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REVIEW ARTICLE

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An update on the current status and future prospects of erectile dysfunction following radical prostatectomy

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Abstract

Background: Radical prostatectomy (RP) and radiation treatment are standard options for localized prostate cancer. Even though nerve-sparing techniques have been increasingly utilized in RP, erectile dysfunction (ED) due to neuropraxia remains a frequent complication. Erectile function recovery rates after RP remain unsatisfactory, and many men still suffer despite the availability of various therapies.

Objective: This systematic review aims to summarize the current treatments for post-RP-ED, assess the underlying pathological mechanisms, and emphasize promising therapeutic strategies based on the evidence from basic research.

Method: Evaluation and review of articles on the relevant topic published between 2010 and 2021, which are indexed and listed in the PubMed database.

Results: Phosphodiesterase type 5 inhibitors, intracavernosal and intraurethral injections, vacuum erection devices, pelvic muscle training, and surgical procedures are utilized for penile rehabilitation. Clinical trials evaluating the efficacy of erectogenic drugs in this setting are conflicting and far from being conclusive. The use of androgen deprivation therapy in certain scenarios after RP further exacerbates the already problematic situation and emphasizes the need for effective treatment strategies.

Conclusion: This article is a detailed overview focusing on the pathophysiology and mechanism of the nerve injury developed during RP and a compilation of various strategies to induce cavernous nerve regeneration to improve erectile function (EF). These strategies include stem cell therapy, gene therapy, growth factors, low-intensity extracorporeal shockwave therapy, immunophilins, and various pharmacological approaches that have induced improvements in EF in experimental models of cavernous nerve injury. Many of the mentioned strategies can improve EF following RP if transformed into clinically applicable safe, and effective techniques with reproducible outcomes.

KEYWORDS

cavernous nerve injury, erectile dysfunction, phosphodiesterase type 5 inhibitors, radical prostatectomy, stem cell therapy

1 | INTRODUCTION

As well as being the second most diagnosed cancer (about 15% of all diagnosed tumors), prostate cancer (PCa) is also the second cause of cancer deaths in men.[1] PCa affected 1.1 million patients in 2012 and is predicted to affect 1.7 million in 2030.[2] North American and European countries have traditionally high PCa incidence rates. However, recently, the numbers have also been significantly increasing in Asia.[3]

The treatment of PCa impacts patients' quality of life and their functional status.[4] Furthermore, PCa patients frequently suffer from decreased sexual function (SF) as a long-term side effect after treatments, impacting their quality of life. To overcome long-term effects, there is a growing need for optimization in treatment selection and posttreatment rehabilitation.

Radical prostatectomy (RP) is one of the standard treatments in localized PCa; radiation treatment (either in the form of external beam RT or brachytherapy) and active surveillance (in selected cases) are other options.[5] Regardless of the advances in surgical techniques and increasingly-utilized robotic procedures, RP has a significant potential to cause cavernous nerve injury (CNI) and resultant pathologic changes in cavernous vasculature.[6]

Neurogenic erectile dysfunction (ED) is a consequence of CNI after RP leading to pathophysiological alterations in the corpus cavernosum (CC) and cavernosal nerve. Prevalence of ED following RP was documented to be between 14% and 90%.[7]

Nitric oxide (NO) is the primary mediator in penile erection, released from the nerves innervating CC and cavernosal endothelium.[8–10] This release of NO activates soluble guanylyl cyclase (sGC), which boosts cyclic guanosine monophosphate (cGMP) levels and induces penile erection.[11–13] Phosphodiesterase inhibition causes accumulation of cGMP and potentiates erection. Based on this mechanism of action, oral phosphodiesterase type 5 inhibitors (PDE5is) are currently considered the first-line ED treatment. However, the response rate to PDE5is is usually lower in post-RP-ED compared to the general ED population.[14]

After RP, achieving a healthy erectile function (EF) is a great struggle for many patients and a real challenge for urologists. Despite the developments in minimally invasive surgery and surgical techniques over time, the recovery of EF remains a long and costly process. Therefore, this systematic review aimed to summarize and update the current treatments for post-RP-ED and, more importantly, to evaluate the underlying pathological mechanisms and promising therapeutic strategies suggested by the evidence from basic research.

1.1 | ED as a frequent complication of RP

CNI during RP is the major cause of ED, which is observed frequently despite advanced surgical methods, particularly nerve-sparing techniques.[15–18] The widely adopted use of nerve-sparing surgical procedures and robot-assisted laparoscopic techniques in RP can not completely prevent post-RP-ED. It may become persistent in some patients.[19]

The main mechanism of postoperative ED is related to CN damage caused by surgery. The direct contact during surgical intervention, mechanical traction, and thermal disturbance resulting from electrocautery use may induce neuronal ischemia, apoptosis, and regional inflammatory reactions, which can cause damage to the CN.[20,21] This damage initiates a cascade of neuropathological events, called Wallerian degeneration, that results in the degeneration of the distal axon and, at the same time, causes a disrupted NO release.[22,23] Attempts are made to prevent the degeneration and fibrosis of the CC caused by the invasion of the surgery itself or the postoperative hypoxic state by oxygenating the penis from an early postoperative stage.[24] Recovery from ED requires rapid regeneration of the CN; otherwise, CNI could result in fibrosis of the CC.[25,26] Elevated reactive oxygen species, CC hypoxia, apoptosis, and the increase in profibrotic factors, such as transforming growth factor-beta1 (TGF-β1), are involved in changing the structure of the CC tissue leading to the decrease in smooth muscle content, damage to endothelium and fibrosis of CC[22,23,27–29] (Figure 1).

Similarly, several studies in a radiation-induced CNI model showed that oxidative stress has a significant role in the pathology of nerve injury.[30–32] Therefore, minimizing oxidative stress can be a feasible approach to CN recovery. Also, it was found that calpain, a calcium-dependent, non-lysosomal neutral cysteine endopeptidase, and its activation have a role in the pathogenesis of CNI related ED.[33] Calpain inhibition improved erectile responses and neuronal NOS (nNOS) expression with a decrease in TGF-β1 and collagen expression in penile tissue from CNI rats.[33] The inhibition of calpain could be a choice among the new approaches to prevent the development of ED after CNI.[33] In another study, S-nitrosylation of endothelial NOS[34] and sGC in penile tissue was investigated as another mechanism for disrupting the NO signaling pathway in CNI-induced ED.[35] Protection of EF by saving the function of the NO/cGMP signaling pathway can be provided by denitrosylation in CNI (Figure 1).[35]

Penile rehabilitation is defined as “the use of any drug or device at or after RP to maximize EF recovery.”[36] Although the efficacy of penile rehabilitation as a concept is not proven yet, various major approaches are already in use. Men with post-RP ED have diverse treatment choices like PDE5is, intracavernosal injections (ICI) of vasoactive agents, vacuum erection devices (VED), and others. The efficiency of penile rehabilitation using prostaglandin E1 injection into the CC was reported first in 1997 by Montorsi et al.[37] These options are only partially successful, which makes the research for more dependable interventions obligatory.

1.1.1 | Animal models of CNI

Rodent models of CNI have a significant role in developing the domain and improving the quality of life of the patients.[38] These models have lower costs compared to models with larger animals. Furthermore, the CN in the rat is a distinct entity that branches off the significant pelvic ganglion on the dorsolateral aspect of the

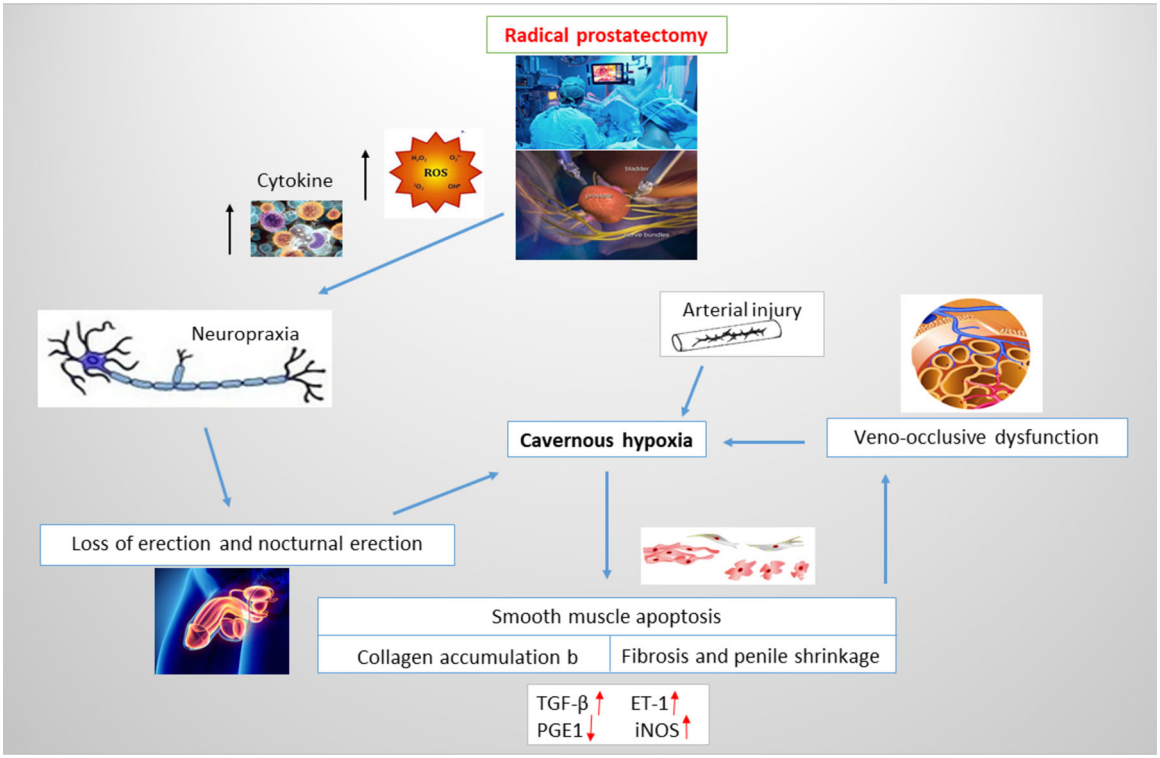

FIGURE 1 The pathophysiological mechanisms of ED after radical prostatectomy. ED, erectile dysfunction [Color figure can be viewed at wileyonlinelibrary.com]

prostate,[39,40] unlike the human CNs, which are part of a neurovascular cluster, which is hard to isolate or dissect, making it more exposed to injury during surgery. In the rat model, crush injury, transection, freeze injury, cautery, and excision have been used to simulate the damage that occurs in RP.[41] Therefore, mentioned models have been frequently used in developing new and efficient strategies for the treatment of post-RP-ED.

1.2 | Surgical techniques for managing postprostatectomy ED

1.2.1 | Penile prosthesis (PP)

PP implantation (PPI) is a last-resort invasive treatment for post-RP ED and ED in general. Although PPI is frequently applied after the failure of conservative methods of penile rehabilitation, it can also be utilized at the earliest time point, which is during RP, to prevent the need for another consecutive surgical intervention. This proactive approach may be helpful in patients with poor preoperative SF and advanced age, who are unlikely to benefit from standard penile rehabilitation and extensive diseases where nerve-sparing is not feasible.

1.2.1.1 | *Clinical studies*

Khoudary et al.[42] were the first to describe simultaneous RP and PP implantation in 1993.[42] Fifty patients with a PP were compared to 72 who underwent RP alone. PP provided an early and satisfactory sexual activity in 96% of men within 3 months.[42] A subsequent analysis from the same group revealed that this approach resulted in a greater overall QOL, a better EF, and more frequent sexual contact than the RP-only group.[43]

Likewise, Mondaini et al.[44] were the first to study simultaneous PPI during laparoscopic RP. They compared postoperative penile length and QoL (using presurgery 36-Item Short-Form Health Survey [SF-36]) with the preoperative values. After 2 years of follow-up, while the penile length was preserved, SF-36 scores improved significantly.[44] The authors concluded that the procedure improved the QoL of patients while maintaining penile length.[44]

Ceruti et al.[45] placed PP reservoirs simultaneously during robotic-assisted radical prostatectomy (RARP) in 5 patients, leaving the prosthesis implantation itself to be performed in a subsequent session. Prosthetic surgery was performed 1.5–2.5 months later. No significant loss in penile length was observed, and all patients resumed continence and satisfactory sexual activity within 4.5 months from RP.[45]

1.2.2 | Nerve grafting after RP

1.2.2.1 | *Preclinical studies*

The restoration of EF by the augmentation of the CNs with nerve grafts was reported in several rat studies.[46–48]

Persistent loss of EF is a result of CNI. This dysfunction usually can not be treated with conventional methods, making the

repairment of the injured nerves an approach with significant potential. As a result, many researchers have been focusing on this area.[49] Muneuchi et al.[50] investigated the effects of autologous sural nerve grafts to repair injured neurovascular bundles, and they observed positive results. However, it's a complex procedure to prepare a sural nerve graft, and the structure and function of the corresponding muscle may deteriorate.

Instead of using nerve grafts from other anatomical structures, Cheng et al.[47] examined the feasibility of autologous vein grafting in a rat model of bilateral cavernous nerve injury (BCNI). It is technically less demanding to harvest a vein graft, and the procedure does not disrupt the anatomical and functional integrity of other neural structures.[47] After the excision of a CN segment, the autologous saphenous vein segment was placed in the injury site bilaterally, with two nerve stems inserted into the veinal lumen.[47] Four months after the surgery, the results showed that autologous vein graft induced regeneration of excised CNs and succeeded in restoring the autonomic EF in rats.[47]

However, in their work, Bessede et al.[46] showed that the inside-out autologous vein grafts failed to improve EF in the CN crush injury rat model 4 weeks after the nerve-sparing surgery.[46]

1.2.2.2 | *Clinical studies*

Despite different studies that supported the probability of immediate nerve regeneration after RP, clinical results showed variability in outcomes and long-term follow-up studies or studies that include a control group are scarce.[48,51] It was found that surrounding neurovascular bundles with dehydrated human amnion/chorion membrane allograft nerve texture accelerates early recovery of EF after RARP.[52] Opposingly, outcomes from a well-designed randomized controlled trial showed no benefits of unilateral nerve grafting after RP.[53]

Immediate interventional nerve grafting of the prostatic plexus with autologous sural or genitofemoral nerves can be used to improve post-RP urinary continence and EF after nerve injury.[48,54–56]

1.3 | Stem cell therapy

1.3.1 | Preclinical studies

Stem cells have the capacity for self-renewal, and as multipotent cells, they can differentiate into at least one other terminal phenotype. There is growing interest in using multipotent stem cell therapy to treat ED[57] (Table 1).

Embryonic stem cells could potentially promote regeneration via replacing existing damaged nerve cells or probably by stimulating host factors to promote nerve growth. Effect of injected neural stem cells on CN renewal, and EF in a nerve crush model showed that preservation of nerve morphology might contribute to the restored EF found in neural stem cells treated groups.[58] It was also reported that improved EF was observed after embryonic neural stem cell therapy.[58] Gu et al.[59] have shown that human placental stem cell treatment significantly increased *in vivo* erectile responses and markers of nerve, endothelial and smooth muscle cells at the end of the 6th and 12th week in rats. Despite these promising results, the problem of ethical issues remains a limiting factor for the research and clinical implementation of embryonic stem cell therapy in humans.

Many studies demonstrated that adipose-derived stem cell (ADSC) therapy alleviates ED after RP.[60,72] ADSCs are readily available and plentiful in adipose tissue and have a great promise in the recovery of ED occurring after RP or different pelvic surgeries. The beneficial effects of ADSCs and lysate injection on vehicle treatment support the supposition that ADSCs show their action by releasing intracellular preformed substances or by the secretion of particular biomolecules. A study showed that ICI of neural-like cells from ADSCs into the site of CNI has regulator effects and leads to the improvement in EF and the renewal of CNs.[61] ICI of adipose-derived stromal vascular fraction, either instantly or 4 weeks after CNI, resulted in a meaningful increase in intracavernosal pressure/mean arterial pressure ratios compared to the vehicle-treated group.[73] Both early and delayed treatment with stromal vascular fraction caused a significant increase in the expression of nNOS, neurofilament, and smooth muscle content in dorsal penile nerves.[62,73]

Intravenous preload of mesenchymal stem cells (MSCs) prevented or reduced postoperative ED in a CNI model.[63] Potential mechanisms include the dispersion of the transplanted cells to the injured area, providing neuroprotection, and preventing neuropraxia. MSCs were infused before CNI, and that suggests that preload of MSCs can help preserve EF. It may be a feasible approach to combine MSC therapy with other available penile rehabilitation therapies to obtain optimal results.[63] The minimizing of enhanced neurogenic adrenergic contractions and potentializing of decreased nitrergic relaxation of CC are the main therapeutic targets in the management of ED after CNI.[74] In a study, ADSC-derived exosomes and bone marrow-derived MSC-derived exosomes reduced pathological alterations in neural anatomy, smooth muscle atrophy, endothelial injury, and collagen deposition. They thus ameliorated the ED following BCNI in rats.[64] The dual strategy of combining ICI of marrow-derived MSCs and oral-long term administration of PDE5i tadalafil seems to be superior to either approach in avoiding this imbalance in the cavernosal tone control and in preserving EF after CNI, suggesting a potential role for this dual strategy in the management of post-RP-ED.[74]

ICI of rats with nonhematopoietic p75-derived multipotent stromal cells obtained from bone marrow may provide a treatment to reduce ED after CNI.[65]

Results showed that ICI of urine-derived stem cells genetically modified with pigment epithelium-derived factor could save EF in rats with BCNI-induced ED by inhibiting the destruction of the nerves, enhancing endothelial function, promoting the smooth muscle cell-to-collagen ratio, and reducing fibrosis and apoptosis of cells in the cavernous tissues.[66]

Smooth muscle progenitor cells can be derived from the autologous peripheral blood, and they differentiate more easily into vascular cells during arterial remodeling than stem cells. Smooth muscle progenitor cell injection thickens the vascular intima and has shown beneficial

TABLE 1 Testing of different stem cell therapies in preclinical animal models and clinical trials in ED linked radical prostatectomy

Study/cell types	Methods	Results/status	Comments	References
Preclinical/embryonic neural stem cells	Injection into the major pelvic ganglion, bilateral cavernosal nerve crush, ICP/MAP measurement	Higher intracavernosal pressures, better neurofilament staining	Improved erectile function	58
Preclinical/human placenta-derived stem cells	Injection into the corpus cavernosum, a pelvic neurovascular injury rat model.	Significant increase of ICP/MAP and markers of neurons, endothelial and smooth muscle cells	Effective restoration of the erectile tissue and function	59
Preclinical/adipose tissue-derived stem cells and stem cell lysate	Intracavernous injection, BCNI rat model, CN electrostimulation at 4 weeks, collected penile tissue for histology.	Significant recovery of erectile function, higher expression of nNOS, less fibrosis and increase smooth muscle content	Improvement and recovery of erectile function	60
Preclinical/neural-like cells from adipose-derived stem cells	Intracavernous injection of one million cells, erectile function assessment at 4 weeks, toluidine blue staining of the dorsal cavernous nerve, neuronal nitric oxide synthase-positive fibers by immunohistochemical staining. the ratio of smooth muscle to collagen by Masson staining.	Increase erectile response, myelinated axons and neuronal nitric oxide synthase-positive fibers and the ratio of smooth muscle to collagen.	Alleviation of cavernous nerve injury and improvement in erectile function.	61
Prelinical/autologous adipose-derived stromal vascular fraction	Intracavernous injection at the time of injury or 4 weeks after injury, functional testing and histologic analysis at 12 wk after CN crush	Increased erectile response and increase in the expression of neuronal nitric oxide synthase and neurofilament in dorsal penile nerves, te smooth muscle-to-collagen ratio	Improvement in erectile function, promotion in nerve regeneration, and prevention of fibrosis of the corpus cavernosum in both early or delayed injection	62
Preclinical/mesenchymal stem cells	Intravenous preload of stem cells	Lower reduction of ICP/MAP and higher expression of glia cell-derived neurotrophic factor and neurturin,.	Prevention or reduction in experimental ED	63
Preclinical/adipose-derived mesenchymal stem cells-derived exosomes and bone marrow-derived mesenchymal stem cell-derived exosomes	Intracavernousal injection of exosomes in BCNI, histologic and western blot analyses.	Significant restoration of ICP/MAP, nNOS expression in the penile dorsal nerves and major pelvic ganglion, protein level of neurofilament in the dorsal nerves, endothelial markers, alpha smooth muscle actin and the ratio of smooth muscle to collagen content.	Alleviation of pathological changes and improvement in the erectile function in BCNI	64
Preclinical/nonhematopoietic p75-derived multipotent stromal cells obtained from bone marrow	Intracavernousal injection in BCNI rat model, ICP/MAP measurement	Significantly higher ICP/MAP. fibroblast growth factor secreted by p75 derived protected cavernous nerve	Effective treatment for ED	65
Preclinical/urine-derived stem cells or urine-derived stem cells genetically modified with pigment epithelium-derived factor	Intracavernous injection, BCNI rat model, recording of ICP/MAP,. immunohistochemistry and Western blot analysis	Significantly enhanced ICP/MAP, increased number of nNOS-positive fibers within the penile dorsal nerves, improved expression of endothelial markers and a smooth muscle marker	Prevention of the destruction of erectile function and the cavernous structure by nerve protection.	66

(Continues)

TABLE 1 (Continued)

Study/cell types	Methods	Results/status	Comments	References
		and content, decreased TGF-β1 and cell apoptosis		
Preclinical/smooth muscle progenitor cells	Intracavernosal injection, ultrastructural analysis	Reduction in apoptosis, maintenace of the structure of adherens junctions and regulation of the stability of corporal vessels.	Restoration of EF	[67]
Clinical phase I/autologous adipose-derived regenerative cells	Intracavernosal transplantation, International index of erectile function-5 and erection hardness score.	Recovery of the erectile function and ability to accomplish sexual intercourse, significant increase in maximum systolic velocity.	Significant improvement in IIEF-5 scores and erectile function	[68]
Stage I of a phase 1/2 clinical trial/ Autologous Bone Marrow-Mononuclear Cells	Intracavernosal injection International Index of Erectile Function-15 and Erection Hardness Scale.	Significantly greater improvement in spontaneous erections, improvement of peak systolic velocity and of % penile nitric oxide release.	Significant improvements of intercourse satisfaction and erectile function domains of the IIEF-15 and Erection Hardness Scale, mprovements of erectile function and penile vascularization	[69]
Stage II of a phase 1/2 clinical trial/ Autologous Bone Marrow-Mononuclear Cells	Intracavernosal injection, International Index of Erectile Function-15	Erectile function improvements similar to those seen in stage I	Significant improvements in International Index of Erectile Function-15 intercourse satisfaction, improvement in erectile function	[70]
Open-label phase I clinical trial/autologous adipose-derived regenerative cells	Intracavernosal injection. international index of erectile function-5 and erection hardness score	Erectile function sufficient for intercourse	Significantly increased international index of erectile function-5 scores	[71]

Abbreviations: BCNI, bilateral cavernous nerve injury; CN, cavernous nerve; EF, erectile function; ICP/MAP, intracavernosal pressure; IIEF, international index erectile function; nNOS, neuronal nitric oxde synthase; TGF-β1, transforming growth factor beta 1.

effects in experimental models of cardiovascular diseases. In a recent study, data showed that treatment caused recovery of EF in a rat model of BCNI by recruiting smooth muscle progenitor cells toward the sinuses in the CC, which maintained the structure of the adherens junctions of the smooth muscle cells by reducing cells apoptosis and increasing the stability of the corporal vessels.[67]

1.3.2 | Clinical studies

Stem cell therapy is a promising approach in regenerative medicine, as it has the potential to recover, prevent, and treat disease. A stem cell application can reverse the structural and neural causes of ED and decrease patient dependence on the temporary benefits and chronic utilization of PDE5is[75,76] (Table 1).

The potential of single ICI of autologous ADSCs freshly isolated after liposuction on ED was investigated.[68] Seventeen men with post-RP-ED refractory to classic methods were included in a prospective phase 1 open-label study.[68] All included patients underwent RP 5–18 months before enrollment and had a follow-up 6 months after intracavernosal transplantation. Eight of the 17 men restored their EF with the ability to complete sexual intercourse successfully, and the IIEF-5 scores continued to rise over the 6 months. The outcomes improved significantly at 6 months, with no observed change at 1 and 3 months. The maximum systolic velocity on Doppler ultrasound increased considerably at 6 months.[68] Twelve-month results of the same study indicated that 8 patients from 15 (53%) with ED after RP restored EF adequate for satisfactory intercourse at 12 months.[71] Even though baseline median IIEF-5 scores showed no change 1 month after the treatment, this effect showed a significant increase after 6–7 months and was maintained at 12 months.[71]

A recent clinical study by Yiou et al.[69] reported the effects of ICI on bone-marrow-derived mononuclear cells in patients with severe RP-ED. Twelve men aged 45–70 years who underwent RP within 6 months to 3 years and had penile arterial insufficiency and corporal veno-occlusive dysfunction on color duplex Doppler ultrasound, with failure of pharmacotherapy, were enrolled in this study.[69] The bone-marrow-derived mononuclear cell injection caused a significant improvement in most of the sexual scores at 6 months, and 9 out of 12 patients achieved successful intercourse with vaginal penetration after medication.[69]

A phase 1/2 pilot clinical trial of cell therapy was reported by Yiou et al.,[70] including intracavernous autologous bone marrow mononuclear cell application to treat post-RP-ED. The EF after 6 months showed significant improvements versus baseline were noted in IIEF-15 intercourse satisfaction and EF domains.[70]

1.4 | Gene therapy

1.4.1 | Preclinical studies

COX-2-10aa-PGIS is a newly engineered protein with COX-2 and prostacyclin synthase activities that transform arachidonic acid rapidly to prostacyclin I2, which is considered a potent smooth muscle relaxant. In a study by Lin et al.,[77] 28 days after the ICI, the results showed that Ad-COX2-10aa-PGIS has a beneficial effect on improving EF in BCNI rats. This improvement appears to be related to its antifibrotic and antiapoptotic mechanisms.[77]

In a previous study,[78] the adenovirus-mediated gene transfer of Smad7 (Ad-Smad7) showed success in the recovery of EF by improving endothelial cell regeneration and showing antifibrotic effects.[78] Thus, antagonizing the TGF-β signaling pathway may offer a promising treatment approach for RP-induced ED.[78]

In another study aimed to evaluate the efficacy of ADSCs infected with a lentiviral vector encoding rat brain-derived neurotrophic factor (BDNF) in a rat model of CNI, rats were injected with ADSCs infected with lenti- rat BDNF after injury.[79] EF was evaluated 4 weeks after injury by intracavernosal pressure measurements. Results demonstrated that compared with the BCNI group, EF recovery was significantly better in the $ADSC_{rBDNF}$ groups.[79]

In a study aimed to show phenotypic modulation in BCNI rats for 7 days and then validate gene therapy with myocardin by sustaining a contractile phenotype in CC smooth muscle cells,[80] the results showed that the gene transfection of myocardin promoted CC smooth muscle cells' contractile protein α-smooth muscle actin, supported calponin expression and prevented synthetic element osteopontin expression.[80] Overexpression of myocardin maintained the contractile phenotype of CC smooth muscle cells, ameliorated BCNI rat ED, promoted cell contractility and suppressed proliferative capacity. In conclusion, myocardin ICI inverted phenotypic modulation by enhancing the activity of serum response factor.[80]

1.5 | Pharmacological approaches

1.5.1 | sGC Stimulators

1.5.1.1 | *Preclinical studies*

A study by Lasker et al.[81] showed that the sGC stimulator BAY 41-8543 enhances EF and synergizes with NO released in an exogenous and endogenous manner. Atropine, along with nerve crush, decreases the reaction to CN stimulation, and BAY 41-8543 could restitute this reaction. The results obtained by atropine, L-NAME, and hexamethonium showed that the response to ICI of acetylcholine is muscarinic receptors-mediated, and the nicotinic receptors have no considerable role in NO release. These results supported the beneficial effects of BAY 41-8543 in the recovery of ED.[81] On the other hand, Lasker et al.[82] examined the effect of BAY 60-2770, another sGC activator, on the EF in rats. BAY 60-2770 enhanced vasodilation and EF. In comparison with the sGC stimulator BAY 41-8543, BAY 60-2770 showed a significant potent erectile activity and had a very mild hypotensive effect in the rat, indicating that it's selective for sGC in penile tissues.[82] Thus BAY 60-2770 like agents, which enhance the catalytic activity of oxidized or heme-free sGC, have the potential in the treatment of ROS mediated NO inactivation related pathological

cases and in cases in which sGC is oxidized and show no response to endogenous or exogenous NO as well as sGC stimulators.[82]

Oudot et al.[83] showed synergistic effects of an sGC stimulator, BAY 60-4552, and vardenafil on the CNs in rats with CNI-induced ED.[83] The study supported that the activation of sGC can have a role in managing CNI-induced ED and may, therefore, be an option for men who experience therapy failures with PDE5is following RP.[83]

1.5.2 | The Role of PDE5is

The introduction of PDE5is in the late 90s has changed the management of ED, causing a massive paradigm shift and these drugs proved to be an effective alternative for patients suffering from ED. The use of PDE5is is the first line of therapy for patients with ED. The inhibition of PDE5 potentiates the relaxing of cavernosal smooth muscle via increasing intracellular cGMP, facilitating achieving and maintaining erections[84] (Table 2).

1.5.2.1 | *Preclinical studies*

In a study of a post-RP model of ED in rats, early and daily sildenafil citrate treatment showed a positive effect on penile weight and the adrenergic and cholinergic systems, which all play a different role in EF[97](Table 2). Another study aimed to evaluate the effects of varying PDE5is on neuronal cell survival and the effectiveness of treatment with nanospheres containing sildenafil in a rat model of BCNI.[85] The results revealed an excellent neuroprotective effect for sildenafil compared to vardenafil and tadalafil. Also, nanospheres containing sildenafil to the site of nerve injury ameliorated EF with less adverse histologic alterations.[85]

An interesting trial evaluated the additional benefits of long-term oral treatment with a PDE5i on the potential capacity of intracavernosal cell therapy to recover EF after CNI.[74] Rats were treated with tadalafil, a single ICI of bone marrow-derived MSCs, or dual therapy with both treatments.[74] Four weeks after BCNI, CC function and intracavernosal pressure responses were evaluated.[74] The results showed that a dual therapeutic strategy combining bone marrow-derived MSCs and tadalafil was superior to either monotherapy in normalizing neurogenic regulation of cavernosal tone and preserving EF following CNI, suggesting using this dual strategy in the potential management of ED after RP.[74]

A previous study examined the effect of udenafil, a PDE5i, on bilateral CN resection-induced penile hypoxia and fibrosis in rats.[86] The animals were orally treated with udenafil for 8 weeks following bilateral CN resection.[86] Results showed that udenafil considerably restored alterations in eNOS and nNOS in the injured group. EF was profoundly impaired in animals that underwent bilateral CN resection, and the treatment with udenafil corrected the impairment.[86] According to another study, the pharmacological effect of udenafil on EF recovery is time- and dose-dependent. Its findings suggest mechanistic insight into the positive effects of udenafil in conserving EF after CNI.[87]

In a study by Kim et al.,[88] after 8 weeks of treatment with mirodenafil, the EF and NOS expression and cGMP level were enhanced in CN-injured rats.[88] The data demonstrate the favorable effects of mirodenafil on EF after BCNI.[88]

1.5.2.2 | *Clinical studies*

In a prospective randomized trial comparing early and late penile rehabilitation with sildenafil citrate in patients after nerve-sparing radical cystoprostatectomy (NSRCP),[98] 18 patients without spontaneous erection 8 weeks after NSRCP were randomized into two groups of erectogenic therapy starting at the 2nd and 6th months after operation.[98] The drug therapy constituted of sildenafil citrate twice weekly to be changed to ICI of prostaglandin E1 if the patient had no response. Both groups completed the treatment at the end of the 6th month. The EF was evaluated at the treatment's beginning and end by the IIEF questionnaire and penile Doppler ultrasonography.[98] The results indicate that in comparison with late erectile rehabilitation, the early rehabilitation program improves the natural recovery of potency faster and maintains a nondrug-mediated erection in men after radical cystoprostatectomy.[98]

The REINVENT clinical trial evaluated the efficiency of daily versus on-demand PDE5i, vardenafil.[84] Over 600 patients who had undergone nerve-sparing RP were randomized into three groups: group 1, daily 10 mg vardenafil and placebo on-demand; group 2, daily placebo plus on-demand vardenafil; and group 3, daily placebo and on-demand placebo.[84] This trial had three phases: 9 months of double-blind treatment, followed by a 2 months washout period, and afterward another 2 months of open-label vardenafil. Based on the results, daily vardenafil therapy did not prove to be superior to on-demand vardenafil.[84] Another study demonstrated a significant difference in IIEF-5 score and time to recovery of EF in patients (n = 36) who underwent a unilateral nerve-sparing RP and received 5 or 10 mg/day vardenafil.[89] These results show that even though the daily low-dose vardenafil leads to considerable recovery of EF, doubling the dosage further improved the outcome.[89]

Patients were divided into three groups; treated with avanafil 100 and 200 mg for 12 weeks and a placebo.[90] Patients were assessed at 4-week intervals with IIEF, sexual encounter profile, and patient diaries. A total of 81% had undergone RP using a robotic technique, and 76% were classified as having severe ED.[90] Avanafil groups significantly improved from baseline compared to placebo in mean IIEF-EF scores, proportions of patients with successful vaginal penetration, and successful sexual intercourse at 12 weeks.[90] In subgroup analyses, these benefits of avanafil 100 and 200 mg were generally independent of baseline severity of ED, age, and type of surgical technique.[90] Similar responses were observed for secondary endpoints for at least one avanafil dosage.[90] For instance, avanafil 200 mg recipients had significantly more significant improvement than placebo recipients in the IIEF-EF orgasmic function, intercourse satisfaction, and overall satisfaction domain scores. In comparison, avanafil 100 mg recipients had significantly greater improvement than placebo recipients in the intercourse satisfaction and overall satisfaction domains.[90] Compared with placebo, at most time points from 15 to 360 min after ingestion of the study drug, both avanafil dosage groups had a higher proportion of men with successful responses.[90]

TABLE 2 Effects of PDE5 inhibitors treatment in preclinical animal models and clinical trials in ED linked radical prostatectomy

Methods	Treatment dose/duration	Results	Comments	References
A rat model of BCNI and cultured neuronal cells	Sildenafil, tadalafil, and vardenafil	Decreased cell death after exposure to H_2O_2 and hypoxia. Increase in ICP/MAP and markers of neurons, endothelial and smooth muscle cells	Sildenafil had more neuroprotective effect than tadalafil and vardenafil	85
A rat model of BCNI	Udenafil, 10 mg/kg for 8 weeks	Amelioration in erectile function, markers of fibrosis, apoptosis, neurons and endothelial	Long-term treatment improves penile hypoxia and fibrosis	86
A rat model of BCNI	Udenafil, 5 and 20 mg/kg for 4 and 8 weeks	Improved erectile function, hypoxia, fibrosis, neuronal and endothelial markers as well as the smooth muscle/collagen ratio in a dose- and time-dependent manner	Chronic treatment preserved erectile.	87
A rat model of CNI	Mirodenafil, 10 and 20 mg/kg for 8 weeks	Improved ICP, the smooth muscle component, nitric oxide synthase expression and cGMP levels	Long-term therapy augmented the erectile function.	88
A rat model of BCNI	Tadalafil, 5 mg/kg for 4 weeks and single intracavernosal injection of bone marrow-derived mesenchymal stem cells	Recovered erectile responses, neurogenic contractions and nitrergic relaxations as well as apoptosis and fibrosis after the combined treatment.	A dual strategy combining stem cell and tadalafil was superior to individual approaches in normalizing erectile function.	74
A randomized, double-blind, multicentre, parallel group study	Nightly and on demand vardenafil after nerve-sparing radical prostatectomy	On-demand vardenafil increased IIEF scores and SEP3 response rates.	On demand vardenafil treatment was efficacious, supporting a paradigm shift towards on demand dosing with PDE5 inhibitors in this patient group.	84
A randomized, prospective, single-center study	Vardenafil, 5 and 10 mg/day after nerve-sparing radical prostatectomy	A significant difference in IIEF-5 score and time to recovery of erectile function after both treatment regiments.	Low-dose vardenafil improved erectile function.	89
A double-blind, placebo controlled, parallel group, phase 3 study	On demand avanafil, 100 and 200 mg for 12 weeks after bilateral nerve sparing radical prostatectomy	Increased in SEP2, SEP3, and mean IIEF.	Avanafil was effective in improving erectile function after prostatectomy.	90
A randomized double-blind trial	Nightly and on-demand sildenafil, 50 mg for 12 months after nerve-sparing minimally invasive radical prostatectomy	No differences in erectile function after both treatment regiments	Erectile recovery does not differ between previously potent men who use sildenafil nightly compared to on-demand.	91
A randomized, double-blind, placebo-controlled trial	Tadalafil, 5 mg once daily and 20 mg on demand for 9 months after nerve-sparing radical prostatectomy	Improvement in IIEF in both tadalafil groups, but recovery in SEP and penile length in the tadalafil once daily group only	Tadalafil once daily was most effective on ED.	92
A multicenter, randomized, double-blind, double-dummy, placebo-controlled trial	Tadalafil, 5 mg once daily and 20 mg tadalafil on demand for 3 months after bilateral nerve-sparing radical prostatectomy	The probability for EF-recovery was significantly higher for once daily	Once daily tadalafil can significantly shorten the time to erectile function recovery.	93
A single-center, prospective, randomized controlled trial	Tadalafil, 20 mg on-demand and 3 times per week for 12 months after bilateral nerve-sparing radical prostatectomy	Improvement in IIEF score in the group using tadalafil three times per week.	Tadalafil three times per week is an efficacious and well-tolerated treatment option for ED.	94

(Continues)

TABLE 2 (Continued)

Methods	Treatment dose/duration	Results	Comments	References
A multicenter, randomized, double-blind, double-dummy, placebo-controlled trial	Tadalafil, 5 mg once-daily and 20 mg on-demand for 9 months	Increased in Erectile Dysfunction Inventory of Treatment Satisfaction total-scores in both treatment regimens.	Chronic treatment improves quality-of-life of patients post- radical prostatectomy.	[95]
A prospective randomized controlled trial	Lodenafil 80 mg/day per week and psychotherapy for 12 weeks after radical prostatectomy	Improvement in intimacy with a partner and satisfaction with their sex life and with no significant worsening of IIEF in the combined treatment group only	The combined treatment led to less deterioration of erectile function and physical aspects, with improvement in intimacy with their partner and satisfaction in their sex life.	[96]
A rat model of bilateral cavernous neurotomy	Sildenafil, 1 mg/kg for 14 days	Positive effects on penile weight and the apoptotic index as well as contratile and relaxant responses	Restorative effects on the adrenergic and cholinergic systems	[97]

Abbreviations: BCNI, bilateral cavernous nerve injury; cGMP, cyclic guanosine monophosphate; CN, cavernous nerve; EF, erectile function; ICP/MAP, intracavernosal pressure; IIEF, international index erectile function; SEP3, sexual encounter profile.

In a double-blind, randomized controlled trial of nightly versus on-demand 50-mg sildenafil citrate treatment for 12 months after nerve-sparing minimally invasive RP, a total of 100 men aged <65 years, with preoperative scores of ≥26 on the EF domain of the IIEF were included.[91] Results showed no significant differences in EF recovery between nightly or on-demand use of sildenafil at any time point after adjusting for potential confounding factors.[91]

The REACT clinical trial evaluated nightly versus on-demand tadalafil.[92] The patients were randomized into three groups: 5 mg daily tadalafil, 20 mg on-demand tadalafil, and placebo. The patients received treatment for 9 months, after a washout period of 6 weeks and afterward, 3 months of daily tadalafil. The results achieved at the end of the first 9 months have shown that daily tadalafil was superior to placebo and on-demand tadalafil.[92] At the end of the drug washout period, the superiority of daily tadalafil was not maintained.[92] After reintroducing daily tadalafil for 3 months, the IIEF and Sexual Encounter Profile-3 scores improved. In terms of penile shortening prevention, the daily usage of tadalafil has demonstrated superior results.[92] Moncada et al.[93] concluded that daily administration of tadalafil speeds up the EF recovery process in a randomized clinical trial. The patients with bilateral nerve-sparing RP were randomized to receive either daily 5 mg tadalafil or on-demand 20 mg tadalafil or placebo for 9 months. The study also included a 6-week drug washout period and another 12 weeks of daily tadalafil for all three groups of patients. The length of the treatment was not sufficient for >50% of the patients to achieve a satisfactory erection recovery. A total of 25% of the patients reached an EF recovery (IIEF-EF ≥22) over a period that ranged between 5.8 and 9.3 months (5.8 months for patients with daily tadalafil vs. 9 months for those with on-demand tadalafil and 9.3 months for patients who have received placebo), the daily administration of tadalafil favoring a faster EF recovery.[93] A single-center, prospective, randomized controlled trial aimed to compare three times per week versus on-demand tadalafil 20 mg after bilateral nerve-sparing RP.[94] There was no significant difference among all groups concerning EF at 6 weeks after the surgery. Twelve months after the surgery, the IIEF score was considerably higher in the group using tadalafil 20 mg three times per week.[94] The results showed that chronic dosing of tadalafil started early after nerve-sparing RP increased and accelerated EF recovery and improved patients' quality of life.[95]

After RARP, the comparative efficacy of a penile rehabilitation program with different PDE5is was investigated. Sildenafil 50 mg every other night was given for the first 3 months after the urethral catheter removal.[99] After the 3-month follow-up visit, PDE5is were used on-demand in the following order: tadalafil 20 mg, sildenafil 100 mg, and vardenafil 20 mg. According to the results, in men with a normal erection before surgery, the overall recovery rate of potency 1 year after RP was 79.7%. However, more than half of these men required PDE5is, and only a quarter returned to the baseline EF.[99]

In a previous study, 53 men undergoing RP for PCa were randomized into four groups; control group, psychotherapy, lodenafil 80 mg/one tablet per week, and psychotherapy plus lodenafil 80 mg/one tablet per week groups. Only the last group had amelioration in

intimacy with a partner and satisfaction with their sex life and without worsening the IIEF-5.[96] These results show that early integral treatment involving group psychotherapy and a PDE5i before and after RP may lead to a more limited EF impairment, superior to either treatment.[96]

1.5.3 | Immunophilin Ligands

1.5.3.1 | *Preclinical studies*

Immunophilins are a class of cellular proteins primarily identified as targets for drugs used in transplantation medicine, like tacrolimus, cyclosporine, and rapamycin.

Focus has recently turned toward immunophilin ligands, such as FK506 and rapamycin, for the treatment of ED. A study demonstrated that the receptors to which they bind were more abundant in nerve tissue than immune cells, implying their role in neuronal functions.[100] Their neuroprotective and nerve-regenerative properties after nerve injury and neurological disease were observed in animal models[101–107] (Table 3).

Prototypical immunophilin ligands, for instance, FK506 and rapamycin, show their effects via binding to FK506 binding proteins (FKBPs), a family of immunophilin proteins placed in the nucleus, cytosol, mitochondria, and endoplasmic reticulum of the cell.[121] Acting as chaperone proteins, they modulate protein folding and trafficking and involve in-cell signaling and transcription.[122] FKBP 12 is the most investigated immunophilin, and studies imply that other FKBPs can also gain interest in CNI-induced ED due to their localization in human penile innervation.[123] Also, a previous study demonstrated that FKBP 12 was localized to penile innervation in the rat and was upregulated after CNI.[124]

FK506 binds to FKBP 12, forming a complex that binds to and blocks calcineurin, thereby producing immunosuppression.[125] Increasing evidence suggests that the mammalian target of rapamycin is involved in cellular growth, proliferation, and survival.[126] Rapamycin exerts immunosuppression via binding to FKBP 12.[127] Furthermore, the administration of FK506 prevented the loss of EF after nerve crush injury.[128]

An initial pilot study using FK1706, a nonimmunosuppressant immunophilin ligand, has improved EF and immunohistochemical evidence of neurotrophic/neuroregeneration in rats.[109,129] Another study showed that high-dose subcutaneous FK1706 therapy significantly improved EF without adverse events over the 8-week course of the treatment in a rat model of bilateral CNI.[110]

The previous data suggested that FK506 activated cellular repair mechanisms and reduced apoptosis in penile and neuronal tissue. At the same time, rapamycin shows its antiapoptotic alterations over a longer time frame, particularly in neuronal tissue.[108]

Dipyridamole is currently used clinically as an antithrombotic drug. It increases cAMP levels by inhibiting phosphodiesterase in platelets.[130] A study showed that dipyridamole treatment did not recover EF in rats with BCNI. Still, the decrease in both the level of TGF-β1 and apoptosis after the treatment could be helpful in protecting penile morphology after CNI. Further studies are needed to understand the effect of different pharmacological doses and long-term therapy with dipyridamole, especially penile hemodynamic response.[131]

1.5.3.2 | *Clinical studies*

Tacrolimus is an immunosuppressant with neuroprotective, neurotrophic, and anti-inflammatory effects. A randomized, double-blind trial compared tacrolimus 2–3 mg daily and placebo in men undergoing RP. Despite supportive animal data[102,124,128] the results showed that treatment had no significant impact on ED[119] (Table 3).

1.6 | Growth factors

1.6.1 | Preclinical studies

A bolus ICI combined with vascular endothelial growth factor (VEGF) and BDNF protein-induced significant improvements in EF and the morphology of CN fibers in CC (Table 3). This VEGF-enhanced neurotrophin treatment may help protect and improve EF after radical pelvic surgery.[132] An ICI with BDNF plus VEGF seems to inhibit degeneration and facilitate regeneration of neurons, including nNOS in the major pelvic ganglia, dorsal nerve, and intracavernosal tissue. It is a suggested therapeutic option for augmenting the improvement of EF following radical pelvic surgery.[132]

In a rat model of CNI, ICI of growth differentiation factor-5 (GDF-5) preserved EF in a dose-dependent manner.[111] Furthermore, increased dosages of GDF-5 reduced TGF-β messenger RNA expression but increased GDF-5 concentrations related to decreased preservation of nNOS-containing nerve fibers in the penis and enhanced intracavernous apoptosis.[112] The association between these effects could be translated as that low-concentration GDF-5 was most effective in preserving EF after CNI.

The application of human ADSCs and nerve growth factor-incorporated hyaluronic acid-based-hydrogel into the CN restored EF in a rat model of CNI.[113] Human ADSC and nerve growth factor-incorporated hyaluronic acid-based -hydrogel treatment resulted in a therapeutic effect on the expression of eNOS and the ratio of collagen to smooth muscle in the CC.[113]

The precursor for a nerve growth factor (proNGF) is involved in neuronal cell apoptosis and microvascular dysfunction through its receptor $p75^{NTR}$.[133] A study aimed to determine the expression of proNGF/$p75^{NTR}$ and the efficacy of proNGF neutralizing antibodies in mice with ED induced by CNI.[134] Mice were injected with anti-proNGF antibody for 2 weeks after undergoing BCNI. Results revealed that blockade of the proNGF/$p75^{NTR}$ pathway preserves the damaged penile neurovascular structure and restores EF in CNI mice, probably via regulating the expression of both neurotrophic and angiogenic factors.[134] Also, the p75 neurotrophin receptor modulator, LM11A-31 treatment, improved ED in CNI mice via increased neurovascular content, cavernous endothelial cells, pericytes, and neuronal processes.[114]

TABLE 3 Effects of immunophilins and growth factors in preclinical animal models and clinical trials in ED linked radical prostatectomy

Study/agent	Methods	Results/status	Comments	References
Preclinical/FK506 and rapamycin	Subcutaneous injection, bilateral cavernosal nerve crush rat model, ICP measurement and western blot analyses.	Attenuation of the decrease in FKBP38 and FKBP65 in penis and major pelvic ganglion.	Preservation of EF.	108
Preclinical/FK1706	Subcutaneous injection, BCNI rat model, CN electrostimulation, immunohistochemistry.	Neural and erectile recovery, higher ICP, restoration of axon shape and staining patterns.	Neuroregeneration and EF recovery.	109
Preclinical/FK1706	Subcutaneous injection, BCNI rat model, CN electrostimulation.	Increase in ICP.	Recovery of EF.	110
Prelinical/GDF-5	Intracavernousal implantation of impregnated collagen sponge, BCNI rat model, CN electrostimulation and histologic analysis at 8 wk.	Increase in ICP, more nNOS-containing nerve fibers.	Recovery of EF and nNOS nerve preservation	111
Preclinical/GDF-5	Intracavernous injection of a slow-release suspension of liquid microparticles, BCNI rat model, CN electrostimulation, PCR and immunohistochemical analyses at 4 wk after CN crush.	Increased ICP, preservation of the penile dorsal nerves and antiapoptotic effects in the CC.	Preservation of EF	112
Preclinical/hADSCs and nerve growth factor-incorporated hyaluronic acid-based-hydrogel	Application of hADSCs above injured CN and immediately covering with nerve growth factor-hydrogel, BCNI rat model, ICP/AP measurement by CN electrostimulation, histological examination.	Prevention of smooth muscle atrophy in the CC, increase in eNOS protein expression.	Recovery of ED	113
Preclinical/Anti-proNGF-Ab	Intracavernous injection, BCNI mouse model measurement of EF by electrical stimulation of CN.	Increased nNOS and neurofilament expression, preservation of the integrity of cavernous sinusoids, such as pericytes, endothelial cells, and endothelial cell-to-cell junctions.	Improvement in EF	6
Preclinical/LM11A-31	Oral administration, cavernous nerve injury mouse model, EF measurement by electrical stimulation, histologic examination and western blot analysis.	Increased neurovascular content, including cavernous endothelial cells, pericytes, and neuronal processes. increase in protein expression of active PI3K, AKT, and eNOS, attenuation of cell death and c-Jun N-terminal kinase signaling.	Significant improvement of EF.	114
Preclinical/bFGF-hydrogel+ BDNF with hADSC	Intracavernosal injection of bFGF-hydrogel and ADSC application covered with BDNF-membrane, BCNI rat model, assessment of ICP/AP at 4 wk, Masson's trichrome staining, immunostaining, western blot and cGMP assay.	Significant increase in smooth muscle/collagen ratio, nNOS content, α-smooth muscle actin expression, and cGMP level.	Improved EF.	115
Preclinical/GGF2	Subcutaneous injection, BCNI rat model, assessment of EF by electrical stimulation of the CN, fluorogold retrograde axonal tracing in major pelvic ganglia, electron microscopy.	Increase in the number of fluorogold-labeled cells in the major pelvic ganglia, decrease in denervated Schwann cells, increase in number of unmyelinated axons per Schwann cell.	Recovery of ED.	116
Preclinical/Dual growth factor incorporated heparin-pluronic/	Intracavernousal injection, BCNI rat model, EF assessment by measurement of ICP and MAP at 4 wk, cGMP level	increase in cGMP, greater upregulation of NOS and eNOS, lower apoptosis, increase in α-smooth muscle actin and CD31 expression.	Recovery of EF	117

TABLE 3 (Continued)

Study/agent	Methods	Results/status	Comments	References
gelatin-poly (ethylene glycol)-tyramine hydrogel	measurement, immunohistochemistry, TUNEL assay, Western blot analyses.			
Preclinical/Insulin like growth factor-1	Injection of loaded microspheres underneath the major pelvic ganglion, BCNI rat model, measurement of ICP/MAP at 2 wk, western blot analysis and immunohistochemistry.	Increase in ICP/MAP, upregulation of the IGF-1 receptors and ERK-1/2, upregulation of nNOS in the MPG.	Improvement in EF	118
Clinical/Randomized, double-blind trial/ Tacrolimus	Oral administration, IIEF.	No significant change in erectile function domain.	Failure in treatment of ED	119
Clinical/Randomized, single-blind, single-surgeon, placebo-controlled exploration study	Dehydrated human amnion membrane placed around the neurovascular bundle and vesicourethral anastomosis during RP.	–	–	120

Abbreviations: BCNI, bilateral cavernous nerve injury; BDNF, brain derived neurotrophic factor; CC, corpus cavernous; CN, cavernous nerve; eNOS, endothelial nitric oxide synthase; ED, erectile dysfunction; EF, erectile function; FKBP, FK binding protein; hADSCs, human adipose tissue derived stem cells; ICP/MAP, intracavernosal pressure/mean areterial pressure; IIEF, international index erectile function; nNOS, neuronal nitric oxide synthase; PCR, real-time polymerase chain reaction; TGF-β1, transforming growth factor beta 1; VEGF, vascular endothelial growth factor; wk, week.

Application of BDNF-immobilized poly-lactic-co-glycolic acid membrane with human ADSC into the CN and fibroblast growth factor (βFGF)-incorporated hydrogel into the CC enabled a nearly normal EF in a rat model of RP-ED.[115] The underlying mechanisms of the improvement are linked to increases in nNOS expression, the ratio of smooth muscle to collagen, eNOS phosphorylation, α-smooth muscle actin expression, and cGMP levels in the rat penile tissue.[115]

Neuregulins are a group of growth factors associated with epidermal growth and function by binding ErbB tyrosine kinase transmembrane receptors (ErbB2-4) and stimulating cellular proliferation, differentiation, and survival in several tissues.[135–138] Neuregulin-1 has a vital role in axoglial signaling during the development of the peripheral nervous system.[139] Moreover, it is increasingly being identified for its neuroprotective and neurorestorative functions during adulthood, conceivably through mediating signals between axons and Schwann cells needed for effective nerve repair.[139,140] Regarding their neuroprotective effects, it can be suggested that neuregulins are likely to be an interesting candidate for protecting the CN and preserving EF following RP. A previous study evaluated if glial growth factor-2 (neuregulin-1β3 type II), a soluble full-length splice variant of the neuregulin-1gene,[139] can promote axonal integrity and preserve EF following BCNI in rats.[116] Data showed that GGF2 recovered EF via preserving unmyelinated nerve fibers in the injured CN in a rat model of CNI.[116]

A study showed that EF was reduced following BCNI, which was restored by treatment with a dual growth factor incorporated heparin-pluronic/gelatin-poly (ethylene glycol)-tyramine hydrogel compared to groups treated with a single growth factor in a rat model of CNI.[117] Also, the dual growth factor treatment enhanced cGMP levels, nNOS, and eNOS expression and decreased apoptosis in the penile tissues.[117]

A previous study showed that pioglitazone improved EF in rats undergoing BCNI.[118] The authors proposed that this effect of pioglitazone was mediated by the insulin-like growth factor-1 pathway. In their study, to eliminate the systemic effects of pioglitazone and evaluate the local delivery of insulin-like growth factor-1, polymeric microspheres were injected underneath the major pelvic ganglion after BCNI in the rat. Results showed that stimulating the insulin-like growth factor-1 receptor at the level of the CN had the potential to mitigate ED in men after RP, but further research is needed to assess its safety as a growth factor in the PCa setting.[118]

1.6.2 | Clinical studies

A study suggested that the human amniotic membrane is likely to recover tissue regeneration and functional outcomes after RP due to its growth factors and unique immune tolerance for it.[120] The efficacy and safety of dehydrated human amnion membrane located around the neurovascular bundle and vesicourethral anastomosis during RP for the treatment of localized PCa patients are examined.[120]

1.7 | Low-intensity extracorporeal shockwave therapy (LI-ESWT)

1.7.1 | Preclinical studies

Several studies have investigated the effect of LI-ESWT on ED in rat models of CNI (Table 4). Li et al.[141] showed that LI-ESWT recovered ED by increasing Schwann cell proliferation and leading to more complete reinnervation of penile tissue with the regeneration of nNOS positive nerves to the penis in rats with CNI.[141]

Supporting, a previous study by Lin et al.[152] showed that LI-ESWT stimulated Schwann and endothelial cell proliferation through increased phosphorylation of Erk1/2. Also, LI-ESWT enhanced the expression of BDNF in the rat penis after BCNI. Moreover, BDNF expression was augmented in Schwann cells *in vitro* after LI-ESWT.[142]

In a previous study, combined treatment of LI-ESWT plus human ADSCs significantly recovered ED through alpha-smooth muscle actin content, nNOS, eNOS expression, and cGMP levels in penile tissue when compared with either treatment in a rat model of post-prostatectomy ED.[143] Also, ADSCs mediated recovery of injured CNs, whereas LI-ESWT enhanced angiogenesis in the cavernosal tissue.[143]

Delayed application of LI-ESWT to the penis and pelvis was associated with restoration of penile hemodynamics in a rodent model of severe pelvic neurovascular injury.[144] These effects seem to be mediated by LI-ESWT-enhanced angiogenesis, activation of Schwann cells, and facilitation of nerve regeneration. Three-dimensional imaging of solvent cleared organs provided high-resolution images of unsectioned CN and major pelvic ganglion and demonstrated superior neuronal integrity in animals treated with LI-ESWT.[144]

1.7.2 | Clinical studies

Shockwave therapy induces neoangiogenesis, recruitment of progenitor cells, modulation of vasodilation, and nerve regeneration in several tissues in humans.[148]

LI-ESWT has achieved popularity as a potential treatment option for ED because data from both *in vivo* and *in vitro* studies have indicated that shockwaves can induce angiogenesis.[153] According to these results, LI-ESWT therapy is likely to increase penile blood flow parameters and endothelial function via stimulating angiogenesis in the penis. However, the underlying therapeutic mechanism of shockwaves is not fully understood. It has been assumed that the targeted tissue is compressed because of the positive acoustic pressure produced by the shock, followed by expansion, which occurs over tensile elements of the tissue.[154] This phenomenon has been described as "cavitation" as it can be seen creating micrometer-sized bubbles that violently expand and collapse.[154,155] The physical forces produced by these cavitation bubbles are highly localized, and they cause a localized stress response on endothelial cell membranes secondary to sheering forces. Then, this shear stress contributes to the release of angiogenic factors and production of NO by the increase in eNOS and nNOS activity, platelet-derived growth factor, and VEGF. Also, shockwaves induce hyperpolarization, activation of the Ras signaling pathway, nonenzymatic synthesis of NO, and upregulation of stress fibers and intercellular gaps.[154,155]

In a clinical study by Frey et al.,[148] men with at least 1 year's history of bilateral nerve-sparing RP-induced ED were given two LI-ESWT sessions (1000 shock waves with energy densities of 20, 15, and 12 mJ/mm^2) in the root of the penis every other week for 6 weeks. In this study, LI-ESWT recovered ED with the amelioration in five-item IIEF scores at 1 month and 1 year after the treatment.[148]

A study by Zewin et al.[149] compared the effects of LI-ESWT with PDE5i therapy in penile rehabilitation after NSRCP. Men were given 12 sessions of penile LI-ESWT in the distal, mid, and proximal penile shaft and the left and right crura with a specialized, focused shock wave probe.[149] The results showed that LI-ESWT or an oral PDE5i in penile rehabilitation post-NSRCP improved EF slightly compared to the control group.[149]

Inoue et al.[156] compared early versus delayed LI-ESWT in 16 patients after RP. Early LI-ESWT was initiated in the 1st or 2nd postoperative week. SF was evaluated with the expanded prostate cancer index composite. LI-ESWT significantly improved SF compared to controls regardless of the time point it was initiated. There was no difference regarding SF between the "early" and "delayed" LI-ESWT groups at all time points.

In a recent RCT, 77 patients were given either tadalafil + LI-ESWT ($n = 36$) or tadalafil alone ($n = 41$) as penile rehabilitation.[157] LI-ESWT consisted of 19,200 impulses over 8 weeks. The main outcome measure was ≥4 point difference in IIEF-5 score favoring the treatment group. Despite a significant difference of median 2 points in IIEF-5 scores, the treatment group's primary end-point of at least 4 points difference was not reached. The authors emphasized the need for further studies before making clear recommendations.

A study examined penile vibratory stimulation effect on the protection and renewal of EF and urinary continence in conjunction with nerve-sparing RP.[134] Data from 68 patients showed that the IIEF-5 score was highest in the penile vibratory stimulation group after surgery, but the difference only reached borderline significance.[134]

1.8 | Intraurethral Alprostadil Injection and Medicated Urethral System for Erection (MUSE)

1.8.1 | Clinical studies

A study by Raina et al.[158] reported that MUSE therapy after bilateral nerve-sparing RP in men resulted in 74% of patients regaining erections (vs. 37% of controls) and a mean IIEF-5 score of 18.9 (vs. 15.8 in the control group).[158]

A multicenter, randomized, prospective penile rehabilitation trial by McCullough et al.[159] compared the effectiveness of nightly

TABLE 4 LI-ESWT and VED Therapies in preclinical animal models and clinical trials in ED linked radical prostatectomy

Methods	Treatment	Results	Comments	References
A rat model of BCNI and internal pudendal bundle injury	LESW at low and high energy	Improved EF via angiogenesis, tissue restoration, regeneration of nNOS activation of Schwann cells	LESW induced endogenous progenitor cell recruitment and Schwann cell activation.	[141]
A rat model of BCNI	Li-ESWT	Increased in BDNF in Schwann cells, the phosphorylation levels of PERK and eukaryotic initiation factor 2a and activating ATF4 in an energy-dependent manner.	Li-ESWT stimulates the expression of BDNF through the activation of the PERK/ATF4 signaling pathway	[142]
A rat model of BCNI	LESW and h-ADSCs	Improved intracavernosal pressure, alpha smooth muscle actin content, protein expression of nNOS and eNOS, cGMP and reduces the apoptotic index after the combined treatment	The combined treatment showed beneficial effect on the recovery of EF.	[143]
A rat model of pelvic neurovascular injury	Li-ESWT therapy	Increased in the ICP/MAP, density of nerves, axons, nNOS, Schwann cells in the dorsal penis.	Li-ESWT ameliorated the negative functional and histologic effects of severe pelvic neurovascular injury.	[144]
A rat model of BCNI	VED therapy	Increased in the ICP/MAP ratio, smooth muscle/collagen ratios, preserved α-smooth muscle actin, eNOS expression and decreased in HIF-1α and TGF-β1 expression, apoptotic indices	VED therapy preserves EF via antihypoxic, antiapoptotic, and antifibrotic mechanisms.	[145]
A rat model of BCNI	VED therapy	Prevented penile shrinkage, increased in cavernous oxygen saturation	VED therapy preserved penile size via increasing cavernous blood oxygen saturation.	[146]
A rat model of BCNI	VED therapy	Improved in penile shortening, peak ICP and ICP drop rate, smooth muscle/collagen ratios and preserved the ultramicrostructure of the tunica albuginea, endothelial and smooth muscle cell	VED prevented penile shrinkage and veno-occlusive dysfunction.	[147]
N/A	6 treatments were given over a 6-week period, using the Duolith SD1 T-Top machine in after radical prostatectomy	A significant improvement in IIEF-5 scores regardless of ED category at baseline	LI-ESWT improved EF after bilateral nerve-sparing radical prostatectomy.	[148]
A randomized controlled trial	12 sessions of penile LI-ESWT using Dornier Aries device after post nerve-sparing radical cystoprostatectomy	Increase in IIEF-EF and EHS scores during all follow-up periods	LI-ESWT recovered potency, although the difference is not statistically significant, but of clinical importance.	[149]
A randomized, controlled trial	Daily penile vibratory stimulation initiated for a period of 6 weeks using FERTI CARE vibrator after nerve-sparing radical prostatectomy	Increased in the IIEF-5 score at 12 months but the difference only reached borderline significance	There was not any significant effect of penile vibratory stimulation.	[134]

(Continues)

TABLE 4 (Continued)

Methods	Treatment	Results	Comments	References
A randomized, controlled trial	VED and/or tadalafil after bilateral nerve sparing robotic prostatectomy	Increased in mean IIEF-5 at months 6, 9, and 12 in the combination group, and in the penile hardness scores at 6 and 9 months.	Men with ED subsequent to prostatectomy had a more rapid and complete return of EF when treated with tadalafil plus VED.	[150]
A randomized, controlled trial	A traditional VED protocol after radical retropubic prostatectomy	Increased in IIEF scores and preserved stretched penile length	Initiating the use of a VED protocol at 1 month improves early sexual function and preserves penile length.	[151]

Abbreviations: ATF4, activating transcription factor 4; BDNF, brain-derived neurotrophic factor; cGMP, cyclic guanosine monophosphate level; ED, erectile dysfunction; EF, erectile function; eNOS, endothelial nitric oxide synthase; HES, erection hardness score; HIF-1α, hypoxia inducible factor-1α; LESW, low-energy shock wave; Li-ESWT, low-intensity extracorporeal shock wave treatment; nNOS, neuronal nitric oxde synthase; PDE5, phosphodiesterase type 5; PERK, protein kinase RNA-like ER kinase; TGF-β1, transforming growth factor beta 1; VED, vacuum erectile device.

intraurethral alprostadil versus sildenafil citrate after nerve-sparing prostatectomy. Intraurethral alprostadil or 50 mg oral sildenafil citrate were given to subjects for 9 months as nightly treatments initiating within 1 month of surgery.[159] After 1-month washout and before sexual activity, subjects self-administered sildenafil citrate (100 mg) for 6 attempts in 1 month. The global assessment question, sexual encounter profile, ED Inventory of Treatment Satisfaction, and measured stretched penile length was significantly better only at 6 months for intraurethral alprostadil as secondary endpoints. Intraurethral alprostadil did not induce significant differences in IIEF- EF domain and intercourse success rates.[159] The rate of spontaneous erection recovery from this drug is still not apparent, and it causes pain that may hinder sexual rehabilitation.

In a clinical study using intraurethral alprostadil injection for 12 months after RP and to evaluate the course and impact on sexual rehabilitation of postinjection penile pain,[160] patients started receiving alprostadil (2.5 mg dosage) and were advised to increase the dose gradually until necessary rigidity is achieved. In patients who were willing and able to use intraurethral alprostadil injection, EF based on the IIEF-15 and Erection Hardness Score improved after 1 year. The pain as the main adverse effect was significant during the first 6 months and decreased over time.[160]

A new topical, noninvasive treatment for ED is alprostadil cream which is the combination of alprostadil and a synthetic PGE1. Its local absorption can be improved directly at the site of effect.[161,162] This makes its use suitable in many circumstances and reduces the risk of adverse events, being systemic adverse events reported in only 3% of the treated population. Its clinical efficacy has been demonstrated in phases II and III trials,[163,164] showing a global effectiveness of up to 83% with the 300 μg dose in patients with severe ED, significantly better than the placebo.[163,164]

1.9 | Vacuum erection devices (VED)

VEDs consist of a clear plastic cylinder connected to an air pump and a vacuum seal placed around the penile base. The manual or electric pump then produces a negative pressure within the cylinder to pull blood into the phallus.[165]

The British Society recommends the management of ED with PDE5i and a VED after RP for Sexual Medicine guidelines.[166] If the erection produced can not be maintained throughout the sexual intercourse, the elastic constriction ring can be placed at the base of the penis for up to 30 min.[166]

Erection with a VED is to be produced mechanically by engorging the corpora and glans with venous blood. This is not dependent on any control of the autonomic or sensory neuronal system. Creating a negative pressure of approximately 150–200 mmHg by VED can increase blood flow into the penis.[167]

Although efficacy rates for VEDs on EF are as high as 90%, rates of satisfaction range between 30% and 70%.[168,169] VEDs have also been used for penile rehabilitation to prevent the progress of ED after RP[170,171] (Table 4).

1.9.1 | Preclinical studies

The effects of VED therapy on ED were investigated at the molecular level in a rat model of BCNI.[145] VED therapy acted on EF by preserving the integrity of smooth muscle and endothelial content, which is provided by antifibrosis, antiapoptosis and antihypoxic mechanisms.[145]

The underlying mechanism of VED in penile rehabilitation after BCNI was analyzed regarding its impact on cavernous oxygen saturation and penile shrinkage.[146] After 4 weeks of therapy, the results showed that penile size was preserved effectively by VED therapy in rats with BCNI. Antihypoxic situation due to increased cavernous blood oxygen saturation is proposed to be the mechanism beneath the beneficial effect of VED therapy.[146]

VED prevented corporeal veno-occlusive dysfunction and penile shrinkage in the BCNI rat models.[147,172] Penile length and intracavernosal pressure of rats were measured after 4 weeks of therapy. Based on the recent data, vacuum therapy is effective to prevent penile shrinkage and veno-occlusive dysfunction in penile rehabilitation, inhibiting apoptosis and activating autophagy. It may be associated with the preservation of structure and function of the tunica albuginea, endothelial cell, and smooth muscle cell contents after 4 weeks of treatment.[147,172]

1.9.2 | Clinical studies

Early initiation of the VED after RP is reported as an effective and simple procedure for penile rehabilitation in numerous clinical trials[145,173–175] (Table 4).

In the first meta-analysis on vacuum therapy for early penile rehabilitation of post-RP men,[176] IIEF-5 score and penile shrinkage were improved significantly in post-RP patients.[176] Thus, early use of vacuum therapy is an effective strategy for preventing ED and penile shrinkage in post-RP men.[176] Moreover, vacuum therapy combined with PDE5i displayed a beneficial effect on penile rehabilitation.[176] Early VED significantly improved IIEF-5 scores with substantially more positive answers for the Encounter Profile question 3 questionnaire.[176]

1.10 | Pelvic floor muscle training (PFMT)

1.10.1 | Clinical studies

The effect of early postoperative pelvic-floor biofeedback training once a week for 3 months on potency recovery after RP[177] was investigated in fifty-two patients. For pelvic-floor biofeedback training, an electromyographic apparatus was used.[177] The IIEF-5 scores were obtained before surgery and 1, 3, 6, and 12 months postoperatively. Patients were considered to have a normal EF when they had a total IIEF-5 score of more than 20. In the treatment group, 47.1% of patients recovered potency 12 months postoperatively, instead of 12.5% in the control group.

In another study,[178] all patients received PFMT for 3 months, and PFMT was organized once a week (first 6 weeks) and once every fortnight (next 6 weeks).[178] Pelvic floor muscles were trained by advanced coordination and analytical exercises, and pelvic floor muscle exercises combined with dual tasks in varying body positions. The primary outcome, EF, improved significantly more in the treatment group than in the control group at 15 months.[178] EF and intercourse satisfaction regarding hardness, length, tumescence, elevation, and persistence of erection were significantly improved between the first and final treatment after 3 months of PFMT.[178]

The effect of perioperative PFMT on early recovery of urinary continence and EF in men undergoing RP[179] was examined in 31 eligible men aged between 45 and 75 years. Based on The IIEF-5 questionnaire evaluating ED, the results demonstrated that the protocol of two supervised PFMT sessions with biofeedback in the preoperative period plus verbal and written instructions to continue the exercises after surgery did not induce a sufficient improvement in continence rates or EF in an early (3 months) evaluation after open retropubic RP.[179]

In a recent randomized controlled trial, early initiation of a high-density (6 sets/day) PFMT before RP had no impact on EF at all time points up to 12 months, compared to "usual care" (3 sets/day) of PFMT.[180]

Although PFMT shows merit in the restoration of EF after RP, scarcity of proper RCTs and the heterogeneity in techniques and protocols of PFMT applied and methodological differences between studies challenge the efforts for generating high-level evidence regarding its efficacy.[181]

1.11 | Other treatment strategies

1.11.1 | Hyperbaric oxygen therapy (HBOT)

Despite the conflicting results in the literature, HBOT is a potential treatment for peripheral nerve injury.[182,183] HBOT shows efficacy in combating infection in compromised tissues, promoting granulation tissue formation, and stimulating angiogenesis.[184]

In a preclinical study, the effects of HBOT have been defined on EF and cavernosal tissue in the rat CNI model.[185] Ten days after CNI, the rats underwent *in vivo* studies for EF. HBOT exhibited a protective effect on ED, and the mechanism seemed to involve neurotrophic and endothelial factors.[185] Cavernosal oxygenation appears as a protective mechanism for EF, and further research may need to answer the question concerning the role of the clinical application of HBOT in patients after RP.[185] The therapeutic effect of stem cell-oxygen-releasing hollow microparticles on ED in a rat model of BCNI was investigated.[186] According to the results, these microparticles improved EF, enhanced cGMP level, and the expression of eNOS and nNOS and reduced fibrosis and apoptosis in the CC when compared with the treatment with only stem cells.[186] Collectively, an oxygen-releasing hollow microparticles system supported prolonged stem cell survival, sustaining the paracrine effect of the stem cells and consequently enhancing EF.[186]

1.11.2 | Platelet-rich plasma

Several studies investigated the effect of platelet-rich plasma on CN regeneration and functional status in a nerve-crush rat model.[132,187] CN electrostimulation was used for EF at 3 months, and results of nerve regeneration demonstrated that the usage of platelet-rich plasma to the site of CNI exerted neuromodulation on the recovery of EF.[132,187]

1.11.3 | Losartan

CNI using a rat model of BCNI causes a decrease in erectile responses and increases apoptosis and oxidative stress.[188] Angiotensin II led to apoptosis and oxidative stress in the CC after CNI and impaired erectile response.[188] Losartan (the angiotensin II type 1 receptor antagonist) significantly prevented corporal apoptosis and oxidative stress by inhibiting the Akt/Bad/Bax/caspase-3 and Nrf2/Keap-1 signaling pathways in the CNI model. Losartan treatment for 4 weeks had a modest effect on EF and significantly prevented corporal oxidative stress and apoptosis.[188]

1.11.4 | Atorvastatin

Recently, atorvastatin treatment in ED in patients who underwent RP was investigated.[189] Patients were randomized to either 80 mg atorvastatin or a placebo daily before undergoing RP. Overall, 118 men with PCa and scheduled for RP were asked to fill out the 5-item version of the IIEF-5 questionnaire before surgery and at 3, 6, 9, and 12 months after surgery. Short-term treatment with atorvastatin before RP conferred no significant benefit on the recovery of the EF in this unselected group of men. However, because the IIEF-5 scores were consistently higher but not statistically significant in the statin part, the authors stress the need for further research regarding the effect of long-term statin treatment on post-RP-ED.[189]

1.11.5 | LIM-kinase 2 (LIMK2) pathway

It has been investigated if ROCK1/LIMK2/Cofilin signaling pathway could be involved in corporal fibrosis after BCNI in male rats to supply the pathophysiologic knowledge on the role of those pathways in the process of ED after RP. The pathway appears to be functional, particularly in the early period after CNI.[190] Although the recovery is incomplete, chronic inhibition of LIMK2 alleviated cavernosal veno-occlusive dysfunction by improving cavernosal fibrosis by normalizing the LIMK2/Cofilin pathway.[191]

In another study, combined inhibition of Jun-amino terminal kinase (JNK) and LIMK2 improved EF by suppressing cavernosal apoptosis and fibrosis via restoration of c-Jun/Bcl-2/Bax and LIMK2/cofilin pathways 10 days after CNI.[192]

In a recent study, a combination of LIMK2 inhibitor and PDE5i did not completely normalize the EF at the acute phase after CNI. However, the degree of improvement by the combined treatment was somewhat greater than that by treatment with LIMK2 inhibitor alone.[193]

1.11.6 | Mitogen-activated protein kinases

The c-Jun N-terminal kinase (JNK) and p38 known as the members of the mitogen-activated protein kinases family have critical roles in the apoptosis of various cells.[194] In an earlier study, it has been shown that an increase in cavernosal apoptosis is accompanied by increased protein expression of phosphorylated JNK and phosphorylated p38 at 4 weeks after CN resection in mice.[195] Currently, it was shown that an increase of JNK phosphorylation is involved in the apoptosis of cavernosal tissue after CNI.[196] Therefore, inhibition of JNK beginning from the immediate post-injury period could help to suppress cavernosal apoptosis.

In a rat model of CNI, JNK inhibition from the early postoperative period did alleviate EF through improving apoptosis of cavernosal tissue related to the JNK-driven pathway.[197] Thus, an early therapeutic strategy targeting the JNK-driven pathway may be able to alleviate cavernosal apoptosis caused by CNI, thereby improving post-RP ED.

1.11.7 | Galanin

Galanin signaling acting in synergy with NO-cGMP in erectile response is upregulated in the major pelvic ganglion in the early phase after CNI, after which it gradually decreases. Based on previous data, galanin upregulation is an essential factor in the endogenous neurodegenerative response to CNI, and modulation of this peptide and its receptors may be of therapeutic significance.[198] Furthermore, galanin has neurotrophic action *in vitro* on neurons isolated from the major pelvic ganglion,[199] and impaired neurite outgrowth was seen by inhibiting endogenous galanin, which primarily occurred in nitrergic neurons. *In vivo* administration of a selective agonist resulted in partial recovery of EF after BCNI.[199]

1.11.8 | Hydrogen sulfide (H_2S)

In a recent study in BCNI rats, H_2S concentrations decreased in penile tissue after BCNI, and NaHS treatment significantly improved erectile response, smooth muscle to collagen ratio, and decreased the expression of osteopontin collagen-I, RhoA, and ROCK1.[200] These results suggest H_2S may be a novel treatment candidate for ED in cases caused by insufficient endogenous penile H_2S production as in CNI.

1.11.9 | Herbal medicine

The most metabolically active extract of Epimedium icariin exerted inhibition on PDE5 *in vitro*.[201,202] In a study by Shindel and colleagues,[203] daily treatment with low-dose, purified icariin improved penile hemodynamic parameters 4 weeks after CNI in a rat model of ED. Improved functional outcomes are observed in icariin-treated animals due to increased penile nNOS and smooth muscle content. These data validate this traditional treatment for erectile problems and appear as a novel and potential strategy to study and treat nerve injuries in human patients.[203]

Administration of Ginko Biloba increases neuronal survival and preserves the nNOS, nerve fiber, and contents of the CC after BCNI. Improvement in EF after treatment with high-dose Ginko Biloba has been observed in a BCNI rat model.[204]

Orally administered *Lycium barbarum* polysaccharides efficiently stimulated recovery of nerve regeneration and erectile functional response[205] being most effective when started on 1st day following CNI compared to 7 and 14 days.

Recently, a flavonol isolated from the stems and leaves of herbs epimedii, icariside II, induced the differentiation of ADSCs to Schwann cells and recovered EF of BCNI rats. The underlying mechanism is possibly involved in regulating microRNA-33 which negatively activated glial cell-derived neurotrophic factor and its p75 neurotrophic receptor.[206]

The administration of Hongjing I granules (a new herbal formula derived from traditional Chinese medicine) improved ED in CNI rats dose-dependent. Furthermore, this herbal treatment increased nNOS expression, Schwann cells viability and promoted neurites regeneration of major pelvic ganglia.[207]

The data mentioned above suggest that several herbal components may protect the peripheral nerve from damage. Also, these alternative natural approaches might protect the cavernosal nerve against crush injury through stimulating the release of neurotrophic factors, increasing neuronal survival, and preserving the nNOS, nerve fibers, and contents of the penile CC.

1.12 | Future perspectives

Although progress in equipment and surgical techniques reduces post-RP ED, the patients may still suffer from neuropraxia, diminished NO production, smooth muscle apoptosis, and penile fibrosis. Radiation-based therapies possibly cause ED via a similar mechanism.[75,76] There is little consensus on the optimal management of ED after RP; however, it is agreed that treatment must be prompt to prevent fibrosis and to increase oxygenation of penile tissue. Increased cavernous hypoxia, apoptosis, and upregulation of profibrotic factors, especially TGF-β1, most probably contribute to ED via structural changes in the cavernosal tissue.

Current treatment regimens rely on PDE5i as first-line therapy combined with other treatment alternatives. Combinations of established treatments will probably be increasingly utilized in the near future as the challenges remain in the clinical adoption of the potential therapeutics which exhibit promising efficacy in the preclinical studies. Moreover, evidence supporting this "combination of established treatments" approach continuously accumulates. A recent systematic review and network meta-analysis evaluated the comparative efficacy of various monotherapies and a combination of approaches in penile rehabilitation.[208] The meta-analysis included studies involving PDE5is, PFMT, vacuum therapy, neuromodulatory therapy, statins, ICIs, hyperbaric oxygenation therapy, and in 8 of them, the combined effect of treatments. Analysis revealed that the combination of VEDs and PDE5is had superior if not equivalent efficacy compared to PDE5 monotherapy or intraurethral alprostadil. A variety of VED plus tadalafil was superior to other interventions regarding the IIEF scores in the 6th month after RP.[208]

Regular or on-demand dosing of PDE5is in penile rehabilitation is another point of debate that should be resolved in the future. Even the most recent meta-analyses reveal conflicting results. According to a network meta-analysis, only regular high-dose PDE5is (regardless of type) was the most effective in restoration of post-RP EF, on-demand dosing being similar to placebo.[209] On the contrary, in another meta-analysis, PDE5is were the most effective strategy in preserving EF compared to placebo, regarding both the mean IIEF score and the ratio of patients with IIEF score >21.[210] However, there was no difference between regular and on-demand PDE5i dosing.

Its fast onset of action and its favorable toxicity profile, and lack of interactions with other drugs make alprostadil cream a therapeutic choice for patients with ED, particularly for individuals who are reluctant to take systemic treatments with adverse events. Further research is needed on novel pharmacological treatment options. For instance, pioglitazone and losartan can be therapeutic agents among men undergoing RP. Recommendations for using pioglitazone and losartan at the clinical level await further support from clinical investigations.

Given the limitations of penile rehabilitation after RP, specific inhibition of JNK and LIMK2 may be a potential mechanism-specific targeted therapy for post-RP ED induced by CNI. Further time-course studies determining treatment effects of JNK and LIMK2/Cofilin inhibition are necessary to make these findings more clinically meaningful. Future studies evaluating the combined JNK inhibitor and LIMK2 inhibitor treatments given at different time points following CNI may determine the maximum protection of cavernosal apoptosis and fibrosis in an animal model of post-RP ED.

The underlying mechanisms of stem cells mainly comprise transdifferentiation and secretion of soluble factors for tissue regeneration, such as endothelial cells, smooth muscle, and cavernous nerves, all of which were damaged to varying degrees in ED. Therefore, stem cell therapy is likely to become a treatment option for ED after RP. The findings from basic research related to ADSCs, the nonhematopoietic p75-derived multipotent stromal cells from adult bone marrow, bone marrow mononuclear cells, neural-like cells, smooth muscle progenitor cells provide support for the therapeutic potential of these treatments on ED after RP. Combined

transplantation of stem cells with PDE-5is, LI-EWST, and growth factors such as glial growth factor-2, NGF-hydrogel, fibroblast growth factor, and BDNF may be effective methods to treat ED following RP and deserve further clinical research. This suggests that protecting the CC smooth muscle cells from fibrosis and apoptosis may represent a more critical treatment goal than nerve protection in future studies using the CNI model.

Vacuum therapy has become an attractive alternative in the case of problems with the PDE5i treatment, such as contraindications or significant side effects. VED is one of three methods used in the clinical setting that improve EF.[96] Early VED had an excellent therapeutic effect in ED patients after RP compared with the controls. The early use of VED is the only method in penile rehabilitation that may be utilized to preserve penile length. Still, the evidence is inadequate, and the proposition is currently doubtful.[145,146,176]

The method of penile vibratory stimulation proved to be acceptable for most patients, and there is a trend towards a better EF with penile vibratory stimulation. Although several studies have evaluated LI-EWST for ED in humans, available data are non-conclusive. Despite the large number of ED patients included in these trials, a common exclusion criterion was prior RP. As a result, there is a lack of evidence examining the efficacy of LI-EWST in patients with post-RP ED. Further explorations of LI-ESWT for ED and 3-dimensional imaging of solvent cleared organs for assessment of microstructural changes are warranted.[144] The use of LI-ESWT was as safe as oral PDE5is. So, LI-ESWT could be an alternative, especially if there are contraindications to PDE5i.[149]

Alprostadil cream combines the efficacy of a well-known therapeutic (alprostadil) with an "easy to use" formulation that does not involve using a systemic route or more invasive topical applications, which has the characteristics to meet all the above-mentioned needs for the treatment of ED.

2 | CONCLUSIONS

ED is frequently observed after RP despite the increasing adoption of minimally-invasive and nerve-sparing surgical techniques. Although it has distinct aspects regarding its etiology and pathophysiology, ED-RP is currently managed using the same treatment options available for standard ED. Limited by the clinical applicability, evidence from basic research suggests a wide variety of possible therapeutic approaches for ED-RP, which should be meticulously investigated for clinical adoption by urologists and the industry.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable – no new data generated.

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