Review Article

# Advances in erectile dysfunction treatment research: a narrative review

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**Background and Objective:** Erectile dysfunction (ED) is one of the common diseases in middle-aged and older men, and its etiology mainly includes vascular diseases, neurological diseases, metabolic disorders, and psychological factors. This review takes the physiological mechanisms of penile erection as a starting point and provides an in-depth look at the major current treatments, which include phosphodiesterase type 5 (PDE5) inhibitors, gene therapy techniques, low-intensity extracorporeal shock wave therapy (Li-ESWT), low-intensity pulsed ultrasound therapy (LIPUS), and psychological treatments. The review further provides a critical analysis and summary of the advantages and limitations associated with each treatment approach. Finally, the article discusses the future directions of ED treatment, emphasizing the importance of integrating personalized and precision medicine principles into treatment planning to identify the most appropriate therapeutic strategy for each patient.

**Methods:** We conducted literature searches on academic platforms such as PubMed, Google Scholar, and Web of Science using the terms "erectile dysfunction", "stem cells", "low-intensity extracorporeal shock wave", "low-intensity pulsed ultrasound", "PDE5 inhibitors", "gene therapy", "penile prosthesis implantation", and "psychosexual therapy" collecting literature published from January 1990 to October 2024.

**Key Content and Findings:** The incidence of ED is showing a trend of becoming more widespread and affecting younger people. We have identified the main risk factors that cause ED, which include psychological disorders, hypertension, cardiovascular diseases (CVDs), and unhealthy lifestyles. On this basis, this study comprehensively reviews the latest research progress of traditional treatment methods and emerging treatment approaches, and analyzes their respective advantages and limitations.

**Conclusions:** As ED treatment technologies continue to advance, the erectile function of numerous patients has seen significant improvement. Looking at the future development trend, combined treatment is expected to become the mainstream strategy for treating ED, and the treatment methods for this condition will gradually move towards personalization and precision.

**Keywords:** Erectile dysfunction (ED); low-intensity extracorporeal shock wave; low-intensity pulsed ultrasound; gene therapy

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## Introduction

Erectile dysfunction (ED) refers to a man's inability to achieve or maintain a full erection for satisfactory sexual intercourse for at least 3 months. One hundred and fifty-two million men worldwide suffered from ED in 1995, and experts predict that the number will increase to 322 million in 2025 (1). From 50% to 100% of men aged 70 years and above suffer from ED, and the incidence of the disease tends to be younger, with the prevalence rate of young men reaching 30% (2), which has a direct impact on the relationship between husband and wife and family harmony (*Figure 1*). At present, the traditional first-line therapeutic drugs are phosphodiesterase type 5 (PDE5) inhibitors, but about 60% of the patients recovered their sexual life after taking them, and nearly 40% of them had no significant effect, which highlights its limitations, so new therapies are needed (3). In recent years, with the in-depth study of the mechanism of ED, gene therapy, stem cell therapy, and other new therapies have emerged and the effect is remarkable. In this article, we synthesize the mechanism of penile erection and the cutting-edge therapeutic strategies for ED. We present this article in accordance with the Narrative Review reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-2025-193/rc).

## Methods

We began the search for articles related to the treatment of ED published from January 1990 to October 2024. This search mainly relied on three database platforms: PubMed, Google Scholar, and Web of Science. To ensure the accuracy of the search results, we set the search keywords as "erectile dysfunction", "stem cells", "low-intensity extracorporeal shock wave", "low-intensity pulsed ultrasound", "PDE5 inhibitors", "gene therapy", "penile prosthesis implantation", and "psychosexual therapy". At the same time, to ensure an accurate understanding of the article content, we limited the search scope to English literature. Through the above search strategy, we aim to achieve comprehensive coverage of the search results while ensuring the rigor of the search (*Table 1*).

## Penile erection physiology

Penile erection is a complex physiological process involving nerve signaling and vascular smooth muscle response, influenced by psychological and physiological factors (4,5). After sensory stimulation, impulses are sent from the hypothalamus or lower sacral medulla, and parasympathetic nerve endings release nitric oxide (NO), which causes smooth muscle cells to undergo diastole and increases blood flow in the cavernous arteries leading to an erection (6,7); dopamine also participates in the regulation. Albersen (8) argued that the role of cavernous corpus cavernosum (CC) fibroblasts has been overlooked in past studies, and Guimaraes' team (9) found that it affects penile diastole through the regulation of norepinephrine. Downregulation of Notch signaling after erection resulted in a large increase in the number of fibroblasts, allowing for longer-lasting erections; thus, modulation of fibroblast numbers offers new possibilities for the treatment of ED (10).

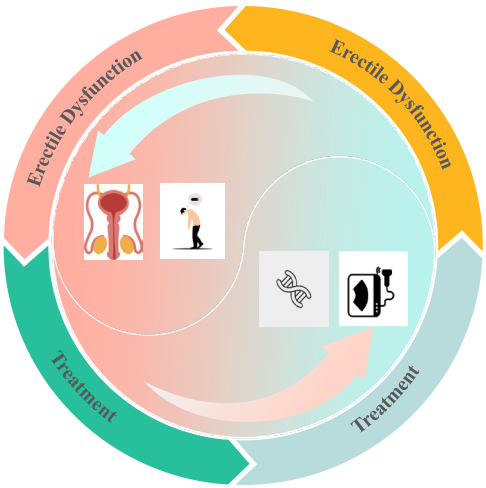


**Figure 1** The impact and treatment of ED. Created by W.J.Y. ED, erectile dysfunction.

## Treatment

### *PDE5 inhibitor*

Since the first PDE5 inhibitor, sildenafil (Viagra), was introduced in 1998, this type of drug has become a first-line treatment option due to its efficiency and safety. Currently, commonly used drugs include sildenafil, tadalafil, vardenafil, and avanafil (11), which were categorized as a class A recommended drug for ED treatment by the Fourth International Consultation on Sexual Medicine in 2015 (ICSM 2015), suggesting that it is efficacious and safe (12). Their mechanism of action is to inhibit PDE5

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**Table 1** Search strategy

| Items | Specification |
|---|---|
| Date of search | October 2024 to December 2024 |
| Databases and other sources searched | PubMed, Google Scholar, and Web of Science |
| Search terms used | "Erectile dysfunction", "stem cells", "low-intensity extracorporeal shock wave", "low-intensity pulsed ultrasound", "PDE5 inhibitors", "gene therapy", "penile prosthesis implantation", and "psychosexual therapy" |
| Time frame | January 1990 to October 2024 |
| Inclusion criteria | (I) All studies must be directly related to the causative factors of ED |
| | (II) All studies must be directly related to the treatment of ED |
| | (III) We limited the language of the study to English to ensure our accurate understanding and analysis of the literature |
| Selection process | All the authors selected the studies together |

ED, erectile dysfunction; PDE5, phosphodiesterase type 5.

activity, reduce cyclic guanosine monophosphate (cGMP) catabolism, and enhance NO to cGMP signaling.

Mulhall's team statistically analyzed PDE5 inhibitor prescriptions in the U.S. from 2012 to 2015, and about half of 100,000 patients chose sildenafil. The data supported this by showing the lowest conversion and treatment overlap rates compared to other PDE5 inhibitors. Continuous administration of sildenafil improves endothelial dysfunction in patients; the drug takes effect 15 minutes after administration and is effective for more than 6 hours, with dosage adjusted on a patient-by-patient basis (13).

PDE5 inhibitors are effective in elderly, depressed, and multimorbid patients but may be less effective or even ineffective in patients with diabetes mellitus (DM) or severe neurological or vascular disease (14,15); in such cases it is recommended to adjust the regimen by switching to a different PDE5 inhibitor or adopting alternative therapies such as sponge injection or urethral drug delivery (16). The drug is well tolerated and side effects are mostly mild, with headache and facial flushing predominating (see *Table 2* for details). The choice needs to emphasize individualization; patients should follow their doctor's instructions regarding whether to take it regularly or on demand according to their frequency of sexual activity while considering occasional versus routine use. They should also consider knowledge about the drug's speed of onset of action, usage guidelines, and adverse effects—this will help them choose the most suitable type for enhancing efficacy or combining with other therapies for comprehensive treatment.

### *Gene therapy*

In recent years, gene therapy has become a hot topic in the scientific community because it provides long-lasting treatment and precise targeting advantages. In particular, it has great potential in the treatment of refractory ED, and penile tissue is regarded as an ideal target for gene therapy because of the slow renewal of vascular smooth muscle cells, ease of injection, and ease of local circulation. The core strategy of gene therapy is to use viral or non-viral vectors to deliver specific genes to target cells or tissues precisely (17). Currently, adenoviruses, as congenital defective viruses, are not associated with human disease and are highly infectious to dividing and nondividing cells, making them a better vector choice (18).

## NO synthase (NOS) and subtype NOS

The NO/cGMP pathway is one of the most studied signaling pathways. In this pathway, NO elevates cGMP levels by activating guanylate cyclase (GC) in the vasculature, which elevates cGMP levels. Enhancement of NO synthesis is therefore a key target for the regulation of various signaling pathways, and Bivalacqua's research team has focused on how to genetically enhance NO levels by using an adenoviral vector carrying the endothelial NOS (eNOS) gene to genetically transfect streptozotocin-induced diabetic rats (19). Forty-eight hours after transfection, they observed a significant increase in eNOS protein expression and cGMP concentration in the CC of the penises of these

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**Table 2** Drug side effect

| Category | Sildenafil | Tadalafil | Vardenafil | Avanafil |
|---|---|---|---|---|
| Duration of drug use | 1 h before sexual activity | ≥30 min before sexual activity | 60 min before sexual activity | As soon as 15 min before sexual activity |
| Duration of medication | 4–8 h | Up to 36 h | 4–8 h | 4–8 h |
| Adverse drug reactions | Headache, flushing, indigestion and nasal congestion, blurred vision | Headache, flushing, dyspepsia and nasal congestion, back pain, myalgia | Headache, flushing, dyspepsia and nasal congestion, blurred vision | Headache and flushing |

rats, which directly suggests that adenoviral vector-mediated transfection of the eNOS gene significantly improves erectile function in rats (20). To further validate this finding, Bivalacqua's team also performed eNOS transfection in rats of different ages and obtained similar positive results (21). In addition, another experiment used adenoviral vectors carrying the neuronal NOS (nNOS) gene to transfect older rats and found that, after 18 days of administration, the rats' erectile function was significantly improved even at low viral loads (22). In addition to this, adenovirus-vectored inducible NOS (iNOS) has also been shown to enhance endothelial function, which provides new perspectives for the study of the NO/cGMP pathway in vascular biology and disease treatment (23).

**RhoA/Rho-kinase**

RhoA belongs to a family of small GTPases that possess the property of activating Rho-associated protein kinase (ROCK). The RhoA-ROCK signaling pathway plays a critical role in regulating vascular smooth muscle contraction, and Hannan's team showed that this signaling pathway is upregulated after bilateral neural CC injury, resulting in penile hypercontraction (24). At the same time, the ratio of eNOS to Rho-kinase tends to decrease with age (25). In addition, Sezen showed that by applying the ROCK inhibitor fasudil, the levels of AKT and P-PTEN in the pelvic ganglion could be effectively restored, and then the signaling pathway of Rho/ROCK/AKT/P-PTEN was constructed (26); this was also supported by the experiments of Wen, who believed that long-term administration of fasudil could, by regulating the PTEN/AKT pathway (27), to the Rho pathway, as a new target for ED treatment, provides a new way to improve organic and hormone-related ED by regulating the dynamic balance between contraction and relaxation of cavernous smooth muscle.

From the results of the above animal experiments, gene therapy has shown good potential for application in the field of ED. However, due to the risk of carcinogenicity in long-term use and the limited duration of its effect, the transition from animal experiments to human clinical research faces greater challenges. With the continuous development of gene technology in the future, gene therapy is expected to become an important means of ED treatment.

### *Low-intensity extracorporeal shock wave therapy (Li-ESWT)*

Li-ESWT has been used for ED treatment since 2010. One study has shown its potential to eradicate ED, and the 2021 European Society of Urology Guidelines for the Management of Male Sexual Dysfunction emphasize its importance and continued use as the preferred first-line therapy for ED (28).

**Mechanism of action**

The prominent effect of Li-ESWT is to stimulate vascular growth-related factors. Nishida established a model of acute infarction, which was observed after 4 weeks of treatment, and found that the ischemic region responded positively to the treatment ($P<0.01$), with no adverse complications such as cardiac arrhythmia during the treatment period (29), while infarction persisted in the untreated control group. This suggests that Li-ESWT can elevate vascular endothelial growth factor (VEGF) expression *in vivo*, and another study has shown that its application alone can cause a variety of vascular growth-related factors to rise in ischemic muscle and promote local capillary regeneration recovery (30). In treating ED, numerous experiments have confirmed that Li-ESWT can activate penile tissue mechanoreceptors, promote neo-angiogenesis and dilation, improve erectile function, and significantly increase International Index of Erectile Function (IIEF) in patients (31-33). Meanwhile, Li-ESWT therapy can significantly activate Schwann cells, promote the release

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**Table 3** The applicable population and contraindications of Li-ESWT

| Category | Recommended population | Description |
|---|---|---|
| Vascular ED | Hypertension, DM, atherosclerosis leading to insufficient blood flow to the penis | Mild to moderate patients (IIEF-5 score 8–21)<br>Preferred for poor response to medication |
| Etiology-specific ED | DMED, pelvic floor vascular nerve injury (e.g., after prostate cancer), trauma or excessive sexual intercourse resulting in cavernous body injury | Serious neurological injury (e.g., spinal cord injury) needs to be ruled out |
| Drug intolerant/ineffective | PDE5 inhibitors ineffective or intolerant of side effects | May be combined with other treatments |
| Young and middle-aged people and those in need of prevention | Young and middle-aged people with weak or insufficiently hard erections, or those who wish to prevent sexual degeneration | Emphasis on early intervention and lifestyle modification |
| Contraindicated population | Anatomical malformations of the penis (Peyronie's disease), coagulation disorders, active infections, severe nerve damage | Needs to be ruled out after evaluation with Doppler ultrasound, hormone testing, etc. |

DM, diabetes mellitus; DMED, diabetic mellitus ED; ED, erectile dysfunction; IIEF, International Index of Erectile Function; Li-ESWT, low-intensity extracorporeal shock wave therapy; PDE5, phosphodiesterase type 5.

of neurotrophic factors, and help repair damaged nerve fibers. It has unique advantages in treating nerve-damaging ED caused by diabetes or pelvic floor surgery. Many experiments have confirmed that Li-ESWT can directly act on Schwann cells to promote the reconstruction and recovery of nerve function (34-36).

**Treatment plan**

Li-ESWT applies to a wide range of patients and is effective in those who are ineffective on PDE5 inhibitors (see *Table 3* for details). There is no consensus on its specific treatment protocol. Animal experiments have shown that a Li-ESWT regimen of 300 shocks 3 times per week for 12 weeks in diabetic mellitus ED (DMED) rats can significantly improve their erectile function (37). In clinical trials, Ruffo's team used the Renova Shockwave System to electrically shock four regions of the penile shaft right and left cavernous body and the right and left crus of the penile crus four times per week, 900 times per region, for a total of 3,600 times and an energy density of 0.09 mJ/mm$^2$ after four sessions, and the patients' IIEF means significantly improved after 3 months (38,39). Experts at the Asia-Pacific Society of Sexual Medicine recommend treating 4 regions of the mid-penile CC and penile pedicle bilaterally with Renova linear shock wave devices, setting the energy flow density to 0.09 mJ/mm$^2$ and frequency to 5 Hz, once a week for a total of four sessions, 900 sessions per region (3,600 total sessions) or adjusted to 5,000 sessions depending on the condition and consolidating the treatment every 6–12 months to alleviate the patient's symptoms (40). The recommendation is a clear treatment plan based on the available evidence.

### *Low-intensity pulsed ultrasound therapy (LIPUS)*

In recent years, LIPUS, as a typical representative of non-invasive physical therapy, has shown remarkable potential in the exploration of ED treatment. LIPUS delivers low-intensity ultrasound pulses precisely to the specific treatment area, regulating tissue repair in the target area and promoting patient treatment and recovery. The output intensity of this technology is lower than that of traditional ultrasound; it is non-invasive, painless, and well-tolerated, with no adverse clinical effects.

**Mechanism of action**

LIPUS accelerates angiogenesis and improves the structure of the CC. Lei's team found that rats treated with LIPUS had elevated CC intracellular pressure, increased endothelial and smooth muscle content, collagen ratio, and elastin fiber number, and enhanced expression of eNOS and nNOS after 2 weeks (41,42). Its mechanism of action is related to the down-regulation of the TGF-β1/Smad/CTGF signaling pathway and also enhances the VEGF secretion capacity of adipose tissue-derived stem cells, which has potential in the treatment of DMED by activating the Piezo-ERK-VEGF signaling pathway (43,44).

LIPUS is effective in ED induced by nerve injury,

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**Table 4** The applicable population and contraindications of LIPUS

| Category | Recommended population | Description |
|---|---|---|
| Vascular ED | Insufficient blood flow to the penis due to hypertension, diabetes, atherosclerosis, etc. | Mild-to-moderate patients (IIEF-5 score 8–21) with poor response to medication are preferentially recommended |
| DMED | Diabetic patients with stable glycemic control (HbA1c ≤7.5%) | LIPUS improves microcirculation and nerve regeneration and is particularly suitable for diabetes-related ED |
| Nerve-damaging ED | Post-radical prostate cancer, pelvic vascular nerve injury, etc. | Works by promoting nerve regeneration and vascular repair, but severe nerve injury (e.g., spinal cord injury) needs to be ruled out |
| Drug intolerant/ineffective | Those who do not respond to PDE5 inhibitors or cannot tolerate the side effects | This can be done alone or in combination with medication to enhance efficacy |
| Young and middle-aged people and those in need of prevention | Those who have insufficient erectile hardness or who wish to prevent sexual deterioration | Emphasize early intervention combined with lifestyle modification |
| Contraindicated population | Anatomical malformations of the penis (e.g., Peyronie's disease), coagulation disorders, active infections, severe psychological disorders | It needs to be ruled out after evaluation by Doppler ultrasound, hormone testing, etc. |

DMED, diabetic mellitus ED; ED, erectile dysfunction; HbA1c, hemoglobin A1c; IIEF, International Index of Erectile Function; LIPUS, low-intensity pulsed ultrasound therapy; PDE5, phosphodiesterase type 5.

Liu's team treated rats with LIPUS for 2 weeks, and the results showed that compared to the nerve injury group, the treatment group had significantly improved erectile function and increased the number of smooth muscle and endothelial cells in the cavernous tissue of the penis, which suggests that LIPUS can promote the repair of damage (45,46). Li's experiment also proved this point (47). Mediated regulation of mechanotransduction does not rely on the classical Hippo signaling pathway, providing a new perspective for understanding its therapeutic mechanism. The above findings confirm the potential of LIPUS for the treatment of neuro-injurious ED and inform future studies.

## Treatment plan

LIPUS, as an emerging therapy, applies to a wide range of people (see *Table 4* for details), but the treatment method has not been standardized. Clinical trials have shown no significant difference in response rates between patient groups treated 3 times per week versus 2 times per week (48). Multicenter studies have noted that LIPUS treatment of both sides of the penile shaft and the crus for 5 minutes twice a week for 4 weeks significantly improves erectile function. Experts from the Asia-Pacific Society of Sexual Medicine recommend using F-type probe grade III with sound intensity 0.2 W/cm$^2$, frequency 1.7 MHz, pulse duration 200 μs, and pulse ratio 1:4 for five minutes on each of the four sites of bilateral penile cavernous body and penile pedicle, 2 to 3 times per week for 1 month; this can improve erectile function in patients with mild-to-moderate ED (49).

However, the sample size of current relevant studies is insufficient; subsequent larger clinical trials and enhanced follow-up are needed. Meanwhile, the clinical application of LIPUS should be combined with PDE5 inhibitors or other therapies to improve overall efficacy.

### *Stem cells*

In recent years, stem cell therapies have provided new avenues for ED treatment. Stem cells are categorized into embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and adult stem cells (ASCs) according to their origin. Among them, ESCs have a strong regenerative capacity, but due to legal and ethical constraints, ASCs are more favored in experimental study and become the first choice of researchers (50).

Adipose-derived stem cells (ADSCs) are cells present in adipose tissue with self-renewal and multidirectional differentiation ability (51). Fandel's team experimented on 100 rats with cavernous nerve injury and found that sponge therapy with ADSCs promoted nerve regeneration and improved ED (52). Fandel *et al*. simulated the experiment on rats with post-prostatectomy ED and showed that ADSCs and their derived cell lysates preserved the

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cavernous structure and reduced the apoptotic index, exhibiting anti-fibrotic and anti-apoptotic properties (52). It can be inferred that ADSC therapy has a significant positive effect on the treatment of DMED (53).

Bone marrow mesenchymal stem cells (BMSCs) are ASCs with self-renewal of mesodermal origin. The Sun's team isolated and cultured BMSCs from rats and then injected them; as a result, the internal pressure (ICP), mean arterial pressure (MAP), and ICP/MAP ratio in the spongy body of the rats' penis increased. An enzyme-linked immunosorbent assay (ELISA) test revealed that levels of multiple factors secreted by BMSCs increased, along with an increase in nerve fibers and nNOS expression in the dorsal penile nerve, indicating that BMSCs have a trophic effect on nerves and can improve erectile function in nerve-damaged rats (54,55). Yiou's team carried out a clinical trial on ED after prostatectomy; after 1 month of treatment with penile cavernous injection of BMSCs, the IIEF score was significantly elevated ($P<0.001$), with an increase in peak penile blood flow rate up to 65%, which verified its clinical effectiveness (56). All these experiments confirmed the effectiveness of BMSCs in improving neurologic injury-related ED and DMED.

In human clinical trials, stem cell therapy for ED has shown initial safety and efficacy reliability, with significant effects on DMED and nerve damage ED. However, this therapy is still in the exploratory stage and lacks the support of long-term and large-scale clinical trial data. In the future, with the development of genetic technology, stem cell therapy is expected to become a mainstream means of ED treatment.

### *Penile prosthesis implantation (IPP)*

IPP is a surgical treatment for patients who have failed to respond to medication and are looking for a single surgical solution to their ED problem. Not only is this method one of the most effective ways to treat ED today, but it also excels in terms of patient satisfaction. Currently, the types of prostheses are mainly categorized into expandable prostheses and semi-rigid prostheses, with the expandable prosthesis commonly used in clinical practice being mostly a three-piece type, whose core structure consists of two cylinders, a liquid pump valve, and a fluid storage capsule.

In recent years, IPP has become the treatment of choice for ED in North America due to its remarkable efficacy, especially for patients who have failed to respond to PDE5 inhibitor therapy and those with spinal cord injuries (57). Thanks to technological innovations, the IPP has achieved a 95% success rate (58), with infection rates as low as 0.46% when using antimicrobial coatings and contactless surgery (59). Postoperative follow-up data showed that patients were highly satisfied with their quality of life and sex life, and believed that the procedure was effective in improving couples' relationships. However, there are still potential risks associated with IPP, which can lead to complications such as postoperative infection, device malfunction, abnormal reservoir position, postoperative pain, and penile shortening (60). It is encouraging to note that with the widespread use of antibiotics and the iterative upgrading of coated implant technology, the risk of postoperative infection has been dramatically reduced, significantly improving the safety and reliability of IPP. These technological breakthroughs provide new hope for patients with severe ED to regain a normal sex life (61,62).

Currently, IPP is controversial due to possible postoperative complications and irreversible damage to the penis. However, in the author's opinion, IPP is expected to become the first-line treatment for ED as the technology of prosthetic materials continues to be revolutionized and the measures to prevent infection become more and more perfect.

### *Vacuum erection device (VED)*

With technological innovation, VED is gradually leaping into the mainstream of ED clinical treatment with its non-invasive advantages. The device is easy to operate, only needing to be worn after applying lubricant on the surface of the penis, using the principle of vacuum negative pressure attraction to guide blood to fill the cavernous body of the penis, thus realizing physiological erection. Patients can complete the treatment independently at home, greatly enhancing convenience and privacy.

Clinical studies have confirmed that VED has significant efficacy for mild to moderate ED patients as well as middle-aged and elderly individuals. Beaudreau's follow-up data on middle-aged and elderly veterans showed that more than 96% of patients recognized the efficacy of VED treatment, and most of their sexual partners were satisfied with the results (63). Shirai's clinical study (64) on the new VED tool Vigor demonstrated that erectile hardness score (EHS) was higher than international standards. Additionally, Shirai's clinical study indicated that patients experienced a significant increase in EHS and IIEF after using this tool, with no adverse effects reported. This series of investigations provides a rationale for widespread use of

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VED in ED treatment.

### *Sexual psychotherapy*

Psychosexual therapy is a treatment that uses psychological methods to cope with psychosexual disorders, and its main avenues cover cognitive-behavioral therapy, psychoanalytic therapy, specialized sex therapy, couples therapy, sensory-focused therapy, and supportive psychotherapy. These approaches are particularly applicable to patients with psychogenic ED.

Group psychotherapy is highly effective in alleviating the condition. Melnik has found that most young ED patients and premature ejaculation patients have psychological problems; early detection and intervention are critical. In addition, Melnik's research has shown that group psychotherapy has a 95% response rate for sexual treatment compared to treating male patients alone. Furthermore, when couples participate in psychotherapy together, the results are better than when men are treated alone (65).

Finally, it should be noted that when psychotherapy fails to achieve significant results, it should be combined with other therapeutic methods for comprehensive intervention. For example, PDE5 inhibitors can be used in conjunction with treatment. From the results of numerous clinical trials, it is clear that the combination of psychotherapy and sildenafil can significantly improve the patient's erectile function (66,67).

### *Lifestyle changes*

In today's society, with an aging population, the incidence of obesity continues to rise, and the prevalence of ED is also increasing steeply. Against this backdrop, it is crucial to adopt a sensible lifestyle that not only prevents ED to a certain extent, but also contributes to the maintenance of overall health (68).

Maintaining a healthy diet can help reduce the risk of ED. A good example is the Mediterranean diet, which uses fruits, vegetables, nuts, whole grains, and fish as the main food sources, supplemented by red meat, processed meats, and refined grains (69,70). This diet improves endothelial function and prevents cardiovascular disease (CVD) in men. In addition, we should try to avoid diets high in sugar and salt as a way of preventing diabetes and high blood pressure, which in turn reduces the likelihood of ED. Obesity is also an important factor in ED. In a weight loss trial involving 110 obese men with ED after a 2-year weight loss intervention, those in the intervention group who participated in physical activity showed significant improvement in their erectile function and overall health. This suggests that weight loss can have a positive effect on ED (71). Additionally, regular physical activity has been shown to play a key role in preventing ED (72). A 9-month exercise intervention showed that exercise increased testosterone levels in men, with significant increases in erection duration and frequency of intercourse within the group (73).

## Conclusions

As the medical field continues to explore the mechanisms of erection and the etiology of ED, and thanks to the continuous improvement of science and technology, the treatment of ED has become more and more diversified. For a long time, PDE5 inhibitors have been the first choice of ED treatment, and their safety, efficacy, and reliability have been widely recognized. However, for some patients who have poor results on PDE5 inhibitors, IPP and VED can be the preferred treatment options. In addition, micro-energy medicine therapies, represented by Li-ESWT and LIPUS, have shown good application potential in the combined treatment of ED. With the continuous progress of regenerative medicine technology, new therapeutic methods represented by stem cell therapy and gene therapy have shown remarkable efficacy in the field of ED treatment. However, most of these methods are still in the stage of animal experiments, and there is still a long way to go before they can be widely applied in clinical practice. Looking to the future, the treatment strategy of ED will certainly move towards precision medicine, and personalized treatment plans will be formulated according to the cause of the patient's illness, to realize personalized and precise medical treatment.

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## Footnote

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## References

1. Ayta IA, McKinlay JB, Krane RJ. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. BJU Int 1999;84:50-6.
2. Nguyen HMT, Gabrielson AT, Hellstrom WJG. Erectile Dysfunction in Young Men-A Review of the Prevalence and Risk Factors. Sex Med Rev 2017;5:508-20.
3. Bechara A, Casabé A, De Bonis W, et al. Twelve-Month Efficacy and Safety of Low-Intensity Shockwave Therapy for Erectile Dysfunction in Patients Who Do Not Respond to Phosphodiesterase Type 5 Inhibitors. Sex Med 2016;4:e225-32.
4. McVary KT. Clinical practice. Erectile dysfunction. N Engl J Med 2007;357:2472-81.
5. Najari BB, Kashanian JA. Erectile Dysfunction. JAMA 2016;316:1838.
6. Gratzke C, Angulo J, Chitaley K, et al. Anatomy, physiology, and pathophysiology of erectile dysfunction. J Sex Med 2010;7:445-75.
7. Sáenz de Tejada I, Angulo J, Cellek S, et al. Physiology of erectile function. J Sex Med 2004;1:254-65.
8. Albersen M. From bystanders to vital contributors: cavernosal fibroblasts' transformative role in erectile physiology and therapeutic prospects. J Sex Med 2024;21:509-10.
9. Guimaraes EL, Dias DO, Hau WF, et al. Corpora cavernosa fibroblasts mediate penile erection. Science 2024;383:eade8064.
10. Ryu JK, Koh GY. Fibroblasts enable penile erection. Science 2024;383:588-9.
11. Wang R, Burnett AL, Heller WH, et al. Selectivity of avanafil, a PDE5 inhibitor for the treatment of erectile dysfunction: implications for clinical safety and improved tolerability. J Sex Med 2012;9:2122-9.
12. Hatzimouratidis K, Salonia A, Adaikan G, et al. Pharmacotherapy for Erectile Dysfunction: Recommendations From the Fourth International Consultation for Sexual Medicine (ICSM 2015). J Sex Med 2016;13:465-88.
13. Mulhall JP, Chopra I, Patel D, et al. Phosphodiesterase Type-5 Inhibitor Prescription Patterns in the United States Among Men With Erectile Dysfunction: An Update. J Sex Med 2020;17:941-8.
14. Gur S, Kadowitz PJ, Gurkan L, et al. Chronic inhibition of nitric-oxide synthase induces hypertension and erectile dysfunction in the rat that is not reversed by sildenafil. BJU Int 2010;106:78-83.
15. Behr-Roussel D, Gorny D, Mevel K, et al. Chronic sildenafil improves erectile function and endothelium-dependent cavernosal relaxations in rats: lack of tachyphylaxis. Eur Urol 2005;47:87-91.
16. Montorsi F, Padma-Nathan H, Glina S. Erectile function and assessments of erection hardness correlate positively with measures of emotional well-being, sexual satisfaction, and treatment satisfaction in men with erectile dysfunction treated with sildenafil citrate (Viagra). Urology 2006;68:26-37.
17. Melman A. Gene therapy for male erectile dysfunction. Urol Clin North Am 2007;34:619-30, viii.
18. Harraz A, Shindel AW, Lue TF. Emerging gene and stem cell therapies for the treatment of erectile dysfunction. Nat Rev Urol 2010;7:143-52.
19. Yoshimura N, Kato R, Chancellor MB, et al. Gene therapy as future treatment of erectile dysfunction. Expert Opin Biol Ther 2010;10:1305-14.
20. Bivalacqua TJ, Usta MF, Champion HC, et al. Gene transfer of endothelial nitric oxide synthase partially restores nitric oxide synthesis and erectile function in streptozotocin diabetic rats. J Urol 2003;169:1911-7.

21. Bivalacqua TJ, Champion HC, Mehta YS, et al. Adenoviral gene transfer of endothelial nitric oxide synthase (eNOS) to the penis improves age-related erectile dysfunction in the rat. Int J Impot Res 2000;12 Suppl 3:S8-17.
22. Magee TR, Ferrini M, Garban HJ, et al. Gene therapy of erectile dysfunction in the rat with penile neuronal nitric oxide synthase. Biol Reprod 2002;67:20-8.
23. Tirney S, Mattes CE, Yoshimura N, et al. Nitric oxide synthase gene therapy for erectile dysfunction: comparison of plasmid, adenovirus, and adenovirus-transduced myoblast vectors. Mol Urol 2001;5:37-43.
24. Hannan JL, Albersen M, Kutlu O, et al. Inhibition of Rho-kinase improves erectile function, increases nitric oxide signaling and decreases penile apoptosis in a rat model of cavernous nerve injury. J Urol 2013;189:1155-61.
25. Ding Z, Shen X, Li Y. Association of nNOS and Rho-kinase with age-associated erectile dysfunction in Sprague-Dawley rats. Exp Ther Med 2017;13:1133-6.
26. Sezen SF, Lagoda G, Musicki B, et al. Hydroxyl fasudil, an inhibitor of Rho signaling, improves erectile function in diabetic rats: a role for neuronal ROCK. J Sex Med 2014;11:2164-71.
27. Li WJ, Park K, Paick JS, et al. Chronic treatment with an oral rho-kinase inhibitor restores erectile function by suppressing corporal apoptosis in diabetic rats. J Sex Med 2011;8:400-10.
28. Salonia A, Bettocchi C, Boeri L, et al. European Association of Urology Guidelines on Sexual and Reproductive Health-2021 Update: Male Sexual Dysfunction. Eur Urol 2021;80:333-57.
29. Nishida T, Shimokawa H, Oi K, et al. Extracorporeal cardiac shock wave therapy markedly ameliorates ischemia-induced myocardial dysfunction in pigs in vivo. Circulation 2004;110:3055-61.
30. Tepeköylü C, Wang FS, Kozaryn R, et al. Shock wave treatment induces angiogenesis and mobilizes endogenous CD31/CD34-positive endothelial cells in a hindlimb ischemia model: implications for angiogenesis and vasculogenesis. J Thorac Cardiovasc Surg 2013;146:971-8.
31. Srini VS, Reddy RK, Shultz T, et al. Low intensity extracorporeal shockwave therapy for erectile dysfunction: a study in an Indian population. Can J Urol 2015;22:7614-22.
32. Kalyvianakis D, Hatzichristou D. Low-Intensity Shockwave Therapy Improves Hemodynamic Parameters in Patients With Vasculogenic Erectile Dysfunction: A Triplex Ultrasonography-Based Sham-Controlled Trial. J Sex Med 2017;14:891-7.
33. Kitrey ND, Gruenwald I, Appel B, et al. Penile Low Intensity Shock Wave Treatment is Able to Shift PDE5i Nonresponders to Responders: A Double-Blind, Sham Controlled Study. J Urol 2016;195:1550-5.
34. Li H, Matheu MP, Sun F, et al. Low-energy Shock Wave Therapy Ameliorates Erectile Dysfunction in a Pelvic Neurovascular Injuries Rat Model. J Sex Med 2016;13:22-32.
35. Wang HS, Ruan Y, Banie L, et al. Delayed Low-Intensity Extracorporeal Shock Wave Therapy Ameliorates Impaired Penile Hemodynamics in Rats Subjected to Pelvic Neurovascular Injury. J Sex Med 2019;16:17-26.
36. Lei H, Liu J, Li H, et al. Low-intensity shock wave therapy and its application to erectile dysfunction. World J Mens Health 2013;31:208-14.
37. Liu J, Zhou F, Li GY, et al. Evaluation of the effect of different doses of low energy shock wave therapy on the erectile function of streptozotocin (STZ)-induced diabetic rats. Int J Mol Sci 2013;14:10661-73.
38. Reisman Y, Hind A, Varaneckas A, et al. Initial experience with linear focused shockwave treatment for erectile dysfunction: a 6-month follow-up pilot study. Int J Impot Res 2015;27:108-12.
39. Ruffo A, Capece M, Prezioso D, et al. Safety and efficacy of low intensity shockwave (LISW) treatment in patients with erectile dysfunction. Int Braz J Urol 2015;41:967-74.
40. Chung E, Lee J, Liu CC, et al. Clinical Practice Guideline Recommendation on the Use of Low Intensity Extracorporeal Shock Wave Therapy and Low Intensity Pulsed Ultrasound Shock Wave Therapy to Treat Erectile Dysfunction: The Asia-Pacific Society for Sexual Medicine Position Statement. World J Mens Health 2021;39:1-8.
41. Lei H, Xin H, Guan R, et al. Low-intensity Pulsed Ultrasound Improves Erectile Function in Streptozotocin-induced Type I Diabetic Rats. Urology 2015;86:1241.e11-8.
42. Tan Y, Guo Y, Reed-Maldonado AB, et al. Low-intensity pulsed ultrasound stimulates proliferation of stem/progenitor cells: what we need to know to translate basic science research into clinical applications. Asian J Androl 2021;23:602-10.
43. Tang J, Feng M, Wang D, et al. Recent advancement of sonogenetics: A promising noninvasive cellular manipulation by ultrasound. Genes Dis 2024;11:101112.
44. Liu S, Jiang C, Hu J, et al. Low-Intensity Pulsed Ultrasound Enhanced Adipose-Derived Stem Cell-Mediated Angiogenesis in the Treatment of Diabetic Erectile Dysfunction through the Piezo-ERK-VEGF Axis.


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Stem Cells Int 2022;2022:6202842.
45. Liu Y, Liu SK, Sun JL, et al. Low-intensity pulsed ultrasound versus low-energy shock wave in the treatment of neurogenic penile erectile dysfunction. Zhonghua Nan Ke Xue 2021;27:694-700.
46. Liu Y, Pan XY, Zhang XX, et al. Role of mechanotransduction mediated by YAP/TAZ in the treatment of neurogenic erectile dysfunction with low-intensity pulsed ultrasound. Andrology 2023;11:1514-27.
47. Li Z, Ye K, Yin Y, et al. Low-intensity pulsed ultrasound ameliorates erectile dysfunction induced by bilateral cavernous nerve injury through enhancing Schwann cell-mediated cavernous nerve regeneration. Andrology 2023;11:1188-202.
48. Chen H, Li Z, Li X, et al. The Efficacy and Safety of Thrice vs Twice per Week Low-Intensity Pulsed Ultrasound Therapy for Erectile Dysfunction: A Randomized Clinical Trial. J Sex Med 2022;19:1536-45.
49. Cui W, Li H, Guan R, et al. Efficacy and safety of novel low-intensity pulsed ultrasound (LIPUS) in treating mild to moderate erectile dysfunction: a multicenter, randomized, double-blind, sham-controlled clinical study. Transl Androl Urol 2019;8:307-19.
50. Yamanaka S. Pluripotent Stem Cell-Based Cell Therapy-Promise and Challenges. Cell Stem Cell 2020;27:523-31.
51. Gir P, Oni G, Brown SA, et al. Human adipose stem cells: current clinical applications. Plast Reconstr Surg 2012;129:1277-90.
52. Fandel TM, Albersen M, Lin G, et al. Recruitment of intracavernously injected adipose-derived stem cells to the major pelvic ganglion improves erectile function in a rat model of cavernous nerve injury. Eur Urol 2012;61:201-10.
53. Garber MG, Carlos ND. Intracavernous administration of adipose stem cells: a new technique of treating erectile dysfunction in diabetic patient, preliminary report of 6 cases. MOJ Cell Sci Rep 2015;2:00018.
54. Sun C, Zhu WD, Liu J, et al. Immediate and delayed intracavernous injection of bone marrow mesenchymal stem cells to improve erectile function in rats with cavernous nerve injury. Zhonghua Nan Ke Xue 2017;23:392-8.
55. Sun C, Lin H, Yu W, et al. Neurotrophic effect of bone marrow mesenchymal stem cells for erectile dysfunction in diabetic rats. Int J Androl 2012;35:601-7.
56. Yiou R, Hamidou L, Birebent B, et al. Safety of Intracavernous Bone Marrow-Mononuclear Cells for Postradical Prostatectomy Erectile Dysfunction: An Open Dose-Escalation Pilot Study. Eur Urol 2016;69:988-91.
57. Kohn TP, Rajanahally S, Hellstrom WJG, et al. Global Trends in Prevalence, Treatments, and Costs of Penile Prosthesis for Erectile Dysfunction in Men. Eur Urol Focus 2022;8:803-13.
58. Wang CM, Wu BR, Xiang P, et al. Management of male erectile dysfunction: From the past to the future. Front Endocrinol (Lausanne) 2023;14:1148834.
59. Eid JF, Wilson SK, Cleves M, et al. Coated implants and "no touch" surgical technique decreases risk of infection in inflatable penile prosthesis implantation to 0.46%. Urology 2012;79:1310-5.
60. Mulcahy JJ. Penile prosthesis infection: progress in prevention and treatment. Curr Urol Rep 2010;11:400-4.
61. Wilson SK, Costerton JW. Biofilm and penile prosthesis infections in the era of coated implants: a review. J Sex Med 2012;9:44-53.
62. Levine LA, Becher EF, Bella AJ, et al. Penile Prosthesis Surgery: Current Recommendations From the International Consultation on Sexual Medicine. J Sex Med 2016;13:489-518.
63. Beaudreau SA, Van Moorleghem K, Dodd SM, et al. Satisfaction with a Vacuum Constriction Device for Erectile Dysfunction among Middle-Aged and Older Veterans. Clin Gerontol 2021;44:307-15.
64. Shirai M, Sano M, Anno Y, et al. Efficacy of a new vacuum erection device (Vigor 2020) for erectile dysfunction: A retrospective study in Japan. Int J Urol 2024;31:1386-92.
65. Melnik T, Soares BG, Nasselo AG. Psychosocial interventions for erectile dysfunction. Cochrane Database Syst Rev 2007;2007:CD004825.
66. Schmidt HM, Munder T, Gerger H, et al. Combination of psychological intervention and phosphodiesterase-5 inhibitors for erectile dysfunction: a narrative review and meta-analysis. J Sex Med 2014;11:1376-91.
67. Melnik T, Soares BG, Nasello AG. The effectiveness of psychological interventions for the treatment of erectile dysfunction: systematic review and meta-analysis, including comparisons to sildenafil treatment, intracavernosal injection, and vacuum devices. J Sex Med 2008;5:2562-74.
68. Horasanli K, Boylu U, Kendirci M, et al. Do lifestyle changes work for improving erectile dysfunction? Asian J Androl 2008;10:28-35.
69. Esposito K, Ciotola M, Giugliano F, et al. Mediterranean diet improves erectile function in subjects with the metabolic syndrome. Int J Impot Res 2006;18:405-10.
70. Esposito K, Marfella R, Ciotola M, et al. Effect of a mediterranean-style diet on endothelial dysfunction

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and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA 2004;292:1440-6.
71. Esposito K, Giugliano F, Di Palo C, et al. Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. JAMA 2004;291:2978-84.
72. Sgrò P, Di Luigi L. Sport and male sexuality. J Endocrinol Invest 2017;40:911-23.
73. White JR, Case DA, McWhirter D, et al. Enhanced sexual behavior in exercising men. Arch Sex Behav 1990;19:193-209.

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