)[13]				
Zanaty 2022, RCT	12 weeks follow-up	17.64 (4.01)	15.72 (3.6)	NR

Study	Details (e.g., timepoint, population)	Intervention	Comparator	Difference between groups
Lei 2021, observational study	3 months following initiation of treatment	21.52 (NR)	21.26 (NR)	p > 0.05
Wang 2023, observational study	4 weeks after final session	16.3 (5.5)	18.3 (6.5)	p > 0.05
Sighinolfi (2022)[18]				
Karakose 2021, observational study	3 months follow-up	7 (2.2)	7 (2.8)	NR
Karakose 2021, observational study	6 months follow-up	13 (3.3)	7 (2.9)	NR
Karakose 2021, observational study	12 months follow-up	18 (3)	9 (3.4)	NR
ESWT vs Platelet-Rich Plasma				
Panunzio (2023)[15]	3 months, 1 observational study (Sajjad 2021)	20.21 (NR)	21.26 (NR)	NR

CI = confidence interval; ED = erectile dysfunction; Li-ESWT = low-intensity extracorporeal shockwave therapy; MD = mean difference; NR = not reported; RCT = randomized controlled trial; SD = standard deviation

Table 6: Summary of Findings by Outcome — International Index of Erectile Function-Erectile Function (also called IIEF-5): Proportion achieving MCID

Study	Details (e.g., timepoint, population)	Intervention	Comparator	Difference between groups
ESWT vs Sham				
Sokolaski (2019)[21]	Last follow-up, all populations, 7 RCTs	228/316	64/240	OR = 8.54 (95%CI 2.64 to 27.63), p = 0.0003, I^2 = 86%
Sokolaski (2019)[21]	Last follow-up, PDE5i-Responders, 4 RCTs	128/189	32/137	OR = 7.26 (95%CI 1.44 to 36.54), p = 0.02, I^2 = 88%
Sokolaski (2019)[21]	Last follow-up, PDE5i non-Responders, 1 RCT	61/75	5/50	OR = 39.21 (95%CI 13.17 to 116.79), p < 0.0001
Sokolaski (2019)[21]	Last follow-up, PDE5i-Responders, kidney transplant recipients, 1 RCT	7/10	1/10	OR = 21.00 (95%CI 1.78 to 248.1), p = 0.02
Sokolaski (2019)[21]	Last follow-up, post radical cystectomy (with bilateral nerve-sparing) ED, 1 RCT	32/42	26/43	OR = 2.09 (95%CI 0.82 to 5.34), p = 0.12
ESWT vs Pharmacological therapy				
Syful (2023)[13]	3 months following initiation of treatment, 1 observational study (Lei 2021)	52.2%	59.4%	p > 0.05
ESWT vs ESWT (different protocol)				
Sokolakis (2019)[21]	1 RCT (Fojecki 2018), IIEF-EF score >5	54%	47%	NS
Sokolakis (2019)[21]	1 RCT (Kalyvianakis 2018), MCID	62%	71%	NR

MCID = minimal clinically important difference; RCT = randomized controlled trial; SD = standard deviation; NR = not reported; NS = not significant

Table 7: Summary of Findings by Outcome — International Index of Erectile Function-Erectile Function (also called IIEF-5): Increase since baseline

Study	Details (e.g., timepoint, population)	Intervention	Comparator	Difference between groups
ESWT vs ESWT (different protocol)				
Sokolakis (2019)[21]	1 RCT (Kalyvianakis 2018), protocol A vs protocol B	+3.1	+5.1	NR
Sokolakis (2019)[21]	1 RCT (Kalyvianakis 2018), protocol A + C vs protocol B + D	+1.8	+1.7	NR
Sokolakis (2019)[21]	1 RCT (Katz 2018), protocol A vs protocol B	No significant difference from baseline	+4.2	NR

NR = not reported; RCT = randomized controlled trial

Table 8: Summary of Findings by Outcome — Erectile Hardness Scale (EHS): Mean (SD) score

Study	Details (e.g., timepoint, population)	Intervention	Comparator	Difference between groups
ESWT vs Sham				
Syful (2023)[13]				
Ong 2022, RCT	1 month follow-up	2.4 (NR)	1.8 (NR)	p = 0.001
Ong 2022, RCT	3 months follow-up	2.7 (NR)	1.7 (NR)	p < 0.001
Ong 2022, RCT	6 months follow-up	2.7 (NR)	1.6 (NR)	p < 0.001
ESWT vs Pharmacological therapy				
Syful (2023)[13]				
Zanaty 2022, RCT	12 weeks follow-up	3.2 (0.76)	3.1 (0.69)	NR
Lei 2021, observational study	3 months following initiation of treatment	NR	NR	p > 0.05
ESWT vs Platelet-Rich Plasma				
Panunzio (2023)[15]	3 months, 1 observational study (Sajjad 2021)	3.04 (NR)	3.89 (NR)	NR

RCT = randomized controlled trial; SD = standard deviation; NR = not reported

Table 9: Summary of Findings by Outcome — Erectile Hardness Scale (EHS): Improvement in EHS score (≥3)

Study	Details (e.g., timepoint, population)	Intervention	Comparator	Difference between groups
ESWT vs Sham				
Yao (2022)[19]	8 RCTs, Improvement to ≥3	Li-ESWT vs control: OR = 5.07 (95% CI 1.78 to 14.44), p = 0.002, I^2 = 80%		
Sokolakis (2019)[21]	Last follow-up, all populations, 8 RCTs	186/363	61/273	OR = 4.35 (95%CI 1.82 to 10.37), I^2 = 69%, p = 0.002
Sokolakis (2019)[21]	Last follow-up, PDE5i-Responders, 5 RCTs	129/274	30/202	OR = 5.02 (95%CI 1.51 to 16.73), I^2 = 75%, p = 0.003
Sokolakis (2019)[21]	Last follow-up, PDE5i non-Responders, 1 RCT	20/37	1/18	OR = 20.00 (95%CI 2.41 to 166.27), p = 0.006
Sokolakis (2019)[21]	Last follow-up, PDE5i-Responders, kidney transplant recipients, 1 RCT	5/10	4/10	OR = 1.50 (95%CI 0.26 to 8.82), p = 0.65
Sokolakis (2019)[21]	Last follow-up, post radical cystectomy (with bilateral nerve-sparing) ED, 1 RCT	32/42	26/43	OR = 2.09 (95%CI 0.82 to 5.34), p = 0.12
ESWT vs Pharmacotherapy				
Sighinolfi (2022)[18]				
Jang 2022, observational study	3 weeks follow-up	14.6% (n=41)	0%	NS
Jang 2022, observational study	1 month follow-up	12.2% (n=41)	5.1% (n=39)	NS
Jang 2022, observational study	3 months follow-up	14.6% (n=41)	5.1% (n=39)	NS
Jang 2022, , observational study	6 months follow-up	29.3% (n=41)	10.3% (n=39)	p = 0.034
ESWT vs ESWT (different protocol)				
Sokolakis (2019)[21]	1 RCT (Fojecki), group A vs group B	34%	24%	NS

RCT = randomized controlled trial; SD = standard deviation; NR = not reported; NS = not significant

Table 10: Summary of Findings by Outcome — Other patient-related outcomes

Study	Details (e.g., timepoint, population)	Intervention	Comparator	Difference between groups
ESWT vs Sham				
Sexual encounter profile (SEP)				
Yao (2022)[19]	3 RCTs, follow-up NR, Answered Yes to question 2	77/112	55/88	OR = 1.27 (95% CI 0.70 to 2.30), p = 0.43, I^2 = 78%
Yao (2022)[19]	3 RCTs, follow-up NR, Answered Yes to question 3	48/112	17/88	OR = 4.24 (95%CI 0.67 to 26.83), p = 0.13, I^2 = 84%
Sexual bother score from Expanded Prostate Cancer Index Composite mean (SD) score				
Sighinolfi (2022)[18]	6 months[a,b], 1 observational study (Inoue 2020)	46.3 (NR)	54.2 (NR)[c]	NR
Sexual function score from Expanded Prostate Cancer Index Composite mean (SD) score				
Sighinolfi (2022)[18]	6 months[b], 1 observational study (Inoue 2020)	19.2 (NR)	17.9 (NR)[c]	NR
Quality of life				
Rosenberg (2023)[17]	1 RCT (Palmieri 2009)	22.68 (4.5)	19.62 (4.5)	MD = 3.06 (95%CI 1.30 to 4.82)
Treatment-related adverse effects				
Rosenberg (2023)[17]	2 RCTs (Chitale 2010, Palmieri 2009), follow-up NR	6/66	2/70	NR[d]
Discontinuation from treatment				
Rosenberg (2023)[17]	2 RCTs (Chitale 2010, Palmieri 2009), follow-up NR	0/66	0/70	NR[d]
ESWT vs Pharmacological therapy				
Self-esteem and relationship (SEAR)				
Syful (2023)[13]	3 months following initiation of treatment, 1 non-randomized study (Lei 2021)	NR	NR	p > 0.05
ESWT vs Platelet-Rich Plasma				
Self-esteem and relationship (SEAR) mean (SD) score				
Panunzio (2023)[15]	3 months, 1 observational study (Sajjad 2021)	45.25 (NR)	48.33 (NR)	NR
Discontinuation from treatment				
Panunzio (2023)[15]	1 observational study	0/30	0/30	
ESWT vs ESWT (different protocol)				
Sexual encounter profile (SEP)				

Study	Details (e.g., timepoint, population)	Intervention	Comparator	Difference between groups
Sokolakis (2019)[21]	1 RCT, protocol A vs protocol B, Question 3	47.4%	65.2%	NR
Sokolakis (2019)[21]	1 RCT, protocol A + C vs protocol B + D, Question 3	61.9%	68.4%	NR

MD = mean difference; SD = standard deviation; NR = not reported

[a] 3-month outcome data also reported, but not extracted

[b] 9- and 12-month data also reported, but both groups had received Li-ESWT at these timepoints

[c] This group received delayed treatment with Li-ESWT 6 months after radical prostatectomy. There is a 3rd group who did not receive Li-ESWT (data not extracted as they are similar to delayed ESWT group at 6 months).

[d] The pooled results includes a study that is not relevant to the present review, therefore the pooled results was not extracted

Table 11: Summary of Recommendations in Included Guidelines

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
Salonia 2024[22]	
Use low-intensity shockwave treatment (Li-SWT) with/without PDE5Is in patients: • with mild vasculogenic ED; • as an alternative therapy in well-informed patients who do not wish to have or are not suitable for oral vasoactive therapy; • who are vasculogenic ED patients who are poor responders to PDE5Is Single-arm trials, randomized controlled trials, and a meta-analysis formed the evidence base. However, authors of the meta-analysis outlined that the level of evidence was low, therefore, careful interpretation of the results is required.	Quality of evidence: not reported Strength rating: Weak
Domes 2021[5]	
We suggest against the use of low-intensity shockwave therapy for patients with erectile dysfunction. The Panel reviewed 7 RCTs comparing Li-SWT to sham treatment. Combining these 7 RCTs there is a statistically significant mean increase in the IIEF-EF score, however, 3 RCTs were high risk of bias. When removing these studies from the meta-analysis, the mean increase in the IIEF-EF score was no longer statistically significant.	Quality of evidence: low levels of certainty in evidence Strength rating: Conditional recommendation
Chung 2021[23]	
"There is a need to define which subgroup of ED population is best suited and the LIESWT protocols including modality of shock waves energy, emission frequency and total energy delivery. The patient selection appears paramount to treatment success and patients with mild-moderate ED, younger age group, those with minimal cardiovascular comorbidities, and absence of diabetes or cavernous nerve are likely going to report high EF recovery and spontaneous erection." (p. 4) Data from systematic reviews and randomized controlled trials were used for this recommendation. The guideline authors state that the outcomes should be interpreted with some caution due to heterogeneity and methodological flaws in the studies.	Level 2; Grade B
"LISWT improves EF scores and penile hemodynamic parameters in men with vasculogenic ED." (p. 5) "Published literature suggests these positive effects of LIESWT to last up to 12 months after treatment." (p. 5) Most published studies do not extend beyond 2 years follow-up, so there is some uncertainty of the clinical long-term significance of this improvement.	Level 1; Grade B Level 2; Grade B
"The clinical adoption of Li-ESWT as an effective treatment option should be restricted to men with mild-moderate vasculogenic ED, either responder or non-responders to PDE5is, and ideally performed in the high specialized centres with documented experience with this type of therapy." (p. 5) This recommendation is supported by multiple systematic reviews that reported on Index of Erectile Function (IIEF) and erectile hardness scores (EHS).	Level 2; Grade B
"LISWT is a safe and well-tolerated procedure without clinically significant adverse events." (p. 6)	Level 1; Grade A

Treatment-related adverse events and drop-out rates due to treatment-related adverse events have been published in clinical trials and systematic reviews.	
Capogrosso 2019[24]	
"Patient-reported outcomes (IIEF, EHS): Current evidence is promising but is still controversial; therefore, a clear clinical recommendation of LISWT for ED cannot be made, and more high-quality studies are needed." (p. 1492) 11 RCTs were identified, but due to high risk of bias, 7 RCTs comparing LISWT to sham control were considered by the committee to assess treatment efficacy. Additionally, 5 meta-analyses were identified, 3 with heterogeneous populations, making it difficult to interpret the results on erectile function outcomes.	Not applicable
"Penile hemodynamics: LISWT significantly improves penile hemodynamic parameters of patients with vasculogenic ED. However, the clinical long-term significance of this improvement is uncertain." (p. 1492) Three sham-controlled trials were identified, all showing a significant improvement in penile blood flow in the actively treated group compared to the control group.	Level 2; Grade C
"Effect endurance: Current data suggest a variable effect of LISWT on EF up to 12 months after treatment. More data are needed to assess the longer-term effects of LISWT." (p. 1492) All studies suffer from short follow-up. One randomized controlled trial reported results at 6 months follow-uup and 1 single-arm cohort study reported 2-year follow-up data.	Level 2; Grade C
"Energy source and type of SW (linear vs focused): Currently, there are no studies comparing the 2 treatment methods. Further research should address the possible differences between focused and linear SW." (p. 1492) Only 2 RCTs used a linear generator, and 1 meta-analysis had a sub-group analysis according to type of generator used. Overall, current evidence is too limited to draw final conclusions on the best shockwave generator.	Not applicable
"There are only few data comparing different treatment protocols with the same SW generator; therefore, a specific protocol cannot be suggested." (p. 1492) Treatment protocols vary widely across the randomized controlled trials, in term of either energy flux density, number of sessions, and length of treatment. No studies directly compared different protocols. Four meta-analyses provided varied results.	Not applicable
"LISWT for patients with vasculogenic ED, either treatment naïve, responders or non-responders to phosphodiesterase type 5 inhibitors (PDE5is), shows encouraging results, but unambiguous evidence for efficacy is lacking, pooled effect size is modest, and evidence quality is low. Patients should be informed about the conflicting results regarding efficacy of this treatment when discussing LISWT." (p. 1492) Randomized controlled trials included vasculogenic ED with mild to severe levels, and only 1 trial included non-responders to PDE5 with another trial including both responders and non-responders. Two meta-analyses showed significant improvement in those with mild ED, with the use of PDE5 increasing the improvement. One of the 2 meta-analyses reported improvement in those with severe ED.	Level 2; grade D
"Safety: LISWT is a safe and well-tolerated procedure without clinically significant adverse events." (p. 1492) No adverse events have been reported in sham-controlled trials or single-arm cohort studies (referencing 12 studies).	Level 1; Grade A

ED = erectile dysfunction; EF = Erectile Function' IIEF-EF = International Index of Erectile Function-Erectile Function; Li-SWT = low-intensity shockwave therapy; PDE5 = phosphodiesterase type 5 inhibitors

Appendix 5: Overlap Between Included Systematic Reviews

Table 12: Overlap in Relevant Primary Studies Between Included HTA and Systematic Reviews

Primary study citation	Syful 2023	Sighinolfi 2022	Sokolakis 2019	Yao 2022
Baccaglini W, et al. J Sex Med 2019; 17(4); 688-94.	Θ	Yes	Θ	Yes
Fojecki GL, et al. J Sex Med 2017; 14: 106–12.	Θ	Θ	Yes	Yes
Kalyvianakis D, et al. J Sex Med 2017;14:891–97.	Θ	Θ	Yes	Yes
Kitrey ND. J Urol 2016; 195:1550–55.	Θ	Θ	Yes	Yes
Ladegaard PBJ, et al. Sex Med 2021; 9(3): 100338.	Θ	Yes	Θ	Yes
Olsen AB, et al. Scand J Urol. 2015;49: 329-33.	Θ	Θ	Yes	Yes
Shendy WS, et al. Andrologia 2021; 53(4): e13997.	Yes	Θ	Θ	Yes
Srini VS, et al. Can J Urol. 2015; 22: 7614-22.	Θ	Θ	Yes	Yes
Vardi Y, et al. J Urol 2012; 187: 1769-75.	Θ	Θ	Yes	Yes
Yamacake KGR, et al. Int J Impot Res 2019; 31:195-203.	Θ	Θ	Yes	Yes
Yee CH, et al. Int JUrol. 2014; 21:1041-5.	Θ	Θ	Yes	Yes
Zewin TS, et al. Int Urol Neph 2018; 50(11): 2007-14.	Θ	Yes	Yes	Yes

Appendix 6: References of Potential Interest

Randomized Controlled Trials

Li-ESWT vs sham

Kalyvianakis D, Mykoniatis I, Pyrgidis N, Kapoteli P, Zilotis F, Hatzichristou D. The effect of combination treatment with low-intensity shockwave therapy and daily tadalafil on severe erectile dysfunction: a double-blind, randomized, sham-controlled clinical trial. J Sex Med. 2024 May 28;21(6):533-538.

Kalyvianakis D, Mykoniatis I, Pyrgidis N, et al. The Effect of Low-Intensity Shock Wave Therapy on Moderate Erectile Dysfunction: A Double-Blind, Randomized, Sham-Controlled Clinical Trial. J Urol. 2022 08;208(2):388-395.

Motil I, Macik D, Sramkova K, Jarkovsky J, Sramkova T. Linear Low-Intensity Extracorporeal Shockwave Therapy as a Method for Penile Rehabilitation in Erectile Dysfunction Patients after Radical Prostatectomy: A Randomized, Single-Blinded, Sham-Controlled Clinical Trial. Urol Int. 2022;106(10):1050-1055.

Li-ESWT with vacuum device vs Li-ESWT vs Vacuum device

Tao R, Chen J, Wang D, et al. The Efficacy of Li-ESWT Combined With VED in Diabetic ED Patients Unresponsive to PDE5is: A Single-Center, Randomized Clinical Trial. Front Endocrinol (Lausanne). 2022;13:937958.

ESWT vs Exercise vs Combine ESWT and exercise

Salama AB, Abdrabo MS, Abouelnaga WA. Effect of physical exercise combined with shockwave therapy on erectile dysfunction in diabetic patients. Arch Med Sci. 2023;19(5):1207-1213.

Energy flux density and frequency of sessions

Kalyvianakis D, Mykoniatis I, Memmos E, Kapoteli P, Memmos D, Hatzichristou D. Low-intensity shockwave therapy (LiST) for erectile dysfunction: a randomized clinical trial assessing the impact of energy flux density (EFD) and frequency of sessions. Int J Impot Res. 2020 May;32(3):329-337.

Radial wave

Sandoval-Salinas C, Saffon JP, Martinez JM, Corredor HA, Gallego A. Are Radial Pressure Waves Effective for the Treatment of Moderate or Mild to Moderate Erectile Dysfunction? A Randomized Sham Therapy Controlled Clinical Trial. J Sex Med. 2022 05;19(5):738-744.

Non-Randomized Studies

Dell'Atti L, Slyusar V, Cambise C. Multimodal treatments based on Tadalafil during acute phase of Peyronie's disease: experience at two referral academic centers. Ir J Med Sci. 2024 Oct;193(5):2301-2306.

Eryilmaz R, Kaplan S, Aslan R, Demir M, Taken K. Comparison of focused and unfocused ESWT in treatment of erectile dysfunction. Aging Male. 2020 Sep;23(3):206-209.

Ghahhari J, De Nunzio C, Lombardo R, et al. Shockwave Therapy for Erectile Dysfunction: Which Gives the Best Results? A Retrospective National, Multi-Institutional Comparative Study of Different Shockwave Technologies. Surg Technol Int. 2022 May 19;40:213-218.

Trishch VI, Mysak AI, Trishch AI, Mandzii AP. Assessment of the treatment effectiveness of men with mild and medium degree of erectile dysfunction. Pol Merkuriusz Lek. 2024;52(1):79-86.

Zasieda Y. Combined Treatment with Focused Low-Intensity Shock-Wave Therapy and Androgen-Stimulation Therapy in Men with Corporal Veno-Occlusive Erectile Dysfunction on the Background of Hypogonadotropic Hypogonadism. Georgian Med News. 2020 Oct(307):49-53.

Guidelines and Recommendations

Guideline published prior to 2019

American Urological Association (AUA). Erectile dysfunction: AUA guideline. 2018. https://www.auanet.org/guidelines-and-quality/guidelines/erectile-dysfunction-(ed)-guideline

Additional References

Systematic Review Protocol

Ergun O, Kim K, Kim MH, Hwang EC, Blair Y, Gudeloglu A, Parekattil S, Dahm P. Low‐intensity shockwave therapy for erectile dysfunction [protocol]. Cochrane Database Syst Rev. 2023 Sep 20;2023(9):CD013166. doi: 10.1002/14651858.CD013166.pub2. PMCID: PMC10510023. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013166.pub2/full

Systematic Review with Questionable ED among participants in primary studies

Man L, Li G. Low-intensity Extracorporeal Shock Wave Therapy for Erectile Dysfunction: A Systematic Review and Meta-analysis. Urology. 2018 Sep; 119:97-103. PubMed: PM28962876

Guideline with non-systematic methodology to identify included studies

Liu JL, Chu KY, Gabrielson AT, et al. Restorative Therapies for Erectile Dysfunction: Position Statement From the Sexual Medicine Society of North America (SMSNA). Sex. 2021 Jun;9(3):100343. PubMed: PM34000480

Schoofs E, Fode M, Capogrosso P, Albersen M; for the European Association of Urology Young Academic Urologists (EAU - YAU) Men's Health Group. Current guideline recommendations and analysis of evidence quality on low-intensity shockwave therapy for erectile dysfunction. Int J Impot Res. 2019 May;31(3):209-217. doi: 10.1038/s41443-019-0132-0. Epub 2019 Mar 25. PMID: 30911110.