

**THE LATEST TRENDS IN THE DIAGNOSIS AND TREATMENT OF ERECTILE
DYSFUNCTION****William Dutton, MD***

MD, Av. Dr. Arnaldo, 455 – Pacaembu, São Paulo, Brazil.

***Corresponding Author: Dr. William Dutton, MD**

MD, Av. Dr. Arnaldo, 455 – Pacaembu, São Paulo, Brazil.

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ABSTRACT

Erectile dysfunction (ED) is a pathological condition of the male body that has a huge negative impact not only on the physical health of a man, but also on his psychological well-being. Also, erectile dysfunction negatively affects the relationship of a man with his sexual partner, destroys the psychological comfort in the personal life of a couple, both married and in a freer relationship, and often causes family breakdown, indirectly affecting the lives of the couple's children. The main non-invasive methods of treatment for erectile dysfunction include maintaining a healthy lifestyle (avoiding bad habits, eating a balanced ration, exercising and playing sports), taking oral medications (mainly phosphodiesterase type 5 inhibitors), topical ointments, intraurethral suppositories and vacuum devices to improve erection. As a rule, first-line ED treatment methods include lifestyle normalization: cessation of smoking, alcohol, fatty and spicy foods, increased physical activity, weight loss, and intake of vitamin and mineral complexes. Of the first-line drugs, the most common are orally administered drugs, mainly in form of pills. In severe cases of erectile dysfunction, invasive treatments are sometimes used, including surgically implanted prosthetic of cavernous bodies of the penis or intracavernous injections. Promising new treatments for erectile dysfunction, developed in recent years, include shock wave therapy, external removable prosthetic devices, intracavernous injections of platelet-rich plasma and stem cells. The goal of this paper is to review the latest advances in the treatment of erectile dysfunction, which have the potential to change the treatment paradigm to achieve the most effective outcome with minimal risk to the patient.

KEYWORDS: Erectile dysfunction, intracavernous injections, external penile prosthesis, treatment paradigm.**INTRODUCTION**

The modern definition of erectile dysfunction (ED) sounds like a regular or chronic inability of a man to achieve a full erection or maintain it for a time sufficient for a normal sexual intercourse. Today, erectile dysfunction is one of the most frequently reported pathologies of sexual sphere in men. Erectile dysfunction affects men of all ages. The largest number of cases of the disease is observed among men over 70 years of age (more than 50% of the total number of cases).^[1] About 33% of ED cases occur in men between the ages of 60 and 70. Approximately 10% of cases occur in men aged 45-60, while the remaining 7% of cases are distributed among younger men. Although 7% seems a small figure, the incidence of ED in men under 45 y.o. has increased significantly in recent years compared to the 2000s.

Most often, primary care physicians are those who report erectile dysfunction among men living in the United States and Canada, thus serving as a link between patients and other more narrow specialists, mainly urologists. Primary care physicians are responsible not only for the primary diagnosis and treatment of ED, but

also for helping patients to navigate among the various treatments available and more narrow specialists.^[2]

The main risk factors contributing to the development of erectile dysfunction include age over forty, coronary heart disease, overweight, hypertension, spinal cord injuries, previous pelvic surgery, and bad habits: smoking, alcohol abuse, drug use. According to research results, the periodic use of even the lightest drug, marijuana, leads to an increase in the risk of erectile dysfunction and other potency disorders at least twofold.^[3]

In a separate category of conditions contributing to the development of erectile dysfunction, psychological factors should be distinguished, such as an unsuccessful sexual experience, self-doubt, psychological trauma, depression, etc.^[4] Not only urology, but also psychology deals with the problem of erectile dysfunction, because a man's sexual health and a decent quality of erection are not only key components of a high quality of life for him, but are also directly related to the psychological, emotional, physical and social well-being of his partner,

in a narrow interpretation, and even his entire family, in a broader interpretation,^[5]

Most patients need qualified help in choosing one or another tactic for treating ED. Due to the fact that in a large number of cases erectile dysfunction is a condition of combined etiology, that is, the cause of which is both physiological and psychological factors, representatives of the American Urological Association (AUA) recommend referring patients with ED to a psychologist or psychotherapist. Psychological counseling is often an adjunct to medical treatment for ED [6]. In some cases, if erectile dysfunction has a purely psychological cause, the help of a mental health professional is the only treatment. It has been proven that professional psychological assistance provided to a patient during medical or invasive treatment of erectile dysfunction increases the patient's responsibility in adhering to the treatment plan, as well as enhances the effect of supportive therapies, such as normalization of lifestyle.^[7] The degree of involvement of the partner is critical to the success of treatment. It has been repeatedly noted that the acceptance of the existing problem and the willingness of the partner to discuss various treatment options, as well as the favorable psychological climate in the couple, significantly contribute to the full restoration of the patient's sexual function.^[8] The treatments used range from conservative, non-invasive to operative, invasive. Despite the fact that the vast majority of patients prefer conservative methods of treatment, invasive ones should not be discounted either. In certain cases, the AUA believes, invasive treatment may be appropriate as first-line therapy.^[9] Current treatment options for ED include lifestyle changes, oral medications, injections into the cavernous bodies of the penis, fixed (implantable) penile prostheses, and, among the latest trends, belted external removable penile prostheses.^[10] Experimental methods of treatment that have still received a sufficiently voluminous evidence base include penile shock wave therapy^[11], external use of ointments with a vasodilating effect, intracavernous injections of stem cells or platelet-rich plasma (PRP). Initial results from clinical studies of these treatments for ED have already shown the first rather encouraging results. It is possible that in the near future they may become part of internationally recognized algorithms for the treatment of erectile dysfunction.^[12]

This paper reviews in details the latest trends in the diagnosis and treatment of erectile dysfunction and aims to help men with erectile dysfunction navigate among the available treatment options and improve their sex lives.

TREATMENT OPTIONS

Health-Improving Lifestyle Changes

The very first treatment that every man who is faced with the problem of erectile dysfunction can afford without the need to consult a specialist is the normalization of his lifestyle. This method has no side effects, it is suitable for absolutely all men, in particular, those who have no

complaints about the level of their potency. This is the safest and most long-term approach to the situation, and although it directly affects the causes of ED, it is quite difficult to implement. In order for a healthy lifestyle to become a rule for a man, become a habit and have the necessary effect, a high level of self-discipline is required. The patient needs to become familiar with what factors present in his life can contribute to the onset of erectile dysfunction. Despite the fact that some risks cannot be eliminated or they can get out of the patient's control, the very fact of being aware of them increases the man's level of concern for his intimate health. The first group of factors that have a negative effect on potency includes decreased physical activity, overweight, unhealthy diet, alcohol, drugs, and smoking.^{[13] [14]} With the proper level of self-discipline, these factors can be completely eliminated by the patient himself. As for the second group of factors, they include concomitant diseases such as diabetes mellitus, arterial hypertension, cardiovascular diseases, impaired lipid and lipoprotein metabolism, metabolic syndrome, hypogonadism, as well as various psychological and psychiatric disorders. Their elimination or control requires medical support, contacting specialists of the relevant profiles. It should be noted that the normalization of the lifestyle can prevent the progression of some of the listed conditions or even contribute to their complete regression, in particular, this applies to arterial hypertension. Thus, it is possible to prevent the development of erectile dysfunction.^[15]

Numerous studies have shown that men who lead a physically active lifestyle are significantly less likely to suffer from potency disorders, including erectile dysfunction, and that increased physical activity helps to improve existing erectile dysfunction.^[16] All things being equal, obesity increases the risk of ED by about 40%.^[17] Normalization of weight in absolutely all cases helps to improve the quality of sexual life. It is important that the normalization of the diet, the elimination of harmful products from it showed an improvement in the course of erectile dysfunction even without a significant decrease in body weight.

Smoking is one of the most detrimental factors that have an extremely negative effect on the course of erectile dysfunction.^[18] Long-term smoking in the history of a man's life significantly increases the risk of erectile dysfunction. The reason for this lies in the fact that smoking contributes to vascular sclerosis, in particular in the penis, where many thin capillaries are in a ball at rest. Smoking can cause them to stick together irreversibly and impair the blood supply to the penis.

It should be noted that, in addition to eliminating the immediate risk factors, the eroticization of some therapeutic practices, such as the application of ointment to the penis or the use of vacuum devices, can contribute to the management of erectile dysfunction. Erotization of erectile aid helps to improve the psychological

environment in couples and increase the effect of treatment.

Medicines for Oral Use

The onset of an erection begins with the activation of the nervous system, which promotes the release of nitric oxide (NO) in the tissues of cavernous bodies of the penis. NO stimulates the production of guanylate cyclase (GC), which causes the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). cGMP causes relaxation of smooth muscle cells contained in the walls of the arteries of the penis, which promotes the dilation of these vessels and induces blood flow to the penis. The increased blood supply is the direct cause of an erection. After some time (normally – after ejaculation), the molecule of enzyme phosphodiesterase type 5 (PDE-5) breaks down cGMP, which allows the penis to return to a sluggish state. It is the effect on the production of phosphodiesterase type 5 (PDE5) that is the mechanism of action of all the most common oral drugs used in modern medicine for the treatment of ED.^[19]

If lifestyle changes do not have a significant positive effect on the course of erectile dysfunction, oral drugs from the group of PDE-5 inhibitors are the first-line drugs. They suppress the production of PDE-5 in cavernous bodies of the penis, which allows to maintain a higher level of cGMP and contributes to the onset of stronger and longer erections. The earliest registered and most widely used PDE5 inhibitor is sildenafil citrate, registered under the Viagra® trademark, patented by Pfizer Inc. Viagra^[20] was registered by the FDA in 1998. More recently registered PDE-5 inhibitors include tadalafil (trademark Cialis®, patent holder Eli Lilly, registered by FDA in 2003), vardenafil (trademark Levitra®, patent holder Bayer Healthcare, registered by FDA in 2003), and avanafil (trademark Stendra®, patent holder Metuchen Pharmaceutical, registered by FDA in 2012).

Sildenafil and vardenafil are the most similar in action. They are absorbed into the bloodstream and begin to act in 30-60 minutes, while the half-life from the body is 3 to 5 hours. The absorption rate increases when the medication is taken on an empty stomach.^[21] Avanafil is absorbed into the bloodstream faster, in 15-30 minutes, the half-life from the body is about 6 hours.^[22] The main difference between tadalafil and other PDE-5 inhibitors is that this substance is absorbed into the blood more slowly (about two hours), and its half-life is much longer, about 18 hours. In addition, the amount of food intake does not affect the absorption of tadalafil into the blood. Of all the PDE5 inhibitors, tadalafil is the only drug officially approved for use on a daily basis.^[23] In addition to treating erectile dysfunction itself, tadalafil is used in the treatment of benign prostatic hyperplasia (BPH) and the relief of lower urinary tract symptoms.^[24] Despite the proven high efficiency of drugs from the group of PDE-5 inhibitors in most cases of erectile

dysfunction, with damage to the nervous system or lack of sexual stimulation, they are ineffective, since it is impossible to stimulate the increase of the NO and cGMP. Consequently, PDE-5 inhibitors may be ineffective for erectile nerve damage, which usually occurs in peripheral neuropathy caused by diabetes mellitus, as well as in patients undergoing radical prostatectomy for prostate cancer.^[25] Also, oral PDE-5 inhibitors may be contraindicated in patients due to incompatibility with other drugs.

Although sildenafil and tadalafil have similar activity, efficacy and side-effect profiles, studies show that from a psychological point of view, patients are more satisfied with tadalafil. In addition, for men who find it difficult to match the timing of PDE-5 inhibitor use to sexual intercourse, or for men who experience unpleasant side effects from high doses of PDE-5 inhibitors, daily low doses of tadalafil may be an appropriate option.^[26] Since 2016, generics of sildenafil have been available to patients, since 2018 – generics of tadalafil.

Injections into the Cavernous Bodies of the Penis

Intracavernous injections, that is, injections of drugs into the cavernous bodies of the penis, are a treatment option used when oral PD-5 inhibitors are ineffective or contraindicated to the patient. Also, their use is advisable in cases where erectile dysfunction occurs against the background of any spinal cord injuries, since in such cases, treatment with oral PDE-5 inhibitors has no effect due to disruption of the nerve connections between the spinal cord and the penis.^[27] They are more effective than oral medications because they act directly on the molecules that regulate the onset of erection, bypassing damaged nerves. The essence of intracavernous administration of drugs is to make an injection directly into the body of the penis (at the lateral base). Typically, prostaglandin E1 (PGE1) is used for treatment, which stimulates the production of cyclic adenosine monophosphate (cAMP), promoting relaxation of smooth muscles in the vascular walls and thus facilitating the onset of an erection. Under the trade marks Edex® and Caverject®, PGE1 was approved by FDA for monotherapy of erectile dysfunction by intracavernous injections. However, apart from monotherapy, PGE1 is used in combination with other drugs such as papaverine and/or phentolamine to enhance the effect. Some patients prefer a combination of any of the other drugs, and some use a cocktail of all three substances.^[28] All three of these drugs are mutually combinable.

The main problem associated with the treatment of erectile dysfunction by intracavernous injections is the possibility of trauma to the penis due to inept drug administration and significant psychological discomfort associated with the need to perform an injection into the penis.^[29] Most men are afraid to carry out such manipulations with their genitals. In this regard, it is of particular importance to conduct a diagnostic (test)

intracavernous injection in the office of a doctor prescribing this treatment option. This is necessary, firstly, in order to determine which dose of drugs is most optimal for a particular patient; secondly, in order to make sure that the patient tolerates such an intervention well, he does not develop systemic side effects, priapism and other unacceptable conditions; thirdly, to familiarize the man with the technique of intracavernous injection for its subsequent independent implementation.^{[30] [31]} It has been reported that men who are familiar with the correct technique of intracavernous injection and overcome their fear of this medical procedure show a higher level of satisfaction with the result of therapy compared with the use of oral PDE5 inhibitors.^[32] General contraindications for therapy with any drugs administered intracavernously are blood clotting disorders, Peyronie's disease and previous episodes of priapism.^[33]

Intraurethral suppositories

A fairly new method that has been successfully used to treat erectile dysfunction that is poorly responsive to oral PDE-5 inhibitors is the use of intraurethral suppositories.^[34] Alprostadil, a synthetic analogue of the natural prostaglandin E1, is used for this type of application. This substance is also used for intracavernous injections, but in recent years more and more men prefer suppositories, despite their relatively lower effectiveness. Sometimes this type of therapy is resorted to by men in whom oral PDE-5 inhibitors turned out to be ineffective, but who fear intracavernous injections. Sometimes this type of therapy is resorted to by men who have not been helped by oral PDE-5 inhibitors, but who fear intracavernous injections. As with intracavernous injections, the American Urological Association recommends that the first dose be administered intraurethrally in the clinic after a decision on this treatment option has been made. With the independent use of suppositories, most often men experience discomfort in the penis, pain in the urethra. It should be noted that when using intraurethral suppositories as a therapy for erectile dysfunction, it is recommended to exclude sex without barrier protection so that the prostaglandin contained in the suppositories does not have a negative effect on the woman's body, especially if a woman is pregnant [35]. The list of contraindications for the use of suppositories for administration into the urethra roughly coincides with those for intracavernous injections.

Vacuum Devices for Normalizing Erection

Most vacuum erectile devices (VEDs) are various penile pump varieties commonly known as a line item in sex shops. Nevertheless, not all devices, which are similar in design to a vacuum pump, are suitable not only for a variety of sexual life and exacerbation of sensations, but for the full treatment of erectile dysfunction. A medically suitable pump is placed on the penis, then a vacuum is created (in most models with a special piston), which causes blood to flow to the penis and promotes the onset

of an erection. Thus, this method is purely mechanical and does not involve any chemically active substances. For severe erectile dysfunction, after the pump is applied, an elastic band or ring is put on the base of the penis to prevent blood flow and help maintain an erection. After removing it, the penis returns to a flaccid state. The mechanical effect provided by vacuum devices leads to an erection in more than 90% of cases of erectile dysfunction, even when other treatments are ineffective. However, a significant number of men complain about the inconvenience of these devices to use and changes in the sensation and sensitivity of the penis, especially when using the retaining ring.^[36]

Caution should be exercised when using vacuum erectile devices in men with bleeding disorders. The most common side effect is bruising on the penis.

Penile Prosthesis

The use of penile prostheses is a surgical invasive treatment that has been used in the treatment of erectile dysfunction since the 1970s. The prosthesis is implanted into the penis, but the device and the technical aspects of the implantation have undergone various changes over the years to optimize the function of the prosthesis, minimize the need for repair and maximize patient satisfaction with this treatment. To date, patients using implanted penile prostheses report the highest levels of sexual satisfaction compared to those taking oral medications or intracavernous injections.^[37]

Modern models of prostheses are divided into inflatable (providing the most physiological erection) and malleable. Malleable devices are semi-rigid structures that are implanted into the cavernous bodies of the penis. They are manually controlled by bending them until the penis reaches the desired position for intercourse. Inflatable prostheses, meanwhile, consists of a fluid-filled cylinders implanted in the penis, a pump hidden in the scrotum, and typically a fluid reservoir implanted into the abdominal cavity. To achieve an erection, the man squeezes the pump in the scrotum, which draws fluid from the reservoir to inflate the cylinders of the penis. Pressing a button on the pump allows fluid to escape from the cylinders and return to the reservoir, causing the penis to return to a flaccid state.^[38] In most cases, apart from serious pelvic injuries, penile prosthetics are not considered first-line therapy for ED. Comprehensive preoperative patient counseling is essential for the successful use of penile prostheses.

The Latest Trends in ED Treatment

Since the existing conventional treatments for ED are not suitable for all patients, research continues to find new, more effective and versatile ways to combat ED. At the moment, they all still have the status of experimental and cannot be applied on a general basis, that is, they can only be used in clinical trials.^[39]

Penile Shockwave Therapy of ED

Low-intensity extracorporeal shockwave therapy (LI-ESWT) studies have been conducted in the treatment of erectile dysfunction since 2010.^[40] This method of treatment is based on improving the functioning of the blood vessels in the penis and promoting the growth of new ones. Thus, shockwave therapy is offered mainly to combat erectile dysfunction of vascular etiology. The first studies showed that LI-ESWT leads to a significant normalization of blood flow in the penis, and the effect is not only temporary, but also persists for at least 6 months after the course of treatment. Some researchers note that after using the LI-ESWT method, patients increase their sensitivity to oral PDE-5 inhibitors. Today, the main goal of scientists studying the effect of low-intensity extracorporeal shockwave therapy on erectile dysfunction is to collect evidence to track the long-term effectiveness of this method and potential side effects.^[41]

Stem Cells Injections

One of the newest methods being considered for the treatment of erectile dysfunction is the use of intracavernous stem cell injections. According to preliminary animal studies, stem cell injections can stimulate the regeneration of the cavernous nerve, which opens up the potential for the use of stem cell therapy for erectile dysfunction in patients with diabetic neuropathy.^[42] Human clinical trials are still in the first phase, but have already shown that stem cell transplantation is well tolerated and shows high levels of efficacy and safety.^[43]

Platelet-Rich Plasma

Platelet-rich plasma (PRP) is able to promote the growth of new blood vessels. This property allows the use of PRP intracavernously in cases of neurogenic erectile dysfunction.^[44] To date, studies have been conducted on only four patients with erectile dysfunction, and there is a need for significant scaling.

External Penile Prosthesis

In cases of ineffectiveness of drug treatment for erectile dysfunction and fear of invasive surgery, erection aids such as external penile prostheses may be used. Their assortment resembles some of the products available in sex shops, such as extensions for the glans penis, devices for keeping the penis in an erect position, a belted phallus prosthesis. They may have additional functions for increasing sexual stimulation, such as vibration. The efficacy and methods of using external prosthetic devices require further research.^[45]

External Use of Ointments

One of the newer treatments for erectile dysfunction is to apply vasodilating or testosterone ointments to the penis. The greatest promise is the use of alprostadil-containing ointments.^[46] The main problem in this case is local allergic reactions.

CONCLUSION

Although classic treatments for erectile dysfunction, which include lifestyle changes, oral medications, intracavernous injections, and implantable penile prostheses, have proven to be effective in treating ED, work to find promising new ways to combat ED remains relevant and ongoing. Alternative methods of treatment have not yet received due recognition in the scientific community due to insufficient research. There is a need for more research to better assess the potential of these treatments.

REFERENCES

1. Male erectile dysfunction and health-related quality of life. Sánchez-Cruz JJ, Cabrera-León A, Martín-Morales A, Fernández A, Burgos R, Rejas J *Eur Urol*, Aug, 2003; 44(2): 245-53.
2. Erectile dysfunction: Current diagnostics and treatment. Leiber C. *Urologe A*, Apr, 2017; 56(4): 519-529. doi: 10.1007/s00120-017-0355-y.
3. Aldemir E., Akyel B., Keskin Gokcelli D., Celikay H., Altintoprak A. E., Coskunol H. A controlled study of sexual function in men with cannabis use disorder: A brief report. *Journal of Substance Use*, 2017; 22(5): 490–493.
4. McCabe MP, Sharlip ID, Lewis R, et al.: Risk Factors for Sexual Dysfunction Among Women and Men: A Consensus Statement From the Fourth International Consultation on Sexual Medicine, 2015. *J Sex Med.*, 2016; 13(2): 153–67. 10.1016/j.jsxm.2015.12.015
5. Melnik T, Soares BG, Nasello AG: Psychosocial interventions for erectile dysfunction. *Cochrane Database Syst Rev.*, 2007; 128(3): CD004825. 10.1002/14651858.CD004825.pub2
6. Psychotherapy for erectile dysfunction: now more relevant than ever. Althof SE, Wieder M. *Endocrine*, Mar-Apr, 2004; 23(2-3): 131-4. doi: 10.1385/ENDO:23:2-3:131.
7. Psychological treatment of erectile dysfunction in men without partners: outcome results and a new direction. B Reynolds PMID: 1920469 DOI: 10.1080/00926239108404955
8. Kukula KC, Jackowich RA, Wassersug RJ: Eroticization as a factor influencing erectile dysfunction treatment effectiveness. *Int J Impot Res.*, 2014; 26(1): 1–6. 10.1038/ijir.2013.29
9. Burnett AL, Nehra A, Breau RH, et al.: Erectile Dysfunction: AUA Guideline. *J Urol.*, 2018; 200(3): 633–41. 10.1016/j.juro.2018.05.004
10. Recent advances in the understanding and management of erectile dysfunction. Krzastek SC, Bopp J, Smith RP, Kovac JR. PMID: 30740217 PMID: PMC6348436 DOI: 10.12688/f1000research.16576.1
11. Low-Intensity Shockwave Therapy Improves Hemodynamic Parameters in Patients With Vasculogenic Erectile Dysfunction: A Triplex Ultrasonography-Based Sham-Controlled Trial. Kalyvianakis D, Hatzichristou D. *J Sex Med.*, Jul,

- 2017; 14(7): 891-897. doi: 10.1016/j.jsxm.2017.05.012.
12. Can we cure erectile dysfunction? Hatzimouratidis K. *Eur Urol*, Aug, 2010; 58(2): 249-50. doi: 10.1016/j.eururo.2010.04.030. Epub 2010 May 8.
 13. Lifestyle modifications and erectile dysfunction: what can be expected? Maiorino MI, Bellastella G, Esposito K. *Asian J Androl*, Jan-Feb, 2015; 17(1): 5-10.
 14. Effects of cigarette smoking on erectile dysfunction. Kovac JR, Labbate C, Ramasamy R, Tang D, Lipshultz LI. *Andrologia*, Dec, 2015; 47(10): 1087-92. doi: 10.1111/and.12393. Epub 2014 Dec 29.
 15. Vasculogenic Erectile Dysfunction: The Impact of Diet and Lifestyle. Ostfeld RJ, Allen KE, Aspry K, Brandt EJ, Spitz A, Liberman J, Belardo D, O'Keefe JH, Aggarwal M, Miller M, Batiste C, Kopecky S, White B, Shah N, Hawamdeh H, Batts T, Blankstein R, Reddy K, Ornish D, Freeman AM. *Am J Med.*, Nov 20, 2020. S0002-9343(20)30918-9. doi: 10.1016/j.amjmed.2020.09.033.
 16. Physical activity and erectile dysfunction: meta-analysis of population-based studies. Cheng JY, Ng EM, Ko JS, Chen RY *Int J Impot Res.*, May-Jun, 2007; 19(3): 245-52.
 17. Metabolically healthy and unhealthy obesity in erectile dysfunction and male infertility. Rastrelli G, Lotti F, Reisman Y, Sforza A, Maggi M, Corona G. *Expert Rev Endocrinol Metab*, Sep, 2019; 14(5): 321-334. doi: 10.1080/17446651.2019.1657827.
 18. Epidemiology and risk factors of lower urinary tract symptoms/benign prostatic hyperplasia and erectile dysfunction. Calogero AE, Burgio G, Condorelli RA, Cannarella R, La Vignera S. *Aging Male.*, Mar, 2019; 22(1): 12-19. doi: 10.1080/13685538.2018.1434772.
 19. Mechanisms of action of PDE5 inhibition in erectile dysfunction. Corbin JD. *Int J Impot Res.*, Jun, 2004; 16(1): S4-7. doi: 10.1038/sj.ijir.3901205.
 20. How does sildenafil affect the male body. Abraham Lincoln Woods. <https://redcross-cmd.org/generic-viagra.html>
 21. Spotlight on vardenafil in erectile dysfunction. Keating GM, Scott LJ. *Drugs Aging*, 2004; 21(2): 135-40. doi: 10.2165/00002512-200421020-00005. PMID: 14960129
 22. Avanafil for erectile dysfunction. Kyle JA, Brown DA, Hill JK. *Ann Pharmacother*, Oct, 2013; 47(10): 1312-20. doi: 10.1177/1060028013501989. Epub 2013 Sep 27. PMID: 24259695
 23. Meta-Analysis of the Long-Term Efficacy and Tolerance of Tadalafil Daily Compared With Tadalafil On-Demand in Treating Men With Erectile Dysfunction. Zhou Z, Chen H, Wu J, Wang J, Zhang X, Ma J, Cui Y. *Sex Med.*, Sep, 2019; 7(3): 282-291. doi: 10.1016/j.esxm.2019.06.006. Epub 2019 Jul 12. PMID: 31307951
 24. Tadalafil for the treatment of benign prostatic hyperplasia. Mónica FZ, De Nucci G. *Expert Opin Pharmacother*, Jun, 2019; 20(8): 929-937. doi: 10.1080/14656566.2019.1589452. Epub 2019 Mar 22. PMID: 30901259
 25. Efficacy and safety of phosphodiesterase type 5 (PDE5) inhibitors in treating erectile dysfunction after bilateral nerve-sparing radical prostatectomy. Cui Y, Liu X, Shi L, Gao Z. *Andrologia*, Feb, 2016; 48(1): 20-8. doi: 10.1111/and.12405. Epub 2015 Feb 15. PMID: 25684196
 26. Efficacy and safety of tadalafil once daily: considerations for the practical application of a daily dosing option. Donatucci CF, Wong DG, Giuliano F, Glina S, Dowsett SA, Watts S, Sorsaburu S. *Curr Med Res Opin*, Dec, 2008; 24(12): 3383-92. doi: 10.1185/03007990802498440. PMID: 1903212.
 27. Intracavernous Injections in Spinal Cord Injured Men With Erectile Dysfunction, a Systematic Review and Meta-Analysis. Chochina L, Naudet F, Chéhense C, Manunta A, Damphousse M, Bonan I, Giuliano F. *Sex Med Rev.*, Jul, 2016; 4(3): 257-269. doi: 10.1016/j.sxm.2016.02.005.
 28. Diagnosis and therapy of erectile dysfunction using papaverine and phentolamine. Zentgraf M, Baccouche M, Jünemann KP. *Urol Int*, 1988; 43(2): 65-75. doi: 10.1159/000281308. PMID: 3291360.
 29. Nelson CJ, Hsiao W, Balk E, et al. : Injection anxiety and pain in men using intracavernosal injection therapy after radical pelvic surgery. *J Sex Med.*, 2013; 10(10): 2559-65. doi: 10.1111/jsm.12271
 30. Acceptability of auto-injection of vasoactive drugs in the treatment of erectile dysfunction]. Ribé Subirà N, Vives A, Jurado C, Rajmil O, Pomerol JM. *Arch Esp Urol.*, Nov, 1999; 52(9): 973-7. PMID: 10633965.
 31. The effects of stress and coping upon the diagnostic intracavernous injection in men with erectile dysfunction. van der Borgh W, Vanderschueren D, Demyttenaere K. *J Psychosom Res.*, Oct, 1995; 39(7): 865-73. doi: 10.1016/0022-3999(95)00027-4. PMID: 8636918.
 32. 26. Belew D, Klaassen Z, Lewis RW: Intracavernosal Injection for the Diagnosis, Evaluation, and Treatment of Erectile Dysfunction: A Review. *Sex Med Rev.*, 2015; 3(1): 11-23. doi: 10.1002/smrj.35.
 33. Intracavernous prostaglandin E1 in erectile dysfunction. Linet OI, Neff LL. *Clin Investig*, Jan, 1994; 72(2): 139-49. doi: 10.1007/BF00184593. PMID: 8186662.
 34. Review of intraurethral suppositories and iontophoresis therapy for erectile dysfunction. Lewis R. *Int J Impot Res.*, Oct, 2000; 12(4): S86-90. doi: 10.1038/sj.ijir.3900584. PMID: 11035393.
 35. Costa P, Potempa AJ: Intraurethral alprostadil for erectile dysfunction: a review of the literature. *Drugs*, 2012; 72(17): 2243-54. doi: 10.2165/11641380-000000000-00000.
 36. Satisfaction with a Vacuum Constriction Device for Erectile Dysfunction among Middle-Aged and Older Veterans. Beaudreau SA, Van Moorlehem K, Dodd SM, Liou-Johnson V, Suresh M, Gould CE. *Clin*

- Gerontol, Oct 4, 2020: 1-9. doi: 10.1080/07317115.2020.1823922.
37. Bernal RM, Henry GD: Contemporary patient satisfaction rates for three-piece inflatable penile prostheses. *Adv Urol.* 2012;2012:707321. 10.1155/2012/707321.
 38. [Surgical treatment of erectile dysfunction]. Pottek TS. *Urologe A.*, May, 2015; 54(5): 676-83. doi: 10.1007/s00120-015-3795-2. PMID: 25987333
 39. SMSNA - SMSNA Position Statement on Restorative Therapies for ED. (accessed 14 November 2018).
 40. Low-Intensity Shockwave Therapy for Erectile Dysfunction. Rizk PJ, Krieger JR, Kohn TP, Pastuszak AW. *Sex Med Rev.*, Oct, 2018; 6(4): 624-630. doi: 10.1016/j.sxmr.2018.01.002. Epub 2018 Mar 22. PMID: 29576441
 41. Controversies in low intensity extracorporeal shockwave therapy for erectile dysfunction. Yang H, Seftel AD. *Int J Impot Res.*, May, 2019; 31(3): 239-242. doi: 10.1038/s41443-019-0124-0. Epub 2019 Feb 11. PMID: 30742044.
 42. Qiu X, Villalta J, Ferretti L, et al.: Effects of intravenous injection of adipose-derived stem cells in a rat model of radiation therapy-induced erectile dysfunction. *J Sex Med.*, 2012; 9(7): 1834-41. 10.1111/j.1743-6109.2012.02753.x
 43. Zhu GQ, Jeon SH, Bae WJ, et al. : Efficient Promotion of Autophagy and Angiogenesis Using Mesenchymal Stem Cell Therapy Enhanced by the Low-Energy Shock Waves in the Treatment of Erectile Dysfunction. *Stem Cells Int.*, 2018; 2018: 1302672. 10.1155/2018/1302672
 44. Wu YN, Wu CC, Sheu MT, et al.: Optimization of platelet-rich plasma and its effects on the recovery of erectile function after bilateral cavernous nerve injury in a rat model. *J Tissue Eng Regen Med.*, 2016; 10(10): E294-E304. 10.1002/term.1806
 45. Tatem A, Kovac JR: External penile prosthesis as a novel approach to the treatment of erectile dysfunction. *Transl Androl Urol.*, 2017; 6(5): S795-S796. 10.21037/tau.2017.11.01
 46. Retention and migration of alprostadil cream applied topically to the glans meatus for erectile dysfunction. Yeager J, Beihn RM. *Int J Impot Res.*, Jan-Feb, 2005; 17(1): 91-5. doi: 10.1038/sj.ijir.3901285. PMID: 15538395