New developments in erectile dysfunction treatments: A role for regenerative medicine

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Abstract

Erectile dysfunction is a highly prevalent issue related to the sexual wellness of millions of men worldwide. While conventional therapies have been successful for many, there remains a significant subset of individuals who do not respond adequately or experience undesirable side effects. This article reviews the emerging field of regenerative medicine as a potential breakthrough in the management of ED. Regenerative therapies, especially platelet-rich plasma (PRP) therapy along with stem cell therapy, provide novel approaches to tackling the fundamental causes of ED. By harnessing the body's natural healing mechanisms, these treatments hold promise for restoring erectile function and improving patients' quality of life. This review explores the mechanisms of action, benefits, and current research findings related to regenerative therapies for ED, emphasizing their potential to revolutionize the treatment landscape for this prevalent condition. As ongoing research continues to shed light on their safety and efficacy, regenerative therapies may pave the way for a brighter future in the management of erectile dysfunction.

Keywords: Erectile dysfunction; Regenerative medicine; Platelet-rich plasma; Stem cell therapy; Quality of life

1 Introduction

Erectile dysfunction (ED) is a prevalent condition that affects a significant number of the male population, especially as men age and the incidence of contributing factors such as chronic diseases and lifestyle-related issues gets higher [1]. This condition is defined as being unable (occasional or habitual) to achieve or preserve a sufficiently strong erection for excellent sexual intercourse [2]. Effective management and treatment options are essential to address the impact of ED on individuals' quality of life and overall well-being [3].

According to many research studies, the prevalence of ED ranges between 3 and 76.5% all over the world [4]. 30 million men throughout Indonesia have been estimated to be suffering from ED [5] and one in every three men is affected by ED [6]. All studies show that the risk of developing ED increases with age. In total, 52% of men had ED, with 40% of men affected at age 40 and nearly 70% affected at age 70, according to the Massachusetts Male Aging Study. Additionally, the prevalence of complete ED increased, going from 5% at age 40 to 15% at age 70 [7]. In a comparable way, a most recent case control study conducted in Indonesia revealed that between the ages of 40 and 49, 2% to 9% of men have ED. The percentage increases to 20% to 40% between the ages of 60 and 69. With a range of 50% to 100%, the oldest age group is those over 70 which has the highest rate [8].

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ED can be caused by aging, diabetes, spinal injuries/nerve disorders, psychogenic issues and drug side effects, as illustrated in Figure 1 [9,10,11,12, 13]. Further factors that contribute to the progression of ED are drug abuse and stress. A high risk of ED and consequently low libido is also posed by the development of diabetes, cardiovascular diseases, and hypertension.

Both conventional and modern pharmacologic approaches have been investigated to address therapeutic alternatives for ED. Hormone regulation and the balance between physical and emotional response are the main concerns of traditional treatments, which also include exercise, acupuncture, and the use of herbal products [14]. Since changing one’s lifestyle is often the first step towards overcoming ED, the scientific community has been exploring alternative treatment options, such as medications or other surgical or non-surgical interventions, in order to accelerate recovery [15]. Even though oral active phosphodiesterase type 5 (PDe5) inhibitors were developed in 1992 and significantly improved ED treatment [16], many ED cases still do not respond to these drugs, which means that new therapeutic approaches other than PDe5 inhibition-mediated activation of the cGMP-cavorous nitric oxide (NO)–guanylate cyclase (GC) pathway are needed to treat these forms of ED. If oral medications such as papaverine, phentolamine, and alprostadil don’t work, intravenous injections of these substances have been demonstrated to be viable alternatives. Nevertheless, these treatments are not a full cure for ED due to their temporary nature. Only in extreme cases usually for elderly patients with fewer sex encounters annually are penile prostheses and vacuum constriction employed [17]. The drawbacks of this ED surgical procedure include its expensiveness, invasiveness, and irreversible effects.

Therefore, it is now possible for scientists to create treatments using cells for the ongoing management of ED with the help of recent developments in regenerative medicine. The potential application of shockwave therapy, platelet-rich plasma (PRP), and stem cells as regenerative therapies for various ailments has been the subject of numerous research investigations [18]. The curative properties of stem cell therapy, platelet-rich plasma, and the combination of them with beneficial agents for the regeneration of damaged cavernous nerves in penile corporeal tissues are explained below, considering multiple basic research studies and clinical trials on the subject.

2 The Physiology of Erection and the Pathophysiology of Erectile Dysfunction

A penile erection is a sophisticated physiological process resulting from the synchronized actions of blood vessels, nerves, and hormones [19]. Major advancements in our understanding of erection physiology have occurred over the past few decades, spanning from the neural pathways of the sympathetic and parasympathetic nervous systems to the biochemical effectors like cyclic adenosine monophosphate (cAMP), nicotinamide (NO), and Ras homologue a (RhoA) [20].

The mechanism of erection is illustrated in Figure 2. When a man experiences sexual arousal, his nerves set off a sequence of events that result in the release of nitric oxide (NO). A compound known as cyclic guanosine monophosphate, or cGMP for short, is more frequently formed as a result of a sequence of biochemical reactions. The smooth muscles in the penis’ erectile tissues relax as a result of this cGMP, greatly increasing blood flow to the corpora cavernosa. The process known as the corporeal veno-occlusive mechanism occurs when cavernosal spaces fill quickly, compressing venules and decreasing venous outflow. A full erection and progressive penile rigidity are the results of a rapid increase in intracavernosal pressure caused by a combination of decreased outflow and increased inflow. The vascular endothelium and nerves respond to sexual stimulation by releasing nitric oxide, which activates cytoplasmic guanylate cyclase and transforms GTP into cGMP. High cGMP concentrations result in the smooth muscle in the helicine and cavernosal arteries relaxing and the lacunar spaces expanding. Intracavernosal pressure rises and cavernosal
venous outflow decreases as a result of the expanding lacunar spaces compressing the subtunical venous plexus against the tunica albuginea, causing penile rigidity [21].

![Figure 2 The mechanism of erection [91].](image)

Smooth muscle contraction occurs around sinusoids and arterioles when sympathetic tonic discharge is resumed following ejaculation or in the absence of erotic stimuli. The venous channels reopen, the arterial flow returns to flaccid levels, and a large amount of blood is expelled from the sinusoidal spaces. Cyclic GMP is dissolved into GMP by phosphodiesterase type 5 during the transition to the flaccid state. It leads to a reduction in cGMP levels, which sets off a reaction in the erectile tissues' smooth muscles. The reduction of artery inflow and the collapse of lacunar spaces are caused by trabecular muscle contraction and penile artery constriction, respectively. When the trabecular muscle contracts, the cavernous bodies' drainage venules decompress, letting blood escape the lacunar areas and causing the penis to become flaccid. An equilibrium between blood flow into and out of the erectile bodies is found in the flaccid penis [22]. As Figure 3 illustrates, the mechanism causing flaccidity or detumescence is highly complex.

![Figure 3 Detumescence and reverting to a Flaccid state [91].](image)

The term "erection dysfunction" (ED) is used to describe the inability to frequently sustain a penile erection strong enough to enable satisfying libido [23]. Erectile dysfunction may result from any illness that impacts the vascular or neural pathways that are necessary for an erection. A deficiency in nerve signaling to the corpora cavernosa is the cause of neurogenic erectile dysfunction [24]. Diabetes, traumatic brain injury, multiple sclerosis (MS), spinal cord injuries, Parkinson's disease, and radical pelvic surgery (including radical prostatectomy) can all lead to secondary deficits. Although they don't directly affect the penis, lesions to the upper motor neurone (above spinal nerve T10) can stop the central nervous system (CNS) from controlling the erection. On the other hand, because of the reduced innervation,
sacral lesions (S2–S4 are usually the cause of reflexogenic erections) result in functional and structural changes [10,25,26,27,28,29,30].

Such injuries alter how the smooth muscle functions by reducing the amount of NO load that is available to it. The primary structural changes include the death of blood vessel endothelial cells and smooth muscle cells, as well as an increase in fibrogenesis cytokines that cause the smooth muscle to become collagenized. Veno-occlusive dysfunction, also known as venous leak, is the outcome of these alterations. Erectile dysfunction is caused by vascular disease and endothelial dysfunction and is brought on by reduced blood flow, arterial insufficiency, or arterial stenosis. The most frequent cause of organic erectile dysfunction is by far vasculogenic erectile dysfunction [31]. Many men believe that erectile dysfunction simply occurs as they age. Even though aging is a known risk factor for erectile dysfunction (ED), only roughly one-third of men over 70 say they do not experience ED. Therefore, doctors shouldn’t automatically assume that aging is the cause of erectile dysfunction.

Erectile dysfunction is associated with the following risk factors: obesity, sedentary lifestyle, tobacco use, and long-term alcohol consumption. These elements may cause hormonal shifts that could result in a sharp decline in testosterone levels and a decline in endothelial function [32, 33, 34]. Systemic endothelial function may be impacted by circulating inflammatory markers as well as chronic inflammation, according to a number of studies. Thus, it’s possible that cardiovascular diseases (CVD) and ED are related to chronic inflammation [35]. Inflammatory marker expression is elevated in relation to the onset and severity of ED. Several markers and mediators, including TNF-α, intercellular adhesion molecule 1, interleukin (IL)-6, IL-10, IL-1β, and C-reactive protein (CRP), were expressed at higher levels in ED patients. Furthermore, ED patients express higher levels of endothelial and prothrombotic factors such as fibrinogen, tissue plasminogen activator inhibitor 1 (PAI-1), von Willebrand factor (vWF), and tPA [36, 37].

Androgens have a significant impact on vascular and penile health because they have cellular targets in smooth muscle and endothelial cells [38]. It increases the survival of endothelial cells, prevent vascular smooth muscle cell proliferation and intimal migration, and lower the expression of pro-inflammatory markers on endothelium [39]. Low levels of testosterone are linked to pathologic structural remodeling and endothelial and smooth muscle cell apoptosis in the penis [40]. In addition, erectile dysfunction may result from hypo- or hyperthyroidism. Additionally, there is a higher chance of developing erectile dysfunction in those with Metabolic Syndrome (MetS) such as depression, dyslipidemia, hypertension, and diabetes mellitus [41]. Many of the risk factors for MetS, especially hypertension, diabetes mellitus, smoking, and high cholesterol, are also linked to ED and coronary artery disease [23]. ED may be brought on by MetS in a few different ways. Obesity is commonly associated with all components of MetS. Hyperinsulinemia and hyperglycemia are linked to insulin resistance, which is facilitated by abdominal obesity [42]. Atypical lipid profiles, hypertension, and vascular inflammation are additional potential outcomes, all of which exacerbate the progression of atherosclerosis.

ED may also be an indication of cardiovascular disease, and there is a strong likelihood that MetS will predispose an individual to ED given these shared pathways [43]. The precise mechanisms underlying the effects of many drugs and medications, including benzodiazepines, β-blockers, clonidine, digoxin, ketoconazole, methyldopa, monoamine oxidase inhibitors, phenobarbital, phenytoin, selective serotonin reuptake inhibitors, spironolactone, thiazide diuretics, and tricyclic antidepressants, can lead to erectile dysfunction [44].

3 Current Therapeutic Approaches for Erectile Dysfunction

It is still difficult to impart erectile functions during a full recovery from ED therapy, even though doing so is vital to regain social and personal confidence. Oral medications along with lifestyle modification, vacuum-assisted equipment, LI-ESWT, intraurethral suppositories, and prosthesis are currently the most popular treatment methods as shown in Figure 4.

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3.1 Using Oral Medication and Lifestyle Changes to Treat ED

The first step toward improving ED remains to make lifestyle modifications. It seems to be helpful to cut back on alcohol and tobacco use in addition to exercising moderately and choosing a healthy diet [45]. Treatment of reduced underlying diseases such as hypertension, diabetes, cardiovascular disease, and mental health conditions may also reduce the risk of ED [46]. Additionally, by transforming the focus from the patient’s perceived disability to the partner’s sexual pleasure, eroticization of ED aids improves both compliance and effectiveness [47]. Thus, lifestyle-related therapies assist in restoring and improving sexual performance in addition to lowering the risk of ED.

Furthermore, it has been demonstrated that treating ED with oral medication from the new class of drugs known as type-5 phosphodiesterase (PDE5) inhibitors is effective. These medications consist of avanafil, tadalafil, vardenafil, and sildenafil. The erection cycle is completed by the production of cGMP and its breakdown by the enzyme phosphodiesterase type 5 (PDE5) [48]. The erection metabolic pathway is the target of several frequently prescribed oral medications, which raise cGMP concentration and enhance erectile function. However, for these drugs to be effective, the patient needs to have a nerve system that is capable of responding to stimuli. Giving CYP3A inhibitors and alpha receptor blocking medications, like azole antifungals, antiretroviral protease inhibitors, and macrolide antibiotics, requires caution [49]. These medications should not be used to treat chest pain. Doctors typically prefer avanafil over other second-generation PDE5I medications because it is both safer and more effective than its first-generation. PDE5I frequently caused migraines, nausea and vomiting, fainting, sweating, nasal congestion, allergies and back pain.

3.2 Using Vacuum Erection Devices to Treat ED

Treating ED nonsurgical is possible with vacuum erection devices. Actually, it’s not a novel concept to use a device consisting of a constriction ring, vacuum pump, and closed-end cylinder to obtain a strong erection for sexual activity. Utilizing vacuum erection devices in the aforementioned circumstances is supported by research done on human penile tissues (cavernous and vascular) and animal models of ED (rats) to identify the primary effects of the device on physiological markers of erectile function. The mechanism by which the vacuum chamber causes an erection is thought to involve lengthening the corporeal sinusoids, boosting blood flow, and inducing negative pressure within the penis. According to the findings, using vacuum devices improves tissue oxygenation, inhibits apoptosis and fibrosis, preserves or aids in the recovery of tissues essential to preserving erectile function, and increases penile blood flow [50,51].

3.3 Using Shockwave Therapy to Treat ED

Since shockwaves (SWs) can move energy and disperse throughout tissue, they are thought to be a useful therapeutic tool. It is anticipated that the targeted tissues will expand over their tensile elements due to compression brought on by the acoustic pressure shock, even though the exact process that drives the impact of SWs on corpora cavernosa is still unknown. Low-intensity extracorporeal shockwave therapy (LI-ESWT) has been suggested as a promising non-invasive treatment option to improve vasculogenic ED because it encourages revascularization and restores blood vessel functions [52, 53].

The therapeutic process that LI-ESWT initiates without triggering damage may enhance injured penile tissue by improving hemodynamic and neovascularization [54]. Additionally, LI-ESWT improves the response of PDE5I non-respondent patients to PDE5I drugs, which results in better erectile function [55]. In order to explore regenerative therapy for persistent wounds, cardiac disorders, and peripheral neuropathy, a great deal of research has been done on the angiogenic stimulation properties of LI-ESWT [56]. In addition to other growth factors, the expression of VEGF and other angiogenic factors may also play a role in this [57].
3.4 Using Intracavernosal Drugs and Intraurethral Suppositories to Treat ED

Medication including prostaglandin E1 (PGE1) muscle relaxant and erectile inducer alone or in combination with papaverine, phentolamine, and vasoactive intestinal peptide (VIP) can be administered using first-line ED therapies like penile corpora. For patients who do not respond to PDE5I treatment, this therapy is thought to be an option [58]. PGE1, papaverine, and phentolamine are combined in TriMix treatment, which seems to be easier to tolerate than intracavernosal injection, which has a higher rate of treatment discontinuation due to pain [59]. Moreover, it has been demonstrated that the restoration of penile blood flow and erectile functions is more successful when alprostadil, an analogue of PGE1, is administered intracavernosally as opposed to intraurethral mode [60]. However, there are some side effects, like a higher risk of urethral infections and penile and urethral pain.

4 Potential Revolution in the Use of Regenerative Medicine in Managing Erectile Dysfunction.

4.1 Platelet-Rich Plasma (PRP) in ED Treatment

Platelet-rich plasma (PRP) derived from blood is suggested as a potential regenerative material for the management of a variety of conditions, such as musculoskeletal and wound disorders [61]. Blood is centrifuged to extract platelet-rich plasma (PRP), which must then be activated in order for the therapeutic biomaterials it contains to be released and have a therapeutic regenerative effect. However, PRP application needs to be customized to the particular type and need of damaged tissues that must be addressed and repaired to effectively guide the regeneration of injured tissues like penile tissue, as shown in Figure 5 [62].

![Figure 5 ED treatment using Platelet-Rich Plasma (PRP) [91].](image)

Platelet-derived biomaterials for the treatment of ED can be made using platelet-rich plasma (PRP). Because blood-derived PRP has a high concentration of growth factors like VEGF, IGF-1, FGF, PDGF, and TGF-β, it can increase the index of erectile function (IIEF-5). It is also necessary for the synthesis of collagen, extracellular matrix, axonal myelination, nerve regeneration, blood flow regulation, angiogenesis, and neuroprotection. Transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) are a few of the growth factors. According to a clinical study, autologous PRP can enhance erectile function by releasing its active biomaterials, which include FGF, VEGF, VEGF-D, PDGF-AA, and PDGF-BB. These biomaterials can have their concentration raised by freezing and thawing. This might be explained by the fact that endogenous NO increased the synthesis of VEGF, which promotes endothelial regeneration through angiogenesis [64].

Despite the fact that the peripheral nervous system can make injured nerves function again, the recovery process is not optimal or complete. Consequently, PRP with a high fibrin matrix can be used as a scaffold or filler to bridge nerve pathways because it releases neurotrophic growth factors that control inflammation, apoptosis, fibrosis, angiogenesis, and muscle atrophy. This encourages the damaged peripheral nerve gap to regenerate quickly [65]. Platelet-derived
prosthetic platelet synthesis (PDP) stability is also linked to this therapeutic rehabilitation process [66]. Platelet-rich fibrin (PRF), which is high in platelets, leukocytes, fibrinogen, fibronectin, and other growth factors, can be created from PRP to alleviate stresses about early washout [67]. This method limits the possibility of decreased blood flow and the quick extraction of biomaterials derived from platelets from the cavernous nerve.

There is evidence in the literature that smooth muscle loss following CN injury is associated with RhoA/ROCK1 signaling and corporal fibrosis [68]. PRP has been shown to preserve myelinated axons, lower the apoptotic index, and increase intracranial pressure in crushed bilateral cavernous nerves [69]. These results imply that RhoA/ROCK1 and S1P signaling may be inhibited and nerve fibrosis may be suppressed by platelet-derived biomaterials. Because TGF-β1 and its Smad and non-Smad pathways are hyperactivated in diabetics, there may be an increase in the amount of collagen in the corpus cavernosum. This can lead to cavernosal fibrosis, which can lead to structural alterations, and severe dysfunction of the corporal veno-occlusive system [70]. Platelet-derived biomaterials, like TGF-β2, IGF-I, and VEGF, may mitigate these pathological features by promoting neural regeneration and nNOS upregulation. It has been shown that PDGF-β is a mitogen for Schwann cells with trophic activity on neurons because neuronal cells express PDGF receptors [71]. Higher levels of PDGF-β are found in peripheral neurons with damaged peripheral nerves, suggesting the importance of this protein for peripheral nerve regeneration [72].

4.2 Stem Cell Therapy in ED Treatment
Stem cells are an exciting prospect for regenerative medicine because of their capacity to proliferate and differentiate into many specific cells to repair damaged tissues, as demonstrated in Figure 6. Stem cell therapy involves three steps: isolating, subculturing, and dividing stem cells. After sorting, post-treatment assessments are carried out and the cells are administered to the damaged cavernous nerve [73].

![Figure 6 ED treatment using Stem Cell based Therapy](91).

Induced pluripotent stem cells (iPSCs), bone marrow-derived stem cells (BMSCs), urine-derived stem cells (UDSCs), neural embryonic stem cells (NESC), and adipose-derived stem cells (ADSCs) are the most studied stem cell types for ED. Stem cells control signaling pathways such as SDF/CXCR4 during repair and regeneration in order to mobilize, multiply, and differentiate into nerve and endothelial cells. Furthermore, these cells release growth factors like VEGF and BDNF to help with angiogenesis and nerve fiber regeneration, respectively. The corpus cavernosum has less fibrosis and more smooth muscle cells when nitric oxide (NO) synthase is upregulated. Stem cells' immunomodulatory and anti-apoptotic qualities eventually prevent further injury to the penile muscles or nerves. Stem cells are an effective regenerative treatment option for ED because they increase meaning arterial pressure (MAP) when combined with other therapies [74].
During repair and regeneration, stem cells are crucial for the restoration of the major pelvic ganglion (MPG) because they secrete growth, neurotropic factors, cytokines, and exosomes. When it comes to delivering regenerative therapies for a range of disorders with negligible side effects, autologous MSCs are the most effective [75]. These MSCs pose no ethical or legal issues because they have a minimal chance of tissue rejection [76]. Additionally, developing cell lines is not necessary for clinical applications utilizing autologous stem cells, making their use economical [77]. Since it can be difficult to obtain enough autologous MSCs from patients with diabetes, autoimmune diseases, elderly patients, and underweight individuals [78, 79], it is not recommended for people with genetic defects or mutations [79]. Allogenic stem cells are especially more beneficial for widespread use because they are uniform, easily accessible, and have already undergone extensive characterization. They also don’t require patient biopsy techniques. However, one significant barrier to clinical use is the stability of allogenic stem cells. We go over the research in detail that examine the ways in which different kinds of stem cells impact conditions brought on by cavernous nerve injury (CNI):

4.2.1 Adipose-Derived Stem Cells (ADSCs) on ED

ADSCs stimulate the corpus cavernosum’s neutralization and vascularization in DMED rats, improving erectile function. Moreover, these compounds have the capacity to protect smooth muscle cells from damage and to suppress fibrosis and inflammation. The efficacy and safety of their use in clinical research, however, are still up for debate [80].

The pre-clinical efficacy of ADSCs in treating ED has also been the subject of similar research. On cavernous nerve regeneration after crush injury in a rat model, it is demonstrated that lenti-rBDNF and ADSCs have a quantifiable neurotrophic effect. Both functional and morphological studies supported the recovery of erectile function. Four weeks later, the erectile response was better, according to the ICP changes and ICP/MAP ratio [81].

4.2.2 Bone Marrow-Derived Mesenchymal Stem Cells on ED

MSCs obtained from bone marrow constitute a noteworthy extra resource for the progress of regenerative medicine. An excess release of β-FGF, β-NGF, VEGF, and IGF-1 may account for the increased ICP/MAP in Sprague-Dawley rats following an intracavernous injection of BMSCs expressing the receptor for p75 nerve growth factor (p75dMSCs) [82]. The amount of muscle, endothelial cells, and neurofilament in cavernous tissues was found to be increased by injecting BMSCs intraperitoneally (IP) and intravenously (IC) in a significant study [83]. The therapeutic efficacy of MSCs could potentially be enhanced through genetic modification via adenovirus-mediated transfecition. This would lead to a significant improvement in erectile function through elevated levels of cGMP and endothelial nitric oxide synthase (eNOS) [84].

4.2.3 Induced Pluripotent Stem Cells (iPSCs) on ED

Since embryonic stem cells (ESCs) present ethical issues, induced pluripotent stem cells, or iPSCs, are being investigated as a possible source of therapeutic use. Sox2, Klf4, c-Myc, and Oct3/4 are the four primary genes that are expressed in somatic cells to generate induced pluripotent stem cells (iPSCs) [85]. Ectoderm, mesoderm, and endoderm are the three germ cells that can be differentiated from iPSCs, similar to ESCs, in contrast to MSCs, which can only differentiate into a limited number of cell lines [86]. Increases in ICP/MAP, eNOS, and S100β content in MPG can be achieved by employing iPSCs to repair cavernous nerve integrity [87].

The paracrine effect and anti-apoptotic activity of iPSCs’ secretome may be responsible for these regenerative effects. Research has also looked at stem cells from different sources, including the skin, skeletal muscles, penile tissues, and umbilical cord, in order to develop regenerative therapies for ED [88]. To aid in the regeneration of the cavernosal nerve following crush injury, neural embryonic stem cells (NES) have also been injected into the MPG and corpus cavernosal tissues [89]. These cells have the capacity to greatly elevate ICP and stimulate nerve fibers that contain NOS and have a higher neurofilament content. The release of substrates from NES for growth factor release, control over demyelination, and axonal extension is the suggested mechanism underlying this therapy. Despite this, because of their pluripotency, iPSCs are a good option for regenerative therapies; however, their clinical use is limited by the risks of genetic alteration, tumor formation, and epigenetic memory [90].

5 Conclusion

As we learn more about the disease’s molecular and cellular pathogenesis, a number of new treatment targets for ED are being developed. Although the preclinical outcomes of using PRP and different types of stem cells are highly encouraging, clinical trials are still necessary to validate these potential treatments. Our long-term goal is to work with biopharmaceutical companies to develop regenerative therapy, which mainly targets therapeutic angiogenesis and
neural regeneration, as a treatment modality that can eventually mitigate the side effects of ED medications currently available on the market.

**Compliance with ethical standards**

**Disclosure of conflict of interest**

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