REVIEW ARTICLE

INNOVATIVE TREATMENT METHODS FOR ERECTILE DYSFUNCTION

Innowacyjne metody terapii zaburzeń erekcji

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Abstract

Erectile dysfunction is a common sexual disorder among men. The complexity of its aetiology, problems with therapeutic efficacy and convenience prompt the search for new solutions that could improve the existing treatment approaches. The article presents a set of innovative surgical, physiotherapeutic and pharmacological solutions for erecqtile dysfunctions, including stem cell therapy, platelet-rich plasma therapy, low energy shock wave therapy, as well as pharmacological innovations using amorphous solid dispersions of phosphodiesterase-5 inhibitors.

Streszczenie

Zaburzenia erekcji są częstym problemem z zakresu dysfunkcji seksualnych mężczyzn. Złożoność ich przyczyn, ograniczenia skuteczności i wygody obecnych metod leczenia, a także powszechność występowania sprawiają, że konieczne jest nieustanne poszukiwanie nowych rozwiązań, które mogłyby ulepszyć dotychczasowe formy leczenia. W artykule przedstawiono przegląd innowacyjnych metod terapii zaburzeń erekcji, które podzielono na metody zabiegowe, fizjoterapeutyczne oraz farmakologiczne. Omówiono m.in. terapię komórkami macierzystymi, terapię osoczem bogatopłytkowym, terapię falą uderzeniową o niskiej energii oraz innowacje farmakologiczne z wykorzystaniem amorficznych stałych dyspersji inhibitorów fosfodiesterazy-5.

Keywords: erectile dysfunction; Li-ESWT; amorphous solid dispersions; phosphodiesterase-5 inhibitors; platelet-rich plasma

Słowa kluczowe: zaburzenia erekcji; Li-ESWT; amorficzne stałe dyspersje; inhibitory fosfodiesterazy-5; osocze bogatopłytkowe

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Introduction

Erectile dysfunction (ED) is the most common type of sexual dysfunction in men. Treatment options include both symptomatic and causal approaches, with differential diagnosis playing a key role in causal treatment [1]. Erectile dysfunction is defined as the inability to achieve or maintain an erection adequate for satisfactory sexual intercourse. Multiple mechanisms may be involved in its pathophysiology. These include vascular, neurogenic, anatomical, hormonal, drug- or substance-induced, and psychogenic factors, which may coexist and mutually exacerbate ED [2]. Since effective ED treatments are still lacking, novel, more effective therapeutic modalities are being explored, including surgical, physiotherapeutic, behavioural, and pharmacological approaches. This prompted us to summarize the latest innovations in ED therapy.

Pharmacological treatments for ED aim to temporarily improve sexual performance rather than address the underlying cause or provide a permanent outcome. Regenerative therapies that may reverse changes leading to EDs include platelet-rich plasma (PRP) injections, low-intensity extracorporeal shockwave (LI-ECSW), and stem cell therapy [3].

Stem cell therapy

Injection of mesenchymal stem cells (stem cell therapy, SCT) or stromal vascular fractions derived, among oth-

ers, from adipose tissue, is one of medical interventions used to treat ED.

To date, most studies have been conducted in rodents. A recent systematic review identified five human studies on SCT for erectile dysfunction. These phase I and II trials included a total of 61 patients. Importantly, none of the studies reported serious adverse events (AEs), and their results were indicative of a positive therapeutic effect. However, the authors of the review emphasize that the limited data in this area warrant further in-depth clinical trials to assess the efficacy and safety of this therapy, particularly in patients with prostate cancer [3].

Platelet-rich plasma

Platelet-rich plasma (PRP) is a natural blood-derived product containing biologically active platelets, which release growth factors such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factor (IGF-1), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF), which stimulate cell growth, proliferation, and differentiation, as well as collagen and elastin production, promoting tissue regeneration and faster wound healing. Growth factors also stimulate angiogenesis, giving rise to new blood vessels. PRP is obtained by centrifuging the patient's venous blood, typically collected from the ulnar vein (approximately 10 mL), using an FDA-approved separation process. The resulting PRP is then injected into corpora cavernosa. Contraindications include blood disorders, cancer, skin lesions at the injection site, and poorly controlled diabetes mellitus [4].

The first randomized, double-blind, placebo-controlled clinical trial was conducted among 60 sexually active patients with mild to moderate ED, forming two equal groups (n = 30): one receiving 10 mL of PRP, and one receiving placebo intracavernosal injections. Participants did not use any other ED treatments during the study. Erectile function was assessed at 1, 3, and 6 months after treatment completion. The results were very promising with improved erectile function in 69% of the study group vs 27% in the placebo group at 6 months. These patients were also more satisfied with the treatment. The results observed at 1 and 3 months were consistent with the final results. No adverse events were reported during the study [5].

Another clinical trial, conducted in a group of 34 patients, showed that PRP intracavernosal injections were particularly beneficial for smokers [6].

According to a 2015–2020 study, PRP injections can be a beneficial addition to low-intensity extracorporeal shock wave therapy (Li-ESWT) in ED patients who had not responded to at least 3 months of treatment with phosphodiesterase type 5 inhibitors (tadalafil at 5 mg daily). The patients were randomised into two groups: Li-ESWT alone and Li-ESWT combined with PRP. Although the increase in IIEF-EF (International Index of Erectile Function – Erectile Function domain) was similar in both groups, the PRP plus Li-ESWT group experienced a 1.5- to 3.5-fold longer duration of vaginal penetration. No adverse events were reported, with all patients on the combination therapy expressing a desire to continue PRP injections [7].

In conclusion, although PRP intracavernosal injections seem to be a potentially safe, innovative and promising treatment approach for ED and improving sexual function in men, further clinical trials are needed to confirm these reports.

Low-intensity extracorporeal shock wave therapy

Low-intensity extracorporeal shock wave therapy (Li-ESWT) is a first-line treatment for erectile dysfunction [8].

Li-ESWT is a form of acoustic wave with unique properties: it generates a sudden rise in pressure that rapidly decreases to a negative value, with propagation speed higher than that of typical sound waves. Li-ESWT energy, generated by electrohydraulic, electromagnetic, or piezoelectric sources, is delivered through an applicator placed on the penis, which is coated with gel to eliminate the air layer. Key treatment parameters include energy density (<0.2 mJ/mm^2), frequency (Hz), and number of pulses. Their selection impacts the therapeutic effect [9]. It is worth noting that there is currently no standardised protocol for Li-ESWT in the treatment of ED, as emphasized in 2018 during the 20th Congress of the European Society for Sexual Medicine (CESSM) and the 21st World Meeting of the International Society for Sexual Medicine (WMISSM) [10].

Research on the use of Li-ESWT in patients with ED was initiated by Gruenwald et al. [11], who described and defined metabolic and tissue processes involved in the formation and development of blood vessel networks. Several mechanisms are thought to underlie the beneficial effects of Li-ESWT in ED, including stimulation of penile tissue mechanoreceptors, reduction of inflammation, recruitment and activation of endothelial progenitor cells (EPCs), and both neuroprotective and neuroregenerative effects [12]. In their studies in rats, Lin et al. [13] demonstrated increased stem cell proliferation in penile tissue after 48 hours and 1 week of Li-ESWT (*in-situ*), with stronger therapeutic effects in young animals compared to middle-aged ones, and higher doses producing greater benefits. In turn, Scorpo et al. [14] demonstrated improved penile microcirculation in men undergoing Li-ESWT (based on Doppler flow analysis).

The beneficial effects of Li-ESWT in ED are observed at 6 and 12 months, but gradually deteriorate, reaching a plateau of about 40% at 5 years post-treatment (according to patients' subjective assessments) [15–17]. It is also noteworthy that Li-ESWT is a non-invasive, safe procedure, and precise targeting of the treatment site helps protect surrounding tissues. However, it is important to note that Li-ESWT for ED may cause discomfort due to the nature of the procedure, and patients should be adequately informed beforehand. A review of available studies showed virtually no adverse reactions to Li-ESWT for ED. Furthermore, our clinical experience indicates that patients describe the procedure as well-tolerated and even relaxing.

Unfortunately, Li-ESWT treatments for ED are not reimbursed in Poland and can be quite costly. This, combined with limited awareness of the method's effectiveness among both patients and medical personnel, as well as the small number of centres offering this treatment in our country, makes Li-ESWT poorly accessible. Based on current research findings, we believe that it is worth promoting Li-ESWT in the treatment of ED.

Innovative pharmacological treatments for ED

Phosphodiesterase-5 inhibitors (PDE5Is) are currently used as the first-line treatment for ED and represent the most common form of pharmacotherapy. In later phases (second-line treatment), other agents such as alprostadil or papaverine may be used, administered either as an intraurethral gel or via intracavernosal injection. PDE5Is are widely tolerated by patients due to their convenient oral formulations (tablets, films, and powders for oral suspension). However, discontinuing PDE5I therapy is very common. Studies indicate poor compliance with PDE5I treatment, despite its high efficacy [18]. Therefore, new pharmacological treatments are being explored, using known substances with improved performance parameters that may enhance compliance.

The mechanism of action of PDE5Is is based on the selective inhibition of phosphodiesterase type 5, an enzyme found in various tissues, including the corpus cavernosum of the penis. As a result, the breakdown of cyclic guanosine monophosphate (cGMP) is inhibited. The accumulated cGMP induces a decrease in smooth muscle calcium ions, leading to relaxation of vascular and cavernous smooth muscle, increased blood flow, and erection. However, nitric oxide (NO), released locally during sexual stimulation as the primary mediator of erection, with cGMP acting as a secondary mediator, is a key factor. Consequently, the effectiveness of PDE5I depends on adequate release of NO, which activates guanylate cyclase to produce cGMP. PDE5Is act only by increasing cGMP levels through inhibition of its degradation [19].

The PDE5I class includes five drugs: sildenafil, tadalafil, vardenafil, avanafil, and udenafil. Udenafil is not approved for use in Poland, the United States, and many other countries. These medications vary in efficacy, as confirmed by a recent meta-analysis of systematic reviews on PDE5Is and erectile dysfunction. Their efficacy as compared to placebo was often dose-dependent in the general population [20]. All five inhibitors have specific dosage ranges. In Poland, the available doses are 25 mg, 50 mg, and 100 mg for sildenafil; 5 mg, 10 mg, and 20 mg for tadalafil; 5 mg, 10 mg, and 20 mg for vardenafil; and 50 mg, 100 mg, and 200 mg for avanafil. The choice of appropriate dose depends on the patient's response. In some cases, physicians may prescribe the maximum dose. In recent years, 10 mg tadalafil has also become available over the counter in Poland. All PDE5Is discussed in this paper belong to the second class of the Biopharmaceutics Classification System (BCS). The second group comprises substances that are poorly soluble in water, but easily penetrate biological membranes, which makes their absorption rate similar to their dissolution rate in water [21–25]. Due to possible adverse reactions, the need for optimal formulations, and the possibility of improving bioavailability while reducing treatment costs, efforts are being made to enhance the water solubility of these compounds.

Amorphous solid dispersions (ASDs) are systems where the amorphous form of a pharmacologically active substance is molecularly dispersed within a carrier matrix that, due to its physicochemical properties, effectively stabilizes the amorphic substance. Their role in stabilization is crucial, as the commercial crystalline forms of active substances such as sildenafil, tadalafil, avanafil, and vardenafil have poor water solubility. Converting them into the more soluble amorphous form improves dissolution but reduces physical stability, necessitating appropriate stabilization. Achieving a physically stable amorphous form of the drug improves bioavailability, which may allow for lower doses of the active substance while maintaining efficacy. Enhanced solubility can also accelerate drug action by facilitating membrane penetration and delivery to the target site [26–28].

The amorphous state of the substance is beneficial due to its improved water solubility and the resulting increase in bioavailability. The process of converting a crystalline form into an amorphous one is referred to as a phase transition as the elemental composition, molecular formula, and structural formula of the molecule remain unchanged. Only the crystal structure changes. The presence of different crystallographic forms of a given substance results from the different spatial arrangement of its molecules. Unlike the crystalline form, the amorphous form exhibits only short-range order, meaning that the molecular positions are not precisely defined. As a result, it shows variable molecular mobility and exists in a less stable, higher-energy state than the crystalline form. This leads to crystallization, resulting in reduced water solubility and bioavailability of the drug. Therefore, efficient stabilization of amorphous forms is essential. In ASDs, stabilization can be achieved by using a carrier with suitable physicochemical properties. Key criteria for carriers include a high glass transition temperature and an amorphous form. Efficiency can be further improved by employing an appropriate excess of carrier [26].

Amorphous solid dispersions of sildenafil

Studies on the formation of sildenafil ASDs with glycyrrhizin and polymeric solubilizer Soluplus, using spray drying as the amorphization method, demonstrated satisfactory performance and an optimal particle size (0.710 µm for a 1:1 drug-to-stabilizer weight ratio). Furthermore, the ASD form showed higher drug release efficiency compared to the pure substance. These results were confirmed in a rat model, where sildenafil ASD led to improved sexual activity compared to its crystalline counterpart [23].

Similar studies on the impact of a stabilizing polymer on the physicochemical stability of sildenafil ASD were published in 2021. In these studies, the substance was amorphized by solvent evaporation using a rotary evaporator. Among the three polymers tested (Kolliphor® P188, Kollidon® 30, and Kollidon® VA64), all improved the solubility of sildenafil ASD compared to its crystalline form. The ASD system with Kollidon® VA64 was selected for

further research as it showed the greatest improvement in dissolution rate compared to crystalline sildenafil. The amorphous nature of the systems was confirmed by X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC). For ASDs with Kolliphor® P188 and Kollidon® 30, the authors observed powder diffraction patterns indicative of a partially crystalline form of the drug, as noted in their study results. The ASD formulation of sildenafil with Kollidon® VA64 was considered amorphous as it lacked the characteristic peak reflections around 20° of 2-theta. However, the diffraction pattern did not include the fully amorphous 'halo' typically seen in a completely amorphous form. This may suggest that the amorphization method is less efficient than, for example, spray drying. When tested in a rat model, the formulation significantly improved male sexual activity [29]. Furthermore, recent research from a Polish centre highlighted the use of a carrier with plasticizing properties, which has (unlike previous studies) a glass transition temperature significantly lower than that of the amorphous substance. This was achieved by using polyvinyl acetate polymer at high concentrations (75% by weight). This led to the conclusion, suggesting areas for further research, that plasticizers may also stabilize ASD systems when used at concentrations at which they no longer accelerate recrystallization, but instead have the opposite effect [30].

Amorphous solid dispersions of tadalafil

Tadalafil was also investigated for physical stability in an ASD prepared by spray drying, using glycyrrhizin as a stabilizing carrier. This resulted in a significant increase in the dissolution rate of tadalafil in the ASD with glycyrrhizin compared to its crystalline form. A significant improvement in sexual parameters was also observed in rats for the formulation with a 1:2 tadalafil-to-glycyrrhizin weight ratio. It maintained physicochemical stability in studies conducted after one month [23].

Other studies have also confirmed the improved solubility of tadalafil in ASD formulations with polymeric carriers compared to its pure crystalline form. This was important as it allowed for comparing various amorphization methods, including solvent evaporation using a rotary vacuum evaporator, spray drying, and melt extrusion. Regardless of the approach used, the dissolution rate increased, although the release profiles differed depending on a given method. The highest dissolution rate was consistently observed in the formulation prepared by solvent evaporation using a rotary vacuum evaporator. Differences in release rates and the amount of drug released likely resulted from the distinct morphologies of particles formed during the individual amorphization processes. Furthermore, the researchers observed that the molecular weight of the polymer carrier affected drug release efficiency: tadalafil release decreased with increasing polymer molecular weight [31].

Amorphous solid dispersions of vardenafil

Vardenafil was also amorphized to explore its physicochemical stability, this time using lyophilization. Formulations were prepared with β-cyclodextrin and hydroxypropylmethylcellulose in various proportions. Optimal solubility in a formulation containing cyclodextrin was achieved with a 1:5 weight ratio of vardenafil to cyclodextrin. All amorphous vardenafil systems, regardless of the polymer used, showed an improved dissolution profile compared to pure crystalline vardenafil. Additionally, the formulation with β-cyclodextrin at a 1:5 ratio exhibited enhanced permeability across biological membranes [32].

Amorphous solid dispersions of avanafil

Avanafil was amorphized to create an ASD incorporated into a self-emulsifying drug delivery system (SEDDS). This formulation (containing lipids, surfactants, cosurfactants, and the drug itself) rapidly formed an oil-in-water (O/W) nanoemulsion. The resulting high-surface-area globules, combined with peristaltic mixing, enhanced the drug's solubility in water. The development of SEDDSs using amorphous avanafil gave rise to formulations that remained stable for six months and exhibited a 3.2-fold increase in bioavailability compared to the commercial crystalline form of the drug [33].

An amorphous form of avanafil was also produced using a three-step process involving solvent precipitation, ultrasound, and high-pressure homogenization, resulting in avanafil stabilized with polyvinyl alcohol. However, this approach was less effective in enhancing solubility compared to nanoparticle sonoprecipitation [34].

The discussed studies on amorphous solid dispersions of PDE5Is highlight a promising research direction focused on enhancing pharmacotherapy by modifying existing, well-known substances. This strategy not only reduces the substantial costs associated with bringing new drugs to market, which can reach billions of dollars, but also improves the bioavailability of existing medications, allows for lower dosages, reduces certain adverse effects, lowers production costs, and ultimately prices for patients. Furthermore, research in this area may alter the drug's release kinetics, potentially resulting in a more rapid onset of action – a factor that could be crucial for improving sexual comfort and quality of life in men with erectile dysfunction.

Conclusions

The innovative ED treatment methods described in this paper are often still at the preliminary preclinical stage. The complexity and prevalence of EDs prompt researchers worldwide to explore increasingly advanced pharmacological and surgical strategies. In the coming years, we can expect a dynamic rise in interest in these approaches, potentially leading to the establishment of new standards for ED treatment.

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