

Review Article

Male sexual health and dysfunction

pISSN: 2287-4208 / eISSN: 2287-4690
World J Mens Health 2021 Jan 39(1): 48-64
<https://doi.org/10.5534/wjmh.200007>



Novel Emerging Therapies for Erectile Dysfunction

Soyeun Kim¹, Min Chul Cho², Sung Yong Cho³, Hong Chung⁴, Mahadevan Raj Rajasekaran⁵

¹Department of Family Medicine, Korea Cancer Center Hospital, ²Department of Urology, SMG-SNU Boramae Medical Center, Seoul, ³Department of Urology, Inje University Ilsan Paik Hospital, Goyang, ⁴Department of Urology, Konkuk University School of Medicine, Chungju, ⁵Department of Urology, San Diego VA Health Care System & University of California, San Diego, CA, USA

Currently, several treatments exist for the improvement of erectile dysfunction (ED). These include medical therapies such as phosphodiesterase type 5 inhibitors (PDE5-Is), invasive methods such as intracavernosal injection therapy of vaso-active substances, vacuum erection devices, and penile prosthesis implants. However, the percentage of patients that are unresponsive to available treatments and who drop out from treatments remains high. Current evidence reveals that the pathogenesis of ED is related to multiple factors including underlying comorbidities, previous surgery, and psychological factors. Diverse approaches using novel molecular pathways or new technologies have been tested as potential therapeutic options for difficult-to-treat ED populations. Melanocortin receptor agonist, a centrally acting agent, showed promising results by initiating erection without sexual stimulation in non-responders to PDE5-Is. Recent clinical and pre-clinical studies using human tissues suggested that new peripherally acting agents including the Max-K channel activator, guanylate cyclase activator, and nitric oxide donor could be potential therapies either as a monotherapy or in combination with PDE5-Is in ED patients. According to several clinical trials, regeneration therapy using stem cells showed favorable data in men with diabetic or post-prostatectomy ED. Low-intensity shock wave therapy also demonstrated promising results in patients with vasculogenic ED. There are growing evidences which suggest the efficacy of these emerging therapies, though most of the therapies still need to be validated by well-designed clinical trials. It is expected that, should their long-term safety and efficacy be proven, the emerging treatments can meet the needs of patients hitherto unresponsive to or unsatisfied by current therapies for ED.

Keywords: Erectile dysfunction; Extracorporeal shockwave therapy; Guanylate cyclase; Melanocortins; Nitric oxide donor; Stem cells

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Erectile dysfunction (ED) is defined as the “consistent inability to attain or maintain a penile erection, or both, sufficient for adequate sexual relations” [1]. It is a common disease that can have an adverse effect on men’s health and quality of life. The prevalence of ED reported in epidemiological data vary depending on

patient age group and definition used. In the United States, it has been reported that ED affects 52% of men aged 40 to 70 years and more than 70% in men older than 70 years [2-4]. In the past, ED was considered a purely psychogenic disorder; however, current evidence suggests that the pathogenesis of ED is related to a multitude of factors. Up to 80% of patients have, at least partly, an organic etiology [5]. ED is associated

Received: Jan 10, 2020 **Accepted:** Jan 27, 2020 **Published online** Mar 16, 2020

Correspondence to: Mahadevan Raj Rajasekaran <https://orcid.org/0000-0003-4188-1628>

Department of Urology, San Diego VA Health Care System, (151) 3350 La Jolla Village Drive, San Diego, CA 92161, USA.

Tel: +1-858-552-7114, **Fax:** +1-858-552-7436, **E-mail:** mrajasekaran@health.ucsd.edu

with many comorbidities and risk factors including age, obesity, smoking, alcohol, diabetes, cardiovascular disease, depression, prior pelvic surgery, and spinal cord injuries, as well as other psychological variables [6-15].

There are various non-invasive and invasive treatments currently available to improve ED. The American Urological Association guidelines acknowledge that any treatment option may be used as a first-line therapy [16]; however, phosphodiesterase type 5 inhibitors (PDE5-Is) are the most commonly suggested and used first-line treatment option. Invasive treatment encompasses intracavernosal injection (ICI) with vaso-active substances, intraurethral suppository of prostaglandin E1 (PGE1, alprostadil), vacuum-assisted erectile device (VED), and penile prostheses [17,18]. Despite the non-invasive nature and excellent efficacy and safety of PDE5-Is, a non-negligible portion of ED patients do not respond to these drugs due to underlying comorbidities or previous surgery [17]. The high prevalence of non- or less-responders combined with the unmet needs in currently available therapies have prompted investigation toward the development of emerging treatment options. Different molecular pathways and diverse approaches must be studied to provide therapeutic options for a larger patient population. In this paper, we conduct a review of current treatments for ED and their limitations, and provide an overview of the novel treatments in development.

CURRENT THERAPIES FOR ERECTILE DYSFUNCTION AND THEIR LIMITATIONS

1. Phosphodiesterase 5 inhibitors

The most commonly used treatment for ED is PDE5-Is. PDE5-Is have been several beneficial effects in erectile dysfunction caused by a variety of factors. Up to 60% of patients who take PDE5-Is as first line on-demand treatment show a good response, defined as erection with sufficient rigidity for penetration [17,19]. Another study showed that 59% of ED patients with type 2 diabetes mellitus taking PDE5-Is had successful intercourse compared to 14 % of those taking a placebo [20]. Tadalafil was approved as a low dose (5 mg) daily regimen, as well as a classical on-demand regimen [21]. Both daily and on-demand dosing of tadalafil have been shown to exhibit the same efficacy [22]. However, daily regimen may increase the ability for spontaneity

of sexual intercourse.

Although the expression of the PDE5 gene is highly detected in penile corpora cavernosa (CC) [23], the PDE5 gene has also been expressed in other portions of the male genital tract, as well as other organs in males, including skeletal muscle, lung, stomach, thyroid, and adrenal gland. This distribution is related to the adverse effects of PDE5-Is. The possible adverse events of this non-invasive drug therapy include myalgia, headache, heartburn, facial flushing, nasal congestion, and vision-related conditions, such as macular degeneration, retinitis pigmentosa, and non-arteritic anterior ischaemic optic neuropathy [24,25]. For PDE5-Is to work, patients with ED must have an intact molecular and nervous system pathway, as well as a degree of sexual stimulation. Therefore, PDE5-Is have shown a lack of efficacy in some disease states affecting the upstream nitric oxide (NO) pathway [25]. These disease states include diabetes with peripheral neuropathy [11,26], denervation after radical prostatectomy (RP) for prostate cancer [27], condition of damaged nerves critical for attaining erection, hypogonadal conditions, and Peyronie's disease (and its subsequent veno-occlusive disease). Therefore, there is a need for additional pharmacological treatment options for ED, especially for those patients who are unresponsive to PDE5-Is.

2. Intracavernosal injection

ICI is a treatment involving the injection of vaso-active substances directly into the CC at the lateral base of the penis *via* a small needle. These vaso-active medications include PGE1 (alprostadil), papaverine, and phentolamine. These medications can be used as a PGE1 monotherapy or as a formula combined with one or two other drugs (bi-mix of papaverine and phentolamine; tri-mix of prostaglandin E1, papaverine, and phentolamine).

ICI may be preferred in certain patients who are poor responders, cannot tolerate oral medications, or who are on medications contraindicated with ED-treating oral medication. Other ideal candidates for intracavernosal agents are patients who have damaged nerves for erection [28]. The main barrier to the use of ICI is patients' understandable fear of injecting the penis [29]. It is known that initial satisfaction rates following ICI are high, and that 94% of patients were satisfied with a successful erection with in-office titration [28,30]. However, dropout rates with ICI are also

high—46% to 80% of patients abandoned treatment in the first year [31,32]. Causes of dropouts included high cost, problem of injection, lack of partner, and desire for a permanent solution [33].

3. Intraurethral prostaglandin E1 suppository

Intraurethral PGE1 suppository (IUS) uses a small intraurethral delivery catheter to place a PGE1 within the urethra for absorption through the CC before sexual intercourse. This is similar to alprostadil ICI, but is less invasive and less effective than ICI [28]. This route of administration may be preferred in patients who are poor responders, are contraindicated for oral medication, or have fear of injectable medications. IUS efficacy was reported to be between 45% and 65% depending on the group of enrolled patients [34,35]. IUS use for post-RP patients showed similar efficacy to sildenafil. However, the dropout rate of the IUS group was higher than that of sildenafil group [36]. The most common side effect and cause of discontinuation was penile or urethral pain [37,38]. Patients with urethral disease, such as urethral stricture, or with high risk for priapism should use IUS with caution. Adverse effects related to dose are dizziness, sweating, and hypotension, [39,40].

4. Vacuum erectile device

The VED is a device placed over the penis. The effect of VED on erection was reported to be over 75% and up to 90% [41,42]. Though the effect of VED on penile rehabilitation following RP remains controversial, a VED may be employed as part of a rehabilitation program to decrease the risk of corporal fibrosis and to assist with erectile function [43]. However, discontinuation rate was also high—up to 30% due to bruising, pivoting at the base of penis, decreased orgasm, problems related to constriction band including pain, and temporary change to penile sensation [44]. It may be difficult for patients with large lower abdominal fat and/or buried penis to use this device because they have a less usable penile shaft. Adverse reactions including petechiae and haematoma have been reported [45]. Caution is necessary in patients taking anti-coagulants because there is a greater risk of penile bruising.

5. Penile prosthesis

The penile prosthesis is a surgically implanted device which has undergone an evolution over the past

40 years, resulting in a more effective and reliable treatment for advanced erectile dysfunction which has failed to respond to other less invasive approaches or where these approaches are contraindicated or unacceptable to the patient.

The most common device implanted in penile surgery is the three-piece inflatable penile prosthesis (IPP) [46]. The 5- and 10-year overall survival of modern prosthetics is estimated to be 90.4% and 86.6%, respectively [47]. Patient satisfaction rate ranges from 90% to 100% and varies by prosthetic device [48,49]. However, IPP may be provided only to those patients who fail more conservative treatment because of its high cost, invasiveness, and myriad potential complications. Complications related to IPP implantation include infection, distal cylinder erosion, auto-inflation, pump migration, and reservoir displacement [50]. Infection is the most serious complication, but since the development of antibiotic and hydrophilic coatings, infection rate is decreasing [48].

EMERGING THERAPIES FOR ERECTILE DYSFUNCTION

1. Centrally acting treatments: melanocortin receptor activator

Melanocortins are a group of central neurochemistry peptides mediating sexual behaviors.

The initiation of erections without sexual stimulation distinguishes the mechanism of action of melanocortin agonists from the PDE5-Is. Melanotan II (MT-II) is a superpotent cyclic alpha-melanocyte-stimulating hormone analog. In a small double-blind placebo-controlled crossover study of psychogenic ED patients, eight out of ten men reported apparent erections with regard to penile rigidity and the significant duration of erection after subcutaneous injection of the MT-II (0.025 mg/kg). Mean duration of tip rigidity of the penis (80%–100%) was 38 minutes with injection of MT-II *versus* 3 minutes with placebo. The most frequent side effects reported were yawning, nausea, and decreased appetite [51]. Another study indicated that the erectogenic action of MT-II was effective not only for treatment of psychogenic ED, but also for treatment of ED from variable organic risk factors [52]. These findings were also confirmed in other double-blind, placebo-controlled crossover study. Ten men with psychogenic ED and

Ten men with organic ED received subcutaneous injections of MT-II. Seventeen out of 20 men reported penile erection from at least one of two injections of MT-II in the absence of visual sexual stimulation (VSS). A total of 68% of subjects with MT-II injections reported increased sexual desire (*versus* 19% in the placebo group). At the preferred dose (0.025 mg/kg), 13% of subjects injected with MT-II reported severe nausea [53]. Furthermore, the reported latency time of 113 minutes is quite long for a clinically useful drug. The addition of erotic stimulation could lead to a more rapid response. Based on the reported adverse effects, such as severe nausea, as well as the long latency time, investigators doubted the clinical utility of MT-II. No further clinical trials have been performed.

Bremelanotide is a carboxylated metabolite of MT-II, and was formerly known as PT-141. Bremelanotide is delivered intranasally using a disposable, single-use, metered dose delivery device. In the phase 1 study, of 32 healthy male subjects, the 10 mg and 20 mg doses of PT-141 resulted in a significantly greater duration of base rigidity $\geq 80\%$. Doses up to 20 mg PT-141 were safely administered to healthy male subjects [54]. In the phase 2A study, the administration of a 20 mg PT-141 dose led to significantly greater duration of base rigidity $\geq 80\%$ compared to placebo. Mean duration of base rigidity $\geq 80\%$ was about 24 minutes at 20 mg dose. The duration of onset was approximately 30 minutes. Single doses up to 20 mg were safely administered and well-tolerated in most ED patients. The most commonly reported adverse events were flushing and nausea [54]. Another study evaluated the effect of stem cell (SC) administration of PT-141 on healthy subjects and on patients with ED who reported an inadequate response to sildenafil. The erectile response increased significantly at 4 mg and 6 mg SC doses of PT-141 with VSS [55]. Single doses up to 10 mg (healthy male subjects) and up to 6 mg (ED patients) of PT-141 were safely administered and well-tolerated. The most common adverse effects were flushing, somnolence, nausea, vomiting, headache, diaphoresis, and lower back pain [55]. In an at-home setting, the 342 ED patients who were non-responsive to sildenafil citrate were randomly divided to receive either PT-141 (10 mg) as an intranasally spray (n=172) or placebo (n=170) between 2 hours and 45 minutes before sexual activity. The efficacy of the treatment was assessed using the international index of erectile function (IIEF) score, the mean intercourse satisfaction

domain, and number of weekly coitus episodes. In the bremelanotide group, 51 subjects (34%) reported significantly better results compared to placebo (9%), including ability to attain and maintain an erection sufficient to allow sexual intercourse, and greater intercourse satisfaction. Reported adverse effects were similar to other studies [56]. A study for co-administration of PT-141 and a PDE5-I was also conducted in 19 men with ED who were responders to sildenafil or vardenafil in order to evaluate an addictive or synergistic effect on erectile response. The erectile response induced by co-administration of PT-141 (7.5 mg) and sildenafil (25 mg) was significantly greater than the response elicited by administration of sildenafil alone [57]. The combination regimen was safe and well-tolerated and did not result in new adverse events or adverse events that were increased in frequency or severity compared with monotherapy [57]. Bremelanotide (Vyleesi™) has recently been approved in the United States for the treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder [58]. Given the promising erectogenic effect and safety, bremelanotide may provide an emerging treatment option to treat male ED patients, as well. However, further well-designed studies are needed to reach firm conclusions on long-term efficacy and safety for treatment of ED. The results of studies about centrally acting agents are summarized in Table 1.

2. Peripherally acting treatments

1) New phosphodiesterase type 5 inhibitors: SLx-2101, phosphodiesterase type 5 inhibitor topical agent, phosphodiesterase type 5 inhibitor sublingual dispersal agent

SLx-2101 is a PDE5-I currently under development. SLx-2101 is particularly interesting because it is metabolized to SLx-2081, an active metabolite. SLx-2081 extends its activity and may therefore clinically provide an even longer duration of benefit to ED patients. The half lives of SLx-2101 and SLx-2081 are 8 to 13 hours and 9 to 14 hours, respectively [59]. A clinical study suggested that a single dose of SLx-2101 was safe and tolerated in healthy volunteers, making it a candidate for once-daily dosing. RigiScan data showed positive effects at 0 to 6 hours post-dose in the absence of VSS for 10, 20, 40 and 80 mg doses and at 24 to 24.5 hours post-dose in the presence of VSS for 20, 40, and 80 mg doses.

Table 1. Summary of emerging therapy for ED: centrally acting agents

Compound	Type of study	Route and dosage of administration	Population studied	Main findings	Date (year)	Author
PT-141	Phase I	Intranasal 7–20 mg	Healthy men (n=30)	Mean duration of base rigidity ≥60% increased from 49.4 to 137.7 min for subjects receiving the 7–20 mg PT-141 doses (placebo: 20.6 min). Flushing and nausea were the most common adverse events reported.	2004	Diamond et al [54]
	Phase IIA		Viagra-responsive ED (n=24)	Mean duration of ≥60% base rigidity was 26.0 and 53.8 min for patients receiving the 7 and 20 mg PT-141 doses (placebo: 18.5 min). Flushing and nausea were the most common adverse events reported.		
PT-141	Phase I	Subcutaneous 0.3–10 mg	Healthy men (n=48)	Erectile response increased at doses greater than 1.0 mg. Mean duration of base rigidity ≥60% increased from 18 to 73 min for subjects receiving the 1.0–10.0 mg PT-141 doses (placebo: 6 min). Single doses up to 10 mg were safely administered and well-tolerated.	2004	Rosen et al [55]
	Phase IIA randomized, double-blind, placebo-controlled crossover study	Subcutaneous 4 or 6 mg	Non-responder to viagra (n=25)	Mean durations of base rigidity at ≥80% were 14 and 17 min for patients receiving the 4 and 6 mg PT-141 doses (placebo: 2 min). Single doses up to 6 mg were safely administered and well-tolerated.		
PT-141	Randomized, double-blind, placebo controlled study	Intranasal 10 mg	Non-responder to sildenafil (n=342)	Positive clinical results (ability to attain and maintain an erection and intercourse satisfaction) were seen in 51 patients (34%) in the PT-141 group compared with 13 patients (9%) in the placebo group.	2008	Safarinejad and Hosseini [56]
Co-administration of PT-141 and a PDE5-i		Intranasal 7.5 mg (with 25 mg sildenafil)	Responders to sildenafil or vardenafil (n=19)	Mean duration of basal rigidity ≥60% was 113 min in co-administration group (sildenafil alone: 70 min). No new adverse event was noted.	2005	Diamond et al [57]

ED: erectile dysfunction, PDE5-i: phosphodiesterase type 5 inhibitor.

Single doses up to 40 mg were well-tolerated. Common side effects included minimal headache, as well as problems with visual effects at the 80 mg dose [59].

Although the efficacy of PDE5-Is was up to 80% in unselected ED patients, a reasonable number of drop-outs was also reported [60]. The main reasons for discontinuation of treatment were the lack of efficacy and presence of side effects. Since the occurrence of side effects increases with both serum levels and exposure time to the drug [61], the design of a novel drug formulation by pharmacokinetic approach including bioavailability and route of administration could improve the safety and efficacy profile of the drug. Given this approach, application of a sildenafil topical cream is one of several new trials for the treatment of ED. A phase IIa study was conducted in 33 men with ED. Patients applied a single 2 g dose of SST-6006 topical cream 5% (delivering 100 mg of sildenafil) or a topical placebo to the penile shaft and glans. Though the study has been completed, the full results of this study have not yet been reported or published [62].

Another route of administration for PDE5-Is is sublingual dispersal. A formulation of oro-dispersible tablets (ODT) is quickly dispersed in the mouth and can be administered without water, making it highly useful in patients with swallowing disorders. Vardenafil ODT was first approved to treat ED by the Food and Drug Administration in 2010 [63]. However, though the ODT formulation of vardenafil increases bioavailability, the therapeutic effects and adverse events were not improved compared to those of vardenafil film-coated tablets (FCT). A phase I clinical trial examined the pharmacokinetics of sildenafil ODT in 36 healthy subjects. Sildenafil ODT had a similar pharmacokinetic profile as the FCT form, and high fat meals reduced the rate of absorption of sildenafil compared to the film-coated form. Considering the food-drug interaction, sildenafil ODT should be taken on an empty stomach [64]. Another study conducted on ED patients showed that sildenafil oro-dispersal film (ODF) not only had the same safety and effectiveness as the FCT, but also produced higher overall satisfaction from patients [65]. A study was performed in 20 patients with psychogenic ED receiving alternatively oral FCT or sublingual ODT or ODF at an equal dosage (50 mg). The serum level of the ODF formulation increased more rapidly than those of both FCT and ODT. Compared to FCT as the reference formulation, the prevalence of headache

in ODF decreased and the duration and intensity of flushing and nasal congestion were lower [66]. Recently, a phase I study of tadalafil ODF was conducted in 36 healthy men. The pharmacokinetics of the tadalafil ODF formulation was similar to those of the FCT formulation. Both ODF and FCT formulations of tadalafil were well-tolerated, and no clinically significant changes from baseline were observed [67].

2) Maxi-K channel activator

Large-conductance Ca (2+)-activated K(+) channels (maxi-K channel), located on the arterial and corporal smooth muscle, are potential options for treatment of ED. NS1619 was one of the first Maxi-K channel activators, and was studied for its therapeutic potential in smooth muscle disorders, including ED. Activation of NS1619 resulted in the recovery of erectile function in diabetic rats [68]. However, its poor response and many adverse events led to interruption of its clinical use [69]. Following the NS1619 investigations, a more selective maxi-K channel, NS11021, has been developed. NS11021 increases potassium currents in vascular smooth muscle, reduces vascular tension of penile arteries and CC strips, and induces erection in anesthetized rats. The efficacy of effect was similar to that of sildenafil [70]. A similar study conducted in human penile small arteries and NS11021 evoked pronounced relaxations that led to erectile response [71]. Currently, andolast is the only candidate drug targeting maxi-K channels for treatment of ED in clinical development. Well-designed clinical studies are needed to evaluate the treatment outcomes of andolast in ED patients.

3) Guanylate cyclase activator

PDE5-I showed a lack of efficacy in many patients with impaired pathway of NO-soluble guanylyl cyclase (sGC)-cyclic guanosine monophosphate (cGMP) signal cascade. Attempting to directly delivery of sGC to smooth muscle cell, regardless of NO could offer a solution for PDE5-I unresponsive patients [72]. Activators of sGC such as BAY60-4552 and BAY 60-2770 reactivate the heme-oxidized sGC in vascular diseases. In an animal study, two-week therapy with BAY 60-2770 fully restored the decreased intracavernosal pressure (ICP) and low level of acetylcholine-induced cavernosal relaxations in obese ED mice [73].

In a study of a combination of BAY60-4552 (1 mg) and vardenafil (10 mg), PDE5-I non-responders showed

downregulation of the NO/cGMP/sGC pathway compared to healthy subjects [72], and the combination therapy had synergistic effects on relaxation of human CC in PDE5-I nonresponders compared to vardenafil (20 mg) alone. However, superiority of a combination therapy over vardenafil alone could not be established.

4) Nitric oxide donors: L-arginine, glyceryl trinitrate

NO is the key mediator of erection from cavernosal nerve endings and partially from penile artery endothelial cells. L-arginine induces endothelial NO. In a phase II study, 26 ED patients treated with the combination formula (L-arginine aspartate 8 g combined with adenosine monophosphate 200 mg) noted improvements in erection hardness score (EHS) and IIEF-5 scores compared to patients treated with placebo. This drug was well-tolerated and there were no severe adverse effects [74]. In a randomized controlled trial evaluating the combination of sildenafil with L-arginine orally on the treatment of ED, a combination group demonstrated improved IIEF-5 scores compared to the sildenafil only group. Except for gastritis, adverse effects did not differ between the two groups [75].

Glyceryl trinitrate (GTN) is a well-established vasodilatory agent with a comprehensive safety profile. GTN's vasodilatory action is thought to result from the release of NO in vascular smooth muscle [76]. Pharmacokinetic and pharmacodynamics studies showed that MED2005 (0.2%, GTN dose of 0.6 mg) has a relatively short half-life and a favorable safety profile [77]. In a recently conducted phase II randomized clinical trial [78], 232 patients received a treatment regimen of MED2005. IIEF scores increased significantly in the MED2005 group compared to the placebo group. The results of the global assessment questionnaire were consistent with IIEF scores. The onset of erection in 70% of patient was less than 10 minutes, and adverse events included mild headache and rhinitis. Improvements in all assessments were present only with mild ED. A European Phase III study, "FM57", is ongoing, with headline data expected at the end of 2019. The results of studies about peripherally acting agents are summarized in Table 2.

3. Regeneration therapy: stem cell

SC therapy is one of the most investigated emerging therapeutic methods for ED. In the last few years,

several small clinical trials have been conducted to determine the safety and efficacy of SC therapy in ED patients. A single-blind study was conducted in seven men with type 2 diabetes and ED. Six of seven ED patients experienced morning erection and penile hardness by the third month after ICI of umbilical cord-derived SCs [79]. The degree of penile hardness by SC therapy only was still insufficient for effective penetration. However, after nine months, three of the seven patients actively treated with SC therapy alone agreed that the treatment had some effect on ED [79]. Haahr et al [80] performed a 6-month follow-up phase I study assessing treatment with autologous adipose-derived regenerative cells (ADRCs) in 17 men with post-RP ED. Eight of 17 subjects reported erectile response adequate for sexual intercourse [80]. The same authors [81] recently reported a 12-month follow-up study showing safety and effectiveness of treatment with ADRCs in 21 patients with post-RP ED. No serious adverse effects were observed during the 12 months of follow-up. Only 8 reversible minor events related to the liposuction were noted. IIEF-5 scores increased significantly at 6 months after treatment, and this improvement was sustained at 12 months. 38% of patients recovered erection sufficient for intercourse in the 12-month observation time. This improvement was observed in patients who had normal pre-operative erectile function and who were continent at inclusion [81]. In a phase I study to determine the effects of placental matrix-derived mesenchymal SCs (PM-MSCs), eight non-responders to ED oral therapy were enrolled and followed for 6 months. No serious adverse effects were noted. The ICI of PM-MSCs induced improvement in blood flow into the penis, which was sustained at 6 months. The penile artery peak systolic velocity improved after 6 months, while no significant changes were noted in either end-diastolic velocity or IIEF scores. Interestingly, three of eight patients recovered to response to PDE5-Is after 3 months post-SC injection [82].

The safety and effect of bone marrow-derived mononuclear cells was assessed in 12 post-RP patients with vasculogenic ED [83]. Significant improvements in intercourse satisfaction and erectile function domains of IIEF-15 and EHS were noted at 6 months follow-up, and clinical benefit was sustained after one year [83]. A longer-term follow-up (mean, 62.1 months) data set collected by the same authors showed a lack of adverse events and slightly decreased erectile function score

Table 2. Summary of emerging therapy for ED: peripherally acting agents

Compound	Type of study	Mechanism of action	Route and dosage of administration	Population studied	Main findings	Date (year)	Author
SLx-2101	Phase IA double-blind, randomized, single dose study	New oral PDE5-I	Oral 5, 10, 20, 40, and 80 mg	Healthy men (n=8)	SLx-2101 was well-tolerated in single doses up to 40 mg. Positive effects were shown at 0–6 h post-dose without VSS for 10, 20, 40, and 80 mg doses. The common side effects are headache and have been minimal.	2006	Prince et al [59]
Vardenafil ODT	Phase I/III	PDE5-I sublingual dispersal agent	Orodispersal 10 mg	Men of broad age range with ED	Vardenafil ODT has a similar pharmacokinetic profile to vardenafil FCT. Vardenafil ODT has significantly greater bioavailability and was well-tolerated.	2011	Heinig et al [63]
Sildenafil ODT	Phase I randomized, open-label, crossover, single-dose study	PDE5-I sublingual dispersal agent	Orodispersal 50 mg	Healthy men (n=36)	Sildenafil ODT without water, was bioequivalent to sildenafil FCT. High fat meals reduced the rate of absorption of sildenafil ODT.	2014	Damle et al [64]
Sildenafil ODF		PDE5-I sublingual dispersal agent	Orodispersal 75 mg	Patients with ED (n=139)	Sildenafil ODF had the same safety and effectiveness of the FCT, was better appreciated by patients in overall satisfaction.	2017	Cocci et al [65]
Sildenafil ODF	Phase I	PDE5-I sublingual dispersal agent	Orodispersal equal dosage of FCT 50 mg	Psychogenic ED patients (n=20)	The serum level of ODF increased faster than those of both FCT and ODT. ODF showed a lower prevalence of headache compared to FCT and improved pattern of flushing and nasal congestion.	2018	De toni et al [66]
Tadalafil ODF	Phase I open-label, randomized sequence, two-period, two-formulation, single-dose, crossover design	PDE5-I sublingual dispersal agent	Orodispersal equal dosage of FCT 20 mg	Healthy men (n=36)	The pharmacokinetics of the tadalafil ODF formulation was similar to those of the FCT formulation. Both ODF and FCT formulations were well-tolerated.	2018	Park et al [67]
L-arginine	Phase II randomized, double-blind, crossover, placebo-controlled comparative clinical trial	NO donors	Oral on demand for 2 wk L-arginine aspartate 8 g +AA 200 mg	ED patients (n=26)	Combination group showed the improvements in EHS and IIEF-scores compared to patients treated with placebo. This drug was well-tolerated and there was no severe adverse effect.	2013	Neuzillet et al [74]
L-arginine	Randomized controlled trial	NO donors	Oral sildenafil 50 mg (every other day) +L-arginine 1 g (3 times daily)	Organic ED (combination=30, sildenafil=29)	Combination group improved IIEF-5 score compared to sildenafil alone group.	2020	El-Wakeel et al [75]
MED2005 (GTN)	Phase II randomized, double-blind, placebo-controlled, crossover trial	NO donors	Topical 0.2% GTN gel	ED patients (n=232)	23% patients showed ≥ 4 points IIEF-EF increase after treatment vs. 14% after placebo. The onset of erection in 70% of patient was less than 10 min. Adverse events were mild headaches and rhinitis.	2018	Ralph et al [78]

ED: erectile dysfunction, PDE5-I: phosphodiesterase type 5 inhibitor, VSS: visual sexual stimulation, ODT: oro-dispersible tablets, FCT: film-coated tablets, ODF: oro-dispersal film, NO: nitric oxid, AA: adenosine monophosphate, EHS: erection hardness score, IIEF: international index of erectile function, GTN: glyceryl trinitrate, IIEF-EF: international index of erectile function-erectile function.

compared with data acquired at the 12-month time point. Repeated injections may be necessary for lasting effect [84]. In a recent study in ED patients with diabetes, ICI of autologous bone marrow-derived mesenchymal SCs (BM-MSCs) was demonstrated to be safe and effective with significant improvement of IIEF-15 and EHS (IIEF-15 ($p=0.04$), erectile function ($p=0.03$), sexual desire ($p=0.04$), intercourse satisfaction ($p=0.04$), and overall satisfaction ($p=0.04$) [85]. Another phase I study with ICI of autologous BM-MSCs was conducted in ten ED patients (five diabetes-associated ED and five post-prostatectomy ED). The study has been completed and full results are pending [86]. The results of studies about stem cell therapy are summarized in Table 3.

4. Therapies using physical energies

1) Low-intensity shock wave therapy

Extracorporeal low-intensity shock wave therapy (LI-SWT) is a potential treatment option for ED. The micro-trauma to cavernosal tissue induced by LI-SWT may stimulate neovascularization and upregulate some factors associated with tissue healing and remodeling [87]. A prospective randomized, sham-controlled study was conducted on 55 patients with vasculogenic ED [88]. The study reported that clinically meaningful improvement of erectile function (international index of erectile function-erectile function [IIEF-EF] and EHS) was shown in 40.5% of the treatment group according to the minimum clinically important differences (MCID) criteria. There were no adverse effects reported. Another randomized clinical trial was conducted to assess changes in penile hemodynamics and IIEF-EF score in patients with vasculogenic ED [89]. For the IIEF-EF score, the MCID criteria for the treatment group were met by 56.7% of the treatment group at one month and by 75% at 12 months. In a more recent randomized clinical trial evaluating the effect of LI-SWT on ED among kidney-transplanted patients, similar findings were reported [90]. Kitrey et al [91] evaluated the long-term efficacy of LI-SWT in 156 ED patients. Efficacy was assessed by IIEF-EF at 6, 12, 18, and 24 months in patients with a successful outcome of LI-SWT according to the MCID at one month. During the follow-up period, clinical beneficial effect decreased from 64% at 1 month to 34% at 2 years. The efficacy lasted longer in mild forms of ED without comorbidity, such as diabetes. Meta-analyses have suggested that LI-SWT

could significantly improve erectile function as evaluated by the IIEF and EHS [92,93]. Therapeutic efficacy could persist for about 3 months. Clinical outcomes were associated with number of shock waves, energy intensity, and duration of treatment [92]. Recent meta-analysis demonstrated that the mean difference of IIEF-EF score between the treatment and sham groups was 4.23 ($p=0.012$) at the 1-month follow-up. No significant adverse events were reported [94]. These studies suggest that LI-SWT appears to produce significant improvement of the IIEF and EHS and appears to be well-tolerated. However, setup of LI-SWT, treatment protocols, and follow-up durations were variable. There were 2 clinical trials that showed no difference between the LI-SWT group and control group [95,96]. Current evidence is promising, but still controversial. Robust evidence from additional randomized controlled trials with standardized protocols and longer-term follow-up procedures is needed. There are several ongoing randomized clinical trials that may help elucidate the role of LI-SWT in the treatment of ED along with producing a standardized treatment protocol [97]. Interestingly, a recent study suggested that the combination of SC therapy and LI-SWT may have synergistic effects in the promotion of angiogenesis and decrease in the destruction of cells [98]. More work needs to be done in this field to better understand the long-term efficacy and safety of this therapy, which still remains investigational at this time.

2) Low-intensity pulsed ultrasound

Another important form of physical therapy in micro-energy therapy is low-intensity pulsed ultrasound (LIPUS). LIPUS delivers pulsed ultrasound to target tissue at intensity less than 3 W/cm^2 . LIPUS therapy improves erectile function, as evidenced by increasing ICP and reversed pathological changes in penile erectile tissue, such as increased endothelial and smooth muscle content, as well as increased expression of endothelial nitric oxide synthase and neuronal nitric oxide synthase in a streptozotocin-induced diabetic rat model. Penile tissue showed decreased collagen and fiber changes with downregulation of transforming growth factor- β 1/Smad/connective tissue growth factor signaling pathway by LIPUS [99].

In the randomized clinical trial conducted in mild to moderate ED [100], during the 12-week follow-up period, IIEF-EF score significantly increased. The response

Table 3. Summary of emerging therapy for ED: stem cell therapy

Compound	Type of study	Route of administration FU duration	Population studied	Main findings	Date (year)	Author
Umbilical cord-derived SCs	Phase I single-blind study	Single ICI 9 mo FU	Type 2 DM with ED (n=7)	6/7 patients experienced morning erection by the third mo and maintained for more than 6 mo.	2010	Bahk et al [79]
Adipose-derived regenerative cells	Phase I open-label, single arm study	Single ICI 6 mo FU	Post-RP ED (n=17)	2/7 patients achieved penetration with the addition of PDE5-I. 8 of 17 men recovered their erectile function and were able to accomplish sexual intercourse. For continent men, 8 of 11 men recovered erectile function. Median IIEF-5 score increased from 7 to 17 for 6 mo after ICI. No serious AE were reported. Minor events related to the liposuction and SC injection at the 1-mo.	2016	Haahr et al [80]
Adipose-derived regenerative cells	Phase I open-label, single arm study	Single ICI 12 mo FU	Post-RP ED (n=21)	8 out of 15 patients (53%) in the continent group reported erectile function sufficient for intercourse at 12 mo. Median IIEF-5 score in continent group increased from 6 to 11 after 6 mo. No serious adverse events occurred.	2018	Haahr et al [81]
Placental-derived stem cells	Phase I/II	Single ICI 6 mo FU	Non-responders to PDE5-I (n=8)	No serious adverse effects were noticed. At 6 mo, PSV ranged from 25.5 to 73.9 cm/s. The increase in PSV was statistically significant (p<0.05). Changes in measured EDV, stretched penile length, width, and IIEF score were not statistically significant.	2016	Levy et al [82]
Bone marrow-mononuclear cells	Phase I/II	Single ICI 12 mo FU	Vasculogenic post-RP ED (n=12)	No serious side effects occurred. At 6 mo vs. baseline, significant improvements of intercourse satisfaction (6.8±3.6, 3.9±2.5; p=0.044) and erectile function (17.4±8.9, 7.3±4.5; p=0.006) domains of the IIEF-15 and (2.6±1.1, 1.3±0.8; p=0.008) were observed.	2016	Yiou et al [83]
Bone marrow-mononuclear cells	Single ICI mean 62.1 mo FU	Post-RP ED (n=18)	No serious side effects occurred. After 6 mo, significant improvements vs. baseline were noted in IIEF-15 intercourse satisfaction (7.8±3.1 vs. 2.2±3.4; p=0.033) and erectile function (18±8.3 vs. 3.7±4.1; p=0.035) domains. After a mean follow-up of 62.1 mo, erectile function scores were slightly lower compared with the 1-y time point.	2017	Yiou et al [84]	
Bone marrow-derived mesenchymal stem cells	Phase I open label clinical trial	Two ICI Safety: 24 mo FU Efficacy: 12 mo FU	Type 2 DM with ED (n=4)	No patients reported significant adverse effects. There was significant improvement of IIEF-15 and EHS; IIEF-15 (p=0.04), erectile function (p=0.03), sexual desire (p=0.04), intercourse satisfaction (p=0.04), and overall satisfaction (p=0.04).	2018	Al Demour et al [85]

ED:erectile dysfunction, FU: follow-up, SC: stem cell, ICI: intracavernosal injection, DM: diabetes mellitus, PDE5-I: phosphodiesterase type 5 inhibitor, Post-RP: post prostatectomy, IIEF: international index of erectile function, AE: adverse events, PSV: peak systolic velocity, EDV: end diastolic velocity, EHS: erection hardness scale.

Table 4. Summary of emerging therapy for ED: therapies using physical energies

Treatment	Type of study	Protocol	Population studied	Main findings	Date (year)	Author
LI-SWT	Prospective, randomized, double-blind, sham controlled study	Duration of session: 20 min Energy intensity: 0.09 mJ/mm ² Frequency: 120 shock waves per min Total of 12 sessions Total of 1,500 pulses per session Schedule: 9 wk protocol (2 sessions per wk for 3 wk-3 wk break-2 sessions per wk for 3 wk) Assessment: 1 mo after last treatment	Vasculogenic ED (37=LI-SWT, 18=sham probe)	54% of treatment group achieved erection hard to penetration (EHS of 3). Meaningful improvement of IIEF score was shown in 40.5% of treatment group according to the MCID criteria. There was no adverse effect reported.	2016	Kitrey et al [88]
LI-SWT	Double-blinded, randomized, sham-controlled trial	Duration of session: 20 min Energy intensity: 0.09 mJ/mm ² Frequency: 160 shock waves per min Total of 12 sessions Total of 1,500 shocks per session Schedule: 9 wk protocol (2 sessions per wk for 3 wk-3 wk break-2 sessions per wk for 3 wk) Assessment: 1, 3, 6, 9, and 12 mo after last treatment	Vasculogenic ED (30=LI-SWT, 16=sham probe)	For the IIEF-EF score, the MCID criteria for the treatment group were met in 56.7% of treatment group at 1 mo, and 75% at 12 mo. Mean peak systolic velocity increased by 4.5 and 0.6 cm/s in the LI-SWT and sham groups (p<0.001).	2017	Kalyianakis et al [89]
LI-SWT	Prospective, randomized, double blinded, sham-controlled study	Duration of session: 10 min Energy intensity: 0.09 mJ/mm ² Frequency: 160 shock waves per min Total of 6 sessions Total of 2,000 shocks per session Assessment: 1, 4, and 12 mo after last treatment Schedule: 3 wk protocol (2 sessions per wk for 3 wk)	ED patients (10=LI-SWT, 10=sham probe)	For the IIEF-EF score, the MCID criteria for the treatment group were met in 56.7% of treatment group at 1 mo, and 75% at 12 mo.	2019	Yamaçake et al [90]
LI-SWT	Retrospective study	Duration of session: 10 min Energy intensity: 0.09 mJ/mm ² Frequency: 120 shock waves per min Total of 12 sessions Total of 1,500 shocks per session Schedule: 9 wk protocol (2 sessions per wk for 3 wk-3 wk break-2 sessions per wk for 3 wk) Assessment: 6, 12, 18, and 24 mo after last treatment	ED patients (156 LI-SWT)	Clinical beneficial decreased from 64% at 1 mo to 34% at 2 y. The efficacy lasted longer in mild form of ED without comorbidity such as diabetes.	2018	Kitrey et al [91]
LI-SWT	Prospective, randomized, double-blinded, placebo controlled study	Duration of each session: 20 min Energy density: 0.09 mJ/mm ² Frequency: 120 shock waves per min Total of 12 sessions Total of 1,500 shocks per session Schedule: 9 wk protocol (2 sessions per wk for 3 wk-3 wk break-2 sessions per wk for 3 wk) Assessment: 1 mo after last treatment	ED patients (30=LI-SWT, 28=sham probe)	No differences of clinical outcomes (EHS and IIEF score) were shown between LI-SWT group and control group.	2014	Yee et al [95]

Table 4. Continued

Treatment	Type of study	Protocol	Population studied	Main findings	Date	Author
Linear LI-SWT	Double-blinded, sham-controlled, randomized clinical trial	Energy density: 0.09 mJ/mm ² Frequency: 300 shock waves per min Total of 10 sessions Total of 600 shocks per session Schedule: 18 wk protocol (once a wk for 5 wk-4-wk break-once a wk for 5 wk-4 wk break) Assessment: 9, 18 wk after first treatment	ED patients (58=LI-SWT 60=sham probe)	No clinically relevant effect (IIEF and EHS score) of linear LI-SWT on ED was found.	2017	Fojecki et al [96]
LIPUS	Multicenter, randomized, double-blind, sham-controlled clinical study	Energy intensity: 300 mW/cm ² Pulse duration time-to-pulse rest time ratio of 1:4 (200 μs:800 μs) at 1,000 Hz and frequency at 1.7 MHz Twice a wk for 4 wk Assessment: 4, 8, and 12 wk after last treatment	Mild to moderate ED (80=LIPUS, 40=sham treated control)	The rate of patients with increased IIEF score ≥3 was 68% which was significantly higher than 20% in control group at 12 wk. The percentage of patients with positive answers to SEP-3 (successful vaginal intercourse) were 73% at 12 wk after treatment which were significantly higher than 29% in control group.	2019	Cui et al [100]

ED: erectile dysfunction, LI-SWT: low-intensity shock wave therapy, EHS: erection hardness score, IIEF: international index of erectile function, MCI: minimum clinically important differences, IIEF-EF: international index of erectile function-erectile function, LIPUS: low intensity pulsed ultrasound, SEP-3: sexual encounter profile questionnaires 3.

rate in LIPUS group was 67.5%, which was 20% higher than the sham group at 3 months. For the sexual encounter profile questionnaires 3, the rate of positive answers for treatment group *versus* control group were met in 73.08% *versus* 28.95% at 12 weeks. There were no treatment-related adverse events reported. LIPUS therapy has potential as a non-invasive valuable therapy for nerve injury-induced ED. Despite promising results in animal studies, investigation of the therapeutic effect of LIPUS on ED in humans is limited. Additional high-quality clinical studies for ED are necessary. The results of studies about therapies using physical energies are summarized in Table 4.

CONCLUSIONS

Although there are several existing treatments for ED including PDE5-Is, ICI therapy of vaso-active substances, vacuum erection devices, and penile prosthesis implants, the percentage of patients that are unresponsive to or unsatisfied by the clinically available treatments remains high. In this context, there have been several scientific advances for innovative ED therapies in the last decade. According to recent clinical trials and pre-clinical studies using human tissues, a centrally acting melanocortin receptor agonist or new peripherally acting agents, including the Max-K channel activator, guanylate cyclase activator, and NO donor have shown promising results in improving erection. Also, combination of these therapies with PDE5-Is may be helpful in treating difficult-to-treat ED populations, such as PDE5-I non-responders. Recent clinical trials suggest that regeneration therapy using SCs could also be a potential candidate for treatment of difficult-to-treat ED populations, such as diabetic or post-prostatectomy ED. Meanwhile, LI-SWT showed favorable results as a monotherapy or in combination with SC therapy in treating patients with vasculogenic ED. There is growing evidence suggesting efficacy of these emerging therapies, although most of the therapies need to be validated by well-designed clinical trials. It is expected that the emerging treatments can meet the needs of patients unresponsive to or unsatisfied by current therapies for ED once their long-term safety and efficacy have been confirmed.

Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: SK, MCC, SYC, MRR. Data curation: SK, MCC. Formal analysis: SK, MCC. Investigation: SK, MCC, SYC, MRR. Methodology: SK, MCC, HC, SYC. Resources: SK, MCC, MRR. Software: SK, MCC. Supervision: SYC, HC, MCC, MRR. Writing – original draft: SK, MCC. Writing – review & editing: SK, MCC, SYC, HC, MRR.

REFERENCES

1. NIH Consensus Conference. Impotence. NIH consensus development panel on impotence. *JAMA* 1993;270:83-90.
2. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol* 1994;151:54-61.
3. Kubin M, Wagner G, Fugl-Meyer AR. Epidemiology of erectile dysfunction. *Int J Impot Res* 2003;15:63-71.
4. Selvin E, Burnett AL, Platz EA. Prevalence and risk factors for erectile dysfunction in the US. *Am J Med* 2007;120:151-7.
5. Yafi FA, Jenkins L, Albersen M, Corona G, Isidori AM, Goldfarb S, et al. Erectile dysfunction. *Nat Rev Dis Primers* 2016;2:16003.
6. Sasayama S, Ishii N, Ishikura F, Kamijima G, Ogawa S, Kanmatsuse K, et al. Men's Health Study: epidemiology of erectile dysfunction and cardiovascular disease. *Circ J* 2003;67:656-9.
7. McCabe MP, Sharlip ID, Lewis R, Atalla E, Balon R, Fisher AD, et al. Risk factors for sexual dysfunction among women and men: a consensus statement from the Fourth International Consultation on Sexual Medicine 2015. *J Sex Med* 2016;13:153-67.
8. Corona G, Rastrelli G, Monami M, Saad F, Luconi M, Luchese M, et al. Body weight loss reverts obesity-associated hypogonadotropic hypogonadism: a systematic review and meta-analysis. *Eur J Endocrinol* 2013;168:829-43.
9. Cao S, Gan Y, Dong X, Liu J, Lu Z. Association of quantity and duration of smoking with erectile dysfunction: a dose-response meta-analysis. *J Sex Med* 2014;11:2376-84.
10. Arackal BS, Benegal V. Prevalence of sexual dysfunction in male subjects with alcohol dependence. *Indian J Psychiatry* 2007;49:109-12.
11. Malavige LS, Levy JC. Erectile dysfunction in diabetes mellitus. *J Sex Med* 2009;6:1232-47.
12. Nehra A. Erectile dysfunction and cardiovascular disease: efficacy and safety of phosphodiesterase type 5 inhibitors in men with both conditions. *Mayo Clin Proc* 2009;84:139-48.
13. Bacon CG, Mittleman MA, Kawachi I, Giovannucci E, Glasser DB, Rimm EB. A prospective study of risk factors for erectile dysfunction. *J Urol* 2006;176:217-21.
14. Dunn KM, Croft PR, Hackett GI. Association of sexual problems with social, psychological, and physical problems in men and women: a cross sectional population survey. *J Epidemiol Community Health* 1999;53:144-8.
15. McCabe MP, Althof SE. A systematic review of the psychosocial outcomes associated with erectile dysfunction: does the impact of erectile dysfunction extend beyond a man's inability to have sex? *J Sex Med* 2014;11:347-63.
16. Burnett AL, Nehra A, Breaux RH, Culkin DJ, Faraday MM, Hakim LS, et al. Erectile dysfunction: AUA guideline. *J Urol* 2018;200:633-41.
17. Hatzimouratidis K, Salonia A, Adaikan G, Buvat J, Carrier S, El-Meliegy A, et al. Pharmacotherapy for erectile dysfunction: recommendations from the Fourth International Consultation for Sexual Medicine (ICSM 2015). *J Sex Med* 2016;13:465-88.
18. Porst H, Burnett A, Brock G, Ghanem H, Giuliano F, Glina S, et al. SOP conservative (medical and mechanical) treatment of erectile dysfunction. *J Sex Med* 2013;10:130-71.
19. Hatzimouratidis K, Hatzichristou DG. A comparative review of the options for treatment of erectile dysfunction: which treatment for which patient? *Drugs* 2005;65:1621-50.
20. Boulton AJ, Selam JL, Sweeney M, Ziegler D. Sildenafil citrate for the treatment of erectile dysfunction in men with Type II diabetes mellitus. *Diabetologia* 2001;44:1296-301.
21. Wrishko R, Sorsaburu S, Wong D, Strawbridge A, McGill J. Safety, efficacy, and pharmacokinetic overview of low-dose daily administration of tadalafil. *J Sex Med* 2009;6:2039-48.
22. Peng Z, Yang L, Dong Q, Wei Q, Liu L, Yang B. Efficacy and safety of tadalafil once-a-day versus tadalafil on-demand in patients with erectile dysfunction: a systematic review and meta-analyses. *Urol Int* 2017;99:343-52.
23. Morelli A, Filippi S, Mancina R, Luconi M, Vignozzi L, Marini M, et al. Androgens regulate phosphodiesterase type 5 expression and functional activity in corpora cavernosa. *Endocrinology* 2004;145:2253-63.
24. Yuan J, Zhang R, Yang Z, Lee J, Liu Y, Tian J, et al. Comparative effectiveness and safety of oral phosphodiesterase type 5 inhibitors for erectile dysfunction: a systematic review and network meta-analysis. *Eur Urol* 2013;63:902-12.
25. Giuliano F, Jackson G, Montorsi F, Martin-Morales A, Riallard P. Safety of sildenafil citrate: review of 67 double-blind

- placebo-controlled trials and the postmarketing safety database. *Int J Clin Pract* 2010;64:240-55.
26. Diabetes Canada Clinical Practice Guidelines Expert Committee, Bebb R, Millar A, Brock G. Sexual dysfunction and hypogonadism in men with diabetes. *Can J Diabetes* 2018;42 Suppl 1:S228-33.
 27. Montorsi F, McCullough A. Efficacy of sildenafil citrate in men with erectile dysfunction following radical prostatectomy: a systematic review of clinical data. *J Sex Med* 2005;2:658-67.
 28. Belew D, Klaassen Z, Lewis RW. Intracavernosal injection for the diagnosis, evaluation, and treatment of erectile dysfunction: a review. *Sex Med Rev* 2015;3:11-23.
 29. Nelson CJ, Hsiao W, Balk E, Narus J, Tal R, Bennett NE, et al. Injection anxiety and pain in men using intracavernosal injection therapy after radical pelvic surgery. *J Sex Med* 2013;10:2559-65.
 30. Heaton JP, Lording D, Liu SN, Litonjua AD, Guangwei L, Kim SC, et al. Intracavernosal alprostadil is effective for the treatment of erectile dysfunction in diabetic men. *Int J Impot Res* 2001;13:317-21.
 31. Althof SE, Turner LA, Levine SB, Risen C, Kursh E, Bodner D, et al. Why do so many people drop out from auto-injection therapy for impotence? *J Sex Marital Ther* 1989;15:121-9.
 32. Weiss JN, Badlani GH, Ravalli R, Brettschneider N. Reasons for high drop-out rate with self-injection therapy for impotence. *Int J Impot Res* 1994;6:171-4.
 33. Mulhall JP, Jahoda AE, Cairney M, Goldstein B, Leitzes R, Woods J, et al. The causes of patient dropout from penile self-injection therapy for impotence. *J Urol* 1999;162:1291-4.
 34. Padma-Nathan H, Hellstrom WJ, Kaiser FE, Labasky RF, Lue TF, Nolten WE, et al. Treatment of men with erectile dysfunction with transurethral alprostadil. Medicated Urethral System for Erection (MUSE) Study Group. *N Engl J Med* 1997;336:1-7.
 35. Williams G, Abbou CC, Amar ET, Desvaux P, Flam TA, Lycklama à Nijeholt GA, et al. Efficacy and safety of transurethral alprostadil therapy in men with erectile dysfunction. MUSE Study Group. *Br J Urol* 1998;81:889-94.
 36. McCullough AR, Hellstrom WG, Wang R, Lepor H, Wagner KR, Engel JD. Recovery of erectile function after nerve sparing radical prostatectomy and penile rehabilitation with nightly intraurethral alprostadil versus sildenafil citrate. *J Urol* 2010;183:2451-6.
 37. Costa P, Potempa AJ. Intraurethral alprostadil for erectile dysfunction: a review of the literature. *Drugs* 2012;72:2243-54.
 38. Guay AT, Perez JB, Velásquez E, Newton RA, Jacobson JP. Clinical experience with intraurethral alprostadil (MUSE) in the treatment of men with erectile dysfunction. A retrospective study. Medicated urethral system for erection. *Eur Urol* 2000;38:671-6.
 39. Fulgham PF, Cochran JS, Denman JL, Feagins BA, Gross MB, Kadesky KT, et al. Disappointing initial results with transurethral alprostadil for erectile dysfunction in a urology practice setting. *J Urol* 1998;160(6 Pt 1):2041-6.
 40. Shabsigh R, Padma-Nathan H, Gittleman M, McMurray J, Kaufman J, Goldstein I. Intracavernous alprostadil alfadex is more efficacious, better tolerated, and preferred over intraurethral alprostadil plus optional actis: a comparative, randomized, crossover, multicenter study. *Urology* 2000;55:109-13.
 41. Price DE, Cooksey G, Jehu D, Bentley S, Hearnshaw JR, Osborn DE. The management of impotence in diabetic men by vacuum tumescence therapy. *Diabet Med* 1991;8:964-7.
 42. Lee M, Sharifi R. Non-invasive management options for erectile dysfunction when a phosphodiesterase type 5 inhibitor fails. *Drugs Aging* 2018;35:175-87.
 43. Liu C, Lopez DS, Chen M, Wang R. Penile rehabilitation therapy following radical prostatectomy: a meta-analysis. *J Sex Med* 2017;14:1496-503.
 44. Levine LA, Dimitriou RJ. Vacuum constriction and external erection devices in erectile dysfunction. *Urol Clin North Am* 2001;28:335-41, ix-x.
 45. Ganem JP, Lucey DT, Janosko EO, Carson CC. Unusual complications of the vacuum erection device. *Urology* 1998;51:627-31.
 46. Segal RL, Camper SB, Burnett AL. Modern utilization of penile prosthesis surgery: a national claim registry analysis. *Int J Impot Res* 2014;26:167-71.
 47. Dick B, Tsambarlis P, Reddy A, Hellstrom WJ. An update on: long-term outcomes of penile prostheses for the treatment of erectile dysfunction. *Expert Rev Med Devices* 2019;16:281-6.
 48. Levine LA, Becher EF, Bella AJ, Brant WO, Kohler TS, Martinez-Salamanca JI, et al. Penile prosthesis surgery: current recommendations from the International Consultation on Sexual Medicine. *J Sex Med* 2016;13:489-518.
 49. Bernal RM, Henry GD. Contemporary patient satisfaction rates for three-piece inflatable penile prostheses. *Adv Urol* 2012;2012:707321.
 50. Hellstrom WJ, Montague DK, Moncada I, Carson C, Minhas S, Faria G, et al. Implants, mechanical devices, and vascular surgery for erectile dysfunction. *J Sex Med* 2010;7(1 Pt 2):501-23.
 51. Wessells H, Fuciarelli K, Hansen J, Hadley ME, Hruby VJ, Dorr R, et al. Synthetic melanotropic peptide initiates erections in men with psychogenic erectile dysfunction: double-blind, placebo controlled crossover study. *J Urol*

- 1998;160:389-93.
52. Wessells H, Gralnek D, Dorr R, Hruby VJ, Hadley ME, Levine N. Effect of an alpha-melanocyte stimulating hormone analog on penile erection and sexual desire in men with organic erectile dysfunction. *Urology* 2000;56:641-6.
53. Wessells H, Levine N, Hadley ME, Dorr R, Hruby V. Melanocortin receptor agonists, penile erection, and sexual motivation: human studies with Melanotan II. *Int J Impot Res* 2000;12 Suppl 4:S74-9.
54. Diamond LE, Earle DC, Rosen RC, Willett MS, Molinoff PB. Double-blind, placebo-controlled evaluation of the safety, pharmacokinetic properties and pharmacodynamic effects of intranasal PT-141, a melanocortin receptor agonist, in healthy males and patients with mild-to-moderate erectile dysfunction. *Int J Impot Res* 2004;16:51-9.
55. Rosen RC, Diamond LE, Earle DC, Shadiack AM, Molinoff PB. Evaluation of the safety, pharmacokinetics and pharmacodynamic effects of subcutaneously administered PT-141, a melanocortin receptor agonist, in healthy male subjects and in patients with an inadequate response to Viagra. *Int J Impot Res* 2004;16:135-42.
56. Safarinejad MR, Hosseini SY. Salvage of sildenafil failures with bremelanotide: a randomized, double-blind, placebo controlled study. *J Urol* 2008;179:1066-71.
57. Diamond LE, Earle DC, Garcia WD, Spana C. Co-administration of low doses of intranasal PT-141, a melanocortin receptor agonist, and sildenafil to men with erectile dysfunction results in an enhanced erectile response. *Urology* 2005;65:755-9.
58. Dhillon S, Keam SJ. Bremelanotide: first approval. *Drugs* 2019;79:1599-606.
59. Prince WT, Campbell AS, Tong W, Sweetnam P, Willett MS, Roesch BG, et al. SLX-2101, a new long-acting PDE5 inhibitor: preliminary safety, tolerability, PK and endothelial function effects in healthy subjects. *J Urol* 2006;175(4S):299-300.
60. Corona G, Rastrelli G, Burri A, Serra E, Gianfrilli D, Mannucci E, et al. First-generation phosphodiesterase type 5 inhibitors dropout: a comprehensive review and meta-analysis. *Andrology* 2016;4:1002-9.
61. Taylor J, Baldo OB, Storey A, Cartledge J, Eardley I. Differences in side-effect duration and related bother levels between phosphodiesterase type 5 inhibitors. *BJU Int* 2009;103:1392-5.
62. Milenkovic U, Campbell J, Roussel E, Albersen M. An update on emerging drugs for the treatment of erectile dysfunction. *Expert Opin Emerg Drugs* 2018;23:319-30.
63. Heinig R, Weimann B, Dietrich H, Böttcher MF. Pharmacokinetics of a new orodispersible tablet formulation of vardenafil: results of three clinical trials. *Clin Drug Investig* 2011;31:27-41.
64. Damle B, Duczynski G, Jeffers BW, Crownover P, Coupe A, LaBadie RR. Pharmacokinetics of a novel orodispersible tablet of sildenafil in healthy subjects. *Clin Ther* 2014;36:236-44.
65. Cocci A, Capece M, Cito G, Russo GI, Falcone M, Timpano M, et al. Effectiveness and safety of oro-dispersible sildenafil in a new film formulation for the treatment of erectile dysfunction: comparison between sildenafil 100-mg film-coated tablet and 75-mg oro-dispersible film. *J Sex Med* 2017;14:1606-11.
66. De Toni L, De Rocco Ponce M, Franceschinis E, Dall'Acqua S, Padrini R, Realdon N, et al. Sublingual administration of sildenafil oro-dispersible film: new profiles of drug tolerability and pharmacokinetics for PDE5 inhibitors. *Front Pharmacol* 2018;9:59.
67. Park SI, Heo SH, Kim G, Chang S, Song KH, Kim MG, et al. Comparison of tadalafil pharmacokinetics after administration of a new orodispersible film versus a film-coated tablet. *Drug Des Devel Ther* 2018;12:935-42.
68. González-Corrochano R, La Fuente J, Cuevas P, Fernández A, Chen M, Sáenz de Tejada I, et al. Ca²⁺-activated K⁺ channel (KCa) stimulation improves relaxant capacity of PDE5 inhibitors in human penile arteries and recovers the reduced efficacy of PDE5 inhibition in diabetic erectile dysfunction. *Br J Pharmacol* 2013;169:449-61.
69. Bentzen BH, Olesen SP, Rønn LC, Grunnet M. BK channel activators and their therapeutic perspectives. *Front Physiol* 2014;5:389.
70. Kun A, Matchkov VV, Stankevicius E, Nardi A, Hughes AD, Kirkeby HJ, et al. NS11021, a novel opener of large-conductance Ca(2+)-activated K(+) channels, enhances erectile responses in rats. *Br J Pharmacol* 2009;158:1465-76.
71. Király I, Pataricza J, Bajory Z, Simonsen U, Varro A, Papp JG, et al. Involvement of large-conductance Ca(2+)-activated K(+) channels in both nitric oxide and endothelium-derived hyperpolarization-type relaxation in human penile small arteries. *Basic Clin Pharmacol Toxicol* 2013;113:19-24.
72. Albersen M, Linsen L, Tinel H, Sandner P, Van Renterghem K. Synergistic effects of BAY 60-4552 and vardenafil on relaxation of corpus cavernosum tissue of patients with erectile dysfunction and clinical phosphodiesterase type 5 inhibitor failure. *J Sex Med* 2013;10:1268-77.
73. Silva FH, Leiria LO, Alexandre EC, Davel AP, Mónica FZ, De Nucci G, et al. Prolonged therapy with the soluble guanylyl cyclase activator BAY 60-2770 restores the erectile function in obese mice. *J Sex Med* 2014;11:2661-70.
74. Neuzillet Y, Hupertan V, Cour F, Botto H, Lebret T. A ran-

- domized, double-blind, crossover, placebo-controlled comparative clinical trial of arginine aspartate plus adenosine monophosphate for the intermittent treatment of male erectile dysfunction. *Andrology* 2013;1:223-8.
75. El-Wakeel LM, Fouad FA, Saleem MD, Saber-Khalaf M. Efficacy and tolerability of sildenafil/l-arginine combination relative to sildenafil alone in patients with organic erectile dysfunction. *Andrology* 2020;8:143-7.
 76. Futura Medical Developments Ltd. Evaluating MED2005 & Nitrostat Bioavailability (FM58) [Internet]. Bethesda: U.S. National Library of Medicine; c2019 [cited 2019 Sep 13]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT04008732>.
 77. Futura Medical. MED2005 clinical programme [Internet]. Guildford: Futura Medical [cited 2019 Sep 13]. Available from: <https://futuramedical.com/what-we-do/med2005/med2005-clinical-programme/>.
 78. Ralph DJ, Eardley I, Taubel J, Terrill P, Holland T. Efficacy and safety of MED2005, a topical glyceryl trinitrate formulation, in the treatment of erectile dysfunction: a randomized crossover study. *J Sex Med* 2018;15:167-75.
 79. Bahk JY, Jung JH, Han H, Min SK, Lee YS. Treatment of diabetic impotence with umbilical cord blood stem cell intracavernosal transplant: preliminary report of 7 cases. *Exp Clin Transplant* 2010;8:150-60.
 80. Haahr MK, Jensen CH, Toyserkani NM, Andersen DC, Damkier P, Sørensen JA, et al. Safety and potential effect of a single intracavernous injection of autologous adipose-derived regenerative cells in patients with erectile dysfunction following radical prostatectomy: an open-label phase I clinical trial. *EBioMedicine* 2016;5:204-10.
 81. Haahr MK, Harken Jensen C, Toyserkani NM, Andersen DC, Damkier P, Sørensen JA, et al. A 12-month follow-up after a single intracavernous injection of autologous adipose-derived regenerative cells in patients with erectile dysfunction following radical prostatectomy: an open-label phase I clinical trial. *Urology* 2018;121:203.e6-13.
 82. Levy JA, Marchand M, Iorio L, Cassini W, Zahalsky MP. Determining the feasibility of managing erectile dysfunction in humans with placental-derived stem cells. *J Am Osteopath Assoc* 2016;116:e1-5.
 83. Yiou R, Hamidou L, Birebent B, Bitari D, Lecorvoisier P, Contremoulins I, et al. Safety of intracavernous bone marrow-mononuclear cells for postradical prostatectomy erectile dysfunction: an open dose-escalation pilot study. *Eur Urol* 2016;69:988-91.
 84. Yiou R, Hamidou L, Birebent B, Bitari D, Le Corvoisier P, Contremoulins I, et al. Intracavernous injections of bone marrow mononucleated cells for postradical prostatectomy erectile dysfunction: final results of the INSTIN clinical trial. *Eur Urol Focus* 2017;3:643-5.
 85. Al Demour S, Jafar H, Adwan S, AlSharif A, Alhawari H, Alrabadi A, et al. Safety and potential therapeutic effect of two intracavernous autologous bone marrow derived mesenchymal stem cells injections in diabetic patients with erectile dysfunction: an open label phase I clinical trial. *Urol Int* 2018;101:358-65.
 86. Pharmicell Co., Ltd. Safety of autologous bone marrow derived mesenchymal stem cells in erectile dysfunction [Internet]. Bethesda: U.S. National Library of Medicine; c2015 [cited 2019 Sep 16]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02344849>.
 87. Gruenwald I, Kitrey ND, Appel B, Vardi Y. Low-intensity extracorporeal shock wave therapy in vascular disease and erectile dysfunction: theory and outcomes. *Sex Med Rev* 2013;1:83-90.
 88. Kitrey ND, Gruenwald I, Appel B, Shechter A, Massarwa O, Vardi Y. Penile low intensity shock wave treatment is able to shift PDE5i nonresponders to responders: a double-blind, sham controlled study. *J Urol* 2016;195:1550-5.
 89. Kalyvianakis D, Hatzichristou D. Low-intensity shockwave therapy improves hemodynamic parameters in patients with vasculogenic erectile dysfunction: a triplex ultrasonography-based sham-controlled trial. *J Sex Med* 2017;14:891-7.
 90. Yamaçake KGR, Carneiro F, Cury J, Lourenço R, Françolin PC, Piovesan AC, et al. Low-intensity shockwave therapy for erectile dysfunction in kidney transplant recipients. A prospective, randomized, double blinded, sham-controlled study with evaluation by penile Doppler ultrasonography. *Int J Impot Res* 2019;31:195-203.
 91. Kitrey ND, Vardi Y, Appel B, Shechter A, Massarwi O, Abu-Ghanem Y, et al. Low intensity shock wave treatment for erectile dysfunction-how long does the effect Last? *J Urol* 2018;200:167-70.
 92. Lu Z, Lin G, Reed-Maldonado A, Wang C, Lee YC, Lue TF. Low-intensity extracorporeal shock wave treatment improves erectile function: a systematic review and meta-analysis. *Eur Urol* 2017;71:223-33.
 93. Clavijo RI, Kohn TP, Kohn JR, Ramasamy R. Effects of low-intensity extracorporeal shockwave therapy on erectile dysfunction: a systematic review and meta-analysis. *J Sex Med* 2017;14:27-35.
 94. Campbell JD, Trock BJ, Oppenheim AR, Anusionwu I, Gor RA, Burnett AL. Meta-analysis of randomized controlled trials that assess the efficacy of low-intensity shockwave therapy for the treatment of erectile dysfunction. *Ther Adv Urol*

- 2019;11:1756287219838364.
95. Yee CH, Chan ES, Hou SS, Ng CF. Extracorporeal shockwave therapy in the treatment of erectile dysfunction: a prospective, randomized, double-blinded, placebo controlled study. *Int J Urol* 2014;21:1041-5.
96. Fojecki GL, Tiessen S, Ooster P. Effect of low-energy linear shockwave therapy on erectile dysfunction-a double-blinded, sham-controlled, randomized clinical trial. *J Sex Med* 2017;14:106-12.
97. Katz JE, Molina ML, Clavijo R, Prakash NS, Ramasamy R. A phase 2 randomized trial to evaluate different dose regimens of low-intensity extracorporeal shockwave therapy for erectile dysfunction: clinical trial update. *Eur Urol Focus* 2018;4:336-7.
98. Zhu GQ, Jeon SH, Bae WJ, Choi SW, Jeong HC, Kim KS, et al. Efficient promotion of autophagy and angiogenesis using mesenchymal stem cell therapy enhanced by the low-energy shock waves in the treatment of erectile dysfunction. *Stem Cells Int* 2018;2018:1302672.
99. Lei H, Xin H, Guan R, Xu Y, Li H, Tian W, et al. Low-intensity pulsed ultrasound improves erectile function in streptozotocin-induced type I diabetic rats. *Urology* 2015;86:1241.e11-8.
100. Cui W, Li H, Guan R, Li M, Yang B, Xu Z, et al. Efficacy and safety of novel low-intensity pulsed ultrasound (LIPUS) in treating mild to moderate erectile dysfunction: a multicenter, randomized, double-blind, sham-controlled clinical study. *Transl Androl Urol* 2019;8:307-19.