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Can Combination Therapy Improve Outcomes in PDE5i-Refractory Erectile Dysfunction? A Systematic Review of Low-Intensity Extracorporeal Shockwave Therapy

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Abstract: -Introduction: Phosphodiesterase type 5 inhibitors (PDE5i) are the first-line treatment for erectile dysfunction (ED) however, some patients experience inadequate therapeutic responses. Low-intensity extracorporeal shockwave therapy (Li-ESWT) has emerged as a restorative treatment that may enhance erectile function and responsiveness to PDE5i. This systematic review evaluated the efficacy and safety of Li-ESWT alone or in combination with PDE5i compared with relevant monotherapy.

Methods: PubMed, Scopus, ScienceDirect, Europe PMC, and Epistemonikos were systematically searched for English-language studies published between 2015 and 2026. RCT and comparative observational studies evaluating Li-ESWT alone or combined with PDE5i in adult men with ED were included. Erectile-function, safety, and secondary clinical outcomes were narratively synthesized because of clinical and methodological heterogeneity. Risk of bias was assessed using RoB 2 and ROBINS-I.

Results: Five studies (420 participants; three RCTs and two prospective non-randomized studies) were included from 492 identified records. Li-ESWT consistently improved erectile-function outcomes. Compared with relevant monotherapy, combination therapy generally produced greater improvements in IIEF-5/IIEF-EF and EHS in selected populations, while another suggest greater durability in treatment effects. Benefits appeared more pronounced in moderate-to-severe ED, whereas Li-ESWT monotherapy may be sufficient in milder disease. Li-ESWT demonstrated short-term efficacy comparable to PDE5i monotherapy, with potential advantages in tolerability and treatment satisfaction. All RCTs had some risk-of-bias concerns, while both non-randomized studies had serious overall risk of bias.

Conclusion: Li-ESWT-based combination therapy may provide greater improvements in erectile-function outcomes than monotherapy in selected patients; however, heterogenity in populations, treatment protocols and methodological limitations precludes definitive conclusions regarding its superiority, particularly in strictly defined PDE5i-refractory ED.

Keywords: Erectile dysfunction; PDE5 inhibitors; low-intensity extracorporeal shockwave therapy; combination therapy; Li-ESWT; systematic review

INTRODUCTION

Erectile dysfunction (ED), defined as the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual activity, is a common male sexual disorder with substantial implications for quality of life, psychological well-being, and intimate relationships. Its prevalence increases with age and is strongly associated with vascular and metabolic risk factors, including diabetes mellitus, hypertension, dyslipidemia, obesity, and cardiovascular disease. Beyond its impact on sexual health, ED may also reflect underlying endothelial and vascular dysfunction. Phosphodiesterase type 5 inhibitors (PDE5i), including sildenafil and tadalafil, have transformed the management of ED and remain a cornerstone of pharmacological treatment. However, their overall efficacy is approximately 60–70%, leaving a clinically important proportion of patients with inadequate treatment response [1,2]

Despite their established efficacy, PDE5i primarily facilitate erections in association with sexual stimulation and do not directly reverse the underlying pathophysiological abnormalities responsible for ED. Approximately 30–35% of patients fail to respond adequately to PDE5i, although some apparent non-responders may be salvaged through optimization of drug use and counseling. True non-responders are often considered for vacuum erection devices, intracavernosal or intraurethral therapies, and penile prosthesis implantation, which may be less acceptable because of their invasiveness or treatment burden[1]. This therapeutic limitation has stimulated interest in restorative approaches capable of improving spontaneous erectile function rather than providing only transient symptomatic support.

Low-intensity extracorporeal shockwave therapy (Li-ESWT) has emerged as a potential restorative treatment for ED. The first clinical pilot study by Vardi et al. (2010) demonstrated improvements in erectile function and penile endothelial parameters following Li-ESWT, establishing the basis for its subsequent investigation in vasculogenic ED. Proposed mechanisms include the induction of angiogenic signaling and neovascularization, improvement of penile microcirculation, recruitment of progenitor cells, tissue remodeling, and

potentially neural repair. Unlike PDE5i, these mechanisms theoretically target components of the underlying vascular pathology of ED. Subsequent studies extended this concept to men responding poorly to PDE5i. Gruenwald et al. (2012) reported improved erectile-function scores and restoration of erections sufficient for intercourse when Li-ESWT was followed by PDE5i therapy, while Palmieri et al. (2020) demonstrated clinically significant improvements in IIEF-EF, EHS, penile hemodynamics, and quality of life with Li-ESWT combined with PDE5i in previous non-responders.

Nevertheless, the comparative and long-term evidence remains uncertain. Clinical studies have differed substantially in patient selection, ED severity, shockwave devices, energy settings, number and frequency of treatment sessions, concomitant PDE5i use, outcome measures, and follow-up duration. Moreover, randomized evidence has produced inconsistent findings, including discrepancies between IIEF and EHS outcomes and uncertainty regarding sustained benefit [3]. Combination therapy is particularly relevant but incompletely resolved. Setiawan et al. (2022) reported greater improvements in IIEF-5, EHS, peak systolic velocity, and VEGF with Li-ESWT plus daily tadalafil than tadalafil alone, suggesting a potentially complementary effect between pharmacological vasodilation and restorative shockwave therapy. More recent comparative evidence also suggests that the magnitude of benefit may vary according to ED severity, emphasizing the need for better treatment stratification.

Therefore, this systematic review aims to synthesize the available evidence on the efficacy and safety of Li-ESWT-based treatment, particularly its use in combination with PDE5 inhibitors, in men with erectile dysfunction with inadequate response to PDE5i therapy, and to determine whether combination strategies provide clinically meaningful advantages over relevant monotherapy approaches. The review will focus on adult men and eligible randomized and observational studies published between 2015 and 2026, evaluating outcomes including IIEF-EF/IIEF-5 or SHIM, EHS, SEP2/SEP3, durability of treatment response, and adverse events. By integrating comparative effectiveness, safety, and durability data, this review seeks to clarify the potential role of Li-ESWT-based combination therapy in the management of difficult-to-treat ED.

MATERIAL AND METHODS

Eligibility Criteria

Studies were selected according to predefined eligibility criteria. Eligible participants were adult men aged ≥18 years with ED including those with documented inadequate response or refractoriness to an adequate trial of PDE5 inhibitor therapy (e.g., ≥4 attempts at maximum

tolerated dose). Studies were included if they evaluated low-intensity extracorporeal shockwave therapy (Li-ESWT) as a primary therapeutic intervention, either as monotherapy or in combination with phosphodiesterase type 5 inhibitors (PDE5i), and provided quantitative clinical outcomes related to erectile function. Randomized controlled trials (RCTs) and comparative or longitudinal observational studies were eligible for inclusion. Only full-text articles published in English between January 2015 and 2026 were considered.

Studies were excluded if they involved patients without ED, untreated ED populations outside the predefined therapeutic context, or patients treated primarily for other conditions, such as Peyronie's disease, without separately extractable ED data. Studies combining Li-ESWT with other therapeutic modalities whose independent effects could not be distinguished, such as stem cell therapy, platelet-rich plasma, or penile prosthesis, were also excluded. Systematic reviews, meta-analyses, narrative or scoping reviews, editorials, commentaries, case reports, insufficiently informative case series or conference abstracts, study protocols, preclinical studies, and studies using therapeutic modalities other than Extracorporeal Shock Wave Therapy and PDE5i data were excluded.

Search Strategy

From July 21 to October 1, 2026, two independent researchers searched the literature. A systematic literature search was conducted across PubMed, Scopus, ScienceDirect, Europe PMC, and Epistemonikos to identify relevant published studies. Search terms were constructed around the principal concepts of erectile dysfunction, low-intensity extracorporeal shockwave therapy, extracorporeal shockwave therapy, phosphodiesterase type 5 inhibitors, and combination therapy, using database-appropriate Boolean operators and controlled vocabulary where applicable.

Data Extraction and Analysis

The electronic search and study selection process were carried out independently by two authors, who extracted the selected studies into a Google Sheet. The remaining authors then reviewed and verified the extracted data for accuracy and eligibility, with disagreements resolved trough discussion.

Risk of Bias Assessment

The methodological quality and risk of bias of the included studies were assessed according to study design. Randomized controlled trials were evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool, which assesses bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results.

Non-randomized studies were assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool, covering bias due to confounding, participant selection, intervention classification, deviations from intended interventions, missing data, outcome measurement, and selection of reported results. Assessments were conducted independently, with disagreements resolved through discussion and consensus. Based on the completed assessments in this review, the three included RCTs generally demonstrated some concerns overall, whereas the two non-randomized studies showed greater methodological limitations, including domains judged to have serious risk of bias. These assessments were considered when interpreting the strength and generalizability of the findings.

Intervention of Interest

The intervention of interest was low-intensity extracorporeal shockwave therapy (Li-ESWT) used as a restorative treatment for erectile dysfunction, either alone or in combination with PDE5i therapy. Particular attention was given to Li-ESWT-based combination therapy, in which Li-ESWT was administered alongside PDE5i such as tadalafil or sildenafil, and its comparative effectiveness relative to Li-ESWT or PDE5i monotherapy.

Given the variability among eligible studies, no single Li-ESWT protocol was imposed regarding the number of treatment sessions, treatment frequency, treatment duration, or concomitant PDE5i regimen. Instead, these characteristics were extracted and considered as potential sources of clinical heterogeneity. Studies involving shockwave therapy combined with additional interventions whose effects could not be independently evaluated, including stem cell therapy, platelet-rich plasma, or penile prosthesis, were excluded.

Outcomes of Interest

The primary outcomes were changes in erectile function measured using validated clinical instruments, primarily the International Index of Erectile Function–Erectile Function domain (IIEF-EF) or Sexual Health Inventory for Men (SHIM) and the Erection Hardness Score (EHS). Outcomes were evaluated using changes from baseline and/or post-treatment measurements at the follow-up periods reported by individual studies.

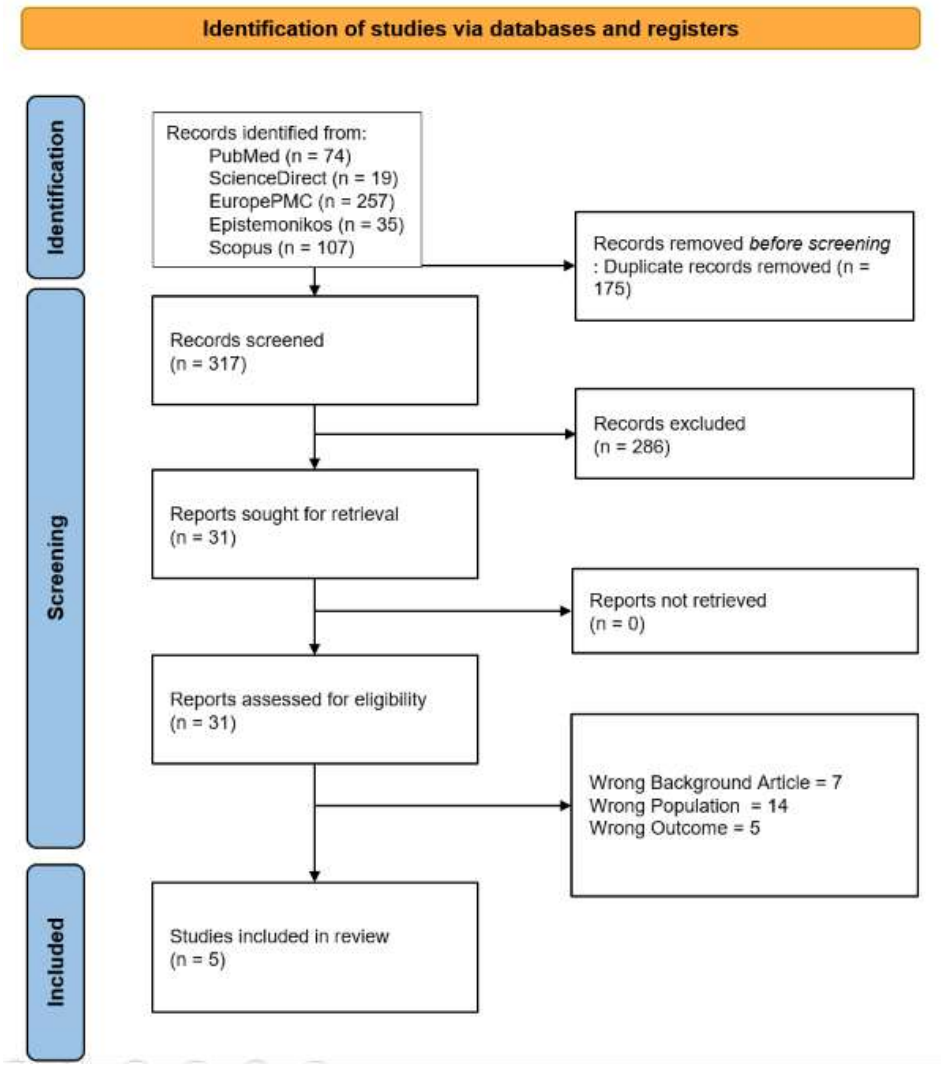
Secondary outcomes included Sexual Encounter Profile questions 2 and 3 (SEP2 and SEP3), durability of therapeutic response, and treatment-related adverse events. SEP2 represented successful vaginal penetration, whereas SEP3 reflected successful completion of intercourse. Treatment durability was evaluated according to the persistence of improvements in erectile-function outcomes during longer-term follow-up after treatment. Safety was assessed according to the incidence and type of adverse events reported during treatment and follow-up. Collectively, these outcomes were used to evaluate whether Li-ESWT-based

combination therapy provided clinically meaningful and potentially more durable benefits compared with monotherapy while maintaining an acceptable safety profile.

RESULTS

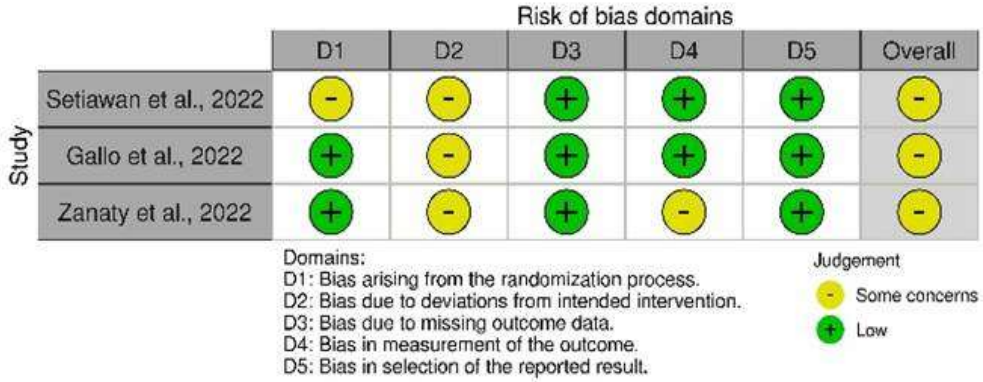
Study Selection and Identification

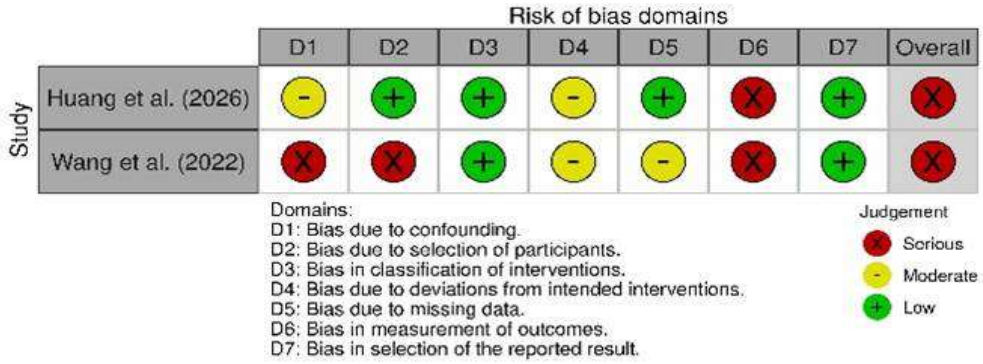
The study selection process is summarized in the PRISMA flow diagram (Figure 1). A total of 492 records were identified through database searches, including PubMed (n = 74), ScienceDirect (n = 19), EuropePMC (n = 257), Epistemonikos (n = 35), and Scopus (n = 107). After removing 175 duplicate records, 317 records underwent title and abstract screening, of which 286 were excluded. Subsequently, 31 full-text reports were retrieved and assessed for eligibility, with no reports unavailable for retrieval. Following full-text assessment, 26 studies were excluded due to inappropriate background (n = 7), population (n = 14), or outcomes (n = 5). Ultimately, five studies met the predefined eligibility criteria and were included in the systematic review (Figure 1).



Risk of Bias Assessment

The risk of bias assessment for the five included studies is summarized in Figure 2. The three randomized controlled trials were evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool, with all studies rated as having some concerns overall, primarily due to concerns related to the randomization process, deviations from intended interventions, and/or outcome measurement. The two non-randomized studies were assessed using the ROBINS-I tool and were judged to have an overall serious risk of bias, with the main concerns arising from confounding, participant selection, outcome measurement, and missing data. Overall, the included evidence demonstrated methodological limitations of varying severity, which should be considered when interpreting the findings of this review (Figure 2).





Summary of the Included Studies

No.	Author (Year)	Study Design	Country	Sample Size (n)	Intervention	Comparator	IIEF Outcome (Pre → Post)	EHS Outcome (Pre → Post)	EDITS	MCID (%)	Li-ESWT Protocol Details
1	**Gallo (2022)**	Prospective, randomized, single-blind	Italy	83 (41 Int; 42 Ctrl)	Li-ESWT + Tadalafil (5mg) + L-Arginine (2500 mg)	Li-ESWT alone	Int: 16.0 → 21.6 (12mo); Ctrl: 16.5 → 19.5	Int: 2.07 → 2.98 (12 mo); Ctrl: 2.12 → 2.76	NR	75.6 % vs 66.7 % (at 12 months)	**Device:** Storz Duolith SD1; **Shocks:** 3,000/session; **Energy:** 0.25 mJ/mm²; **Freq:** 6 sessions (1x/week); **Areas:** 6 sites (4 shaft, 2 crura)

2	**Setiawan (2022)**	Randomized clinical trial (pre-post)	Indonesia	26 (14 Exp; 12 Ctrl)	Li-ESWT + Tadalafil (2.5mg/day)	Tadalafil 2.5mg/day	Exp: 15.5 → 23.5; Ctrl: 16.5 → 21.0	Exp: 2 → 4; Ctrl: 2 → 3	NR	**NR**	**Device:** BTL-6000 SWT; **Shocks:** 1,500/session; **Energy:** 0.09 mJ/mm²; **Freq:** 8 sessions (2x/week); **Areas:** 5 sites (3 shaft, 2 crura)
3	**Huang (2026)**	Prospective, multi-center, non-randomized	China	188 (135 Comb; 53 Mono)	Li-ESWT + Tadalafil (5mg/day)	Li-ESWT Monotherapy	**Mean Increase:** 4.60 (Comb) vs 2.92 (Mono)	**Post (Mo-Se):** 2.70 (Comb) vs 2.30 (Mono)	NR	56.2 % vs 20.0 % (Moderate–Severe ED)	**Device:** Renova (Direx); **Shocks:** 5,000/session; **Energy:** 0.09 mJ/mm

											^{2}; **Freq:** 4 sessions (1x/week); **Areas:** Penile crus & corpus cavernosum
4	**Wang (2022)**	Prospective, non-randomized controlled	China	72 (42 Li-ESWT; 30 Ctrl)	Li-ESWT	On-demand Sildenafil (100mg)	Li-ESWT: 8.6 → 16.3; Ctrl: 7.1 → 18.3	**NR**	57.9 vs 54.7	59.5% vs 80.0%	**Device:** Omnispec ED1000; **Shocks:** 1,500/session; **Energy:** 0.09 mJ/mm^2; **Freq:** 12 total sessions (2x/week in 2 cycles)

5	**Zanaty (2022)**	Prospective, randomized trial	Egypt	51 (25 Li-ESWT; 26 Ctrl)	Li-ESWT	On-demand Tadalafil (20mg)	Li-ESWT: 11.16 → 17.64; Ctrl: 10.08 → 15.72	Li-ESWT: 1.64 → 3.20; Ctrl: 1.48 → 3.10	NR	**NR**	**Device:** PiezoWave2 (Wolf); **Shocks:** 6,000/session; **Depth:** 15mm; **Freq:** 6 sessions (2x/week); **Areas:** Penile shaft & crura

Five studies published between 2022 and 2026, comprising a total of 420 participants, were included in this systematic review. The studies were conducted across diverse geographical settings, including Italy, Indonesia, China, and Egypt, reflecting evidence derived from both European and Asian populations. Three studies employed randomized controlled designs (Gallo et al., Setiawan et al., and Zanaty et al.), whereas two were prospective non-randomized controlled studies (Huang et al. and Wang et al.). Sample sizes varied substantially, ranging from 26 participants in Setiawan et al. to 188 participants in Huang et al., with considerable variation in the allocation of participants between intervention and comparator groups.

Considerable clinical heterogeneity was observed in the therapeutic protocols across the included studies, particularly regarding the frequency and duration of low-intensity extracorporeal shockwave therapy (Li-ESWT), concomitant use of phosphodiesterase type 5 inhibitors (PDE5i), and treatment duration. Gallo et al. evaluated six weekly Li-ESWT sessions combined with daily tadalafil and L-arginine compared with Li-ESWT monotherapy, whereas

Setiawan et al. investigated twice-weekly Li-ESWT for four weeks in combination with low-dose daily tadalafil compared with tadalafil alone. Similarly, Huang et al. compared four weekly Li-ESWT sessions combined with daily tadalafil against Li-ESWT monotherapy. In contrast, Wang et al. evaluated a nine-week Li-ESWT protocol against on-demand sildenafil, while Zanaty et al. compared six Li-ESWT sessions with on-demand tadalafil. Thus, the included studies encompassed two principal therapeutic comparisons: Li-ESWT-based combination therapy versus monotherapy and Li-ESWT versus PDE5i pharmacotherapy. These variations in study design, treatment schedule, pharmacological co-interventions, and comparator groups demonstrate substantial methodological and clinical diversity across the evidence base and should be considered when interpreting the comparative effectiveness of Li-ESWT-based treatment strategies

Descriptive Analysis of Treatment Effectiveness and Clinical Outcomes

Across the five included studies, Li-ESWT consistently demonstrated beneficial effects on erectile function, either as monotherapy or in combination with phosphodiesterase type 5 inhibitors (PDE5i), although the magnitude of benefit varied according to treatment strategy and baseline erectile dysfunction (ED) severity. Gallo et al. reported that adjunctive daily tadalafil and L-arginine enhanced both the efficacy and durability of Li-ESWT compared with Li-ESWT alone, with particularly favorable outcomes among younger patients and those with mild ED. Similarly, Setiawan et al. demonstrated that Li-ESWT combined with daily tadalafil was superior to tadalafil monotherapy, producing greater improvements in erectile function as well as objective vascular and angiogenic parameters, including peak systolic velocity (PSV) and vascular endothelial growth factor (VEGF). These findings suggest that combining Li-ESWT with pharmacological therapy may provide complementary therapeutic effects extending beyond symptomatic improvement to potentially enhance penile vascular function.
The relative benefit of combination therapy appeared to be influenced by baseline ED severity. Huang et al. found that both Li-ESWT monotherapy and Li-ESWT combined with tadalafil were clinically effective; however, combination therapy produced greater benefits among patients with moderate-to-severe ED, whereas Li-ESWT monotherapy appeared sufficient for those with mild ED. This finding suggests that treatment intensification through the addition of PDE5i may be particularly advantageous in patients with greater baseline erectile impairment, while monotherapy may remain an appropriate therapeutic option for less severe disease.

Direct comparisons between Li-ESWT and PDE5i therapy further demonstrated that improvements in erectile function were achievable with either treatment approach, although

differences were observed in patient-centered outcomes, tolerability, and cost. Wang et al. reported improvement in erectile function with both Li-ESWT and on-demand sildenafil; however, Li-ESWT resulted in greater overall treatment satisfaction and higher partner satisfaction regarding the duration of sexual intercourse. Similarly, Zanaty et al. found that Li-ESWT achieved short-term efficacy comparable to on-demand tadalafil while demonstrating a substantially more favorable safety profile, with adverse events occurring in 8% of the Li-ESWT group compared with 44% of the tadalafil group. Nevertheless, this potential safety advantage was accompanied by a higher treatment cost for Li-ESWT.

Overall, the findings indicate that Li-ESWT is an effective therapeutic modality for ED, while its combination with PDE5i may enhance the magnitude and, potentially, the durability of clinical benefit compared with either modality alone. The incremental advantage of combination therapy appears particularly relevant in patients with moderate-to-severe ED, whereas Li-ESWT monotherapy may provide sufficient benefit in milder disease. In comparisons with PDE5i therapy, Li-ESWT showed broadly comparable improvements in erectile function while potentially offering advantages in treatment satisfaction and tolerability. However, differences in study design, Li-ESWT protocols, PDE5i regimens, baseline ED severity, outcome definitions, and follow-up duration introduce substantial clinical heterogeneity; therefore, these findings should be interpreted as a descriptive synthesis rather than definitive evidence of superiority across all treatment strategies.

Adverse Events, Safety, and Other Clinical Outcomes

Safety and other secondary outcomes were assessed heterogeneously across the five included studies, with differences in the reporting of treatment-related adverse events, patient and partner satisfaction, psychosocial outcomes, vascular parameters, and treatment costs. Overall, Li-ESWT was generally well tolerated, with no major safety concerns identified across the included studies. Gallo et al. primarily evaluated treatment efficacy using IIEF-EF, EHS, and achievement of the minimal clinically important difference (MCID), while reporting that the addition of daily tadalafil and L-arginine to Li-ESWT was safe and well tolerated. Similarly, Setiawan et al. incorporated objective vascular and biological assessments, including peak systolic velocity (PSV) measured by color Doppler ultrasonography and plasma vascular endothelial growth factor (VEGF) levels, alongside IIEF-5 and EHS. These findings provided additional evidence of potential vascular effects associated with combination therapy beyond improvements in erectile function alone.

Treatment-related adverse events were more explicitly evaluated in the studies by Huang et al., Wang et al., and Zanaty et al. Huang et al. assessed adverse events alongside

clinical outcomes, including IIEF-5, EHS, Clinical Global Impression (CGI), and MCID, providing a broader evaluation of both therapeutic effectiveness and tolerability. Wang et al. additionally assessed treatment satisfaction using the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) questionnaires for both patients and partners. Although both Li-ESWT and on-demand sildenafil improved erectile function, Li-ESWT was associated with greater overall treatment satisfaction and higher partner satisfaction regarding the duration of sexual intercourse, indicating potential patient-centered benefits beyond conventional erectile function scores.

The most pronounced difference in treatment-related adverse effects was reported by Zanaty et al., who found that side effects occurred in 8% of patients receiving Li-ESWT compared with 44% of those receiving on-demand tadalafil, despite broadly comparable short-term efficacy between the two treatments. This finding suggests a potentially more favorable tolerability profile for Li-ESWT compared with pharmacological therapy. However, the study also identified higher financial costs associated with Li-ESWT, highlighting an important trade-off between tolerability and treatment affordability. The inclusion of the Self-Esteem and Relationship (SEAR) questionnaire further demonstrated the relevance of psychosocial and relationship-related outcomes when evaluating the overall clinical impact of ED treatment.

Collectively, the available evidence suggests that Li-ESWT has a favorable safety and tolerability profile, with additional potential benefits in treatment satisfaction and patient-centered outcomes. Combination approaches involving Li-ESWT and PDE5i also appeared to be generally well tolerated, although the extent and consistency of adverse-event reporting varied substantially among studies. Importantly, direct safety comparisons remain limited because adverse events were not uniformly defined, measured, or reported across all five studies. Therefore, while the findings support the overall safety of Li-ESWT-based therapy, conclusions regarding its comparative safety advantage over PDE5i or combination therapy should be interpreted cautiously given the heterogeneity of safety assessments and the limited number of included studies.

DISCUSSION

This systematic review aimed to determine whether low-intensity extracorporeal shockwave therapy (Li-ESWT), particularly when combined with phosphodiesterase type 5 inhibitors (PDE5i), provides greater clinical benefit than relevant monotherapy strategies in men with erectile dysfunction (ED), with particular interest in patients who respond inadequately to PDE5i. This question is clinically important because ED substantially affects

sexual function, psychological well-being, interpersonal relationships, and quality of life, while approximately one-third of patients may respond inadequately to first-line PDE5i and subsequently require more burdensome second-line therapies, including intracavernosal or intraurethral agents, vacuum erection devices, or penile prosthesis implantation [4–7]. Li-ESWT is particularly attractive in this setting because, unlike PDE5i, which predominantly facilitate erections through pharmacological potentiation of the nitric oxide–cyclic guanosine monophosphate (NO–cGMP) pathway, Li-ESWT has been proposed as a restorative intervention capable of modifying the vascular substrate underlying vasculogenic [8,9]. Across the five included studies comprising 420 participants, Li-ESWT consistently improved erectile-function outcomes either alone or as part of combination therapy, although treatment effects varied substantially according to baseline ED severity, treatment protocol, comparator, and follow-up duration. Combination strategies generally produced greater improvements in IIEF-EF/IIEF-5 and EHS than relevant monotherapy in selected populations; Setiawan et al. additionally demonstrated improvements in peak systolic velocity (PSV) and vascular endothelial growth factor (VEGF), providing objective support for vascular effects beyond questionnaire-based improvement, while Gallo et al. reported that adjunctive tadalafil and L-arginine enhanced the magnitude and persistence of benefit after Li-ESWT [10,11]**.** Direct comparisons with pharmacotherapy showed that Li-ESWT achieved broadly comparable short-term erectile-function improvement to on-demand PDE5i, while potentially providing advantages in tolerability, treatment satisfaction, and partner-reported outcomes [12,13]. Nevertheless, these findings should not be interpreted as definitive evidence that combination therapy is universally superior. Rather, they indicate a pattern of potential incremental benefit, particularly in patients with greater baseline dysfunction, while substantial heterogeneity precluded meaningful quantitative pooling. Therefore, the current findings represent a descriptive narrative synthesis rather than a pooled meta-analytic estimate of treatment superiority.

The findings of this review are broadly consistent with previous clinical trials and evidence syntheses suggesting that Li-ESWT can improve erectile function and, importantly, may restore responsiveness to PDE5i in selected previous non-responders. The first clinical pilot investigation by Vardi et al. demonstrated improvement in erectile function and penile endothelial parameters after Li-ESWT, establishing the initial clinical rationale for using shockwaves as a disease-modifying rather than purely symptomatic treatment [14]. A subsequent randomized, double-blind, sham-controlled study provided evidence that these improvements were associated with physiological effects beyond placebo [15]. Particularly relevant to refractory

disease, Gruenwald et al. demonstrated clinically meaningful improvement in severe ED patients responding poorly to PDE5i; 72.4% achieved an EHS ≥3 following treatment, indicating restoration of rigidity sufficient for penetration [8]. Kitrey et al. subsequently strengthened this concept in a double-blind sham-controlled trial demonstrating that Li-ESWT could shift a proportion of PDE5i non-responders into responders [16]. Similar benefits have been reported by Bechara et al. in PDE5i failures, with improvements in IIEF-EF, EHS, SEP2, and SEP3 that persisted in many responders during longer-term follow-up [17,18], while Palmieri et al. demonstrated significant improvements in erectile function, penile hemodynamics, and quality of life when Li-ESWT was combined with PDE5i in previous non-responders [2]. Their multicenter study reported an increase in mean EHS from 2.19 to 3.40, PSV from 27.79 to 41.66 cm/s, and normalization of previously abnormal penile hemodynamics in 71.4% of affected patients, supporting a physiological correlate of clinical improvement. Earlier randomized trials have also reported favorable outcomes with Li-ESWT compared with sham, including Olsen et al., who reported that 57% of treated patients could achieve intercourse without medication compared with 9% in the placebo group [19]. Meta-analyses by Lu et al. (2017) and Clavijo et al. (2017) similarly reported significant improvements in erectile-function outcomes after Li-ESWT, while Sokolakis and Hatzichristodoulou (2019) found an overall therapeutic signal across randomized trials. However, not all evidence has been uniformly positive. Yee et al. (2014), Fojecki et al. (2017), and other sham-controlled investigations demonstrated smaller, inconsistent, or non-durable effects, emphasizing that efficacy depends strongly on patient selection, device characteristics, treatment intensity, and outcome definitions. Long-term evidence also suggests gradual attenuation in some patients [20] Thus, the principal advantages of Li-ESWT include its non-invasive nature, favorable tolerability, potential restoration of spontaneous erectile function, and possible conversion of PDE5i non-responders into responders; disadvantages include repeated clinic-based treatment, specialized equipment, higher upfront cost, uncertain durability, and lack of consensus regarding optimal energy flux density, number of shocks, anatomical treatment sites, treatment frequency, and device type [9,21]. These inconsistencies support a more nuanced interpretation: Li-ESWT appears biologically active and clinically beneficial in selected patients, but its effectiveness is unlikely to be uniform across all ED phenotypes.

The biological rationale for combining Li-ESWT with PDE5i is based on their complementary mechanisms. PDE5i such as sildenafil and tadalafil inhibit PDE5-mediated degradation of cGMP, thereby potentiating endogenous NO-dependent cavernosal smooth-muscle relaxation and facilitating penile arterial inflow during sexual stimulation [22]. However,

this pharmacological mechanism depends on sufficient upstream NO production and functional endothelial tissue; consequently, severe endothelial dysfunction associated with diabetes, hypertension, dyslipidemia, smoking, aging, and cardiovascular disease may limit PDE5i responsiveness [23,24]. Li-ESWT, by contrast, delivers low-energy acoustic impulses that generate controlled mechanical shear stress and microtrauma within cavernosal and perivascular tissues, activating mechanotransduction pathways involved in tissue repair and vascular regeneration [25–27]. Experimental evidence suggests that shockwaves may stimulate VEGF expression, endothelial nitric oxide synthase activity, recruitment and activation of progenitor cells, endothelial proliferation, neovascularization, improved microvascular perfusion, smooth-muscle preservation, and potentially neural regeneration [26–30]. This mechanistic complementarity is particularly evident in Setiawan et al., where tadalafil alone improved clinical outcomes and PSV without a comparable increase in VEGF, whereas Li-ESWT plus tadalafil produced greater improvements in IIEF-5, EHS, PSV, and VEGF [11]. The investigators proposed that tadalafil primarily improves vasodilation, while Li-ESWT-induced shear microtrauma stimulates pro-inflammatory and pro-proliferative signals, including VEGF, potentially promoting new vascular formation within cavernosal tissue. Thus, PDE5i may provide relatively rapid functional support while Li-ESWT progressively improves the vascular environment necessary for sustained erectile responsiveness. Nevertheless, increased circulating VEGF should be regarded as supportive evidence of angiogenic signaling rather than direct proof of structural cavernosal neovascularization. Regarding safety, the available evidence generally indicates that Li-ESWT is well tolerated, with most reported adverse events being absent, mild, or transient. Zanaty et al. reported treatment-related adverse effects in only 8% of Li-ESWT recipients compared with 44% receiving on-demand tadalafil, although Li-ESWT incurred substantially higher financial costs [13] Combination therapy was also generally well tolerated in Gallo et al. and Setiawan et al. [10,11]**.** Palmieri et al. reported no major treatment-related adverse events, although one patient developed penile curvature and a palpable plaque diagnosed as Peyronie's disease; causality was not established [2] Consequently, Li-ESWT should be described as having a favorable observed safety profile, rather than being definitively safer, because existing trials remain too small and follow-up too limited to reliably detect rare or delayed adverse events.

Several additional findings from this review have important clinical implications. First, treatment response appears to be influenced by baseline ED severity. The included evidence suggests that Li-ESWT monotherapy may provide sufficient benefit in some patients with mild disease, whereas combination therapy may provide a larger incremental advantage in

moderate-to-severe ED. This observation supports treatment stratification rather than a universal combination approach. It is also consistent with evidence that age, ED duration, baseline severity, and vascular comorbidities may predict long-term response to Li-ESWT [20] Second, the definition of PDE5i refractoriness is critical. Apparent non-response may result from incorrect drug administration, inadequate dosing, insufficient treatment attempts, lack of sexual stimulation, poor adherence, or inadequate counseling rather than true pharmacological failure [4,5]. Your protocol appropriately defined true non-response as inability to achieve penetrative rigidity, generally EHS ≤2, despite optimized maximum PDE5i doses over repeated attempts. However, the five included studies did not uniformly apply this definition, meaning that evidence from broader ED populations cannot be automatically generalized to true PDE5i-refractory disease. Third, clinically meaningful response should not be limited to statistical changes in mean IIEF scores. Achieving EHS ≥3, crossing the minimal clinically important difference in IIEF-EF, restoring successful penetration or intercourse through SEP2/SEP3, improving sexual quality of life, increasing patient and partner satisfaction, and converting a PDE5i non-responder into a responder may be more clinically relevant endpoints [8,16,31]**.** Fourth, durability remains clinically important. Bechara et al. reported maintenance of improvements in many PDE5i non-responders at 12 months [18] while Kitrey et al. demonstrated that response may decline over longer follow-up [20] Gallo et al. similarly observed attenuation over time despite greater persistence of benefit with adjunctive tadalafil and L-arginine [10] Therefore, Li-ESWT should not yet be described as permanently curative. Finally, patient-centered outcomes may influence therapeutic choice independently of IIEF scores. Wang et al. found broadly comparable erectile-function improvement between Li-ESWT and sildenafil but reported greater overall treatment and partner satisfaction with Li-ESWT [12] whereas Zanaty et al. identified a trade-off between better tolerability and substantially greater cost [13] Clinically, these findings suggest that Li-ESWT-based combination therapy may occupy a useful therapeutic position between optimized oral pharmacotherapy and more invasive second-line interventions. For a true PDE5i non-responder, restoring sufficient vascular responsiveness to make oral medication effective may itself constitute a major therapeutic success, even if complete medication independence is not achieved. Patient selection should therefore incorporate ED etiology, baseline severity, cardiovascular and metabolic comorbidities, confirmation of optimized prior PDE5i exposure, treatment preferences, accessibility, cost, and willingness to complete repeated treatment sessions.

The evidence base has several strengths but also important methodological weaknesses. Strengths include the use of validated erectile-function instruments such as IIEF-EF/IIEF-5 and

EHS [31] assessment of clinically meaningful outcomes such as MCID and treatment durability, and—in selected studies—the integration of objective measures including penile Doppler PSV, EDV, VEGF, quality of life, SEAR, CGI, and patient/partner EDITS outcomes. The five included studies also incorporated three randomized controlled designs and two prospective non-randomized comparative designs across Italy, Indonesia, China, and Egypt, broadening geographical representation. Nevertheless, only 420 participants were included overall, individual sample sizes varied substantially, and several methodological limitations reduce certainty. All three RCTs were judged to have some concerns in the RoB 2 assessment, whereas both non-randomized studies had an overall serious risk of bias, particularly from confounding, participant selection, missing data, and outcome measurement. There was also substantial clinical heterogeneity in ED severity and etiology, definitions of PDE5i response, shockwave generator type, energy flux density, number of shocks, anatomical treatment sites, treatment frequency and duration, concomitant PDE5i type and dose, comparator interventions, outcome definitions, and follow-up periods. Such heterogeneity has repeatedly been identified as a major limitation in previous reviews and meta-analyses [21,32,33]. Importantly, concomitant treatment also complicates causal attribution: Gallo et al. combined Li-ESWT with both tadalafil and L-arginine, meaning that improved durability cannot be attributed specifically to Li-ESWT–PDE5i synergy [10] Similarly, differences between focused, linear, electromagnetic, electrohydraulic, and other shockwave systems limit direct comparability and challenge the assumption that "Li-ESWT" represents a single standardized intervention [9,21]. The greatest limitation relative to the review title is indirectness of population: not all five included studies specifically enrolled strictly confirmed PDE5i-refractory patients. Consequently, while the totality of evidence suggests that Li-ESWT-based combination therapy may enhance erectile outcomes and potentially restore pharmacological responsiveness in selected patients, definitive superiority specifically in true PDE5i-refractory ED remains unproven. Future studies should therefore be adequately powered, multicenter, randomized, double-blind, sham-controlled trials using standardized definitions of PDE5i non-response, harmonized Li-ESWT parameters, standardized PDE5i regimens, and clinically meaningful responder outcomes including IIEF-EF MCID, EHS ≥3, SEP2/SEP3, restoration of PDE5i responsiveness, medication independence, quality of life, and patient/partner satisfaction. Follow-up of at least 12–24 months is necessary to establish durability, retreatment requirements, long-term safety, predictors of response, and cost-effectiveness before combination therapy can be recommended routinely for PDE5i-refractory ED.

CONCLUSION AND FUTURE RESEARCH

This systematic review suggests that Li-ESWT-based combination therapy may improve erectile function more effectively than monotherapy in selected men with erectile dysfunction, with benefits reflected across erectile-function outcomes and potentially greater durability of response. However, the substantial heterogeneity in patient populations, Li-ESWT protocols, concomitant PDE5i regimens, comparator groups, and study designs limits definitive conclusions regarding the superiority of combination therapy, particularly in strictly defined PDE5i-refractory ED. Future research should prioritize large, multicenter, adequately powered randomized controlled trials specifically enrolling well-defined PDE5i non-responders, with standardized Li-ESWT parameters and PDE5i regimens, consistent clinically meaningful outcomes such as IIEF-EF/SHIM, EHS, and SEP2/3, and longer follow-up. Such studies are needed to determine the optimal combination regimen, identify predictors of treatment response, establish long-term durability and safety, and clarify which patients are most likely to benefit from Li-ESWT-based combination therapy.

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