Reviewing the evidence for shockwave- and cell-based regenerative therapies in the treatment of erectile dysfunction

Robert Drury, Caleb Natale and Wayne J. G. Hellstrom

Abstract: Erectile dysfunction (ED) is both a common and complex disease process. Existing ED treatments do not always achieve adequate results. There is clinical interest in employing regenerative therapies, including low-intensity extracorporeal shockwave therapy (Li-ESWT), platelet rich plasma (PRP), and stem cell therapy (SCT), in the treatment of ED as adjunct or alternative treatments. Here, we present evidence for emerging shockwave- and cell-based regenerative therapies for the treatment of ED following a thorough review of the existing PubMed literature pertaining to Li-ESWT, PRP, and SCT in relation to the treatment of ED. Li-ESWT causes microtrauma in tissue that hypothetically upregulates angiogenesis and recruits stem cells. Several large-scale systematic reviews and meta-analyses have reported that Li-ESWT improved ED in humans. Additionally, evidence has commenced to show that Li-ESWT may be effective against two recognized and complex etiologies of ED: diabetic and neurogenic. PRP delivers an autologous sample rich in growth factors to damaged tissue. Animal model studies have demonstrated improved erectile function recovery as well as preservation of cavernous nerve axons. Studies with PRP in humans are limited. SCT utilizes the regenerative potential of stem cells for healing of damaged tissue. In the treatment of ED, SCT has been used in the setting of diabetic and post-prostatectomy ED. Results of human studies are varied, although SCT treatments did result in increased erectile rigidity with some patients recovering the ability to achieve penetration. While these regenerative therapies show potential to augment the current treatment regimen for ED, there is a paucity of evidence to support the safety and efficacy of these treatments. Further research is necessary to define the role of these alternative therapies in the treatment of ED.

Keywords: erectile dysfunction, extracorporeal shockwave therapy, platelet rich plasma, regenerative medicine, stem cell therapy

Introduction
Erectile dysfunction (ED) is defined as a man’s continuous (≥ 3 months) inability to attain and/or maintain a penile erection sufficient for satisfactory sexual intercourse.¹ Though a common condition in men over 40 years old, evidence suggests increasing prevalence in younger men.² Many risk factors (e.g., obesity, hypertension) and comorbidities (e.g., cardiovascular) may contribute to the development of ED.³⁻⁵ The American Urological Association (AUA) states that the clinical workup for ED should include several constituents, including medical and psychosocial elements.⁶ Since 1998, phosphodiesterase type 5 inhibitors (PDE5i) have been used as a mainstay of initial treatment for ED.⁷ Though generally safe for ED treatment, PDE5i may be ineffective or they may have side effects that make them less desirable to certain patients.⁸⁻¹⁰ Additional treatment options for ED exist, including vacuum erection devices, intracavernosal vasoactive injections, and penile prosthetics.⁹¹⁰ The AUA states that patients...
should be informed of all non-contraindicated treatment modalities for ED as potential first-line therapies, regardless of invasiveness or irreversibility. Even with multiple treatment options available for ED, some patients continue to have suboptimal outcomes. Therefore, additional treatments are being investigated, including regenerative therapies. Regenerative therapies aim to restore function via replacement or regeneration of human cells, tissues, or organs. Regenerative therapies for the treatment of ED include low-intensity extracorporeal shockwave therapy (Li-ESWT), platelet rich plasma (PRP), and stem cell therapy (SCT) (Table 1).

**Low-intensity extracorporeal shockwave therapy**

Extracorporeal shockwave therapy was first used in 1980 to treat renal calculi. It has since been used to treat other pathologies, such as gallstones and parotid gland stones. In 1988, Rompe et al. created a grading system that suggested lower energy flux density shockwave therapy might be safe for use in soft tissue. This realization was the origin of Li-ESWT. Li-ESWT has since become recognized for its potential clinical therapeutic effects in the treatment of various musculoskeletal pathologies, Peyronie's disease, chronic prostatitis/chronic pelvic pain syndrome, chronic wound treatments, and several cardiovascular pathologies. In 2010, Li-ESWT began to be explored as an alternative means of treating ED, with the first randomized controlled trial (RCT) published in 2012.

The benefits of Li-ESWT stems from its ability to induce microtrauma. A shockwave is a type of longitudinal acoustic wave that is composed of three sequential parts: a short pulse, a rapid increase to max positive acoustic pressure (the "shock"), and a prolonged period of negative pressure. The shockwave causes damage both directly via the mechanical stress of the high-amplitude shockwave itself, and indirectly via the growth and violent collapse of cavitation bubbles in fluid, particularly blood vessels. The body responds to this microtrauma by upregulating several physiologic compounds and processes.

When Li-ESWT is applied to tissue, the microtrauma induces angiogenesis through the upregulation of growth factors (e.g., vascular endothelial growth factor). Additionally, Li-ESWT recruits stem cells and progenitor cells to the site of injury, which may further contribute to the formation of new blood vessels. The potential benefit of increased angiogenesis in those patients with vasogenic ED is readily apparent. Sufficient vasodilation is also essential to erectile function, and Li-ESWT has demonstrated increased production of vasodilatory nitric oxide in affected tissues. Li-ESWT may even play a role in nerve regeneration. Through facilitating accelerated debris clearing and reduced neuronal scarring in regenerating nerves, as well as increasing Schwann cell proliferation, Li-ESWT may help treat ED caused by neuropathic etiologies.

Several large-scale systematic reviews and meta-analyses have been performed on Li-ESWT, all of which reported promising results. A 2019 study

---

**Table 1.** Shockwave- and cell-based regenerative therapies for ED.

| Type of therapy | Proposed method of action | AUA guideline on therapy |
|-----------------|---------------------------|--------------------------|
| Li-ESWT         | Produces microtrauma in penile tissue that upregulates angiogenesis and recruits stem cells | Li-ESWT should be considered investigational since insufficient evidence exists to recommend for or against its use in the treatment of ED |
| PRP             | Delivers an autologous sample rich in growth factors to damaged penile tissue | PRP should not be offered to patients except in the setting of an institutional review board-approved experimental clinical research protocol |
| Intracavernosal SCT | Utilizes the regenerative potential of stem cells for healing damaged penile tissue | SCT should be considered investigational. Additionally, there is no data for the most effective source or dose of SCT |

AUA, American Urological Association; ED, erectile dysfunction; Li-ESWT, low-intensity extracorporeal shockwave therapy; PRP, platelet-rich plasma; SCT, stem cell therapy.
by Dong et al. investigated the effects of Li-ESWT using the International Index of Erectile Function erectile function domain (IIEF-EF) and the Erection Hardness Score (EHS) questionnaires, as compared with sham therapy.47 Using data from January 2010 to June 2018, they performed a systematic search of seven well known databases (e.g., MEDLINE) to obtain RCTs on the effects of Li-ESWT on ED. Seven RCTs met their criteria and were included, involving a total of 522 participants. The meta-analysis revealed that Li-ESWT-treated men showed significant improvement on both ED questionnaires. Compared with the sham group, the Li-ESWT pooled mean on the IIEF-EF score increased significantly from baseline to follow up [mean difference (MD): 1.99 points; 95% confidence interval (CI) (1.35, 2.63); p<0.00001]. Additionally, a significant increase in the IIEF-EF of the Li-ESWT treatment group was observed [MD: 3.62; 95% CI (2.99, 4.25); p<0.00001]. A significant increase was also seen on the EHS questionnaires in four studies [odds ratio (OR): 16.02; 95% CI (7.93, 32.37); p<0.00001]. No adverse effects were reported.

A similar meta-analysis by Sokolakis and Hatzichristodoulou was performed using the IIEF-EF and EHS questionnaires.48 Data from January 2010 to September 2018 was collected from five databases (e.g., Web of Science) and only sham-controlled RCTs were used. A total of 10 RCTs met their criteria, involving 873 patients in total. Li-ESWT improved ED significantly in the pooled data in both patient-subjective and patient-objective outcomes [IIEF-EF: 3.97; 95% CI (2.09–5.84); p<0.0001, EHS ≥ 3: OR: 4.35; 95% CI (1.82–10.37); p=0.0009, and peak systolic velocity: +4.12; 95% CI (2.30–5.94); p<0.00001, respectively]. There were no major adverse effects caused by Li-ESWT; however, one study reported a patient experienced local irritation from Li-ESWT and another study reported that a patient was diagnosed with Peyronie’s disease 6 months after treatment.

Evidence has begun to indicate that Li-ESWT may be effective against two specific, more complicated etiologies of men with ED: diabetic and neurogenic. ED is often difficult to treat in diabetic patients because of the angiopathic and neurogenic effects of diabetes.49–51 A 2019 study illustrated the efficacy of Li-ESWT in treating diabetic patients with ED.52 Specifically, the researchers collected data from five double-blind, sham-controlled trials and subdivided patients into two groups, based on whether their ED had previously responded to treatment with PDE5i. A total of 350 PDE5i responders (PDE5i-R) with vasogenic ED were identified, 61 of which had diabetes. A total of 53 PDE5i non-responders (PDE5i-NR) were found, 48 of which had diabetes. The study utilized multiple questionnaires (e.g., IIEF-EF) and demonstrated that Li-ESWT therapy was effective in treating ED in both diabetic subgroups. Specifically, the minimal clinically important difference in IIEF-EF scores was significantly higher in Li-ESWT versus sham group at the 1, 6, and 12-month follow-up visits post-Li-ESWT therapy (p<0.001). The researchers concluded that Li-ESWT was safe and effective for patients with diabetes-associated ED. However, further large RCTs in diabetic patients with ED are limited.

ED due to neuronal injury following invasive procedures (e.g., radical prostatectomy) also poses a difficult condition to manage.53–55 Animal studies have assessed the effects of Li-ESWT on neuronal regeneration, finding that Li-ESWT may increase Schwann cell proliferation,46 increase neurotrophin-3 expression,56 protect peripheral nerves from diabetes-associated inflammation and oxidative stress,57 and suppress neuronal cell death in gliocytes.58 Several animal studies have also revealed that Li-ESWT may be beneficial in specifically rejuvenating injured penile nerves by increasing key neuronal elements (e.g., Schwann cells, brain-derived neurotrophic factor) 59–61; one study even demonstrated that this benefit to cavernous nerves may potentially be enhanced by the addition of human adipose-derived stem cells concurrent with treatment by Li-ESWT.62 However, studies regarding neuronal-based ED in human subjects remain limited. One study included patients (n=18) who had undergone bilateral nerve-sparing radical prostatectomy and reported that their IIEF-EF improved slightly postoperatively with Li-ESWT, though not to a clinically significant extent.63 A similar result was observed in patients (n=42) after nerve-sparing radical cystoprostatectomy who reported clinically significant improvements, though the improvements were not statistically significant.64 No severe adverse effects from Li-ESWT were seen in either study. Therefore, though there are clinical studies emerging regarding the effects of Li-ESWT on neurogenic ED, there is a fundamental need for further studies with larger sample sizes.55,65
The use of Li-ESWT for ED appears promising, though the collective supporting evidence is still underdeveloped. One holistic analysis by Yang and Seftel listed several weaknesses and unknowns regarding Li-ESWT treatment for ED,9 including the use of varied questionnaires (e.g., IIEF-EF) in measuring erectile improvement after Li-ESWT that makes pooling data difficult, the lack of subjective (e.g., IIEF-EF) versus objective (e.g., evaluation of penile blood flow) data on erectile improvement following Li-ESWT, the exclusion of non-vasculogenic ED patients (e.g., male hypogonadism) from Li-ESWT studies, the benefit of Li-ESWT on ED over time, and the lack of a published treatment protocol. For example, the treatment protocols vary in the amount of shocks delivered per session and the total amount of shocks delivered during treatment. In one particular clinical trial, 2400 shocks/session-week were used for a total of 8 weeks (19,200 shocks total),66 whereas another study performed 2000 shocks biweekly for 3 weeks (12,000 shocks total).67 A recent meta-analysis analyzed 14 clinical studies and found that the number of shocks per session ranged from 1500 to 5000 and that the length of treatment varied from 6 to 9 weeks.68 To address this variance, one recent review recommended starting with 18,000 shocks total over a condensed period of 6 weeks.69 However, one of the main difficulties in establishing a treatment protocol is the lack of published data about the long-term adverse effects of Li-ESWT and how those effects are affected by shocks per session and total shocks delivered.

Since the usage of Li-ESWT in treating ED is relatively new and most studies are short-term in nature, there is insufficient data on whether Li-ESWT treatment of ED produces any long-term adverse effects. Furthermore, there is insufficient data on whether those adverse effects are affected by various treatment protocols. With that being noted, to date, no significant short- or long-term side effects from the usage of Li-ESWT in ED have been identified.

Thus, one of the first steps in making Li-ESWT more standardized and beneficial to patients with ED is elucidating any long-term adverse effects of Li-ESWT for ED and whether those effects are affected by shocks delivered per session and total shocks delivered. This information would provide clinicians with a specific protocol for how much shock to deliver and for what length of time. Additionally, it would elucidate any possible contraindications for Li-ESWT and thus help clinicians tailor treatment to each individual patient.

With all these unknowns still remaining, it is clear why the United States Food and Drug Administration has yet to approve Li-ESWT for ED. Furthermore, the AUA states that Li-ESWT should be considered investigational, as insufficient evidence exists to recommend for or against its use in the treatment of ED.6

**Platelet-rich plasma**

PRP describes a biological therapy containing a supraphysiologic concentration of platelets, proteins, and other components of plasma that stimulate growth and repair in various target tissues. The value of this therapy is postulated to be explained by the abundance of growth factors contained within the sample,70 including platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), and fibroblast growth factor (FGF). These growth factors affect stem cell recruitment, inflammatory reaction response, angiogenesis, and wound healing.71 The first medical application of PRP was in hematology, with the applied therapy intended to transfuse a large number of platelets.72 Platelet-derived therapies have since been trialed in a range of medical and surgical fields for their perceived value in wound healing and tissue regeneration. Among others, platelet-based therapies have been used in rheumatology for the treatment of tendinopathies73; dermatology for treatment of alopecia, acne, and burns;74,75; maxillofacial surgery for degenerative joint disorders76; and orthopedic surgery and sports medicine for a variety of conditions.77 In urology, PRP has been used in the treatment of ED, Peyronie’s disease, and stress urinary incontinence.71,78

PRP is generally produced by processing an autologous blood sample. After obtaining the blood through venipuncture, a one- or two-step centrifugation process separates plasma from leukocytes and red blood cells. This is followed by an activation step to prompt release of therapeutic factors. Proposed stimulants for activation include thrombin, calcium, chloride, collagen cryopreservation, and freeze drying.79 Standard platelet concentrate for transfusion historically contains $0.5 \times 10^{11}$ platelets per unit.72 Modified PRP preparation techniques can be used to produce PRP products with varied concentrations of
platelets, leukocytes, and fibrin.72 Although the mechanism behind the efficacy of PRP in ED is not well elucidated, the proposed effect of the treatment derives from the concentration of biologically active growth factors within the medium. Platelets are involved in a variety of homeostatic functions that include regeneration and wound healing. To accomplish these roles, platelets contain a wide range of growth factors, including PDGF, TGF-β, VEGF, FGF, insulin-like growth factor (IGF), connective tissue growth factor (CTGF), and basic fibroblast growth factor (bFGF).79 The roles of these factors include angiogenesis; collagen synthesis; myogenesis; and proliferation and migration of endothelial, smooth muscle and mesenchymal cells.79,80 Emerging evidence suggests that growth factors within platelets are involved in the upregulation of neuronal nitric oxide synthase and neural regeneration, which may indicate potential benefit of PRP in the treatment of ED.81,82

Research investigating the efficacy of PRP in the treatment of ED is limited, with most available evidence derived from animal models. A 2009 study by Ding et al. investigated the effect of PRP injection on regenerative capacity in a bilateral cavernosal nerve (CN) crush injury model82; 24 rats were divided into the three groups of sham operation, bilateral CN crush injury followed by injection of PRP at the site of injury, and bilateral CN crush injury without further intervention. The study assessed erectile function at 3 months through maximal intracavernous pressure (ICP) with electrostimulation. Nerve regeneration was assessed through toluidine blue staining of the CN nerve and NADPH-diaphorase staining of the penile tissue. Rats in the PRP treatment group demonstrated increased maximal ICP, an increased number of myelinated CN axons on toluidine blue staining and more NADPH-diaphorase positive nerve fibers, compared with the non-PRP operation groups. Rats in the sham operation showed the greatest number of myelinated axons and NADPH-diaphorase positive nerve fibers overall. The authors concluded that the application of PRP could have led to a reparative effect on the CN and peripheral nerves.

In their 2012 study, Wu et al. conducted a similar experiment,81 observing that the crush injury group without subsequent PRP treatment (vehicle only) showed significantly worse ED compared with the sham operation group. The crush injury group treated with PRP showed lower ICP after electrostimulation at 1 month, although this was not statistically significant. The PRP-treated group also exhibited a significantly greater number of preserved myelinated CN axons compared with the vehicle-only group. mRNA expression of TGF-β1 was also decreased significantly in the PRP group compared with the vehicle-only group. These results support the conclusion that PRP serves to increase the number of myelinated axons and ultimately facilitates recovery of erectile function. In 2016, the same group conducted an experiment attempting to determine the effect of the concentration of growth factors within the PRP on reparative outcomes82; 24 rats were divided randomly into a sham operation group or groups treated with nerve crush injury followed by intracavernosal injection of general PRP, optimized PRP containing a higher amount of PDGF, or normal saline. The study results suggest that optimized PRP containing a high level of PDGF is more stable and facilitates recovery of erectile function.

Human studies of the efficacy and safety of PRP are limited. A retrospective study of 17 patients treated with PRP included four treated for ED and one treated for a combination of ED and Peyronie’s disease.78 In this study, two tubes of 9 ml whole blood were centrifuged at 6000 r/min for 6 min; 10% CaCl₂ solution was added to the PRP in a 1:10 ratio. Average yield was approximately 5.5 ml of injectable platelet rich fibrin matrix. Between 4 and 9 ml of solution was injected during each treatment session. The authors reported that no patient suffered from reduced erectile function as measured by the IIEF-5 scores, with average improvement of 4.14 points after PRP therapy. The authors also reported four minor adverse events in the overall group of 17 patients, including pain at injection site and penile bruising, without any major adverse events.

Overall, there is not sufficient evidence to support the use of PRP in the treatment of ED. While this is an exciting treatment that is being used in many different fields of medicine, the efficacy of this treatment in humans is largely theoretical. Increased understanding of the mechanism behind the clinical application of PRP should precede clinical adoption of this treatment. Animal models may be the key to determining the ideal protocol for preparing PRP. It is likely that further elucidation of these protocols will allow for progression to more clinical trials. As research on human subjects is extremely limited, future
Studies should include both control groups and comparisons with available treatments, particularly PDE-5i. The AUA guidelines state that PRP should not be offered to patients except in the setting of an institutional review board-approved experimental clinical research protocol. However, PRP is widely available in many countries in direct-to-consumer clinics. These clinics provide “P shots,” often at very high prices per treatment. These PRP therapy clinics rely on consumer advertising, largely through the internet. Further research is required to determine if PRP is an effective and safe therapy for ED, or just a short-lasting trend.

**Stem cell therapy**

Stem cells are clonogenic, self-renewing cells that have the ability to undergo proliferation, self-renewal, and differentiation into multiple cell phenotypes. Stem cell therapies (SCT) seek to harness the regenerative potential of stem cells for the repair of injured or damaged tissues. The utilization of adult stem cells has allowed for easier access to stem cells, leading to higher likelihood of utility in regenerative medicine. SCTs have the potential to revolutionize the treatment of conditions as broad as muscular dystrophy, diabetes, and neurodegeneration. In many cases, however, technology that seeks to apply these therapies in clinical practice remains in a nascent phase. The etiologies of ED are numerous and include damage to the neurovascular bundle or neuropraxia during radical prostatectomy; nerve damage, endothelial dysfunction, and oxidative stress in the setting of diabetes mellitus; and accumulation of fibrous plaque and veno-occlusive ED in the setting of Peyronie’s disease. Animal models have been developed to evaluate the benefit of SCT in the treatment of ED for each of these etiologies.

The utility of SCT is conceived to lie in the transformation, paracrine signaling, and differentiation of stem cells into specialized cells (smooth muscle, epithelial, Schwann, and neuronal). The specific mechanism(s) of SCT is not well defined and may vary by cell lineage. Evidence from a diabetic rat model in which cavernosal tissue was transplanted with bone marrow-derived mesenchymal stem cells (BM-MSC) observed evidence of differentiation into endothelial and smooth muscle-like cells in the corpus cavernosum, which could be a possible explanation for improvement of erectile function in treated cavernosal cells compared with untreated diabetic model rats. Other animal model studies using adipose tissue-derived stem cells (ADSC) indicate that paracrine action might be an important mechanism by which stem cells play a role in regeneration of endothelial and smooth muscle cells.

Albersen et al. documented evidence of a paracrine mechanism of ADSCs in a neurogenic rat model with CN crush injury when they found comparable functional recovery in rats treated with ADSCs and ADSC-derived lysate despite having no live stem cells injected or identified upon inspection in the latter group. Exosomes are also believed to contribute to the efficacy of stem cells in regeneration of tissues through the migration of proteins, microRNA, and nucleic acids that decrease apoptosis and promote angiogenesis. A study evaluating the treatment of ED with muscle-derived stem cells (MDSC) using a CN crush injury rat model found evidence of stem cells within the tissue as well as near normal erectile function after 4 weeks. The authors postulated that the stem cells had proliferated and differentiated into muscle cells and neuronal cells, mitigating, and reversing the ED caused by the crush injury. A study comparing the efficacy of delivery of stem cells intracavernosally versus peri-prostatically at the time of the operation observed that erectile function recovery was similar with each method, but that the intracavernosal method primarily resulted in the prevention of corpuscal smooth muscle deterioration while the periprostatic method mainly induced nerve regeneration.

Several studies have evaluated the efficacy of SCT for the treatment of ED in humans. Bahk et al. infused $1.5 \times 10^7$ human umbilical cord stem cells into both corpus cavernosa of seven diabetic patients suffering from ED. Six of the patients regained morning erections by the third month and maintained the erections for 6 months. SCT prompted increased rigidity that was not sufficient for penetration, although two patients achieved penetration and orgasm with the addition of PDE5i prior to intercourse. The control group, which consisted of three patients injected with saline, did not experience changes in penile rigidity. There were not any reported adverse events. A similar case series was published in 2015 that utilized ADSCs, injecting $1.5 \times 10^7$ cells intracavernosally in diabetic patients with ED. These investigations noted that morning erections returned in five of six men by 95 days and continued for more than 4 months. Three
patients were able to achieve penetrative sex and orgasm with the aid of PDE5i. There were not any reported adverse events. A 2016 study evaluated the effectiveness of placental matrix-derived mesenchymal stem cells on patients with ED. These authors reported that SCT led to improved erections as measured by significant increases in peak systolic velocity from baseline at 3 months ($p < 0.05$) and 6 months ($p < 0.01$). Changes in stretched penile length, end diastolic velocity and IIEF scores were not changed significantly at 6 weeks, 3 months, or 6 months. Some patients reported pain at the injection site. Haahr et al. reported the results of a phase I open-label single-arm study that included 17 patients suffering from ED after radical prostatectomy who were treated with ADSCs. They reported that 8 of the 17 men recovered erectile function and were able to perform sexual intercourse. After subsetting for only continent men, 8 of 11 recovered erectile function, with a median IIEF score increasing from 7 (95% CI 5–12) to 17 (6–23) which revealed a statistically significant mean difference of 0.57 (0.38–0.85, $p = 0.0069$). Some patients reported pain during the harvesting procedure, and one patient reported a hematoma after injection. A 2016 phase I/II pilot clinical trial utilized bone marrow derived mononuclear cells (BM-MNC) for the treatment of ED after radical prostatectomy. A total of 12 patients were divided into four groups, with the groups receiving varying doses of BM-NMC from $2 \times 10^7$ to $2 \times 10^9$ cells. The authors reported significantly improved IIEF domains of intercourse satisfaction (6.8 versus 3.9, $p = 0.044$) and erectile function (17.4 versus 7.3, $p = 0.006$), as well as increased erection harness (2.6 versus 1.3, $p = 0.008$) at 6 months compared with baseline. Groups receiving higher doses of BM-NMC demonstrated significantly greater improvement in spontaneous erections. No adverse events were reported.

While available literature communicates potential for the efficacious treatment of ED with SCT in diabetics and post-prostatectomy patients, there is not sufficient evidence to merit clinical recommendations for this treatment outside of well-designed clinical trials. Future studies may help to determine which variety of stem cells produce optimal results, if any. Additionally, it is unclear which concentration of stem cells, treatment duration, and dosing schedule are most appropriate. These gaps in knowledge likely represent barriers prohibiting clinical trials from being undertaken. Understanding the mechanism behind the clinical application of SCT for the treatment of ED may further elucidate some or all of these questions. For this reason, animal model studies would be appropriate. The AUA guidelines indicate that intracavernosal stem cell therapy should be considered investigational, noting that no evidence exists of a most effective source or dose of SCT. Although published risks include only minor events (e.g., pain at the site of injection, hematoma), the paucity of available data does not allow for the elucidation of the complete risk profile of this form of ED treatment.

Gene therapy, an alternative form of cellular based therapy which consists of injections of novel genetic material via vector to treat disease, is another potential future therapy for ED. Proposed targets using gene therapy in the treatment of ED include nitrous oxide synthase, pigment epithelium-derived factor and vascular endothelial growth factor. Gene therapy has the advantage of potentially long-lasting treatment effects due to the low rate of smooth muscle turnover, but this therapy comes with risk of severe inflammatory reactions. Research supporting gene therapy for the treatment of ED remains in its infancy.

**Conclusion**

Despite advancements in the understanding of ED, there remains a need for better treatments of this common and often complex condition. Traditional therapies (e.g., lifestyle changes, PDE5i, vacuum erection device, intracavernous vasoactive injections, penile prostheses) are effective, although some patients do not achieve an adequate response to these therapies or are unwilling or unable to undergo such treatment. Novel regenerative therapies have revealed promise as alternative or adjunctive therapies in the treatment of ED. The current body of research to support the use of these methods is limited. In general, these therapies have demonstrated limited side effect profiles, but data to their efficacy is also lacking. Due to this paucity of data, these treatments are not recommended for ED outside of experimental environments. Thus, we recommend these treatments be utilized only for patients with refractory ED who are willing to undergo experimental treatment for their ED. Of the regenerative therapies reviewed herein, Li-ESWT is the treatment with the strongest evidence for its usage. However, additional research highlighting
the safety and efficacy of LiESWT, PRP, and SCT is necessary before these regenerative therapies are included in the standard repertoire of ED treatments. It is possible that the further elucidation of the pathophysiology behind ED will allow for clinicopathologically targeted therapies for treatment. This could allow these experimental therapies to be targeted to specific patient populations, such as those with neurogenic or diabetes-associated ED.

Author contributions
Conception and design: all authors; acquisition and analysis of data: RD, CN; writing – original draft: RD, CN; writing – revision: WH; final approval: all authors.

Conflict of interest statement
The author(s) declare that there is no conflict of interest.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD
Wayne J. G. Hellstrom https://orcid.org/0000-0003-1284-959X

References
1. Montorsi F, Adaikan G, Becher E, et al. Summary of the recommendations on sexual dysfunctions in men. J Sex Med 2010; 7: 3572–3588.
2. Nguyen HMT, Gabrielson AT and Hellstrom WJG. Erectile dysfunction in young men—a review of the prevalence and risk factors. Sex Med Rev 2017; 5: 508–520.
3. Shamloul R and Ghanem H. Erectile dysfunction. Lancet 2013; 381: 153–165.
4. Christensen BS, Grønbaek M, Osler M, et al. Associations between physical and mental health problems and sexual dysfunctions in sexually active Danes. J Sex Med 2011; 8: 1890–1902.
5. Raheem OA, Su JJ, Wilson JR, et al. The association of erectile dysfunction and cardiovascular disease: a systematic critical review. Am J Mens Health 2017; 11: 552–563.
6. Burnett AL, Nehra A, Breau RH, et al. Erectile dysfunction: AUA guideline. J Urol 2018; 200: 633–641.
7. Rizk PJ, Krieger JR, Kohn TP, et al. Low-intensity shockwave therapy for erectile dysfunction. Sex Med Rev 2018; 6: 624–630.
8. Yafi FA, Sharlip ID and Becher EF. Update on the safety of phosphodiesterase type 5 inhibitors for the treatment of erectile dysfunction. Sex Med Rev 2018; 6: 242–252.
9. Yang H and Selft AD. Controversies in low intensity extracorporeal shockwave therapy for erectile dysfunction. Int J Impot Res 2019; 31: 239–242.
10. Ciocanel O, Power K and Eriksen A. Interventions to treat erectile dysfunction and premature ejaculation: an overview of systematic reviews. Sex Med 2019; 7: 251–269.
11. Chaussy C, Brendel W and Schmiedt E. Extracorporeally induced destruction of kidney stones by shock waves. Lancet 1980; 2: 1265–1268.
12. Tandan M and Reddy DN. Extracorporeal shock wave lithotripsy for pancreatic and large common bile duct stones. World J Gastroenterol 2011; 17: 4365–4371.
13. Tandan M, Reddy DN, Santosh D, et al. Extracorporeal shock wave lithotripsy of large difficult common bile duct stones: efficacy and analysis of factors that favor stone fragmentation. J Gastroenterol Hepatol 2009; 24: 1370–1374.
14. Capaccio P, Torretta S and Pignataro L. Extracorporeal lithotripsy techniques for salivary stones. Otolaryngol Clin North Am 2009; 42: 1139–1159.
15. Rompe JD, Kirkpatrick CJ, Küllmer K, et al. Dose-related effects of shock waves on rabbit tendo Achilles. A sonographic and histological study. J Bone Joint Surg Br 1998; 80: 546–552.
16. Lei H, Liu J, Li H, et al. Low-intensity shock wave therapy and its application to erectile dysfunction. World J Mens Health 2013; 31: 208–214.
17. Diercks R, Bron C, Dorrestijn O, et al.; Dutch Orthopaedic Association. Guideline for diagnosis and treatment of subacromial pain syndrome: a multidisciplinary review by the Dutch orthopaedic association. Acta Orthop 2014; 85: 314–322.
18. Larsson ME, Käll I and Nilsson-Helander K. Treatment of patellar tendinopathy—a systematic review of randomized controlled trials. Knee Surg Sports Traumatol Arthrosoc 2012; 20: 1632–1646.
19. Atesok K, Fu FH, Wolf MR, et al. Augmentation of tendon-to-bone healing. J Bone Joint Surg Am 2014; 96: 513–521.
20. Li P-C, Chen X, Zhu X-B, et al. Low-intensity extracorporeal shockwave therapy for Peyronie’s disease: a preliminary study of 32 cases. Zhonghua Nan Ke Xue 2018; 24: 340–346. [in Chinese]

21. Krieger JR, Rizk PJ, Kohn TP, et al. Shockwave therapy in the treatment of Peyronie’s disease. Sex Med Rev 2019; 7: 499–507.

22. Burnett AL, Nehra A, Breau RH, et al. Erectile dysfunction: AUA guideline. J Urol 2018; 200: 633–641.

23. Yuan P, Ma D, Zhang Y, et al. Efficacy of low-intensity extracorporeal shock wave therapy for the treatment of chronic prostatitis/chronic pelvic pain syndrome: a systematic review and meta-analysis. Neurourol Urodyn 2019; 38: 1457–1466.

24. Dariy EV, Tirsy KA and Grigoriev NA. [Efficiency assessment of low-intensity shockwave therapy in the treatment of chronic pelvic pain syndrome]. Urologiia 2020; 46–50. [in Russian]

25. Omar MT, Gwada RF, Shaheen AA, et al. Extracorporeal shockwave therapy for the treatment of chronic wound of lower extremity: current perspective and systematic review. Int Wound J 2017; 14: 898–908.

26. Dumfarth J, Zimpfer D, Vögele-Kadletz M, et al. Prophylactic low-energy shock wave therapy improves wound healing after vein harvesting for coronary artery bypass graft surgery: a prospective, randomized trial. Am J Surg 2008; 86: 1909–1913.

27. Li H and Liu ML. Cardiac shock wave therapy: an alternative non-invasive therapy for refractory angina. Eur Rev Med Pharmacol Sci 2018; 22: 5402–5410.

28. Kassimis G, Didagelos M, De Maria GL, et al. Shockwave intravascular lithotripsy for the treatment of severe vascular calcification. Angiology 2020; 71: 677–688.

29. Manchanda A, Aggarwal A, Aggarwal N, et al. Management of refractory angina pectoris. Cardiol J 2011; 18: 343–351.

30. Khadzegova AB, Shkol’nik EL, Kopeleva MV, et al. [Shock-wave therapy: novel direction in the treatment of ischemic heart disease]. Kardiologiya 2007; 47: 90–94. [in Russian]

31. Burneikaitė G, Shkolnik E, Ėculiškienė J, et al. Cardiac shock-wave therapy in the treatment of coronary artery disease: systematic review and meta-analysis. Cardiovasc Ultrasound 2017; 15: 11.

32. Khattab AA, Brodersen B, Schuermann-Kuchenbrandt D, et al. Extracorporeal cardiac shock wave therapy: first experience in the everyday practice for treatment of chronic refractory angina pectoris. Int J Cardiol 2007; 121: 84–85.

33. 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: 243–248.

34. 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: 1769–1775.

35. Cleveland RO and McAteer JA. Shock-wave lithotripsy. In: Smith AD, Preminger G, Badlani G, et al. (eds) Smith’s Textbook of Endourology. Hoboken, NJ: Wiley-Blackwell, 2012, pp.527–558.

36. Katz JE, Clavijo RI, Rizk P, et al. The basic physics of waves, soundwaves, and shockwaves for erectile dysfunction. Sex Med Rev 2020; 8: 100–105.

37. Young Academic Urologists Men’s Health Group, Fode M, Hatzichristodoulou G, et al. Low-intensity shockwave therapy for erectile dysfunction: is the evidence strong enough? Nat Rev Urol 2017; 14: 593–606.

38. Nishida T, Shimokawa H, Oi K, et al. Extracorporeal cardiac shock wave therapy markedly ameliorates ischemia-induced myocardial dysfunction in pigs in vivo. Circulation 2004; 110: 3055–3061.

39. Sokolakis I, Dimitriadis F, Psalla D, et al. Effects of low-intensity shock wave therapy (LiST) on the erectile tissue of naturally aged rats. Int J Impot Res 2019; 31: 162–169.

40. Aicher A, Heesschen C, Sasaki K, et al. Low-energy shock wave for enhancing recruitment of endothelial progenitor cells: a new modality to increase efficacy of cell therapy in chronic hind limb ischemia. Circulation 2006; 114: 2823–2830.

41. Gotte G, Amelio E, Russo S, et al. Short-time non-enzymatic nitric oxide synthesis from L-arginine and hydrogen peroxide induced by shock waves treatment. FEBS Lett 2002; 520: 153–155.

42. Huang JJ, Shi YQ, Li RL, et al. Angiogenesis effect of therapeutic ultrasound on HUVECs through activation of the PI3K-Akt-eNOS signal pathway. Am J Transl Res 2015; 7: 1106–1115.
43. Ciampa AR, de Prati AC, Amelio E, et al. Nitric oxide mediates anti-inflammatory action of extracorporeal shock waves. *FEBS Lett* 2005; 579: 6839–6845.

44. Andersson KE. Mechanisms of penile erection and basis for pharmacological treatment of erectile dysfunction. *Pharmacol Rev* 2011; 63: 811–859.

45. Hausner T, Pajer K, Halat G, et al. Improved rate of peripheral nerve regeneration induced by extracorporeal shock wave treatment in the rat. *Exp Neurol* 2012; 236: 363–370.

46. Schuh CM, Hausner T and Redl HR. A therapeutic shock propels Schwann cells to proliferate in peripheral nerve injury. *Brain Circ* 2016; 2: 138–140.

47. 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: 155798319846749.

48. Sokolakis I and 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: 177–194.

49. Cellek S, Cameron NE, Cotter MA, et al. Pathophysiology of diabetic erectile dysfunction: potential contribution of vasa nervorum and advanced glycation endproducts. *Int J Impot Res* 2013; 25: 1–6.

50. Feldman HA, Goldstein I, Hatzichristou DG, et al. Impotence and its medical and psychosocial correlates: results of the Massachusetts male aging study. *J Urol* 1994; 151: 54–61.

51. Tamás V and Kempler P. Sexual dysfunction in diabetes. *Handb Clin Neurol* 2014; 126: 223–232.

52. Spivak L, Shultz T, Appel B, et al. Low-intensity extracorporeal shockwave therapy for erectile dysfunction in diabetic patients. *Sex Med Rev*. Epub ahead of print 1 August 2019. DOI: 10.1016/j.sxmr.2019.06.007.

53. Liu C, Lopez DS, Chen M, et al. Penile rehabilitation therapy following radical prostatectomy: a meta-analysis. *J Sex Med* 2017; 14: 1496–1503.

54. Cui Y, Liu X, Shi L, et al. Efficacy and safety of phosphodiesterase type 5 (PDE5) inhibitors in treating erectile dysfunction after bilateral nerve-sparing radical prostatectomy. *Andrologia* 2016; 48: 20–28.

55. Zou ZJ, Liang JY, Liu ZH, et al. Low-intensity extracorporeal shock wave therapy for erectile dysfunction after radical prostatectomy: a review of preclinical studies. *Int J Impot Res* 2018; 30: 1–7.

56. Lee JH and Kim SG. Effects of extracorporeal shock wave therapy on functional recovery and neurotrophin-3 expression in the spinal cord after crushed sciatic nerve injury in rats. *Ultrasound Med Biol* 2015; 41: 790–796.

57. Chen YL, Chen KH, Yin TC, et al. Extracorporeal shock wave therapy effectively prevented diabetic neuropathy. *Am J Transl Res* 2015; 7: 2543–2560.

58. Yahata K, Kanno H, Ozawa H, et al. Low-energy extracorporeal shock wave therapy for promotion of vascular endothelial growth factor expression and angiogenesis and improvement of locomotor and sensory functions after spinal cord injury. *J Neurosurg Spine* 2016; 25: 745–755.

59. Wang B, Ning H, Reed-Maldonado AB, et al. Low-intensity extracorporeal shock wave therapy enhances brain-derived neurotrophic factor expression through PERK/ATF4 signaling pathway. *Int J Mol Sci* 2017; 18: 433.

60. 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: 22–32.

61. 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: 493–501.

62. Jeon SH, Shrestha KR, Kim RV, et al. Combination therapy using human adipose-derived stem cells on the cavernous nerve and low-energy shockwaves on the corpus cavernosum in a rat model of postprostatectomy erectile dysfunction. *Urology* 2016; 88: 226.e1–e9.

63. Frey A, Sønksen J and Fode M. Low-intensity extracorporeal shockwave therapy in the treatment of postprostatectomy erectile dysfunction: a pilot study. *Scand J Urol* 2016; 50: 123–127.

64. 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: 2007–2014.

65. Usta MF, Gabrielson AT and Bivalacqua TJ. Low-intensity extracorporeal shockwave
therapy in the treatment of erectile dysfunction following radical prostatectomy: a critical review. Int J Impot Res 2019; 31: 231–238.

66. 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: 688–694.

67. 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: 195–203.

68. Lu Z, Lin G, Reed-Maldonado A, et al. Low-intensity extracorporeal shock wave treatment improves erectile function: a systematic review and meta-analysis. Eur Urol 2017; 71: 223–233.

69. 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: 27–35.

70. Marx RE. Platelet-rich plasma: evidence to support its use. J Oral Maxillofac Surg 2004; 62: 489–496.

71. Raheem OA, Natale C, Dick B, et al. Novel treatments of erectile dysfunction: review of the current literature. Sex Med Rev. Epub ahead of print 3 July 2020. DOI: 10.1016/j. smr.2020.03.005.

72. Dohan Ehrenfest DM, Rasmusson L and Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leukocyte- and platelet-rich fibrin (L-PRF). Trends Biotechnol 2009; 27: 158–167.

73. Southworth TM, Naveen NB, Tauro TM, et al. The use of platelet-rich plasma in symptomatic knee osteoarthritis. J Knee Surg 2019; 32: 37–45.

74. Gupta AK, Cole J, Deutsch DP, et al. Platelet-rich plasma as a treatment for androgenetic alopecia. Dermatol Surg 2019; 45: 1262–1273.

75. Merchán WH, Gómez LA, Chasoy ME, et al. Platelet-rich plasma, a powerful tool in dermatology. J Tissue Eng Regen Med 2019; 13: 892–901.

76. Bousnaki M, Bakopoulou A and Koidis P. Platelet-rich plasma for the therapeutic management of temporomandibular joint disorders: a systematic review. Int J Oral Maxillofac Surg 2018; 47: 188–198.

77. Mlynarek RA, Kuhn AW and Bedi A. Platelet-Rich Plasma (PRP) in orthopedic sports medicine. Am J Orthop (Belle Mead NJ) 2016; 45: 290–326.

78. Matz EL, Pearlman AM and Terlecki RP. Safety and feasibility of platelet rich fibrin matrix injections for treatment of common urologic conditions. Invest Urol 2018; 59: 61–65.

79. Liu MC, Chang ML, Wang YC, et al. Revisiting the regenerative therapeutic advances towards erectile dysfunction. Cells 2020; 9: 1250.

80. Epifanova MV, Gvasalia BR, Durashov MA, et al. Platelet-rich plasma therapy for male sexual dysfunction: myth or reality? Sex Med Rev 2020; 8: 106–113.

81. Wu C-C, Wu Y-N, Ho H-O, et al. The neuroprotective effect of platelet-rich plasma on erectile function in bilateral cavernous nerve injury rat model. J Sex Med 2012; 9: 2838–2848.

82. Ding XG, Li SW, Zheng XM, et al. The effect of platelet-rich plasma on cavernous nerve regeneration in a rat model. Asian J Androl 2009; 11: 215–221.

83. Scott S, Roberts M and Chung E. Platelet-rich plasma and treatment of erectile dysfunction: critical review of literature and global trends in platelet-rich plasma clinics. Sex Med Rev 2019; 7: 306–312.

84. Madl CM, Heilshorn SC and Blau HM. Bioengineering strategies to accelerate stem cell therapeutics. Nature 2018; 557: 335–342.

85. Trounson A and McDonald C. Stem cell therapies in clinical trials: progress and challenges. Cell Stem Cell 2015; 17: 11–22.

86. Mandai M, Watanabe A, Kurimoto Y, et al. Autologous induced-stem-cell-derived retinal cells for macular degeneration. N Engl J Med 2017; 376: 1038–1046.

87. Barba M, Di Taranto G and Lattanzi W. Adipose-derived stem cell therapies for bone regeneration. Expert Opin Biol Ther 2017; 17: 677–689.

88. Gokce A, Wang JC, Powers MK, et al. Current and emerging treatment options for Peyronie’s disease. Res Rep Urol 2013; 5: 17–27.

89. Costa C, Soares R, Castela A, et al. Increased endothelial apoptotic cell density in human diabetic erectile tissue—comparison with clinical data. J Sex Med 2009; 6: 826–835.

90. Jordan GH. The use of intralesional clostridial collagenase injection therapy for Peyronie’s
91. Peak TC, Anaissie J and Hellstrom WJ. Current perspectives on stem cell therapy for erectile dysfunction. Sex Med Rev 2016; 4: 247–256.

92. Qiu X, Lin H, Wang Y, et al. Intracavernous transplantation of bone marrow-derived mesenchymal stem cells restores erectile function of streptozocin-induced diabetic rats. J Sex Med 2011; 8: 427–436.

93. Huang YC, Ning H, Shindel AW, et al. The effect of intracavernous injection of adipose tissue-derived stem cells on hyperlipidemia-associated erectile dysfunction in a rat model. J Sex Med 2010; 7: 1391–1400.

94. Garcia MM, Fandel TM, Lin G, et al. Treatment of erectile dysfunction in the obese type 2 diabetic ZDF rat with adipose tissue-derived stem cells. J Sex Med 2010; 7: 89–98.

95. Albersen M, Fandel TM, Lin G, et al. Injections of adipose tissue-derived stem cells and stem cell lysate improve recovery of erectile function in a rat model of cavernous nerve injury. J Sex Med 2010; 7: 3331–3340.

96. Chen F, Zhang H, Wang Z, et al. Adipose-derived stem cell-derived exosomes ameliorate erectile dysfunction in a rat model of type 2 diabetes. J Sex Med 2017; 14: 1084–1094.

97. Woo JC, Bae WJ, Kim SJ, et al. Transplantation of muscle-derived stem cells into the corpus cavernosum restores erectile function in a rat model of cavernous nerve injury. Korean J Urol 2011; 52: 359–363.

98. You D, Jang MJ, Lee J, et al. Comparative analysis of periprostatic implantation and intracavernosal injection of human adipose tissue-derived stem cells for erectile function recovery in a rat model of cavernous nerve injury. Prostate 2013; 73: 278–286.

99. Bahk JY, Jung JH, Han H, et al. Treatment of diabetic impotence with umbilical cord blood stem cell intracavernosal transplant: preliminary report of 7 cases. Exp Clin Transplant 2010; 8: 150–160.

100. Garber M and Carlos N. Intracavernous administration of adipose stem cells: a new technique of treating erectile dysfunction in diabetic patient, preliminary report of 6 cases. MOJ Cell Sci Rep 2015; 2: 5–8.

101. Levy JA, Marchand M, Iorio L, et al. Determining the feasibility of managing erectile dysfunction in humans with placental-derived stem cells. J Am Osteopath Assoc 2016; 116: e1–e5.

102. Haahr MK, Jensen CH, Toysenki NM, et al. Safety and potential effect of a single intracavernous injection of autologous adipose-derived regenerative cells in patients with erectile dysfunction following radical prostatectomy: an open-label phase I clinical trial. EBioMedicine 2016; 5: 204–210.

103. Yiou R, Hamidou L, Birebent B, et al. Safety of intracavernous bone marrow-mononuclear cells for postradical prostatectomy erectile dysfunction: an open dose-escalation pilot study. Eur Urol 2016; 69: 988–991.

104. Matz EL, Scarberry K and Terlecki R. Platelet-rich plasma and cellular therapies for sexual medicine and beyond. Sex Med Rev. Epub ahead of print 13 August 2020. DOI: 10.1016/j.smvr.2020.07.001.

105. Patel DP, Pastuszak AW and Hotaling JM. Emerging treatments for erectile dysfunction: a review of novel, non-surgical options. Curr Urol Rep 2019; 20: 44.