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PRACA POGLĄDOWA
REVIEW

Modern treatment approaches for erectile dysfunction – review

Nowoczesne podejścia terapeutyczne w leczeniu dysfunkcji erekcyjnej – przegląd

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ABSTRACT

Erectile dysfunction (ED) is a significant public health issue that affects both patients' quality of life and their intimate relationships. While phosphodiesterase type 5 inhibitors (PDE5-Is) are the standard first-line treatment, a substantial proportion of patients fail to achieve satisfactory results. Growing interest in alternative treatment approaches has led to the exploration of novel therapies, including botulinum neurotoxin (BoNT). BoNT increases penile tissue blood supply by relaxing corpora cavernosa smooth muscle by inhibiting the release of acetylcholine. In this review, BoNT as a new agent in the treatment of ED and comparison with the safety and efficacy of advanced techniques like endovascular therapy, stem cell therapy, platelet-rich plasma therapy, and low-intensity shockwave therapy is discussed. The mechanisms of action, clinical trial results, and possible limitations of these approaches are discussed. According to recent research, BoNT is a potential alternative for ED patients who are not responsive to traditional treatments. Additional studies, however, are required to establish optimal dosing regimens and determine the long-term benefits of these new therapeutic approaches.

KEYWORDS

erectile dysfunction, modern treatment, botulinum toxin, sexual health

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STRESZCZENIE

Zaburzenia erekcji (*erectile dysfunction* – ED) są istotnym problemem zdrowia publicznego, wpływającym zarówno na jakość życia pacjentów, jak i ich relacje intymne. Chociaż inhibitory fosfodiesterazy typu 5 (*phosphodiesterase type 5 inhibitors* – PDE5-Is) stanowią standardowe leczenie pierwszego rzutu, znaczna część pacjentów nie osiąga zadowalających rezultatów. Rosnące zainteresowanie alternatywnymi metodami leczenia doprowadziło do eksploracji nowych terapii, w tym neurotoksyny botulinowej (*botulinum neurotoxin* – BoNT). BoNT zwiększa dopływ krwi do tkanek prącia poprzez rozluźnienie mięśni gładkich ciał jamistych dzięki hamowaniu uwalniania acetylocholiny. W niniejszym przeglądzie omówiono BoNT jako nowy środek w leczeniu ED oraz porównano bezpieczeństwo jej stosowania i skuteczność z zaawansowanymi metodami, takimi jak terapia endowaskularna, terapia komórkami macierzystymi, terapia osoczem bogatopłytkowym oraz terapia falą uderzeniową o niskiej intensywności. Omówiono mechanizmy działania, wyniki badań klinicznych oraz możliwe ograniczenia tych metod. Według najnowszych badań BoNT jest obiecującą alternatywą dla pacjentów z ED, którzy nie reagują na tradycyjne leczenie. Konieczne są jednak dodatkowe badania w celu ustalenia optymalnych schematów dawkowania oraz określenia długoterminowych korzyści nowych podejść terapeutycznych.

SŁOWA KLUCZOWE

dysfunkcja erekcyjna, nowoczesne leczenie, toksyna botulinowa, zdrowie seksualne

Introduction

Erectile dysfunction (ED) is a condition characterized by persistent difficulties in achieving or maintaining an erection sufficient for satisfactory sexual intercourse. This issue has a significant impact on public health and the quality of life of men worldwide. According to estimates, ED currently affects over 150 million men globally, and by 2025, this number could increase to approximately 300 million [1].

ED is particularly common in older age groups – affecting approximately 20% of men aged 40–50, with its prevalence increasing to 50% among men over the age of 70 [2].

Importance of the problem

ED is not limited to physiological aspects – it also has a significant impact on mental health, interpersonal relationships, and overall life satisfaction. Numerous studies indicate that individuals suffering from ED are more likely to experience depression, anxiety, and low self-esteem [3].

The partners of men struggling with ED often experience dissatisfaction in their relationships, which can negatively affect the quality of the relationship. Additionally, ED can be an indicator of underlying cardiovascular diseases, such as atherosclerosis, hypertension, or diabetes [4]. Both the direct costs associated with the treatment and diagnosis of ED and the indirect costs, including loss of work productivity and social burdens, have a significant impact on healthcare system budgets [5].

Current treatment methods

Traditional treatment of ED is primarily based on pharmacotherapy using phosphodiesterase type 5 inhibitors (PDE5-Is), such as sildenafil, tadalafil, vardenafil and the newest such as avanafil or udenafil. These medications work by increasing the availability of nitric oxide (NO) in the smooth muscles of the corpora cavernosa, promoting their relaxation and improving blood flow [6]. Although these medications are effective for most patients, they do not provide the expected improvement in approximately 30–40% of cases. Additionally, side effects such as headaches, vision disturbances, or nasal congestion may lead some patients to discontinue therapy. Alternative treatment methods include prostaglandin injections (e.g. alprostadil), vacuum pumps, and surgical procedures such as penile prosthesis implantation. While these options can be effective in certain cases, they are often considered invasive, costly, and difficult to use on a daily basis.

New therapeutic approaches

In recent years, increasing attention has been given to innovative methods for treating ED. One of the most promising solutions is the use of botulinum neurotoxin (BoNT). Primarily known for its applications in aesthetic medicine and neurology, BoNT works by relaxing smooth muscles through the inhibition of acetylcholine release at neuromuscular junctions [7].

Additionally, BoNT affects the regulation of the autonomic nervous system, which may support the mechanisms responsible for the erection process. Current studies indicate that BoNT may be particularly effective in patients who do not respond to PDE5-Is and in cases of ED with mixed etiology. Due to its minimal side effects and long-lasting therapeutic effect (up to six months), BoNT could serve as a viable alternative to more invasive treatment options.

Aim of the study

The aim of this review is to present the potential use of BoNT in the treatment of ED and to compare it with other modern therapeutic approaches. This article will discuss the mechanisms of action of BoNT, findings from preclinical and clinical studies, as well as the

potential benefits and limitations of this approach. Additionally, the review will explore innovative ED treatment strategies, including platelet-rich plasma (PRP) therapy, stem cell therapy, low-intensity shockwave therapy (LI-SWT), endovascular treatment methods, and the impact of regular physical activity, particularly aerobic exercise, on erectile function. The goal is also to identify areas requiring further research to improve the understanding and optimization of novel ED therapies.

The analysis included clinical studies, randomized controlled trials, and case series focusing on BoNT and the range of modern therapeutic approaches to ED discussed above. Studies that did not directly address these therapies or their effects on erectile mechanisms were excluded, as well as research focusing solely on traditional treatments, such as PDE5-Is, without reference to innovative therapeutic approaches.

Causes of ED

ED is a multifactorial condition. It can result from both organic and psychogenic causes. Below are the most significant organic factors:

1. Vascular factors: Atherosclerosis of the penile arteries and other circulatory disorders can significantly reduce blood flow to the corpora cavernosa [8].
2. Neurogenic factors: Spinal cord injuries, diabetic neuropathy, or pelvic surgeries can lead to impaired nerve signal transmission, preventing a proper response to sexual stimulation [9].
3. Hormonal factors: Testosterone deficiency, hyperprolactinemia, and thyroid dysfunction can lead to decreased libido and the inability to achieve an erection [10].

Psychological factors, such as stress, depression, relationship difficulties, or fear of failure, play a significant role in the development of ED, especially in young men. Stress activates the sympathetic nervous system, which can hinder the parasympathetic responses necessary for achieving an erection. Depression is associated with decreased levels of key neurotransmitters, including dopamine and serotonin, which are crucial for experiencing pleasure and sexual motivation. Additionally, reduced oxytocin levels, which play a role in emotional bonding and sexual function, may further contribute to erectile difficulties, particularly in the context of relationship distress [11]. Relationship problems, such as a lack of emotional intimacy, can exacerbate these issues, creating a vicious cycle of mutual tension and withdrawal [12].

The role of smooth muscles in ED

Smooth muscles of the corpora cavernosa play a crucial role in the erection process. Their relaxation allows proper blood flow and penile engorgement. Excessive smooth muscle tension, often associated with autonomic nervous system dysfunctions, is one of the main pathophysiological mechanisms in ED.

The autonomic nervous system, which regulates smooth muscle tension, operates based on a balance between the sympathetic and parasympathetic systems. A disruption of this balance, caused, for example, by diabetic neuropathy, can prevent proper vasodilation and blood flow to the penis [13].

Treatment using new technologies in the context of ED

Treatment with BoNT

Botulinum neurotoxin type A (BoNT-A) may play a significant role in the treatment of ED, especially in patients with excessive smooth muscle tension. BoNT-A works by blocking the release of acetylcholine at neuromuscular synapses, leading to muscle relaxation. In the context of ED, BoNT-A can restore autonomic balance and improve blood flow by relaxing the vessels in the corpora cavernosa [10]. A summary of all available studies on the use of BoNT-A is presented in Table I.

Table I. Publications investigating treatment with botulinum toxin type A

Publication	Study population	Applied treatment	Conclusions
Giuliano et al. [14]	A total of 85, 44, and 23 men received two, three, and four doses of BTX/A ic, respectively.	This retrospective case series evaluates the effectiveness of repeated off-label X/A injections (onabotulinumtoxinA 100 U, incobotulinumtoxinA 100 U, or abobotulinumtoxinA 500 U) in men with ED unresponsive to PDE5-Is or PGE1-ICIs, defined by an IIEF-EF score < 26.	The overall response rate was 77.5%, with higher rates in mild (85.7%) and moderate (79%) ED. Response increased with repeated injections: 67.5%, 87.5%, and 94.7% after the second, third, and fourth injections. Changes in IIEF-EF were similar across injections. Four men reported mild penile pain, and one experienced a burning sensation. Repeated BTX/A injections with PDE5-Is or PGE1-ICIs resulted in effective, sustained responses and acceptable safety.
Abdelrahman et al. [15]	A double-blind, randomized, placebo-controlled study involving 70 patients with PDE5I-resistant ED collected data on EHS, PSV, EDV, SHIM, and SEP-2&3 at the start.	The treatment group (n = 35) received 100 units of BoNT-A in 2 ml saline via ICI, while the control group (n = 35) received 2 ml saline. EHS, PSV, and EDV were assessed at 2 weeks, and SHIM, SEP-2, SEP-3, and GAQ-Q1&Q2 at 2, 6, and 12 weeks post-treatment.	Two weeks after treatment, the treated group showed significant improvements in EHS, PSV, EDV, and GAQ-Q1 ($p < 0.001$) compared to the control. After 6 and 12 weeks, the treated group also showed improvements in SHIM scores, SEP-2, and GAQ-Q1 and Q2. At 6 weeks, the treated group had a 5-point increase in SHIM, with 53% achieving erections sufficient for vaginal penetration. BoNT-A is a safe and effective treatment for PDE5I-resistant ED.
Giuliano et al. [16]	Data from a retrospective, uncontrolled study conducted at a single center were analyzed, involving 47 patients with ED, consecutively recruited, who were insufficiently responsive to existing pharmacological treatment.	Patients treated with PDE5-Is or IC PGE1 injections received additional IC abobotulinumtoxinA (250 or 500 U) as a free combination with their existing therapy.	The response rate to IC abobotulinumtoxinA with prior pharmacological treatment was 54% at 6 weeks. Two patients experienced mild penile pain. Effectiveness was not influenced by ED etiology or risk factors, but less severe ED had a higher response rate. Preliminary evidence suggests IC abobotulinumtoxinA may be a safe adjunctive therapy for ED unresponsive to standard treatment, pending confirmation in clinical trials.
El-Shaer et al. [17]	A prospective, randomized, double-blind, placebo--controlled study was conducted from July 2016 to February 2019, involving 176 patients who were randomly assigned (1:1:1) to one of the treatment sequences, with follow-up for 6 months.	The Botox 100 U group (BTX-100; 62 patients), the Botox 50 U group (BTX-50; 59 patients), or the placebo group (55 patients).	Both the BTX-100 and BTX-50 groups showed significant improvements in SHIM, EHS, SEP, GAS, and Doppler parameters ($p < 0.001$), with maximal improvement at 3 months. Approximately 40% of patients were able to engage in sexual intercourse. No significant improvement was observed in the placebo group ($p = 0.264$). At 6 months, BTX-100 showed a statistically significant advantage over BTX-50 ($p < 0.01$).
Giuliano et al. [18]	66 men with difficult-to--treat ED.	IncobotulinumtoxinA 100 U ICI as an adjunctive therapy.	The response rate to incobotulinumtoxinA ICI was 52%, with no impact from ED etiology or severity (except spinal cord injury). A clinically significant response to the first injection predicted the need for a second (OR = 5.6). Three men experienced mild penile pain during the injection.
Abdel Raheem et al. [19]	A prospective, double-blind, randomized study involving 70 patients with ED unresponsive to PDE5-Is and ICI therapy.	Patients were randomly assigned to treatment (100 units BoNT-A) or control (1 mL saline) groups, with 35 patients in each. Penile duplex ultrasound and EHS were assessed at baseline and 2 weeks post-treatment. SHIM, SEP, and GAQ questionnaires evaluated outcomes at 6 and 12 weeks.	In the treated group, significant improvements were observed in peak systolic velocity, end-diastolic velocity, EHS, and SHIM score ($p < 0.001$). SEP-1 and SEP-2 responses were higher in the treated group, as were GAQ-1 and GAQ-2 responses. No adverse events occurred, and improvements were sustained at the 12-week follow-up.

BTX/A, X/A, BoNT-A – botulinum toxin type A (alternative abbreviations used in some studies); ED – erectile dysfunction; PDE5-Is – phosphodiesterase type 5 inhibitors; PGE1 – prostaglandin E1; ICI – intracavernosal injection; IIEF-EF – International Index of Erectile Function – Erectile Function domain; EHS – Erection Hardness Score; PSV – peak systolic velocity; EDV – end-diastolic velocity; SHIM – Sexual Health Inventory for Men; SEP-2&3 – Sexual Encounter Profile questions 2 and 3; GAQ-Q1&Q2 – Global Assessment Questionnaire questions 1 and 2; IC – intracavernosal; GAS – Global Assessment Score.

Other innovative treatment methods for ED

Table II presents publications on other innovative treatment methods for ED.

Table II. Publications investigating other innovative treatment methods for erectile dysfunction

Publication	Study population	Applied treatment	Conclusions
1	2	3	4
Platelet rich plasma			
Masterson et al. [20]	61 men with mild to moderate ED (IIEF score 11–25).	Two injections of PRP or placebo, administered one month apart.	PRP was safe but showed no significant difference in efficacy compared to placebo.
Poulios et al. [21]	The study included 60 sexually active male patients aged 40––70 years with mild to moderate ED. Participants were required to be in stable heterosexual relationships and refrain from using other ED treatments during the study.	Participants were randomly assigned to receive two ICIs of either PRP or a placebo (normal saline), with a one-month interval between treatments. PRP was prepared using an FDA-approved separation system.	The study found that PRP injections significantly improved erectile function compared to the placebo. At the six-month follow-up, 69% of PRP-treated patients showed a clinically meaningful improvement, compared to 27% in the placebo group. No adverse effects were reported, indicating that PRP may be a safe and effective treatment for mild to moderate ED.
Shaher et al. [22]	The study included 100 men aged 45–65 with mild to moderate ED. Participants were randomly assigned to two groups: one receiving PRP treatment and the other receiving a placebo (saline injections).	The PRP group received three ICIs (3 mL per corpus cavernosum) at 15-day intervals. The placebo group received the same volume of saline injections. Follow-up assessments were conducted at 1, 3, and 6 months.	PRP treatment significantly improved erectile function compared to placebo, with the highest improvement observed at the 3-month follow-up. At 6 months, 70% of PRP patients achieved a clinically meaningful improvement, compared to 16% in the placebo group. No major adverse effects were reported, suggesting PRP is a safe and promising treatment for mild to moderate ED.
Saltzman et al. [23]	The study enrolled 60 men aged 30–80 with mild to moderate ED (IIEF-EF score 12–25), all in stable heterosexual relationships and providing informed consent.	Participants were randomly assigned to receive either PRP injections and low-intensity SWT or placebo (saline injections and sham SWT). The treatment lasted five weeks, with PRP and SWT in weeks 1 and 5, and additional SWT sessions in weeks 2–4.	The study aims to evaluate the safety and efficacy of combined PRP and SWT therapy for ED. The primary outcome focuses on adverse events, while secondary outcomes include improvements in erectile function based on the IIEF-EF score and reduction in the need for PDE5-Is. If successful, this approach could offer a regenerative treatment option for ED.
Zaazaa et al. [24]	80 patients with ED who had a refractory response to PDE5-Is for at least 6 months.	Patients were randomly assigned to four groups: saline (placebo), PRFM injection, PGE-1 injection, and PRFM + PGE-1 combination. Intracorporeal injections were given weekly for 8 weeks, with follow-ups at 1, 2, 3, and 6 months.	The combination of PRFM and PGE-1 showed significant improvement in erectile function scores compared to the other groups. However, despite the improvements, patients still had mild to moderate ED. The treatment is not recommended as a standalone therapy for ED but may enhance response to ICI home therapy in patients resistant to oral PDE5-Is.
Aerobic exercises			
Leitão et al. [25]	45 men (aged 40–59) with ADAM, experiencing ED and low testosterone levels.	Participants were divided into four groups: (1) control + placebo, (2) control + *Eurycoma longifolia* (200 mg daily), (3) concurrent training + placebo, and (4) concurrent training + *Eurycoma longifolia*. The interventions lasted for 6 months, with exercise performed 3 times a week.	The combination of *Eurycoma longifolia* supplementation and concurrent training led to the most significant improvements in erectile function and testosterone levels. While both interventions had benefits separately, their combined effect was superior, suggesting a synergistic impact on male sexual health.
Rislanu et al. [26]	30 men (aged 25–65) diagnosed with ED. Participants were randomly assigned to two groups.	One group received electrical stimulation therapy, and the other performed aerobic exercise for six weeks (two sessions per week). Erectile function was assessed using the IIEF-5 before and after treatment.	Both treatments improved erectile function, but electrical stimulation showed significantly better results compared to aerobic exercise. This suggests that electrical stimulation may be a more effective non-invasive option for managing ED.
La Vignera et al. [27]	50 middle-aged men (48––62 years) with arterial ED. A control group of 20 men was also included.	A structured aerobic physical activity program: 150 minutes of moderate-intensity aerobic exercise per week for 3 months. The control group did not participate in the exercise program.	Aerobic physical activity significantly improved erectile function, endothelial health, and metabolic parameters. The exercise group showed higher IIEF-5 scores, better penile vascular function, and reduced endothelial apoptosis compared to the control group.

cd. tab. II

1	2	3	4
		Stem cell therapy	
Al Demour et al. [28]	4 male patients (aged 49–60) with diabetes-related ED resistant to standard treatments.	Two consecutive ICIs of autologous BM-MSCs were administered, with follow-ups over 12 months to assess safety and efficacy.	The treatment was well tolerated, with no significant adverse effects. Patients showed improvements in erectile function, with increased IIEF-15 and EHS. The results suggest that BM-MSC therapy may be a promising option for diabetic patients with refractory ED.
Levy et al. [29]	8 men aged 40–70 with chronic ED who did not respond to oral treatments.	Injection of PM-MSCs into the corpora cavernosa. Patients were monitored for 6 months.	Stem cell treatment led to a significant increase in penile blood flow. Three patients achieved erections without medication, while others required lower doses. Further studies with larger samples are needed to confirm effectiveness.
You et al. [30]	10 men with ED due to radical prostatectomy or diabetes mellitus, unresponsive to PDE5-Is.	Injection of autologous BMSCs into the corpus cavernosum. Patients were monitored for 12 months.	The treatment was safe, with no severe adverse events directly related to BMSC injection. Some patients showed an improvement in erectile function, but further research is needed to confirm long-term efficacy.
Koga et al. [31]	38 men with ED, aged 31–79, including patients with diabetes, hypertension, or a history of priapism.	Injection of a cultured conditioned medium derived from exfoliated deciduous dental pulp stem cells (SHED-CM) into the corpus cavernosum, administered in three sessions over several weeks.	97.4% of patients showed improved erectile function, with an average IIEF-5 score increase of 64.4%. Nearly half achieved scores indicating no ED. No adverse events were reported. Further studies are needed to confirm long-term efficacy.
		Low-intensity shockwave therapy	
Kennady et al. [32]	33 men with organic ED were randomized to shockwave therapy (n = 17) or sham treatment (n = 16). After one month, the sham group crossed over to receive shockwave therapy.	Participants received LiSWT for ED, with efficacy evaluated using the SHIM score and EHS at 1 month. Erectile function was further assessed at 1, 3, and 6 months post-treatment.	LiSWT significantly improved erectile function, with a mean SHIM score increase of 5.5 points at 6 months ($P < .001$). 54.6% of men showed clinically significant improvement, and 68% of those with an initial EHS < 3 improved to ≥ 3. The study supports LiSWT's long-term effectiveness in organic ED.
De Oliveira et al. [33]	The study included 25 ED patients, divided into two groups: 13 with ED ≤ 24 months and 12 with ED > 24 months.	Patients received LiSWT for ED, with effectiveness assessed using the IIEF-5 questionnaire at baseline, 6 weeks, and 3 months. Penile Doppler ultrasound was done before and 6 weeks after treatment to evaluate vascular changes.	LiSWT is a safe, non-invasive, and repeatable treatment for ED, showing significant improvements in erectile function and penile vascular parameters. The results indicate that the duration of ED does not negatively impact the effectiveness of the therapy.
Kalyvianakis et al. [34]	48 men with severe vasculogenic ED were randomized to LiST plus tadalafil (n = 34) or sham therapy plus tadalafil (n = 17) in a double-blind trial. 3 patients were excluded (n = 3).	Participants received 12 LiST sessions (three times weekly) and daily tadalafil 5 mg for four weeks. Erectile function was assessed via IIEF-EF and SEP diary at 1 and 3 months. Primary outcome: IIEF-EF at 3 months. Secondary outcomes: IIEF-EF at 1 month, SEP responses, and adverse events.	LiST plus tadalafil significantly improved IIEF-EF scores vs. sham plus tadalafil at 1 and 3 months ($P \leq .002$). More patients achieved a clinically important IIEF-EF improvement, though SEP responses were not statistically significant. No adverse events were reported, suggesting added benefit of LiST in severe vasculogenic ED.
Kalyvianakis et al. [35]	This randomized study included 97 PDE5 inhibitor users with vasculogenic ED, divided into four groups based on LiST frequency and EFD. Groups received LiST twice or three times weekly. 89 patients completed the 6-month follow-up.	Participants underwent 12 LiST sessions (two or three times weekly) with EFD 0.05 or 0.10 mJ/mm². Erectile function was assessed via IIEF-EF, SEP diary, and penile ultrasonography. Primary outcome: erectile function improvement. Secondary outcomes: MCID achievement and PSV changes at 3 months.	All groups showed significant improvement in IIEF-EF, SEP3, and PSV ($p < 0.001$), with no difference between session frequencies. Higher EFD (0.10 mJ/mm²) showed a trend toward better efficacy but lacked statistical significance. No adverse effects were reported. Further research is needed.

cd. tab. II

1	2	3	4
Olsen et al. [36]	This randomized, placebo--controlled study included 112 men with organic ED. Participants were assigned to LI-ESWT (n = 51) or placebo (n = 54), with both patients and clinicians blinded. After 10 weeks, the placebo group received active treatment.	LI-ESWT participants received five treatment sessions over five weeks. ED was assessed at screening and at 5, 12, and 24 weeks using interviews, EHS, and IIEF-15. The placebo group initially received sham treatment but later underwent active therapy after 10 weeks.	At five weeks post-treatment, 57% of men in the LI-ESWT group achieved erection sufficient for intercourse without medication vs. 9% in the placebo group (p = 0.0001). While EHS showed significant improvement, no statistical difference was noted in the IIEF-EF domain. After 24 weeks, 19–23% maintained this effect. Larger, long-term studies are needed to confirm LI-ESWT's potential as a cure.
		Endovascular treatment methods	
Aschenbach et al. [37]	This study retrospectively analyzed 29 men diagnosed with ED caused by veno--occlusive dysfunction. Diagnosis was confirmed through pharmacocaverno-sometry and cavernosography. All participants underwent endovascular embolization therapy via a transfemoral approach.	The procedure involved catheter placement at the target vascular sites, followed by embolization using N-butyl-2-cyanoacrylate (Histoacryl®). The primary endpoints included technical success, clinical improvement, and the occurrence of complications.	Endovascular embolization demonstrated a high technical success rate (93.1%), with failure occurring in two patients due to anatomical challenges. Clinically, 88.8% of successfully treated patients experienced improvement in erectile function. Specifically, 40.7% progressed from poor tumescence and no rigidity (E1) to good tumescence with intermediate rigidity (E4), while 29.6% regained normal rigidity (E5), and 18.5% achieved improved tumescence with poor rigidity (E3). Only 11.1% showed no change in erectile function. The procedure was performed without complications, making it a safe and effective therapeutic approach for veno-occlusive ED.

ED – erectile dysfunction; IIEF – International Index of Erectile Function; PRP – platelet-rich plasma; FDA – Food and Drug Administration; ICI – intracavernosal injection; IIEF-EF – International Index of Erectile Function – Erectile Function domain; SWT – shockwave therapy; PDE5-Is – phosphodiesterase type 5 inhibitors; PRFM – platelet-rich fibrin matrix; PGE-1 – prostaglandin E1; ADAM – androgen deficiency in the aging male; BM-MSCs, BMSCs – bone marrow--derived mesenchymal stem cells; EHS – Erection Hardness Score; PM-MSCs – placental matrix-derived mesenchymal stem cells; SHED-CM – stem cells from human exfoliated deciduous teeth – conditioned medium; LiSWT, LiST, LI-ESWT – low-intensity shockwave therapy (alternative abbreviations used in some studies); SHIM – Sexual Health Inventory for Men; SEP – Sexual Encounter Profile; EFD – energy flux density; MCID – minimal clinically important difference; PSV – peak systolic velocity.

Discussion

The management of ED has evolved significantly over the past decades, shifting from traditional pharmacological approaches to innovative therapeutic strategies targeting the underlying pathophysiology of the disorder. This discussion critically evaluates the potential of BoNT as an emerging treatment for ED and juxtaposes its efficacy and safety profile against other novel interventions.

Challenges in current treatment approaches

Despite the widespread use of PDE5-Is such as sildenafil and tadalafil, approximately 30–40% of patients fail to achieve satisfactory therapeutic outcomes [16]. The limited efficacy of PDE5-Is in certain patient populations, particularly those with endothelial dysfunction, diabetes mellitus, or neurogenic ED, underscores the need for alternative treatment options [15]. Additionally, common side effects, including headaches, visual disturbances, and nasal congestion, often lead to discontinuation of therapy [17]. More invasive solutions, such as penile prosthesis implantation, while effective, are associated with surgical risks and high costs [18], further highlighting the necessity of exploring less invasive, yet efficacious alternatives.

Botulinum toxin: a paradigm shift in ED management

BoNT, primarily recognized for its neuromuscular blockade properties, has emerged as a promising agent in the treatment of ED by modulating smooth muscle tone in the corpora cavernosa [10]. Its mechanism of action involves inhibition of acetylcholine release at neuromuscular junctions, leading to prolonged smooth muscle relaxation and improved penile blood flow [14]. Clinical studies demonstrate encouraging outcomes, with significant improvements in Erection Hardness Score (EHS), peak systolic velocity (PSV), and Sexual Health Inventory for Men (SHIM) scores in BoNT--treated patients resistant to PDE5-Is [15]. Notably, repeated injections appear to enhance therapeutic efficacy, with response rates improving from 67.5% after the second injection to 94.7% after the fourth [14]. However, BoNT therapy is not without its limitations. While adverse effects are generally mild, including transient penile pain and burning sensations [17], the optimal dosing regimen and long-term safety profile require further elucidation [18]. Additionally, the lack of standardized administration protocols presents

a challenge in achieving consistent therapeutic outcomes across different patient populations [10].

Comparative analysis of emerging therapies

Several other innovative therapeutic modalities have been explored for ED management, including:

1. PRP therapy
   PRP therapy has gained attention for its regenerative properties, promoting angiogenesis and tissue repair [21]. Clinical studies indicate that PRP injections result in significant improvements in erectile function, with approximately 69% of treated patients experiencing clinically meaningful benefits at six--month follow-up [22]. However, some trials report no significant difference compared to placebo [20], necessitating further research to clarify its efficacy.
2. Stem cell therapy
   Stem cell-based approaches aim to restore erectile function through cellular regeneration and neoangiogenesis [28]. Preliminary trials involving mesenchymal stem cell (MSC) injections have demonstrated promising results, particularly in diabetic and post-prostatectomy patients [29]. Nevertheless, concerns regarding the scalability, cost, and ethical considerations of stem cell therapy remain unresolved [30].
3. LI-SWT
   LI-SWT has been shown to stimulate neovascularization and improve penile hemodynamics [32]. Randomized controlled trials indicate significant improvements in erectile function, with a mean SHIM score increase of 5.5 points at six months [33]. Notably, combination therapy with LI-SWT and PDE5-Is has yielded superior results compared to monotherapy [34].
4. Endovascular techniques
   Penile artery stenting and embolization procedures have emerged as viable options for patients with vasculogenic ED refractory to medical therapy [37]. Studies suggest that endovascular embolization can restore erectile function in up to 88.8% of patients with veno-occlusive dysfunction [37]. However, these techniques require specialized expertise and are associated with procedural risks [37].

Future research directions and clinical implications

While current findings underscore the potential of BoNT as an effective treatment for ED, several key questions remain unanswered. Future research should focus on optimizing dosing regimens, refining patient selection criteria, and evaluating long-term outcomes [18]. Additionally, investigating synergistic treatment strategies – such as combining BoNT with LI-SWT or regenerative therapies – may enhance therapeutic efficacy [15]. Large-scale, multicenter randomized controlled trials are essential to establish evidence--based guidelines for integrating BoNT into clinical practice [17].

Conclusions

Based on the analysis of available clinical studies, BoNT-A appears to be a promising and safe therapeutic option for patients with ED, particularly those unresponsive to conventional treatments such as PDE5-Is. The reviewed evidence suggests that BoNT-A may offer significant improvements in erectile function with a favorable safety profile, especially when used as an adjunct to other therapies. However, due to the heterogeneity of study designs and limited long-term data, further well-designed randomized trials are necessary to establish standardized dosing protocols, assess durability of effect, and define optimal patient selection criteria.
In addition, regenerative and neuromodulatory approaches such as PRP, stem cell therapy, LI-SWT, and endovascular techniques also show potential but require further validation. In our opinion, the future of ED management lies in a personalized, multimodal strategy that combines pharmacological, procedural, and lifestyle-based interventions, tailored to the etiology and severity of the condition.

Authors' contribution

Study design – K. Nikel
Data collection – J. Smolarczyk, M. Piegza
Manuscript preparation – K. Nikel, M. Stojko
Literature research – K. Nikel, M. Stojko

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