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ANDROLOGY/SEXUAL MEDICINE
REVIEW

Innovative trends and perspectives for erectile dysfunction treatment: A systematic review

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KEYWORDS

Erectile dysfunction;
PDE5 inhibitors;
Herbal treatment;
Stem cells;
Shockwave therapy

ABBREVIATIONS

ADSCs, adipose tissue-derived stem cells;
cGMP, cyclic guanosine monophosphate;
cNOS, constitutive nitric oxide synthase;
ED, erectile dysfunction;
FDA, USA Food and Drug Administration;
(hUCB-)MSCs,

Abstract ***Objective:*** To review contemporary knowledge concerning the innovative trends and perspectives in the treatment of erectile dysfunction (ED).

Methods: Medline was reviewed for English-language journal articles between January 2000 and March 2016, using the terms 'erectile dysfunction treatments', 'new trends' and 'perspectives'. In all, 114 original articles and 16 review articles were found to be relevant. Of the 76 cited papers that met the inclusion criteria, 51 papers had level of evidence of 1a–2b, whilst 25 had level of evidence of 3–4. Criteria included all pertinent review articles, randomised controlled trials with tight methodological design, cohort studies, and retrospective analyses. We also manually reviewed references from selected articles.

Results: Several interesting studies have addressed novel phosphodiesterase type 5 inhibitors (PDE5Is), orodispersible tablets, their recent chronic use, and combination with other agents. A few controlled studies have addressed herbal medicine as a sole or additional treatment for ED. Experimental studies and exciting review papers

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(human umbilical cord blood) mesenchymal stem cells;
ICI, intracavernosal injection;
LI-ESWT, low-intensity extracorporeal shockwave therapy;
NO, nitric oxide;
PDE5Is, phosphodiesterase type 5 inhibitors;
RP, radical prostatectomy;
SC, stem cell;
sGC, soluble guanylate cyclase;
VED, vacuum erectile device;
VEGF, vascular endothelial growth factor

have addressed stem cells as novel players in the field of ED treatment. Other recent articles have revised the current status of low-intensity extracorporeal shockwave therapy in the field of ED. A few articles without long-term data have addressed new technologies that included: external penile support devices, penile vibrators, tissue engineering, nanotechnology, and endovascular tools for ED treatment.

Conclusions: The current treatment of ED is still far from ideal. We expect to see new drugs and technologies that may revolutionise ED treatment, especially in complex cases.

Introduction

Erectile dysfunction (ED) is a worldwide condition and its prevalence is anticipated to increase from 152 million in 1995 to 322 million by 2025 [1]. This projection indicates a growing need to re-evaluate ED therapeutic strategies and mandates robust steps to validate the innovative dugs and technologies that may revolutionise ED treatment. Over the past half century, ED treatment has rapidly evolved and continues to change with more available novel methods of treatment.

Fifty years ago, psychotherapy was the mainstay treatment and undoubtedly was limited in its success. During the 1970s, penile prostheses combined with psychotherapy remained popular but relatively inaccessible. In the 1980s, intracavernosal injection (ICI) emerged, followed by intraurethral therapy in the mid-1990s. The true revolution in the non-surgical management of ED was with the introduction of oral phosphodiesterase type 5 inhibitors (PDE5Is) in the late 1990s and subsequently. PDE5Is rapidly became the patient-friendly method of ED treatment and are currently considered as first-line monotherapy [2]. Currently, three PDE5Is are widely available, i.e., sildenafil, vardenafil and tadalafil. New PDE5Is, including avanafil, udenafil, and mirodenafil are now in clinical use in a few countries, and other compounds are under development [3]. However, PDE5I therapy does have limitations, especially for patients who may need organic nitrates for the treatment of angina.

Low-intensity extracorporeal shockwave therapy (LI-ESWT) has recently been used for treating ED [4,5]. Clinical studies have shown that LI-ESWT has the potential to affect PDE5I non-responders, with few adverse effects. The mechanism of action of LI-ESWT for ED is related to increased expression of vascular endothelial growth factor (VEGF) smooth muscle and endothelial content through recruitment of endogenous mesenchymal stem cells (MSCs) [6]. In the near future, LI-ESWT might be a promising treatment for patients with organic ED. However, further widespread evidence-based basic and clinical studies are needed to confirm its safety and efficacy.

Recently, stem cell (SC) therapy has become a focus of experimental and clinical research for the treatment of ED. Numerous studies have investigated the capacity of SCs for both self-renewal and directed differentiation and hence have confirmed that SCs represent great promise for regenerative medicine. Different therapeutic forms of SCs have been developed, including multiple sources of SCs or progenitor cells, gene-transfected SCs, SC lysates, and SCs seeded on tissue matrices [7]. Furthermore, SCs have been shown to be able to functionally regenerate damaged tissues, depending on the stimuli or signals that they receive [8,9]. Several types including bone-marrow MSCs, adipose tissue-derived SCs, and muscle-derived SCs, have been investigated for neural, vascular, endothelial or smooth muscle regeneration in animal models of ED. Several studies have investigated the potential curative effect of SCs with varying populations and strategies [10]. Currently, SC therapy appears to be one of the most promising treatments of ED.

In summary, the current mainstay treatments for ED are derived from four principal options that consist of: oral therapy, vacuum erectile devices (VEDs), penile injection or intraurethral suppositories, and penile prosthesis. However, of note we are approaching an era

Table 1 Innovative trends in treatment of ED.

I. Phosphodiesterase type 5 inhibitors (PDE5Is)
a. Novel PDE5Is
b. Tadalafil once-daily
c. PDE5Is for LUTS
II. Soluble guanylate cyclase (sGC) activators
a. BAY 60-2770
b. BAY 41-2272
III. Herbal treatment
a. Herbal combinations
b. Resveratrol
c. Pyrazolopyrimidinone analogues
d. Neuromedin B
IV. Stem cells
a. Adipose tissue-derived stem cells (ADSCs)
b. human umbilical cord blood mesenchymal stem cells (hUCB-MSCs)
c. Bone marrow-derived stem cell
d. MSCs and muscle-derived stem cells
e. Combined stem cell and shockwave therapy
V. Low-intensity extracorporeal shockwave therapy (LI-ESWT)
a. The underlying mechanisms of how LI-ESWT improves erection
b. Limitations of LI-ESWT
VI. Vacuum erection device (VED)
VII. External penile support devices
VIII. Penile vibrators
IX. Impulse magnetic-field therapy
X. Tissue engineering
XI. Nanotechnology
XII. Endovascular tools

where new drugs and promising technology in medicine are rapidly growing and quickly becoming applicable. Despite recent advances, satisfactory ED treatment continues to be a clinically challenging entity. Probably, combined therapy may gain widespread acceptance for more refractory and complex cases of ED. The role of these advances in the treatment of ED is broadening and more options will soon be available.

The present systematic review provides insight into the innovative drugs, technological advances, devices, and promising research in the field of ED treatment (Table 1).

Methods

Medline was reviewed for English-language journal articles between January 2000 and March 2016, using the terms 'erectile dysfunction treatments', 'new trends' and 'perspectives'. In all, 114 original articles and 16 review articles were found to be relevant. Of the 76 cited papers that met the inclusion criteria, 51 papers had a level of evidence of 1a–2b and 25 had a level of evidence of 3–4. Criteria included all pertinent review articles, randomised controlled trials with tight methodological design, cohort studies, and retrospective analyses. We also manually searched the references from selected articles for additional relevant publications.

Results

Several interesting studies have addressed the novel PDE5Is, orodispersible tablets, their recent chronic use, and combination with other agents. A few controlled studies have addressed herbal medicine as a sole or additional treatment for ED. Experimental studies and exciting review papers have addressed SCs as novel players in the field of ED treatment. Other recent articles have reviewed the current status of LI-ESWT in the field of ED. A few articles, without long-term data, have addressed new technologies that included external penile support devices, penile vibrators, tissue engineering, nanotechnology, and endovascular tools for ED treatment.

Phosphodiesterase type 5 inhibitors (PDE5Is)

Novel PDE5Is

TPN729MA is a novel selective PDE5I that is currently under development in China for the treatment of ED. In 2015, Gao et al. [11] characterised the preclinical pharmacokinetics of TPN729MA and predicted its human pharmacokinetics using a physiologically based pharmacokinetic model. They found that TPN729MA had good preclinical pharmacokinetics and showed the benefits of using a physiologically based pharmacokinetic model to predict pharmacokinetics in humans. Meanwhile, Wang et al. (2013) [12] investigated the *in vitro* inhibitory potency and selectivity of TPN729MA on PDE isozymes and its efficacy in rat and dog models, they concluded that TPN729MA is a potent PDE5I with a balanced selectivity profile. TPN729MA showed excellent potency both *in vitro* and *in vivo* and a longer effect on erectile function than sildenafil in the rat and dog models.

Ahn et al. (2009) [13] studied another PDE5I, udenafil, and examined its effects on ED and constitutive nitric oxide synthase (cNOS) expression levels in the corpus cavernosum of diabetic rats. They found that udenafil modulated cNOS expression and also had an inhibitory role in cyclic guanosine monophosphate (cGMP) degradation. Further, udenafil demonstrated the ability to compensate for the diabetes-associated changes in the corpus cavernosum.

Tadalafil once-daily

Kim et al. (2014) [14] conducted a study on the comparative efficacy of tadalafil once-daily in men with ED who were partially responders to as-needed sildenafil, tadalafil, or vardenafil. They concluded that tadalafil once-daily is a viable alternative to as-needed PDE5I therapy in men with ED. However, Hatzichristou et al. (2015) [15] explored the impact of patient characteristics and associated comorbidities on treatment continuation rates, effectiveness, and satisfaction in patients with ED, who started or switched to tadalafil 5 mg once-

daily. They concluded that treatment continuation rate or satisfaction does not seem to be significantly affected by the presence of comorbidities in men who choose ED treatment using tadalafil 5 mg once-daily. The magnitude of treatment effectiveness was affected by certain baseline characteristics and comorbid conditions. Formerly, Buvat et al. (2014) [16] studied the continuation and effectiveness of tadalafil once-daily during a 6-month observational study of ED. They found that $>86\%$ of men starting/switching to tadalafil once-daily at baseline continued this plan for $\geqslant 6$ months when they were involved in treatment decision-making. For diabetes-induced ED, chronic administration of PDE5I was studied by Choi et al. [17], who evaluated the effect of chronic administration of PDE5I combined with glycaemic control on diabetes-induced ED. They found that this combined treatment resulted in restoration of overt diabetes-induced ED and it was better than monotherapy with insulin or a PDE5I. Furthermore, Ramirez et al. (2015) [18] reported that 3-month PDE5I therapy enhances insulin sensitivity and improves markers of endothelial function. PDE5Is were also shown to increase testosterone levels, which may further contribute to improved erectile function [19]. All these data are consistent with new findings indicating that PDE5Is may have a beneficial effect on survival in a cohort of men with type 2 diabetes [20]. Another interesting study suggested that combined therapy with testosterone and a PDE5I is safe and effective in treating hypogonadal patients with ED who failed to respond to testosterone monotherapy [21].

PDE5I for LUTS

Recent interesting studies investigated the use of PDE5Is as an effective treatment for both ED and LUTS independently. They assumed that men who have both ED and LUTS/BPH, and are concerned about their sexual dysfunction, might benefit from single-agent, holistic treatment with PDE5I [22].

Soluble guanylate cyclase (sGC) activators

BAY 60-2770

Some patients do not respond to PDE5Is because of very low endogenous nitric oxide (NO) formation and increased oxidative stress, which can inactivate NO and inhibit the activity of sGC. A new class of agents called sGC activators has been shown to increase the catalytic activity of oxidised or heme-free sGC and promote vasodilation in experimental animals when responses to NO donors and sGC stimulators are severely attenuated. BAY 60-2770 is a sGC activator that increases the activity of oxidised sGC; however, the effects of BAY 60-2770 on erectile function have not been determined [23]. Another study showed that BAY 60-2770 would be effective in the treatment of ED when NO bioavailability is reduced, after pelvic nerve injury, and when sGC is oxidised [24]. Furthermore, a more recent study showed that the relaxation induced by the sGC activator, BAY 60-2770, was increased after sGC oxidation and unaltered in the absence of NO. Thus, this class of substances may have advantages over sGC stimulators or PDE5Is for treating patients with ED and extensive endothelial damage [25].

BAY 41-2272

In contrast to the classical NO donors, BAY 41-2272 directly stimulates sGC and increases the sensitivity of the enzyme to NO, generating significant amounts of cGMP by stimulating the sGC via NO-independent mechanisms. Through this mechanism, BAY 41-2272 produces a variety of effects, including anti-aggregatory, anti-proliferative, and vasodilatory effects [26]. In rats, 4-week therapy with BAY 41-2272 prevented the impaired corpus cavernosum relaxations of rats treated chronically with L-NAME, indicating that accumulation of cGMP into erectile tissue counteracts the NO deficiency [27].

Herbal treatment

Herbal combinations

Herbal medicine is assumed to be advantageous because it is ‘natural’; moreover, it can be used to treat isolated symptoms in addition to maintaining general well-being. Shin et al. (2015) [28] focused on the ability of oriental herbs to enhance physical health, including sexual function. They reviewed the current status of Korean preclinical or clinical studies of the application of oriental herbs to sexual medicine such as Korean ginseng, Korean red ginseng (*Panax ginseng*), extract of tissue-cultured Korean mountain ginseng, *Ginkgo biloba*, *Rubus coreanus*, *Schisandra chinensis*, *Epimedium koreanum*, *Lepidium meyenii*, male silkworm extract, *Artemisia capillaris*, *Cuscuta chinensis*, garlic, mixtures of multiple plants. They emphasised the beneficial effect of these herbs over Western-style drugs for treating ED. Pavan et al. (2015) [29] also concluded that plants and extracts containing polyphenols, especially a class of compounds called kraussianones, appear to be particularly effective and promising in the treatment of ED. Kotirum et al. (2015) [30] reported on the efficacy of Tongkat Ali (*Eurycoma longifolia*) herbal extract on erectile function improvement. A histopathological study conducted by Ayuob et al. (2014) [31], on the chronic use of *Ferula harmonis* in mice to enhance erectile function, found that chronic administration significantly decreased the level of testosterone and partially impaired fertility. Histopathological degenerative changes and a significant reduction in oestrogen receptor β expression were observed in the fertility organs: testes, epididymis, and seminal vesicle.

For combined therapy, a study conducted by Ferrini et al. (2015) [32] found that an oral combination of ginger, *Muira puama*, *Paullinia cupana* and L-citrulline seems to be as effective as daily PDE5I therapy in either delaying or reversing the onset of the ageing-related histological and functional characteristics associated with ED.

Resveratrol

Bai (2015) [33] found that resveratrol improved diabetes-associated ED in rats. Combined therapies with resveratrol and sildenafil have a synergistic effect in improving ED. The mechanisms might be attributed to its anti-oxidative properties and upregulation of the NO-cGMP signalling pathway.

Pyrazolopyrimidinone analogues

Sawant et al. (2015) [34] stated that a novel pyrazolopyrimidinone analogue (compound-4a) may act as new alternative and as potent inhibitor of PDE5 compared with the classic PDE5Is sildenafil, vardenafil, tadalafil, and avanafil. They found that the new compound had better *in vivo* efficacy and good physicochemical properties.

Neuromedin B

Nishimatsu et al. (2015) [35] reported that neuromedin B restored erectile function via protection of the cavernosal body and survival enhancement of the associated nerves. Ultimately, in the future, neuromedin B may be a useful tool in the treatment of patients with ED with severely damaged cavernosal bodies.

Stem cells (SCs)

Adipose tissue-derived SCs (ADSCs)

SC research is now emerging as a new modality in the treatment of ED. Recently, Chen et al. (2016) [36] investigated the mechanism by which ADSCs can ameliorate cavernosal nerve injury-induced ED in rats. They found that ICI of ADSCs improved erectile function, repaired the nerve, and corrected penile fibrosis. Another recent preclinical study by Soebadi et al. (2016) [37] showed evidence of SCs as a potential curative treatment for ED, and further early phase clinical trials are currently being performed. They concluded that both MSCs (stromal) from bone marrow and ADSCs had produced positive effects on erectile function in various animal models of ED. Liu et al. (2015) [38] found that treatment with hepatocyte growth factor-modified ADSCs could significantly enhance the beneficial effect of ADSCs on erectile function in diabetic rats, and this effect might be closely related to the down-regulation of the $TGF\beta_1$-Smad signalling pathway.

Yang et al. (2015) [39] found that ICI of ADSCs resulted in substantial recoveries of erectile function after cavernosal nerve cryoinjury. They claimed that the effects may be achieved through the elevated level of neurotrophic factors in penile tissue and subsequent neuroregenerative effects. In another condition with structural deformity of the penis, Gokce et al. (2015) [40] studied the effect of local injection of ADSCs or ADSCs and interferon α-2b on the reduction of Peyronie's-like manifestations. They hypothesised that these effects might be due to a decrease in the expression of tissue inhibitors of metalloproteinases. This study documented that transplantation of genetically modified ADSCs, with or without human interferon α-2b, attenuated Peyronie's-like changes and enhanced erectile function in a rat model.

Human umbilical cord blood MSCs (hUCB-MSCs)

Song et al. [41] (2016) hypothesised that ICI of brain-derived neurotrophic factor-hypersecreting hUCB-MSCs can ameliorate ED in a rat model of cavernosal nerve electrocautery injury. They concluded that the mechanism could be via enhancement of the recovery of erectile function, promotion of the cavernosal nerve regeneration, and inhibition of corpus cavernosum fibrosis after cavernosal nerve electrocautery injury in a rat model. Recently, Levy et al. (2016) [42] conducted a human study on a very limited number of patients to determine the feasibility and effects of using placental matrix-derived MSCs in the treatment of patients with ED. Two patients for whom previous oral therapies failed had the ability to sustain erections on their own. At the 3-month follow-up, one additional patient was able to achieve erections on his own. This is one of the first human studies to report on the feasibility of using SC therapy to treat patients with ED. Further investigations with larger sample sizes should be conducted

Bone marrow-derived SCs

Yiou et al. (2015) [43] studied ICI of bone marrow-mononuclear cells as a promising treatment approach for post-radical prostatectomy (RP) ED. They concluded that there were significant improvements in erectile function and penile vascularisation, whilst no serious side-effects were encountered.

MSCs

Yiou et al. (2016) [44] studied the regenerative properties of MSCs and reported the ability of MSCs to repair multiple types of damage, especially those seen after RP. Also Xu et al. (2015) [45] found that muscle-derived SCs in rat corpus cavernosum may have therapeutic potential in the treatment of organic ED. In a prevention study, Takayanagi et al. (2015) [46] showed that i.v. preloading of MSCs before cavernosal nerve injury could prevent or reduce experimental ED.

Recently, Xin et al. (2016) [47] performed a search of PubMed for articles related to contemporary evidence regarding: (i) SC niche and SC biological features *in vitro*; (ii) localisation and mobilisation of endogenous SCs; (iii) existing evidence of penile endogenous SCs and their possible mode of mobilisation in a wide range of basic studies. They concluded that numerous evidences hold the promise that endogenous SCs would be a novel therapeutic approach to ED treatment.

Combined SC and low-intensity extracorporeal shockwave therapy (LI-ESWT)

In a study of combined methods of ED treatment, Jeon et al. (2015) [48] investigated combined therapeutic efficacy of human ADSCs application on injured cavernosal nerve and LI-ESWT on the corpus cavernosum in a rat model of post-RP ED. In their study, hADSCs showed effect on recovery of injured cavernosal nerve and LI-ESWT improved angiogenesis in the corpus cavernosum.

Low-intensity extracorporeal shockwave therapy (LI-ESWT)

Several previous clinical and experimental studies had demonstrated the effect of LI-ESWT on erectile function [4–6]. A more recent pilot study on 58 patients with mild-to-severe ED aimed to assess the safety and efficacy of LI-ESWT on patients with vasculogenic ED. Erectile function was evaluated by the International Index of Erectile Function and Sexual Encounter Profile and Global Assessment questionnaires, at baseline and at 1, 3, and 6 months after treatment. The preliminary results suggested that LI-ESWT could add a new perspective to the treatment of ED [49]. Furthermore, in a pilot study conducted on patients who had undergone robot-assisted bilateral nerve-sparing RP, the authors suggested that LI-ESWT may improve erectile function in such patients [50].

The underlying mechanism of how LI-ESWT improves erection

The mechanism of LI-ESWT is far from clearly understood. Several studies have explored the possible mechanism with diabetic animal models. These studies have shown the beneficial effect of LI-ESWT on ameliorating injured tissues or cells including neovascularisation, and improvement of smooth muscle and endothelial cells in the penis of diabetic ED animal models. At the same time recruiting endogenous MSCs with up-regulation of α-smooth muscle actin, von Willebrand factor, neuronal NOS, and VEGF, and down-expression of the receptor for advanced glycation end products [51,52].

Limitations of LI-ESWT

To date, the total number of treated patients is relatively low. In addition, the standardisation of the technique is not well established and the current protocol, shared by most studies, is empirical and preliminary. Furthermore, the target population who will benefit from this technique has not yet been adequately defined. Finally, there are insufficient data on the underlying mechanism of action of LI-ESWT at the cellular, histological, and molecular levels. Long-term, multicentre studies are needed to discover the optimal treatment protocols and the modifications to improve efficacy and durability [53].

Vacuum erectile devices (VEDs)

Although the VED was first approved by the USA Food and Drug Administration (FDA) in 1982 [54] and recommended as one of the alternative treatments for organic ED by the AUA in 1996 [55], it was not a very popular treatment for ED until the concept of penile rehabilitation was introduced in patients with prostate cancer after RP. The mechanism of VED therapy for ED after RP was not clear. Recent studies with the use of a unique rat model showed that VED therapy preserves erectile function through anti-hypoxic, anti-apoptotic, and anti-fibrotic mechanisms by improving the arterial blood flow into the penis [56,57].

Due to the unpredictable response of PDE5I in the treatment of refractory ED, the use of the VED has resurged and is becoming the first-line therapy in the treatment of ED after RP. Currently, the combined therapy of VED with either PDE5I or ICI was advocated for post-RP ED [58]. Another study, evaluated the efficacy of adding VED in diabetic men with severe ED who were PDE5I non-responders. The authors found that combined use of sildenafil and a VED significantly enhanced erectile function and improved the outcome [59].

External penile support devices

A recent mechanical device called 'Erektor' is applied externally with no need for surgical intervention. It is introduced to strengthen penile rigidity and enhance length and is used only during sexual intercourse. The device was introduced by Global Life Technologies and has received media coverage in the *Urology Times* magazine (http://business.highbeam.com/137412/article-1G1-200116245/external-support-device-alternative-ed-medications) [60]. This external support device is composed of two rings attached to an interspaced rigid rod. The penile shaft is placed within the rings and the rigid rods lie along the ventral aspect of the penis. The penile shaft is stretched when the device is worn and intercourse may then ensue. Each device is individually

customised to the patient's phallic length. Similar devices with better configuration and function are required to help patients with end-organ failure who may not be eligible for, or cannot afford, penile implants.

Penile vibrators

The first penile vibratory stimulation in a man with spinal cord injury was reported with a hand-held device in 1970 [61]. Refinements in technique, advancements in technology, and portability led to the first approval of penile vibratory stimulator (Viberect) by the FDA for ED treatment in July 2011. The device has received a remarkable media and commercial interest after its FDA approval. The mechanism of action is proposed to be through vibratory stimulation to branches of the pudendal nerve alongside the penile shaft. Stimulation of the pudendal nerve causes a reflex parasympathetic erection through an activation of the parasympathetic pathway by pelvic nerves and non-adrenergic non-cholinergic fibres [62]. The Viberect device applies external stimulation of cavernosal nerve fibres that induces NO release from nerve terminal endings [63]. Another proposed option for using the device is for penile rehabilitation after nerve-sparing RP. Prospective controlled clinical trials are necessary to evaluate its long-term efficacy.

Impulse magnetic-field therapy

Magnetic fields in adequate forms and doses can increase oxygen uptake by the cell, enhance blood circulation, and reverse functional impairment. Magnetic-field therapy has gained interest in the field of sexual medicine. A pioneer study investigated impulse magnetic-field therapy on patients with neurogenic ED and healthy volunteers. The study concluded that magnetic stimulation is a simple, noninvasive method that could induce penile engorgement and indicated this therapy might be suitable for patients with ED [64]. Another double-blind, placebo-controlled study assessed the efficacy of 3 weeks of impulse magnetic-field therapy for ED and found that impulse magnetic-field therapy improved erectile function [65]. However, prospective well-designed controlled clinical studies are required to evaluate its long-term efficacy and to verify the safety profile and side-effects.

Tissue engineering

The construction of a biological penile prosthesis has gained much interest in recent decades. The earliest known biological reconstruction of the penis due to ED was in 1936, when bone cartilage, the 'artificial os penis' was used to create scaffolding for post-traumatic penile reconstruction [66]. However, due to the poor cosmesis and function of the penis, this type of surgery was discarded [67,68]. Other studies have shown the ability to grow cartilaginous rods by seeding bovine chondrocytes onto a polyglycolic acid polymer infrastructures and further successful implantation of these cartilage rods into the corporal spaces of rabbits [68]. Several lines of research and developments have emerged in the field of tissue engineering for corporal bodies and tunica albuginea replacement and repair. Seeding human corporeal smooth muscle cells on polymer scaffolds to create a neo-corpora has been reported [69]. Further studies have examined the implantation of smooth muscle cells and endothelial cells seeded onto three-dimensional corporal collagen matrices and demonstrated the creation of a neo-corpora, which exhibited good intracorporeal pressures to attain erection [70]. Such new technology and innovative biological substitutes will open the door for the treatment of ED and replacement of the injured, diseased, or malfunctioning penis. Although, to date, there has been no real application of these innovations in men; however, the future of innovative biological substitutes as alternatives to a penile prosthesis seems very promising.

Nanotechnology

Basically, nanoparticles are packages of molecules that are similar in size to viruses, which can be synthesised to encapsulate biologically active materials. In the field of ED management these nanoparticles can carry active agents such as PDE5Is. This technology can help to topically deliver the active agents to the penile shaft to achieve erection, whilst minimising the side-effect profiles of oral or other methods of delivery.

An experimental investigation, using of tadalafil, sialorphin and NO to create topical gel nanoparticles was reported. Nanoparticles encapsulating erectogenic agents were applied to the glans and penile shaft of rats. The control group consisted of a similar group of rats that received nanoparticles without the encapsulated erectogenic agents, applied in the same area and in a similar manner. The results revealed a significant erectile and intracavernosal pressure response in the experimental group vs the control group [71]. In a more recent study, Lin et al. (2016) [72] used ADSCs magnetised with nano-Shuttle magnetic nanoparticles to create nano-ADSCs. They found that magnetisation of ADSCs with nano-Shuttle magnetic nanoparticles kept ADSCs in the corpus cavernosum and improved ADSC therapy for ED in a rat model. However, to date, there are no clinical data for humans. The application of this technology to provide localised therapy for ED may soon enter into practice to provide a new option for

patients who are looking for more conservative treatment. A nanoparticle delivery system may ultimately revolutionise the therapy for ED. Hence, further studies are warranted to fulfil the criteria of efficacy and safety of this innovative technology.

Endovascular tools

Although microsurgical vascular reconstruction for penile artery insufficiency has been possible for several decades, this kind of procedure had not stood the test of time and unfortunately resulted in a wide range of complications. Furthermore, the AUA had not supported such procedures. Recently, new technology using a peripheral stent system had gained a lot of interest. Zotarolimus-Eluting for the treatment of ED was the first trial to investigate the use of the drug-eluting stent. It was launched in 2009 in patients with ED caused by internal pudendal artery stenosis refractory to PDE5I. The results of the study showed improvement in erectile function in a high portion of patients [73]. No adverse events or complications were reported. Long-term larger scale controlled trials are needed to confirm using stents as an option for patients with arteriogenic ED.

Balloon dilatation of the internal pudendal artery secondary to peripheral arterial disease has also been reported. Babaev and Jhaveri (2012) [74] reported significant improvement in erectile function after balloon dilatation of the internal pudendal. Various sized drug-eluting coronary stents were additionally positioned within the pudendal artery with a favourable outcome. All patients were discharged on the same day and reported improvement of erectile function during the follow-up period.

In patients with a veno-occlusive dysfunction, endovascular treatment with selective embolisation therapy has shown to be a safe and effective method of treatment for ED. Herwig and Sansalone (2015) [75] evaluated the effectiveness of pelvic vein embolisation with the sclerosing agent aethoxysclerol using an aeroblock technique for the treatment of ED due to venous leakage in men using sildenafil. This new pelvic veno-ablation technique was effective, minimally invasive, and cost-effective. All patients were able to perform sexual intercourse without the need for the previously used dosage of PDE5I. This new method may help those patients with contra-indications to PDE5Is, or in patients who cannot afford the frequent usage of expensive oral medication or PDE5I non-responders. Another study reported the effect of embolisation of the dorsal penile vein with a mixture of *N*-butyl-2-cyanoacrylate tissue adhesive and LIPIODOL ULTRA. The results revealed recovering from poor erection in 24/27 (88%) of the patients with no complications [76]. However, prospective well-designed controlled clinical studies are required to approve and validate the procedure.

Conclusions

There is emerging information and novel technology available to improve upon even the well-established treatments for ED treatment. This information will probably open the door for advancement and promotion of ED treatment. The current treatment of ED is still far from ideal. We expect to see new drugs and technologies that may revolutionise ED treatment, especially in complex cases. The dream of ED becoming a curable condition may be feasible in the near future.

Conflicts of interest

None.

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None.

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