Energy-Based Therapies for Erectile Dysfunction
Current and Future Directions

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KEYWORDS

• Low-intensity shock wave therapy • Radial shock wave therapy • Restorative therapy
• Erectile dysfunction

KEY POINTS

- A growing body of data supports shock wave therapy as a safe and effective treatment modality for erectile dysfunction (ED), particularly in men who are responders to phosphodiesterase-5 inhibitor (PDE5i) therapy.
- There are important distinctions regarding energy source and transfer that must be carefully considered when interpreting existing data and applying them to practice.
- Published studies on shock wave treatment for ED are limited by short follow-up durations, lack of heterogeneity in patient selection, and variability in shock wave treatment protocol.

INTRODUCTION

Erectile dysfunction (ED) is defined as the consistent or recurrent inability of a man to attain and/or maintain a penile erection sufficient for sexual activity and is a common condition worldwide.[1] ED has been shown to be associated with a variety of comorbidities that affect both patients' physical and mental health, including cardiovascular disease, anxiety, and depression.[2] The prevalence of ED is expected to increase throughout the world, with some estimates predicting that 322 million men will be affected globally by 2025, a 111% increase from 1995.[3] Although there are many therapeutic options available for men with ED, management has changed little since the approval of phosphodiesterase-5 inhibitors (PDE5i) in 1998.[4] Approximately, 30% of men do not respond to PDE5i therapy and many others find that these medications cause undesirable side effects.[5] As a result, PDE5is have been reported to have discontinuation rates of approximately 4% per month and almost 50% after 1 year.[6] In the setting of PDE5i failure, the next steps in management typically involve more invasive therapy, including injections of erectogenic medications and penile prosthesis. Therefore, there is a clear need for new, noninvasive treatment options for men with ED.

Energy-based therapies have been proposed as a novel, nonsurgical, restorative treatment option for ED. A variety of energy sources have been used, most prominently shock waves. Shock waves are a form of acoustic energy that can be targeted and focused on highly specific anatomic regions.[7] Shock waves are known to have mechanically disruptive effects, impacts on tissue regeneration, and anti-inflammatory properties. These properties have made shock wave energy of interest for several medical applications.[8] Examples of use include the management of

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nephrolithiasis, in calcific coronary plaque modification, and musculoskeletal regeneration.[9–11]

Shock wave therapy for use in ED typically uses either low-intensity extracorporeal shock wave therapy (Li-ESWT) or radial shock wave therapy. Li-ESWT is similar to extracorporeal shock wave therapy (ESWT) that is used in other medical applications, except that it works at a lower energy level and the shock waves are spread over a larger focal volume.[12] Radial shock waves, however, are pressure waves that use maximum pressures that are approximately 100 times lower and pulse durations that are about 1000 times longer than Li-ESWT.[13,14] **Fig. 1** demonstrates the differences in the waveforms between Li-ESWT and radial shock wave therapy. Because of differences between these types of shock waves, radial shock wave therapy is classified as an FDA Class I device and does not require medical supervision, whereas Li-ESWT is a class II device, requiring medical supervision. As there is little to no peer-reviewed published literature regarding the efficacy of radial shock waves in the treatment of ED, this technology will not be considered in this article.

The mechanism by which Li-ESWT may improve erectile function remains unclear but is thought to stem at least in part from stimulation of mechanosensors throughout the endothelium in the penile vasculature. This stimulation in turn induces neoangiogenic processes allowing for greater blood flow throughout the corpus cavernosum.[15] In addition to neoangiogenesis, rat models of ED have shown that Li-ESWT may induce migration of progenitor cells that can improve microcirculation and contribute to nerve regeneration.[16] Li-ESWT has also been thought to contribute to the overall decline in cell stress responses and inflammation in penile tissue, which can further contribute to increased blood flow and smooth muscle relaxation.[15] In fact, Lue et al. used a rat model of pelvic neurovascular injuries to demonstrate that Li-ESWT can induce endogenous progenitor cell recruitment and subsequent Schwann cell activation allowing for angiogenesis along with tissue and nerve regeneration.[17] Similar findings have been demonstrated in many other animal models of ED and there have been numerous proposed specific cellular pathways implicated.[18] This is of particular interest as Li-ESWT for the management of ED is generally regarded as safe, with few to no reported adverse effects.[19]

Since Li-ESWT was introduced in 2010, there have been numerous randomized controlled trials (RCTs), as well as meta-analyses evaluating, and in most cases supporting, the efficacy of Li-ESWT.[20–23] Despite this, multiple sexual health organizations and guidelines remain restrictive in their endorsement of this technology, recommending use only in the setting of an institutional review board (IRB)-approved clinical trial.[24–26] Nevertheless, interest in this technology for ED remains quite high.[27,28] In this article, we critically analyze the literature to determine which men are most likely to benefit from Li-ESWT for ED and to delineate data necessary to establish whether or not Li-ESWT will be a new standard of care in ED management.[29] Most studies of Li-EWT have been conducted on men with vasculogenic ED. Moreover, few if any studies have evaluated the efficacy of Li-ESWT in men with ED related to radical pelvic surgery, neurogenic ED, and diabetes.

LITERATURE REVIEW

Phosphodiesterase-5 Inhibitor Responders

Many RCTs investigating the use of Li-ESWT in ED treatment have focused on efficacy in men who are responders to PDE5i therapy. This is an important group to study as it represents the majority of patients with ED and Li-ESWT has the potential to reduce or even eliminate reliance on medication. This is of particular import for men with contraindications to PDE5i use, such as those taking nitrates for angina, and those who have moderate to severe side effects.[30]

The first peer-reviewed published investigation of Li-ESWT for ED was a prospective cohort study by Vardi and colleagues in 20 PDE5i responsive men with vasculogenic ED with International Index of Erectile Function Erectile Function Domain (IIEF-EF) scores between 5 and 19 as well as abnormal nocturnal penile tumescence parameters. All participants underwent a 4-week PDE5i washout period. The participants were administered LI-ESWT to the penile shaft and crura at 5 different sites for 2 sessions a week for 3 weeks with a total of 1500 shocks per treatment. This protocol was repeated after a 3-week period of no treatment. This pilot study was quite successful, with a significant increase in mean IIEF-EF scores from 13.5 ± 4.1 to 20.9 ± 5.8 at 1-month follow-up. Improvements in mean IIEF-EF score remained unchanged at 6-month follow-up, with half of the participants no longer requiring PDE5i therapy.[20]

These promising results led to further study by this same group. In 2012, the first randomized, double-blind, sham-controlled trial of Li-ESWT was reported. In this study, 67 men with ED who were PDE5i responders were randomized to receive Li-ESWT therapy or sham therapy after a 4-week PDE5i washout period. The Li-ESWT cohort received 2 treatment sessions per week for 3 weeks, which were repeated after a 3-week

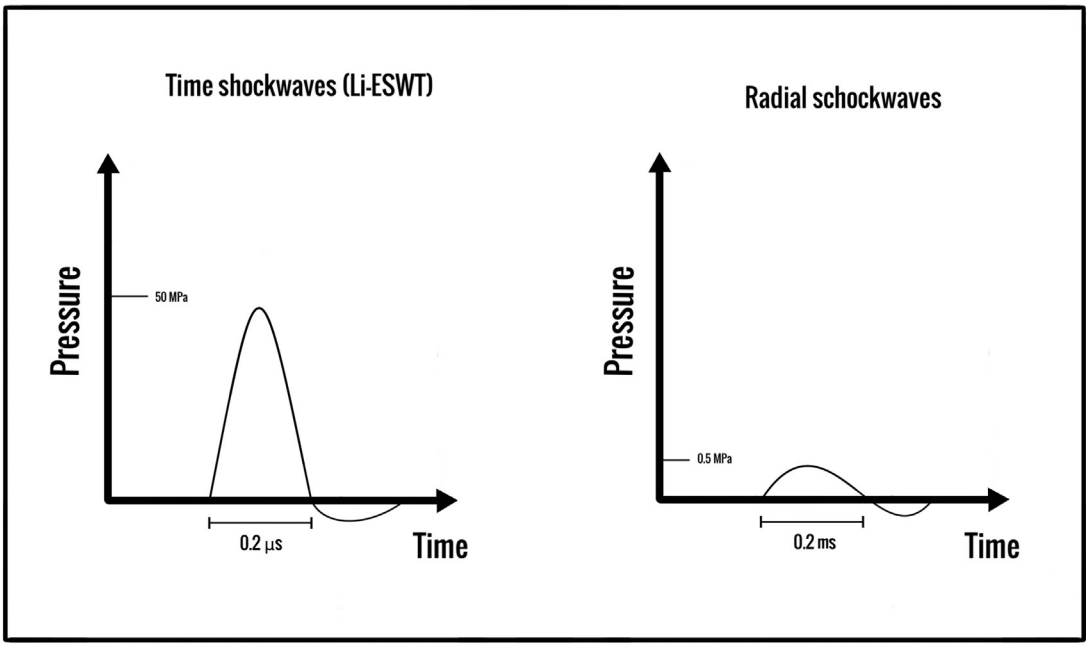

Fig. 1. Waveforms of true shockwaves (Li-ESWT) versus radial shockwaves.

period of no treatment. The participants received 1500 shocks in each treatment session. The authors measured erectile function before the first treatment as well as 1 month after the final treatment. Both cohorts had similar baseline measures of erectile function with a mean IIEF-EF score of 11.5 ± 0.86 and 12.6 ± 0.75 in the sham and treatment group, respectively. There was a significant improvement in erectile function in the treatment group at 1-month follow-up, with a mean IIEF-EF increase of 6.7 ± 0.9 versus 3.0 ± 1.4 in the Li-ESWT and placebo cohorts, respectively. Importantly, more than 40% of the men in the treatment group were newly able to achieve erections hard enough for penetration in the treatment group compared with none in the placebo.[31]

Numerous subsequent studies on Li-ESWT for ED have yielded similar results. In a recent meta-analysis conducted by Sokolakis and colleagues, 6 of the 13 RCTSs on Li-ESWT for ED were focused on men who were PDE5i responders and all of these studies demonstrated a positive effect of Li-ESWT on ED compared with placebo.[22] These results are encouraging but substantial limitations remain to be addressed. The follow-up durations in the RCTs that have been conducted have been quite short, with 4 of the 6 RCTs focusing on PDE5i responders in the aforementioned meta-analysis having follow-up durations of under 6 weeks.[21] This is important as studies evaluating the efficacy of Li-ESWT in patients with even mild forms of ED have shown that the benefits of treatment are not durable at 2 years in at least a quarter of patients.[32] Therefore, it is essential that additional RCTs with longer follow-up durations be conducted to understand how the extent to which patients may experience durable benefit from this therapy.

Phosphodiesterase-5 Inhibitor Nonresponders

PDE5i nonresponders represent a unique group that could significantly benefit from Li-ESWT.[33] Men who fail PDE5i often must turn to more invasive treatment options, including intracorporal injections or surgery for placement of an inflatable penile prosthesis. Unfortunately, studies reporting the efficacy of Li-ESWT in PDE5i nonresponders are scant and until recently have been limited to prospective single-arm cohort studies. Both of the most recent meta-analyses by Dong and colleagues and Sokolakis and colleagues included only one RCT by Kitrey and colleagues that focused on PDE5i nonresponders.[21,22,34] Since these two meta-analyses were published, a more recent randomized, double-blind, sham-controlled trial was conducted in 2020 in which 76 patients with vascular ED who were nonresponders to PDE5i therapy were assigned to either Li-ESWT or a sham probe. The participants had a baseline median IIEF-EF score of 12 (IQR 8–17) and 13 (IQR 8–17) in the treatment and placebo group,

respectively, as well a median baseline Erection Hardness Score (EHS) score of 2 (IQR 1–3) in both groups. At the 3-month follow-up, the median change in IIEF-EF from baseline in the Li-ESWT and sham group was 3.5 (IQR 0–10) and −0.5 (IQR -11 to 1) respectively. At 6 months, 52.5% of participants in the treatment group had an EHS of greater than 2, which is consistent with erections sufficient for penetration, compared with 27.8% in the sham group.[35] Overall, this study showed how Li-ESWT can provide a modest improvement in erectile function in specific groups of patients who are nonresponders to PDE5i therapy. Nevertheless, similar to the majority of RCTs studying Li-ESWT in PDE5i responders, this study was limited by its short follow-up duration of only 6 months. In addition, this study did not reach a clinically significant endpoint which is defined as the minimally clinically important difference in IIEF-EF scores, which varies with a baseline level of erectile function, and is defined as 2, 5, and 7 in those with mild, moderate, and severe ED, respectively.[36] In addition, other than the study by Kitrey and colleagues described below, this is the only sham-controlled RCT evaluating the use of Li-ESWT in PDE5i nonresponders.[30,34]

Li-ESWT was shown to convert men from PDE5i nonresponders to PDE5i responders in one sham-controlled RCT. Kitrey and colleagues conducted a prospective, randomized, double-blind placebo-controlled study in 58 patients with vasculogenic ED who stopped using PDE5i therapy because of a lack of efficacy. Participants had a median IIEF-EF score of 7 and 8 in the treatment and placebo group, respectively, and all participants had an EHS of 2 or less with PDE5i therapy. At 1-month follow-up, 54.1% of participants in the treatment group were able to achieve an erection hard enough for vaginal penetration with PDE5i therapy compared with 0% in the placebo group.[34] A therapy that may allow men to become PDE5i responders may of great utility as an alternative to proceeding to invasive treatments. Although these results are intriguing, data from longer duration studies with a large sample size are necessary before Li-ESWT can be recommended to men who are PDE5i nonresponders.

Erectile Dysfunction in Diabetic Men

In 2019, Spivak and colleagues identified and analyzed 5 double-blind, sham-controlled trials that did not exclude men with diabetes. The study extracted data on 109 men with diabetes who underwent Li-ESWT. Of these, 61 men were PDE5i responders and 48 were nonresponders. Li-ESWT was effective in both groups of diabetic patients, with a mean change in IIEF-EF scores between the treatment and placebo groups of 6.4 (1.6 ± 3.4 vs 8.0 ± 5.5), 4.8 (3.6 ± 5.2 vs 8.4 ± 5.0), and 5.4 (5.4 ± 0.5 vs 5.9 ± 5.1) at 1, 6, and 12 months after the last shock wave treatments, respectively. Among PDE5i nonresponders, 55% were responsive to PDE5i after Li-ESWT corresponding to a change in mean IIEF-EF at 1 month follow-up from −0.5 ± 2.0 to 5.4 ± 5.9 in the placebo and experimental group in this cohort, respectively. As would be expected, PDE5i responders had better outcomes than the PDE5i nonresponders.[37] Although this study speaks to the efficacy of Li-ESWT in this population, dedicated RCTs for diabetic men need to be conducted to better determine the extent to which this therapy may be beneficial in this population. Furthermore, men should be further classified by the extent and control of their diabetes to better elucidate which diabetic men may most benefit from Li-ESWT.

Erectile Dysfunction in Men after Pelvic Surgery

There are certain patient populations for whom Li-ESWT trials have failed to find any efficacy. This has held especially true in men who have undergone radical prostatectomy or radical cystoprostatectomy. Radical pelvic surgery was an exclusion criterion for most RCT evaluating Li-ESWT for ED. Baccaglini and colleagues led the first RCT of Li-ESWT for ED related to nerve-sparing radical prostatectomy. The study enrolled 92 men who were randomly assigned to either receive a PDE5i or combination therapy with Li-ESWT and PDE5i postoperatively following removal of the transurethral catheter. All men received 5 mg/d of tadalafil postoperatively and the Li-ESWT cohort received one session of Li-ESWT per week with 2400 shocks per session for a total of 8 weeks. At 8-week follow-up, the men in the combination therapy cohort were found to have an improvement in median IIEF-EF score compared with the PDE5i only cohort with a median IIEF-EF score of 12 (IQR 9.3–15.8) and 10.0 (IQR 7.0–11.0), respectively. However, despite statistical significance, the study did not reach the primary clinical endpoint defined as a ≥4-point difference in mean IIEF-EF scores between the arms.[38] A similar study by Zewin and colleagues evaluated the role of Li-ESWT for ED in male patients who underwent nerve-sparing cystoprostatectomy. The study included 128 patients who were randomized to Li-ESWT, PDE5i, or control arm. All men had received surgery within 5 years of the date the study was conducted. The

participants in the Li-ESWT cohort received 12 sessions of Li-ESWT with a total of 1500 shocks per treatment session. Patients in the Li-ESWT and control arms did not use adjunctive PDE5i. Potency recovery rates, defined as $\geq$5 point increase in IIEF-EF score and/or erection sufficient for vaginal penetration, at 9-month follow-up were 76.2%, 79.1%, and 60.5% in the Li-ESWT, PDE5i, and control arms, respectively. The researchers did not find a statistically significant difference in erectile function between these groups at any follow-up periods.[39] Furthermore, potency recovery rates in this study were likely higher than other nerve-sparing cystectomy series because of the young age of the patients (53 $\pm$ 6 years) and because all surgeries were carried out by a single expert surgeon. Overall, existing data suggest that although Li-ESWT may be safe in postpelvic surgery patients, it is unlikely to be effective as a monotherapy.

Erectile Dysfunction in Men after Renal Transplant

ED is prevalent in over half of sexually active male renal transplant patients.[40] ED in renal transplant patients is often multifactorial, involving vascular, neurogenic, and pharmacologic causes. Furthermore, there is some concern that PDE5i may alter serum levels of immunosuppressive drugs.[41] In the only sham-controlled RCT in this population, Yamacake and colleagues recruited 20 patients with a minimum interval of 6 months postrenal transplant who were equally randomized among a Li-ESWT and placebo group. All participants were required to discontinue PDE5i use at least a month before treatment and throughout the study period. The Li-ESWT cohort received 2 treatment sessions per week for 3 weeks with a total of 2000 shocks per session. The 2 cohorts had similar baseline IIEF-EF scores of 10.9 $\pm$ 5.1 and 14.9 $\pm$ 3.0 and the mean change in IIEF-EF scores at 4 month follow-up were 6.3 and 1.6 for the Li-ESWT and placebo cohorts, respectively.[41] Although small, this study suggests that renal transplant patients with ED may benefit from Li-ESWT.

Optimal Low-Intensity Extracorporeal Shock Wave Therapy Protocols

The studies that have evaluated the efficacy of Li-ESWT in ED treatment have had significant heterogeneity in their treatment protocols. Unfortunately, the number of trials investigating unique treatment protocols has also been quite limited. The recent

Table 1
Summary of the limitations of current RCTs evaluating Li-ESWT in ED treatment

Limitation	Description
Professional urologic and sexual health associations have advised restricting Li-ESWT use in ED to clinical trials.	Lack of unequivocal evidence and long-term follow-up duration have led to skepticism about the true efficacy of Li-ESWT in ED.
Most RCTs evaluating Li-ESWT in ED have limited follow-up durations.	The most recent meta-analyses of RCTs report follow-up durations between 1 mo and 1 y. Prospective cohort studies that have been conducted with lengthier follow-up durations report diminished efficacy after 1 y.
Many of the RCTs evaluating Li-ESWT in ED are not adequately powered or are missing power calculations altogether.	Approximately, half of the RCTs included in the most recent meta-analyses are missing power calculations. Limited sample sizes and lack of appropriate power calculations lead to uncertainty of the trial's statistical accuracy.
Treatment protocols that have been used in the RCTs evaluating Li-ESWT in ED have not been consistent.	RCTs have used varying treatment durations, number of shocks, and types of shockwave lithotripters. This leads to ambiguity as to the most efficacious protocol in ED treatment.
There are certain patient populations in which Li-ESWT in ED has not been shown to be effective or there is limited data.	The RCTs that have been conducted on men who have underwent pelvic surgery have not shown Li-ESWT to be effective. Limited data exist in diabetic men.

meta-analysis by Sokolakis and colleagues identified only 3 RCTs that compared two different Li-ESWT protocols.[22] In one of these RCTs, Katz and colleagues compared a protocol involving 5 daily sessions of 720 shocks to 6 daily sessions of 600 shocks for a period of 2 weeks. Men who were taking a PDE5i were assigned a 4-week washout period before starting the study and remained free of PDE5i use throughout the study. Although both protocols involved a total of 3600 shocks throughout the course of the study, the first protocol failed to show any difference in IIEF scores at 6 months while the second protocol showed a significant increase of 4.2 points in mean IIEF scores.[29] This indicated that the intense daily application of shocks failed to produce the same results as distributing fewer shocks over a longer period. Kalyvianakis and colleagues also led an RCT involving 42 PDE5i responders in which they tried to compare the efficacy of Li-ESWT in patients who received either 6 (Group A) or 12 (Group B) treatment sessions within a 6-week period. Men who were taking PDE5is underwent a 4-week washout period and remained free of PDE5i use throughout the study. All participants received 5000 shocks per treatment session. Furthermore, those who completed 6-month follow-up were offered 6 additional sessions. The researchers found that when examining the impact of the total number of sessions received, 62%, 74%, and 83% of patients achieved an MCID in IIEF-EF score compared with baseline after 6, 12, and 18 sessions, respectively.[42] As a whole, this study demonstrated that the total number of Li-ESWT sessions has a significant impact on the efficacy of treatment. It also demonstrated that there may be a benefit in retreating patients at specific intervals. Although the current literature gives us some understanding of how to optimize treatment protocols, a larger number of RCTs and meta-analyses comparing protocols must be conducted. This will allow for less heterogeneity and the identification of specific protocols that can best benefit patients.

SUMMARY

Numerous RCTs have demonstrated the efficacy of Li-ESWT in ED treatment. Furthermore, the safety of Li-ESWT has been well-established with none of the RCTs included in recent meta-analyses reporting any significant adverse effects.[21,22] Both urologists and patients have also expressed great interest in this novel therapy.[27,43] Nevertheless, RCTs that have been conducted have not used consistent treatment protocols and additional studies are required to determine which treatment protocols (in terms of number of shocks, location of shocks, intervals between treatment, and frequency of treatment sessions) are optimal. It is conceivable that patient factors may modulate treatment response and that there may not be an optimal "one-size-fits-all" approach.

Currently, most of the successful studies on Li-ESWT in ED treatment have been on men with vasculogenic ED, particularly those who are still responsive to PDE5i. Li-ESWT appears to lack efficacy in men who have undergone pelvic surgery. Other populations, including diabetic men and men who have had a renal transplant, have been incompletely evaluated as to the efficacy of Li-ESWT for ED. Therefore, additional studies in carefully categorized populations are necessary to properly evaluate what populations may best benefit from Li-ESWT.

It is also crucial to assess the long-term efficacy of Li-ESWT to determine how it may best be incorporated into ED treatment. The short follow-up duration of most current RCTs, as well as the small number of men recruited, creates a disadvantage in determining who would best benefit from Li-ESWT and how it can be optimally incorporated into treatment plans.

Overall, despite the growing evidence of efficacy, these limitations have led major urologic and sexual health societies to restrict Li-ESWT as an experimental treatment.[24,26] **Table 1** summarizes the limitations of the RCTs evaluating the use of Li-ESWT in ED treatment. Appropriately powered RCTs with longer follow-up durations, homogenous treatment protocols, and diverse patient populations are required to determine the role of Li-ESWT in ED management. Until such data become available, clinicians should use Li-ESWT only in the context of appropriate patient counseling and safety protocols.

CLINICS CARE POINTS

- Li-ESWT is a noninvasive restorative treatment option for ED with minimal adverse effects.
- Numerous small RCTs have demonstrated the efficacy and safety of Li-ESWT for the management of ED.
- The bulk of data on Li-ESWT for ED has been focused on short-term efficacy in PDE5i responders, a population in which there is evidence for substantial efficacy.

- There are few RCTs on the use of Li-ESWT for ED treatment in PDE5i nonresponders and nonvascular ED.
- Limitations in existing clinical trials of Li-ESWT for ED include short follow-up durations, small sample sizes, and variability in treatment protocols.
- Future studies to expand the prime-time use of Li-ESWT in ED will need to focus on conducting additional RCTs with more diverse patient populations, longer follow-up durations, and larger sample sizes.

REFERENCES

1. Raheem OA, Natale C, Dick B, et al. Novel treatments of erectile dysfunction: review of the current literature. Sex Med Rev 2020;9(1).
2. Christensen BS, Grønbæk M, Osler M, et al. Associations between physical and mental health problems and sexual dysfunctions in sexually active danes. J Sex Med 2011;8(7):1890–902.
3. Goldstein I, Goren A, Li VW, et al. Epidemiology update of erectile dysfunction in eight countries with high burden. Sex Med Rev 2020;8(1):48–58.
4. Moon DG. Evolution of phosphodiesterase-5 inhibitors. World J Mens Health 2015;33(3):123–4.
5. Giuliano F, Joussain C, Denys P. Safety and efficacy of intracavernosal injections of abobotulinumtoxinA (Dysport(®)) as add on therapy to phosphosdiesterase type 5 inhibitors or prostaglandin E1 for erectile dysfunction-case studies. Toxins (Basel) 2019;11(5).
6. Corona G, Rastrelli G, Burri A, et al. First-generation phosphodiesterase type 5 inhibitors dropout: a comprehensive review and meta-analysis. Andrology 2016;4(6):1002–9.
7. Gruenwald I, Appel B, Kitrey ND, et al. Shockwave treatment of erectile dysfunction. Ther Adv Urol 2013;5(2):95–9.
8. Kamel FH, Basha M, Alsharidah A, et al. Efficacy of extracorporeal shockwave therapy on cervical myofascial pain following neck dissection surgery: a randomized controlled trial. Ann Rehabil Med 2020;44(5):393–401.
9. Cao L, Wang YQ, Yu T, et al. The effectiveness and safety of extracorporeal shock wave lithotripsy for the management of kidney stones: A protocol of systematic review and meta-analysis. Medicine (Baltimore) 2020;99(38):e21910.
10. Karimi Galougahi K, Patel S, Shlofmitz RA, et al. Calcific Plaque Modification by Acoustic Shock Waves: Intravascular Lithotripsy in Coronary Interventions. Circ Cardiovasc Interv 2020;14(1):e009354. https://doi.org/10.1161/CIRCINTERVENTIONS.120.009354.
11. Simplicio CL, Purita J, Murrell W, et al. Extracorporeal shock wave therapy mechanisms in musculoskeletal regenerative medicine. J Clin Orthop Trauma 2020;11(Suppl 3):S309–18.
12. Zou Z-J, Tang L-Y, Liu Z-H, et al. Short-term efficacy and safety of low-intensity extracorporeal shock wave therapy in erectile dysfunction: a systematic review and meta-analysis. Int Braz J Urol 2017;43(5):805–21.
13. McClure SR, Sonea IM, Evans RB, et al. Evaluation of analgesia resulting from extracorporeal shock wave therapy and radial pressure wave therapy in the limbs of horses and sheep. Am J Vet Res 2005;66(10):1702–8.
14. Katz JE, Clavijo RI, Rizk P, et al. The basic physics of waves, soundwaves, and shockwaves for erectile dysfunction. Sex Med Rev 2020;8(1):100–5.
15. Sokolakis I, Dimitriadis F, Teo P, et al. The basic science behind low-intensity extracorporeal shockwave therapy for erectile dysfunction: a systematic scoping review of pre-clinical studies. J Sex Med 2019;16(2):168–94.
16. Lin G, Reed-Maldonado AB, Wang B, et al. In situ activation of penile progenitor cells with low-intensity extracorporeal shockwave therapy. J Sex Med 2017;14(4):493–501.
17. Li H, Matheu MP, Sun F, et al. Low-energy shock wave therapy ameliorates erectile dysfunction in a pelvic neurovascular injuries rat model. J Sex Med 2016;13(1):22–32.
18. Liu T, Shindel AW, Lin G, et al. Cellular signaling pathways modulated by low-intensity extracorporeal shock wave therapy. Int J Impot Res 2019;31(3):170–6.
19. Chung E, Cartmill R. Evaluation of clinical efficacy, safety and patient satisfaction rate after low-intensity extracorporeal shockwave therapy for the treatment of male erectile dysfunction: an Australian first open-label single-arm prospective clinical trial. BJU Int 2015;115(Suppl 5):46–9.
20. Vardi Y, Appel B, Jacob G, et al. Can low-intensity extracorporeal shockwave therapy improve erectile function? A 6-month follow-up pilot study in patients with organic erectile dysfunction. Eur Urol 2010;58(2):243–8.
21. Dong L, Chang D, Zhang X, et al. Effect of low-intensity extracorporeal shock wave on the treatment of erectile dysfunction: a systematic review and meta-analysis. Am J Mens Health 2019;13(2).1557988319846749.
22. 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. Int J Impot Res 2019;31(3):177–94.
23. Clavijo RI, Kohn TP, Kohn JR, et al. Effects of low-intensity extracorporeal shockwave therapy on

erectile dysfunction: a systematic review and meta-analysis. J Sex Med 2017;14(1):27–35.
24. Hatzimouratidis K, Giuliano F, Moncada I, et al. EAU guidelines on erectile dysfunction, premature ejaculation, penile curvature and priapism 2019.
25. Burnett AL, Nehra A, Breau RH, et al. Erectile dysfunction: AUA guideline. J Urol 2018;200(3):633–41.
26. POSITION STATEMENT: ED Restorative (Regenerative) Therapies (shock waves, autologous platelet rich plasma, and stem cells). Sexual Medicine Society of North America. Available at: https://www.smsna.org/V1/images/SMSNA_Position_Statement_RE_Restorative_Therapies.pdf. Accessed December 22, 2020.
27. Capogrosso P, Di Mauro M, Fode M, et al. Low-intensity extracorporeal shockwave therapy among urologist practitioners: how the opinion of urologists changed between 2016 and 2019. Int J Impot Res 2020.
28. Towe M, El-Khatib F, Osman M, et al. "Doc, if it were you, what would you do?": a survey of Men's Health specialists' personal preferences regarding treatment modalities. Int J Impot Res 2020.
29. Katz JE, Molina ML, Clavijo R, et al. A phase 2 randomized trial to evaluate different dose regimens of low-intensity extracorporeal shockwave therapy for erectile dysfunction: clinical trial update. Eur Urol Focus 2018;4(3):336–7.
30. Schoofs E, Fode M, Capogrosso P, et al, for the European Association of Urology Young Academic Urologists Men's Health G. Current guideline recommendations and analysis of evidence quality on low-intensity shockwave therapy for erectile dysfunction. Int J Impot Res 2019;31(3):209–17.
31. Vardi Y, Appel B, Kilchevsky A, et al. Does low intensity extracorporeal shock wave therapy have a physiological effect on erectile function? Short-term results of a randomized, double-blind, sham controlled study. J Urol 2012;187(5):1769–75.
32. Kitrey ND, Vardi Y, Appel B, et al. Low intensity shock wave treatment for erectile dysfunction-how long does the effect last? J Urol 2018;200(1):167–70.
33. Patel P, Fode M, Lue T, et al. Should low-intensity extracorporeal shockwave therapy be the first-line erectile dysfunction treatment for nonresponders to phosphodiesterase type 5 inhibition? Eur Urol Focus 2019;5(4):526–8.
34. Kitrey Noam D, Gruenwald I, Appel B, et al. Penile low intensity shock wave treatment is able to shift PDE5i nonresponders to responders: a double-blind, sham controlled study. J Urol 2016;195(5):1550–5.
35. Vinay J, Moreno D, Rajmil O, et al. Penile low intensity shock wave treatment for PDE5I refractory erectile dysfunction: a randomized double-blind sham-controlled clinical trial. World J Urol 2020;39:2217–22. https://doi.org/10.1007/s00345-020-03373-y.
36. Rosen RC, Allen KR, Ni X, et al. Minimal clinically important differences in the erectile function domain of the International Index of Erectile Function scale. Eur Urol 2011;60(5):1010–6.
37. Spivak L, Shultz T, Appel B, et al. Low-Intensity Extracorporeal Shockwave Therapy for Erectile Dysfunction in Diabetic Patients. Sex Med Rev 2019. https://doi.org/10.1016/j.sxmr.2019.06.007. S2050-0521(19)30072-1.
38. Baccaglini W, Pazeto CL, Corrêa Barros EA, et al. The role of the low-intensity extracorporeal shockwave therapy on penile rehabilitation after radical prostatectomy: a randomized clinical trial. J Sex Med 2020;17(4):688–94.
39. Zewin TS, El-Assmy A, Harraz AM, et al. Efficacy and safety of low-intensity shock wave therapy in penile rehabilitation post nerve-sparing radical cystoprostatectomy: a randomized controlled trial. Int Urol Nephrol 2018;50(11):2007–14.
40. Malavaud B, Rostaing L, Rischmann P, et al. High prevalence of erectile dysfunction after renal transplantation. Transplantation 2000;69(10):2121–4.
41. Yamaçake KGR, Carneiro F, Cury J, et al. Low-intensity shockwave therapy for erectile dysfunction in kidney transplant recipients. A prospective, randomized, double blinded, sham-controlled study with evaluation by penile Doppler ultrasonography. Int J Impot Res 2019;31(3):195–203.
42. Kalyvianakis D, Memmos E, Mykoniatis I, et al. Low-intensity shockwave therapy for erectile dysfunction: a randomized clinical trial comparing 2 treatment protocols and the impact of repeating treatment. J Sex Med 2018;15(3):334–45.
43. Patel P, Huang C, Molina M, et al. Clinical trial update on shockwave therapy and future of erectile function restoration. Int J Impot Res 2019;31(3):206–8.