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Effects of Low-Intensity Extracorporeal Shockwave Therapy on Erectile Dysfunction: A Systematic Review and Meta-Analysis

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Abstract

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Introduction

Low-intensity extracorporeal shock wave therapy (Li-ESWT) has been proposed as an effective non-invasive treatment option for erectile dysfunction (ED).

Aim

To use systematic review and meta-analysis to assess the efficacy of Li-ESWT by comparing change in erectile function as assessed by the erectile function domain of the International Index of Erectile Function (IIEF-EF) in men undergoing Li-ESWT vs sham therapy for the treatment of ED.

Methods

Systematic search was conducted of MEDLINE, EMBASE, and ClinicalTrials.gov for randomized controlled trials that were published in peer-reviewed journals or presented in abstract form of Li-ESWT used for the treatment of ED from January 2010 through March 2016. Randomized controlled trials were eligible for inclusion if they were published in the peer-reviewed literature and assessed erectile function outcomes using the IIEF-EF score. Estimates were pooled using random-effects meta-analysis.

Main Outcome Measures

Change in IIEF-EF score after treatment with Li-ESWT in patients treated with active treatment vs sham Li-ESWT probes.

Results

Data were extracted from seven trials involving 602 participants. The average age was 60.7 years and the average follow-up was 19.8 weeks. There was a statistically significant improvement in pooled change in IIEF-EF score from baseline to follow-up in men undergoing Li-ESWT vs those undergoing sham therapy (6.40 points; 95% CI = 1.78–11.02; $I^2 = 98.7%$; $P < .0001$ vs 1.65 points; 95% CI = 0.92–2.39; $I^2 = 64.6%$; $P < .0001$; between-group difference, $P = .047$). Significant between-group differences were found for total treatment shocks received by patients ($P < .0001$).

Conclusion

In this meta-analysis of seven randomized controlled trials, treatment of ED with Li-ESWT resulted in a significant increase in IIEF-EF scores.

Key Words:

[Erectile Dysfunction](#), [Shock Waves](#), [Randomized Controlled Trial](#), [Meta-Analysis](#)

Consultation on Sexual Medicine 2015

The Journal of Sexual Medicine, Vol. 13, Issue 2

Standards for Clinical Trials in Male and Female Sexual Dysfunction: III. Unique Aspects of Clinical Trials in Male Sexual Dysfunction

The Journal of Sexual Medicine, Vol. 14, Issue 1

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Introduction

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Erectile dysfunction (ED) is when a man is unable to achieve or maintain an erection for satisfactory sexual performance. ED is estimated to affect one in every five men and, given the aging male population and increasing prevalence of comorbid conditions, it is likely to become even more prevalent.¹ Phosphodiesterase type 5 inhibitors (PDE5is) are often effective in treating patients with ED and are associated with few side effects; however, a significant proportion of men do not respond to therapy.² In men who do not respond to PDE5is or cannot tolerate them because of side effects, options such as medicated urethral suppositories for erection, intracorporeal injections, and penile prostheses are available.³ Although these treatment options can be effective, long-term usage rates are hindered by side effects and potential complications.⁴ Furthermore, these treatments attempt to improve erectile function without treating the underlying pathophysiology of ED.⁵

Low-intensity extracorporeal shockwave therapy (Li-ESWT) has been proposed as a treatment option for ED with minimal side effects. Vardi et al⁶ first reported on the use of Li-ESWT for ED; their rationale was extrapolated from cardiac literature reporting improvements in neovascularization. Recent studies of a diabetic rat model have recently supported the notion that Li-ESWT indeed might induce structural changes that regenerate penile tissue.⁷

Aims

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Given the availability of several randomized sham-treatment-controlled trials studying the effects of Li-ESWT in the treatment of ED, we performed a meta-analysis to determine whether this novel treatment improves erectile function in men with ED when assessed by the International Index of Erectile Function erectile function domain (IIEF-EF) compared with men undergoing sham therapy.^{8, 9, 10, 11, 12, 13, 14} In addition, from our review of the literature, we sought to provide formal recommendations for future randomized controlled trials.

Methods

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Search Strategy

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Randomized controlled trials published from January 2010 (the year that SWT was first used as a treatment for ED⁶) through March 2016 that reported on using the IIEF-EF score for men with ED receiving Li-ESWT were identified using electronic searches of MEDLINE, EMBASE, and ClinicalTrials.gov. Additional studies were identified by scanning the reference lists of articles identified, searching relevant conference abstracts, and corresponding with study investigators using the approach recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁵ A flow diagram for study selection is presented in [Figure 1](#). The computer-based searches combined terms: “[(shockwave) OR (shock wave) AND erectile dysfunction].”

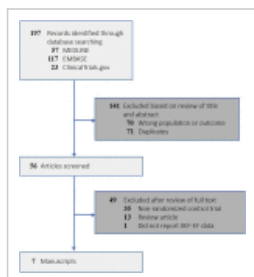


Figure 1
Flow diagram for study selection.

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Inclusion Criteria and Trial Selection

Studies were included if they were randomized controlled trials of Li-ESWT for ED that reported on the use of the IIEF-EF, a validated six-question questionnaire that assesses erection frequency, erection firmness, penetration ability, maintenance frequency, maintenance ability, and erection confidence on a scale of 0 to 5.¹⁶ The most comprehensive publication was used when there were several involving the same study population. Abstracts of randomized controlled trials from relevant conferences were included in this analysis in accordance with recommendations of the Cochrane Handbook for Systematic Reviews section 6.2.2.4.¹⁷

Data Extraction

The following information was extracted independently by two trained investigators using a standardized form: authors and publication year, year of study, publication type, practice setting, duration of follow-up, population, SWT regimen, IIEF-EF (six-question form), participant inclusion and exclusion criteria, sample size, geographic locale in which the study took place, mean or median participant age, and model of Li-ESWT machine. All discrepancies were resolved by discussion and adjudication of a third reviewer. Study investigators from most studies were contacted to obtain further information.

Quality Assessment

The risk of bias in the included randomized trials was assessed using the Cochrane Risk of Bias Assessment tool in the domains of randomization, sequence generation, allocation concealment, blinding, completeness of outcome data, selective outcome reporting, and other potential sources of bias.¹⁷ Domains were independently assessed by two trained investigators (R.I.C. and T.P.K.). All discrepancies were resolved by discussion and adjudication by a third reviewer. Summary for risk of bias were generated with RevMan 5.2.¹⁸

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Meta-Analysis

in IIEF-EF scores measured before initiating and then after treatment with Li-ESWT or placebo were calculated for each study. Overall differences were calculated by pooling the study-specific estimates using random-effects meta-analysis that included between-study heterogeneity.¹⁹ Between-study heterogeneity was assessed by standard χ^2 tests and the I^2 statistic (ie, percentage of variability in prevalence estimates because of heterogeneity rather than sampling error or chance)^{20, 21} and by comparing results from studies grouped according to prespecified study-level characteristics (total treatment shocks, mean participant age, baseline IIEF-EF score, and duration of follow up) using stratified meta-analysis and meta-regression.^{22, 23} The influence of individual studies on the overall summary estimates was examined by serially

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excluding each study in a sensitivity analysis.²⁴ Bias secondary to small study effects was investigated using the funnel plot and the Egger test.^{25, 26} All analyses were performed using R 3.2.2 (R Foundation for Statistical Computing).²⁷ Statistical tests were two-sided and used a significance threshold of a *P* value less than .05.

Main outcome measures

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Difference in pooled change in IIEF-EF score from baseline to follow-up in men treated with Li-ESWT was compared with that in those treated with sham therapy.

Results

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Study Characteristics

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Seven randomized controlled trials involving 602 participants were included in this meta-analysis (Table 1). Six studies used the Omnispec ED1000 (Medispec Ltd, Yehud, Israel) and one study used an ESWT device from Richard Wolf GmbH (Knittlingen, Germany). The mean number of participants per study was 86.4 (range = 53–135), the mean age was 60.7 years, mean baseline IIEF-EF score was 9.2, and mean follow-up was 19.8 weeks (range = 13–56). All seven studies used sham therapy for the control group using shockwave probes that looked and sounded similar to the active treatment probe. All seven studies included men with vasculogenic ED and excluded men with neurogenic ED. Four studies included men with mild, mild to moderate, moderate, and severe ED. One study included only men with mild to moderate, moderate, and severe ED. One study included only men with mild ED while on PDE5i. Two studies did not specify the severity of ED for the included patients. Seven studies consisted of regimens of two treatments per week for 3 weeks, then 3 weeks without treatment, followed by 3 weeks of two treatments per week—for a total of 18,000 total treatment shocks. One study had a regimen of one treatment every 5 weeks, 4 weeks without treatment, followed by 5 weeks with one treatment per week—for a total of 6,000 total treatment shocks. All studies included in the present analysis used an energy flux density of 0.09 mJ/mm². Five studies took place in Asia, two in Europe, and one in North America. All seven trials studied IIEF-EF score as a primary outcome. Five studies were published as journal articles and two studies were published as abstracts. Further inclusion and exclusion criteria are listed in Table 1. For most studies, the risk of bias was low. However, the risk of bias was unclear for several domains of published abstracts (eFigures 1 and 2).

Table 1

Selected characteristics of seven studies included in this systematic review

Study	Year	Duration of follow-up (wk)	Weeks of treatment	Treatments/wk	Shocks per treatment	Total treatment shocks	Sample Size (n)
Kitrey et al ⁸	2016	13	6	2	1,500	18,000	37
Feldman et al ⁹	2015	13	6	2	1,500	18,000	84
Fojecki and Osther ¹⁰	2015	18	10	1	600	6,000	63

Srini et al ¹¹	2015	13	6	2	1,500	18,000	95
Hatzichristou and Kalyvianakis ¹²	2015	56	6	2	1,500	18,000	30
Yee et al ¹³	2014	13	6	2	1,500	18,000	30
Vardi et al ¹⁴	2012	13	6	2	1,500	18,000	40

[View Table in HTML](#)

ED = erectile dysfunction; IIEF-EF = International Index of Erectile Function erectile function domain; PDE5i = phosphodiesterase type 5 inhibitor; SHIM = Sexual Health Inventory for Men.

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Effect of Li-ESWT on Change in IIEF-EF Score

There was a statistically significant improvement in pooled change in IIEF-EF score from baseline to follow-up in men treated with Li-ESWT compared with those receiving sham therapy (6.40 points; 95% CI = 1.78–11.02; $I^2 = 98.7\%$; $P < .0001$ vs 1.65 points; 95% CI = 0.92–2.39; $I^2 = 64.6\%$; $P < .0001$; between-group difference, $P = .047$; [Figure 2A, B](#)). For each study the control group was subtracted from the treatment group to determine the between-group mean difference, which was meta-analyzed (4.17 points; 95% CI = -0.5 to 8.3; $I^2 = 98.8\%$; $P < .0001$; [Figure 2C](#)). The sensitivity analysis demonstrated that, for the sham treatment group, no individual study affected the overall prevalence estimate by more than an absolute difference of 0.5 point. For the Li-ESWT group, two studies (Fojecki and Ooster¹⁰ and Sirini et al¹¹) were found to affect the overall prevalence estimate by an absolute difference of 0.5 point ([eTable 1](#)).

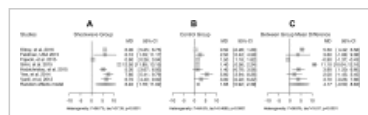


Figure 2 Forest plot of change in International Index of Erectile Function erectile function score for men undergoing low-intensity extracorporeal shockwave therapy vs sham therapy.

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Effect of Li-ESWT on Change in IIEF-EF Score According to Study-Level Characteristics

Among the seven studies, no between-group differences were noted in sub-analyses that controlled for the potential confounders of duration of follow-up, age of participant, and baseline IIEF-EF scores ($P > .05$ for all comparisons; [Table 2](#)). A significant between-group difference was observed for total treatment shocks when compared by stratified meta-analysis ($P < .001$; [Figure 3](#)).

Table 2

Meta-regression by age and total shock energy

Meta-regression	Slope	Lower CI	Upper CI	Q	P value
Control arm					
Duration of follow-up	-0.01	-0.07	0.06	0.080	.78
Age (y)	-0.04	-0.37	0.30	0.05	.83
Baseline IIEF-EF score	0.15	-0.31	0.60	0.39	.53
Treatment arm					
Duration of follow-up	-0.05	-0.36	0.26	0.10	.75
Age (y)	-0.41	-0.95	0.14	2.16	.14
Baseline IIEF-EF score	-0.37	-2.80	2.07	0.09	.77

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IIEF-EF = International Index of Erectile Function erectile function domain.

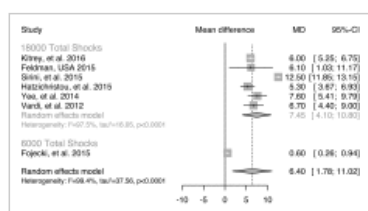


Figure 3 Sub-analyses by total treatment shocks.

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Assessment of Publication Bias

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Visual inspection of the funnel plot showed minimal asymmetry for the treatment group, suggesting that the pooled estimates were unlikely to be importantly biased secondary to small study effects (eFigure 3). The Egger regression asymmetry test supported this finding (treatment: $z = 0.14$; $P = .89$). In comparison, visual inspection of the funnel plot showed significant asymmetry for the sham group; the Egger regression asymmetry test supported this (control: $z = 2.11$; $P = .03$). This asymmetry occurs from an increased number of small studies that reported improvement during sham therapy, which is opposite any publication bias.

Discussion

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This systematic review and meta-analysis of seven randomized controlled trials involving 691 men demonstrated a statistically significant improvement in IIEF-EF score of men with ED undergoing Li-ESWT compared with men undergoing sham therapy. This positive result suggests that Li-ESWT might clinically improve erectile function in men with ED.

It has been previously determined that a change of four points in the IIEF-EF score is the minimum clinically important difference, which indicates a difference that might be clinically meaningful to patients and potentially change management.²⁸ For the trials included in this study, the combined improvement in IIEF-EF score was 4.17 after treatment with Li-ESWT, which is greater than the minimum clinically important difference. Of note, one randomized controlled trial was not included in the meta-analysis because pre- and post-treatment IIEF-EF scores were not reported and were not available after attempting to contact the investigators.²⁹ This study found no difference between the treatment and control groups at 5 weeks. This study used a different device than the seven included studies (Duolith SD1, Storz, Switzerland) and had a longer follow-up time of 24 months.

The mechanism of action that leads to improvement in IIEF scores in men treated with Li-ESWT has not been elucidated completely. In vitro and animal studies have shown that SWT can promote neovascularization and expression of pro-angiogenesis markers resulting in remodeling of tissue.^{30, 31, 32} Studies on the effect of SWT on penile tissue in rats have shown improvement in erectile function and regeneration of endothelium, smooth muscle, and nerves expressing neuronal nitric oxide synthase.^{7, 33} Although no histologic or gene expression studies have been carried out in human tissue, using an established protocol, several groups have reported a statistically significant improvement in flow-mediated dilatation in patients treated with Li-ESWT, indicating improvement in penile hemodynamics and endothelial function.^{8, 14, 34} A recent study of mice as a model of type 2 diabetes treated with Li-ESWT found that Li-ESWT improved erectile function, but not through the expected mechanism dependent on nitric oxide and cyclic guanosine monophosphate.³⁵ Thus, currently, Li-ESWT is believed to be effective primarily by regenerating microvasculature and improving penile hemodynamics; this could explain why it has been studied mainly in men with vasculogenic ED and not in men with neurogenic ED.

This study is not the first meta-analysis to publish on Li-ESWT and ED.³⁶ In a meta-analysis published by Lu et al,³⁶ men with ED, Peyronie's disease, and chronic pelvic pain were included. With this heterogeneous population, they found the average IIEF-EF score difference between the treatment group and the control group was 2.00. In the present study, the average IIEF-EF score difference was 4.17, a clinically significant improvement. In addition, Lu et al included randomized controlled trials and cohort studies. With the inclusion of cohort studies, Lu et al presented their meta-analytic findings at a level of evidence of 2a. Although we emphasize that we are not the first to report a systematic review and meta-analysis on the use of Li-ESWT in the treatment of ED, our study differs in that it is the first to publish on a homogenous population of men with only ED. Furthermore, our meta-analysis includes only randomized controlled trials and thus can be regarded as level 1a evidence.

Our study has important strengths and limitations. This is the first meta-analysis published on Li-ESWT that specifically reports on only men with ED, demonstrating a significant clinical and statistical improvement. All seven trials included were randomized controlled trials with sham therapy. However, most included trials had small samples; the largest study included in our meta-analysis had only 135 men.¹¹ Two studies were published as abstracts. Study investigators

for the abstracts were contacted for further information, and we received, for our review, a prepared report for one and a study protocol for the other. Although we are uncertain of the current publication status of these two abstracts, we are confident after thorough review of the data presented that the quality of evidence presented is similar to those presented in the peer-reviewed articles. Follow-up was limited to approximately 1 year in most studies and only one study provided follow-up data beyond 1 year.¹² Data on the use of PDE5i during Li-ESWT treatment were available in five studies; the remainder did not report these data. The study by Kitrey et al⁸ was the only one in which patients used PDE5i during the SWT phase. Our study also had increased heterogeneity ($I^2 = 99.4\%$), which can be attributed to two studies (Fojecki and Osther¹⁰ and Sirini et al¹¹) that, when systematically omitted from the sensitivity analysis, caused the overall effect to change by more than 0.5. One possible cause for this heterogeneity could be treatment regimen and subject selection. The study published by Fojecki and Osther showed minimal difference between the treatment and sham groups, which can be explained by the variation in treatment protocol. Fojecki and Osther used a total of 6,000 treatment shocks over 10 weeks, whereas all other studies used 18,000 treatment shocks over 9 weeks. Conversely, Sirini et al described a greater average treatment effect compared with all other treatment groups, which might be explained by their subject selection. The study by Sirini et al is the only one that screened men by ultrasound for vasculogenic ED; thus, they might have selected study participants who were more apt to respond to Li-ESWT. When these two trials are omitted, the heterogeneity significantly decreases ($I^2 = 0\%$) and the total treatment effect is 6.17, very similar to the original calculated treatment effect of 6.40.

Currently, it is unclear where Li-ESWT fits in the current treatment algorithm for ED. The most recent update to the European Association of Urology guidelines on male sexual dysfunction lists SWT as a potential treatment option for ED, but the association refrains from giving any recommendations at this time because of the immaturity of available data.³ The American Urological Association currently does not include SWT in its guideline on management of ED. Because no prior meta-analysis has been performed synthesizing only randomized controlled trials, this study sheds light on the effectiveness of Li-ESWT in treating ED.

However, as with many therapies, patient selection is likely to be crucial in maximizing the benefits of Li-ESWT. Results of the two randomized controlled trials in this study and the single-arm studies show that factors such as older age, several comorbidities, longer duration of ED,^{37, 38} lower baseline IIEF-EF score, and poor initial response to PDE5i can undermine the overall effect of Li-ESWT in the improvement of the IIEF-EF score.^{8, 13, 39, 40} Although our findings indicate an improvement for those undergoing Li-ESWT, more randomized controlled trials are warranted before the acceptance of this treatment becomes widespread. From our review of the literature, we put forth these recommendations for future studies: future studies should be randomized; subjects should be screened by penile Doppler ultrasound and nocturnal penile tumescence to ensure only men with vascular ED are included; the duration of follow-up should be longer than 3 months; other treatment schedules ought to be trialed to determine optimum effect; control groups should undergo sham treatment; PDE5is should be stopped completely and with appropriate washout periods; all studies should be registered on trial registry sites; and all studies should report all adverse events. It seems reasonable that future trials should start with using 18,000 shocks. Because no significant adverse effects have been reported, a more condensed protocol shorter than 6 weeks could be attempted. However, spacing out treatments could end up being more beneficial because of some yet unknown effect on penile physiology.

Conclusion



In this meta-analysis of randomized controlled trials evaluating the effect of Li-ESWT on ED, the improvement in IIEF-EF scores was statistically significant for men who underwent Li-ESWT compared with those who underwent sham therapy. However, more stringent randomized controlled trials are warranted before there is widespread acceptance of this treatment.

Statement of authorship



Category 1

(a) Conception and Design

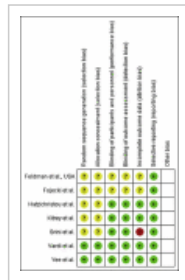
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- (b) Acquisition of Data
Raul I. Clavijo; Taylor P. Kohn; Jaden R. Kohn
- (c) Analysis and Interpretation of Data
Raul I. Clavijo; Taylor P. Kohn; Ranjith Ramasamy
- Category 2
- (a) Drafting the Article
Raul I. Clavijo; Taylor P. Kohn; Jaden R. Kohn; Ranjith Ramasamy
- (b) Revising It for Intellectual Content
Raul I. Clavijo; Taylor P. Kohn; Jaden R. Kohn; Ranjith Ramasamy
- Category 3
- (a) Final Approval of the Completed Article
Raul I. Clavijo; Taylor P. Kohn; Jaden R. Kohn; Ranjith Ramasamy

Supplementary data

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eTable 1
Sensitivity analysis



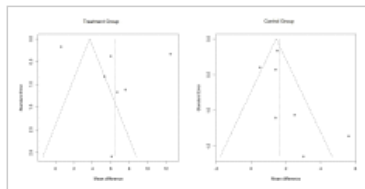
eFigure 1
Risk bias summary.

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eFigure 2
Risk bias graph.

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eFigure 3
Assessment of small study effects by funnel plot.

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