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Review

An update on the use of stem cell therapy for erectile dysfunction

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Abstract *Objective:* This systematic review aimed to analyze animal and human trial data to better understand the efficacy of stem cell therapy (SCT) for erectile dysfunction (ED) and the obstacles that may hinder its application in this field.
Methods: We searched electronic databases, including PubMed and Scopus, for published studies with the Medical Subject Heading terms of "erectile dysfunction" (AND) "stem cell therapy" (OR) "erectile dysfunction" (AND) "clinical trial of stem cell therapy" (OR) "stem cell therapy" (AND) "sexual dysfunction". The search was limited to English-language journals and full papers only. The initial search resulted in 450 articles, of which 90 relevant to our aims were included in the analysis.
Results: ED is a multifactorial disease. Current treatment options rely on pharmacotherapy as well as surgical options. Patients may have side effects or unsatisfactory results following the use of these treatment options. SCT may restore pathophysiological changes leading to ED rather than treating the symptoms. It has been evaluated in animal models and shown promising results in humans. Results confirm that SCT does improve erectile function in animals with different types of SC use. In humans, evidence showed promising results, but the trials were heterogeneous and limited mainly by a lack of randomization and the small sample size. Many challenges could limit future research in this field, including ethical dilemmas, regulation, patient recruitment, the cost of therapy, and the lack of a standardized SCT regimen. Repairing and possibly replacing diseased cells, tissue, or organs and eventually retrieving normal function should always be the goals of any therapy, and this can only be guaranteed by SCT.

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Conclusion: SCT is a potential and successful treatment for ED, particularly in patients who are resistant to the classic therapy. SCT may promote nerve regeneration and vascular cell regeneration, not only symptomatic treatment.

1. Introduction

Erectile dysfunction (ED) is the inability to achieve or maintain an erection sufficient for satisfactory sexual performance. It is common, affecting at least 12 million American men. The condition can be caused by vascular, neurologic, psychological, or hormonal factors [1]. The treatment of ED requires lifestyle modification, reduction of comorbid vascular risk factors, and the treatment of organic or psychosexual dysfunction with either pharmacotherapy alone or in combination with the psychosexual therapy [2]. The American Urological Association guidelines acknowledge that any treatment option may be used as a first-line therapy [3]. Phosphodiesterase type 5 inhibitors (PDE5-Is) are the most commonly suggested and used first-line treatment option. Invasive treatment encompasses intracavernosal injection (ICI) with vasoactive substances, the intraurethral suppository of prostaglandin E1 (alprostadil), the vacuum-assisted erectile device, and penile prostheses [4]. Despite the favorable clinical data of PDE5-Is, high dropout rates exist. Up to 50% of patients stop treatment owing to issues such as cost, inadequate efficacy, and adverse events [5]. Moreover, ICI therapy has its complications. Priapism is a significant concern, as are pain, ecchymosis, and hematoma formation. Discontinuation rates are not insignificant, with rates of >50% over 5 years reported in some series [6].

The high prevalence of non- or less-responders combined with the unmet needs in currently available therapies has prompted investigation toward the development of new treatment options. Interest in stem cell (SC) technology for erectile restoration is increasing. The exact mechanism of benefit, however, remains unclear.

SCs can be located at the injured site of the body, stimulating angiogenesis, tissue regeneration, immunomodulation, anti-inflammatory, and anti-fibrotic factors, which have attracted their use in the treatment of many conditions. SC therapy (SCT) holds the potential to revolutionize the treatment of several chronic conditions [7]. Numerous animal studies involving the administration of various SC types for ED have reported improvement in erectile response [8]. There are only 11 published trials involving fewer than 130 patients with ED of different etiologies (idiopathic, diabetic, or after radical prostatectomy [RP] or cystectomy). These trials mainly assess the safety and feasibility of SCT, but none is designed to demonstrate its efficacy [9–19].

We performed a concise review to summarize all the available literature on the management of ED using SCT. This review focuses on the main barriers that affect the development of SCT in this area.

2. Material and methods

We searched electronic databases, including PubMed and Scopus, for published studies that analyzed the role of the following Medical Subject Headings terms: "erectile dysfunction" (AND) "stem cell therapy" (OR) "erectile dysfunction' (AND) "clinical trial of stem cell therapy" (OR) "stem cell therapy" (AND) "sexual dysfunction".

This was done to ensure the comprehensive inclusion of articles related to the use of SCT in ED treatment. Only English-language articles were considered. The initial search resulted in 450 articles. After review, we initially excluded 360 papers that were not relevant (duplicated, case report, or editorial). Reference lists for several of the manuscripts identified via the search were reviewed, and additional relevant citations were obtained from these. After the review, 90 articles were selected based on their clinical relevance related to the aim. Data extraction was performed by the authors (Moussa M, Chakra MA, Yassine AA, Boaz J, Jida M, and Klampke F).

3. Rational to use SCT for ED

3.1. Pathophysiology of ED

The main etiologies of ED are vascular, neurologic, psychological, and hormonal. Neurogenic ED is caused by the inappropriate transmission of signals to the corpora cavernosa. It can be related to central or peripheral causes. The common peripheral etiology is cavernous nerve (CN) injury (CNI), especially in radical surgery such as prostatectomy and cystectomy. This led to decreased secretion of nitrous oxide (NO) from CN endings, prolonged relaxation of corpora muscles, and then structural changes in the penile tissue [20]. As it is known, the classic treatments such as PDE5-Is and ICI have failed in neurogenic ED, so there is a need for new targeted treatments. The Ras homolog gene family member A (*RhoA*) signaling in the penis activates Rho-associated protein kinase (ROCK) and thus promotes smooth muscle contraction and decreases erection. Thus, any drug that inhibits this pathway could help. In addition, brain-derived nerve growth factor and vascular endothelial growth factor (VEGF) could help in nerve regeneration [21]. Any therapy that enhances those neurotrophins could improve neurogenic ED [22].

Diabetic ED is a more complex disease. Mechanisms suggested are decreased NO synthesis, upregulation of the RhoA/ROCK pathway, structural changes, and impaired cyclic guanosine monophosphate-dependent kinase-1 [23]. Additional mechanisms, such as impaired angiogenesis and

increased free radicals from high glucose, could contribute to ED [24]. Also, impaired endothelial function could lead to a reduction in the bioavailability of NO, and a vicious circle may be generated [25].

3.2. Mechanism of action of SCT in ED

SCT has the potential to alter underlying disease mechanisms, regenerate tissue, and offer a cure for the disease. Adipose-derived SCs (ADSCs) improved damaged erectile function (EF) in an animal model [26]. Several possible mechanisms underlying the treatment were proposed. The cell-based mechanism indicated that ADSCs differentiated into local functional cells, including smooth muscle cells (SMCs) and endothelium. In addition, the growth factor-based mechanism indicated that the growth factors secreted from ADSCs had a neurotrophic effect to promote nerve regeneration [26]. The mechanisms suggested by SC to restore ED are illustrated in Fig. 1.

The possibility of using mesenchymal SCs (MSCs) in the treatment of ED is enticing not only because these cells are known to secrete various growth factors that are beneficial in ED, such as insulin-like growth factor-1, VEGF, and fibroblast growth factor 2, but also because of their anti-inflammatory activities [27]. From a histopathology explanation, as it is known, the penile corpora cavernosum are composed of sinusoids that are lined with a single layer of endothelial cells (ECs) and are surrounded by multiple layers of circular and longitudinal cavernous SMCs (CSMCs). In men with ED, there is often an alteration or reduction of EC and CSMC contents. SCs are believed to be able to differentiate into various cell types, including ECs, SMCs, Schwann cells, and neurons. Therefore, SCT for ED was based on the hypothesis that transplantation of SCs into the penis through ICI might replenish the depleted EC and/or CSMC pools [28].

In acute ED models like post-RP or radical cystectomy, the mechanism of action of SCs is presumed to be paracrine action. In contrast, in chronic ED, like in diabetes mellitus or aging, the theoretical method of SC action is postulated to be both engraftment and cellular differentiation [29].

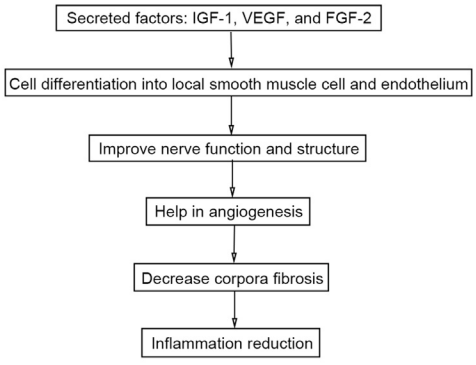

Figure 1 Mechanisms suggested for stem cell therapy in erectile function restoration. IGF-1, insulin-like growth factor 1; VEGF, vascular endothelial growth factor; FGF-2, fibroblast growth factor 2.

4. Preclinical trials supporting the use of SCs for ED

4.1. Data presentation

4.1.1. Animal studies using multipotent SCs

Numerous animal studies involving the administration of various SC types for ED have reported improvement in erectile response. Attempts have been made to determine which cell type performs best [30]. In acute animal models, such as those with CNI-induced ED, engraftment and differentiation have not been observed. Instead, SCs are believed to interact with the host tissue in a paracrine fashion [31]. Kendirci et al. [32] tested the effects of transplanting non-hematopoietic adult bone marrow SCs (multipotent SCs) into the corpus cavernosum (CC) in a rat model of bilateral CN crush injury. Rats injected with typical multipotent stromal cells had partial EF rescue compared with animals that received p75-derived multipotent stromal cells [32]. In another trial, Xu et al. [33] concluded that ADSCs-based micro-tissue (MT) resulted in a better restoration of EF than the traditional single-cell strategy in a rat model of bilateral CNI. Albersen et al. [34] reported that penile injection of both ADSC and ADSC-derived lysate can improve recovery of EF in a rat model of neurogenic ED. In a rat model of post-prostatectomy ED, human ADSCs show an effect on the recovery of CNI, and low-energy shock wave therapy (SWT) improves angiogenesis in the CC. While ADSC injection plays a role in the recovery of the CNI, the low-energy SWT results in significantly increase expressions of VEGF and vascular supply to the penis [35]. In addition, transplantation of induced pluripotent SC-derived MSCs in a rat model significantly improved ED induced by CNI. It can restore the expression of von Willebrand factor, endothelial NO synthase, smooth muscle actin, and desmin, which indicates the alleviation of endothelial and smooth muscle tissue of the penis [36].

4.1.2. Animal studies using exosomes (Exos) form SCs

Exos isolated from MSC culture supernatants could ameliorate CNI-induced ED in rats by inhibiting apoptosis. Therefore, this cell-free therapy has great potential for application in the treatment of ED [37]. Interestingly, ICI of MSC-Exos could be an effective treatment to ameliorate EF in a rat model of arterial injury, which is mainly caused by atherosclerosis and trauma [38]. Chen et al. [39] demonstrated that ICI of ADSC-derived Exos could ameliorate ED in diabetic rat models. ICI of ADSCs-based MT improves EF and histopathological changes in diabetic rats. MT injection has a higher retention than ADSC injection, and MT treatment improves neuronal nitric oxide synthase (nNOS) expression, and smooth muscle and endothelial contents in diabetic rats, while also better ameliorating local inflammation in CC [40]. Pigment epithelium-derived factor-transfected ADSCs could have a potential effect on treating ED in rat models. Pigment epithelium-derived factor overexpression also results in

higher survival rates and decreases apoptosis in ADSCs [41]. In addition, it is proven that ADSCs expressing VEGF produce a therapeutic effect and restore EF in diabetic rats by enhancing VEGF-stimulated endothelial function and increasing the contents of smooth muscle and pericytes [42].

4.1.3. Animal studies using other types of SCs

A study was conducted by Feng et al. [43] in diabetic rat models to investigate the role of human umbilical cord MSCs (HUCMSCs) in managing ED. They found that HUCMSCs improved EF in diabetic rats. HUCMSCs restore EF by attenuating diabetes-induced ferroptosis. Hypoxic preconditioning of MSCs is an effective approach to enhancing their therapeutic effect for ED in the rat model. This may be due to their augmented angiogenesis and neuroprotection [44]. ICI of bone marrow-derived MSCs is effective in improving nerve regeneration in diabetic rats [45].

A population of SCs can be easily isolated from voided human urine. Urine-derived SCs (UDSCs) have a similar phenotype to MSCs and can be reprogrammed into induced pluripotent SCs. Having simple, safer, and low-cost SCs such as UDSCs increases their use in clinical practice [46]. UDSCs express MSC markers and secrete several proangiogenic growth factors. It could induce improvement of EF in Type 2 diabetic rats by recruiting resident cells and increasing the endothelial expression and contents of smooth muscle [47]. The use of SC-derived extracellular vesicles (EVs) is a novel strategy for cell-free SCT. UDSC-EV transplantation can ameliorate ED in diabetic rats. Its mechanism may involve the delivery of proangiogenic microRNA [48]. Even the topical application of UDSC-EVs combined with hyaluronic acid in the treatment of ED in diabetic rats has been proven effective [49]. Impaired autophagy is involved in cavernosal endothelial dysfunction and ED in diabetic rats. ICI of UDSCs upregulates autophagic activity in the cavernosal endothelium, contributing to ameliorating cavernosal endothelial dysfunction and finally improving the ED induced by diabetes [50]. Galhom et al. [51] compared the effects of transplantation of UDSCs or their lysate (UDSC-L) into the CC of diabetic rats with ED. They concluded that both UDSCs and UDSC-L can repair the structure and ultrastructure of CC in the rat model. However, UDSC-L is considered better than UDSCs because the latter have decreased survivability with time. Icariside II, when added to ADSCs, could potentiate their ability to restore EF in rats [52].

In another trial, instead of injecting SCs in the CC, SCs were injected in the periprostatic region (around the CN) or around the major pelvic ganglion (MPG) [53—56]. When using ICI combined with periprostatic or MPG injections, this may potentiate the effect of SCs to restore histological changes but not the EF in animal models. It is important to note that the two techniques may address different types of pathophysiology when restoring EF [59,60]. In one study, intravenous infusion of bone marrow-derived MSCs after CNI decreased postoperative ED in a rat model of CNI [61]. Other preclinical studies demonstrated that overexpression of some receptors like relaxin family peptide receptor 1 and peroxiredoxin 2 in ADSCs could enhance the activity of those cells that exert ED treatment [62,63]. At the genetic level, programmed cell death 4 has also been determined as a putative gene under the regulatory control of microRNA-21-5p (miR-21-5p), and it can play an important role in ED. It was found that MSC-derived exosomal miR-21-5p suppressed the expression of programmed cell death 4 and ED in rats with diabetes mellitus [64]. The small EVs from melatonin-pretreated MSCs could help in the restoration of ED in rat models [65]. Exos derived from miR-301-3p-overexpressing ADSCs could help in the restoration of EF in an ED model induced by hypoxia simulating the obstructive sleep apnea scenario in humans [66]. MSC-Exos could preserve EF by inhibiting fibrosis [67]. In post-RP model simulation, injection of ADSC-Exos or bone marrow-derived MSC-Exos could restore pathological changes in ED cases [68]. Exos derived from UDSCs could significantly ameliorate tunica fibrosis and EF in the Peyronie's disease model [69].

Li et al. [70] performed a meta-analysis to compare the efficacy of different SCT for diabetic ED in rats. Ten studies with 302 rats were enrolled in this meta-analysis. Pooled analysis of these studies showed a beneficial effect of SCT in improving EF of diabetic rats (standardized mean difference: 4.03, 95% confidence interval: 3.22—4.84, $p<0.001$) [70]. In another review, the effect of ADSC therapy and its influential factors on the treatment of ED in rats were assessed [71]. Twenty studies with a total of 248 rats were included in this meta-analysis. The data indicated that ADSC therapy recovered EF and regenerated cavernous structures in ED rats [71]. Park et al. [72] evaluated the effects of ADSCs on CNI-induced ED in rats. Nineteen studies were included in the final meta-analysis. It was concluded that ADSCs might be effective in improving EF. However, non-blinded outcome assessors might cause detection bias and overestimate treatment efficacy when proper blinding of studies was tested [72]. Wani et al. [73] performed a network meta-analysis of animal studies to investigate the role of SCT in the management of ED secondary to CNI in rats. Twenty-nine animal studies were included. Pooled analysis of these studies showed a beneficial effect of SCT in improving EF in rats with bilateral CNI using network meta-analysis (95% confidence interval: 15—42; $p<0.001$) [73]. An additional meta-analysis was conducted by Shan et al. [74] to evaluate the effects and influential factors of SC transplantation on ED rats with CNI. Twelve studies with 319 rats were enrolled in their analysis. Pooled analysis results confirmed the efficacy of SC transplantation. Whereas subgroup analysis results showed that treatment effects were not related to follow-up time, SC species, SC sources, markers, or delivery approaches in the transplantation [74].

An overview of preclinical studies explaining the details of SCT used and the main results is summarized in Table 1.

4.2. Critical review of preclinical trial results

After years of exploration in many preclinical trials, the current mechanism of SCT for organic ED has been

Table 1 Summary of results of preclinical studies on stem cell therapy for ED reported.

Study	Type of stem cells used	Source of stem cell	Mode of delivery	ED induction mechanism	Results summary
Kendirci et al., 2010 [32]	• Multipotent stromal cell	Rat	IC	• CNI	• Rats injected with typical multipotent stromal cells had partial EF rescue
Xu et al., 2014 [33]	• ADSC and ADSC-based MT	Rat	IC	• CNI	• EF, the contents of smooth muscle and endothelial cells, and the number of nNOS-positive nerves were significantly ameliorated in the MT group than those in the traditional ADSC group
Albersen et al., 2010 [34]	• ADSC and ADSC-derived lysate	Rat	IC	• CNI	• Both ADSC and lysate treatments resulted in significant recovery of EF • nNOS content was preserved in both the ADSC and lysate groups
Jeon et al., 2016 [35]	• h-ADSC	Human	CN	• CNI	• h-ADSCs showed effect on the recovery of injured CN
Chen et al., 2019 [36]	• ADSC and iMSC	Human	IC	• CNI	• iMSCs and adMSCs had similar beneficial effect on recovery of EF
Ouyang et al., 2018 [37]	• MSC and MSC-Exos	Rat	IC	• CNI	• MSC-Exos could ameliorate CNI-induced ED in rats with similar potency to that observed in the MSC-treated group
Liu et al., 2019 [38]	• MSC and MSC-Exos	Cell bank	IC	• Arteriogenic	• MSC-Exos could ameliorate rat EF with similar potency compared with the MSC group
Chen et al., 2017 [39]	• ADSC and ADSC-derived Exos	N/A	IC	• Diabetic ED model	• IC injection of ADSC-derived Exos could ameliorate diabetic-induced ED rat
Zhou et al., 2017 [40]	• ADSC and ADSC-based MT	Rat	IC	• Diabetic ED model	• MT injection had a higher retention than ADSC injection and improved EF
Lu et al., 2016 [41]	• ADSC and PEDF-transfected ADSC	Rat	IC	• Diabetic ED model	• ADSCs restored EF • PEDF overexpression resulted in higher survival rates and decreased apoptosis of ADSCs
Liu et al., 2013 [42]	• ADSC and ADSC-modified with the *VEGF* gene	Human or rat	IC	• Diabetic ED model	• IC injection of ADSCs expressing VEGF has more efficiently promoted the recovery of EF
Feng et al., 2022 [43]	• HUCMSC	Human	IC or VI	• Diabetic ED model	• HUCMSCs can effectively and safely alleviate ED and attenuate diabetes-induced ferroptosis in CC
Wang et al., 2015 [44]	• AMSC and HP-AMSC	Rat	IC	• Diabetic ED model	• Hypoxic preconditioning of MSCs is an effective approach to enhance their therapeutic effect on ED
Sun et al., 2012 [45]	• BM-MSC and BM-MSC-conditioned medium	N/A	IC	• Diabetic ED model	• IC BM-MSC injection is effective in improving nerve regeneration in diabetic rats
Ouyang et al., 2014 [47]	• UDSC and UDSC-FGF2	Human	IC	• Diabetic ED model	• Paracrine effect of UDSCs or UDSC-FGF2 induced improvement of EF in diabetic rats
Ouyang et al., 2019 [48]	• UDSC-EV	Human	IC	• Diabetic ED model	• UDSC-EV transplantation can ameliorate EF in diabetic rats • Its mechanism involves the delivery of proangiogenic miRNA

Table 1 (*continued*)

Study	Type of stem cells used	Source of stem cell	Mode of delivery	ED induction mechanism	Results summary
Zhuang et al., 2022 [49]	• UDSC-EV and UDSC-EV-HA	Human	Local	• Diabetic ED model	• Topical application of UDSC-EVs-HA in the treatment of ED in diabetic rats has been proven effective
Galhom et al., 2022 [51]	• UDSC and UDSC-L	Rat	IC	• Diabetic ED model	• Both UDSCs and UDSC-L can repair the structure and ultrastructure of CCs and improve the copulatory functions in the diabetic rat model
Zheng et al., 2018 [52]	• I-PSC	Rat	IC	• CNI	• ADSCs treated with Icariside II markedly preserved the EF of the CNI model rats
Yang et al., 2020 [53]	• ADSC-V and ADSC G&V	Rat	MPG	• CNI	• ADSCs co-overexpressed VEGF and GDNF-induced synergistic effects and could be a potential tool for recovering EF
Kim et al., 2013 [54]	• h-ADSC	Human	CN	• CNI	• Transplantation of hADSCs and NGF-hydrogel into damaged CN improved EF
You et al., 2013 [55]	• h-BMSC	Human	IC with/ without PI	• CNI	• PI of h-BMSCs potentiates recovery of EF by IC of h-BMSCs via regeneration of nNOS-containing nerve fibers
Fang et al., 2016 [56]	• d-MSC and r-BM-MSC	Rat	IC and PI	• CNI	• PI of d-MSCs effectively restored EF in rats with CNI
Kim et al., 2012 [57]	• MSC, MSC plus matrixen	Rat	MPG	• CNI	• The functional and histological restoration was observed in the rats with CNI • The effect of MSCs on recovery of EF might be improved by using a cell carrier such as Matrixen
Kim et al., 2012 [58]	• MSC-rAd/hBDNF and MSC	Rat	MPG	• CNI	• Combination treatment with MSCs and BDNF resulted in better functional and histological preservation in ED than MSCs alone
You et al., 2013 [59]	• h-ADSC	Human	PI and/or IC	• CNI	• PI and IC injections of ADSCs were equally effective in recovering penile erection
Bochinski et al., 2004 [60]	• ENSC	N/A	MPG or IC	• CNI	• IC injection ENSCs can improve EF in a rat model of neurogenic impotence
Matsuda et al., 2018 [61]	• MSC	Rat	REJV	• CNI	• Intravenous infusion of MSCs after CNI decreases postoperative ED
Chen et al., 2023 [62]	• PRDX2-ADSC	Rat	Culture-based	• CNI	• Overexpression of PRDX2 in ADSCs enhanced the therapeutic effect of ADSCs by inhibiting ferroptosis
Huo et al., 2020 [63]	• MSC-Exos containing miR-21-5p	Rat	IC	• Diabetic ED model	• MSC-Exos can transport miR-21-5p to cavernous muscle and inhibit its apoptosis
Sun et al., 2023 [64]	• RXFP1-ADSC	Rat	IC	• Diabetic ED model	• RXFP1-ADSCs had more potent efficacy than regular ADSCs
Chen et al., 2023 [65]	• MT-EV and NC-EV	Rat	IC	• CNI	• Transplantation of MT-EVs could significantly alleviate ED

(*continued on next page*)

Table 1 (*continued*)

Study	Type of stem cells used	Source of stem cell	Mode of delivery	ED induction mechanism	Results summary
Liang et al., 2021 [66]	• miR-301-3p-overexpressing ADSC	Rat	N/A	• Hypoxia-induced ED	• miR-301a-3p-overexpressing Exos treatment had significant therapeutic effects in the ED model
Song et al., 2020 [67]	• MSC-Exos *vs.* CCSMC-Exos	Rat	IC	• Diabetic ED model	• CCSMC-Exos or MSC-Exos could preserve EF
Li et al., 2018 [68]	• ADSC-Exos and BMSC-Exos	N/A	IC	• CNI	• ADSC-Exos and BMSC-Exos therapy could significantly alleviate pathological changes associated with ED and improve EF
Yang et al., 2020 [69]	• UDSC-Exos	Human	IC	• Peyronie's disease rat model	• UDSC-Exos could significantly ameliorate tunica fibrosis and EF

CN, cavernous nerve; IC, intracavernous; CNI, CN injury; EF, erectile function; ADSC, adipose-derived stem cell; MT, micro-tissue; nNOS, neuronal nitric oxide synthase; h-ADSC, human ADSC; CC, corpus cavernosum; MSC, mesenchymal stem cell; iMSC, induced pluripotent stem cell-derived MSC; Exos, exosomes; MSC-Exos, MSC-derived Exos; ED, erectile dysfunction; N/A, not applicable; VEGF, vascular endothelial growth factor; HUCMSC, human umbilical cord MSC; VI, tail vein injection; HP-AMSC, hypoxia-preconditioning-adipose derived MSC; BM, bone marrow; BM-MSC, BM-derived MSC; d-MSC, neural differentiated MSC; r-BM-MSC, rat BM-MSC; PI, periprostatic implantation; UDSC, urine-derived stem cell; FGF2, fibroblast growth factor 2; EV, extracellular vehicle; UDSC-EV, EV secreted by UDSC; HA, hyaluronic acid; I-PSCs, icariside II promoted ADSCs' proliferation and differentiation to Schwann cells; UDSC-L, lysate derived from UDSCs; GDNF, glial cell-derived nerve growth factor; ADSC-V, ADSCs that were genetically modified by VEGF; ADSC-G&V, ADSCs that were genetically modified by VEGF and GDNF; MPG, major pelvic ganglion; NGF-hydrogel, nerve growth factor-incorporated HA-based hydrogel; h-BMSC, human BM-derived MSC; BDNF, brain-derived neurotrophic factor; MSC-rAd/hBDNF, MSC infected with recombinant adenoviruses expressing human BDNF; ENSC, embryonic neural stem cell; REJV, right external jugular vein; PRDX2, peroxiredoxin 2; RXFP1, relaxin family peptide receptor 1; MT-EV, EV derived from melatonin-pretreated MSC; NC-EV, EV derived from ADSC without preconditioning; CCSMC, corpus cavernosum smooth muscle cells; MSC-Exos, MSC-derived Exos; BMSC-Exo, BMSC-derived Exos; UDSC-Exos, UDSC-derived Exos; adMSC, adipose-derived MSC; PEDF, pigment epithelium-derived factor.

clarified. There are two major hypotheses explaining this mechanism. First, SCT can repair and replace CNs. SCs differentiate into CN cells, SMCs, or ECs [75]. Second, SCT could heal penile tissue through a paracrine effect which induces anti-inflammatory and anti-apoptotic effect [76].

In most of the animal studies, intracavernosal pressure (ICP), and the ratio of ICP and mean arterial pressure were analyzed to assess EF. There are limited data that show that those parameters are considered a reliable method to measure EF. Stimulation and pressure (mean arterial pressure and ICP) monitoring have been used in numerous studies with various rat models exploring many aspects of EF. Certain issues make a rat model to be not a true physiological one—possible interference of anesthetic agents with the erectile response and involvement of invasive surgical techniques [77]. The need to anesthetize the animal might influence the physiology and pharmacological response of erection [78].

A rat model of ED after CNI has been used in most animal studies [32—37,52—62,65,68]. Although the precise anatomy may differ from species to species, the overall framework of rat pelvic autonomic innervation is remarkably similar to that of humans and other animals [79]. In summary, there are different types of CNI ranging in severity from crush to excision. Functional and morphological studies have shown that the severity of injury escalates from crush to freezing, transection, and excision [80]. It is known that multiple variables are in operation between the nerve injury and the downstream fibrotic effects of the corporal tissue [81]. Other studies were using a diabetic rat model for ED [33—45]. Data suggest that the ancillary penile nerves, which originate from the MPG, have a complementary role to the CN in the autonomic motor innervation of the penis in rats [82]. This nerve remains intact in rat models with CNI, and may influence the degree of ED in those models. Until heterogeneity is addressed, it will be difficult to determine which model could simulate the real scenario.

The most common route of administration of SCs was intracavernosal [32—34,36—45,47,48,51,52,63—65,67—69]. In other trials, SCs or combined with ICI were injected directly into the CN or MPG [53—60]. Intravenous routes or local administration were also used [49,61]. Until heterogeneity is addressed, it will be difficult to determine which route of administration could best address EF recovery.

Many limitations were not considered in preclinical trials. These are as follows: the age of the rat involved in the experiment, absence of rat comorbidities, and spontaneous recovery of EF of the rat after 6 months [83]. Kim et al. [84] assessed the pathophysiological consequences and spontaneous recovery after CN crush injury in the rat model. Significant spontaneous recovery of EF was observed at 6 months after CN crush injury. This may indicate that the recovery of EF after SC injection in the CNI rat model may be related to the time effect but not the cells.

Preclinical trials were including rats without comorbidities according to their young age. This cannot simulate the real-life scenario as most of the patients with ED are suffering from multiple comorbidities at an older age [85].

5. Clinical trials supporting the use of SCs for ED

5.1. Data presentation

Eleven clinical trials with limited participants have been described [9—19]. The results of those trials are summarized in Table 2. All studies had institutional review board approval but none of these studies mentioned information about the cost of treatment.

Concerning study design, only one study was a randomized trial [9], and the others were single-blind non-controlled [11—14,16—19], or controlled trials [10,15]. Concerning the SC type used, it includes ADSCs, bone marrow-derived MSCs, Wharton's jelly-derived SCs, and placental matrix-derived SCs. Concerning primary endpoints of the studies, they mainly included the safety, tolerability, and efficacy of SCT. Concerning the sample size, it was small in all studies ranging from 4 to 22 patients. The tolerability of SCT was excellent as there was no major side effect reported in all trials. The follow-up duration from all studies was short and it ranged from 3 months to 12 months. The majority of the studies showed the improvement in EF due to SCT in patients, including the improvement in penile vascular flow, the International Index of Erectile Function score, and Erectile Hardness Scale score. The regimen used was variable in each trial, and it can include one injection [9,10,12,14—19] or two injections [11,13] separated by at least 1 month.

5.2. Critical review of clinical trial results

Based on clinical data in this review [9—19], findings indicated that SCT is a promising modality of treatment. Clinical efficacy is measured using the International Index of Erectile Function score, which is improved in the majority of trials. In some of the studies, this efficacy is assessed objectively using penile Doppler sonography parameters such as end-diastolic velocity and peak systolic velocity [9,11,16,17].

When comparing SC types, Wharton's jelly SCs are derived with relatively high efficiency and bear a substantially increased proliferation capacity whilst largely sustaining the expression of typical immunophenotypic markers, whereas ADSC exhibits a reduced proliferation potential showing typical signs of senescence at an early stage [86]. Wharton's jelly SCs are widely multipotent and have the advantages of being able to be scaled up easily and not inducing teratomas [87]. The optimal cell type, concentration, and dosing for injection remain to be determined as there is no standardized protocol used in human trials.

Evidence mainly consists of small, open-label, single-arm trials in which the SC has been used, with significantly distinct study protocols. There is a need to conduct randomized controlled trials that measure the effectiveness of this new intervention or treatment. Although no study is likely on its own to prove causality, randomization reduces bias [88]. However, the question remains: which type of control should be used

Table 2 Summary of results of clinical studies on SCT for ED reported.

Study	Study design	Type of the SC used	Regimen used (cells)	Mode of delivery	ED etiology	Patient, *n*	F/U, month	Outcome[a]	
								Baseline	After SCT
Bahk et al., 2010 [15]	• Single-blinded	• Human umbilical cord blood SC	• 1.5×10^7	IC	• DM	• Tx group: 7 • Ctrl group: 3	11	• Number of erections: 1	• Number of erections: 2.3
Yiou et al., 2016 [17]	• Non-randomized trial	• BM-mononuclear cell	• 4 doses: 2×10^7, 2×10^8, 1×10^9, and 2×10^9	IC	• RP	• 12	6	• IIEF-IS: 3.9±2.5 • IIEF-EF: 7.3±4.5	• IIEF-IS: 6.8±3.6 • IIEF-EF: 17.4±8.9
Haahr et al., 2016 [18]	• Open-label and single-arm	• Adipose-derived regenerative cell	• 2.2×10^7	IC	• RP	• 17	6	• IIEF - Ctrl group: 7 - Tx group: 5	• IIEF - Ctrl group: 17 - Tx group: 5
Levy et al., 2016 [16]	• Open-label and single-arm	• Placental matrix-derived MSC	• N/A	IC	• Organic	• 8	6	• PSV: 23.1—49.3 • IIEF: 21—54	• PSV: 50.7—73.9 • IIEF: 23—63
Yiou et al., 2017 [14]	• Open-label and single-arm	• BM-mononuclear cell	• 1×10^9	IC	• RP	• 6	6	• IIEF-IS: 2.2±3.4 • IIEF-EF: 3.7±4.1	• IIEF-IS: 7.8±3.1 • IIEF-EF: 18±8.3
Al Demour et al., 2018 [13]	• Open-label and single-arm	• BM-derived MSC	• 30×10^6 cells/4 mL injected at baseline and at 30 days	IC	• DM	• 4	12	• EHS: 1 • IIEF-15: 10	• EHS: 2.75 • IIEF-15: 42.5
You et al., 2021 [12]	• Open-label and single-arm	• Human BM-derived MSC	• 30×10^7	IC	• DM (5 patients) and RP (5 patients)	• 10	12	• IIEF: 18.1±10.7	• IIEF: 23.3±15.8
Al Demour et al., 2021 [11]	• Open-label and single-arm	• Allogeneic Wharton's jelly-derived MSC	• 20×10^6 cells/4 mL	IC	• DM	• 22	12	• IIEF-5: 11.5±2.7 • EHS: 1.7±0.7	• IIEF-5: 13.6±4.2 • EHS: 2.4±0.7
Mirzaei et al., 2021 [9]	• Randomized single-blinded	• Autologous MSC	• $50—60\times10^6$	IC	• DM	• Tx group: 10 • Ctrl group: 10	6	• IIEF - Tx group: 7.2±2.1 - Ctrl group: not change	• IIEF - Tx group: 10.6±4.7 - Ctrl group: not change
Moussa et al., 2021 [10]	• Single-blinded	• Autologous ADSC	• N/A	IC	• RC	• Tx group: 5 • Ctrl group: 5	6	• IIEF-5 - Tx group: 5 - Ctrl group: not change	• IIEF-5 - Tx group: 18.6 - Ctrl group: not change
Fode et al., 2023 [19]	• Case series	• Autologous ADSC	• N/A	IC	• Organic	• 10	3	• 3/10 men achieved an improvement equal to or greater than the minimal clinically important difference according to their baseline IIEF-EF score	

ED, erectile dysfunction; F/U, follow-up; BM, bone marrow; SC, stem cell; ADSC, adipose-derived SC; SCT, SC therapy; IC, intracavernous; DM, diabetes mellitus; Tx, treatment; Ctrl, control; SD, standard deviation; RP, radical prostatectomy; EF, erectile function; IIEF, International Index of Erectile Function; IS, intercourse satisfaction; PSV, peak systolic velocity; N/A, not applicable; EHS, Erection Hardness Score; RC, radical cystectomy; MSC, mesenchymal stem cell.

[a] Data are presented as mean±SD, range, or median.

in future trials to test the effectiveness of SCs in treating ED?

Finally, long-term follow-up studies are needed to determine the possible efficacy and adverse effects of SCT on cell growth. The follow-up time in most of the human trials was a maximum of 12 months. Published results of SC trials to treat other health conditions have included 5 years of follow-up and this may have an impact on treatment efficacy as it can fade with time [89].

SCT could be an important option for patients who are unresponsive to PDE5-Is. It was reported that diabetic patients are less responsive to PDE5-Is and require higher dosing, which can increase side effects and affect compliance [90]. Constitutional changes such as remarkably decreased levels of NO and low testosterone may explain the failure of PDE5-Is in those patients [91]. Despite the use of PDE5-Is for penile rehabilitation post-RP, it should be used in combination therapy as the response rate to PDE5-Is is low (15%) when used alone [92]. It is important to mention that up to 35% of men are unresponsive to PDE5-Is, and many patients may have tachyphylaxis or decreased responsiveness after repeated doses. This may complicate the treatment options for ED [93].

Other alternatives to medical treatment of ED include the use of low-intensity SWT and platelet-rich plasma (PRP). Low-intensity SWT is effective in the short term, but long-term treatment efficacy is limited and may be preserved for mild ED [94]. The evidence supporting the use of PRP for ED is limited. Only one randomized trial was performed by Poulios et al. [95]. Results are promising, but patients with severe ED were excluded from the trials; those patients have the greatest need for new therapies.

6. Barriers that may affect the advancement of research using SCT to treat ED

Significant limitations to future studies include costs and patient recruitment. SCT is not patentable; this blocks private sponsorship of clinical trials since pharmaceutical companies have no economic interest [96]. Although there are no data assessing the cost versus benefit of SCT for ED, extrapolated data from other applications showed a meaningful assessment of the cost-effectiveness of these advanced therapies. A study was performed by Nagpal et al. [97] to examine economic evaluation studies of SCT in neurological disorders. They identified an incremental cost per quality-adjusted life year gained, also known as the incremental cost-effectiveness ratio, compared to standard care. In another study, authors showed that both autologous and allogeneic MSCs were more cost-effective than fecal diversion in the treatment of Crohn's disease in an academic medical center and even in a worst-case scenario with a 100% chance of all complications for MSC treatment and 0% chance of complications for fecal diversion [98].

In an online review of costs between clinics in the USA, the costs of different emerging treatments for ED were compared. The average cost per SCT injection was $5291; PRP per injection was $1336; and SWT per session was $413 [99]. Over a 5-year period, malleable prosthesis insertion was found to be the least expensive therapy for ED per patient ($3150), followed by ICI ($3450) and inflatable prosthesis ($9000) [100]. A cost-utility analysis should be considered with multiple limitations including direct and indirect costs. A long-term analysis and quality of life impact should always be computed in addition to any direct cost of therapy.

The fact that SCT is rather a new domain makes it subject to scientific, ethical, and legal controversies that are yet to be regulated. Leading countries in the field have devised guidelines serving that purpose [101]. In Japan, two laws have been implemented to promptly deliver regenerative medicine to patients. These include an accelerated approval scheme for clinical trials that shows a reasonable likelihood of clinical benefit; in addition, the laws divide regenerative medicine into three categories depending on the potential risks [102]. Under certain strict criteria, the United States Food and Drug Administration (FDA) allows the use of cell therapy in the framework of regulatory guidelines governing disease transmission, without premarket approval or biologic license application. The criteria under this title specify that "the human cells, tissues, and cellular and tissue-based products are minimally manipulated; intended for homologous use; not combined with other active agents; without a systemic effect; and—if with a systemic effect—administered autologously or to first-/second-degree blood relatives" [103].

In the USA, a few states have introduced or enacted legislation requiring clinics to inform patients that the SCT being offered is not FDA-approved or requires the registration of SCT with the state. However, Texas went the opposite direction, passing legislation in 2017 and 2019 that allows patients to access unregulated SCT and protect physicians administering these interventions [104]. The legal frame for cell-derived medicinal products in European Union (EU) is based on EU regulation (1394/2007), which was issued in 2008. SCs are most often considered advanced therapy medicinal products in the EU and are classified by the Committee for Advanced Therapies. The clinical development should comply with updated EU regulations. In the directive 2009/120, it was stated that "due to the specific nature of advanced therapy medicinal product, a risk-based approach may be applied to determine the extent of quality, non-clinical and clinical data to be included in the marketing authorization application" [105]. As can be seen, the reference legal documents in the area of SC research do not establish clear and stable limits for this type of research [106].

SCT is not currently part of the routine recommended treatment for ED. The current American Urological Association and the European Association of Urology guidelines for the management of ED consider intracavernosal SCT as investigational [107]. The Sexual Medicine Society of North America considers SCT as a restorative therapy. Therefore, it should be reserved for clinical trials and not offered in routine clinical practice [108].

Safety measures could also contribute to challenges when using SCT for ED. Although the safety profile is excellent when analyzing human trials, there are some concerns of the contribution of MSCs in prostate cancer. MSCs with tri-

lineage differentiation potential are identified in prostate tissue from a subset of men with prostate cancer [109]. MSC proangiogenic, anti-apoptotic, and immunomodulatory properties may act together as tumor promoters [110]. Additional data make these concerns more complicated to resolve. Schweizer et al. [111] tested the use of systemically infused allogeneic MSCs before prostatectomy. Enrolled subjects received a single intravenous infusion 4—6 days before prostatectomy. MSCs were undetectable in all subjects, and the study was stopped early for futility [111]. It was found that 45.8% of MSCs spontaneously transformed into malignant cells after 1 month in culture. Though this phenomenon is still controversial, it is important to note that the culture condition should be tightly controlled to minimize the negative change in SCs [112]. Tumorigenesis risk following cell therapy or organ transplantation induced by induced pluripotent SCs may be prevented by irradiation [113].

Allogeneic SC transplantation has been used to treat ED, but there are concerns concerning its immunogenicity. Autologous MSCs are easy to obtain and lack immune rejection after infusion. Allogeneic MSCs may be also immunogenic and these cells can induce an immune memory response under appropriate conditions [114]. In the literature, evidence suggests that the alloreactivity risks of implanted allogeneic cells to the recipients are minimal and do not cause severe adverse reactions in patients [115]. In terms of efficacy, there is a paucity of trials that test the efficacy of autologous versus allogenic SCs for ED. In a rat model, ICI of both autologous and allogeneic MSCs improves EF in a rat model of CNI. In certain cases, allogeneic MSCs might be a more effective product [116].

In the end, the absence of a standardized regimen of SCT can be a major problem when testing its application for ED patients. The cell type, injection concentration, course of treatment, and evaluation endpoint of the treatment effect have not yet been determined [117]. Most SCs are washed out immediately after ICI. In an animal model, the magnetization of ADSCs with NanoShuttle magnetic nanoparticles kept those cells in the CC and improved the SCT of ED [118].

In future trials conducted to assess the efficacy of new emerging treatments for ED, a standardized regimen is important. The lack of this regimen in SCT is the same problem encountered when testing the use of linear SWT or PRP [119,120]. Conducting more trials to investigate the efficacy of linear SWT or PRP will be less challenging than trials of the use of SCT due to the cost of treatment and the funding available.

Barriers that may encounter SC research field for ED are illustrated in Fig. 2.

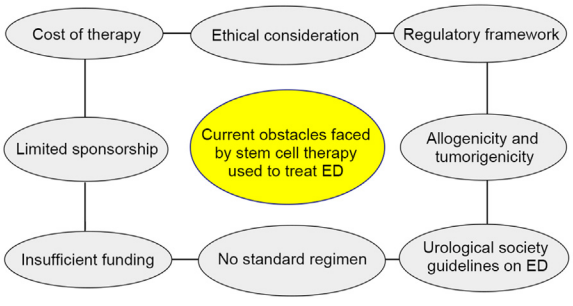

Figure 2 Barriers that may encounter stem cell research in ED treatment. ED, erectile dysfunction.

7. Conclusion

Evidence suggests that SCT is an effective and promising option for ED especially in refractory cases. SCT could induce nerve restoration and vascular cell recovery instead of only symptomatic treatment. The challenge in this area is that many problems need to be solved to provide more advanced clinical trials. Those problems can range from the lack of a standardized regimen to the high ethical and immunologic debates when SCT is applied. However, instead of only criticizing this type of treatment, everyone should help to build robust evidence in this novel era of regenerative medicine.

Author contributions

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Conflicts of interest

The authors declare no conflict of interest.

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