TECHNOLOGY REVIEW (MINI-HTA)

EXTRACORPOREAL SHOCKWAVE THERAPY FOR THE TREATMENT OF ERECTILE DYSFUNCTION

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
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EXECUTIVE SUMMARY

Background

At present, treatment of erectile dysfunction (ED) mainly includes a step-wise method to modify risk factors, optimise the medical comorbidities, and to carry out medical treatments like vasoactive agents given through cavernous body and phosphodiesterase type 5 inhibitors (PDE5i) administered orally; besides, a penile prosthesis may also be implanted in advanced cases. While many patients are satisfied with these treatments, others are not due to the poor efficacy or inability to use them. Furthermore, the above therapeutic means mainly aim to enhance erectile function but do not address the pathophysiological factors. Hence, shockwave therapy has been suggested as an alternative. The clinical term for this treatment used by urologists is low-intensity extracorporeal shockwave therapy (LI-ESWT). This therapy involves applying shockwaves to the penile shaft at a specified energy setting for a predetermined number of shocks per minute and for a set treatment duration and number of treatments. While its mechanism of action is still not completely elucidated, the low-intensity energy from shockwave therapy stimulates new blood vessel growth through a process called angiogenesis. This increases penile blood flow, which may improve erectile function. Although the number of systematic reviews/ meta-analyses is increasing, results were somewhat varied and there were inherent challenges in deciphering treatment outcomes due to variations in treatment protocols and patient populations. Given the controversy and lack of clarity surrounding LI-ESWT, as well as the increasing number of clinicians who are offering the treatment, this technology review was requested by the Director of Medical Practise Division, Ministry of Health Malaysia (MOH) to evaluate whether LI-ESWT can be used as an alternative to standard treatment for ED in Malaysia.

Objective/ aim

The objective of this technology review was to assess the effectiveness, safety, and economic implication of LI-ESWT as a treatment option for men with ED.

Results and conclusions:

Search results

A total of **491** records were identified through the Ovid interface and PubMed. No duplicates references were found; **491** potentially relevant titles were screened using the inclusion and exclusion criteria. Of these, **69** relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the **69** full text articles, **13** were included. **Fifty-six** were excluded as those primary studies were already included in systematic review and meta-analysis (n=16), irrelevant study design (n=20), irrelevant intervention (n=13), and review articles (n=7). All full text articles finally selected for this review comprised of six systematic review and meta-analysis, four randomised controlled trials (RCTs), one prospective cohort study, and two quasi-experimental studies. The studies were conducted mainly in Europe, Asia, and Latin America.

Efficacy/ effectiveness

There was substantial fair level of retrievable evidence to suggest that LI-ESWT improved erectile function regarding patient-subjective outcomes relative to those who received placebo/ sham control treatment for ED. Findings in general indicated that:

i. LI-ESWT increased the International Index of Erectile Function-Erectile Function domain (IIEF-EF) score with a mean difference (MD) between 2.00 and 3.20 points ($p<0.0001$).

ii. LI-ESWT improved the Erection Hardness Score (EHS ≥3) with odds ratio (OR) between 4.35 and 10.40 points ($p<0.0001$).

iii. Patients treated by LI-ESWT developed a good therapeutic effect that lasts for at least 3 to 6 months.

iv. Patients who had mild or moderate ED and without comorbidities ($p<0.001$) had better therapeutic efficacy after treatment than patients with more severe ED ($p=0.30$) or comorbidities ($p=0.33$).

v. LI-ESWT showed a significant effect (improved IIEF score) on early recovery in penile rehabilitation of ED following radical prostatectomy (weighted mean difference [WMD] -2.04; 95% CI: -3.72 to -0.35; $p=0.02$).

vi. The combination of LI-ESWT and pelvic floor muscle exercise improved IIEF-EF score for the treatment of diabetic patients with ED (17.5 ± 2.72 versus 13.40 ± 2.85; $p<0.001$).

vii. In patients with ED unresponsive to PDE5i, LI-ESWT showed improvement in efficacy parameters (IIEF-EF, EHS, Sexual Encounter Profile diaries) and responded positively to the Global Assessment Question (GAQ) in 60% of patients treated.

viii. LI-ESWT versus on-demand 20 mg tadalafil has a comparable therapeutic efficacy at 12 weeks when comparing the baseline values to the follow-up variables for IIEF-5 (17.64 ± 4.01; $p<0.001$ within the Li-ESWT group and 15.72 ± 3.6; $p<0.001$ within the tadalafil group) and EHS (3.2 ± 0.76; $p<0.001$ within the LI-ESWT group and 3.1 ± 0.69; $p<0.001$ within the tadalafil group).

ix. LI-ESWT had similar efficacy as on-demand 100 mg sildenafil for general ED patients as measured by IIEF-5 and EHS scores ($p>0.05$ at baseline and third month).

x. Adjuvant daily therapy with L-arginine 2,500 mg and tadalafil 5 mg improved erectile function in terms of IIEF-EF and EHS scores ($p<0.0001$). The increase in both scores was statistically significant at all follow-up visits at 1, 6, and 12 months ($p<0.0001$).

Safety

There was substantial fair level of retrievable evidence to suggest that LI-ESWT was generally safe with low incidence of minor adverse effects (AEs) and well-tolerated by patients during the treatment of ED. Overall, studies reported that LI-ESWT was not associated with any chronic pain, discomfort or treatment-related AEs (minor skin bruises, haematoma, haematuria, urinary retention) during the sessions or the follow-up. The most common mild side effects were headache and dizziness, dyspepsia, stinging sensation, and local penile pain. There was no participant discontinuation due to AEs. However, the United States Food and Drug Administration (US FDA) has not yet approved shockwave therapy as a treatment for ED.

Organisational:

There was no retrievable evidence in the context of procedural time points and training or learning curve related to LI-ESWT for ED. However, different LI-ESWT setup parameters such as energy flux density (EFD) and number of pulses, and different treatment protocols including treatment frequency and length of course resulted in differences in reported efficacy. Given this information, recent evidence has demonstrated that the improvement in IIEF was better in the group with lower energy density (EFD 0.09 mJ/mm^2 versus EFD 0.1-0.2 mJ/mm^2; MD 3.81; 95% CI: 2.07 to 5.55; $p<0.0001$) while administering more shockwaves reported a significant increase in IIEF compared with delivering fewer shockwaves (number of pulses 3,000: MD 2.86; 95% CI: 1.54 to 4.19; $p<0.0001$). Shorter course of <6 weeks reported a significant increase in the IIEF (MD: 2.11; 95% CI: 0.98-3.25; $p=0.0003$).

With regard to treatment satisfaction, patients and their partners in the LI-ESWT group had similar total Erectile Dysfunction Inventory of Treatment Satisfaction questionnaires (EDITS) and EDITS Index scores as those in the sildenafil group. However, more patients and their partners in the LI-ESWT group were very satisfied and somewhat satisfied with the duration of intercourse compared with those in the sildenafil group. The improvement effect sustained 1-month after treatment without any additional active intervention, implying that LI-ESWT exerted a genuine physiologic effect on cavernosal tissue.

There are several international organisations that have published guideline recommendations surrounding LI-ESWT including the American Urological Association (AUA; 2018), Asia-Pacific Society for Sexual Medicine (APSSM; 2020), European Society of Sexual Medicine (ESSM; 2019), and European Association of Urology (EAU; 2020). All organisations acknowledge LI-ESWT as a potential treatment for ED with promising early clinical studies.

Economic implication

The cost-effectiveness of LI-ESWT for the treatment of ED has not yet been formally evaluated. However, cost associated to use this treatment is higher than self-administered 20 mg tadalafil on-demand, as reported in one prospective study. For each participant (n=51), the average number of sessions in the shockwave group was six sessions with an average total cost of USD 500.00, while the average of the medical treatment group was 30 tablets throughout the study costing about USD 62.50 ($p<0.001$).

Conclusion

A substantial body of retrievable evidence has demonstrated that LI-ESWT as compared to placebo/ sham is a safe and well-tolerated treatment with modest improvement in erectile function and hardness among patients with ED, and an effect that lasts up to 3 to 6 months. Above all, LI-ESWT appears most likely to benefit younger men and in patients with mild or moderate ED and few medical comorbidities such as diabetic and radical prostatectomy. In addition, LI-ESWT may optimize response to PDE5i or enhance medication response in PDE5i “non-responders”. A comparable short-term therapeutic efficacy was shown by the application of LI-ESWT with on-demand sildenafil or tadalafil for ED patients. Adjuvant daily therapy with L-arginine and tadalafil, however, increased efficacy and duration of benefits of LI-ESWT. Lower energy density, increased number of pulses per treatment, and shorter treatment courses resulted in better therapeutic efficacy, especially regarding IIEF improvement.

Methods

A systematic review was conducted. Review protocol and search strategy was developed by the main author while literature search was conducted by an *Information Specialist* who searched for published articles related to LI-ESWT for the treatment of ED. The following electronic databases were searched through the Ovid interface: MEDLINE (R) ALL 1946 to 31st March 2023, EBM Reviews - Health Technology Assessment 4th Quarter 2016, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to 28th March 2023, EBM Reviews - Cochrane Central Registered of Controlled Trials February 2023, EBM Reviews - Database of Abstracts of Review of Effects 1st Quarter 2016, and EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016. Parallel searches were run in PubMed, US FDA and INAHTA database while additional articles were retrieved from reviewing the bibliographies of retrieved articles. The search was limited to articles on human. There was no language limitation in the search. The last search was conducted on 4th April 2023.

TABLE OF CONTENTS

ABBREVIATION

AEs	Adverse events or adverse effects
AUC	Area under the ROC curve
BMI	Body mass index
CASP	Critical Appraisal Skills Programme
CI	Confidence interval
DM	Diabetes mellitus
ED	Erectile dysfunction
EDITS	Erectile Dysfunction Inventory of Treatment Satisfaction questionnaires
EDV	End-diastolic velocity
EFD	Energy Flux Density
EHS	Erection Hardness Score
ESW	Extracorporeal shockwave
GAQ	Global Assessment Question
IIEF	International Index of Erectile Function
IIEF-EF	International Index of Erectile Function-Erectile Function domain
INAHTA	International Network of Agencies for Health Technology Assessment
LI-ESWT	Low-intensity extracorporeal shockwave therapy
MaHTAS	Malaysian Health Technology Assessment Section
MCID	Minimal clinically important difference
MD	Mean difference
MOH	Ministry of Health
OR	Odds ratio
PDE5i	Phosphodiesterase type 5 inhibitors
PSV	Peak systolic velocity
RI	Resistance index
RCT	Randomised controlled trial
RD	Risk difference
RoB	Cochrane Risk of Bias Tool
ROBIS	National Collaborating Centre for Methods and Tools
SEAR	Self-Esteem and Relationship questionnaires
SEP	Sexual Encounter Profile
US FDA	United States Food and Drug Administration
VEGF	Vascular endothelial growth factor
WMD	Weighted mean differences

1.0 BACKGROUND

Erectile dysfunction (ED) is the incapacity to attain or sustain penile erection for a sufficient period to achieve successful sexual intercourse.[1-2] It is common in adult men older than 40 years. An estimated of 30-50% of men between the ages of 40-70 years suffer from moderate or severe ED based on data from the United States and Europe.[3-4] Similar trends were seen in Malaysia as well, whereby 69.5% of men aged 40 years and above in primary care clinics reported ED to some extent.[5] The prevalence of ED increases with age and comorbid conditions. Some of the risk factors associated with ED include general health status of the individual, diabetes mellitus, cardiovascular disease, hypertension, obesity, hyperlipidaemia metabolic syndrome, abdominal-pelvic interventions, and other genitourinary disease (benign prostatic hyperplasia, psychiatric disorders, etc). Smoking, medications, and hormonal factors also are well-defined risk factors.[6]

The evaluation of ED involves a detailed history from the patient, and preferably the partner as well; physical examination and laboratory tests. Clinical diagnosis of ED is usually made using validated questionnaires. A commonly used self-administered questionnaires are the International Index of Erectile Function (IIEF) and the Erection Hardness Score (EHS). The IIEF addresses five domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. Depending on the response, patients can be classified as having severe (5 to 7), moderate (8 to 11), mild to moderate (12 to 16), mild (17 to 21) and no ED (22 to 25).[7] The EHS was based on self-estimated rigidity, categorised using a scale of 1-4: ([1]-the penis is larger but not hard, [2]-the penis is hard but not hard enough for penetration, [3]-the penis is hard enough for penetration but not completely hard, and [4]-the penis is completely hard and fully rigid for coitus).[8]

Treatment options for ED begins with lifestyle modification followed by medical therapy. The first-line drugs for ED are phosphodiesterase type 5 inhibitors or PDE5i (sildenafil, avanafil, vardenafil, and tadalafil). Although they are effective, the relief is only temporary, do not improve spontaneous erections, and they provide no permanent improvement. In addition, the side-effects caused by PDE5i such as visual impairment, dyspepsia, myalgia, and back pain are difficult for patients to tolerate. Especially for patients taking antihypertensive drugs, the combination of PDE5i will have a slight synergistic effect. For various reasons, 35% of patients may not respond to PDE5i.[9-10] In medication refractory patients or in those with intolerable side effects, published guidelines encourage clinicians to discuss established treatment - vacuum erection devices, self-administered intracavernosal injection of erectogenic agents, intraurethral suppositories, and penile prosthesis placement. Such treatment modalities, however, are used as second- or even third-line approaches, yet long-term use is associated with complications and unwanted side-effects.[11] Therefore, they are not the best choice for treating ED.

For some years, low-intensity extracorporeal shockwave therapy (LI-ESWT) has been implemented as a new therapeutic method for the treatment of ED with encouraging outcomes, but has not yet been widely recognised. This therapy involves applying low intensity shockwaves to the penile shaft at a specified energy setting for a predetermined number of shocks per minute and for a set treatment duration and number of treatments. It is claimed that the energy from shockwave therapy stimulates new blood vessel growth through a process called angiogenesis. This increases penile blood flow, which may improve erectile function.[12] Due to the minimally-invasive nature of this approach, LI-ESWT is an attractive treatment modality for many patients and clinicians, and has been included as a first-line therapy for this disease in the latest guidelines of the European Association of Urology (EUA) 2018.[13] In past years, although the number of systematic reviews/ meta-analyses increased, results were somewhat varied and there was inherent challenges in deciphering treatment outcomes due to variations in treatment protocols (energy settings, number of shocks delivered, duration of therapy, etc.) and patient populations.

Given the controversy and lack of clarity surrounding LI-ESWT, as well as the increasing number of clinicians who are offering the treatment, this technology review was requested by the Director of Medical Practice Division, Ministry of Health Malaysia (MOH) to evaluate whether LI-ESWT can be used as an alternative to standard treatment for ED in Malaysia.

2.0 OBJECTIVE / AIM

The objective of this technology review was to assess the effectiveness, safety, and economic implication of LI-ESWT as a treatment option for men with ED.

3.0 TECHNICAL FEATURE

Extracorporeal shockwave (ESW) is a special sound wave carrying energy which has different functions in clinical application. According to the different energy density levels of ESW, higher than 0.60 mJ/mm^2 is consider high energy; 0.28-0.60 mJ/mm^2 is medium energy; and 0.08-0.28 mJ/mm^2 is low energy.[14] High energy density ESW focus on mechanical damage characteristics, so it is often used in lithotripsy treatment (kidney stones). Medium energy density ESW has anti-inflammatory function and it is often used in surgery such as tendinitis, synovial bursitis, and nonbinding fracture. Low energy density ESW can promote angiogenesis and improve its blood supply and it is often used in chronic injury, musculoskeletal recovery, and cardiovascular disease.[15-17] Studies have reported that the important mechanism of ED is vascular endothelial function injury or disorder [18-19] and LI-ESWT can stimulate the expression of angiogenesis-related factors such as vascular endothelial growth factor (VEGF), so as to promote vascular regeneration.[20-22] As a result, LI-ESWT has been widely used in clinical treatment of ED.[23] However, the evidence for its use is still debated at present, while lacking Food and Drug Administration (FDA) approval for ED.

The mechanism of action of LI-ESWT is still not completely elucidated. However, it has been identified that: (I) LI-ESWT can effectively induce angiogenesis, increase the expression of VEGF and other angiogenic factors, promote the formation of blood vessels in the corpus cavernosum of the penis, and cause penis hyperaemia, thus promoting penis erection; [24] and (II) LI-ESWT is conducive to remodelling of cavernous tissue in smooth muscle cells, increases penile microvascularization,[25] induces muscle cell differentiation,[26] and improves erection.

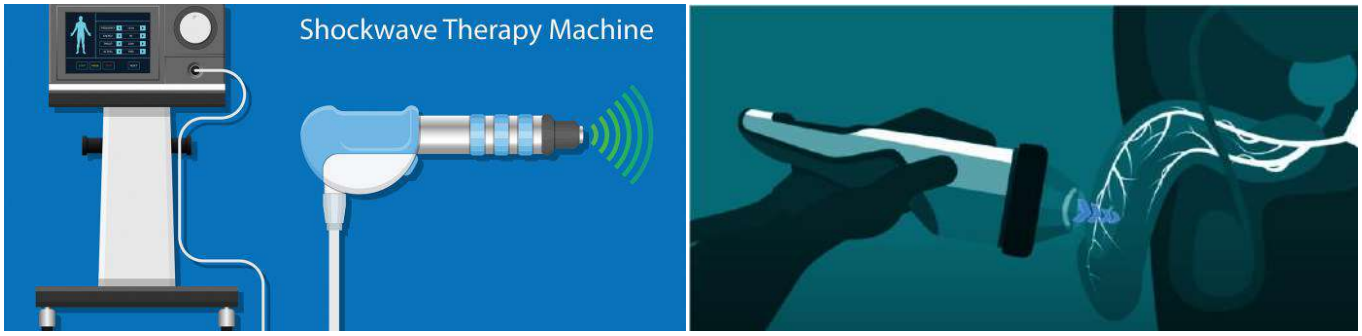

Figure 1: Low-intensity extracorporeal shockwave therapy for the treatment of erectile dysfunction

4.0 METHODS

A systematic review was conducted. Search strategy was developed by the main author and an *Information Specialist*.

4.1 SEARCHING

The following electronic databases were searched through the Ovid interface:

- MEDLINE® All < 1946 to 31st March 2023>
- EBM Reviews - Health Technology Assessment 4th Quarter 2016
- EBM Reviews - Cochrane Database of Systematic Reviews 2005 to 28th March 2023
- EBM Reviews - Cochrane Central Registered of Controlled Trials February 2023
- EBM Reviews - Database of Abstracts of Review of Effects 1st Quarter 2016
- EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016

Other databases: PubMed, US FDA, INAHTA

General databases such as Google and Yahoo were used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles. The search was limited to articles on human. There was no language limitation in the search. **Appendix 1** showed the detailed search strategies. The last search was conducted on 4th April 2023.

4.2 SELECTION

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria. Relevant articles were then critically appraised depending on the type of the study design. Studies were graded according to *US/ Canadian Preventive Services Task Force* (**Appendix 2**). All data were extracted and summarised in evidence table as in **Appendix 3**.

The inclusion and exclusion criteria were:

Inclusion criteria:

a.	**Population**	Men, adults, 18 years of age or older with erectile dysfunction (ED)
b.	**Intervention**	Extracorporeal shockwave therapy or low intensity extracorporeal shockwave therapy of the penis
c.	**Comparator**	**1-Pharmacologic therapy:** phosphodiesterase-5 inhibitors (PDE5i), sildenafil (Viagra), tadalafil (Cialis) **2-Medication refractory patients or in those with intolerable side effects:** intracavernosal injections, intraurethral suppositories **3-Medical devices:** vacuum erection devices, penile prosthesis placement **4-Combination therapy** of 1, 2, and 3 above **5-Placebo** (or sham treatment)
d.	**Outcomes**	**Effectiveness:** Improvement in erection parameters/ erectile function satisfactory for penetration and successful intercourse (evaluated by validated questionnaire), sexual quality of life **Safety:** Adverse events (AEs) related to treatment **Organisational issues:** procedural time, training or learning curve **Economic implications:** Cost, cost-effectiveness, cost-utility analysis
e.	**Study design**	HTA reports, systematic review with/out meta-analysis, randomised controlled trial (RCT), cohort, diagnostic, case-control, economic evaluation studies
f.	Full text articles published in English	

Exclusion criteria:

a.	**Study design**	Case report, case series, animal study, laboratory study, narrative review
b.	Non-English full text articles	

5.0 RESULTS

Search results

An overview of the search is illustrated in **Figure 3**. A total of **491** records were identified through the Ovid interface and PubMed. No duplicates references were found; **491** potentially relevant titles were screened using the inclusion and exclusion criteria. Of these, **69** relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the **69** full text articles, **13** were included. **Fifty-six** were excluded as those primary studies were already included in systematic review and meta-analysis (n=16), irrelevant study design (n=20), irrelevant intervention (n=13), and review articles (n=7). All full text articles finally selected for this review comprised of six systematic review and meta-analysis, four RCTs, one prospective cohort study, and two quasi-experimental studies. The studies were conducted mainly in Europe (United Kingdom, Germany, Italy, Spain, Denmark, Austria, Greece, Turkey), Asia (Japan, China, Korea, Hong Kong, Australia, India, Egypt, Malaysia), and Latin America (Argentina, Brazil, Mexico).

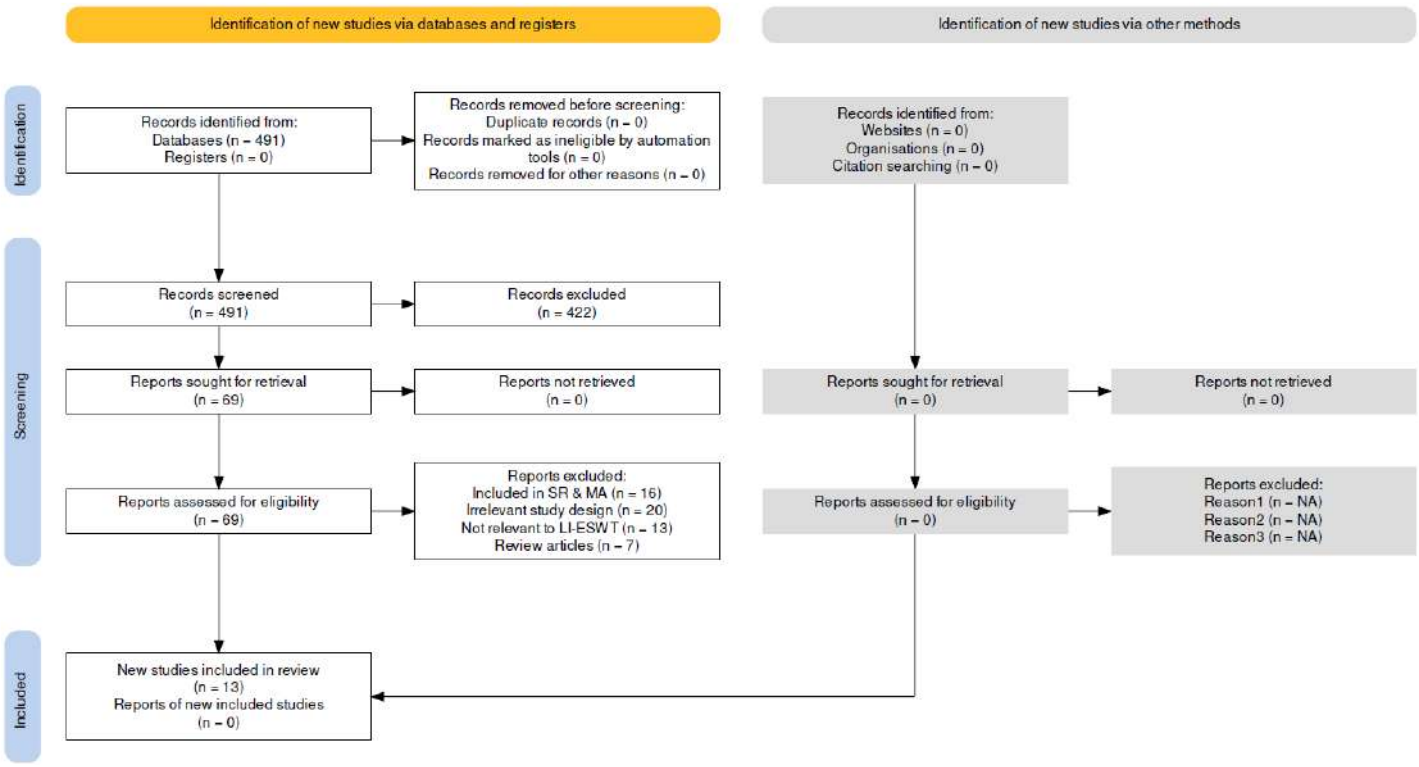

Figure 3: Flow chart of retrieval of articles used in the results

Quality assessment of the studies

The risk of bias or quality assessment (methodology quality) of all retrieved literatures was assessed depending on the type of the study design. These assessments involved answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias: using the relevant checklist of National Collaborating Centre for Methods and Tools (ROBIS) [27] for systematic review and meta-analysis, a revised Cochrane Risk of Bias Tool (RoB 2) for randomised controlled trials [28], Critical Appraisal Skill Programme (CASP) checklist for observational study [29], and The Joanna Briggs Institute (JBI) Critical Appraisal tools for Quasi-Experimental Studies (non-RCT).[30] All full text articles were graded based on guidelines from the *U.S. / Canadian Preventive Services Task Force*.[31]

Risk of bias assessment for included systematic review and meta-analysis

Six studies were included in this assessment and were judged to have an overall high risk of bias following uncertainty in the data collection or risk of bias assessment processes. Most of the studies were retrospective in nature. The main concern in RCTs included were related to selection bias, introduced by attrition of study participants (**Figure 4.1**).

Review	Phase 2				Phase 3
	1-STUDY ELIGIBILITY CRITERIA	2-IDENTIFICATION AND SELECTION OF STUDIES	3-DATA COLLECTION AND STUDY APPRAISAL	4-SYNTHESIS AND FINDINGS	RISK OF BIAS IN THE REVIEW
Lu Z et al. 2016 [32]	☺	☺	☹	☺	☹
Brunckhorst O et al. 2019 [33]	☺	☺	☹	☺	☹
Sokolakis I et al. 2019 [34]	☺	☹	☺	☹	☹
Liu S et al. 2022 [35]	☺	☺	☺	☺	☺
Yao H et al. 2022 [36]	☺	☺	☺	☺	☺
Rho BY et al. 2022 [38]	☺	☺	☹	☺	☹

☺ low risk; ☹ high risk ? unclear risk

Figure 4.1: Risk of bias assessment for systematic review and meta-analysis using ROBIS

Risk of bias assessment for included RCT

All studies were rated to have an overall low risk of bias as shown in **Figure 4.2**. The method of randomisation was stated while random sequence generation and allocation concealment were performed adequately. Outcomes were analysed using intention to treat analysis while selective reporting was considered to have a low risk of bias as all pre-specified outcomes were reported and analysed.

Review	Risk of bias domains					
	D1	D2	D3	D4	D5	Overall
	Bias arising from the randomisation process	Bias due to deviations from intended intervention	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	
Ong WLK et al. 2022 [37]	☺	☺	☺	☺	☺	☺
Shendy WS et al. 2021 [39]	☺	☺	☺	☺	☺	☺
Gallo L et al. 2022 [40]	☺	☺	☺	☺	☺	☺
Zanaty F et al. 2022 [41]	☺	☺	☺	☺	☺	☺

☺ low risk; ☹ high risk ? unclear risk

Figure 4.2: Risk of bias assessment for RCT using RoB 2

Risk of bias assessment for included cohort using CASP

Based on the CASP checklist, the study had low risk of bias (**Figure 4.3**).

Review	Risk of bias domains					
	D1	D2	D3	D4	D5	Overall
	Selection of cohort	Exposure accurately measures	Outcome accurately measures	Confounding factors	Follow-up and timing	
Bechara A et al. 2016 [42]	☺	☺	☺	☺	☺	☺

☺ low risk; ☹ high risk ? unclear risk

Figure 4.3: Risk of bias assessment for cohort study using CASP

Risk of bias assessment for included non-RCT using JBI

Two studies were included in this assessment and were summarised in **Figure 4.4**. All were judged to have overall low risk of bias.

Review	Risk of bias domains									
	D1	D2	D3	D4	D5	D6	D7	D8	D9	Overall
	Cause and effect	Participants similar	Treatment similar	Control	Multiple measurement	Follow-up	Outcomes - same	Outcomes - reliable	Statistical analysis	
Lei Q et al. 2021 [43]	☺	☺	☺	☺	☺	☺	☺	☺	☺	☺
Wang D et al. 2023 [44]	☺	☺	☺	☺	☺	☺	☺	☺	☺	☺

☺ low risk; ☹ high risk ? unclear risk

Figure 4.4: Risk of bias assessment for quasi-experimental study using JBI

5.1 EFFICACY/ EFFECTIVENESS

5.1.1 Low-intensity extracorporeal shockwave therapy (LI-ESWT) versus placebo/ sham-controlled treatment for ED

A systematic review of the evidence regarding LI-ESWT for patients with ED was undertaken with a meta-analysis by Lu Z et al. (2016) to identify the efficacy of the treatment modality. A total of 14 studies involving 833 patients were included. These studies were performed by different medical centres in different countries. Most of these patients had an organic aetiology such as a vascular lesion and a nerve injury. The overall meta-analysis of the data revealed that LI-ESWT increased the International Index of Erectile Function (IIEF) (mean difference [MD] 2.00; 95% CI: 0.99 to 3.00; p<0.0001) and improved the Erection Hardness Score (EHS) (risk difference [RD] 0.16; 95% CI: 0.04 to 0.29; p=0.01). Moreover, therapeutic efficacy could last at least three months. Patients who had mild or moderate ED (MD 2.86; 95% CI: 1.54 to 4.19; p<0.0001) and the ED patients who had no comorbidities (MD 2.36; 95% CI: 1.19 to 3.53; p<0.0001) benefited more from LI-ESWT than the patients with severe ED (p=0.30) or with comorbidities (p=0.33).[32, level II-1]

Brunckhorst O et al. (2019) assessed the long-term effect of LI-ESWT on vasculogenic ED patients. Eleven articles (5 RCTs and 6 non-randomised) representing a total of 799 patients were included in the review. Nine of the 11 studies found a statistically significant increase in erectile function utilising either IIEF or EHS scores after LI-ESWT at over 6-month follow-up (median International Index of Erectile Function-Erectile Function Domain [IIEF-EF] score improvement from baseline at six months 5.3, range 2.6-10.7). When assessing studies with follow-ups of greater than six months, there appeared to be limited improvement in IIEF scores beyond this time period (change in IIEF-EF scores of between -2 and 0.1). Three out of five studies demonstrated a gradual decline in erectile function with two showing a plateauing of results. However, none of these studies demonstrated a decrease in erectile function below baseline post intervention. Subgroup analysis revealed increasing age appears to reduce responsiveness to LI-ESWT treatment in long-term follow-up studies. Furthermore, ED severity, PDE5i responsiveness, and co-morbidities may also influence its effectiveness; however, results are inconsistent.[33, level II-1]

Another systematic review and meta-analysis by Sokolakis I et al. (2019) investigated the efficacy of LI-ESWT for ED, and reported primary outcomes using IIEF-EF scores/ questionnaires were included. Ten RCTs (873 patients; mean age 58 years) with vasculogenic ED, either PDE5i-responders or PDE5i-non-responders were selected for the meta-analysis. Pooled data of these studies showed that LI-ESWT could significantly improve erectile function in men with ED regarding both patient-subjective outcomes (IIEF-EF: 3.97; 95% CI: 2.09 to 5.84; p<0.0001, EHS $\geqslant$3: odds ratio [OR]: 4.35; 95% CI: 1.82 to 10.37; p=0.0009) and patient-objective outcomes (peak systolic velocity [PSV]: 4.12; 95% CI: 2.30 to

5.94; p<0.00001). In the subgroup of patients with vasculogenic ED that were PDE5i-responders, a significant difference in IIEF-EF change from baseline was observed (MD: 4.12; 95% CI: 1.30 to 6.95; p=0.004) favouring the LI-ESWT group. Subgroup analysis regarding the duration of follow-up using the IIEF-EF scores at 1-, 3-, 6-, and 12-months follow-up showed that the positive effect of LI-ESWT lasts for 12 months, although it could be weaker with time.[34, level II-1]

Eleven RCTs including 814 male patients were enrolled in the recent systematic review and meta-analysis by Liu S et al. (2022). The pooled results suggested that ED patients who received LI-ESWT had markedly improved IIEF-EF (MD: 2.77 points; 95% CI: 1.74 to 3.79; p<0.001) and EHS scores (OR: 10.40 points; 95% CI: 5.60 to 19.31; p<0.001) relative to those who received placebo treatment. There were nine articles that mentioned the ED severity, based on IIEF score or responds to PDE5i. Compared with placebo, LI-ESWT alleviates ED symptoms in patients, particularly those who have mild or moderate ED.[35, level I]

Yao H et al. (2022) carried out a meta-analysis of 16 RCTs (n=1,064) to systematically evaluate the efficacy of LI-ESWT in the treatment of ED. The results reported that after one month (MD 3.18; 95% CI: 1.38 to 4.98; p=0.0005), three months (MD 3.01; 95% CI: 2.04 to 3.98; p<0.00001), and six months follow-up (MD 3.20; 95% CI: 2.49 to 3.92; p<0.00001), the improvement of IIEF in the LI-ESWT group was better than that in the control group. Besides, eight articles provided data on the improvement of patients with baseline EHS $\leqslant$2 to EHS $\geqslant$3 after treatment; the LI-ESWT group was also significantly better than the placebo group (OR 5.07; 95% CI: 1.78 to 14.44; p=0.002). However, the positive response rate of Questions 2 and 3 of the Sexual Encounter Profile (SEP) was not statistically significant (SEP2: OR 1.27; 95% CI: 0.70 to 2.30; p=0.43; SEP3: OR 4.24; 95% CI: 0.67 to 26.83; p=0.13). Subgroup analysis also suggested that treatment plans with an energy density of 0.09 mJ/mm2 (MD 3.81; 95% CI: 2.07 to 5.55; p<0.0001) and pulses number of 1,500 to 2,000 (MD 4.80; 95% CI: 2.61 to 7.00; p<0.0001) are more beneficial to IIEF in ED patients. In addition, IIEF improvement was more pronounced in patients with moderate ED after LI-ESWT (MD 4.24; 95% CI: 2.88 to 5.59; p<0.00001).[36, level I]

A prospective, randomised, double-blinded, sham controlled single centre trial was conducted in Penang General Hospital, Malaysia between August 2019 till July 2020 and follow-up was carried out until December 2020. Study subjects were recruited by opportunistic screening from general outpatient and urology clinics. Others were directly referred by physicians for treatment of ED. A total of 51 patients (median age 59 years) were included in this study of which 27 patients underwent a 4-week course of LI-ESWT while 24 patients were not given shockwave therapy. Measurements using validated five-item version (IIEF-5) questionnaire scores and EHS at the beginning and the end of the treatment (1 month) and 3-, 6-month after therapies were recorded. The study indicated that mean IIEF-5 scores were significantly improved in the treatment arm compared to worsening of scores in the sham arm after 1-month (14.1 versus 9.3; p<0.001), 3-month (14.9 versus 8.6; p<0.001), and 6-month (14.2

versus 7.9; p<0.001) post-treatment. When evaluating for success of treatment (defined as IIEF score improvement of more than five points), only 15%, 22% and 26% of patients in the treatment arm achieved such results at 1-, 3- and 6-month, respectively. None of the patients in the sham arm had a 5-point increment. A significant improvement of EHS was demonstrated at 1-month (2.4 versus 1.8; p=0.001), 3-month (2.7 versus 1.7; p<0.001), and 6- month (2.7 versus 1.6; p<0.001) in the treatment arm compared to sham arm. With regards to significant improvement in EHS (defined as EHS of 3 or more), 44%, 63% and 63% of patients in the treatment arm achieved significant erection hardness, at 1-, 3- and 6-month, respectively. In the sham arm, only 8%, 8% and 4% of patients achieved this at similar time intervals.[37, level I]

5.1.2 Low-intensity extracorporeal shockwave therapy (LI-ESWT) following radical prostatectomy versus placebo/ sham-controlled treatment for ED

Erectile dysfunction is a well-known complication of radical prostatectomy and since there was few LI-ESWT studies in this group, Rho BY et al. (2022) published the most recent systematic review and meta-analysis to investigate the efficiency of LI-ESWT. Five papers (460 patients who underwent radical prostatectomy or radical cystoprostatectomy and had normal sexual function before surgery) were included in the meta-analysis. The endpoint was the change in IIEF scores after LI-ESWT. The study showed that the ED recovery rate in patients receiving LI-ESWT was significantly higher than the control group, 3-4 months after LI-ESWT (weighted mean differences [WMD]; -2.04; 95% CI: -3.72 to -0.35; p=0.02). However, in the long-term (9-12-month) analysis involving two studies, the results were not statistically significant (WMD: -5.37; 95% CI: -12.42 to 1.69; p=0.14).[38, level II-1]

5.1.3 Low-intensity extracorporeal shockwave therapy (LI-ESWT) versus placebo/ sham-controlled treatment for diabetic ED

Shendy WS et al. (2021) evaluated the effectiveness of LI-ESWT in the management of ED in 42 diabetic patients (41-55 years with a confirmed diagnosis of ED and diabetic polyneuropathy). They were randomly allocated to one of two groups: shock wave group (n=21) treated with LI-ESWT plus pelvic floor muscle training and control group (n=21) treated with pelvic floor muscle exercise and sham therapy by a shockwave. The erectile function was scored according to the IIEF-5. Colour-coded duplex sonography (5-10 MHz probes) was used for the evaluation of penile perfusion. The systolic and diastolic velocities (cm/s) were performed at 10 and 30 minutes for both cavernous arteries. The highest values obtained were recorded. The following Doppler indices of the right and left cavernous arteries: peak systolic velocity (PSV), end-diastolic velocity (EDV) and resistance index (RI) were recorded. The assessment was done before and three months after treatment. Regarding the baseline Doppler measurements, there were no significant differences in the three Doppler indices of the right and left cavernous arteries between the two groups. After treatment, PSV of the right and left cavernous arteries increased significantly in the two

groups. However, the post-treatment PSV was significantly higher in the LI-ESWT group compared to the sham group (p<0.001, for both arteries). There was no significant change of EDV of the two cavernous arteries after treatment in the two groups. The RI of right and left cavernous arteries increased significantly in the LI-ESWT group, but not in the sham group. The five-item version of the IIEF-EF increased significantly in the LI-ESWT group (p<0.001) but not in the control group (p=0.194). In the LI-ESWT group, 15 (71%) patients achieved erection sufficient for penetrative intercourse versus 2 (9.5%) patients in the control group (p<0.001).[39, level I]

5.1.4 Combination of low-intensity extracorporeal shockwave therapy (LI-ESWT) and oral therapy versus LI-ESWT alone for ED

A two-arm, prospective, randomised, single-blinded trial was designed by Gallo L et al. (2022) to investigate a therapeutic protocol for ED based on the combination of LI-ESWT, tadalafil, and L-arginine. Recruited patients (n=83) completed the domain IIEF-EF and the EHS questionnaires at baseline and were randomly assigned in two groups: 41 in Group A (LI-ESWT with tadalafil 5 mg for 3 months and daily L-arginine 2,500 mg for 6 months) and 42 in Group B (LI-ESWT without oral therapy). Follow-up visits were scheduled 1, 6, and 12 months after the last LI-ESWT application. The main outcome measures were the changes from baseline to every follow-up visit in IIEF-EF and EHS scores. The percentage of patients who reached a minimal clinically important difference (MCID) in IIEF-EF were also evaluated. The study demonstrated that the mean IIEF-EF scores in group A were 16.0 ± 4.0, 24.8 ± 3.4, 23.3 ± 4.6, and 21.6 ± 5.5 at baseline, 1, 6, and 12 months of follow-up, whereas in group B the mean IIEF-EF scores were 16.5 ± 4.1, 22.7 ± 4.2, 21.5 ± 4.5, and 19.5 ± 4.9, respectively. An increased in mean EHS score were also reported in group A from 2.07 ± 0.72 at baseline to 3.39 ± 0.59, 3.17 ± 0.67, and 2.98 ± 0.72 at 1, 6, and 12 months, respectively, and in group B from 2.12 ± 0.80 at baseline to 3.07 ± 0.78 and 2.95 ± 0.76 at 1 and 6 months, respectively. The percentage of men who reached a MCID was 100% and 88.1% at 1 month, 87.8% and 76.2% at 6 months, and 75.6% and 66.7% after 1 year for group A and group B, respectively. The degree of response to treatment and the duration of benefits were greater in younger men and in patients affected by mild ED.[40, level I]

5.1.5 Low-intensity extracorporeal shockwave therapy (LI-ESWT) versus on-demand tadalafil (*Cialis, Adcirca*) for ED

In an RCT by Zanaty F et al. (2022), 50 adults with ED for at least 12 months and in a stable marriage relationship were randomised to the LI-ESWT or tadalafil group. Patients in the LI-ESWT group received six sessions (2 per week) while other patients self-administered tadalafil on-demand at a dose of 20 mg each hour before each event of sexual intercourse. The outcomes were assessed using the IIEF-5 score, EHS, and Self-Esteem and Relationship (SEAR) questionnaire before, at 6- and 12-week after treatment. An improvement of 5 points or greater from IIEF-5 score baseline and an increase in EHS score

from 2 or less at baseline to 3 or more, and a positive change in SEAR questionnaire score were considered significant. Considering the results, there were no significant differences in baseline IIEF-5 score and baseline EHS between the two groups (11.16 ± 4.2 and 10.08 ± 3.8; p>0.34). The IIEF-5 score increased significantly from baseline to 16.36 ± 3.8 (p<0.001) at 6-week and to 17.64 ± 4.00 (p<0.001) at 12 weeks within the LI-ESWT group, and the IIEF-5 score also increased significantly from baseline to 17.52 ± 2.75 (p<0.001) at 6-week and to 15.72 ± 3.6 (p<0.001) at 12 weeks within the tadalafil group. The median change in IIEF-5 score in the LI-ESWT and tadalafil groups was 5.2 and 7.4 at the 6-week and 6.4 and 5.6 at the 12 weeks follow-up. Mean EHS also statistically higher at six and 12 weeks within both groups. The SEAR questionnaire scores, which showed the negative effects of ED on the psychological condition and positive effects of successful treatment for both groups, were not statistically a significantly difference at baseline (p=0.3) but showed an improvement comparing baseline values to follow-up variables for both groups (p<0.001).[41, level II-1]

5.1.6 Low-intensity extracorporeal shockwave therapy (LI-ESWT) in patients whose ED was unresponsive to PDE5i treatment

Bechara A et al. (2016) reported the long-term results of an open-label, longitudinal, and observational study on LI-ESWT involving 50 patients (median age 64.8 years; duration of ED 70.5 months) who are non-responders to PDE5i treatment. Patients were treated with a four-session LI-ESWT protocol. During active treatment and follow-up, all patients remained on their regular high on-demand or once-daily PDE5i dosing schedules. Effectiveness was assessed using the IIEF-EF, SEP2 and SEP3 diaries, EHS, and Global Assessment Question (GAQ) at baseline and at 3-, 6-, 9-, and 12-month after treatment. Findings recorded that 80% (40/50) of patients completed the treatment and follow-up while 60% (24/40) showed improvement in efficacy parameters in all four assessments and responded positively to the GAQ. These changes were significant from the first follow-up (3 months after treatment). By the third month after treatment, 91.7% (22/24) of responders to LI-ESWT maintained efficacy parameters up to the last follow-up visit 12 months after treatment. Improvements in the IIEF-EF score was higher whenever ED was more severe, with changes of 13.0, 10.5, 6.8, and 4.5 points for patients with severe, moderate, mild to moderate, and mild ED, respectively.[42, level II-2]

5.1.7 Low-intensity extracorporeal shockwave therapy (LI-ESWT) versus on-demand sildenafil (*Viagra*) for ED

There has been no comparative analysis of these two treatments using validated instruments. Herein, Lei Q et al. (2021) designed a prospective non-randomised interventional study of 110 men who underwent initial screening, including medical history and physical examinations. After a 4-week washout period of past ED treatment, patients entered one of two active treatment groups, either 9-week LI-ESWT or 100 mg on-demand sildenafil. The primary outcome was effectiveness as measured by IIEF-5, with other measurements,

including the EHS and Self-Esteem and Relationship (SEAR) questionnaires consisting of Confidence Domain and Relationship Domain. A total of 78 participants of diverse pathogeneses (psychogenic, organic, and mixed ED) completed the study; 46 in the LI-ESWT and 32 in the sildenafil group. At baseline, the IIEF-5 score was equal in both groups (14.09 ± 3.75 in the LI-ESWT group and 13.0 ± 4.20 in the sildenafil group, adjusted for age). The mean score in IIEF-5 for LI-ESWT and sildenafil was 19.0 ± 5.75 and 24.5 ± 4.3 at first month follow-up ($p<0.01$), and 20.52 ± 5.92 and 20.59 ± 6.40 at third month follow-up ($p>0.05$). Improvement of the IIEF-5 score was higher in the first month follow-up in the sildenafil group, with no statistically significant difference at the third month follow-up. The EHS and SEAR were similar to IIEF-5, which was equal at baseline, higher in the sildenafil group in the first month, but equal again in the third month. According to MCID criteria, a 7-score improvement of severe patients and 5-score improvement of mild and moderate patients were recorded as positive results. In the third month, 24 participants (52.2%) in the LI-ESWT group and 19 (59.4%) in the sildenafil group reported positive results ($p>0.05$). In the third month, the ratio of patients who achieved clinical cure defined by IIEF-5 >26 was 21.9% in the sildenafil and 15.2% in the LI-ESWT group ($p>0.05$).[43, level II-2]

The most recent study by Wang D et al. (2023) also compared erectile function status in patients who received sildenafil (100 mg on-demand) or LI-ESWT (9 weeks). A total of 72 participants were enrolled; 42 in the LI-ESWT group and 30 in the sildenafil group. Patient in the two groups have similar demographic profiles except for age (33.9 ± 6.2 in the LI-ESWT group versus 31.2 ± 5.2 in the sildenafil group; $p<0.05$). The erectile function was evaluated using the erectile function domain of the IIEF-EF questionnaires. Four weeks after the final session, the mean score in IIEF-EF for LI-ESWT and sildenafil was 16.3 ± 5.5 and 18.3 ± 6.5 ($p>0.05$), respectively.[44, level II-2]

Summary of studies related to the efficacy/ effectiveness of LI-ESWT for ED are shown in **Table 1**.

5.2 SAFETY

According to the safety assessment, LI-ESWT was generally safe with low incidence of minor AEs and well-tolerated by patients during the treatment of ED. Overall, studies reported that LI-ESWT was not associated with any chronic pain, discomfort or treatment-related AEs (minor skin bruises, haematoma, haematuria, urinary retention) during the sessions or the follow-up.[34-35, 37, 39, 42] The most common mild side effects were headache and dizziness, dyspepsia, stinging sensation, and local penile pain. There was no participant discontinuation due to AEs.[40-41, 43-44] Despite the clinical research and the science behind this pill-free treatment has been supported by several studies that have turned up with encouraging results, the FDA has not yet approved shockwave therapy as a treatment for ED. This means it is presently still seen as an investigational or experimental treatment.

Table 1: Efficacy/ effectiveness of LI-ESWT for ED reported by the included studies

Study	Patient characteristic/ disease	Follow-up duration	Intervention		Findings
			Treatment	Control	
Lu Z et al. 2016 SR & MA	833 general ED, vascular lesion and nerve injury	3-12 month	LI-ESWT	Sham	▪ LI-ESWT improved IIEF (MD 2.00; 95% CI: 0.99 to 3.00; p<0.0001) and EHS (RD 0.16; 95% CI: 0.04 to 0.29; p=0.01) ▪ Therapeutic efficacy could last at least 3 months ▪ Patients with mild- moderate ED had better therapeutic efficacy after treatment than patients with more severe ED or comorbidities
Brunckhorst O et al. 2019 SR	799 vasculogenic ED	6-24 month	LI-ESWT	Placebo/sham	▪ LI-ESWT improved IIEF-EF with results lasting to over 6 months
Sokolakis I et al. 2019 SR & MA	873 vasculogenic ED, PDE5i-responders or PDE5i-non-responders	12 months	LI-ESWT	Sham	▪ LI-ESWT improved erectile function regarding patient-subjective outcomes (IIEF-EF: +3.97; 95% CI: 2.09 to 5.84; p<0.0001, EHS ≥3: OR 4.35; 95% CI: 1.82 to 10.37; p=0.0009) ▪ PDE5i-responders - a significant difference in IIEF-EF (MD 4.12; 95% CI: 1.30 to 6.95; p=0.004) favouring LI-ESWT ▪ Therapeutic efficacy could last at least 12 months
Liu S et al. 2022 SR & MA	814 general ED	Between 7-week and 12 months	LI-ESWT	Placebo/sham	▪ LI-ESWT improved IIEF-EF (MD 2.77; 95% CI: 1.74 to 3.79; p<0.001) and EHS (OR: 10.40; 95% CI: 5.60 to 19.31; p<0.001) ▪ LI-ESWT alleviates ED symptoms in patients, particularly those who have mild or moderate ED
Yao H et al. 2022 SR & MA	1,064 general ED	1, 3 and 6 months	LI-ESWT	Placebo/sham	▪ LI-ESWT improved IIEF-EF (1 month [MD 3.18; 95% CI: 1.38 to 4.98; p=0.0005], 3 months [MD 3.01; 95% CI: 2.04 to 3.98; p<0.00001], and 6 months follow-up [MD 3.20; 95% CI: 2.49 to 3.92; p<0.00001]) and EHS (OR 5.07; 95% CI: 1.78 to 14.44; p=0.002) ▪ IIEF improvement was more pronounced in patients with moderate ED
Rho BY et al. 2022 SR & MA	460 radical prostatectomy	3-9 month	LI-ESWT	Placebo/sham	▪ LI-ESWT improved IIEF (WMD -2.04; 95% CI: -3.72 to -0.35; p=0.02)
Ong WLK et al. 2022 RCT	51 vasculogenic ED	1, 3 and 6 months	LI-ESWT	Sham	▪ LI-ESWT improved IIEF-EF (1-month [14.1 versus 9.3; p<0.001], 3-month [14.9 versus 8.6; p<0.001], and 6-month [14.2 versus 7.9; p<0.001] and EHS (1-month [2.4 versus 1.8; p=0.001], 3-month [2.7 versus 1.7; p<0.001], and 6- month [2.7 versus 1.6; p<0.001]
Shendy WS et al. 2021 RCT	42 general ED and diabetic polyneuropathy	3-month	LI-ESWT + pelvic floor muscle	Sham + pelvic floor muscle	▪ LI-ESWT improved IIEF-EF (17.5 ± 2.72 versus 13.40 ± 2.85; p<0.001)
Gallo L et al. 2022 RCT	83 general ED	1, 6, and 12 months	LI-ESWT + tadalafil + L-arginine	LI-ESWT without oral therapy	▪ IIEF-EF scores in treatment group: 16.0 ± 4.0, 24.8 ± 3.4, 23.3 ± 4.6, and 21.6 ± 5.5 at baseline, 1, 6, and 12 months of follow-up, whereas in control group: 16.5 ± 4.1, 22.7 ± 4.2, 21.5 ± 4.5, and 19.5 ± 4.9, respectively ▪ An increased in mean EHS score in treatment group from 2.07 ± 0.72 at baseline to 3.39 ± 0.59, 3.17 ± 0.67, and 2.98 ± 0.72 at 1, 6, and 12 months, respectively, and in control group from 2.12 ± 0.80 at baseline to 3.07 ± 0.78 and 2.95 ± 0.76 at 1 and 6 months, respectively
Zanaty F et al. 2022 RCT	50 general ED	6 and 12 weeks	LI-ESWT	Self-administered on-demand 20 mg tadalafil	▪ Both groups showed significant improvement when comparing the baseline values to the follow-up variables for IIEF-5 (17.64 ± 4.01; p<0.001 at 12 weeks within the LI-ESWT group and 15.72 ± 3.6; p<0.001 within the tadalafil group) and EHS (3.2 ± 0.76; p<0.001 at 12 weeks within the LI-ESWT group and 3.1 ± 0.69; p<0.001 within the tadalafil group)
Bechara A et al. 2016 Cohort	50 general ED unresponsive to PDE5i	12 months	LI-ESWT	-	▪ LI-ESWT showed improvement in efficacy parameters in all assessments (IIEF-EF, SEP2 and SEP3, EHS) and responded positively to the GAQ in 60% of patients ▪ The efficacy response was maintained for 12 months (91.7% of patients) ▪ Improvements in the IIEF-EF score was higher whenever ED was more severe, with changes of 13, 10.5, 6.8, and 4.5 points for patients with severe, moderate, mild to moderate, and mild ED, respectively

Study	Patient characteristic/ disease	Follow-up duration	Intervention		Findings
			Treatment	Control	
Lei Q et al. 2021 Non-RCT	78 diverse pathogeneses (psychogenic, organic, and mixed ED)	First- and third-month following initiation of treatment	LI-ESWT	Self-administered on-demand 100 mg sildenafil	▪ In the third month, IIEF-5 was 21.52 in LI-ESWT group and 21.26 in sildenafil group (p>0.05) ▪ The EHS and SEAR improvement was similar in the two groups (p>0.05 at baseline and third month) ▪ Proportion of improvement defined by MCID criteria was 52.2% in LI-ESWT group and 59.4% in sildenafil group (p>0.05)
Wang D et al. 2023 Non-RCT	72 general ED	4 weeks after the final session	LI-ESWT	Self-administered on-demand 100 mg sildenafil	▪ Mean score in IIEF-EF for LI-ESWT and sildenafil was 16.3 ± 5.5 and 18.3 ± 6.5 (p>0.05), respectively

SR & MA, systematic review & meta-analysis; RCT, randomized controlled trial; ED, erectile dysfunction; LI-ESWT, low-intensity extracorporeal shockwave therapy; IIEF, International Index of Erectile Function; IIEF-EF, International Index of Erectile Function-Erectile Function domain; MD, mean difference; RD, risk difference; PDE5i, phosphodiesterase type 5 inhibitors; CI, confidence interval; EHS, Erection Hardness Score; OR, odds ratio; WMD, weighted mean differences; SEP2 and SEP3, Sexual Encounter Profile diaries; GAQ, Global Assessment Question; SEAR, Self-Esteem and Relationship questionnaires; MCID, minimal clinically important difference

5.3 ORGANISATIONAL ISSUES

5.3.1 Treatment protocol

Different LI-ESWT setup parameters such as EFD and number of pulses, and different treatment protocols including treatment frequency and length of course resulted in differences in reported efficacy. In their systematic review and meta-analysis involving 14 studies (n=883), Lu Z et al. (2016) showed that the improvement in IIEF was better in the group with EFD 0.09 mJ/mm^2 compared with EFD 0.1-0.2 mJ/mm^2, although neither group reached statistical significance. Studies administering more shockwaves (number of pulses 3,000) reported a significant increase in IIEF (MD: 2.86; 95% CI: 1.54 to 4.19; p<0.0001) compared with the studies delivering fewer shockwaves. Regarding duration of treatment, shorter course of <6 weeks reported a significant increase in the IIEF (MD: 2.11; 95% CI: 0.98-3.25; p=0.0003).[32] Another meta-analysis by Yao H et al. (2022) also suggested that treatment plans with an energy density of 0.09 mJ/mm^2 (MD 3.81; 95% CI: 2.07 to 5.55; p<0.0001) and pulses number of 1,500 to 2,000 (MD 4.80; 95% CI: 2.61 to 7.00; p<0.0001) was more beneficial to IIEF in ED patients.[36] Indeed, there was no retrievable evidence in the context of procedural time points and training or learning curve related to LI-ESWT for ED.

5.3.2 Treatment satisfaction

Improvement in erectile function using LI-ESWT has been validated in clinical trials. However, no comparative study of LI-ESWT versus sildenafil has been conducted concerning the satisfaction aspect. Herein, Wang D et al. (2023) performed a comparative analysis of the two treatments using validated instruments to assess ED treatment satisfaction of both, patients and their partners. Treatment satisfaction were evaluated using the Erectile Dysfunction Inventory of Treatment Satisfaction questionnaires (EDITS). The study demonstrated that the total EDITS score and index score of both, the patient version and

partner version were similar in the two groups. More detailed analysis of each question in EDITS indicated that a significantly higher number of patients and partners in the LI-ESWT group responded 3 or 4 (very satisfied or somewhat satisfied) to question 1 in the patient and partner version assessing overall satisfaction with treatment than those in the sildenafil group. Furthermore, patients and partners gave the same response to question 6 in the EDITS patient version and question 4 in the partner version, respectively, which address the satisfaction with the duration of intercourse.[44, level II-2]

5.3.3 Guidelines

There are several international organisations that have published guideline recommendations surrounding LI-ESWT including the American Urological Association (AUA; 2018), Asia-Pacific Society for Sexual Medicine (APSSM; 2020), European Society of Sexual Medicine (ESSM; 2019), and European Association of Urology (EAU; 2020).[45-48] All organisations acknowledge LI-ESWT as a potential treatment for ED with promising early clinical studies. The treatment appears safe with minimal risk for serious AEs. The majority of AEs seen in the randomised trials were mild and transient, and there have been no dropouts reported as a result of treatment AEs.[46] However, due to heterogeneity in the literature surrounding treatment protocols and study populations, further investigation is necessary before it can be label as “standard of care” outside the scope of clinical research. Accordingly, LI-ESWT is recommended by the EAU as a first-line treatment alternative in patients with vasculogenic ED who are uninterested or unable to tolerate oral therapy and who are poor PDE5i responders, but this is based on weak evidence.[48] The APSSM similarly suggests that LI-ESWT be offered to men with mild/ moderate vasculogenic ED who do or do not respond to PDE5i (level 2; grade b).[46] The AUA and ESSM, in contrast, consider LI-ESWT as deserving of more investigation or experimental, respectively.[45, 47]

5.4 ECONOMIC IMPLICATION

There was no retrievable evidence on the cost-effectiveness or other economic analysis related to LI-ESWT for ED. However, a prospective study of 51 men with ED revealed that LI-ESWT is more costly compared to self-administered 20 mg tadalafil on-demand. For each participant, the average number of sessions in the shockwave group was six sessions with an average total cost of USD 500.00, while the average of the medical treatment group was 30 tablets throughout the study costing about USD 62.50 ($p<0.001$).[41, level II-1]

5.5 LIMITATIONS

We acknowledge some important limitations in our review and these should be considered when interpreting the results. The selection of the studies and appraisal was done by one reviewer. Although there was no restriction in language during the search, only the full text

articles in English published in peer-reviewed journals were included in the report, which may have excluded some relevant articles and further limited our study numbers. Most of the studies included small sample sizes and the follow-up was relatively short, limited to approximately one year, which does not allow drawing any conclusions for a longer period of time. An increased heterogeneity was also observed among the studies, which can be attributed mainly to the treatment protocol of LI-ESWT for ED that has not been standardized, and there is still no unified standard for energy setting, treatment interval, type of ED patients, age of ED patients, treatment of combined diseases, disease duration of ED, etc. Therefore, in the process of clinical treatment, the whole condition of ED patients should be evaluated, and the individualized LI-ESWT scheme should be considered.

6.0 CONCLUSION

A substantial body of retrievable evidence has demonstrated that LI-ESWT as compared to placebo/ sham is a safe and well-tolerated treatment with modest improvement in erectile function and hardness among patients with ED, and the effect lasted up to 3 to 6 months. Above all, LI-ESWT appears most likely to benefit younger men and in patients with mild or moderate ED and few medical comorbidities such as diabetic and radical prostatectomy. In addition, LI-ESWT may optimize response to PDE5i or enhance medication response in PDE5i “non-responders”. A comparable short-term therapeutic efficacy was shown by the application of LI-ESWT with on-demand sildenafil or tadalafil for ED patients. Adjuvant daily therapy with L-arginine and tadalafil, however, increased efficacy and duration of benefits of LI-ESWT. Lower energy density, increased number of pulses per treatment, and shorter treatment courses resulted in better therapeutic efficacy, especially regarding IIEF improvement.

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8.0 APPENDIX

APPENDIX 1: LITERATURE SEARCH STRATEGY

OVID MEDLINE® ALL <1946 to March 31, 2023>

1. MEN/
2. m#n.tw.
3. ADULT/
4. adult*.tw.
5. ERECTILE DYSFUNCTION/
6. Impotence.tw.
7. (erectile adj dysfunction).tw.
8. (male adj impotence).tw.
9. (male adj2 sexual impotence).tw.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. EXTRACORPOREAL SHOCKWAVE THERAPY/
12. (shock wave adj2 therap*).tw.
13. (extracorporeal adj3 shock wave therap*).tw.
14. (extracorporeal adj2 shockwave therap*).tw.
15. 11 or 12 or 13 or 14
16. PHOSPHODIESTERASE 5 INHIBITORS/
17. (pde 5 adj1 inhibitor*).tw.
18. (pde-5 adj inhibitor*).tw.
19. (phosphodiesterase 5 adj2 inhibitor*).tw.
20. phosphodiesterase type 5 inhibitor*.tw.
21. SILDENAFIL CITRATE/
22. viagra.tw.
23. revatio.tw.
24. citrate.tw.
25. sildenafil.tw.
26. acetildenafil.tw.
27. homosildenafil.tw.
28. hydroxyhomosildenafil.tw.
29. (sildenafil adj (citrate or desmethyl or lactate or nitrate)).tw.
30. TADALAFIL/
31. Cialis.tw.
32. Tadalafil.tw.
33. VASODILATOR AGENTS/
34. vasodilator*.tw.
35. vasorelaxant*.tw.

36. (vasoactive adj antagonists).tw.
37. (vasodilator adj (agent* or drug*)).tw.
38. PENILE PROSTHESIS/
39. (artificial adj penis).tw.
40. (penis adj prosthes#s).tw.
41. (penile adj (implant* or prosthes#s)).tw.
42. PENILE IMPLANTATION/
43. (penile adj implantation*).tw.
44. (penile adj2 prosthes#s implantation*).tw.
45. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44
46. 10 and 15 and 45

Other Databases

PubMed
INAHTA
US FDA

} Same MeSH and keywords as per MEDLINE search

APPENDIX 2: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS

DESIGNATION OF LEVELS OF EVIDENCE

I	Evidence obtained from at least one properly designed randomized controlled trial.
II-I	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

APPENDIX 4: EVIDENCE TABLE

Evidence Table : Effectiveness/ safety/ organisational/ economic implication
Question : What is the effectiveness, safety, and cost-effectiveness of extracorporeal shock wave therapy for the treatment of erectile dysfunction?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comments
1. Lu Z, Lin G, Reed-Maldonado A et al. Low-intensity extracorporeal shock wave treatment improves erectile function: A systematic review and meta-analysis. Eur Urol. 2016; http://dx.doi.org/10.1016/j.eururo.2016.05.050	**Systematic review and meta-analysis** A comprehensive search of the PubMed and Embase databases for studies on low-intensity extracorporeal shock wave treatment (LI-ESWT) and erectile dysfunction (ED) was performed. The abstracted data were analysed with RevMan 5.3 software. The risk of bias in the included studies was assessed by the Cochrane Collaboration's tool. Publication bias was presented in funnel plots. The International Index of Erectile Function (IIEF) and the Erection Hardness Score (EHS) were the most commonly used tools to evaluate the therapeutic efficacy of LI-ESWT.	II-1	A total of 14 studies involving 833 patients were included. These studies were performed by different medical centres in different countries. Most of these ED patients had an organic etiology such as a vascular lesion and a nerve injury. Of the 14 studies, seven were RCTs and were included for meta-analysis.	Low-intensity extracorporeal shock wave treatment (LI-ESWT)	Sham-controlled treatment (without delivering any energy/ with a gel pad that prevent the passage of energy/ with an element that block delivery of shockwaves/ with a sham pad that prevent shockwaves/ with a cap used to prevent LI-ESWT/ with a shock wave absorbent material/ with a probe that did not generate shockwaves	Between 1 and 12 months	The overall meta-analysis of the data revealed that: i. LI-ESWT increased the IIEF and improved the erectile function of ED patients (mean difference [MD] 2.00; 95% CI: 0.99 to 3.00; $p<0.0001$). ii. Patients treated by LI-ESWT developed a good therapeutic effect by 3 months (MD 2.71; 95% CI: 1.51 to 3.91; $p<0.0001$). iii. The patients who had mild or moderate ED (MD 2.86; 95% CI: 1.54 to 4.19; $p<0.0001$) and the ED patients who had no comorbidities (MD 2.36; 95% CI: 1.19 to 3.53; $p<0.0001$) benefited more from LI-ESWT than the patients with severe ED ($p=0.30$) or with comorbidities ($p=0.33$). iv. Lower energy density (EFD 0.09 mJ/mm^2), increased number of pulses (3,000), and shorter treatment courses of <6 week resulted in better therapeutic efficacy. v. LI-ESWT improves the erectile hardness of the penis for ED patients, especially at 1 month after treatment (risk difference [RD] 0.47; 95% CI: 0.38 to 0.56; $p<0.00001$), and that this improvement lasts for at least 3 months (RD 0.16; 95% CI: 0.04 to 0.29; $p=0.01$).	Most of the included RCTs did not describe the details of randomisation or blinding, and the potential biases involved are unclear.

Evidence Table : Effectiveness/ safety/ organisational/ economic implication
Question : What is the effectiveness, safety, and cost-effectiveness of extracorporeal shock wave therapy for the treatment of erectile dysfunction?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comments
2. Brunckhorst O, Wells L, Teeling F et al. A systematic review of the long-term efficacy of low-intensity shockwave therapy for vasculogenic erectile dysfunction. Int Urol Nephrol. 2019; 51(5): 773-781	**Systematic review** Electronic databases, MEDLINE (via PubMed) and Scopus, were systematically searched. The primary outcome measure extracted for clinical efficacy included erectile function measures such as the International Index of Erectile Function-Erectile Function domain (IIEF-EF) or EHS scores after LI-ESWT at long-term follow-up of over 6 months. Additionally, subgroup analysis of LI-ESWT effectiveness was conducted via assessment of population cohorts including age, phosphodiesterase 5 inhibitors (PDE5i) responsiveness, presence of vascular co-morbidities and smoking status.	II-1	Eleven articles (five RCTs and six non-randomised) representing a total of 799 vasculogenic ED patients were included in the review.	Low-intensity extracorporeal shock wave therapy (LI-ESWT)	Placebo/ sham-controlled treatment	Between 1 and 24 months	**Long-term efficacy of LI-ESWT** Nine of the eleven studies found a statistically significant increase in erectile function utilising either IIEF or EHS scores after LI-ESWT at over 6-month follow-up (median IIEF-EF score improvement from baseline at 6 months 5.3, range 2.6-10.7). When assessing studies with follow-ups of greater than 6 months, there appeared to be limited improvement in IIEF scores beyond this time period (change in IIEF-EF scores of between −2 and 0.1). Three out of five studies demonstrated a gradual decline in erectile function with two showing a plateauing of results. However, none of these studies demonstrated a decrease in erectile function below baseline post intervention. **Effect of LI-ESWT on specific population cohorts** Increasing age appears to reduce responsiveness to LI-ESWT treatment in long-term follow-up studies. Furthermore, ED severity, PDE5i responsiveness, and co-morbidities may also influence its effectiveness; however, results are inconsistent at present.	Selection bias (attrition of study participants). Five RCTs demonstrated small numbers of participants, with all being single centre trials. Sham or double blinded nature of the trials.

Evidence Table : Effectiveness/ safety/ organisational/ economic implication
Question : What is the effectiveness, safety, and cost-effectiveness of extracorporeal shock wave therapy for the treatment of erectile dysfunction?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comments
3. 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. International Journal of Impotence Research. 2019; 31(3): 177-194	**Systematic review and meta-analysis** Aim: to evaluate the efficacy of LI-ESWT for ED, identify the ideal treatment population and treatment protocol, and provide recommendations for future research in the field. Systematic research (Medline, Embase, The Cochrane Library, Scopus, and Web of Science) for relevant clinical studies was performed. Only clinical studies that investigated the efficacy of LI-ESWT for ED only, and reported primary outcomes using IIEF-EF scores/ questionnaires were included. Both RCTs and cohort studies were included, but the meta-analysis was performed only for sham-controlled RCTs.	II-1	Ten RCTs including 873 patients with vasculogenic ED, either PDE5i-responders or PDE5i-non-responders were selected for the meta-analysis. The mean age was 58 (range 27–81) years.	Low-intensity extracorporeal shock wave therapy (LI-ESWT)	Sham-controlled treatment	12 months	Pooling data of these studies showed that LI-ESWT could significantly improve erectile function in men with ED regarding both patient-subjective outcomes (IIEF-EF: +3.97; 95% CI: 2.09 to 5.84; $p<0.0001$, EHS ≥ 3: odds ratio [OR]: 4.35; 95% CI: 1.82 to 10.37; $p=0.0009$) and patient-objective outcomes (peak systolic velocity [PSV]: +4.12; 95% CI: 2.30 to 5.94; $p<0.00001$). In the subgroup of patients with vasculogenic ED that where PDE5i-responders, a significant difference in IIEF-EF change from baseline was observed (MD: 4.12; 95% CI: 1.30 to 6.95; $p=0.004$) favouring the LI-ESWT group. Subgroup analysis regarding the duration of follow-up using the IIEF-EF scores at 1-, 3-, 6-, and 12-months follow-up showed that the positive effect of LI-ESWT lasts for 12 months, although it could be weaker with time. All studies reported that LI-ESWT for ED was not associated with any pain, discomfort or side-effects such as ecchymoses of haematuria.	Most included trials had small samples and short follow-up time. An increased heterogeneity due to treatment protocol and patient selection.

Evidence Table : Effectiveness/ safety/ organisational/ economic implication
Question : What is the effectiveness, safety, and cost-effectiveness of extracorporeal shock wave therapy for the treatment of erectile dysfunction?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comments
4. Liu S, Pu J, Li X et al. Effects of low-intensity extracorporeal shockwave therapy on erectile dysfunction: A systematic review and meta-analysis. J Coll Physicians Surg Pak. 2022; 32(09): 1181-1186	**Systematic review and meta-analysis** Aim: to examine the effectiveness of LI-ESWT on improving ED in the male patients based on IIEF-EF score or EHS relative in relation to those who received placebo treatment, and provide a formal recommendation based on the literature review for future RCTs. The Medline and Embase databases were systemically searched. The primary endpoint was IIEF-EF score/ questionnaire or EHS.	I	Eleven RCTs including 814 male patients were enrolled.	Low-intensity extracorporeal shock wave therapy (LI-ESWT)	Placebo/ sham-controlled treatment	Between 7-week and 12 months	The seven eligible studies suggested that relative to placebo treatment, male ED patients receiving LI-ESWT had markedly increased IIEF-EF scores (MD: 2.77 points; 95% CI: 1.74 to 3.79; I^2=66%; p<0.001). Besides, patients were followed up at 1, 3, 6, 9, and 12 months and 7 weeks, and it was found that the patients receiving Li-ESWT had evidently elevated IIEF scores (MD: 2.96 points; 95% CI: 2.31 to 3.61; I^2=48%; p<0.001). Similarly, patients receiving LI-ESWT treatment had dramatically elevated EHS scores in relation to those taking placebo treatment (OR: 10.40 points; 95% CI: 5.60 to 19.31; I^2=66%; p<0.001). There were 7 RCTs mentioning EHS scores with different total pulses, which reported that the EHS scores evidently elevated following the LI-ESWT (OR: 9.37; 95% CI: 5.65 to 15.52; I^2=61%; p<0.001). There were 9 articles that mentioned the ED severity, based on IIEF score or responds to PDE5i. Compared with placebo, LI-ESWT alleviates ED symptoms in patients, particularly those who have mild or moderate ED. None of the enrolled studies reported any severe adverse reaction.	Each study showed a low-risk due to selective reporting or incomplete outcome data. Majority of the articles only carry out follow-up for about one year.

Evidence Table : Effectiveness/ safety/ organisational/ economic implication
Question : What is the effectiveness, safety, and cost-effectiveness of extracorporeal shock wave therapy for the treatment of erectile dysfunction?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comments
5. 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. Am J Mens Health. 2022; 16(2): doi:10.1177/15579883221087532	**Systematic review and meta-analysis** Aim: to evaluate the efficacy of LI-ESWT in the treatment of ED from PubMed, EMBASE, and Cochrane databases. The data were analysed by Review Manager Version 5.4.	I	A total of 16 RCTs including 1,064 participants were included to evaluate the effectiveness of LI-ESWT in the treatment of ED. There was no significant difference in mean age and severity of ED between the LI-ESWT and the placebo group.	Low-intensity extracorporeal shock wave therapy (LI-ESWT)	Placebo/ sham-controlled treatment	1-, 3-, 6-month	Fifteen articles mentioned IIEF. The results reported that after 1 month (MD 3.18; 95% CI: 1.38 to 4.98; p=0.0005), 3 months (MD 3.01; 95% CI: 2.04 to 3.98; p<0.00001), and 6 months follow-up (MD 3.20; 95% CI: 2.49 to 3.92; p<0.00001), the treatment group can significantly increase the IIEF of ED patients compared with the control group. Eight articles provided data on the improvement of patients with baseline EHS ≤2 to EHS ≥3 after treatment. There was a significant difference in the number of people of EHS improvement between the treatment group and the control group (OR 5.07; 95% CI: 1.78 to 14.44; p=0.002). The positive response rate of Questions 2 and 3 of the Sexual Encounter Profile (SEP) was not statistically significant (SEP2: OR 1.27; 95% CI: 0.70 to 2.30; p=0.43; SEP3: OR 4.24; 95% CI: 0.67 to 26.83; p=0.13). **Subgroup analysis:** The results of this meta-analysis suggest that treatment plans with an energy density of 0.09 mJ/mm^2 (MD 3.81; 95% CI: 2.07 to 5.55; p<0.0001) and pulses number of 1,500 to 2,000 (MD 4.80; 95% CI: 2.61 to 7.00; p<0.0001) are more beneficial to IIEF in ED patients. In addition, IIEF improvement was more pronounced in patients with moderate ED after LI-ESWT (MD 4.24; 95% CI: 2.88 to 5.59; p<0.00001).	

Evidence Table : Effectiveness/ safety/ organisational/ economic implication **(RADICAL PROSTATECTOMY)**
Question : What is the effectiveness, safety, and cost-effectiveness of extracorporeal shock wave therapy for the treatment of erectile dysfunction?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comments
6. Rho BY, Kim SH, Ryu JK et al. Efficacy of low-intensity extracorporeal shock wave treatment in erectile dysfunction following radical prostatectomy: a systematic review and meta-analysis. J. Clin. Med. 2022; 11: 2775	**Systematic review and meta-analysis** Aim: to investigate the efficiency of LI-ESWT in ED following radical prostatectomy (RP). A literature search of all publications was conducted using the Ovid-Embase, PubMed, and Cochrane Library databases. The endpoint was the change in IIEF scores after LI-ESWT.	II-1	Five papers (460 patients who underwent RP or radical cystoprostatectomy and had normal sexual function before surgery) were included in the meta-analysis.	Low-intensity extracorporeal shock wave therapy (LI-ESWT)	Placebo/ sham-controlled treatment	3-9 months	In IIEF scores performed 3-4 months after LI-ESWT, patients receiving LI-ESWT showed statistically significantly better results (weighted mean differences [WMD]; -2.04; 95% CI: -3.72 to -0.35; p=0.02) than the control group. However, there were two studies that measured the results after 9-12 months and no statistical difference between the two groups (WMD: -5.37; 95% CI: -12.42 to 1.69; p=0.14) were observed.	Level of evidence was low. Therefore, careful interpretation of the results is required.

Evidence Table : Effectiveness/ safety/ organisational/ economic implication
Question : What is the effectiveness, safety, and cost-effectiveness of extracorporeal shock wave therapy for the treatment of erectile dysfunction?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comments
7. Ong WLK, Lechmiannandan S, Lim YL et al. Early outcomes of short-course low intensity shockwave therapy (LiSWT) for erectile dysfunction: A prospective, randomized, double-blinded, sham-controlled study in Malaysia. Andrologia. 2022; 54(9): e14518	**Randomised controlled trial** A prospective, randomised, double-blinded, sham controlled single centre trial was conducted in Penang General Hospital, Malaysia. Study subjects were recruited by opportunistic screening from general outpatient and urology clinics. Others were directly referred by physicians for treatment of ED. All eligible patients were randomized into Arm 1 or Arm 2 with an equal allocation ratio (1:1). The randomisation sequence was computer generated by the study coordinator. The subjects and clinicians who were responsible for the data collection, were blinded to the treatment protocols. Measurements using validated five-item version of the International Index of Erectile Function (IIEF-5) questionnaire scores and EHS and of the adverse events of the therapy, at the beginning and the end of the treatment (1 month) and 3, 6 months after therapies were recorded.	I	A total of 51 patients (median age 59 years) were recruited for this study of which 27 patients underwent a 4-week course of LI-ESWT while 24 patients were not given shockwave therapy (sham therapy).	Low-intensity extracorporeal shock wave therapy (LI-ESWT)	Placebo/ sham-controlled treatment	1, 3 and 6 months	The mean IIEF-5 scores were significantly improved in the treatment arm compared to worsening of scores in the sham arm after 1 month (14.1 versus 9.3; $p<0.001$), 3 months (14.9 versus 8.6; $p<0.001$), and 6 months (14.2 versus 7.9; $p<0.001$) post treatment. When evaluating for success of treatment, defined as IIEF score improvement of more than five points, only 15%, 22% and 26% of patients in the treatment arm achieved such results at 1, 3 and 6 months, respectively. None of the patients in the sham arm had a 5-point increment. A significant improvement of EHS was demonstrated at 1 month (2.4 versus 1.8; $p=0.001$), 3 months (2.7 versus 1.7; $p<0.001$), and 6 months (2.7 versus 1.6; $p<0.001$) in the treatment arm compared to sham arm. With regards to significant improvement in EHS, defined as EHS of 3 or more, 44%, 63% and 63% of patients in the treatment arm achieved significant erection hardness, at 1, 3 and 6 months, respectively. In the sham arm, only 8%, 8% and 4% of patients achieved this at similar time intervals. No adverse events such as minor skin bruises, hematoma, haematuria, urinary retention and chronic pain were reported.	

Evidence Table : Effectiveness/ safety/ organisational/ economic implication **(DIABETIC)**
Question : What is the effectiveness, safety, and cost-effectiveness of extracorporeal shock wave therapy for the treatment of erectile dysfunction?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comments
8. Shendy WS, Elsoghier OM, El Semary MM et al. Effect of low-intensity extracorporeal shock wave therapy on diabetic erectile dysfunction: Randomised control trial. Andrologia. 2021; 53: e13997. https://doi.org/10.1111/and.13997	**Randomised controlled trial** Aim: to assess the effectiveness of LI-ESWT in the management of ED in diabetic patients with mixed vasculogenic and neurogenic causes as confirmed by nerve conduction and Doppler studies. The erectile function was evaluated by the IIEF-5. The score ranges from 1 to 25 and classifies ED severity with the following breakpoints: severe (1–7/25), moderate (8–11/25), mild to moderate (12–16/25), mild (17-21/25) and no ED (22–25/25). Colour-coded duplex sonography (5-10 MHz probes) was used for the evaluation of penile perfusion. The systolic and diastolic velocities (cm/s) were performed at 10 and 30 min for both cavernous arteries. The highest values obtained were recorded. The following Doppler indices of the right and left cavernous arteries: peak systolic velocity (PSV), end-diastolic velocity (EDV) and resistance index (RI) were recorded.	I	A total of 42 patients (41-55 years with a confirmed diagnosis of ED and diabetic polyneuropathy) were included in the final analysis. They were randomly allocated to one of two groups: shock wave group (n=21) treated with LI-ESWT plus pelvic floor muscle training and control group (n=21) treated with pelvic floor muscle exercise and sham therapy by a shockwave.	Low-intensity extracorporeal shock wave therapy (LI-ESWT) plus pelvic floor muscle training	Pelvic floor muscle exercise and sham therapy by a shockwave	The assessment was done before and three months after treatment.	Regarding the baseline Doppler measurements, there were no significant differences in the 3 Doppler indices of the right and left cavernous arteries between the two groups. After treatment, PSV of the right and left cavernous arteries increased significantly in the two groups. However, the post-treatment PSV was significantly higher in the LI-ESWT group compared to the sham group ($p<0.001$, for both arteries). There was no significant change of EDV of the two cavernous arteries after treatment in the two groups. The RI of right and left cavernous arteries increased significantly in the LI-ESWT group, but not in the sham group. IIEF-EF increased significantly in the LI-ESWT group ($p<0.001$), but not in the control group ($p=0.194$). In the LI-ESWT group, 15 (71%) patients achieved erection sufficient for penetrative intercourse versus 2 (9.5%) patients in the control group ($p<0.001$). No study participants reported any pain or adverse events during the sessions or the follow-up.	Small sample size and short-term follow-up.

Evidence Table : Effectiveness/ safety/ organisational/ economic implication **(COMBINATION ORAL THERAPY)**
Question : What is the effectiveness, safety, and cost-effectiveness of extracorporeal shock wave therapy for the treatment of erectile dysfunction?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comments
9. Gallo L, Pecoraro S, Sarnacchiaro P. Adjuvant daily therapy with L-arginine 2,500 mg and tadalafil 5 mg increases efficacy and duration of benefits of low-intensity extracorporeal shock wave therapy for erectile dysfunction: A prospective, randomized, single-blinded study with 1-year follow-up. Investig Clin Urol. 2022; 63(1): 83-91	**Randomised controlled trial** Aim: to investigate a therapeutic protocol for ED based on the combination of LI-ESWT, tadalafil, and L-arginine. Recruited patients completed the domain IIEF-EF and the EHS questionnaires at baseline and were randomly assigned in two groups. The percentage of patients who reached a minimal clinically important difference (MCID) in IIEF-EF were also evaluated. *MCID was defined as an increase in IIEF-EF score of 2 points for patients with baseline mild ED (IIEF-EF scores of 18–25) and of 5 points for patients with baseline moderate ED (IIEF-EF scores of 11–17).	I	A total of 83 individuals were randomly assigned; 41 in Group A (treatment) and 42 in Group B (control). At baseline, the two groups were homogeneous for all the features evaluated in the study.	LI-ESWT with tadalafil 5 mg for 3 months and daily L-arginine 2,500 mg for 6 months	LI-ESWT without oral therapy	Follow-up visits were scheduled 1, 6, and 12 months after the last LI-ESWT application	The mean IIEF-EF scores in group A were 16.0 ± 4.0, 24.8 ± 3.4, 23.3 ± 4.6, and 21.6 ± 5.5 at baseline, 1, 6, and 12 months of follow-up, whereas in group B the mean IIEF-EF scores were 16.5 ± 4.1, 22.7 ± 4.2, 21.5 ± 4.5, and 19.5 ± 4.9, respectively. An increased in mean EHS score were also reported in group A from 2.07 ± 0.72 at baseline to 3.39 ± 0.59, 3.17 ± 0.67, and 2.98 ± 0.72 at 1, 6, and 12 months, respectively, and in group B from 2.12 ± 0.80 at baseline to 3.07 ± 0.78 and 2.95 ± 0.76 at 1 and 6 months, respectively. The percentage of men who reached a MCID was 100% and 88.1% at 1 month, 87.8% and 76.2% at 6 months, and 75.6% and 66.7% after 1 year for group A and group B, respectively. The degree of response to treatment and the duration of benefits were greater in younger men and in patients affected by mild ED. Low incidence of minor adverse effects was reported in both groups. Some patients experienced a stinging sensation during LI-ESWT, especially at the perineal level.	Absence of a placebo group and the lack of evaluation of hemodynamic parameters.

Evidence Table : Effectiveness/ safety/ organisational/ economic implication **(VERSUS TADALAFIL)**
Question : What is the effectiveness, safety, and cost-effectiveness of extracorporeal shock wave therapy for the treatment of erectile dysfunction?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comments
10. Zanaty F, Badawy A, Kotb H et al. Efficacy and safety of low-intensity extracorporeal shock wave therapy versus on-demand tadalafil for erectile dysfunction. Arab J Urol. 2022; 20(4): 189-194	**Randomised clinical trial** Participants were randomized to the LI-ESWT group or Tadalafil group by the electronic method. Patients in the LI-ESWT group received 6 sessions (2 per week). Patients in the Tadalafil group self-administered Tadalafil on-demand at a dose of 20 mg each hour before each event of sexual intercourse. The outcomes were assessed using the IIEF-5 score, EHS, and SEAR questionnaire before, at 6 and 12 weeks after treatment. Treatment-related side effects and costs were recorded too. An improvement of 5 points or greater from IIEF-5 score baseline and an increase in EHS score from 2 or less at baseline to 3 or more, and a positive change in SEAR questionnaire score were considered significant.	II-1	A total of 50 adults with ED for at least 12 months and in a stable marriage relationship were included. The mean age at the time of the LI-ESWT group was 43.7 years and in the Tadalafil group was 47.0 years.	Low-intensity extracorporeal shock wave therapy (LI-ESWT)	Self-administered on-demand Tadalafil at a dose of 20 mg	6 and 12 weeks	There were no significant differences in baseline IIEF-5 score and baseline EHS between the two groups (11.16 $\pm$ 4.2 and 10.08 $\pm$ 3.8; $p>0.34$). IIEF-5 score increased significantly from baseline to 16.36 $\pm$ 3.8 ($p<0.001$) at 6 weeks and to 17.64 $\pm$ 4.00 ($p<0.001$) at 12 weeks within the LI-ESWT group, and the IIEF-5 score also increased significantly from baseline to 17.52 $\pm$ 2.75 ($p<0.001$) at 6 weeks and to 15.72 $\pm$ 3.6 ($p<0.001$) at 12 weeks within the Tadalafil group. The median change in IIEF-5 score in the LI-ESWT and Tadalafil groups was 5.2 and 7.4 at the 6-week and 6.4 and 5.6 at the 12-week follow-up. Mean EHS also statistically higher at 6 and 12 weeks within both groups. The SEAR questionnaire scores, which show the negative effects of ED on the psychological condition and positive effects of successful treatment for both groups, were not a statistically significant difference at baseline ($p=0.3$) but showed an improvement comparing baseline values to follow-up variables for both groups ($p<0.001$). There was a notable statistical difference between the two groups regarding the side effects as the shockwave group was with mild side effects (2 cases [8%] with tolerable penile pain, 1 case [4%] with skin bruises) and no deformity recorded, while there were noticeable side effects on the Tadalafil group ($p<0.05$); 11 of 25 patients had side effects (44%): 5 patients suffered from muscle pain (20%), 4 patients suffered from headache (16%), and 2 patients suffered from nausea (8%). LI-ESWT is more costly compared to Tadalafil. For each participant, the average number of sessions in the shockwave group was 6 sessions with an average total cost of USD 500.00, while the average of the medical treatment group was 30 tablets throughout the study costing about USD 62.50 ($p<0.001$).	Small number of participants and short-term follow-up.

Evidence Table : Effectiveness/ safety/ organisational/ economic implication **(NON-RESPONDERS TO PDE5I)**
Question : What is the effectiveness, safety, and cost-effectiveness of extracorporeal shock wave therapy for the treatment of erectile dysfunction?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comments
11. Bechara A, Casabé A, De Bonis W et al. Twelve-month efficacy and safety of low-intensity shockwave therapy for erectile dysfunction in patients who do not respond to phosphodiesterase type 5 inhibitors. Sex Med. 2016; 4(4): e225-e232	**Cohort study** This open-label, longitudinal, and observational study investigated an uncontrolled population of 50 consecutive patients whose ED was unresponsive to PDE5i treatment. Patients were treated with a four-session LI-ESWT protocol. During active treatment and follow-up, all patients remained on their regular high on-demand or once-daily PDE5i dosing schedules. Effectiveness was assessed using the IIEF-EF, questions 2 and 3 from the Sexual Encounter Profile (SEP2 and SEP3) diaries, EHS, and Global Assessment Question (GAQ) at baseline and at 3, 6, 9, and 12 months after treatment. Patients were considered responders to LI-ESWT whenever they showed improvement in erection parameters in all four assessments and responded positively to the GAQ. Adverse events were also recorded.	II-2	Eighty percent of patients (40/50) completed the treatment and follow-up. Ten patients with were excluded because of loss to the first follow-up. Median age was 64.8 years and duration of ED was 70.5 months.	Low-intensity extracorporeal shock wave therapy (LI-ESWT)	-	12 months	No statistically significant difference was found for age, duration of ED, comorbidities, and dysfunction severity when comparing responders to LI-ESWT (24/40) with non-responders to LI-ESWT (16/40). Sixty percent (24/40) of patients showed improvement in efficacy parameters in all four assessments (IIEF-EF, SEP2, SEP3, and EHS) and responded positively to the GAQ. These changes were significant from the first follow-up (3 months after treatment). By the third month after treatment, 91.7% (22/24) of responders to LI-ESWT maintained efficacy parameters up to the last follow-up visit 12 months after treatment. Improvements in the IIEF-EF score was higher whenever ED was more severe, with changes of 13, 10.5, 6.8, and 4.5 points for patients with severe, moderate, mild to moderate, and mild ED, respectively. No patient reported treatment-related adverse events.	Lack of a placebo group prevents a proper comparison of the effects of LI-EWST.

Evidence Table : Effectiveness/ safety/ organisational/ economic implication **(VERSUS VIAGRA)**
Question : What is the effectiveness, safety, and cost-effectiveness of extracorporeal shock wave therapy for the treatment of erectile dysfunction?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comments
12. Lei Q, Wang D, Liu C et al. Comparison of the efficacy and safety of low-intensity extracorporeal shock wave therapy versus on-demand sildenafil for erectile dysfunction: a prospective non-randomized study. Transl Androl Urol. 2021; 10(2): 860-868	**Non-randomised interventional study** After a 4-week washout period of past ED treatment, patients entered one of 2 active treatment groups. The primary outcome was effectiveness as measured by IIEF-5, with other measurements, including the EHS and Self-Esteem and Relationship (SEAR) questionnaires consisting of Confidence Domain and Relationship Domain. The number of adverse events assessed therapeutic safety.	II-2	A total of 78 participants of diverse pathogeneses (psychogenic, organic, and mixed ED) completed the study; 46 in the LI-ESWT and 32 in the sildenafil group. Overall, 26.9% (21/78) of the participants were psychogenic.	9-week of LI-ESWT	Self-administered sildenafil on-demand at a dose of 100 mg	First- and third-month following initiation of treatment	At baseline, the IIEF-5 score was equal in both groups (14.09 ± 3.75 in the LI-ESWT group and 13.0 ± 4.20 in the sildenafil group, adjusted for age). The mean (SD) score in IIEF-5 for LI-ESWT and sildenafil was 19.0 ± 5.75 and 24.5 ± 4.3 at first month follow-up ($p<0.01$), and 20.52 ± 5.92 and 20.59 ± 6.40 at third month follow-up ($p>0.05$). Improvement of the IIEF-5 score was higher in the first month follow-up in the sildenafil group, with no statistically significant difference at the third month follow-up. The EHS and SEAR were similar to IIEF-5, which was equal at baseline, higher in the sildenafil group in the first month, but equal again in the third month. According to MCID criteria, a 7-score improvement of severe patients and 5-score improvement of mild and moderate patients were recorded as positive results. In the third month, 24 participants (52.2%) in the LI-ESWT group and 19 (59.4%) in the sildenafil group reported positive results ($p>0.05$). In the third month, the ratio of patients who achieved clinical cure defined by IIEF-5 >26 was 21.9% in the sildenafil and 15.2% in the LI-ESWT group ($p>0.05$). **Safety** There was no participant discontinuation due to adverse events. The most common treatment-emergent adverse events in the sildenafil group were flushing, headache and dizziness, and dyspepsia. The most common treatment-emergent adverse events in the LI-ESWT group were headache and dizziness, dyspepsia, and local penile pain.	Number of participants was not large enough for subgroup comparison concerning psychogenic, vascular, and mixed causes.

Evidence Table : Effectiveness/ safety/ organisational/ economic implication **(TREATMENT SATISFACTION)**
Question : What is the effectiveness, safety, and cost-effectiveness of extracorporeal shock wave therapy for the treatment of erectile dysfunction?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comments
13. Wang D, Wang SJ, Li YJ et al. The treatment satisfaction in patients and their partners treated with low-intensity extracorporeal shock wave therapy and sildenafil: a prospective non-randomized controlled study. Patient Prefer Adherence. 2023; 17: 583-589	**Prospective, non-randomized, controlled clinical trial** After a 4-week washout period of past treatment, participants entered one of two active treatment group - either 9-week LI-ESWT (treatment group) or 100 mg on-demand sildenafil therapy (control group) according to their intention of treatment. The primary outcome was the satisfaction of the patients and their partners, as measured using the Erectile Dysfunction Inventory of Treatment Satisfaction questionnaires (EDITS). The erectile function was evaluated using the erectile function domain of the IIEF-EF questionnaires.	II-2	A total of 72 participants (young men) were enrolled (42 in the LI-ESWT group and 30 in the sildenafil group). Patient in the two groups have similar demographic profiles except for age (31.2 $\pm$ 5.2 in the sildenafil group versus 33.9 $\pm$ 6.2 in the LI-ESWT group; $p<0.05$).	9-week of LI-ESWT	Self-administered sildenafil on-demand at a dose of 100 mg	4 weeks after the final session	Four weeks after the final session, the mean (SD) score in IIEF-EF for LI-ESWT and sildenafil was 16.3 $\pm$ 5.5 and 18.3 $\pm$ 6.5 ($p>0.05$), respectively. The total EDITS score and index score of both, the patient version and partner version, were similar in the two groups. More detailed analysis of each question in EDITS indicated that a significantly higher number of patients and partners in the LI-ESWT group responded 3 or 4 (very satisfied or somewhat satisfied) to question 1 in the patient and partner version assessing overall satisfaction with treatment than those in the sildenafil group. Furthermore, patients and partners gave the same response to question 6 in the EDITS patient version and question 4 in the partner version, respectively, which address the satisfaction with the duration of intercourse. No participant discontinuation due to adverse events was observed. The only treatment-emergent adverse events in the sildenafil group were flushing and headache (1/30, 3.3%). Other than local penile pain (1/42, 2.4%), no adverse effects were encountered in the Li-ESWT group.	A small cohort and short-term follow-up. Penile hemodynamics were not measured to confirm the improvement of cavernous blood inflow or penile rigidity. Subgroup comparison was not applied to identify different etiologic groups.