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REVIEW

Stem-cell therapy for erectile dysfunction

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KEYWORDS

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ABBREVIATIONS

ED, erectile dysfunction;
PD, Peyronie's disease;
CNI, cavernous nerve injury;
RP, radical prostatectomy;
CC, corpus cavernosum;
PDE5 (I), phosphodiesterase type 5 (inhibitor);

Abstract ***Introduction:*** Erectile dysfunction (ED) is the most common sexual disorder that men report to healthcare providers, and is the male sexual dysfunction that has been most investigated. Current treatments for ED focus on relieving the symptoms of ED and therefore tend to provide a temporary solution rather than a cure or reversing the cause. Recently, therapies based on stem cells (SCs) have had an increasing attention for their potential to restore erectile function. Preclinical studies showed that these cells might reverse the pathophysiological changes leading to ED, rather than treating the symptoms of ED. This review is intended to provide an overview of contemporary reports on the use of SCs to treat ED.

Methods: We made an extensive search for reports on SC-based therapy for the management of ED, published in English between 1966 and 2013, using the search engines SciVerse-sciencedirect, SciVerse-scopus, Google Scholar and Pubmed, with the search terms 'erectile dysfunction', 'stem cells', 'multipotent stromal cells', 'adipose (tissue) derived stem cells', 'bone-marrow derived stem cells', 'animal model', 'diabetes', 'ageing', 'Peyronie's Disease' and 'cavernous nerve injury'.

Results: Fifty-four papers were identified and contributed, either as an original research report or review thereof, to this review. Several preclinical studies addressed SC-based therapies for the recovery of erectile function caused by a variety of both chronic and acute conditions. Overall, these studies showed beneficial effects of SC therapy, while evidence on the mechanisms of action of SC therapy varied between

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NO, nitric oxide;
(e)(n)NOS, (endothelial) (neuronal) NO synthase;
(A)(E)(H)(M) SC, (adult) (embryonic) (haematopoietic) (mesenchymal) stem cell;
AD, adipose tissue-derived;
BM, bone marrow-derived;
MD, muscle-derived;
SVF, stromal vascular fraction;
MPG, major pelvic ganglion;
GFP, green fluorescent protein

studies. One clinical trial investigated the short-term effects of SC therapy in diabetic patients with ED. Two more clinical trials are currently recruiting patients.

Conclusions: The rapidly expanding and highly promising body of preclinical work on SC-based medicine providing a potential cure for ED, rather than merely symptom relief, is indicative of the increasing interest in regenerative options for sexual medicine over the past decade. Clinical trials are currently recruiting patients to test the preclinical results in men with ED.

Introduction

Erectile dysfunction (ED) is defined as the consistent inability to obtain or maintain an erection for satisfactory sexual intercourse [1]. Notwithstanding variations in definitions and methods, various large-scale studies (both cross-sectional and longitudinal) confirm the global presence of this disease, with an estimated overall prevalence rate of 10–20% worldwide [2]. There is a strong correlation between age and ED, with the prevalence increasing steadily from 6.5% in men aged 20–39 years to 77.5% in those aged ⩾75 years. While previously ED was believed to be primarily due to psychological causes, currently the vast majority of cases have been attributed to the underlying organic disease [3]. In many cases ED is the result of systemic changes in diseases such as diabetes and atherosclerosis, and in the (patho)physiological process of ageing, as illustrated by the convincing epidemiological data cited above [4]. However, also more localised diseases have been linked to ED, such as Peyronie's disease (PD), and iatrogenic causes such as cavernous nerve injury (CNI) during radical prostatectomy (RP) for clinically localised prostate cancer [5]. RP results in significant damage to the neurovascular bundles and autonomic innervation of the penis, resulting in 'either-or-not' temporary denervation of the penis and severe end-organ damage, as evidenced by smooth muscle apoptosis and fibrosis of the corpus cavernosum (CC) [6]. The latter type of ED has been extensively investigated in the light of the possible application of stem cell (SC) therapy for the cure of ED [7].

The recognition of nitric oxide (NO) as the main erectogenic (gaso)transmitter in the erectile tissue has led to the development of phosphodiesterase type 5 (PDE5) inhibitors (PDE5-i) [8]. The efficacy of PDE5-i depends on the integrity of the NO pathway, so it is clear that patients in whom this pathway is deranged or defective might benefit much less than would the general population from treatment with PDE5-i [2]. Diseases in which the availability of NO is reduced include severe diabetes with neuropathy and endothelial dysfunction, metabolic syndrome, and down-regulation or deactivation of NO synthase (NOS) expression, which can occur in denervation of the erectile tissue after RP, atherosclerosis, advanced age, and hypogonadism [2]. Furthermore, in severe ED there is also a downregulation of targets activated by the NO pathway [9]. Overall efficacy rates of PDE5-i are currently 60–70% with on-demand treatment regimens [10]. Men who persistently fail to respond to PDE5-i might require intracavernous injections of vasoactive substances, e.g. prostaglandin E1 and papaverine, to regain erectile function, and when these treatments fail patients must resort to the surgical implantation of inflatable penile prostheses. It is clear that current pharmacotherapies for ED are aimed at providing symptom relief and do not represent a curative approach [11]. Despite this, patients report that the most important treatment outcome and measure of success is the ability of a therapy for ED to cure them of their disease [12]. Thus an ideal future therapy for ED would focus on identifying a disease-specific therapy with curative intent. Various groups worldwide are currently involved in investigating how cell-based therapy, specifically SCs, might be of use in reversing different pathophysiological processes in the establishment of ED to halt or reverse the development of this prevalent sexual dysfunction. While these studies are mainly conducted in a preclinical setting, clinical trials are starting to emerge based on positive preclinical results, and the outcome of these studies might change the approach towards ED.

While we are aware that SC research is ongoing in other areas of andrology, based on our field of expertise, in the present review we focus on the current evidence to support the use of SCs for treating ED, and discuss SC-based strategies in several diseases leading to organic ED.

Stem cells

SCs are by definition capable of self-renewal (which means they can make exact copies of themselves, indefinitely) and differentiation into various phenotypes [13]. They can functionally and structurally regenerate damaged tissues, depending on the stimuli or signals they receive [13]. When a SC divides, both daughter cells have the potential either to remain as SCs or to become a more specialised type of cell, e.g., muscle, red blood or brain. Tissue regeneration is the result of two principles of cell division, which are also the backbone of the maintenance of the SC population, i.e., asymmetrical replication, in which one daughter cell becomes a SC and the other a more differentiated cell, and stochastic differentiation, in which one SC gives rise to two daughter SCs and a neighbouring SC gives rise to two more differentiated daughter cells.

The hierarchy of multi-lineage differentiation classifies SCs as being totipotent, pluripotent, multipotent, progenitor and precursor cells. In the earliest stages of development, the totipotent zygote and morula (or early blastocyst cells) give rise to a fully differentiated adult organism. After just a few divisions into development the totipotency is lost. At this stage there are pluripotent cells that give rise to cells of all three germ layers (ectoderm, mesoderm and endoderm), but are no longer capable of giving rise to extra-embryonic tissues [14]. Embryonic SCs (ESCs), isolated from the inner cell mass of the blastocyst, are the commonest example of pluripotent cells [13]. Multipotent SCs, such as haematopoietic SCs (HSCs) and mesenchymal (stromal) SCs (MSCs), are isolated from the developing germ layer and their descended adult organs, can renew themselves and differentiate into any cell type within their germ layer [7]. Unipotent cells are progenitor cells or precursor cells with a limited capacity for self-renewal and they differentiate into only one defined cell type, such as epithelial cells [13]. The harvesting of ESCs requires the destruction of human embryos and this has raised significant ethical and political restrictions. These barriers have prompted the search for alternative SC sources including adult SCs (ASCs).

SC types

In ED research, three types of ASC are commonly used, including adipose tissue-derived SCs (ADSCs), bone marrow-derived SCs (BMSCs), and muscle-derived SCs (MDSC). All of these SCs have been defined as MSCs, indicating that they can differentiate into various cell types within the mesodermal germ line, such as muscle, fat and bone cells [15]. They are further characterised by their surface marker expression, which is highly similar between ADSCs and BMSCs, and might differ slightly in MDSCs, and thus raise the question whether these three populations are derived from the same lineage [14]. MDSCs are isolated from a striated muscle biopsy and require cultural expansion to gain sufficient cell numbers for therapy. BMSCs are isolated from the mononuclear fraction of the bone marrow by aspiration, and either cultured BMSCs or the whole mononuclear fraction (containing many cell types, among which are BMSCs) can be used for cell therapy, as illustrated by a multitude of clinical trials using both cultured and uncultured cellular products. ADSCs are a distinct population of MSCs residing in the perivascular niche of adipose tissue [16,17]. The possibility of harvesting large amounts of tissue (> 100 g) allows for direct re-injection of cells (the stromal vascular fraction, SVF) in the same surgical procedure during which they were harvested [18].

Besides multipotent or even pluripotent differentiation, SCs (in particular MSCs) have strong paracrine capacities, and these cells have been recognised as producers of growth factors and cytokines [19,20]. In this sense it is possible and increasingly believed that MSCs have their beneficial effects on damaged or diseased tissues by releasing various molecular mediators, which in turn stimulate the host tissue to initiate a regenerative or healing response to disease or injury. This hypothesis is supported in many different preclinical studies using MSCs, in various disciplines, in which there is functional and structural tissue regeneration in the absence of cell incorporation, or even cell differentiation [21]. In ED, various studies from different groups have made similar observations, as detailed below. In addition, functional results on the recovery of erectile function have been either replicated by injection with SC-derived soluble molecules in the form of lysate or conditioned culture medium, or blunted by blocking certain trophic factor-initiated signalling pathways [21–23]. Therefore, it is increasingly believed that MSCs do not need to engraft in the host tissue to generate a beneficial (structural or functional) response to cellular therapy.

Results and mechanisms of action

Because of limited space, not all the available studies are discussed in full. We selected studies representing important advances in SC therapy for ED, both in efficacy and in understanding the mechanism of action of cellular therapy. However, all SC studies that were identified using the search criteria noted above are summarised in Table 1 [22–45].

CNI

Bochinski et al. [24] reported the first attempt to use SCs to restore erectile function after CNI. They injected neural ESCs labelled with green fluorescent protein either into the CC or next to the major pelvic ganglion (MPG, in which the cell bodies of the cavernous neurons are located, in the rat). These authors reported a significant improvement in erectile function. In the treated groups, staining for neurofilament and neuronal NOS (nNOS) showed greater neuro-regeneration or nerve preservation than in injured controls. Of interest, in both treated groups there was no direct evidence of engrafted SCs after harvesting the tissue. The authors suggested that transplanted SCs might not require prolonged residence in the tissue to exert their function. Instead, the mechanism of action might have been by growth factor expression, inhibition of demyelination, or as an initial lattice of cellular substrate. Kendirci et al. [32] replicated these results by injecting the CC of rats after CNI with BMSCs expressing selected neurotrophin receptors. There was an improvement in erectile function and increased erectile responses to electrostimulation of the cavernous nerve at 4 weeks after a CNI (crush) and injection with SCs. These authors thus concluded that the nerves had regenerated. These cells were also genetically labelled with GFP, and engraftment in the erectile tissue was rare. The few engrafted cells had a fibroblast-like appearance, and did not express any markers to confirm that transdifferentiation had replaced dead or diseased host cells. Kendirci et al. further found that these SCs were capable of secreting large amounts of neurotrophic factors, a discovery that was later confirmed in ADSCs in vitro by Zhang et al. [46]. Albersen et al. [21] tested the application of ADSCs in the CNI rat model. Besides ADSCs, they injected the CC of another group of rats with ADSC-derived lysate. Lysate treatment exposes injured tissues to soluble factors contained in ADSCs, without allowing live cells to directly act on the host tissue [47]. In that study, both ADSCs and ADSC-lysate improved the erectile responses to cavernous nerve stimulation at 4 weeks after injection, and both therapies partly restored the smooth muscle content of the penis, decreased CC fibrosis, and importantly, restored nNOS expression in the dorsal penile nerves. In agreement with previous studies, few engrafted ADSCs (which were marked with the fluorescent thymidine analogue EdU) were detected in the CC after 4 weeks. The combination of a lack of engraftment and the beneficial effects of lysate injection provided evidence for paracrine interactions between ADSCs and host tissue. These results mark a change in the understanding of the mechanisms of action of SC therapy, as it was previously thought that SCs have the potential to engraft in, and repopulate, diseased target organs [48].

The absence of injected SCs in the penis of these rats raised the question of what the fate of these cells might be after they had disappeared from the CC [11,34,36]. Because the CC is a highly perfused structure (and is essentially a modified blood vessel [49]), it is probable that injected SCs are flushed out and reach the systemic circulation soon after the injection. This hypothesis was tested by Fandel et al. [34] and Lin et al. [36], who labelled ADSCs with EdU and examined the behaviour and migration of these cells after injection into the CC. The ADSCs disappeared quickly from the CC and reached either a niche resembling their usual site (the perivascular space in the bone marrow) or the MPG. Interestingly, in those rats in which there was migration towards the MPG there was a time-dependent increase in penile nNOS levels, suggesting that the migration of ADSCs towards the injured MPG was essential for neuro-regeneration. Qiu et al. [38] reported similar beneficial functional effects, and the migration of SCs towards the MPG after pelvic irradiation in rats as a model of ED induced by radiation. Another recent study of Qiu et al. [18] showed the potential for clinical translation of these findings, in that autologous adipose SVF could improve erectile function and preserve neuro-anatomical integrity in a long-term study (3 months).

Diabetes, ageing and metabolic syndrome

In ED induced by chronic disease processes there have been different results. First, the migratory behaviour of SCs has not been investigated. However, it is likely that in the absence of an acute event such as an injury (and thus in the absence of local chemoattractant release), SCs are less likely to migrate to certain tissues to aid in the regenerative process [11]. It can be hypothesised that these cells are distributed throughout the body and ameliorate the systemic disease state, and in that way also improve symptoms such as ED. Supporting this hypothesis is a human trial using umbilical cord SCs for diabetes-related ED in seven patients. After an intracavernous transplant with these cells, blood glucose levels decreased, anti-diabetic medication dosages were reduced, and glycosylated haemoglobin levels improved for up to 4 months [50].

Second, there was engraftment and differentiation of injected SCs in the CC in some studies, although the methods for detecting cells vary between studies in terms of reliability and sensitivity to erroneous interpretation [49]. Furthermore, the extent to which this incorporation of cells contributes to the cure of ED remains controversial.

Ageing

A study by Bivalacqua et al. [26], involving intracavernous injections with BMSCs alone or with BMSCs

Table 1 An overview of preclinical SC studies targeting ED (adapted from [11]). The erectile function was improved in all studies.

Ref.	Pathophysiology	Type of SC	Time of evaluation	Tissue/molecular effects
[24]	CNI (rat)	Neuronal ESC	3 months	Improved neurofilament staining in dorsal and cavernous nerves. No evidence of incorporation of SCs
[25]	CNI (crush, rat)	MDSC	2 + 4 weeks	Increased cavernous level of axonal marker. Persistent LacZ expression (used as cell marker)
[26]	Ageing (rat)	BMSC or BMSC modified with eNOS	7 + 21 days	Cells expressing LacZ found in erectile tissue up to 21 days. Increased eNOS expression and activity, increased cGMP levels
[27]	Ageing (rat)	MDSC	2 + 4 weeks	Co-location of DAPI, α-smooth muscle actin and smoothelin Increased α-smooth muscle actin
[28]	CN resection (rat)	Bone marrow mononuclear fraction	3 + 5 weeks	Improved nNOS and eNOS levels, decreased apoptosis
[29]	Ageing (rat)	BMSC	3, 4 weeks, 3 + 4 months	Increased cGMP in CC, markedly dilated sinusoidal spaces in the CC
[30]	DM type II (rat)	ADSC	3 weeks	Increased nNOS levels in dorsal penile nerve endothelial cells in CC. No significant SC incorporation
[31]	Hyperlipidaemia (rat)	ADSC	4 weeks	Increased nNOS levels in dorsal penile nerve and endothelial cells in CC. No significant SC incorporation
[32]	CNI (crush, rat)	BMSC selected for p75 neurotrophin	4 weeks	Rare long-term engraftment of GFP-positive cells, showing mesenchymal morphology (no receptor expression or differentiation)
[21]	CNI (crush, rat)	ADSC or ADSC-derived lysate	4 weeks	Preservation of nNOS and smooth muscle content in the penis Prevention of cavernous fibrosis. No significant cell incorporation
[33]	Diabetes type I (rat)	BMSC	4 weeks	Increased smooth muscle and endothelial markers. Few CM-DiI (cell marker)-positive cells at 4 weeks co-located with smooth muscle and endothelial markers
[34]	CNI (crush, rat)	ADSC	1,3,7,28 days	Increased smooth muscle: collagen ratio in the erectile tissue + time-dependent increase in nNOS expression in dorsal nerve after intracavernous injection. Injected cells recruited to the MPG in injured rats, not in sham, soon after injury, but not permanently engrafted
[35]	CNI (crush, rat)	MDSC	4 weeks	Increased cGMP levels in penile tissue
[36]	CNI (crush, rat)	ADSC	2 or 7 days	Both autologous and allogeneic ADSCs exit the CC within days of injection and CNI; migrates preferentially towards bone marrow
[37]	Diabetes type I (rat)	BMSC	4 weeks	Increased smooth muscle and endothelial markers. Enhanced penile VEGF expression
[18]	CNI (crush, rat)	SVF	3 months	Improved nNOS and neurofilament staining in the dorsal penile nerve. Improved smooth muscle/collagen ratio in erectile tissue
[38]	Pelvic irradiation	ADSC	6 weeks	Improved nNOS expression in dorsal penile nerve and MPG, improved smooth muscle content, EdU (cell marker)-positive cells migrated into the MPG
[39]	CNI (crush, rat)	BMSC	4 weeks	Improved nNOS and eNOS levels
[22]	Diabetes type I (rat)	BMSC or BMSC-conditioned culture medium	4 weeks	In-vitro: secretion of neurotrophic molecules by BMSC. *Invivo*: improved nNOS and neurofilament staining in the dorsal penile nerve. Time-dependent decrease in number of BMSCs in CC after injection
[40]	CNI (crush, rat)	ADSC embedded in a BDNF membrane	4 weeks	Increased smooth muscle/collagen ratio, nNOS content, phospho-eNOS protein expression, and cGMP level
[41]	Diabetes type I (rat)	ADSC	4 weeks	This result absent after genetic knock-down of andromedullin Increased VE-cadherin and eNOS.
[23]	Diabetes type [1] SVF	2 weeks	This result absent after adding a VEGF blocker. Increased eNOS	(mouse) phosphorylation, and cGMP expression. Increased cavernous VEGF-A expression
[42]	CNI (crush, rat)	ADSC	3 months	Increased nNOS levels
[43]	CNI (crush, rat)	ADSC in NGF-hydrogel	4 weeks	Increased smooth muscle content, increased eNOS levels
[44]	CNI (crush, rat)	BMSC	4 weeks	Improved smooth muscle content, improved nNOS expression
[45]	CNI (crush, rat)	ADSC	4 weeks	Improved smooth muscle content

BDNF, bone-derived neurotrophic factor; VEGF, vascular endothelial growth factor.

modified by endothelial NOS (eNOS) in rats with ageing-associated ED, showed an improvement in erectile function. Based on the immunohistochemistry results showing smooth-muscle markers and endothelial markers co-locating with the SC label, the authors concluded that the mechanism of action involved the incorporation and differentiation of the injected SCs into host tissue cells. These findings were confirmed by Abdel-Aziz et al. [29], who traced GFP-labelled BMSCs back to the CC at 3–4 months after injection. However, this group did not investigate the differentiation of BMSCs into host cell types such as endothelium. Nolazco et al. [27] injected MDSCs into the penis of aged rats, after which there was activation of α-smooth muscle actin promoter, suggesting the conversion of these cells into smooth muscle-like cells, or at least an activation of the motility and contractility properties of these injected cells. These authors confirmed this hypothesis with immunofluorescence imaging, reporting the complete co-location of smooth muscle actin and the nuclear stain with which the injected cells were labelled (DAPI), leading them to conclude that SCs could replace cavernous smooth muscle cells that are lost or functionally damaged in the penis during the ageing process, and by doing so, restore the normal compliance of the tissue. However, it is very unlikely that injected SCs would be able to completely replace the smooth muscle compartment (there was a total overlap in DAPI and smooth muscle staining). This observation might be a result of using DAPI as a tracking label, as it does not penetrate the intact membrane of living cells well [49]. Furthermore, DAPI binds DNA non-covalently and thus can leak from the labelled cells after transplantation and be adsorbed by host cells, resulting in a false-positive detection. Nonetheless, there was a functional improvement, which might be explained by other processes, such as a paracrine induction of regeneration, rather than incorporation and differentiation [20].

Diabetes and metabolic syndrome

Both BMSCs and ADSCs have been extensively investigated in diabetic animals. Sun et al. [22] and Qiu et al. [33] showed that injection with uncommitted BMSCs into the CC results in increased erectile function on stimulating the cavernous nerve, compared with untreated diabetic controls. The authors claimed that this effect was the result of an increased content of endothelium and smooth muscle in the CC. They also reported elevated levels of the neuronal markers for nNOS and neurofilament in dorsal penile nerves. Similar to how Albersen et al. [21] had approached paracrine mechanisms in the CNI rat model, this group was able to partly replicate the beneficial effects of SC injection by an injection with BMSC-conditioned medium, indicating that paracrine interactions of cells with the host tissue might also have a role in the diabetic model [22]. These authors attributed the effects to a cocktail of neurotrophins, which were present at high levels in the conditioned medium. The same authors also evaluated the number of SCs that remained in the CC, and concluded that SCs disappeared from the penis soon after (within days) injection. At 4 weeks after injection, there were almost no labelled cells in the CC of these rats, supporting their statement on possible paracrine mechanisms of action. Also Garcia et al. [30] and Huang et al. [31] reported improved erectile function in the absence of significant cell incorporation in animal models of type 2 diabetes and hyperlipidaemia, respectively, after an intracorporeal injection with ADSCs. Thus, whereas in CNI the mechanisms of action of SC therapy for ED are becoming clear, there is still debate on the role that SCs might have in the cure of ED in diseases with no acute cause of onset. In ageing, some authors reported cell incorporation, while in diabetes and metabolic syndrome, convincing evidence for cell engraftment remains scarce.

PD

Castiglione et al. [51] were the first to report the potential benefit of ADSCs in PD. They injected xenogeneic (human) ADSCs into the tunica albuginea of rats with experimentally induced PD, during the acute phase of the disease. Local injection into the site of inflammation resulted in the prevention of elastosis and fibrosis of the tunica, and interestingly, rescued the erectile function in these rats, as shown by a complete restoration of the intracavernous pressure increase during electrostimulation of the cavernous nerve at 5 weeks after injection. After 5 weeks, only a few labelled ADSCs were found in the penises of the treated rats. While this study provided a ‘proof of principle’ for the efficacy of SCs in treating PD, most patients present to their healthcare provider with later stages of PD, and thus these results cannot be directly translated into a clinical application [52]. However, Ferretti et al. [53] targeted the disease in the chronic phase and injected autologous ADSCs into rats with established Peyronie’s plaques and penile curvature, in a novel model for PD established by their laboratory. These authors showed that injection with SCs into the plaque after mechanical penile remodelling resulted in decreased penile curvature at 2 months after the injection. It was proposed that neo-angiogenesis is a potential mechanism that could explain this phenomenon. These two studies hint at a novel application of SC therapy within the field of ED, and although only providing a ‘proof of concept’ to date, might provide future hope for men dealing with this difficult-to-treat disease. However, more work is needed both in the translational plane and in elucidating how these effects are established. Most preclinical studies in other diseases linked to inflammation and fibrosis suggest that there is immunomodulation, thereby limiting the host response to injury and preventing the onset of fibrosis. Another proposed mechanism is the induction of phenotypical changes in resident fibroblasts, shown by reduced collagen and increased hyaluronic acid production in fibroblasts co-cultured with MSCs [51]. Furthermore, the direct interaction of MSCs with the extracellular matrix has been proposed, based on their ability to secrete matrix-modulating enzymes [54].

Conclusions and future perspectives

The rapidly expanding and highly promising body of preclinical work in SC medicine providing a potential cure for ED, rather than merely symptom relief, is indicative of the interest that has arisen for regenerative options in sexual medicine over the past decade. Company interest and the emergence of two large clinical trials aimed at testing SC therapy in men with ED further substantiate the promise of these novel treatment strategies. The results of these two trials, one testing ADSCs and one testing BMSCs, are eagerly awaited and expected to appear within the next 2–3 years, but the convincing results acquired in the animal studies worldwide provide great hope that we can cure patients with ED, or at least render PDE5i-nonresponders responsive to oral medication, within the next decade.

Conflict of interest

None.

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None.

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