



Systematic review on the safety and effectiveness of restorative therapies for erectile dysfunction

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Abstract

Introduction: Several restorative (or regenerative) therapies have been proposed in the past 15 years to reverse the underlying pathophysiology associated with erectile dysfunction.

Objectives: The aim of this International Society for Sexual Medicine-commissioned review of restorative therapies for erectile dysfunction was to systematically review the literature to determine the safety and efficacy of these therapies.

Methods: A systematic review of MEDLINE, EMBASE, CINAHL, and the Cochrane CENTRAL database of controlled trials was performed to identify comparative studies published from January 2010 through November 2023. Two reviewers performed study selection and data extraction. Five restorative therapies were assessed: low-intensity extracorporeal shockwave therapy (focused or radial), intracorporal stem cell injections, intracorporal platelet-rich plasma injections, and low-intensity pulsed ultrasound. Outcomes of interest included adverse events and changes in validated erectile function symptom scores. The Cochrane Risk of Bias and ROBINS-I tools were used to evaluate the risk of bias of randomized controlled trials and observational studies, respectively.

Results: A total of 36 studies were included, 30 randomized controlled trials and 6 non-randomized studies. Most of these studies ($n = 23$) evaluated focused shockwave therapy. Results for focused shockwave therapy compared to sham were mixed. While some sham-controlled trials reported statistically significant improvements in erectile function scores favoring focused shockwave therapy, other trials found no significant difference between groups. Additionally, many studies (78%) did not report or compare the minimal clinically important difference (MCID) in erectile function. Among those that did, further methodological concerns including the use of MCID thresholds with instruments for which no MCID has been validated (ie, IIEF-5) and reporting a combined MCID in cohorts with mixed severity of erectile function limit confidence in the result. Other restorative therapies also report limited and inconsistent evidence.

Conclusions: The data regarding focused shockwave therapy for erectile dysfunction remains mixed, with some trials showing benefit compared to sham and others showing no difference. The heterogeneity of treatment protocols, methodological limitations across studies, and inconsistent MCID reporting preclude definitive conclusions about clinical efficacy. All restorative therapies, including focused shockwave therapy, require further investigation in well-designed trials with standardized protocols and validated outcome measures before routine clinical use can be recommended.

Keywords erectile dysfunction, restorative therapies, low intensity shockwave therapy, platelet-rich plasma, stem cells, low intensity pulse ultrasound.

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Introduction

Erectile dysfunction (ED) remains a significant health challenge, affecting millions of men worldwide, with profound impacts on their quality of life and relationships.¹ Over the years, therapeutic approaches have predominantly focused on alleviating the symptom rather than targeting the underlying pathophysiological mechanisms with curative intent. More recently, compelling evidence has accumulated regarding the role of restorative therapies and ED.^{2–4} The aim of these therapies resides in their name, “to restore erectile function” despite the complex pathophysiology of ED involving vascular, neurological, hormonal, and psychological factors.⁵

Restorative therapies can potentially promote angiogenesis and nerve regeneration to modulate inflammatory responses.^{2,3} *Low-intensity extracorporeal shockwave therapy* (Li-ESWT) utilizes acoustic waves to promote neovascularization and tissue regeneration in the corpora cavernosa of the penis. These acoustic waves can be generated by electrohydraulic, electromagnetic, or piezoelectric sources, each producing distinct wave characteristics. Two primary types of energy distribution are available, focused and radial. Focused waves concentrate energy at a specific point, whereas radial waves disperse energy along a line. This distinction in energy delivery may have important implications for treatment protocols and potential efficacy differences, such as the number of treatment sessions required to see an improvement. In 2015, Lei et al.⁶ published a study demonstrating that *low-intensity pulse ultrasound* (LIPUS) can effectively improve ED in a diabetic rat model. LIPUS is a non-invasive therapy that uses specific ultrasound waves to stimulate penile tissue, promoting nerve regeneration, angiogenesis, and tissue repair, thereby in theory, improving erectile function.⁶ *Platelet-rich plasma* (PRP) therapy, while controversial, has also gained increasing attention as it is theorized to promote tissue repair and angiogenesis in the corpora cavernosa of the penis. PRP therapy involves the extraction of a patient's own blood, which is then centrifuged to separate PRP from other blood components. The effects of PRP are driven by growth factors and cytokines contained in platelets, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor- β (TGF- β).^{7–9} *Stem cell therapy* has also gained attention as a potential treatment for ED. The rationale lies in their capabilities to replace malfunctioning or damaged erectile tissue and restore its original baseline function.² Preclinical studies have shown promising results, but translating these findings into clinical practice remains challenging due to issues of cell survival, engraftment, and potential safety concerns.

The aim of the present systematic review, commissioned by the International Society of Sexual Medicine, is to conduct a comprehensive narrative-based systematic review on the safety and efficacy of restorative therapies for ED.

Methods

Study design

This systematic review is reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.¹⁰ A protocol was prospectively registered in the PROSPERO database (CRD42024311280).

Literature search

An experienced medical information specialist developed and tested the search strategies through an iterative process in consultation with the review team. The MEDLINE strategy was peer-reviewed by another senior information specialist using the PRESS Checklist.¹¹

Using the multifile option and deduplication tool available on the Ovid platform, we searched Ovid MEDLINE ALL, Embase Classic+Embase, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. We also searched CINAHL on Ebsco. All searches were executed on November 25, 2023. The MEDLINE search strategy is available in [Appendix 1](#).

The strategies utilized a combination of controlled vocabulary (eg, “Erectile Dysfunction”, “Extracorporeal Shockwave Therapy”, “Stem Cells”) and keywords (eg, “erectile function”, “LI-ESWT”, “mesenchymal”). Study design filters were applied for systematic reviews/meta-analyses, RCTs, non-RCTs, and observational studies. Vocabulary and syntax were adjusted across the databases. There were no language restrictions. Where possible, animal-only records, case studies, conference proceedings, preprints, and other irrelevant publication types were removed. Records were downloaded and deduplicated using EndNote version 9.3.3 (Clarivate Analytics) and uploaded to DistillerSR (Evidence Partners, Ottawa, Canada).

One reviewer performed supplemental searching for gray literature and published studies not identified in the electronic database search through: (1) targeted clinical trial registries (ie, ClinicalTrials.gov and the International Clinical Trials Registry Platform), (2) websites of organizations, (3) scanning the references of all included studies and from relevant systematic reviews, and (4) searching for full-text publications of relevant conference abstracts.

Inclusion criteria

Studies were included if they met the following criteria:

Population. Men with the primary presentation of ED, defined as clinician-diagnosed inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance with an international index of erectile function (IIEF-5), also known as the Sexual Health Inventory of Men, score ≤ 21 or IIEF-EF domain score of ≤ 25). Men with psychogenic ED, neurological pathology, prior radical prostatectomy, or radiation therapy to the pelvis were excluded. We also included studies with mixed populations if the results were disaggregated.

Intervention. Restorative therapy, including (1) focused Li-ESWT, (2) radial Li-ESWT, (3) LIPUS, (4) intracorporeal PRP injections, and (5) intracorporeal stem cell injections.

Comparators. Sham, no treatment/waitlist, different treatment protocols, other restorative therapies.

Outcomes. (1) change in validated erectile function symptom scores from baseline using either the IIEF-EF or IIEF-5; (2) binary minimal clinically important difference (MCID) in the erectile function from the IIEF-EF domain defined as an increase in the baseline IIEF-EF score of ≥ 2 for men with mild ED, ≥ 5 for men with moderate ED, and ≥ 7 for men with severe ED¹²; and (3) adverse events (AEs). Note that the MCID thresholds described above were derived and validated specifically for the IIEF-EF domain.¹² There

are no validated MCID thresholds for the IIEF-5 (Sexual Health Inventory for Men) score. Therefore, studies applying MCID thresholds to IIEF-5 scores should be interpreted with caution, as they have not been validated.

Study designs. RCTs, non-RCTs (ie, prospective comparative cohort studies, before and after studies, and interrupted time series).

Study selection

We conducted screening using a two-staged approach. First, two reviewers independently, and in duplicate, screened all records based on the title and abstract. We resolved any disagreements by consensus or by involving a third reviewer. Second, two reviewers independently, and in duplicate, screened all records included during the first stage of screening against the inclusion criteria. Prior to both stages of screening, we conducted a pilot exercise to ensure consistency among reviewers in applying eligibility criteria.

Data extraction

Using DistillerSR, one reviewer extracted study characteristics and outcome data using a pre-tested data extraction form. A second reviewer verified the extracted data. Disagreements were resolved through discussion and consensus.

Risk of bias assessment

One reviewer independently assessed the risk of bias (RoB) of each included study, and a second reviewer verified the assessments. Disagreements were resolved through discussion. For RCTs, we used the Cochrane RoB tool for RCTs.¹³ As all outcomes included in this review are patient reported, the domain specific questions (ie, blinding of patients/personnel, blinding of outcome assessors) were judged only once. For non-randomized studies, we used the Cochrane RoB in Non-randomized Studies of Interventions (ROBINS-I),¹⁴ using a staged approach. First, studies were assessed if relevant confounders were considered in an adjusted analysis. If this was not done, no further assessment was performed, and studies were considered as having high RoB.

Data synthesis

Study characteristics are summarized narratively in the text. Summary tables are organized for each comparison and separated for each outcome. Data are presented as frequencies and percentages, medians and interquartile ranges, and means and standard deviations (SD), as they were reported in the primary studies. Where provided in the studies, we have extracted the measure of statistical significance (ie, *P*-value) to evaluate differences between comparisons. Emphasis was placed on sham-controlled trials to reduce potential placebo effects from any therapy. Meta-analysis was not performed given the heterogeneity of the devices used and treatment protocols in the studies, because of unclear and high risk of bias across the studies, and/or both. We acknowledge that meta-analytic methods exist to address heterogeneity (eg, random-effects models, subgroup analyses); however, the combination of clinical heterogeneity in treatment protocols, the

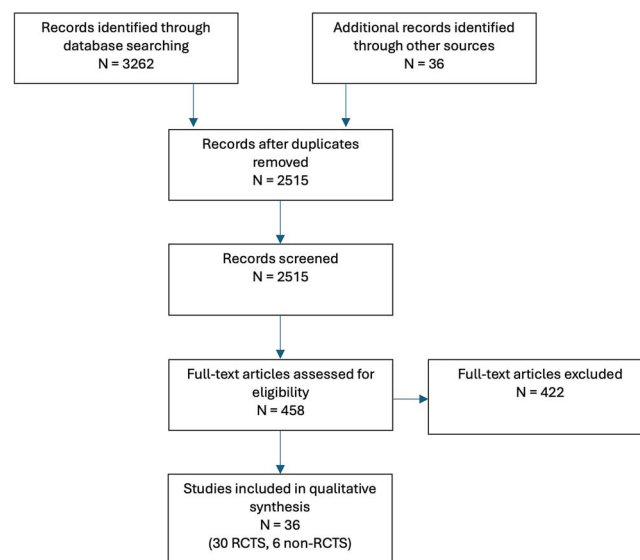


Figure 1 Flow chart of study selection.

preponderance of unclear or high risk of bias across studies, and concerns about data quality led us to determine that a quantitative synthesis would not yield meaningful pooled estimates. Instead, a narrative synthesis emphasizing the direction and consistency of findings across studies is provided.

Results

A total of 2515 unique records were screened for eligibility at the title and abstract level, with 458 evaluated based on the full text publication. Finally, 36 studies were included, 30 RCTs and 6 observational studies (Figure 1), with 11 treatment comparisons. Table 1 summarizes the treatment comparisons, number of studies, and outcomes reported for each comparison.

Risk of bias assessments

RoB across the domains in the Cochrane RoB tool varied (Figure 2A). A lack of reporting was the main reason why domains were assessed an unclear. Overall, three RCTs were judged as low risk of bias, 11 were judged as unclear risk of bias, and 16 were judged as high risk of bias (Supplemental Table 1). None of the non-randomized studies provided adjusted analysis to account for confounders, so all were rated as high RoB.

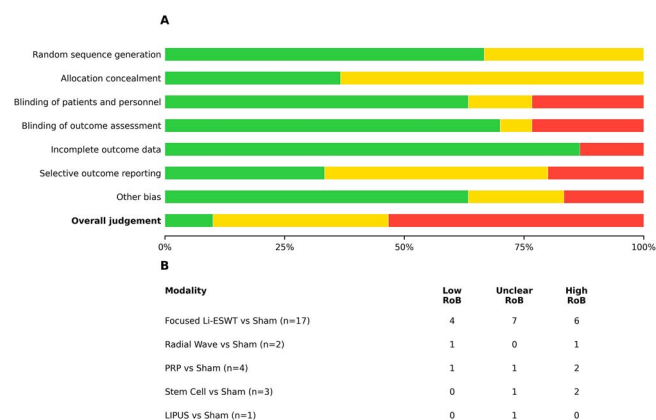
The distribution of risk of bias varied by modality (Figure 2B). For focused Li-ESWT versus sham, only 4 of 17 RCTs (24%) were rated as low risk of bias. All studies evaluating stem cell therapy were rated as high or unclear risk of bias. The evidence base for PRP includes one study rated as low risk of bias (Masterson 2023). One additional PRP study (Poulios 2021) was initially assessed as low risk using standard RoB domains, but was reclassified as high risk based on concerns detailed below regarding placebo response patterns and data handling.

Sham Design and Fidelity. The quality of sham interventions varied across studies and may affect the validity of treatment comparisons. Sham designs included: (1) identical devices with standoff attachments preventing energy transmission but producing similar sounds (Chung 2023, Kalyvianakis 2022); (2) specially manufactured sham probes generating identical

Table 1 Included studies by comparisons.

Intervention	Comparison	Studies	IIEF-EF	IIEF-5	MCID	AE
Focused Li-ESWT	Sham	17 RCTs	✓	✓	✓	✓
Focused Li-ESWT	Pharmacotherapy	1 RCT 1 non-RCT	✓	✓		✓
Focused Li-ESWT	Different Schedules	3 RCTs	✓		✓	✓
Focused Li-ESWT	Radial SW Therapy	1 non-RCT		✓		✓
Radial SW Therapy	Sham	1 RCT 1 non-RCT	✓	✓	✓	✓
Radial SW Therapy	No Sham	1 RCT		✓		
LIPUS	Sham	1 RCT		✓		✓
LIPUS	Different Schedules	1 RCT	✓			✓
PRP Injection	Sham	4 RCTs	✓	✓	✓	✓
PRP Injection + Li-ESWT	Li-ESWT alone	1 non-RCT		✓		✓
Stem cell therapy	Sham	1 RCT 2 non-RCTs		✓		✓

Abbreviations: AE = adverse events; EF = erectile function domain; IIEF = International Index of Erectile Function; Li-ESWT = low-intensity shockwave therapy; LIPUS = low intensity pulse ultrasound; MCID = minimally clinical important difference; PRP = platelet rich plasma; SW = shockwave.

**Figure 2** Cochrane risk of bias domains (A) and distribution of risk of bias across modalities (B).

noise and vibrations without delivering shockwave energy (Kalyvianakis 2017); (3) placebo gel pads designed to prevent shockwave emission while appearing identical to active pads (Fojecki 2017); and (4) devices turned on but not activated or with energy settings reduced to imperceptible levels. The adequacy of participant blinding was infrequently assessed or reported. Given that some shockwave devices produce perceptible sensations during treatment, studies using less sophisticated sham designs may be subject to unblinding, which could inflate treatment effects.

Beyond formal risk of bias assessment, several additional methodological concerns were identified that affect the interpretation of findings across the included studies. These are detailed in the following section.

Methodological concerns in the included literature

Beyond the formal risk of bias assessment, several methodological concerns warrant discussion as they affect the interpretation of findings across the included studies.

MCID Measurement Issues. The MCID for erectile function improvement has been validated only for the IIEF-EF domain, with thresholds of ≥ 2 points for mild ED, ≥ 5 points for moderate ED, and ≥ 7 points for severe ED.¹² However, several studies applied these or similar thresholds to the IIEF-5 instrument, for which no MCID has been established nor validated. Studies reporting MCID outcomes using the IIEF-5 include Kennady et al. (2023),¹⁵ Ong et al. (2022),¹⁶ and others. Results from these studies should be interpreted with appropriate caution.

Unusual Placebo Response Patterns. Historically, ED treatment trials typically demonstrate a placebo response, with some proportion of men in sham arms reporting improvement. However, several Li-ESWT trials demonstrated unusual patterns: Kalyvianakis et al. (2022)¹⁷ reported that 0% of sham-treated men achieved MCID at 3 months versus 79% in the treatment group; Kennady et al. (2023)¹⁵ reported 0/16 sham-treated men achieved MCID; and Ong et al. (2022)¹⁶ reported 0/24 sham-treated men achieved MCID at any time point through 6 months. Additionally, some studies showed worsening erectile function in the sham arm (eg, Kim et al. 2020,¹⁸ Vinay et al. 2021¹⁹), which is atypical for placebo arms in ED trials. These patterns raise questions about sham design adequacy, patient expectations, or other unreported methodological factors. The expected placebo response in ED device and injection trials is approximately 3 points on the IIEF-EF (eg, Masterson 2023). Studies demonstrating substantially lower or negative placebo responses—such as the -0.2 point change observed in one PRP trial at 6 months—deviate markedly from expected values and raise concerns about blinding adequacy, outcome ascertainment, or data handling procedures.

Mixed Populations and MCID Determination. Several studies included patients with mixed severity of ED (eg, mild to severe) and did not stratify results by baseline severity. Since the MCID thresholds differ substantially by severity category (≥ 2 for mild, ≥ 5 for moderate, ≥ 7 for severe), studies that used a single MCID threshold across mixed populations—or that reported overall MCID results without stratification—may have systematically over- or under-estimated treatment response rates depending on the severity distribution of their sample.

Data Reporting Inconsistencies. Some studies demonstrated inconsistencies between tabulated data, figures, and reported statistical analyses. For example, in some cases, manually calculating changes from reported baseline and follow-up values did not match the change scores reported in the text or tables. While such discrepancies may reflect rounding or different analytical approaches, they introduce uncertainty in the interpretation of individual study results and limit the ability to verify reported findings.

Undisclosed Imputation Methods. Examination of supplementary data from some studies revealed evidence of last observation carried forward (LOCF) imputation that was not disclosed in the methods. In one instance, a substantial proportion of follow-up values were identical to prior timepoint values, suggesting missing data were imputed without acknowledgment. Inconsistent application of imputation, where some patients with missing data were marked as dropouts while others had values carried forward, further raises concerns about data handling and selective reporting.

Outcomes: Focused Li-ESWT vs sham

Overall, 17 RCTs evaluated focused Li-ESWT compared to sham.^{15–31} Studies were conducted in 14 countries, with sample sizes ranging from 20 to 135 participants. Patients had stable sexual relationships, had predominantly vasculogenic ED, with varying degrees of ED (mild to severe). The level of PDE5i response varied across studies (eg, non-responsive, partially responsive, good response). Most studies did not include men with significant underlying co-morbidities, except for Yamaçake et al. (2018)³⁰ who included patients who had undergone renal transplantation at least six months before the study. Most studies did not exclude men with common cardiovascular diseases such as hypertension and hyperlipidemia. Information about the study participants, presence of diabetes, devices used, treatment protocols, duration of treatment, and outcomes are available in [Supplemental Table 2](#).

Erectile function

Erectile function was measured using the IIEF-EF score, IIEF-5 score, and MCID at various timepoints.

International Index of Erectile Function—Erectile Function Domain

Of the 17 included RCTs, 12 reported IIEF-EF domain scores (the remaining 5 studies reported IIEF-5 scores instead; see below).^{15,17–19,21–25,28,29,31} These 12 studies reported outcomes across 15 data points at varying follow-up times, as not all studies reported at all timepoints. Nine of the 15 data points showed a statistically significant difference favoring Li-ESWT over sham ([Table 2](#)).

1 month follow-up ($n=6$). Three studies^{15,17,29} reported statistically higher mean scores in the Li-ESWT than in the sham group. Olsen et al. (2015)²⁴ reported that there were no significant differences between groups without providing mean scores. Srini et al. (2015)²⁸ did not report a statistical measure of difference between the groups, but the mean IIEF-EF scores were 22.0 in the Li-ESWT group and 10.6 in the sham group. Lastly, Yee et al. (2014)³¹ reported no statistical difference between groups.

7 weeks follow-up ($n=1$). Kim et al. (2020)¹⁸ reported that scores increased significantly from baseline to 7 weeks within the Li-ESWT group ($P < .001$) compared to the sham group.

3 months follow-up ($n=2$). Both studies^{17,25} reported significantly better scores in the Li-ESWT group.

6 months follow-up ($n=4$). Two studies^{22,23} reported statistically higher scores in the Li-ESWT group, Vinay et al. (2021)¹⁹ reported no difference between groups, and Fojecki et al. (2017)²¹ did not report a statistical measure of difference between groups, but the sham group reported a higher mean score (14.3) than the Li-ESWT group (12.8).

12 months follow-up ($n=2$). Kalyvianakis et al. (2017)²² found that the increase in IIEF-EF scores stayed statistically significant at the 12-month follow-up in the group receiving Li-ESWT. As reported at 6-months follow-up, Fojecki et al. (2017)²¹ reported no statistical difference between groups.

International Index of Erectile Function-5

Five RCTs reported the IIEF-5 at various follow-up times across seven data points.^{16,20,26,27,30}

1 month follow-up ($n=1$). Ong et al. (2022)¹⁶ did not report on statistical significance between groups, however the mean score in the Li-ESWT group was higher than that of the control group, 14.07 and 9.3, respectively.

3 months follow-up ($n=4$). Two studies^{26,27} reported statistically higher scores in the Li-ESWT group than in the sham group. The other two studies^{16,30} did not report on statistical significance between groups, however the mean score in the Li-ESWT group was higher than that of the control group for both studies.

6 months follow-up ($n=2$). Chung et al. (2023)²⁰ reported a statistically significant mean difference between groups. Ong et al. (2022)¹⁶ did not report on statistical significance between groups, however, as was reported at 1- and 3-months follow-up, the mean score in the Li-ESWT group was higher than that of the control group at 6-months follow-up (14.19 and 7.88, respectively).

Minimally clinical important difference

Three RCTs reported on the proportion of those who reached the MCID in both groups from baseline to follow-up.^{15–17} Fojecki et al. (2017)²¹ only reported this for the sham group. Notably, two of these studies (Kennady et al. 2023¹⁵ and Ong et al. 2022¹⁶) used the IIEF-5 rather than the IIEF-EF domain and should therefore be interpreted with caution.

1 month follow-up ($n=3$). Kalyvianakis et al. (2022)¹⁷ reported a statistically significantly higher number of men reaching MCID in the Li-ESWT group than the sham group. Statistical significance was not reached in Ong et al. (2022),¹⁶ with four men in the Li-ESWT group and zero men in the sham group reaching MCID. Although a measure of statistical significance was not provided in Kennady et al. (2023),¹⁵ more men in the Li-ESWT group reached an MCID compared to the control group, 8/17 compared to 0/16, respectively. Note that the absence of any placebo response (0% MCID achievement) in the sham arms of multiple studies is unusual compared to historical ED trial data and may reflect methodological factors rather than true treatment effects.

3 months follow-up ($n=2$). Both studies^{16,17} reported a statistically significant difference, with more men in the Li-ESWT group reaching MCID compared to sham.

Table 2 Included studies by comparisons.

Study	N	ED Severity	Outcome Measure	1 mo	3 mo	6 mo	12 mo	Favors Li-ESWT?
Chung 2023	60	Mild-Mod	IIEF-5	—	—	✓	—	Yes*
Fojecki 2017	126	Mixed	IIEF-EF	—	—	✓	✓	No
Kalyvianakis 2017	46	Mixed	IIEF-EF	—	—	✓	✓	Yes*
Kalyvianakis 2022	70	Moderate	IIEF-EF, MCID	✓	✓	—	—	Yes*
Kennady 2023	40	Mild-Mod	IIEF-EF, MCID†	✓	—	—	—	Yes*
Kim 2020	60	Moderate	IIEF-EF	✓‡	—	—	—	Yes*
Kitrey 2016	55	Severe	IIEF-EF	✓	—	✓	—	Yes*
Olsen 2015	105	Mixed	IIEF-EF	✓	—	—	—	No
Ong 2022	58	Mild-Mod	IIEF-5, MCID†	✓	✓	✓	—	Mixed§
Ortac 2021	60	Mild	IIEF-EF	—	✓	—	—	Yes*
Shendy 2021	80	Diabetic	IIEF-5	—	✓	—	—	Yes*
Sramkova 2020	66	Mild-Mod	IIEF-5	—	✓	—	—	Yes*
Srini 2015	135	Mixed	IIEF-EF	✓	—	—	—	NR
Vardi 2012	60	Mild-Mod	IIEF-EF	✓	—	—	—	Yes*
Vinay 2021	71	Mixed	IIEF-EF	—	—	✓	—	No
Yamaçake 2018	42	Transplant	IIEF-5	—	✓	—	—	NR
Yee 2014	20	Mild-Mod	IIEF-EF	✓	—	—	—	No
Studies at timepoint				9	6	7	2	

Abbreviations: IIEF-EF = International Index of Erectile Function – Erectile Function domain; IIEF-5 = International Index of Erectile Function-5 (Sexual Health Inventory for Men); MCID = Minimal Clinically Important Difference; mo = months; Mod = Moderate; NR = Not reported/unclear Symbols: ✓ = Outcome reported at this timepoint, — = Outcome not reported at this timepoint; * = Statistically significant difference favoring Li-ESWT ($P < .05$); † = MCID calculated using IIEF-5; no validated MCID exists for this instrument; ‡ = 7 weeks follow-up; § = Statistically significant on continuous IIEF-5 but not on MCID at some timepoint.

6 months follow-up ($n = 1$). Ong et al. (2022)¹⁶ reported that the difference between groups remained statistically significant at 6-months follow-up, with more men in the Li-ESWT group reaching MCID ($P = .011$).

Adverse events

Fourteen (of the 17) RCTs reported on AEs experienced by study participants (see [Supplemental Table 3](#)). Participants in four studies reported AEs,^{21,24,25,27} which were more commonly reported in those who received Li-ESWT. AEs were mild and included local irritation, mild discomfort during application of therapy, slight burning or tingling sensation after treatment, headache, fatigue/tiredness, dysuria, nausea, mild fever.

In summary, among the 17 RCTs evaluating focused Li-ESWT versus sham, results were heterogeneous. Approximately half of the studies reporting IIEF-EF outcomes found statistically significant differences favoring Li-ESWT, while the remainder found no significant difference. Among the limited studies reporting MCID outcomes, methodological concerns—including the use of unvalidated MCID thresholds with the IIEF-5 and the unusual absence of placebo response—limit the conclusions that can be drawn about clinically meaningful benefit.

Outcomes: Focused Li-ESWT vs pharmacotherapy

One RCT³² and one non-randomized study³³ compared Li-ESWT therapy to pharmacotherapy. Studies were conducted in Egypt

and China, with sample sizes of 51 and 95 participants. Both studies included patients with vasculogenic ED in stable sexual relationships. The level of PDE5i response was not specified in either study. Information about the study participants, devices used, treatment protocols, duration of treatment, and outcomes are available in [Supplemental Table 4](#).

Erectile function

Erectile function was measured using the IIEF-EF and IIEF-5 scores. Overall, there was no difference in erectile function between participants treated with Li-ESWT or pharmacotherapy.

International index of erectile function—erectile function domain

Wang et al. (2023)³³ report results at 4 weeks follow-up, with no statistical difference between the two groups.

International index of erectile Function-5

Zanaty et al. (2022)³² report results at 6- and 12-weeks follow-up, with no statistical difference between groups at either time point.

Adverse events

Both studies reported AEs in both groups. Zanaty et al. (2022)³² reported more side effects in the Tadalafil group than the Li-ESWT group ($P < .05$). Two participants (8%) in the Li-ESWT group experienced AEs (minimal penile pain, mild penile bruises) and 11 participants (44%) in the Tadalafil group experienced muscle pain, headache, and nausea. In Wang et al. (2023),³³ no participants discontinued the study due to AEs, however, one participant in

the Sildenafil group experienced flushing and headache and one participant in the Li-ESWT group experienced local penile pain.

Outcomes for different schedules of focused Li-ESWT

Three RCTs compared different schedules of Li-ESWT.^{34–36} Two studies were conducted in Greece^{34,35} and one in the USA,³⁶ with sample sizes of 43, 87, and 97 participants. All studies included patients with vasculogenic ED in stable sexual relationships. The level of PDE5i response was not specified in two studies,^{34,35} with the third study being in non-responders.³⁶ Different schedules of focused Li-ESWT included 1 session per week for 6 weeks, 2 sessions per week for 6 weeks, 3 sessions per week for 4 weeks, and 5 sessions per week for 1 week. Information about the study participants, devices used, treatment protocols, duration of treatment, and outcomes are available [Supplemental Table 5](#).

Erectile function

International index of erectile function—erectile function domain

All three studies reported IIEF-EF scores at 6 months follow-up and there was no statistical difference between the different treatment groups.^{34–36}

Minimal clinically important difference

Kalyvianakis et al. (2020)³⁵ reported the proportion of men who achieved MCID at 6 months. Across the four treatment groups, 71 to 87% of the men reached a MCID over that follow-up period.

Adverse events

No treatment-related side effects were reported in any of the studies. However, Patel et al. (2020)³⁶ reported that two patients (5%) in Group A developed worsening erectile function.

Outcomes: Focused vs radial shockwave therapy

Erylimaz et al. (2020)³⁷ conducted a non-randomized study in Turkey, comparing focused Li-ESWT versus radial waves and included 20 participants in each group. The treatment schedule for both groups was 2 sessions per week for 3 weeks, followed by no treatment for 3 weeks, and then another 2 sessions per week for 3 weeks. Information about the study participants, devices used, treatment protocols, duration of treatment, and outcomes are available in [Supplemental Table 6](#).

Erectile function

International index of erectile Function-5

The mean IIEF-5 scores increased by 5.34 in the focused group and 6.3 in the radial wave group at 3-months follow-up, however no measure of statistical significance was provided.³⁷

Adverse events

No complications were observed in either group.³⁷

Outcomes: Radial wave therapy vs sham

Two studies evaluated radial wave therapy against sham therapy. Sandoval-Salinas et al. (2022)³⁸ conducted an RCT in Colombia of 80 men with vasogenic ED. Ismail et al. (2022)³⁹ conducted a non-randomized study in Egypt of 40 men with diabetic ED, all of whom were also taking a 12-week daily administration of 5-mg tablet of Tadalafil. Information about the study participants, devices used, treatment protocols, duration of treatment, and outcomes are available in [Supplemental Table 7](#).

Erectile function

International index of erectile function—erectile function domain

Sandoval-Salinas et al. (2022)³⁸ reported no statistical difference between groups at both 6 weeks (end of treatment) and 10 weeks (1 month) follow-up.

International index of erectile Function-5

IIEF-5 scores in Ismail et al. (2022)³⁹ increased from baseline in both groups at 1-, 3-, and 6-months follow-up. Differences between groups were statistically significant at 1- and 3-months follow-up but were no longer significant at 6-month follow-up.

Minimal clinically important difference

In Sandoval-Salinas et al. (2022),³⁸ the sham group numerically outperformed the radial wave treatment group on MCID achievement at both time points. At 6 weeks (end of treatment), 47.5% (19/40) of men in the sham group achieved MCID compared to only 35% (14/40) in the radial wave treatment group—a 12.5 percentage point difference favoring sham. This pattern persisted at 10 weeks (1-month follow-up), with 32.5% (13/40) in the sham group versus 22.5% (9/40) in the treatment group maintaining MCID—a 10 percentage point difference again favoring sham. Although no measure of statistical significance was reported for these between-group comparisons, these findings are notable: not only did radial wave therapy fail to demonstrate superiority over sham, but the numerical trend favored the sham condition. This is inconsistent with a true treatment effect and raises questions about the mechanisms of action proposed for shockwave therapy in ED.

Adverse events

In Sandoval-Salinas et al. (2022),³⁸ no patients withdrew due to side effects. One patient in each group reported facial flushing due to Sildenafil. One patient reported superficial abrasions of the dermis in the penis during the second session of radial shockwave therapy. Ismail et al. (2022)³⁹ did not report on this outcome.

Radial wave therapy vs No sham

Setiawan et al. (2022)⁴⁰ performed a RCT in Indonesia comparing radial wave therapy plus 2.5 mg daily tadalafil ($n = 14$) to 2.5 mg daily tadalafil alone ($n = 12$) in men with vasogenic ED. Information about the study participants, devices used, treatment protocols, duration of treatment, and outcomes are available in [Supplemental Table 8](#).

Erectile function

International index of erectile Function-5

Men in both groups experienced significant improvement in IIEF-5 scores from a baseline to 4 weeks follow-up, and the difference between groups was statistically significant ($P = .047$).⁴⁰

Adverse events

AEs were not reported in this study.

Outcomes: Low intensity pulse ultrasound vs sham

Cui et al. (2019)⁴¹ carried out a RCT across five centers in China comparing LIPUS to sham therapy in 120 men in stable sexual relationships with mild to moderate vasogenic ED. All men were PDE5i responders and LIPUS or sham was offered over 2 sessions per week for 4 weeks. Information about the study participants, devices used, treatment protocols, duration of treatment, and outcomes are available in [Supplemental Table 9](#).

Erectile function

International index of erectile Function-5

At 4-, 8-, and 12-weeks, both groups reported an increase in IIEF-5 from baseline, however these scores were significantly higher in the LIPUS group ($P < .001$ at all follow-up times).⁴¹

Adverse events

A few men reported mild pain at week 1, 2, and 3 in the LIPUS group, with no one reporting mild pain at weeks 4 onward. No men reported moderate or severe pain in either group at any time and no AEs were related to dropouts.⁴¹

Outcomes for different schedules of LIPUS

One RCT conducted in China by Chen et al. (2022)⁴² investigated the efficacy of 16 treatments of LIPUS, either offered as 2 sessions per week for 8 weeks or as 3 sessions per week for 6 weeks. A total of 323 men with vasogenic mild to moderate ED patients participated. Information about the study participants, devices used, treatment protocols, duration of treatment, and outcomes are available in [Supplemental Table 10](#).

Erectile function

International index of erectile function—erectile function domain

IIEF-EF scores significantly increased from baseline in both groups, however, the difference between groups was not statistically significant at 3 months follow-up ($P = .34$).⁴²

Adverse events

No treatment-related adverse events were reported, and no patients reported a Visual Analog Scale (VAS) pain score higher than 2.⁴²

Outcomes: Platelet rich plasma (PRP) injection vs sham

Four RCTs compared PRP to sham therapy.^{43–46} Study sizes range from 59 to 100 participants and included men with vasogenic

ED. Information about the study participants, preparation and injection protocol for PRP injections, duration of treatment, and outcomes are available in [Supplemental Table 11](#).

Erectile function

International index of erectile function—erectile function domain

Both RCTs^{45,46} reported statistically significant differences between the PRP and sham groups. Poullos et al. (2021)⁴⁵ reported a significant adjusted mean difference (aMD) after 6 months follow-up (aMD 3.9 [95% CI 1.8 to 5.9], $P = .001$). Shaher et al. (2023)⁴⁶ reported statistically significant differences in the IIEF-EF scores at 1-, 3-, and 6-months follow-up ($P < .001$ at all follow-up times).

International index of erectile Function-5

Masterson et al. (2023)⁴⁴ reported an increase in IIEF-5 scores from baseline at 1-, 3-, and 6-months follow up for both groups, however, the difference between groups was not statistically significant at any time point.

Minimal clinically important difference

Two of the three RCTs reported statistically significant differences between the PRP and sham groups.^{43,46} Khalef et al. (2023)⁴³ reported a risk difference of 42% (95%CI 18 to 66), $P < .001$, with more men in the PRP group reaching MCID, however, MCID was not formally defined or referenced. Masterson et al. (2023)⁴⁴ reported no significant difference in MCID reached between groups at 1-, 3- and 6-months follow-up, whereas Shaher et al. (2023)⁴⁶ reported significant differences of MCID between groups at 1-, 3- and 6-months follow-up ($P < .001$ all follow-up times).

Adverse events

AEs were most commonly reported as different measures of pain, specifically, the mean pain with injection on a scale of 1 to 10,⁴⁴ treatment induced pain,⁴⁵ and using VAS,⁴⁶ with little difference between groups. There were few other AEs reported, and they were considered mild (eg, new plaque, hematoma). Khalef et al. (2023)⁴³ did not report if there were any AEs.

Outcomes: Platelet rich plasma + shockwave therapy vs shockwave therapy alone

Geyik et al. (2021)⁴⁷ conducted a non-randomized controlled trial with 214 men with vasogenic ED, who were poor PDE5i responders. The combination therapy group ($n = 91$) received both PRP injection and Li-ESWT therapy and the comparison group ($n = 93$) received Li-ESWT therapy alone. Information about the study participants, PRP preparation and protocol, devices used, treatment protocols, duration of treatment, and outcomes are available in [Supplemental Table 12](#).

Erectile function

International index of erectile Function-5

Both groups saw significant improvements from baseline to 6 months, and the difference between groups was also statistically significant at 6 months follow-up ($P = .001$).⁴⁷

Adverse events

No AEs were reported in either group.⁴⁷

Outcomes: Stem cell injection vs sham

One RCT⁴⁸ and two non-randomized studies^{49,50} compared stem cell therapy to sham. Study sizes ranged from 10 to 26 participants. Mirzaei et al. (2021)⁴⁸ and Bahk et al. (2010)⁴⁹ included men with diabetic ED who were non-responders to PDE5i. von Schwarz et al. (2021)⁵⁰ included men with vasogenic ED and did not specific PDE5i response. Each participant in the stem cell group received a single injection, and comparisons differed in each study. Information about the study participants, stem cell preparation, injection protocol, and comparison groups, and outcomes are available in [Supplemental Table 13](#) and [14](#).

Erectile function

International index of erectile Function-5

All three studies reported an increase in the IIEF-5 score from baseline to 6 months follow-up in the stem cell therapy group, with little or no increase in the control groups. The difference between the stem cell therapy and the control group was statistically significant ($P < .05$) in von Schwarz et al. (2021)⁵⁰ which compared stem cell therapy to a historical control group who received a single saline injection. There was no statistical difference between groups ($P = .87$) in Mirzaei et al. (2021)⁴⁸ which compared stem cell therapy to pretending to obtain oral mucosa in the control group. It is unknown if there is any statistical difference in Bahk et al. (2010),⁴⁹ as they report individual question results for the IIEF-5 and do not report if there were any differences between stem cell group and the saline injection group.

Adverse events

Mirzaei et al. (2021)⁴⁸ reported that no patients in either group reported injection-related complications. Bahk et al. (2010)⁴⁹ did not report if there were any AEs. Last, patients in both groups in von Schwarz et al. (2021)⁵⁰ study reported pain after injection, 7/20 in the stem cell therapy group and 2/6 in the saline injection group.

Discussion

This systematic review provides a comprehensive narrative synthesis of the available literature evaluating restorative therapies for ED. The review highlights both the potential promise and the substantial limitations of the current evidence base in a field that continues to evolve.

Among the various restorative therapies summarized, focused Li-ESWT has the largest body of evidence, though results across trials are mixed. While several RCTs reported statistically significant improvements in erectile function scores favoring Li-ESWT over sham, others found no significant difference between groups (eg, Fojecki et al. 2017,²¹ Yee et al. 2014,³¹ Vinay et al. 2021¹⁹). Among studies reporting MCID outcomes, interpretation is limited by several factors: use of MCID thresholds with the IIEF-5 (for which no MCID has been validated), unusual absence of placebo response in sham arms, and mixed patient populations that complicate MCID determination. One study reported sustained benefits at 12 months,²² though this represents limited data from which to draw conclusions about durability of effect.

Despite the promise of Li-ESWT, considerable heterogeneity exists among the treatment protocols, including variations in energy flux density, frequency, duration, and number of treatment sessions, without a clear superiority of one schedule over another. These inconsistencies limit our ability to determine an optimal treatment regimen. Additionally, while adverse effects were infrequent and mild, standardized reporting was lacking. When comparing Li-ESWT to other treatments, for example, pharmacotherapy and radial wave therapy, no difference was observed, although this was only evaluated in three studies with limited enrollment. Importantly, radial wave therapy in two studies was not found to demonstrate significant improvement when compared to sham therapy.^{38,39}

Interestingly, an apparent paradox emerges when examining the literature on shockwave therapy. A non-randomized study has found no difference between focused and radial wave therapy.³⁷ Radial wave therapy also showed no significant benefit compared to sham in two studies, yet focused therapy was superior to sham in several (though not all) trials. This inconsistency may reflect differences in energy delivery mechanisms, treatment protocols, patient populations, or methodological factors across studies. Alternatively, it may suggest that the observed benefits of focused Li-ESWT in some trials could be influenced by factors other than the specific treatment mechanism, such as the placebo effect, regression to the mean, or study-specific biases. Further head-to-head comparisons with rigorous methodology are needed to clarify these relationships.

In 2021, the Asia-Pacific Society for Sexual Medicine⁵¹ summarized the latest evidence on LIPUS for ED treatment and proposed that LIPUS therapy could improve erectile function and penile hemodynamics by inducing neovascularization and promoting tissue regeneration. They suggested that more rigorous, larger-scale, multicenter randomized placebo-controlled trials were needed before LIPUS can be established as a new standard for male ED treatment. Only one RCT, published in 2019, was identified in this review,⁴¹ highlighting that more robust studies still need to be performed to evaluate the efficacy and safety of LIPUS.

Other emerging therapies such as PRP and stem cell injections have garnered significant interest due to their theoretical restorative potential.^{52,53} However, the clinical data, identified in this systematic review, remains inconclusive, as some studies reported improvements in erectile function scores with PRP versus placebo, others found no significant difference compared to placebo. The inconsistency may stem from variability in PRP preparation methods, injection protocols, and small sample sizes. Although not formally included in this review as they were published after the search date, we are aware of two RCTs that evaluated PRP compared to placebo. Ragheb et al. (2024)⁵⁴ reported no statistical difference between treatment groups and Zaazaa et al. (2025)⁵⁵ reported some statistical differences between the four groups, particularly the group who received a combination of platelet-rich fibrin matrix and prostaglandin E-1. Stem cell therapies, though biologically compelling, are currently supported by only a few small trials, often with methodological limitations, such as non-randomized designs and insufficient control arms. Long-term safety data are also lacking.

This systematic review has several important limitations. Firstly, a meta-analysis was not undertaken. While meta-analytic methods exist to address heterogeneity (eg, random-effects models), the combination of substantial clinical heterogeneity in treatment protocols, the preponderance of unclear or high risk of bias, and concerns about data quality and unusual findings (such as absent placebo responses) led us to conclude that pooled estimates would not be meaningful or reliable. Secondly, formal risk of bias tools may not capture all methodological concerns relevant to this literature. For example, several studies rated as low risk of bias nonetheless had issues such as: application of MCID thresholds to instruments for which no MCID has been validated (IIEF-5), unusual placebo response patterns that deviate from historical norms in ED trials, mixed severity populations without stratified analyses, and inconsistencies between reported data in tables and figures. These concerns, while not captured in standard risk of bias domains, affect the confidence we can place in individual study findings. Third, defining the “ideal patient population” for these therapies remains unresolved, limiting the generalizability of findings.

Further domains were judged as unclear RoB mainly due to poor reporting, which did not allow us to assess the RoB for some domains. Primary authors of future studies should follow reporting guidelines, CONSORT for RCTs⁵⁶ and STROBE for observational studies,⁵⁷ to increase the ability for readers to assess the RoB of their studies. Second, we used a staged approach to assessing the RoB of non-randomized studies. The first question in ROBINS-I relates to bias due to confounding. As none of the included non-randomized studies reported an adjusted analysis, we considered them to be at high risk and determined that additional consideration of other risk would not change our final judgment.

This review highlights the urgent need for better-designed studies in this field. Limitations in the published literature should be acknowledged and improved upon. Most studies did not report a MCID in erectile function improvement. Initiatives, such as the Core Outcome Measures in Effectiveness Trials (COMET) may contribute to a standardized set of outcomes for these studies (comet-initiative.org/). Specific to focused Li-ESWT, the most promising restorative therapy currently available, studies elucidating the ideal treatment protocol are needed to guide clinical practice. A combination of restorative therapies may still prove to be efficacious pending future studies.⁵⁸ The mechanisms of action for both Li-ESWT and PRP on a theoretical basis suggest likely synergistic effects. Hence, this avenue of investigation should continue, informed by the best protocol for treatment efficacy of both Li-ESWT and PRP.

Future trials should adhere to minimum reporting standards to facilitate interpretation, replication, and evidence synthesis. Including: (1) clear specification of the sham comparator design and assessment of blinding adequacy; (2) explicit reporting of whether focused or radial energy was used; (3) stratification of results by ED severity with application of appropriate MCID thresholds; (4) use of the IIEF-EF domain rather than the IIEF-5 when reporting MCID outcomes, as only the former has validated MCID thresholds; (5) reporting of individual patient data or responder analyses to complement mean change scores; and (6) pre-registration of trial protocols and statistical analysis plans to reduce the risk of selective reporting. In further detail:

Sham comparator design

- Provide detailed description of sham device/procedure, including how it mimics the active treatment (sound, vibration, sensation, appearance)
 - Report whether sham and active treatments are perceptually distinguishable to participants
 - Assess and report blinding adequacy (eg, post-treatment questionnaire asking participants to guess allocation)
 - For shockwave therapy, specify whether sham probes were manufacturer-designed or improvised (eg, standoff attachments, deactivated devices, placebo gel pads)

Energy source and device specifications

- Clearly specify whether focused or radial shockwave energy was used
- Report device manufacturer and model
- Report energy flux density (mJ/mm²), frequency (Hz), total pulses per session, and number of treatment sites
- Describe tissue penetration depth if known
- For combination therapies, report specifications for each modality separately

Participant subgroups and baseline characteristics

- Report ED severity distribution at baseline using validated categories (mild, mild-to-moderate, moderate, severe) based on IIEF-EF domain scores
- Report PDE5i response status (naïve, responder, partial responder, non-responder) using standardized definitions
- Report ED etiology (vasculogenic, neurogenic, mixed) and duration
- Report relevant comorbidities (diabetes, cardiovascular disease, hypertension, hyperlipidemia) with frequencies
- Stratify outcomes by ED severity when mixed populations are enrolled

MCID Reporting

- Use the IIEF-EF domain (not IIEF-5) when reporting MCID, as validated thresholds exist only for this instrument
- Apply severity-specific MCID thresholds: ≥ 2 points for mild ED, ≥ 5 points for moderate ED, ≥ 7 points for severe ED
- When enrolling mixed severity populations, report MCID achievement stratified by baseline severity category
- Report both the proportion achieving MCID and mean change scores with standard deviations to allow for future meta-analyses
- Clearly define the MCID threshold used and provide citation for its validation

Follow-up and outcome assessment

- Report outcomes at standardized timepoints (eg, 1, 3, 6, and 12 months post-treatment) to facilitate cross-study comparisons
- Clearly distinguish between end-of-treatment and post-treatment follow-up assessments
- Report attrition at each timepoint with reasons for dropout

- Use intention-to-treat analysis as the primary analysis, with per-protocol as sensitivity analysis

Adverse events

- Use standardized adverse event reporting (eg, CTCAE grading)
- Report all adverse events, not only treatment-related events
- Distinguish between acute (during/immediately after treatment) and delayed adverse events

Adherence to established reporting guidelines (CONSORT for RCTs, STROBE for observational studies) and prospective trial registration would substantially improve the quality and interpretability of future research in this field.

In summary, the evidence for focused Li-ESWT in the treatment of vasculogenic ED remains mixed and inconclusive. While some trials suggest potential benefit compared to sham, others do not, and methodological limitations across the literature—including inconsistent MCID reporting, unusual placebo response patterns, and heterogeneous protocols—preclude definitive conclusions about clinical efficacy. The distinction between statistical significance and clinical meaningfulness is critical: even where statistically significant differences are observed, the clinical relevance of these differences for individual patients remain uncertain. All restorative therapies, including focused Li-ESWT, should be considered investigational. Their use outside of clinical trials should involve shared decision-making with patients about the uncertain evidence base. Further well-designed studies with standardized protocols, validated outcome measures appropriately applied, and adequate sham controls are urgently needed to establish whether any of these therapies provide clinically meaningful benefit.

Author contributions

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[equal], Data curation [equal], Funding acquisition [equal], Methodology [equal], Supervision [equal], Validation [equal], Visualization [equal], Writing—original draft [equal], Writing—review & editing [equal]).

Supplementary material

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Conflicts of interest

I.G. serves on the Scientific Advisory Board for SoftWave TRT; all other authors declare no conflicts of interest.

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