ARTICLE

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Restorative therapy clinical trials for erectile dysfunction: a scoping review of endpoint measures

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Given the lack of regulatory approval for restorative therapies for the treatment of erectile dysfunction, we hypothesized that clinical trials would vary in methodology and endpoint measurements. Our objective was to analyze methodological approaches and outcome measures of clinical trials evaluating restorative therapies for erectile dysfunction. Data was extracted from clinicaltrials.gov on trials which contained the keywords "erectile dysfunction". We evaluated trials initiated between 2004 and 2021 which listed a restorative therapy intervention. We identified 95 trials investigating energy-based/shockwave therapies (60/95), stem cell therapies (25/95), platelet-based therapies (6/95), and others (4/95). Only 41.1% of the trials evaluated safety. The most common efficacy endpoint was International Index of Erectile Function and Sexual Health Inventory for Men, and only 29.5% utilized penile Doppler. Thirty (31.6%) trials had been completed yet only 3 (3.2%) have published results. We found substantial heterogeneity in methodological approach in the trials. Subjective measures of erectile function were commonly reported, but definitions of inclusion criteria and objective outcome measures were inconsistent. These results provide a basis for the design of future clinical trials to improve the quality of trial data and aid in the development of standardized criteria for erectile dysfunction clinical trials.

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INTRODUCTION

Erectile Dysfunction (ED) is defined as the inability to attain or maintain an erection sufficient for sexual intercourse [1]. ED is one of the most prevalent sexual health conditions worldwide and is known to significantly affect the quality of life of affected men [2]. The recent increase in modifiable risk factors for ED has caused an increased prevalence of ED in recent years, with some estimates predicting that 322 million men will be affected globally by 2025 [3]. The rise in ED incidence has resulted in an increasing demand for treatment options. Current medical treatment options include oral phosphodiesterase-5 inhibitors, vacuum-assisted erection devices, intraurethral suppositories, intracavernosal vasodilator injections, and penile implants [4]. However, none of these treatments can reverse ED pathophysiology and none can restore normal penile function or spontaneous erections [5].

A variety of tools exist to determine the severity of ED [6]. These tools include both subjective, patient-reported outcome measures, which capture the patients' view of their symptoms, and objective functional assessments and practical measures, which are generally task-based and scored on a predefined criterion.

Restorative therapies represent a new generation of treatments which aim to reverse the underlying changes that cause ED. Examples of restorative therapies for ED include shockwave therapy [7], injectable platelet-rich plasma (PRP) [8], and stem cell therapy (SCT) [9, 10]. The goal of these treatments is to cure or lessen symptomatology without causing side effects. Notably, restorative therapies have been investigated in the context of other diseases, such as plantar fasciitis [11]; however, there is currently insufficient evidence from randomized controlled clinical trials to support the safety and efficacy of these therapies for ED. Given the lack of regulatory agency approval for any restorative therapy for the treatment of ED, the Sexual Medicine Society of North America has established positions statements on their use. Restorative therapies should only be, "conducted under research protocols in compliance with Institutional Review Board approval" [12].

Nevertheless, patients continue to seek restorative therapies despite a conspicuous lack of regulation by the United States Food and Drug Administration (FDA) or credible associations [13]. With the expansion of clinics offering restorative therapy for ED, it is imperative to investigate them further for safety, efficacy, and standardization to inform eventual regulation or association guidelines.

Previous reviews of studies evaluating the efficacy of SCT [14] and shockwave therapy [15] for ED found significant limitations, such as short follow-up durations and small sample sizes. To date, no study has investigated the whole array of methodological approaches and objective outcome measures in restorative therapy clinical trials. We hypothesize that clinical trials vary in methodology and endpoint measurements. The objective of the present study is to systematically review and analyze all clinical trials that are utilizing restorative therapies for ED to assess

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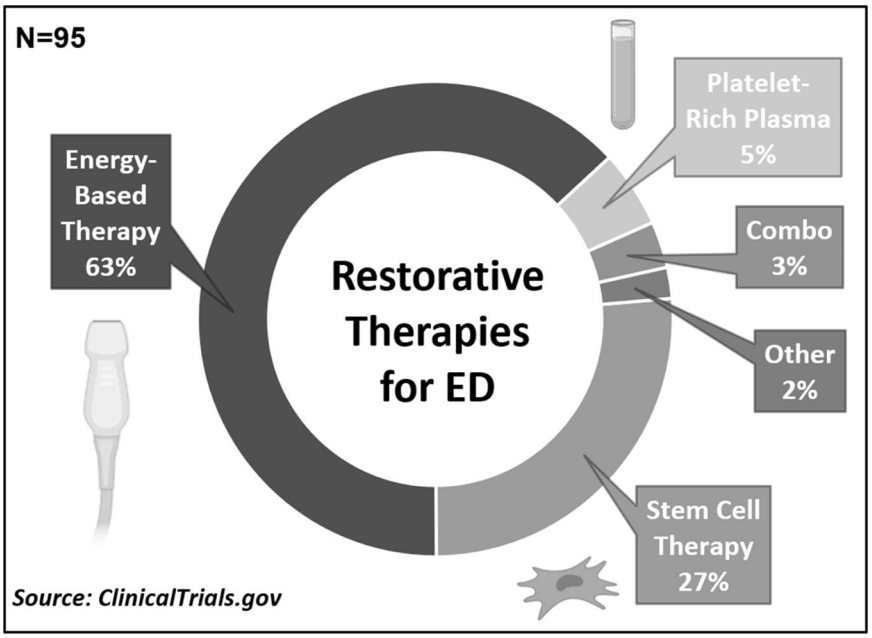

Fig. 1 Restorative therapies used in clinical trials. Source: ClinicalTrials.gov; $N = 95$.

experimental design, outcome assessments, and availability of published data.

METHODS

Data was extracted from clinicaltrials.gov, the largest database of clinical trials cleared by the US FDA, on 10/27/2021 and included all trials which contained the keywords "erectile dysfunction". We evaluated trials initiated between 2004 and 2021 which listed a restorative therapy as the intervention. This included energy-based/shockwave therapies, PRP therapy, and SCT, among others. We recorded whether each trial implemented Doppler ultrasound [16], International Index of Erectile Function (IIEF) [17], Sexual Health Inventory for Men (SHIM) [18], Erectile Hardness Scale [19], endothelial function assessment [20], and safety assessment.

RESULTS

We identified 515 trials for ED in the clinicaltrials.gov database. Of these, 95 (18.4%) investigated a restorative therapy (Fig. 1). The trials investigated the effects of energy-based therapies (60/95), SCT (25/95), platelet-based therapies (6/95), gene therapy (1/95), Hyperbaric Oxygen Therapy (1/95), or a combination thereof (2/95). A total of 15,839 male participants were enrolled or are anticipated for enrollment in the trials.

Most trials were conducted at a single study site (77/95, 81.1%), and half were conducted in an academic setting (48/95, 50.1%). Randomization was utilized in 63.2% (60/95) of trials, yet only 30.1% were double-blinded (29/95). About half of the trials (47/95, 49.5%) were open-label, meaning the participant was aware of the treatment allocation.

Only 41.1% of the trials evaluated safety. The most common efficacy endpoints were the patient self-reported questionnaires, the IIEF and SHIM, and only 30% of trials utilized penile Doppler ultrasound (Fig. 2).

A total of 30 (31.6%) trials have been completed, yet only 3 (3.2%) have made their results available on clinicaltrials.gov. Among these, enrollment (≥80% planned sample size) was achieved in one trial (1/3), and retention (≥75% enrolled subjects) occurred in two of the three trials. A separate search was done on PubMed to determine if any of the clinical trials had published results that were not listed on their clinical trial website. Publications were identified from eight of the trials, which outlined preliminary or final results [8, 21–27], (Table 1).

DISCUSSION

Meeting the increased demand for effective treatments for ED, restorative therapies are advancing the field of andrology and sexual medicine. However, despite the large number of clinical trials, there remains a need to improve the quality of trial design, data collection, and standardized criteria for ED clinical trials. Identification of clinical trial methodological approaches as well as primary and secondary outcomes are necessary for the translation of these novel therapeutics into the clinical setting, as well as to improve the rigor and reproducibility of restorative therapies overall.

In this study, we systematically evaluated multiple aspects affecting the trajectory of clinical translation among research trials conducted between 2004 and 2021 which listed a restorative therapy as the intervention for ED.

Subjective measures of ED, such as the IIEF [17] and the SHIM [18], are regularly used. These questionnaires are readily self-administered in research or clinical settings. The IIEF demonstrates the sensitivity and specificity for detecting treatment-related changes in patients with ED [28]. In addition, studies established the SHIM as a useful indicator of ED, and this measure has had positive scientific impact on understanding and improving male sexual function [29]. However, these outcome measures may be less effective in determining underlying restorative physiological changes in penile tissue than Doppler ultrasound or endothelial function assessments [30].

Penile duplex Doppler ultrasound (PDDU) is a minimally invasive tool to evaluate erectile hemodynamics and determining accurate location of deep penile arteries [31, 32]. However, PDDU protocols have marked heterogeneity and no clear consensus for normative measurements, making the interpretation of results challenging [33]. Furthermore, when arterial inflow is normal but the erectile response is poor and there is antegrade diastolic flow throughout the examination, this is called an indeterminate result or a mixed arterial and venous ED. The diagnosis of mixed arterial and venous ED cannot be made using PDDU because venous competence cannot be assessed in a patient with arterial

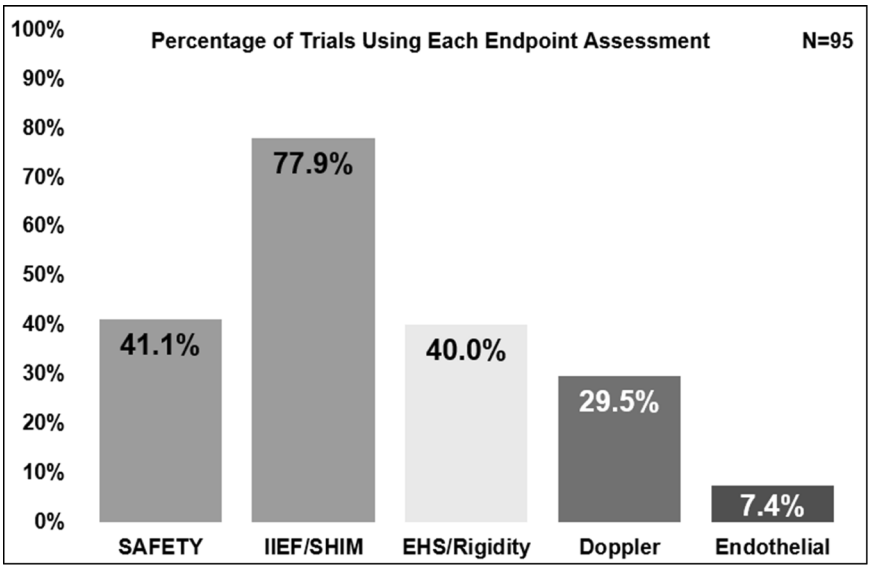

Fig. 2 Common endpoints assessed in clinical trials. Source: ClinicalTrials.gov; *N* 95; Abbreviations: IIEF International Index of Erectile Function, SHIM Sexual Health Inventory for Men, EHS Erection Hardness Scale, Doppler Penile doppler ultrasound.

insufficiency [34]. All in all, using PDDU as a measure of erectile function may only be used in certain circumstances.

Endothelial function is most commonly assessed via brachial artery ultrasound to determine flow-mediated vasodilation. Another method of measuring endothelial function includes culturing the circulating Endothelial Progenitor Cell—Colony Forming Units (EPC-CFUs) obtained from peripheral blood samples [35]. Improvements in these two methods are correlated with one another [36].

Endothelial function may be impaired in ED patients with no apparent cardiovascular disease or diabetes mellitus [37]. Erection occurs with nitric oxide (NO) release from the vascular endothelial cells leading to subsequent arterial dilation [38]. The reduction in endothelial cell production of NO results in the negative impact on the smooth muscles in the corporal bodies and results in less relaxation of the smooth muscle cells with decrease in blood supply and resulting ED. A similar phenomenon is well known to impact the coronary arterial system resulting in cardiovascular disease [39]. ED is frequently, if not usually, directly related to endothelial dysfunction, and the release of NO by the vasculature of the penile arteries is directly related to the function of intact, healthy endothelium [39]. In the face of endothelial dysfunction, the process of erection fails to occur in a normal fashion [40]. All 7 trials [41–47] measuring endothelial function as an endpoint utilized either SCT or Li-SWT, and 1 trial utilized a combination of Li-SWT and PRP [41]. While there are no published results, the assessment of endothelial function (whether through flow-mediated vasodilation or EPC-CFUs) may be an effective measure of erectile function recovery.

This study provides an extensive review of clinical trials utilizing restorative therapies for ED. Limitations are that clinical trials not registered under FDA did not appear in our search and therefore were not included.

Future Directions—Recommendations for Future Clinical Trials

To standardize clinical trial design for investigating novel therapies for ED, researchers should examine protocols and results from already established therapies. The nature of a diagnosis of ED warrants a consideration into the subjective nature of the disease. For this reason, currently available recommendations for clinical trial designs continue to endorse the IIEF as the most validated and reproducible tool to determine endpoints [48]. However, a significant bias in the administration and interpretation of the questionnaire exists across trials. Several studies deviate from incorporating all items of the questionnaire or focusing on specific aspects related to the trial. This has the potential to introduce significant measurement bias. In order to draw final conclusions and hopefully create more effective therapies for patients, it is imperative to adopt a systematic way of collecting data regarding outcome improvements in its entirety, whether through questionnaires, PDDU, or endothelial function assessment.

Another equally important outcome worth capturing is partner satisfaction at the completion of the trial. The IIEF currently lacks a survey of whether the therapy was beneficial in restoring normal sexual functioning, and incorporating the partner's impression and thoughts would imbue the questionnaire with a sense of respect for both parties. This can potentially be addressed by including surveys such as the Treatment Satisfaction Scale which assesses treatment response for both the patient and the partner [49].

To minimize selection bias, a clinical trial investigating therapies for ED should also ensure that the patient population captured in the study is representative of the demographics, symptoms, and complaints of the general population suffering from ED. Because restorative therapies for ED are experimental by nature, the patient population enrolled may come from large academic centers with appropriate funding. This raises a few key issues. For example, the patients who ultimately need referral to a tertiary specialist may be different in many regards than those who receive treatment at primary community centers that lack the necessary resources and expertise to manage a condition that causes significant distress to patients [50]. The progression of their disease may be so advanced at tertiary centers that any minor benefit from a restorative therapy would be detected and recorded as a successful outcome. Although enrolling patients from primary community centers in a clinical trial is considerably challenging, striving to make these considerations before launching a clinical trial is judicious from a methodological standpoint.

CONCLUSION

There is substantial heterogeneity in methodological approach in clinical trials evaluating restorative therapies for ED. Subjective measures of erectile function are commonly reported, but definitions of inclusion criteria and objective outcome measures

Table 1. Results from selected published clinical trials.

Reference	NCT#	Study Disease	Restorative Therapy	Sample Size	Results
Poulios et al. [8]	NCT04050020	ED	PRP	60	Significant difference in the number of participants attaining a MCID and the IIEF-EF score at 1- and 3-months between placebo and treatment groups.
Bieri et al. [21]	NCT03699943	ED	Autologous BM concentrate	140	Significant improvement in IIEF scores at 6 months
Hadanny et al. [22]	NCT02619383	ED	HBOT	30	Significant improvement in IIEF and in penile vasculature using perfusion MRI.
Yiou et al. [23]	NCT01089387	Post Prostatectomy ED	BM-MNCs	6	Significant improvement in two IIEF categories (intercourse satisfaction, and erectile function) after 6 months.
Levy et al. [24]	NCT02398370	ED	Placental derived MSCs	8	Significant increase in peak systolic velocity at 6 months. Three patients for whom previous oral therapies failed had the ability to sustain erections on their own.
Fode et al. [25]	NCT01067261	Post Prostatectomy ED	Vibratory Stimulation	68	Improvement in IIEF with borderline significance.
Katz et al. [26]	NCT03067987	ED	LI-SWT	103	No difference in IIEF between two schedules of shockwave administration.
You et al. [27]	NCT02344849	Post Prostatectomy ED & DM ED	BM-MSCs	10	Significant improvement in IIEF scores at 1 month

NCT national clinical trials identification number, *ED* erectile dysfunction, *PRP* platelet-rich plasma, *BM* bone marrow, *MSC* mesenchymal stem cells, *HBOT* hyperbaric oxygen therapy, *DM* Diabetes Mellitus, *MNC* mononuclear cells, *LI-SWT* low-intensity shockwave therapy, *IIEF-EF* International Index of Erectile Function Questionnaire—Erectile Function subdomain, *MRI* magnetic resonance imaging.

are inconsistent. These results provide a basis for the design of future clinical trials to improve the quality of trial data and aid in the development of standardized criteria for ED clinical trials.

DATA AVAILABILITY

The data that support the findings of this study are available from www.clinicaltrials.gov.

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AUTHOR CONTRIBUTIONS

RS conceived of the research question that led to the submission, acquired data, and helped draft the manuscript. RG acquired data and helped draft the manuscript. TM contributed to interpretation of the results and revised the manuscript. AS helped with interpretation of results and revised the manuscript. RR helped interpret the results and revised the manuscript. All authors approved of the final version of the manuscript and agreed to be accountable for all aspects of the work to ensure that questions related to accuracy or integrity of any part of the work are appropriately investigated and resolved.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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