REVIEW ARTICLE

News and future perspectives of non-surgical treatments for erectile dysfunction

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The significant discontinuation rate of available therapies and the paucity of curative options promoted the research on potential novel treatments suitable for erectile dysfunction patients. The aim of this study was to provide a summary of available evidence regarding the news and future perspectives related to the non-surgical treatment of erectile dysfunction. A narrative review of the literature was performed. A comprehensive search in the MEDLINE, Embase, and Scopus databases was done. Papers in English-language, published until April 2022, were included. No chronological restriction was applied. Retrospective and prospective clinical studies, as well as meta-analyses, were considered. Oro-dispersible formulations of phosphodiesterase type 5 inhibitors are particularly indicated in patients who have difficulty in swallowing solid dosage form; in addition, they constitute a discrete route of administration not requiring water. Low-intensity extracorporeal shock wave therapy is indicated in mild vasculogenic erectile dysfunction and in patients with vasculogenic erectile dysfunction poorly responsive to phosphodiesterase type 5 inhibitors. Stem cell therapy, platelet-rich plasma injections, and gene therapy seem promising regenerative treatments for selected patients with erectile dysfunction. Novel oral formulations of drugs commonly used in erectile dysfunction patients have recently become part of standard clinical practice. Regenerative treatments have been emerging in recent years and could become routine curative options in the near future. Further well-designed randomized controlled trials are needed to provide conclusive evidence on this topic and guide appropriate recommendations.

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INTRODUCTION

Oral phosphodiesterase type 5 inhibitors (PDE5Is) are the traditional first-line therapeutic option for ED [1]. Cognitive behavioral therapy combined with medical treatment can maximize the outcomes [2]. Intracavernous injections of vasoactive agents (e.g., alprostadil) are indicated in patients with ED not responding to PDE5Is and as a first-line therapeutic option in subjects with contraindications (e.g., nitrate medications) or concerns (e.g., drug interactions, side effects) with PDE5Is [1, 3]. Topical formulations of vasoactive agents are also available, they constitute a less invasive but also less effective alternative to intracavernous injections [1, 4, 5]. Vacuum erection devices constitute a non-pharmacological alternative in selected patients [1, 6]. Penile prosthesis implantation is indicated if the other treatments fail or when the patient asks for a definitive solution [1]. This is associated with a high patient satisfaction rate [7, 8]. Despite the limited evidence, treatments for ED are frequently combined to improve their effectiveness, especially in unresponsive patients [9–11]. In addition, despite the high efficacy and safety profile, a significant discontinuation rate for all available ED therapeutic options has been reported: 4.4–76% with PDE5Is, 18.6–79.9% with intracavernous injections of vasoactive agents, 30% with penile prostheses [12]. Ineffectiveness, adverse events (AEs), and costs seem some of the most relevant obstacles which can lead to the discontinuation of the treatments [13, 14]. In particular, a recent meta-analysis reported that PDE5Is were associated with a mean discontinuation rate of 4% per month (~50% after 1 year). Partner-related problems and lack of efficacy were the most important causes of the interruption of the therapy [15].

In the last few years, some new PDE5I oro-dispersible formulations have been introduced in the market [16]. In addition, emerging evidence regarding new ED treatments mainly based on regenerative therapy has been produced including extracorporeal shock wave [17], stem cells [18] and platelet-rich plasma (PRP) [19] therapy. The aim of this study was to provide a summary of available evidence regarding the news and future perspectives related to the non-surgical treatment of ED.

MATERIALS AND METHODS

A narrative review of the literature was performed. A comprehensive search in the MEDLINE Embase, and Scopus databases was done including a different combination of the following keywords:

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"erectile" "erection", "sex", "sexual", "dysfunction", "impotence", "intercourse", "penis", "penile", "treatment", "therapy", "cure", "management", "perspectives", "future", "news", "novel", "innovative", "emerging", "PDE5I", "stem cells", "shockwaves", "ESWT", "platelets", "plasma", "PRP", "gene", "oral", "topical", "regenerative", "restoration", "vacuum device".

Only English-language papers published until April 2022 were included in the analysis. No chronological restriction was applied. Retrospective and prospective clinical studies, as well as meta-analyses, were considered. Conference abstracts, case reports, letters to the editor, editorial comments, and animal studies were excluded. Small case series (≤10 cases), surveys, and narrative reviews were included due to the expected paucity of data in the literature. The reference lists of selected papers were used to search other relevant articles. According to the expert opinion of the authors, articles reporting significant news and perspectives on the non-surgical treatment of ED were included. According to the predefined type of review, the results were qualitatively described, as reported in the primary studies, without quantitative synthesis.

The main characteristics and findings of studies included in the review were summarized in Table 1. The evidence rating and the guideline recommendations on emerging non-surgical treatments for ED covered in the review were reported in Table 2.

RESULTS

PDE5I: is there any news?

Oro-dispersible formulations. Sildenafil, vardenafil, tadalafil, and avanafil are the most used PDE5Is [20]. Although head-to-head trials comparing the efficacy and safety of PDE5Is are still lacking, available data suggest similar efficacy and safety profiles [21, 22].

PDE5Is are traditionally administered orally as film-coated tablets (FCT). In the last few years, oro-dispersible tablets (ODT) and, even more recently, oro-dispersible films (ODF) have been developed and marketed. Sildenafil is the most common PDE5I available in all these new forms [23]. ODT and ODF are particularly indicated in patients who have difficulty swallowing solid dosage forms [1]. In addition, ODT and ODF in particular constitute a discrete route of administration not requiring water which patients may simply prefer. These advantages could improve patient acceptance and compliance compared to traditional formulation.

A randomized, open, two-way cross-over study in 53 healthy male volunteers found that FCT and ODF of sildenafil 100 mg had similar bioavailability in terms of maximum concentration (Cmax) and the area under the concentration-time curve (AUC0-t). AEs occurred at similar rates for both formulations with mild-to-moderate severity [24]. A further randomized, two-way cross-over study on 12 healthy male volunteers showed that the sublingual or supralingual administration of ODF of sildenafil 50 mg had a comparable pharmacokinetic and safety profile [25]. A single-center open-label uncontrolled study evaluated the role of ODF of sildenafil 100 mg in 65 patients with ED after RP. The study showed that ODF resulted in a significant improvement of the five-item version of the International Index of Erectile Function (IIEF-5) score, Sexual Encounter Profile question-2 and 3 (SEP-2, SEP-3) [26]. A multicenter, Italian, cross-over study compared sildenafil 100 mg FCT and sildenafil 75 mg ODF in 139 patients with ED for 4 weeks after 2 weeks of wash-out. The article showed that the ODF formulation resulted in similar safety and effectiveness of the FCT, but was better appreciated by patients in overall satisfaction [27].

Topical formulations. Nanotechnology is based on using solid-lipid biodegradable nanoparticles (SLNs) made up of lipid medium (solid) that is stabilized by surfactants in the aqueous media. The surfactant is adsorbed over SLNs surface during lipid matrix solidification. This approach allows to topically deliver molecules otherwise not adsorbed through lipid matrices such as cutis and mucosae [28]. Pharmacokinetic studies showed that nanoparticle-based drug delivery could be successfully used for several PDE5Is, including sildenafil [29], tadalafil [30], vardenafil [31], and avanafil [32]. However, available data are too limited to draw final conclusions on the topic [33].

Nutraceutical alternatives. The use of nutraceuticals in ED is currently a hot topic. The wide availability of these products (also online and without prescription) and the perception of them as "more natural and safer than drugs" by patients could justify their widespread sale [34]. The use of nutraceuticals in ED has a very ancient history and is rooted in traditional Chinese medicine and Ayurvedic medicine [35]. Promising findings emerged from several studies on Panax ginseng [36], Lepidium meyenii [37], Crocus sativus [38], L-arginine [39], L-citrulline [40], Tribulus terrestris [41], Epimedium [42], Muira puama [43], and Ginkgo biloba [44]. Patients with mild ED, subjects with sporadic ED, men unwilling to take PDE5Is, patients with contraindications for PDE5Is (e.g., coadministration of nitrates), and subjects resistant to PDE5Is alone could benefit from these nutraceuticals [36, 37]. However, the available studies on the topic are methodologically heterogeneous and generally of low quality, often reporting contradictory results [34, 35]. Therefore, the evidence supporting nutraceuticals in ED is still limited and there is no specific recommendation from the European Association of Urology guidelines [1].

Regeneration therapy: a not-so-distant future?

Low-intensity extracorporeal shock wave therapy (Li-ESWT). Vardi et al. published the first clinical study that assessed the efficacy of Li-ESWT for ED in 2010 [45], therefore it can be considered a recently introduced treatment. Li-ESWT represents a physical therapy method based on mechanical shear stress. It induces neoangiogenesis and enhances local blood flow with consequent improvement of penile vascularization [46]. Accordingly, a pilot prospective, single-arm, open study enrolling 30 patients with vasculogenic ED showed that Li-ESWT promotes neovascularization through the Power Doppler assessment. More specifically, the authors found that the number of helicine arteries, penile brachial pressure index, and peak systolic velocity (PSV) were significantly improved after the treatment ($p < 0.0001$) [47]. Neuro-regeneration, immune regulation, fibrosis reduction, and stem cell recruitment and activation are other suggested mechanisms of action [46, 48]. High heterogeneity among shockwave generators, type of shockwaves delivered, set-up parameters, and treatment protocols hinder research on the topic [49, 50]. To date, despite relevant differences in technology and inclusion criteria, several meta-analyses have described a statistically significant improvement in IIEF scores after Li-ESWT, both from baseline and compared to sham therapy [51, 52]. However, large heterogenicity exists between individual trials and the mean IIEF difference between Li-ESWT and sham arms ranged from ~ +2–4 points [53]. According to data derived from the studies on PDE5Is, this slight improvement in the IIEF represents an effective clinical outcome only in patients with a milder form of ED at baseline [54]. Some meta-analyses found that lower energy flux density (0.09 mJ/mm^2) and an increased number of pulses (at least 3000 pulses per session) were associated with improved erectile outcomes [55, 56]. However, more randomized trials are needed to demonstrate whether therapeutic efficacy is positively correlated with energy density.

According to current guidelines [1, 49], Li-ESWT can be suggested to well-informed patients with mild vasculogenic ED or vasculogenic ED patients who are poorly responsive to PDE5Is and represents a well-tolerated treatment option. However, it should be emphasized that current evidence is still poor but

Table 1. Main characteristics and findings of studies included in the review.

First author	Year of publication	Study design	Number of patients	Follow-up	Main findings
ODF of PDE5Is					
Radicioni [24]	2017	Randomized, cross-over	53	NA	Similar bioavailability in terms of Cmax and AUC0-t between ODF and FCT of sildenafil 100 mg. Similar rates of AEs with mild-to-moderate severity
Cocci [27]	2017	Multicenter, prospective, cross-over	139	4 weeks	Similar safety and effectiveness between ODF of sildenafil 75 mg and FCT of sildenafil 100 mg, but greater overall satisfaction with ODF
Loprete [25]	2018	Randomized, cross-over	12	NA	Similar pharmacokinetic and safety profile of sublingual and supralingual administration of ODF (sildenafil 50 mg)
Pavone [26]	2020	Retrospective, uncontrolled	65	3 months	Significant improvement of IIEF-5 score, SEP-2, and SEP-3 after ODF of sildenafil 100 mg in patients with ED after RP
Li-ESWT					
Scroppo [47]	2021	Prospective, uncontrolled	30	1 month	Significant improvement of the number of helicine arteries, penile brachial pressure index, PSV
Lu [55]	2017	Meta-analysis	833	Variable among the included studies	Significant improvement of erectile outcomes with lower energy flux density (0.09 mJ/mm^2) and increased number of pulses (at least 3000 pulses per session)
Libo [56]	2018	Meta-analysis	637	Variable among the included studies	Significant improvement of erectile outcomes with lower energy flux density (0.09 mJ/mm^2) and increased number of pulses (at least 3000 pulses per session)
SCT					
Bahk [18]	2010	Prospective, uncontrolled	7	9 months	Regained morning erection, increased rigidity, increased desire
Levy [69]	2016	Prospective, uncontrolled	8	6 months	Erections with no pharmacologic assistance ($n = 3$) or with only a low-dose of oral medications ($n = 4$)
Haahr [71]	2016	Prospective, uncontrolled	17	6 months	No overall change in IIEF-5 score but improvement in subgroup of continent patients with ED after RP
Yiou [72]	2017	Prospective, uncontrolled	12	62.1 months	Slightly lower IIEF scores at end of follow-up compared to the values at 12 months in patients with ED after RP
Mirzaei [70]	2021	Randomized controlled, single-blinded	20	6 months	Significant improvement of IIEF-5 score during the months after the SCT. Significant difference in the IIEF-5 score compared to the control group
PRP injections					
Matz [59]	2018	Retrospective, uncontrolled	17	15.5 months	Significant improvement of IIEF-5 score. Well-tolerated (only pain at the injection site and mild penile bruising)
Geyik [61]	2021	Retrospective, comparative	184	6 months	Significant improvement of IIEF-EF score with no significant difference between the groups (Li-ESWT vs. Li-ESWT + PRP). Well-tolerated (only pain at the injection site and mild penile bruising)
Poulios [62]	2021	Randomized, placebo controlled	60	6 months	Significant improvement of IIEF-EF score in the PRP group compared to placebo group. No AEs
Gene therapy					
Melman [75]	2006	Prospective, uncontrolled	11	24 weeks	Significant improvement of IIEF-EF score after a single intracavernous injection of *h*Maxi-K. No serious AEs nor dose-related side effects

ED erectile dysfunction, *PDE5Is* phosphodiesterase type 5 inhibitors, *ODF* oro-dispersible films, *FCT* film-coated tablets, *Li-ESWT* low-intensity extracorporeal shock wave therapy, *SCT* stem cell therapy, *PRP* platelet-rich plasma, *AE* adverse event, *IIEF* International Index of Erectile Function, *NA* not available, *Cmax* maximum concentration, *AUC0-t* area under the concentration-time curve, *SEP* sexual encounter profile question, *RP* radical prostatectomy, *PSV* peak systolic velocity.

Table 2. Emerging non-surgical treatments for ED.

Treatment	Evidence[a]	Guideline recommendations[b]
Oro-dispersible formulations of PDE5Is	Low	Indicated in patients who have difficulty swallowing solid dosage forms[c]
Li-SWT	Moderate	Indicated in mild vasculogenic ED, vasculogenic ED poorly responsive to PDE5Is
SCT	Very low	None
PRP injections	Very low	None
Gene therapy	Very low	None

ED erectile dysfunction, *PDE5Is* phosphodiesterase type 5 inhibitors, *Li-ESWT* low-intensity extracorporeal shock wave therapy, *SCT* stem cell therapy, *PRP* platelet-rich plasma.
[a]According to GRADE (Grading of Recommendations, Assessment, Development and Evaluations).
[b]According to EAU (European Association of Urology) Guidelines 2022 [1].
[c]It is a suggestion in the main-text, not a recommendation.

promising, and more high-quality studies are needed. In addition, the long-term clinical effects of this treatment are still under investigated.

Platelet-rich plasma (PRP) injections. PRP is defined as autologous blood plasma with supraphysiologic concentrations of activated platelets. It is generally obtained from an autologous blood sample. More specifically, after the blood is obtained, it is centrifuged to separate plasma from leukocytes and red blood cells, concentrating platelets [57]. The therapeutic effects of PRP would result from high concentrations of growth factors contained within platelets, including platelet-derived growth factor, vascular endothelial growth factor, epidermal growth factor, fibroblast growth factor, insulin-like growth factor. These factors are involved in vascular development, recruitment and proliferation of smooth muscle and endothelial cells, and neuronal regeneration [19]. There are few studies on penile injection of PRP in patients with ED, in addition, several papers are conference abstracts or written in non-English languages (see also Table 1). Chalyj et al. in 2015 described the first clinical study on PRP for ED [58]. A retrospective uncontrolled study was conducted on 17 patients suffering from organic ED ($n = 4$), Peyronie's disease (PD) ($n = 11$), ED plus PD ($n = 1$), or female stress urinary incontinence ($n = 1$). After PRP injections, among ED and/or PD patients who had completed the IIEF-5 questionnaire ($n = 7$), no subject described a worsening of erectile function. Mean IIEF-5 score improved by 4.14 points after treatment. PRP injections were well-tolerated in all cases. Three patients reported mild pain at the injection site, 1 of them also noted mild penile bruising [59]. It was proposed that the combined regenerative therapy for ED could provide a greater benefit than a single regenerative treatment due to the overlap and integration of different mechanisms of action [60]. A retrospective comparative study between Li-ESWT ($n = 93$) and Li-ESWT plus PRP ($n = 91$) in patients with PDE5Is refractory ED found that IIEF-EF scores significantly improved in both groups after treatment, with no significant difference in mean IIEF-EF score. PRP was well-tolerated in all cases, and no systemic AE was recorded during the study. All patients undergoing PRP reported temporary pain at the injection site, 26.4% of them had mild penile bruising after the injection without bleeding [61].

The first randomized controlled trial (RCT) on PRP was conducted on 60 patients with mild and moderate ED. After 6 months, a minimal clinically important difference in IIEF-EF was achieved by 69% and 27% of subjects in the PRP and placebo group, respectively. The baseline-adjusted mean between-group-difference in the IIEF-EF score was 3.9 points (95% CI: 1.8–5.9 points). No AE was reported during the study [62].

Although some preliminary results suggest that PRP can be successfully used in ED patients, available data are limited by small sample size, short follow-up, and/or lack of controls. Neither standardized methods to prepare PRP nor standardized treatment protocols are available [63].

Stem cell therapy (SCT). Stem cells are well known for their capacity of self-renewal and the potential for differentiation into mature cell types or tissue. Depending on their potential for differentiation, stem cells are classified as totipotent, pluripotent, or multipotent stem cells [64]. Embryonic stem cells (ESCs) and mesenchymal stem cells (MSCs) are pluripotent and multipotent cells, respectively. MSCs can be isolated from organs and can differentiate into any cell type within their germ tissue. Stromal vascular fraction (SVF) is freshly isolated heterogeneous cell fraction derived from the adipose tissue, including stromal and stem cells. ESCs have two main advantages over MSCs and SVF, the first of which is their ability to proliferate for longer periods of time, the second is their capacity to differentiate into a broader range of cell types [65]. However, owing to the ethical conflict that surrounds ESCs, their use in research has been limited and, as such, MSCs and SVF are a more feasible option for research and therapeutic applications [66].

MSCs can be isolated from several sources, including adipose tissue (ASCs), bone marrow (BMSCs), amniotic fluid (AFSCs), placenta (PSCs), and urine (USCs) [67]. The cellular mechanisms underlying the therapeutic effect of MSCs on ED is partially understood. A paracrine activity via growth factors, cytokines, and exosomes was supposed to be the main mechanism of action of MSCs [68]. While basic science results for stem cells and SVF are encouraging and have generated significant findings about the mechanisms of penile tissue regeneration, clinical results are limited and not robust [64]. Currently, there are a few small trials sharing similar protocols and involving a small sample size (see also Table 1). Bahk et al. published the first clinical study on the SCT for ED in 2010, showing regained morning erection, increased rigidity, and increased desire [18]. In a phase I study evaluating intracavernous injection of PSCs, eight non-responders to ED oral therapy were enrolled. After SCT, three patients achieved erections with no pharmacologic assistance and four subjects needed only a low-dose of oral medications [69]. A recent randomized single-blinded clinical trial on 20 diabetic subjects with ED compared intracavernous injections of autologous MSCs extracted from oral mucosa and normal saline intracavernous injections. In the intervention group, the mean IIEF-5 scores showed a significant ascending trend during the 6 months after the injection ($p = 0.01$); besides, a significant difference in the IIEF-5 score was found compared to the control group ($p = 0.02$). PSV and resistive index were not significantly different between the two groups, but an improving trend was recorded in the intervention group [70]. An open-label phase I single-arm study on 17 men with post-RP ED undergoing intracavernous injections of autologous ASCs found no overall effect, although a post hoc analysis in a small subset of continent patients did experience an increase in their IIEF-5 score [71]. Another paper investigating 12 patients with post-RP ED undergoing BMSCs intracavernous injections reported after a mean follow-up of 62.1 months that IIEF scores were slightly lower compared to the values recorded

after 12 months; therefore, repeated injections could be necessary for lasting effect [72].

No serious complication was described in the available literature, with several studies reporting no AEs. Pain at the injection site, which is usually resolved within 48 h, was the most frequently recorded side effect [70–72]. The vast majority of the available data on the topic had a small sample size, no control group, and other relevant methodological limitations. In addition, there is no consensus on the optimal dose or delivery route of SCT to significantly improve erectile function, making comparisons impossible [60]. These issues do not allow conclusions to be drawn about the efficacy and safety of SCT, despite the first encouraging basic science results.

Gene therapy. Gene therapy aims to transform the function of existing cell populations. It can be administered with vectors (usually of viral origin) or without (naked DNA). Despite the considerable advances in gene therapy knowledge in the last decade, parallel progress in the ED treatment area has been very limited. Consequently, the literature on the topic is extremely poor and mainly preclinical [68, 73]. Gene therapy for ED could be indicated for selected patients, such as men taking nitrates or not responding to PDE5Is. Besides, it has different intrinsic advantages: First of all, the penis is easily accessible, so the gene can be administered directly into the cavernous tissue without entering the systemic circulation. Then, corporal smooth muscle cells have a relatively low turnover rate, so the transferred gene can be expressed for long periods. Moreover, gap junctions connect corporal smooth muscle cells, allowing relatively low transfection efficiency. Finally, transduced genes can impact any aspect of the erectile process by selectively altering the expression of a given molecular target [73].

Although several preclinical studies provided promising results [74], only a study in human was published in 2006. In this phase I trial with no control group and a follow-up of 24 weeks, 11 patients with moderate to severe ED received a single intracavernous injection of *h*Maxi-K, a naked DNA plasmid carrying the gene *hSlo*, the gene for the α (pore-forming) subunit of the Ca^{2+} activated K^+ channel (Maxi-K). Several types of K^+ channels are present in the plasma membranes of the human corpora cavernosa. When these channels open, they allow K^+ to flow out of the smooth muscle cells; consequently, a hyperpolarization occurs, which limits the entry of Ca^{2+} entry, resulting in the relaxation of the cavernous tissue. Therefore, a gene transfer that causes overexpression of a K^+ channel gene in the corporal tissue could be theoretically used in the ED treatment. No serious AEs nor dose-related side effects were recorded. Besides, no plasmid was detected in the semen of patients. Mean IIEF-EF score improved in the two higher dose groups (5000 µg and 7500 µg), beginning 2 weeks after gene transfer and persisting in both cases during the 24 weeks of follow-up [75]. Despite this gene therapy's potential safety and efficacy, no subsequent researches were published on the topic.

CONCLUSIONS

ED is a condition that can generally be treated effectively. Lifestyle modification and optimization of the associated morbidities should be the first approach in all patients. ODF represents an intriguing discrete, not requiring water, new PDE5I formulation, which can potentially improve patient adherence and satisfaction compared to "traditional" formulations. Data derived from other PDE5I novel formulations are too preliminary to draw final conclusions. Li-ESWT represents a potential approach in patients with mild vasculogenic ED or vasculogenic ED not responding to PDE5Is. However, more data are advisable to support the use of Li-ESWT in other categories of ED patients and define its long-term outcomes. Other regenerative treatments for ED are emerging in recent years and could represent further options in the near future; however, there is not yet enough data to support their use in the clinical setting. Further well-designed RCTs are needed to improve the evidence on this topic and provide appropriate recommendations.

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The authors declare no competing interests.

ADDITIONAL INFORMATION

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