



Low-intensity shock wave therapy for the treatment of vasculogenic erectile dysfunction: a narrative review of technical considerations and treatment outcomes

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Abstract: Erectile dysfunction (ED) impacts a significant portion of the aging male population. Standard treatments such as oral medications, intracavernosal injections, intraurethral suppositories, vacuum erection aids, and penile prosthesis placement have stood the test of time. Recently, there has been a growing interest in the concept of regenerative medicine with the goal of restoring or renewing functional tissue. Low intensity shock wave therapy (LiSWT) is one example of a regenerative therapy. A strong body of basic science data suggests that shockwaves, when applied to local tissue, will encourage blood vessel and nerve regeneration. Clinical evidence supports the use of LiSWT to treat conditions ranging from ischemic heart disease, musculoskeletal injuries, and even chronic non-healing wounds. LiSWT is also being used to treat male sexual dysfunction conditions such as Peyronie's Disease and ED. The first studied application of LiSWT for ED was published in 2010. Since then multiple randomized, sham-controlled trials have sought to evaluate outcomes for this novel therapy in men with vasculogenic ED. Additionally, several meta-analyses are available with pooled data suggesting that LiSWT results in a significantly greater improvement in erectile function relative to sham-control. Despite these promising findings, the current body of literature is marred by significant heterogeneity relating to treatment protocols, patient populations, and follow-up duration. Further work is necessary to determine optimal device technologies, patient characteristics, and treatment duration prior to considering LiSWT as standard of care for men with ED.

Keywords: Stem cells; platelet rich plasma; regenerative; shockwave

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Introduction

Erectile dysfunction (ED) refers to the inability to achieve and/or sustain an erection satisfactory for sexual intercourse. An estimated 30–50% of men between the ages of 40–70 years of age suffer from moderate or severe ED based on data from the United States and Europe (1,2). Treatment begins with lifestyle modification followed by medical therapy with phosphodiesterase-5 inhibitors (PDE5i). In medication

refractory patients, or in those with intolerable side effects, published guidelines encourage clinicians to discuss established treatment such as vacuum erection devices, self-administered intracavernosal injection of erectogenic agents, intraurethral suppositories, and penile prosthesis placement (3).

Over the past several years, there has been considerable interest in the concept of “regenerative” therapies for ED

treatment. This is logical, as ED results in anatomic and functional changes to the erectile tissue characterized by progressive cavernosal fibrosis (4). Regenerative treatments include injections of stem cells, platelet rich plasma, and low-intensity shockwave therapy (LiSWT). There is amassing animal data suggesting that these approaches may result in angiogenesis and neurogenesis, thereby “restoring” dysfunctional erectile tissue (5). To date there is limited human data to support regenerative therapies as a reliable treatment for ED. Also, the patient characteristics associated with treatment success are unclear. This has not stopped a barrage of clinics throughout the world from offering regenerative therapies for ED, sometimes with unsubstantiated claims of benefit, aggressive marketing campaigns, and exorbitant out of pocket fees (6).

Shock wave therapy (SWT) has been widely used for many years to treat many conditions. It was first described 40 years ago for the treatment of renal stones (7) and later for bone non-unions (8), chronic wounds (9), ischemic heart disease (10) and more recently for sexual dysfunction including Peyronie’s Disease and erectile dysfunction (ED) (11,12). High-energy SWT (10–20 kV) is used to fragmentize urinary tract stones whereas SWT using lower energy settings ($<0.2 \text{ mJ/mm}^2$) has been proposed to treat other conditions based on animal model data showing potential regenerative properties through angiogenesis and neurogenesis (7,8).

Due to the minimally-invasive nature of this approach, SWT is an attractive treatment modality for many patients and clinicians. Of the ED regenerative therapies, LiSWT has the largest body of literature, including several randomized-controlled trials and meta-analyses (9). The results are somewhat varied, and there inherent challenges in deciphering treatment outcomes due to variations in treatment protocols (energy settings, number of shocks delivered, duration of therapy, etc.) and patient populations. Also, not all shockwave technologies are created equal and many of the devices used in commonplace are unlikely to exert any effect on erectile tissue (10). Given the controversy and lack of clarity surrounding LiSWT, as well as the increasing number of clinicians who are offering LiSWT within and outside various research protocols, herein we sought to provide a comprehensive review of LiSWT for the treatment of vasculogenic ED with emphasis on mechanism of action, device technology, published data, and future considerations (11). We present the following article in accordance with the Narrative Review Checklist (available at <http://dx.doi.org/10.21037/tau-20-1286>).

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Mechanism of action

A shockwave refers to an acoustic disturbance with the ability to (I) carry energy, and (II) propagate through a medium (10,12). The waveform itself is characterized by a high peak pressure which is achieved rapidly, and a subsequent pressure decay. The wave causes local tissue compression followed by expansion related to the tensile force of the involved tissue (13). This creates tissue stress which is hypothesized to induce neovascularization and neuronal regeneration, in part through recruitment and activation of local progenitor cells (14,15).

In normal physiological conditions, vascular endothelial cells (EC) are frequently exposed to fluid shear stress created by turbulent blood flow. The forces induce cellular changes through a process known as “mechanotransduction”, which is defined as a (bio)chemical response to mechanical stimuli (16). Mechanotransduction modulates EC physiology via intracellular and extracellular signaling pathways, mainly mediated by vascular endothelial growth factor (VEGF), nitric oxide synthase (NOS), and platelet derived growth factor (PDGF) leading to angiogenic gene expression in ECs (17,18).

Through effects on local tissue, SWT is hypothesized to mimic fluid shear stress, stimulating VEGF and other local factor expression to enhance local angiogenesis, particularly at low energy settings (19). Hatanaka *et al.* demonstrated *in vitro* that SWT increased levels of VEGF and endothelial nitric oxide synthase (eNOS), and that caveolin-1 and β_1 -integrin, constitutive proteins of caveolae, which are invaginated organelles found in the plasma membrane and responsible for cell migration, are integral for SWT-induced angiogenesis (20). Also, Sokolakis *et al.* found that LiSWT was associated with increased VEGF expression in the erectile tissue of naturally aged rats, as well as Liu *et al.*, in streptozotocin-induced diabetic rats (21,22). Assaly *et al.*, in a study involving rats with hypertension-induced ED, showed that LiSWT enhanced angiogenesis in cavernosal tissue as shown by CD31 immunohistochemical expression, but there was no significant upregulation of NOS (23). The authors suggested that, although nitric oxide (NO) presence is known to be fundamental for physiological penile erection (and the pathway by which PDE5i act), the effect of LiSWT may be in part NO-independent and therefore beneficial for patients with vasculogenic ED and insufficient PDE5i response.

Table 1 Contemporary lithotripsy technology used in erectile dysfunction

	Omnispec ED 1000 (Medispec, MD, USA)	Duolith SD1 (Storz Medical AG, Tägerwil, Switzerland)	Aries 2 (Dornier MedTech GmbH, Wessling, Germany)	Renova (Direx System GmbH, Wiesbaden, Germany)	PiezoWave 2 (Richard Wolf GmbH, Knittlingen, Germany)
Technology	Electrohydraulic	Electromagnetic	Electromagnetic	Electromagnetic	Piezoelectric
Maximal energy density (mJ/mm ²)	0.23	1.24	0.31	0.09	1.05
Frequency (Hz)	1–3	1–8	1–5	1–5	1–8
Focus penetration depth (mm)	0–80	0–125	0–50	0–40	0–40
Advised protocol	EFD 0.09 mJ/mm ² 1,500 shocks/session 12 sessions (2/week) (3 weeks treatment, 3 weeks no treatment, 3 weeks treatment)	EFD 0.15–0.25 mJ/mm ² 3,000 shocks/session 5 sessions (1/week) or 12 sessions (2/week)	EFD 0.05 mJ/mm ² 5,000 shocks/session 6 sessions (1 /week)	EFD 0.09 mJ/mm ² 3,600 shocks/session 4 sessions (1/week)	EFD 0.16 mJ/mm ² 4,000 shocks/session 6 sessions (1/week)

Mechanical perturbations may also induce neuronal regeneration (“neurogenesis”) through local mechanisms (24). In a rat model of pelvic neurovascular injuries, Li *et al.* demonstrated, both *in vitro* and *in vivo*, that LiSWT improved erectile function not only by increasing the generation of new blood vessels but also by penile nerve regeneration through increased number and proliferation of Schwann cells, which are critical for nerve growth and regeneration (25). Lin *et al.* demonstrated that LiSWT also has the ability to activate local penile progenitor cells in a rat model, suggesting another mechanism for tissue regeneration through vascular and neuronal regeneration (26).

In conclusion, the mechanisms underlying LiSWT in the context of erectile tissue regeneration are not fully understood but likely involve angiogenesis and neurogenesis, namely mediated by growth factor expression and nerve regeneration. Local activation and recruitment of progenitor cells may also play a role. Thus, from a theoretical perspective, this approach, as compared with our standard historical treatment approaches, has the potential to restore erectile function.

Technical specifications

Shock waves are high-pressure acoustic waves characterized by a single rapid and focused pulse followed by a low-tensile phase (10,12). These waves are generated by machines called lithotripters. There are three types of lithotripters

in common use: electrohydraulic, electromagnetic and piezoelectric (12,27,28). Electrohydraulic waves are generated by applying high voltage to electrodes to generate a spark. This produces a high-amplitude spherical wave which is then focused by a reflector. Electromagnetic waves are formed by pulling apart a metal membrane away from an electromagnetic coil using a high voltage electric pulse. The rapid forward movement of the membrane creates a planar acoustic pulse, and the shockwave is focused by an acoustic lens or reflector. Piezoelectric technology uses piezoelectric crystals that expand rapidly and synchronously when a high-voltage electric pulse is applied to them, creating a pressure wave. These crystals are distributed in a spherical way to focus the energy and do not require a lens or a reflector. Contemporary lithotripter machines differ from each other regarding specific settings, namely energy flux density (EFD), penetration depth, and frequency (*Table 1*). Also, each manufacturer has its own recommended protocol, including number and frequency of sessions and number of shocks per session (10,12). Differences amongst machine technologies/protocols and the absence of head-to-head studies make it challenging to determine the superiority of one machine and/or protocol over another.

An important consideration that is often overlooked by patients and practitioners alike is the concept of linear versus radial wave application. This is a distinction that merits further clarification. Radial pressure waves are often described as “standard” shockwaves, but in essence they act

similar to sound waves with a lower peak pressure and rapid outward propagation (10,12,29). This results in a much shallower depth of penetration. In contrast, linear (focused) shockwave devices waves have a distinct focal point and a greater depth of penetration. Radial wave generating devices are classified as “class 1 medical devices” by the United States Food and Drug Administration (FDA) (29). This means that “professionals” are not required to have additional training prior to offering the therapy to patients and there is limited regulatory oversight. In contrast, linear-wave devices are considered as “class 2 medical devices” and require FDA approval to ensure safety and treatment efficacy in the United States. Currently, the majority of providers in the United States who are offering SWT outside of a rigorous research protocol, and especially those without urologic and sexual dysfunction expertise, are using radial-wave technology (i.e., class 1 medical device), whereas the true clinical benefit may lie in the application of linear-wave technologies (i.e., class 2 medical device) (30). Unfortunately, several of the published study protocols that have evaluated LiSWT do not specify the type of ultrasound applicator probe which has significant implications on the conclusions that can be drawn with respect to one technology over another (10).

Review of published clinical data

Randomized, sham-controlled clinical trials

Vardi *et al.* first described LiSWT to treat ED in a 2010 pilot study involving 20 men with PDE5i-responsive erectile dysfunction (31). After a one-month period off all oral pharmacotherapy for ED (i.e. washout), participants underwent six sessions of penile LiSWT over a nine-week period. Follow-up at four-weeks revealed a significant increase in International Index of Erectile function-Erectile Function Domain (IIEF-EF) scores, from a mean 13.5 (out of maximum 30 points), to a mean 20.9, $P < 0.001$). These benefits were maintained at three and six-month follow-up, with an average increase of 7.1 points ($P = 0.001$) (31). Improvements in penile hemodynamics were also seen. The authors subsequently carried out the first randomized, double-blinded, sham-controlled trial with 67 men suffering from vasculogenic, PDE5i-responsive ED who were randomized to LiSWT versus a sham (placebo) procedure using a similar protocol to the original pilot study (32). At one-month follow-up, the mean IIEF-EF in the treatment group increased by +6.7 points, compared with +3.0 points

for the sham-therapy arm ($P = 0.032$). Moreover, 65% of men in the treatment arm achieved a ≥ 5 -point improvement, compared with 20% in the sham arm ($P = 0.0001$). Once again, penile hemodynamics were significantly improved in the treatment arm.

Since that time, multiple retrospective, single-arm prospective, and randomized-controlled trials have been published. This includes 11 randomized, sham-controlled trials evaluating the impact of LiSWT on men with vasculogenic ED (Table 2) (32-42). Results are somewhat mixed owing in part to differences in patient populations, study design, outcomes assessed, follow-up duration, and the type of shockwave technology utilized. Treatment protocols differ in the number of shockwaves delivered with each treatment, location of the applied shockwaves, energy settings, and the number of treatments administered. Also, as discussed above, the type of shockwave transducer (i.e., linear versus radial) may impact the likelihood that a treatment effect is actually delivered at the level of the target tissue. Many of the available LiSWT included in the published literature have capabilities for both wave-types depending on the transducer (10). Unfortunately, in some instances the specific transducer used was not delineated, thereby adding additional uncertainty with the ability to draw definitive conclusions.

In total, 7/11 (64%) sham-controlled trials showed a statistically significant increase in IIEF scores in the treatment arm when compared with the control arm. IIEF scores (either IIEF-EF or IIEF-5) in the treatment arm ranged from +1–12.5 points, depending on the specific study (32,35,36,38-42). 3/11 trials (27%) did not show a benefit favoring LiSWT over sham (33,34,37). For example, in their study of 58 patients using a similar shockwave protocol to the original trial by Vardi *et al.*, Yee and colleagues did not identify any significant difference in outcomes, although they did identify a small benefit in subgroup analysis of men with “severe ED” (37). Trials from Fojecki *et al.* and Olsen *et al.* similarly failed to show a significant difference in outcomes for LiSWT compared with sham-control (33,34). Motil and colleagues did not include a statistical analysis, but their results appear to favor LiSWT over sham, with >80% of patients in the treatment arm achieving a minimal clinically important difference (MCID) in IIEF scores (38). This refers to a change in IIEF scores based on the severity of underlying ED prior to treatment, as defined by Rosen *et al.* (43).

The majority of randomized trials to date have assessed

Table 2 Randomized, sham-controlled trials evaluating outcomes with low-intensity shockwave lithotripsy for vasculogenic erectile dysfunction

Study Info	Trial design	# Treated [control]	Patient characteristics	Device	Treatment protocol					Follow-up duration	Treatment outcomes	
					# shocks/treatment	Frequency of shocks	Energy flux density	Treatment duration	# of treatments		Objective questionnaire results	P value
Vardi <i>et al.</i> (2012)	Randomized, double-blind, sham-controlled	40 [20]	PDE5i responders Vascular ED	Omnispec ED1000	1,500	120/min	0.09 mJ/mm ²	15 mins	12	1 month post	-Tx: +6.7 (+/-0.9) in IIEF -Sham: 3.0 (+/- 1.4) in IIEF	0.0322
Olsen <i>et al.</i> (2015)	Randomized, double-blind, sham-controlled	51 [54]	PDE5i responders Vascular ED	Storz Duolith SD1	3,000	NA	0.15 mJ/mm ²	NA	5	6 wks post	-Tx: 34% w/>5-pt increase in IIEF-EF -Sham: 22% w/>5-pt increase in IIEF-EF	0.67
Yee <i>et al.</i> (2014)	Randomized, double-blind, sham-controlled	28 [30]	Vascular ED	Omnispec ED 1000	1,500	120/min	0.09 mJ/mm ²	20 mins	12	1 month post	-Tx: +5.3 (+/- 5.5) in IIEF vs. Sham: +3.8 (+/- 3.6) in IIEF -Post-hoc analysis suggested significant benefit over sham in subgroup of men with "severe ED"	0.24
Srini <i>et al.</i> (2015)	Randomized, controlled, double-blind, Sham-controlled	60 [17]	PDE5i responders Vascular ED		1,500	120/min	0.09 mJ/mm ²	15 mins	12	1-month post for comparison between sham and tx groups 12-month post for treatment arm	1-month: -Tx: +12.5 (+/-2.2) in IIEF; -Sham: +1.4 (+/-1.9) in IIEF 12-month: -Tx: +8.7 (+/- 2.0) in IIEF	<0.0001
Kitrey <i>et al.</i> (2016)	Randomized, double-blind, sham-controlled	37 [18]	Vascular ED PDE5i non-responders	Omnispec ED10000	1,500	120/min	0.09 mJ/mm ²	15 mins	12	1 month post	-Tx: +5 (median; IQR 0–0.95) in IIEF; MCID (40.5%, n=15) -Sham: +0 (median; IQR -1–1.25) in IIEF; MCID 0% (n=0)	0.0006
Fojecki <i>et al.</i> (2017)	Randomized, double-blind, sham-controlled Cross-over study	58 [60]	Vascular ED PDE5i responders	Wolf PiezoWave/FBL10	1,500	N/A	0.09 mJ/mm ²	15 mins	12	12 months post	-No significant difference in IIEF after active tx vs. sham (38% tx "success" rate in each group) -Low tx satisfaction (50% in sham group and 51% in tx group based on EDITS)	0.92
Motil <i>et al.</i> (2016)	Randomized, single-blind, sham-controlled	75 [50]	Vascular ED PDE5i responders	Wolf PiezoWave/FBL10	4,000	480	0.16 mJ/mm ²	33 mins	4	1-month post	-Tx: 81.3% pts (61/75) achieved MCID in IIEF-5 -Sham: 10% pts (5/10) showed improvement in IIEF-5	NA
Kalyvianakis <i>et al.</i> (2017)	Randomized, double-blinded, sham-controlled trial	30 [16]	Vascular ED PDE5i responders	Omnispec ED1000	1,500	160	0.09 mJ/mm ²	20	12	3 months post	-Tx:56.7% pts achieved MCID in IIEF-EF at 3-mo -Sham: 12.5% pts achieved MCID in IIEF-EF at 3 mo	0.003
Yamacake <i>et al.</i> (2019)	Randomized, double-blind, sham-controlled Cross-over study	10 [10]	Vascular ED Previous renal transplant	Swiss DolorClast	2,000	200	0.09 mJ/mm ²	10 mins	6	3 months post	-Tx: + 6.3 in IIEF-5 vs. Sham: + 1.6 in IIEF-5 -IIEF-5 ↑ by >5-pts in 70% of tx group and 10% of Sham group	0.018
Vinay <i>et al.</i> (2020)	Randomized, double-blind, sham-controlled	40 [36]	Vascular ED	Direx Renova electromagnetic device	5,000	N/A	0.09 mJ/mm ²	N/A	4	1, 3, and 6 months post	1-month: -Tx: +1 (median; IQR -1, 6) in IIEF; -Sham: 0 (median; IQR -8, 4) in IIEF 3-month: -Tx: +3.5 (median; IQR 0, 10) in IIEF; Sham: -0.5 (median; IQR -11, 1) in IIEF 6-month: -Tx: 53% w/EHS >2; Sham: 28% w/EHS >2	1-month: 0.07; 3-month: 0.0004
Kim <i>et al.</i> (2020)	Randomized, double-blind, sham-controlled study	38 [43]	Mild or moderate vascular ED	MT 2000H (electromagnetic)	3,000	NA	20 mJ/mm ² (base) 15 mJ/mm ² (shaft) 12 mJ/mm ² (distal penis)	NA	12	7 wks post	-Tx: mean +5.1 in IIEF (mean EHS: 3.1 +/- 0.6) -Sham: mean 2.2 pts in IIEF (mean EHS: 2.4 +/- 0.9)	<0.001

the effect of LiSWT for vasculogenic ED, but there have been at least two randomized, sham-controlled trials that evaluated treatment outcomes in men suffering from post-pelvic surgery ED. Zewin *et al.* carried out a study involving 128 men with a history of nerve-sparing cystoprostatectomy due to muscle invasive bladder cancer (44). Patients were randomized to one of three arms: LiSWT-only, PDE5i-only, and no-treatment (control). 76%, 79%, and 61% of patients recovered “potency” at 9-months after cystoprostatectomy, respectively. There was a statistically significant difference in IIEF-EF scores amongst all three treatment groups relative to baseline (postoperative), although there was no significant difference in the degree of recovery between the groups. Another study by Baccaglini *et al.* randomized patients to daily PDE5i (tadalafil 5-mg) starting after catheter removal versus PDE5i plus shockwave starting 6-weeks after radical prostatectomy (45). The primary clinical end-point for this trial was a four-point or greater increase in the mean IIEF-5 score favoring the treatment arm. The median baseline IIEF-5 scores for the treatment and control arm were similar (21 and 22 points, respectively; $P=0.510$). The study endpoint was defined at 3-weeks after the last LiSWT application or 16 weeks after prostatectomy. As expected, there was a drop in IIEF-5 scores compared with preoperative, but the median IIEF-5 was significant greater for the LiSWT arm (12; IQR 9.3, 15.8) compared with the control arm (10; IQR 7, 11; $P=0.006$). However, this did not meet the pre-specified study endpoint criteria and the clinical implications of a two-point difference are questionable.

Meta-analyses

Given the variability seen in published outcomes, several groups have attempted to collate the data through meta-analyses to further delineate any beneficial effects with LiSWT on vasculogenic ED (46-53). As is seen in *Table 3*, despite significant differences in study inclusion criteria and technology considerations, all of the meta-analyses to date have shown a significant increase in IIEF scores (i.e., erectile function) for patients treated with LiSWT, both from baseline and relative to sham therapy. The mean difference (MD) in the IIEF between the treatment and sham arms ranged from approximately +2–4 points. Moreover, Sokolakis and Hatzichristodoulou found that patients treated with shockwave therapy were 8.5 times more likely to achieve a MCID in their IIEF score (43,48).

Who is likely to benefit from LiSWT?

Several analyses also sought to identify patient and treatment factors associated with improved outcomes. In their systematic review and meta-analysis involving 14 studies (883 patients), Lu *et al.* showed that the IIEF of patients with mild ED increased significantly after LiSWT relative to sham [mean difference (MD) 2.86; 95% CI: 1.54–4.19; $P<0.0001$], whereas patients with moderate and severe ED did not show a significant increase (49). IIEF increased more notably when LiSWT was combined with PDE5i use (MD 4.20; 95% CI: 0.16–8.24; $P=0.04$), supporting combination therapy. In contrast, a recent meta-analysis from Dong *et al.* found that patients with moderate and/or severe ED experienced greater improvements in their mean IIEF scores relative to patients with mild ED (MD: 3.95; 95% CI: 2.44–5.46; $P<0.00001$) (53). Regarding technical specifications, the number of shocks per session varied between 1,500 to 5,000, but the biggest improvement was seen with >3,000 (49). EFD varied from 0.09 to 0.25 mJ/mm². In their analysis of 9 studies ($n=637$ patients), Man and Li found that lower EFD (0.09 *vs.* 0.1–0.2 mJ/mm²; MD 4.14; 95% CI: 0.87–7.42; $P=0.01$), increased number of shocks (>3,000 per session; MD 5.11; 95% CI: 3.18–7.05; $P=0.0001$) and a shorter total treatment course (<6 weeks; MD 3.73; 95% CI: 0.54–6.93; $P=0.02$) were all associated with improved outcomes.(51) It is important to emphasize that none of the included studies was specifically powered to evaluate these factors.

Discussion

The treatment paradigm for managing vasculogenic ED has remained relatively stagnant for the last two decades. In men who are unresponsive or intolerant of oral medications, we rely on vacuum erection devices, intracavernosal injections, intraurethral suppositories, and the gold-standard penile prosthesis. The latest iteration of the American Urological Association (AUA) guidelines shifted the discussion, positing that a rigid “stepwise” approach, wherein a patient was required to try and fail one option before moving on to the next, was preventing many patients from receiving the treatment needed to optimize their sexual function (3). Regenerative therapies have the potential to revolutionize our age-old approaches, given the perpetual push to develop novel, effective, and less invasive treatments for our patients. The underlying mechanisms for these treatments are sound-animal models supporting tissue regeneration by

Table 3 Meta-analyses reviewing outcomes with low-intensity shockwave lithotripsy to treat erectile dysfunction

Study Info	Number of studies included	Number of patients	Study inclusion criteria	Findings	Other
Angulo <i>et al.</i> (2017)	12	636	Vascular ED	LiSWT resulted in a greater increase in IIEF-EF at 1-month relative to baseline, and to a greater degree relative to sham (MD 2.78; P<0.001) Response relative to sham at 3–6 months unclear	N/A
Man and Li (2017)	9 RCTs	637	Vascular ED; Peyronie’s Disease + ED; Pelvic pain + ED	LiSWT significantly increased IIEF (MD 2.54; P=0.004) and EHS (Risk difference 0.16; P=0.01)	IIEF scores increased significantly for patients with mild or severe ED (versus moderated ED where the increase Lower energy density (0.09 mJ/mm ²), increased # of pulses (>3,000), and shorter treatment course (<6 weeks) resulted in greater improvements Only 1/3 rd of studies have good blinding and 44% of studies had unclear risk of bias in randomization
Zou <i>et al.</i> (2017)	4 RCTs	277	Vascular ED	“Effective treatment” RR for LiSWT vs. placebo was 2.50 (95% CI: 0.74, 8.45) based on IIEF-EF “Effective treatment” RR for LiSWT vs. placebo was 8.31 (95% CI: 3.88, 17.78) based on EHS	9-week protocol resulted in better results versus 5-week protocol
Lu <i>et al.</i> (2016)	7 RCTs	833	Vascular ED; Peyronie’s + ED	LiSWT resulted in a greater increase in IIEF-EF at 1-month relative to baseline, and to a greater degree relative to sham (MD 2.00; 95% CI: 1.19, 3.53; P<0.001) LiSWT resulted in a significant greater increase in EHS at 1-month (RD 0.47; 95% CI: 0.38, 0.56; P<0.00001) and 3-months (RD 0.16; 95% CI: 0.04, 0.29; P=0.001) after treatment	On sub-group analysis, the difference in IIEF was significant at 3-months f/u, but not after only 1-month Patients with “mild” ED had a significant increase in IIEF, whereas those with “moderate” or “severe” ED did not Lower EFD (0.09 mJ/mm ²), greater number of shocks, and shorter treatment duration resulted in greater improvements in IIEF
Clavijo <i>et al.</i> (2017)	7 RCTs	602	Vascular ED	LiSWT resulted in a 4.17-point (95% CI: –0.5, 8.3; P<0.0001) difference relative to sham-control	No difference seen in sub-analysis controlling for follow-up, participant age, and baseline IIEF-EF scores

Table 3 (continued)

Table 3 (continued)

Study Info	Number of studies included	Number of patients	Study inclusion criteria	Findings	Other
				IIEF-EF score increased by mean 6.4 points (95% CI: 1.78, 11.02) for the LiSWT compared with mean 1.65 points (95% CI: 0.92, 2.39; P<0.0001)	Greater number of shocks associated with greater improvement in IIEF score
Campbell <i>et al.</i> (2019)	7 RCTs	607	Vascular ED	LiSWT resulted in a significantly greater increase in IIEF-EF relative to sham (MD 4.13; 95% CI: 0.80, 7.47; P=0.015) Patients who underwent LiSWT were more likely to experience an improvement in EHS (RR 6.63; 95% CI: 1.59, 27.71; P=0.0095)	N/A
Sokolakis and Hatzichristodoulou (2019)	10 RCTs	873	Vascular ED	LiSWT resulted in a significantly greater increase in IIEF-EF relative to sham (MD 3.97; 95% CI: 2.09, 5.84; P=0.03) % of patients achieving a MCID in IIEF-EF in the LiSWT group was significantly greater relative to sham (OR 8.54; 95% CI: 2.64, 27.63; P=0.0003)	Subgroup analysis of PDE5i responders revealed a significantly greater increase in IIEF-EF from baseline and a greater proportion of patients achieving MCID
Dong <i>et al.</i> (2019)	7 RCTs	522	Vascular ED	IIEF scores at 1-month after tx were significantly improved relative to baseline in the LiSWT treated patients compared with sham (MD 1.99 points; 95% CI: 1.35, 2.63; P<0.0001)	N/A

neovascularization and neurogenesis. However, translating these findings into human data with evidence of clinically meaningful positive outcomes is mandatory prior to upending the status quo.

Data continues to amass with respect to LiSWT as a treatment for vasculogenic ED. At least 11 randomized, sham-controlled trials have sought to evaluate treatment outcomes, with >60% showing a statistically significant increase in IIEF scores favoring LiSWT (mean improvement ranging from 1–12.5 points). Studies in other populations such as those with pelvic surgery have shown a benefit as well (35,44). To this end, of the at least eight available meta-analyses, all have supported a statistically significant increase in IIEF-scores with LiSWT (46–53). Due to significant heterogeneity in the study protocols, what remains unknown is what patient characteristics will optimize outcomes with LiSWT. There are some signals from the meta-analyses. For example, Lu *et al.* found that patients with mild ED had a significant improvement over sham, whereas those with moderate and severe ED did not (49). Also, Sokolakis and Hatzichristodoulou

reported that PDE5i responders were more likely to achieve MCID criteria (48). Others such as Clavijo *et al.* reported conflicting results with respect to baseline IIEF-score and likelihood of response, and there are non-randomized studies showing that PDE5i non-responders may be “salvaged” with LiSWT (50). A recent multi-center, prospective, single-arm series from Palmieri *et al.* found that LiSWT, when combined with PDE5i therapy, resulted in an average increase in IIEF-EF score of 8.6 points in PDE5i “non-responders” (54). 71% achieved a MCID in their IIEF-EF scores, and 68% had an EHS ≥ 3 (i.e., rigidity sufficient for penetration). Interestingly, ED symptom duration does not appear to influence results based on a result study from De Oliveira *et al.* (55).

We must also consider treatment protocols which include potential variations in energy settings, number of applied shocks, and treatment duration. Patel *et al.* found no difference in treatment success in their phase II trial comparing a similar number of shocks (3,600) delivered over one versus two weeks (56). Kalyvianakis *et al.* similarly did not identify a significant difference in outcomes based

on the number of sessions administered per week (two versus three) and varying energy-flux density (0.05 *vs.* 0.1 mJ/mm²) (46). In contrast to this, a meta-analysis found that applying a greater number of shocks (at least 3,000) and using a lower EFD (0.09 *vs.* 0.1–0.2 mJ/mm²) may optimize outcomes (49). Future work must focus on delineating the technical settings that will enhance outcomes for our patients if this therapy is to be considered a mainstay.

A final important caveat when offering a treatment is the longevity of positive results. Put another way—do the beneficial effects persist after the treatment has ceased? As seen in *Table 2*, the majority of available studies assessed short term outcomes at 1–3 months post-treatment. In their 2018 study, Kitrey *et al.* sought to further evaluate the persistence of symptom improvement after LiSWT (57). The authors followed 156 patients included in several different previous study protocols. 99/156 patients (64%) were classified as treatment successes at one-month (based on achieving a MCID in IIEF-EF). However, by two years post-treatment, only 53% (53/99) of these original treatment “successes” were able to maintain the beneficial effects of LiSWT without maintenance therapy. 0% of patient with baseline diabetes mellitus or “severe” ED maintained the beneficial effects at two years, as compared to 76% in those with “mild” baseline ED and no diabetes. This underscores the importance of patient selection and pre-treatment counseling to ensure the highest likelihood of success.

There are several national and international organizations that have published guideline recommendations surrounding LiSWT including the AUA (2018), Asia-Pacific Society for Sexual Medicine (APSSM; 2020), European Society of Sexual medicine (ESSM; 2019), and European Association of Urology (EAU; 2020) (3,58–60). All organizations acknowledge LiSWT as a potential treatment for ED with promising early clinical studies. The treatment appears safe with minimal risk for serious adverse events. The majority of adverse events seen in the randomized trials were mild and transient, and there have been no dropouts reported as a result of treatment adverse effects (58). This is true even amongst patients considered higher risk such as those on anti-coagulation or anti-platelet therapy for cardiovascular disease (61). However, due to heterogeneity in the literature surrounding treatment protocols and study populations, further investigation is necessary before we can label LiSWT as “standard of care” outside the scope of clinical research. Accordingly, LiSWT is recommended by the EAU as a first-line

treatment alternative in patients with vasculogenic ED who are uninterested or unable to tolerate oral therapy and who are poor PDE5i responders, but this is based on weak evidence (60). The APSSM similarly suggests that LiSWT be offered to men with mild/moderate vasculogenic ED who do or do not respond to PDE5i (level 2; grade b) (58). The AUA and ESSM, in contrast, consider LiSWT as deserving of more investigation or experimental, respectively (3,59).

Conclusions

Vasculogenic ED is common, and regenerative therapies have the potential to transform our historical treatment paradigms. LiSWT is one such approach that, based on promising animal model data, encourages tissue regeneration through various mechanism including angiogenesis, neurogenesis, and progenitor cell recruitment. Several early single-arm studies and multiple randomized, sham-controlled trials support a possible therapeutic benefit for men with vasculogenic ED. Based on the currently available data, LiSWT appears most likely to benefit patients with mild/moderate ED and few medical comorbidities. LiSWT may optimize response to PDE5i or enhance medication response in PDE5i “non-responders”. Linear ultrasound probes (as opposed to radial) should be considered standard of care. They are the only probes that have been consistently shown to benefit patients based on the available literature, although in practice radial shockwave probes are commonplace. Future work is needed to investigate device technologies, therapeutic administrative protocols (number of shocks, treatment duration), and patient characteristics associated with optimal treatment outcomes. In the meantime, appropriate pre-treatment expectations must be discussed at the outset. Patients should be adequately counseled regarding what is known and unknown about LiSWT, particularly as it pertains to treatment protocols and study populations within the context of clinical studies.

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Footnote

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