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Erectile Dysfunction: Update on Clinical Management

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Abstract

Background and objective: Erectile dysfunction (ED) is a common condition affecting patients' quality of life. Clinical management has changed over the past three decades, with new diagnostic and therapeutic options available. Our aim was to provide an overview of novel evidence regarding clinical management of ED.
Methods: A non-systematic literature review was conducted to identify relevant studies on the diagnosis and treatment of erectile dysfunction. The review encompassed pharmacological, regenerative, and surgical approaches, summarising recent advances and highlighting persisting gaps in clinical practice.
Key findings and limitations: ED is a common reason for seeking medical consultation. The correlation between ageing and ED prevalence is rooted in neurovascular tissue impairment. Medical history, along with the use of validated questionnaires, still represents the mainstay of ED assessment because of the lack of reliable imaging tests. The most widely used and effective treatment is an oral phosphodiesterase type 5 inhibitor, but this is lifelong therapy that is associated with high dropout rates. Among novel regenerative treatments, low-intensity shockwave therapy is supported by more evidence, although high-quality trials and long-term data are lacking. More conclusive evidence is needed for platelet-rich plasma injections and stem cell treatment. Botulinum neurotoxin and new emerging oral drugs are also under investigation.
Conclusions: Several treatment options are available for ED. Clinical tailoring of treatment for individual patients and rigorous research are crucial for further advances.

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Patient summary: Erectile dysfunction (ED) is a common medical problem. Various types of treatment can improve ED, but there is still no cure for this condition.

1. Introduction

Erectile dysfunction (ED) is one of the most common conditions affecting men worldwide [1]. According to the latest epidemiology studies, up to 71% of men will experience ED at some point in their life [1]. These numbers provide insight into the high social impact of this condition. For this reason, research aimed at improving quality of life for men suffering from ED has been active field over the past three decades. Despite these efforts, numerous questions remain unanswered regarding both the pathophysiology and the treatment of ED [2]. An ideal treatment capable of fully restoring normal and spontaneous erectile function (EF) has yet to be discovered.

2. Methods

A comprehensive, non-systematic literature review was conducted to identify original studies and review articles related to the diagnosis and treatment of ED, encompassing publications up to February 2024. The search strategy focused on peer-reviewed sources indexed in PubMed and Embase, utilising the following keywords: 'erectile dysfunction', 'diagnosis', 'medical treatment', 'regenerative therapies', 'shockwave', 'platelet-rich plasma', 'stem cells', 'Botulinum neurotoxin', 'surgical treatment', and 'penile prosthesis implantation'. The collected data were narratively synthesised to present an updated summary of current diagnostic and therapeutic approaches, and to highlight ongoing challenges and unmet needs in the management of ED.

3. Results

3.1. Epidemiology and etiology of ED

The prevalence of ED increases with age: data from the Massachusetts Male Aging Study (MMAS) showed that mild to moderate ED affects 52% of men aged >40 yr, and the prevalence of severe ED rises from 5% to 15% with advancing age [3]. By contrast, <10% of men aged <40 yr report ED [4]. While global epidemiology data confirm the high prevalence of ED among patients aged 40–80 yr, there are some geographical variations [1,5]. Heterogeneity among epidemiology studies in terms of the methodology for ED assessment and population characteristics significantly affects the prevalence rates reported. The MMAS [3] reported overall ED prevalence of 52% among men aged 40–70 yr in the Boston area. A similar European study found ED prevalence of 19.2% among men aged 30–80 yr [6]. In the Multinational Survey on the Aging Male study involving 12 815 men aged 50–80 yr from the USA, UK, Germany, Netherlands, France, Spain, and Italy, ED prevalence was 49% [7]. Epidemiology surveys conducted in South America have revealed similar data [8]. The Global Study of Sexual Attitudes and Behaviours revealed that ED prevalence is highest in Southeast Asia (28.1%) [9]. Overall, data from the most up-to-date systematic review [1] show that ED rates range from 13% to 71% for men aged 40–80 yr, with slight differences among continents, as summarized in Fig. 1.

The etiology of ED can be broadly categorized as primary organic (vasculogenic, neurogenic, hormonal, iatrogenic, post-traumatic, or a combination of these factors) or primary psychogenic. Organic ED often coexists with other systemic diseases, including diabetes, cardiovascular diseases, and metabolic disorders [10,11]. Most of these conditions share a common pathophysiological pathway involving neurovascular impairment; in the penis, this eventually leads to a fibrotic process at the level of the cavernous bodies [12]. Iatrogenic ED also accounts for a significant proportion of cases. The ED can be drug-induced or secondary to therapeutic interventions such as pelvic surgery and radiotherapy [2]. Drug-induced ED is frequently observed: according to the US Food and Drug Administration (FDA) adverse event reporting system, more than 40% of ED reports are attributed to use of 5α-reductase inhibitors or neuropsychiatric medications [13]. In addition to the well-known organic causes of ED, psychogenic ED remains a significant yet often underdiscussed condition. Psychogenic ED is primarily linked to psychological conditions, including stress, anxiety, and depression, that disrupt neurochemical pathways involved in sexual arousal [2,14]. Depression in particular increases the risk of ED and is often worsened by certain antidepressants [15].

3.2. ED assessment

Diagnosis of ED is based on a clinical history. Validated psychometric tools are recommended for defining the severity of ED and assessing other sexual function domains [2]. Among these tools, the International Index of Erectile Function (IIEF) [16], and its short form (IIEF-5), and the Erection Hardness Scale (EHS) [17] are the questionnaires most commonly used in clinical practice. Other diagnostic tools, including blood tests to assess the patient's metabolic and hormonal profile, can help in identifying the most probable etiology of ED [2]. Routine use of imaging is not suggested by clinical guidelines, mainly because of low diagnostic accuracy for assessment of ED [2]. Penile dynamic duplex Doppler ultrasound for detection of vasculogenic ED, for instance, has several limitations [18,19]. There is no clear consensus regarding the ideal parameter cutoffs for defining arteriogenic ED and a low predictive value for corporal veno-occlusive dysfunction (CVOD) [20,21]. Likewise, novel

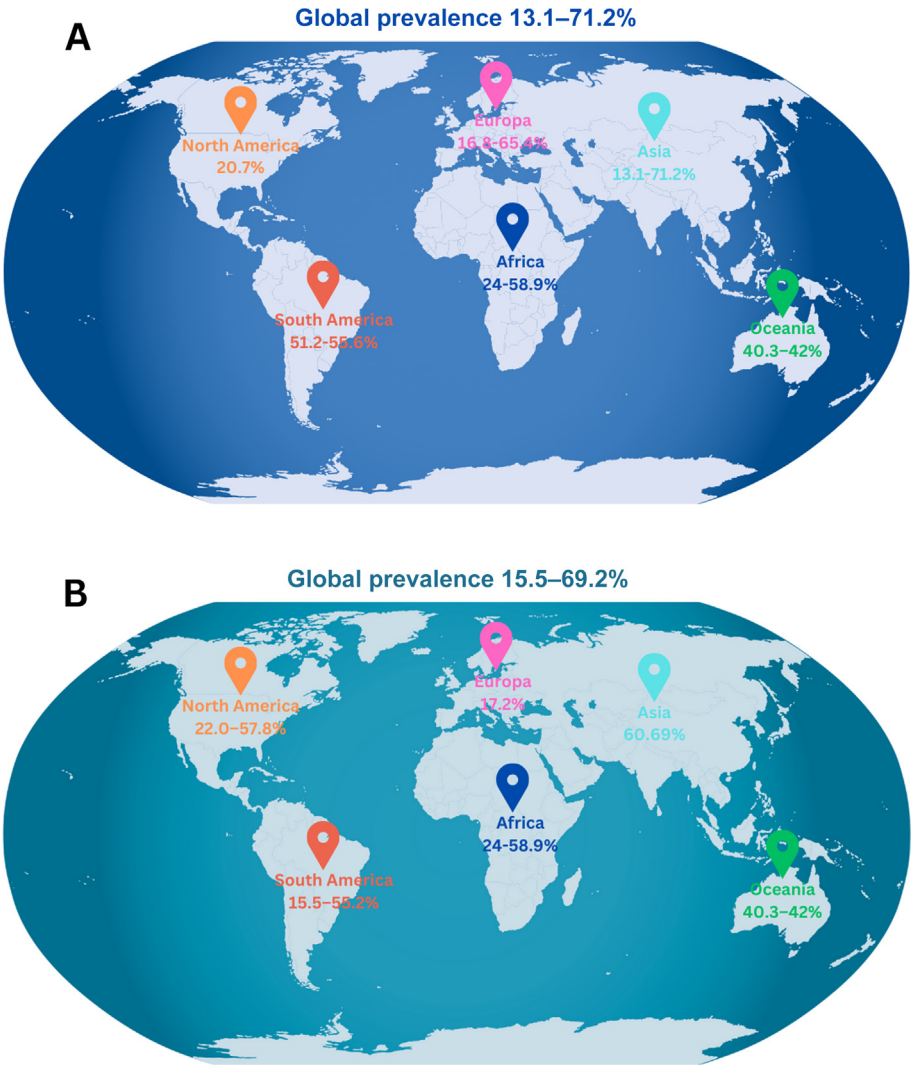

Fig. 1 – Overall global prevalence of erectile dysfunction assessed using (A) International Index of Erectile Function (IIEF), IIEF-5, or IIEF variants and (B) Massachusetts Male Aging Study (MMAS)-derived self-assessment.

modalities including penile magnetic resonance imaging and penile shear wave elastography have not yet proved to be convenient and reliable tools for assessment of corpora integrity in routine clinical practice [21–24]. Nocturnal penile tumescence and rigidity testing (NPTR) has traditionally been used to distinguish organic ED from psychogenic ED [22] and newer wireless wearable devices that offer affordability and ease of use may revive interest in NPTR [23]. Wearable electronic devices and gadgets for ED assessment are increasing in popularity among patients for tracking of sexual function [25]. This technology can measure physiological parameters and provide data on physiological changes during sexual activity [26]. One of the marketed examples is the Tech Ring (FirmTech; https://myfirmtech.com), which functions as both a penoscrotal constriction ring and a sexual health monitor [25], although assessment of physiological erections may be altered by the constriction ring itself. The device is equipped with sensors to track and report the number, duration, and firmness of erections and provides real-time feedback and health metrics. The ADAM sensor [24,27] is another ring-like device that provides information on penile tumescence during sleep, but extensive evaluation is required.

3.3. *Conducting clinical research on ED treatments*

When evaluating the literature on ED treatments, an understanding of the principles of trial design is essential. Randomized controlled trials (RCTs) are necessary for determining the efficacy and safety of treatments, and placebo-controlled designs are crucial because of a placebo response rate of 25–35% in ED studies [28]. Trial design choices (parallel or crossover) should consider whether the medication has immediate or delayed effects. Multicenter trials are preferable because of better generalizability of the results [28]. Studies must be adequately powered, typically for demonstration of significant differences in results for validated instruments such as the IIEF-EF.

Proper patient categorization between organic and psychogenic ED is critical, although definitive classification

remains challenging [29]. The use of validated instruments, such as the IIEF erectile function domain (IIEF-EF) and the Sexual Health Inventory for Men, helps in reducing investigator and patient bias. To prevent biased reporting, inventory completion should be performed by personnel who are not investigators [28].

Clinical trials should be of sufficient duration (typically 8–12 wk) to demonstrate a consistent response, with patients attempting sexual relations once or twice weekly. Long-term efficacy should be assessed via 6–12-mo open-label trials [28].

Collection of safety data in phase 3 trials is crucial, although any sample size based on efficacy endpoints may be underpowered for assessment of adverse event rates. Data collection methods can influence the numbers and types of adverse events recorded [28].

3.4. ED management

The treatment landscape for ED has changed over the past three decades, although solid clinical data supporting clinical implementation of most of the emerging treatment options are still lacking. Fig. 2 summarizes the available and emerging treatments for ED.

Implementation of lifestyle changes is crucial in both preventing and treating ED [2]. These factors include regular maintenance of a healthy weight, regular physical exercise, a well-balanced diet, effective stress management, smoking cessation, reduction of alcohol intake, and enhancement of sleep quality [30]. Such lifestyle interventions can have a beneficial effect on general vascular health, hormone levels, and psychological wellbeing, all of which are elements linked to ED [30]. Oral drugs, penile injections, alprostadil cream and pellets, vacuum devices, and penile implants are all significant options for the management of ED.

In addition to the generally recognized organic causes of ED, psychogenic ED is a noteworthy but frequently overlooked element. For patients with psychogenic ED, addressing underlying psychological issues, including depression, is essential for effective management [2]. This typically requires psychological counseling and, when necessary, pharmacological interventions [2]. An exploration of the treatment strategies for psychogenic ED is beyond the focus of this paper.

3.4.1. Phosphodiesterase type 5 inhibitors: new evidence

ED can be managed with various pharmacological and non-pharmacological treatments, which are often tailored according to the underlying etiology and individual patient and partner preferences. Nevertheless, first-line pharmacological treatment for ED is often a phosphodiesterase type 5 inhibitor (PDE5I) [2]; several RCTs and meta-analyses have largely proved the overall good efficacy and safety profile of these agents [31,32]. Recent research has placed a greater emphasis on the cardiovascular safety of PDE5I agents. Kloner et al [33] conducted a retrospective analysis of data from a large insurance claims database and found a 19% decrease in the occurrence of major adverse cardiovascular events and a 44% decrease in overall mortality among individuals exposed to tadalafil in comparison to those not exposed to PDE5Is. Given that ED is often an early marker of cardiovascular disease, this underscores the importance of assessing cardiovascular health in patients presenting with ED [34].

In addition to potential benefits for cardiovascular health, PDE5Is have demonstrated preventive effects in various other health disorders [35]. For example, research has shown that PDE5Is have renoprotective properties [36]. Indeed, boosting of nitric oxide-cyclic guanosine monophosphate (NO-cGMP) signaling protects kidney function via regulation of blood flow and direct protection of kidney tissue through multiple cellular mechanisms [36], which are advantageous in conditions such as diabetic nephropathy and chronic kidney disease. PDE5Is also have potential advantages in heart failure, as they enhance car-

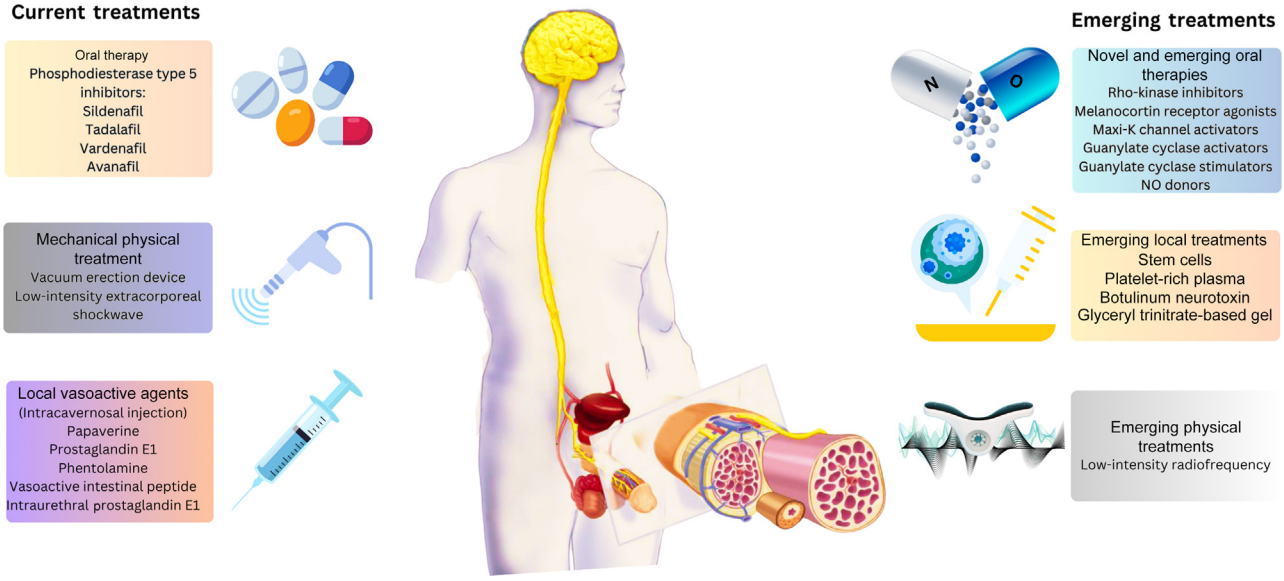

Fig. 2 – Current and emerging treatments for erectile dysfunction.

diac function and decrease myocardial stress [35]. Furthermore, a growing body of data suggests potential PDE5I involvement in reducing cognitive decline [37], anticancer effects mediated by different mechanisms (eg, cell growth arrest; chemotherapy sensitization; modulation of immune responses [38]), and the treatment of immunological disorders and systemic sclerosis [39]. All of these findings need to be confirmed in large clinical trials.

Significant treatment discontinuation rates have been reported for all available PDE5I agents, ranging from 4.4% to 76% [40]. The most common reason for treatment dropout include lack of efficacy (42%), costs (37%), partner reluctance (14.6%), and side effects (11.8%) [40]. Strategies for management of nonresponders and poor responders to PDE5Is should include dose optimization, and proper patient counseling regarding the timing of administration and the need for sexual stimulation [2]. The combination of daily tadalafil and an on-demand PDE5I [41] and the use of PDE5Is along with a supplements such as L-arginine or mechanical equipment such as a vacuum erection device could be a successful strategy [42]. Testosterone replacement medication could also potentially improve response rates in patients with hypogonadism [42].

3.4.2. *Intracavernous pharmacological treatment*

Intracavernos injections (ICI) of vasoactive agents was one of the first treatments for ED and is currently considered a valid option for patients with no response to PDE5Is [2]. Alprostadil is the only agent approved for intracavernous treatment of ED, with success rates ranging from 87% to 93.5% [43]. Adverse effects include pain, priapism (1%), and penile fibrosis (2%) [43]. Alprostadil can also be delivered via the urethra using two distinct formulations: a cream that enhances alprostadil penetration through the urethral meatus (VITAROS) [44] and a pellet specifically formulated for intraurethral administration of alprostadil (125–1000 μg; MUSE) [45]. Overall, 30–65.9% of patients are able to achieve erections adequate for sexual intercourse with these formulations [2,44,45].

Bimix and Trimix are combinations of off-label vasoactive agents that are often used to treat ED in patients who are poor responders to alprostadil, and have a good efficacy profile [46,47]. This combination therapy has similar side effects to alprostadil monotherapy, but lower rates of penile pain because of the lower alprostadil doses used. Invicorp is a medication approved in Scandinavia that combines vasoactive intestinal peptide (25 μg) and phentolamine mesylate (1–2 mg) [48]. Clinical trials demonstrated that this combination is efficacious for ICIs in >80% of males with ED, even in cases in which other treatments have been unsuccessful [48].

Botulinum neurotoxin type A (BoNT-A) has also been investigated as a potential treatment for ED. Botulinum neurotoxin originates from the bacterium *Clostridium botulinum*, which generates a toxin that causes temporary flaccid paralysis by impeding release of acetylcholine at the presynaptic membrane [49]. Animal studies indicate that BoNT-A ICIs can increase intracavernosal pressure and lead to a pro-erectile effect [50,51]. This effect results from relaxation of cavernosal smooth muscle due to inhibition of noradrenaline release by adrenergic neurons, which decreases overall sympathetic tone and facilitates erection following stimulation [52]. Since BoNT-A also blocks the release of acetylcholine from parasympathetic neurons, erection is dependent on the NO produced by non-adrenergic non-cholinergic neurons [52]. Considering these effects, BoNT-A appears to enhance erections.

Two double-blind RCTs have examined the effect of BoNT-A in ED patients who are unresponsive to PDE5Is or pro-erectile drug injections. In the study by Abdelrahman et al [53] 70 ED patients who were unresponsive to PDE5Is received either a single BoNT-A injection of 100 IU or saline. Both groups continued to use high-dose PDE5Is on demand. At 6 wk, the treatment group reported a 5-point increase in mean IIEF-5 score, whereas the placebo group reported no improvement. Furthermore, 53% of patients in the treatment group reported achievement of erections suitable for vaginal penetration at 6 wk after injection. This figure declined to 32% at 12 wk, but was still higher than the 3% in the placebo group at both 6 and 12 wk. Similar findings were obtained in a second placebo-controlled trial involving patients who were unresponsive to PDE5Is or Trimix [54]. Mild local side effects were reported in both trials, with no systemic complications.

Overall, these data suggest that BoNT-A could be an asset in delaying surgical treatment in patients who are unresponsive to medical treatment for ED. However, larger trials are needed to validate these findings and ascertain the efficacy and safety of BoNT-A for ED treatment. Current international guidelines still consider this treatment as experimental [2].

3.4.3. *Regenerative therapies*

During the initial marketing of PDE5Is, a study revealed that ED patients ranked cure first among variables for outcome success [55]. Many patients experience insufficient responses to PDE5Is and permanent clinically meaningful improvements in ED remain unachievable via medication, lifestyle changes, or surgery. Although daily PDE5I use has improved sexual spontaneity, many patients still desire permanent improvement of unassisted EF [56]. Regenerative medicine, an experimental branch of medicine in which the aim is to regrow, repair, or replace damaged tissues, has potential as a curative treatment for ED. Several options, including both allogeneic and autologous cellular or platelet-based injectables and low-intensity shockwave therapy (SWT), have shown beneficial effects in animal models of ED, and the theoretical concept is appealing [57–59]. Changes in the penile microenvironment are characteristic of advanced ED and researchers have been attempting to reverse these changes using regenerative therapies [57–59]. However, it should be borne in mind that ED is largely secondary to systemic disease, as are the penile changes observed. Therefore, there is a limited rationale for therapies directed solely at the penis. Moreover, our understanding of the penile microarchitecture and cellular functions remains incomplete [60]. Consequently, results for these therapeutic innovations must be interpreted with caution, considering that their limited effect sizes probably result from an incomplete understanding and opportunistic

Table 1 – Summary of current evidence on regenerative therapies for erectile dysfunction

Category	Autologous stem cells	Low-intensity shockwave therapy	Platelet-rich plasma
Evidence from animal studies	More than 40 studies on animal models have shown positive findings. Most studies showed that SCs can prevent fibrosis of the corpora, but only 2 studies showed a reversible effect.	20 animal studies using ED models (diabetic, obese, or hypertensive rats; rats with cavernous nerve injury; and naturally aged rats) showed improvements in penile hemodynamic parameters, tissue remodeling, neoangiogenesis, and nerve regeneration.	5 animal studies using ED models (diabetic rats or rats with cavernous nerve injury) showed improvements in penile hemodynamic parameters and nerve regeneration.
Evidence from human clinical trials	LOE 2–4: - 1 RCT showed a benefit of mesenchymal SCs over placebo (saline) - 15 single- or two-arm phase 1/2 trials assessed safety and tolerability using ADSCs, BMSCs, and UDSCs.	LOE 1: A meta-analysis of RCTs showed a benefit over placebo in terms of IIEF-EF scores and penile hemodynamic parameters.	LOE 2: Three RCTs: 2 trials showed a benefit over placebo in terms of IIEF-EF score; 1 trial showed no benefit over placebo.
Magnitude of the effect in human clinical trials	- RCT: 3.4-point improvement in IIEF-5 in the treatment group at 6 mo. - Other trials: controversial findings showing 5–15-point improvements in IIEF-EF scores.	- 2–4-point improvement in IIEF-EF in the treatment group at 6–12 mo. - 4 cm/s improvement in peak systolic velocity on penile Doppler ultrasound.	- 3–4-point improvement in IIEF-EF at 6 mo in positive RCTs.
Safety	No major treatment-related AEs observed. Common side effects include temporary mild pain, redness, bruising, or irritation at injection sites.	No major treatment-related AEs observed. Common side effects include pain at the treatment site and bruising.	No major treatment-related AEs observed. Common side effects include pain at the treatment site and bruising.
Standardized protocol	No standardized protocol available regarding the type of SCs, number of injections and optimal patient profile.	No standardized protocol available regarding the number and timing of treatment sessions, EFD, or frequency. Data from RCTs are in favor of using devices delivering focused shockwaves rather than radial-linear waves.	No standardized protocol available regarding the number and timing of injections, the optimal platelet concentration needed, or the PRP activation method.
Clinical guideline recommendations	EAU: no recommendation provided. AUA: no recommendation provided.	EAU: LISWT could be proposed as an alternative treatment in patients with mild to moderate vasculogenic ED or nonresponders to PDE5Is. AUA: LISWT should be used only in the context of clinical trials.	EAU: PRP should be used only in the context of clinical trials. AUA: PRP should be used only in the context of clinical trials.

ADSCs = adipose-derived SCs; AEs = adverse events; AUA = American Urological Association; BMSCs = bone marrow–derived SCs; EAU = European Association of Urology; ED = erectile dysfunction; EFD = energy flux density; IIEF International Index of Erectile Function; IIEF-EF = IIEF erectile function domain; LISWT = low-intensity shockwave therapy; LOE = level of evidence; PDE5I = phosphodiesterase type 5 inhibitor; PRP = platelet-rich plasma; RCT = randomized controlled trial; SCs = stem cells; UDSCs = urine-derived SCs.

testing of therapies not specifically designed for this purpose. Table 1 summarizes the current evidence on regenerative therapies for ED according to data from primary sources and reflecting the collective expert opinion of the authors.

3.4.3.1. SWT. In the past two decades, low-intensity SWT has been extensively investigated as a regenerative treatment for ED [61]. It is believed that the mechanical energy produced by acoustic shockwaves triggers restoration of cavernosal tissue via various pathways, including enhanced neoangiogenesis due to release of VEGF, recruitment of progenitor stem cells, nerve recovery, and regeneration directly through stimulation of neuronal proliferation or indirectly via activation of Schwann cells, an increase in the production of vasodilatory NO in affected tissues, and an anti-inflammatory effect [57]. However, these hypotheses are grounded in data from animal studies, mainly murine ED models, which limits direct replication in human ED [57].

Despite inconclusive evidence on the biological effects of SWT on cavernosal tissues, more than 20 RCTs and 14 meta-analyses have investigated the efficacy of SWT for ED treatment [61]. Overall, these trials are affected by several limitations that reduce the quality of the evidence provided. (1) The majority of the trials included a small number of patients, with the largest trial of only 118 patients reporting no advantage of SWT over placebo [62]. (2) Patient selection remains an issue, as several trials lack details about the characteristics of the population treated, which potentially included men with psychogenic ED, making it difficult to identify the cohorts that could really benefit from SWT. (3) There is no standardized treatment protocol in terms of the treatment schedule or the amount of energy to be delivered. In addition, although the large majority of these trials reported a benefit in terms of EF improvement after SWT in comparison to placebo, the effects observed appear to be small and may not be perceived as significant by patients in clinical practice. A recent analysis of pooled data revealed a mean increase of 3.01 points in IIEF-EF score (95% confidence interval 2.04–3.98; $p < 0.00001$) at 3 mo after SWT treatment in patients with vasculogenic ED [63], which might not fulfill the minimally clinical important difference (MCID) criterion for the IIEF-EF score for some patients.

Despite these considerations, the excellent safety profile of SWT and the costs related to this out-of-pocket therapy

have led to wide its use as a treatment option for ED. The European Association of Urology is the only international society to date to formally recommend this treatment as an option for patients with mild ED [2]; other international guidelines advise caution regarding SWT use and still consider the treatment as investigational [64,65].

3.4.3.2. Platelet-rich plasma. The aim of platelet-rich plasma (PRP) treatment is to address various pathophysiological aspects of ED, including vascular issues, nerve protection and growth, tissue repair, and inflammation [66]. The patient's own platelets are concentrated to enrich growth factors for tissue healing. However, the exact mechanisms via which PRP facilitates EF recovery are still not fully understood [66]. At present there are no standardized protocols for PRP preparation, and the market offers a plethora of centrifugation devices that produce different PRP doses, depending on their ability to concentrate platelets [66,67].

Although PRP has been considered for urological conditions since the early 2010s, conclusive evidence regarding its efficacy is limited. Animal studies have suggested the potential of PRP in repairing nerves and enhancing EF after injury [66]. Human clinical trials using PRP either as monotherapy or in combination with other modalities (SWT or PDE5Is) have produced mixed results [68]. In the first RCT, 60 patients with mild to moderate vasculogenic ED were assigned to receive two injections of 10 ml of PRP (n = 30) or placebo (n = 30) [69]. At 1-mo, 3-mo, and 6-mo follow-up, the proportion of patients reporting a clinically meaningful improvement in IIEF-EF score was significantly higher in the treatment group: 69% experienced an improvement at 6 mo after PRP therapy, versus 27% in the placebo group ($p < 0.001$). Similar results were obtained by Shaher et al [70] in a second RCT involving 100 patients, while a trial by Masterson et al [71] in a cohort of 61 men with mild to moderate ED found no marked difference in IIEF-EF, MCID, or penile duplex ultrasound results between the PRP and placebo groups.

PRP therapy is widely marketed online and is primarily provided by clinics specialized in cosmetic or naturopathic medicine, often under supervision by cosmetic surgeons or general practitioners. However, the costs of this treatment are largely undisclosed, which obscures the financial aspect of PRP therapy for ED [58]. The paucity and low quality of the evidence does not support current use of PRP treatment in routine clinical practice.

3.4.3.3. Stem cell therapy. The aim of stem cell therapy (SCT) in the ED setting is to regenerate damaged tissue to restore normal EF [12]. Basic science studies have shown that stem cells can self-renew and differentiate into various mature cell types, which makes them suitable for regenerative therapies, while animal studies have demonstrated the potential of stem cells to cure ED by improving various aspects of penile function, including mitigation of penile fibrosis [12]. However, these studies have limitations, and the scarcity of high-quality clinical evidence makes it challenging to translate the findings to human clinical applications [72,73].

Clinical studies on SCT for ED have primarily focused on safety and feasibility, involved fewer than 400 patients, and applied varying methodologies [59]. The studies also used different stem cell types (mostly of adipose tissue, bone marrow, or mesenchymal origin) and were not designed to demonstrate definitive efficacy [59]. Therefore, the actual therapeutic potential of SCT for ED remains unclear. The future of SCT for ED treatment will rely on the development of well-designed, multicenter, placebo-controlled RCTs to determine the optimal stem cell sources and their safety, effectiveness, doses, and administration routes. There is also a need to identify the type of patient and ED severity most suited to SCT. Until then, SCT should be considered experimental and restricted to clinical trials [74].

3.4.4. New potential treatments for ED: Rho-associated inhibitors and more

Novel pharmaceutical targets for the treatment of organic ED have been discovered that act at either the peripheral or central level. The Rho-kinase ROCK2 has a crucial function in contraction of smooth muscle in the cavernosal region by increasing intracellular Ca^{2+} levels [75]. Enhanced ROCK2 activity is therefore associated with ED. Animal models have demonstrated the effectiveness of Rho-kinase inhibitors in enhancing EF via a mechanism that is not NO-dependent [76–80]. Notably, the Rho-kinase inhibitor fasudil was able to restore penile hemodynamics and decrease pelvic atherosclerosis in animal models [81]. Such findings indicate the potential of a novel class of drugs for ED treatment, particularly in individuals with impaired NO function due to conditions such as diabetes and hypertension, who do not respond to PDE5Is [82]. Nevertheless, the effectiveness of these agents for ED has not been evaluated in human clinical trials because the Rho-kinase system is present in all vascular beds and there is thus a risk of marked decreases in blood pressure with these drugs [83].

Maxi-K channel activators are increasingly being recognized for their ability to induce relaxation of smooth muscle in the body, which is essential to achieve penile erection [84–86]. Gene therapy to enhance EF by introducing the Maxi-K channel gene into penile tissues has been investigated [84–86]. Animal models have demonstrated improvements in sexual behavior and enhanced EF [85,86]. In the only small phase 1 human trial published, this approach showed improvements in IIEF-EF scores without negative side effects [84].

Soluble guanylate cyclase (sGC) activators could be effective in overcoming the drawbacks of PDE5Is, especially in individuals with compromised NO-sGC-cGMP signaling pathways in conditions such as diabetes and hypertension [87]. sGC contains an NO-independent site that can be activated by sGC stimulators, which augments the enzyme function of sGC and leads to smooth muscle relaxation at the level of the corpora. Animal studies have revealed that sGC activators can reverse reduced intracavernosal pressure and promote cavernosal relaxation [88–90]. However, clinical use of these compounds is still limited because of the risk of systemic hypotension [87].

Use of the NO donors L-arginine and glyceryl trinitrate (GTN) is a traditional but continuously evolving approach

[82,87]. L-Arginine increases endothelial NO production and can enhance ED outcomes when coupled with sildenafil, as evidenced by improvements in IIEF-5 scores in clinical trials [91]. GTN, a widely recognized vasodilator, functions by releasing NO in the smooth muscle of blood vessels. Recent pharmacokinetic and pharmacodynamic research has revealed the efficacy of a recently approved (FDA and European Medicines Agency) GTN-based gel (MED2005) that has a brief half-life and positive safety profile [92].

Beside peripheral pharmacological agents, other therapeutic agents that act on the central nervous system (CNS) have been investigated [87]. At the CNS level, several potential pharmacological targets, including melanocortin, dopamine, serotonin, and oxytocin receptors, are directly involved in EF and sexual desire [87]. Research suggests that melanotan-II, a melanocortin receptor agonist, and its derivative bremelanotide enhance erections without sexual stimulation by stimulating melanocortin receptors at the hypothalamus level in men with ED of either psychogenic or organic etiology [87,93,94]. Apomorphine, which was released in 2000, is a dopamine receptor agonist that can induce erections, but is extremely limited by side effects (mainly nausea and vomiting) [95]. Novel selective dopamine-4 receptor agonists are currently under investigation and appear to be promising because of a better tolerability profile [96,97]. Buspirone, which acts by modulating serotonin receptors, and bupropion, which increases dopamine and norepinephrine levels in the brain, are currently approved for the treatment of depression and anxiety disorders, but have also shown a positive effect in enhancing sexual desire and erections [98].

In summary, these new treatments address different facets of the complex pathogenesis of ED. However, the lack of significant evidence supporting the efficacy and safety of these compounds has limited their use in clinical practice.

3.4.5. *New medical devices*

Novel medical devices to assist patients in reaching desirable EF have been developed and investigated. Xialla, a constriction ring for CVOD [99], has a unique anchoring mechanism that may optimize venous trapping. Although the device shows promise for improving EF, the evidence is limited to conference abstracts [100–102] and external validation is lacking. Other constriction devices, such as the Eddie by Giddy [103] and Loop Ring by Maintain [25], have also entered the market.

Low-intensity radiofrequency has recently been introduced as a regenerative treatment for men with mild to moderate ED. Vertica is an innovative device that uses low-frequency radiofrequency to enhance the collagen content and structure of the corpus cavernous, and thus improve the veno-occlusive mechanism [104]. The device is designed for self-appliance and home use. In the pivotal clinical trial conducted with 32 patients with ED (mean age 59.5 ± 9.8 yr), 12 sessions with the Vertica device (twice a week in month 1, and once a week in month 2) were associated with significant improvements in IIEF (43.7 ± 7.8 vs 60.9 ± 10.8; $p < 0.01$), IIEF-EF (16.8 ± 3.1 vs 24. ± 4.4; $p < 0.001$), and EHS (2.2 ± 0.8 vs 3.2 ± 0.5; $p = 0.01$) scores [104]. While these initial findings are encouraging, further multicenter, long-term, randomized, and sham-controlled clinical studies are necessary to clarify the effectiveness of the Vertica device and investigate the characteristics of ED patients who are most likely to benefit from this treatment.

3.4.6. *Surgery for ED: the era of implants*

Penile prosthesis implantation remains the last bastion of ED treatment in refractory cases, and can also be considered in patients who prefer a definitive therapy and are not compliant with medical treatment [2]. Numerous advances in materials and surgical techniques over time have led to increases in patient satisfaction and a decrease in complication rates [105]. Data show satisfaction rates of 92–100% after proper preoperative counseling [106–108]. Infection and mechanical failure are the most common complications: infection rates of 1–2% have been reported in the most up-to-date series [109]. A recent meta-analysis showed that the penile prosthesis survival rate is as high as 76.8% at 10 yr [110].

Newer penile prosthesis designs in development seek to broaden the range of patients who can safely use implants while enhancing functionality and spontaneity by providing alternatives to manual pump activation and the need for reservoir placement. Advances in material science and technology have allowed novel innovations, such as nickel and titanium alloy-plated "malleable" implants with properties that change depending on the temperature [111,112]. Activated by external magnetic induction wands, these implants can achieve rigidity similar to that of inflatable devices, but have better flaccidity than traditional malleable implants in their inactive state [111,112].

Other technical modifications include the development of "one-piece" hydraulic devices that use external remote-controlled piezoelectric pumps to shift fluid from reservoirs integrated within the cylinders to achieve device activation and deactivation [113]. Such devices would eliminate the need for manual pumps or reservoirs and could represent safer options for cases in which reservoir placement would be difficult. While these advances have not yet been implemented in clinical practice, they are close on the horizon and represent the next phase in the evolution of penile prosthetic devices.

4. Discussion

ED remains one of the most common reasons for seeking medical consultation, and ED prevalence increases with age, although a significant percentage of men may suffer from bothersome ED at younger ages [2]. ED should be considered a symptom rather than a disease, as it has proven to be a reliable proxy for undetected systemic conditions [114,115].

After the advent of Viagra in 1998, several therapeutic options for ED emerged, including other PDE5Is, mechanical devices, regenerative therapies, and surgical treatments. PDE5Is have demonstrated the highest magnitude of improvements in EF and satisfaction in comparison to other treatments, with low side-effect rates and good compliance [2]. However, the main limitation of PDE5Is is their inability to definitively cure ED, so dependence is lifelong. Moreover,

a non-negligible proportion of patients do not respond to PDE5Is.

Recent research has focused on the development of treatments capable of permanently restoring normal EF. SCT, while extensively studied, still lacks strong clinical evidence [59]. Regenerative treatments such as SWT have shown promising results for mild to moderate vasculogenic ED, although questions regarding efficacy remain [63]. Likewise, PRP ICIs have yielded controversial results in initial controlled trials [66,70,71].

Other intriguing treatments, including ICIs of botulinum neurotoxin for nonresponders to medical treatments, radiofrequency for CVOD, and novel oral therapies, still require more data to draw conclusions regarding their efficacy [2,59,63,66,70,71,99,115].

5. Conclusions

A diverse array of treatments is currently available for ED. Physicians should tailor every treatment to the patient's clinical characteristics and expectations. There remains a need for further high-quality studies to define the role of novel and emerging treatments.

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