4 Erectile Dysfunction: Medical Therapy and Rehabilitation

Alessandro Palmieri, Marco Capece, Angelo di Giovanni, and Carlo D'Alterio

4.1 Introduction

Medical treatment for erectile dysfunction (ED) has dramatically evolved in the last decades. However, to set realistic expectations with the patient, a correct counselling is fundamental. Every kind of medical treatment must be discussed with the patient regarding risk factors, prognostic factors, treatment alternatives, correct drug use, and adverse reactions [1].

The advent of oral phosphodiesterase 5 inhibitors (PDE-5Is) has been a revolutionary change in the management of ED, since those drugs have high efficacy, ease of use, good tolerability, and low to moderate adverse reactions. Oral PDE-5Is were considered a first-line treatment choices, whereas at the present time, other medical and physical therapies may be used in the first instance for selected patients. Those include vacuum devices, intraurethral agents, intracavernosal injection therapy, extracorporeal shock wave therapy, and hormonal treatment.

4.1.1 Oral Pharmacotherapy: PDE-5Is

Phosphodiesterase 5 inhibitor (PDE-5I) drugs are the most common drugs for the management of erectile dysfunction.

The four molecules synthesized and approved by the European Medicines Agency (EMA) are as follows:

- Sildenafil citrate, the first drug approved for the management of erectile dysfunction in 1998 by the FDA
- Vardenafil approved in 2003
- Tadalafil also approved by the FDA in 2003
- Avanafil approved in 2012

However, they are not initiators of erection and an adequate sexual stimulation is required [2].

PDE5-Is are actually effective in about 65% of patients; the effectiveness of this type of drug is defined as the patient's ability to undertake sufficient sexual intercourse [3].

The choice of the molecule must be personalized; adequate counselling is essential in order to investigate patients' comorbidities, the frequency of intercourses, and expectations [4].

A. Palmieri (✉) · M. Capece · A. di Giovanni
C. D'Alterio
Department of Neurosciences, Reproductive Sciences and Odontostomatology, University of Naples Federico II, Naples, Italy
e-mail: info@alessandropalmieri.it

C. Bettocchi et al. (eds.), *Practical Clinical Andrology*,
https://doi.org/10.1007/978-3-031-11701-5_4

4.1.1.1 Pharmacokinetic and Pharmacodynamic Features

The endothelial cells of the corpora cavernosa release nitric oxide (NO), which activates guanylate cyclase, further enhancing the synthesis of cyclic guanosine monophosphate (cGMP).

cGMP is an intracellular second messenger molecule that causes relaxation and vasodilatory effect in smooth muscle cells. It is degraded and inactivated by the enzyme phosphodiesterases. At least 11 different subtypes are currently known.

In the human corpus cavernosum, there are a greater percentage of PDE-2, PDE-3, PDE-4, and PDE-5. The latter phosphodiesterase is the most widely expressed form within the corpus cavernosum. The drugs used for erectile dysfunction are competitive inhibitors of PDE-5; therefore, they enhance the releasing effect of nitric oxide. Inhibiting the activity of the enzyme responsible for the degradation of GMPc, they allow an accumulation of the cyclic nucleotide in response to nitrergic stimulation. The end result is calcium sequestration from the cytoplasm to the endoplasmic reticulum with arteriolar and trabecular smooth muscle relaxation and venous vasoconstriction [5].

Sildenafil

Sildenafil was the first erectile dysfunction drug that hits the world market in 1998 [6]. His discovery was accidental; in fact, originally, the drug was to be used for the treatment of hypertension and angina pectoris. The drug did not prove effective for this purpose, but patients reported unexpected penile erections [7].

Sildenafil takes effect 30–60 min after its administration with a half-life of 4–8 h [8]. Its action can last up to 12 h after the drug intake. Its effectiveness is reduced after a large meal or with the ingestion of fatty foods [9].

The dosages available on the market are 25 mg, 50 mg, 75 mg, and 100 mg.

A placebo-controlled study evaluated the improvement of erection in 465 patients using different dosages of sildenafil. After 24 weeks of treatment in the dose-response study, improved erections are reported in 56%, 77%, and 84% of the men taking 25, 50, and 100 mg of sildenafil, respectively [10].

The most common side effects are headache (16%), flushing (10%), and dyspepsia (7%). Other side effects include nasal congestion, diarrhoea, and changes in vision [7].

Vardenafil

Vardenafil was introduced in 2003. It is effective 30 min after the intake. Most patients report satisfactory erections within 15 min [11].

It is available in the market in doses of 5 mg, 10 mg, and 20 mg. The starting dose is 10 mg, and it can be modified according to the patient's response [12]. A 10 mg orodispersible dose was also recently introduced to the market.

The absorption of vardenafil is reduced after a fatty meal [9].

The most frequent side effects include facial flushing and nasal congestion (9–11%) [13].

After 12 weeks of treatment with vardenafil, a placebo control study showed a statistically significant improvement in erections in 66%, 76%, and 80% of patients taking 5 mg, 10 mg, and 20 mg formulation, respectively [14].

Tadalafil

Tadalafil was approved in the United States in November 2003 [15]. It has particular pharmacokinetic properties. Absorption does not appear to be influenced by the intake of fatty meals or alcohol [16]. The peak of the serum concentration is reached about 2 h after the ingestion differently from sildenafil, vardenafil, and avanafil that require 1 h. In addition, the half-life of the molecule (t½) is around 17.5 h [17, 18]. Therefore, a chronic administration of tadalafil enhances erectile function up to 36 h and may restore a more physiological sexual intercourse [19, 20]. However, tadalafil's prolonged half-life has higher risk of long-lasting adverse effects than other PDE5-Is. Indeed up to 30% of men taking tadalafil report side effects lasting longer than 1–2 h [21].

Avanafil

Avanafil is the latest d approved. It was launched on the market in 2013 [22]. The available formulations are 50 mg, 100 mg, and 200 mg, and the recommended starting dose is 100 mg [17].

Avanafil is rapidly absorbed and quickly eliminated after an oral administration.

Avanafil has the highest selectivity for phosphodiesterase 5 among PDE5-Is, thus side effects are minimized. Adverse effects are generally consistent with the known pharmacology of PDE5-Is, and the most commonly reported adverse events are headaches, flushing, backpain, nausea, muscle cramps, and fatigue. Besides most of this events are mild and self-resolving [18].

The active ingredient is effective 15 min after the intake. The absorption of avanafil is reduced from fatty meals, and its duration is approximately 6 h [23].

Hellstrom et al. showed successful attempts within 15 min in 64%, 67%, and 71% after avanafil dosages of 50 mg, 100 mg, and 200 mg, respectively [23].

Patients suffering from chronic renal failure or hepatic insufficiency do not require a dosage modification [24].

4.1.1.2 The Right Molecule for the Right Patient

The choice of the best PDE-5Is is not supported by any double or triple blind study that compares the effectiveness of the different drugs.

This choice depends on the patient's characteristics such as frequency of intercourse (occasional or regular use with 3 weekly or more intercourse), treatment expectations tolerability, and side effects.

In a recent meta-analysis, *Chen* et al demonstrated that patients affected by ED seeking for an immediate efficacy should start with Sildenafil 50 mg while the others could benefit of Tadalafil 10 mg that has higher tolerability [25].

4.1.1.3 Pharmacological Interactions

The association of NO-donor drugs and PDE-5Is can lead to a cGMP accumulation. Such condition can result in hypotension and cardiogenic shock. Therefore, the intake of nitrates is an absolute contraindication for PDE-5I administration [26].

Considering the pharmacokinetic characteristic, patients treated with PDE5-Is experiencing chest pain must delay any nitro-glycerine intake up to 12, 24, and 48 h for avanafil, sildenafil/vardenafil, and tadalafil, respectively [21].

4.1.1.4 Cardiovascular Safety

The use of PDE-5I has not shown negative side effects on the cardiovascular system; in fact, there is no increase in the rate of myocardial infarction in patients assuming those drugs.

Chronic or on-demand use is well tolerated with a similar safety profile for the various molecules [27, 28].

All molecules that inhibit phosphodiesterase 5 are contraindicated in the following situations:

- Patients with resting hypotension (blood pressure <90/50 mmHg)
- Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmias over the past 6 months
- Patients with hypertension (blood pressure >170/100 mmHg)
- Patients with angina during sexual intercourse
- Patients with unstable angina
- Patients with congestive heart failure

4.1.1.5 Non-responders

Some patients do not respond adequately to oral PDE-5Is; this mainly happens for two reasons:

1. Incorrect use of the drug
2. Lack of actual efficacy of the prescribed molecule

Regarding the incorrect use, patients must be informed about the correct intake procedure.

McCullough suggests carrying out the PDE-5Is treatment for at least 6/8 weeks before establishing its ineffectiveness [29]. The most frequent causes of incorrect use are as follows:

1. Failure to use an adequate dosage.
2. Lack of or inadequate sexual stimulation.

3. Search for intercourse ignoring the right timing of the drug. In fact, there is a period of time between the intake and the pharmacological action in which the drug will be ineffective. Moreover, some patients require a longer time for the drug to start acting [30, 31].

Furthermore, the absorption of the drug can be delayed by the intake of fatty foods or a large meal.

The clinician is always required to verify that the patient has taken an official drug. Unfortunately, a black market has increased over the last decades; thus, the efficacy and safety of unauthorized and uncontrolled tablets cannot be guaranteed.

In addition to that, *Marchal Escalona* et al. recently reported that a polyformism of the PDE5A gene encoding the PDE-5 enzyme may affect the efficacy of the drugs. Thus, there may be variability in the clinical response of the clinical response in subjects using PDE5i [32].

4.1.1.6 On-Demand Vs Daily Treatment

Recently, there has been a great interest in daily PDE5I administration as a new and innovative approach to manage erectile dysfunction. The advantage of daily intake for the management of erectile dysfunction is the complete separation of drug use from sexual activity, eliminating the unpleasant effect indicated by patients as "I feel drugs control my sex life" or "I wish they would. my erections came more spontaneously" [33]. The main goal of ED therapy is to achieve an improvement in erectile function; however, this improvement is not the only factor for sexual satisfaction. In fact, self-confidence and spontaneity of erection may play an important role in increasing the general satisfaction of patients [34]. In this regard, a study observed that patients who started ED treatment with tadalafil once a day (OaD) reported greater improvement in self-esteem and sexual spontaneity than patients who started treatment with sildenafil on-demand. On the other hand, there were no significant differences between the two regarding the improvement of IIEF-EF, of orgasmic function, of the domains of general satisfaction, and of the EDITS score [35].

Regarding tolerability, it is important to emphasize that chronic administration of tadalafil does not appear to result in up-regulation of PDE5 in human penile tissue, an effect which has been observed in rat penile tissue continuously exposed to high doses of sildenafil [36, 37]. This means that the phenomenon of tachyphylaxis occurs against sildenafil and over time, the drug loses its effectiveness since more PDE5 enzymes are produced and the concentration of the drug is no longer sufficient to ensure its inhibition. On the other hand, tadalafil does not seem to show a loss of its efficacy over time due to tachyphylaxis. An additional benefit of tadalafil OaD is that overall drug exposure can be reduced in men who engage sexual intercourse more than twice a week, and side effects can be minimized in men who have difficulty tolerating higher doses of PDE5I [33, 38].

The SURE multicenter study was one of the first trials to investigate the usefulness of chronic tadalafil dosing: 4262 men with ED were treated with 20 mg of tadalafil three times per week or 20 mg on-demand in a 12-day cross-over project [39]. The results of this study showed that over 60% of men in both arms of the study reported normalization of erectile function. Over 70% of men in both groups reported being able to successfully penetrate and complete intercourse. There were no differences in the success rate between routine and on-demand dosing for any efficacy parameter. There was a substantial difference in the timing of intercourse between the treatment arms: within 4 h of taking the drug, 53% of the on-demand arm attempted intercourse while only 29% of the OaD arm attempted intercourse within this time limit. This suggests a greater flexibility in the OaD group. Although efficacy data showed no differences, the three times weekly dosing regimen for tadalafil was preferred by only 43% of enrolled patients; therefore, on-demand therapy was preferred by most men. Anyway, in the SURE study, it is evident that routine dosing may be a good option too.

The impact of daily tadalafil dosage on female partner satisfaction with sexual activity has also

been a topic of recent interest and research. A partner preference study on sildenafil on-demand versus tadalafil OaD indicated that 79% of female partners preferred tadalafil OaD, citing a more relaxed approach to sexual intimacy and greater flexibility with respect to the timing of intercourse. Based on this, it can be inferred that such flexibility would be attractive to many patients' partners [40].

However, it has to be stated that in some studies, side effects were more common at higher doses of tadalafil, but this dose-response relationship was not confirmed in all studies. In general, the incidence of these side effects decreases over time with chronic therapy [38].

4.1.1.7 PDE5-I in Penile Rehabilitation

The advent of PDE-5I drugs has also introduced an innovation in the treatment of ED following radical prostatectomy (RP) and other major pelvic surgeries. It should be emphasized that ED is poorly responsive to PDE5Is in patients who underwent radical prostatectomy. However, these drugs are considered first-line therapy in patients who have undergone nerve sparing (NS) surgery regardless of the surgical technique used [41, 42]; their effectiveness has been demonstrated, and they have therefore entered the therapeutic protocols according to the European Association of Urology guidelines [43].

The use of sildenafil is controversial: although several studies have proven the efficacy of both high-dose on-demand and OaD administration, a 2016 randomized study denies any benefit of sildenafil OaD in restoring ED post-RP [44].

Vardenafil 10 mg and tadalafil 20 mg on-demand are both effective on improving the erectile function of patients who underwent NS prostatectomy [42–45]. Tadalafil 5 mg OaD showed the same effectiveness. In addition, if introduced as a therapy immediately after surgery, it helps the recovery of post-operative erectile function and the maintaining of penile length. In contrast, tadalafil on-demand has not showed these features [46]. However, the therapeutic effects are lost once the drug is discontinued, even after 9 months of treatment [47].

4.1.2 Vacuum Erection Devices

Vacuum device is a manual or electric pump used to obtain mechanical erection in a vacuum chamber. The dispositive consists in a plastic tube where the penis is allocated. When the patient starts the device, the chamber reaches vacuum and the penis is engorged with venous blood. A constriction ring can be placed at the base of the penis in order to keep the erection during a sexual intercourse. Differently from a physiological or pharmacologically induced erection, the portion of the penis next to the ring is not rigid. It may lead to a penile bend effect, moreover the penis skin can result cold and dusky. The ejaculation can be difficult due to the uncomfortable and painful ring positioning. As described by *Montague* et al., an extreme negative pressure can lead to penile injury. Thus patients with bleeding disorders or on anticoagulant therapy should avoid vacuum therapy [48].

In the literature, minor complications such as inability to ejaculate, bruising, petechiae, numbness, and pain are described. Skin necrosis as a major complication can usually be avoided by removing the ring within 30 min [49].

Vacuum device therapy has a satisfaction rates range between 27% and 94% despite the cause of ED [49, 50]. However, a percentage from 50% to 64% patients stop the treatment after 2 years [51].

Patients with infrequent sexual intercourse and comorbidities may benefit from the treatment described below, as it is drug-free and non-invasive [49, 50, 52].

4.1.3 Alprostadil

Prostaglandine E-1 and its synthetic formulation known as alprostadil is the only intracavernous and transurethral therapy, approved by FDA, to treat ED. The drug is absorbed by the urethra to the corpus spongiosum and then to the corpus cavernosum.

Alprostadil operates stimulating adenyl cyclase. The latter increases the cAMP level and

decreases the intracellular calcium involving the subsequent relaxation of arterial and trabecular smooth muscle [53].

4.1.3.1 Topical Route

The topical route (200 and 300 μg VITAROS) is less invasive than the other formulations. It is a cream with a permeation enhancer that facilitates the urethral absorption. Patients suffering from mild-to-severe erectile dysfunction can benefit from this treatment. Although the literature is not rich in data, significant improvement in IIEF-Erectile Function domain score are reported vs placebo [54]. Systemic side effects are infrequent while local effects such as penile erythema, penile burning, and pain are usually self-limiting within 2 h [55, 56].

4.1.3.2 Intraurethral Route

The intraurethral route (125–1000 μg MUSE, medicated urethral system for erection) consists of small semisolid pellets managed into the distal urethra using an adequate device.

If penile rigidity is not reached, a ring at the root of the penis can be useful to keep erection enhancing the veno-occlusive mechanism.

Patients reported a successful rate about 50% [57]. One-third of patients reported penile and/or scrotal pain or discomfort. About 10% of patient's partners using intraurethral alprostadil reported vaginal discomfort after ejaculation. Hypotension and syncope have also been described in 1–5.8%. Local pain is the most common side effect reported (29–41%), while hypotension occurs in about 1.9% and 14% of cases. Urethral bleeding and urinary tract infection (UTI) are reported in 5% and 0.2% of cases respectively and are strictly related to the mode of administration. Priapism is extremely rare, reported in less than 1% of cases [58–60].

4.1.3.3 Intracavernous Injection

Intracavernous injection (ICI) allows the chemical erection of the corpora cavernosa.

It is considered the most effective non-surgical treatment for PDE5-I non-responders (approximately 25% of patients [61]) or those that cannot tolerate side effects of oral agents [62, 63].

ICI treatment does not present systemic side effects (since no change in peripheral blood vessels are observed) or drug interactions. The onset is rapid and independent from sexual stimulations [61].

Alprostadil is the only drug approved by FDA for intracavernous injections with a success rate of 70–75% with a median dose of 12–15 mg [53]. Once injected in the corpora cavernosa the drug allows relaxation of smooth muscle fibres and the consequential vasodilatation that lead to the erectile mechanism. Alprostadil is metabolized within 60 min by the 15-hydroxy dehydrogenase, which is very active in human corpora cavernosa [53].

The most common side effects reported are pain or burning sensation usually at the injection site or during the erection (11–15%). Fibrosis and small hematomas are reported too. Priapism is considered the most severe side effect, but it is reported in only 1–3% of patients [64].

Fibrosis (1–3%) can lead to nodule, diffuse scarring, plaque, or curvature. A 5 min compression above the injection site could prevent scar tissue formation [65].

4.1.4 Extracorporeal Shockwave Therapy

4.1.4.1 Introduction

The shockwaves (SW) are acoustic waves that deliver energy when focused on an anatomical target. The focused SW simulate a microtrauma in the tissues that eventually stimulate the release of endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF) and proliferating nuclear cell antigen (PCNA) [66]. Thus neo-angiogenesis and subsequent improvement of bloodstream are facilitated [67, 68].

4.1.4.2 ESWT and Vascularization

The effect of SW has been under investigation for a long time. Both in vitro and in vivo studies are present in the literature investigating whether the shockwaves improve the vascularization. The cavitation and shear-stress are the main physical mechanisms involved. The cavitation is provoked by the compression of the positive

phase of the SW, followed by the rapid expansion of the tissue. As the cavitation is highly focused, the SW stress the cellular wall of the endotheliocytes [69, 70].

Several studies demonstrated the biochemical effects of the SW, such as the hyperpolarization of the cellular membrane and the activation of RAS and eNOS [71–73].

The rationale of applying the SW to treat the ED comes from several studies on animals: the hypothesis is to improve the endothelial function and angiogenesis in the corpora cavernosa.

4.1.4.3 ESWT and Stem Cells

The SW stimulate the recruitment of the circulating epithelial progenitor cells (EPC) through the expression of chemotactic factors (SDF-1, VEGF) [74]. Evidence suggests the role of the SW in the differentiation of mesenchymal stem cell in bone-forming cell in the bone tissue. This process might be mediated by TGF-beta and VEGF-A [75].

Nurzynska et al. [76] observed that SW promote the proliferation and differentiation of cardiomyocytes, smooth-muscle cells, and endotheliocytes.

4.1.4.4 ESWT and Erectile Dysfunction

Some studies on animal models of ED dysfunction induced by diabetes demonstrated that SW induce regeneration of nerves, endothelium, and smooth muscle [67, 77].

A recent metanalysis of seven randomized controlled trials on 602 men showed a significant improvement of the IIEF-Erectile Function domain score after SW therapy. The mean improvement of the score was 4.17. This improvement was clinically significant [78].

However, the patient must be selected to maximize the effect of SW: age, comorbidities, longtime ED, low IIEF-EF domain score, and poor response to PDE5-i might negatively affect the outcome of SW therapy [79, 80].

In 2015, an analysis of eight studies by *Feldman* et al. [81] on 604 patients showed that SW are safe and effective in both responders and non-responders to PDE-5I.

4.1.4.5 ESWT Protocol

For the treatment of ED, the delivery of 14,400 shockwaves in 4 weeks is suggested. In each session, 3600 hits are delivered with an energy flux density of 0.09 mJ/mm, 1800 are delivered on the shaft (900 for each corpus cavernosum), and 1800 are delivered to the perineum (900 for each crus penis). Each session lasts about 20 min and is performed in office without anaesthesia [79].

4.1.4.6 ESWT Adverse Effects

The shockwaves therapy has virtually no adverse effects. On animal models of cardiac ischemia, no adverse effects were observed [82].

In a recent metanalysis, *Feldman* et al. [81] involving 604 patient only observed mild adverse effects, self-limiting, and self-resolving.

References

1. Frühauf S, Gerger H, Schmidt HM, Munder T, Barth J. Efficacy of psychological interventions for sexual dysfunction: a systematic review and meta-analysis. Arch Sex Behav. 2013;42(6):915–33. https://doi.org/10.1007/S10508-012-0062-0.
2. Hatzimouratidis K, et al. Pharmacotherapy for erectile dysfunction: recommendations from the fourth International Consultation for Sexual Medicine (ICSM 2015). J Sex Med. 2016;13(4):465–88. https://doi.org/10.1016/J.JSXM.2016.01.016.
3. Carson CC. Phosphodiesterase type 5 inhibitors: state of the therapeutic class. Urol Clin North Am. 2007;34(4):507–15. https://doi.org/10.1016/J.UCL.2007.08.013.
4. Dunn ME, Althof SE, Perelman MA. Phosphodiesterase type 5 inhibitors' extended duration of response as a variable in the treatment of erectile dysfunction. Int J Impot Res. Mar. 2007;19(2):119–23. https://doi.org/10.1038/SJ.IJIR.3901490.
5. Alan LRK, Wein J, Partin AW, Peters CA. Campbell-Walsh urology. Elsevier; 2015.
6. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. N Engl J Med. 1998;338(20):1397–404. https://doi.org/10.1056/NEJM199805143382001.
7. Giuliano F, Jackson G, Montorsi F, Martin-Morales A, Raillard P. Safety of sildenafil citrate: review of 67 double-blind placebo-controlled trials and the postmarketing safety database. Int J Clin Pract. 2010;64(2):240–55. https://doi.org/10.1111/J.1742-1241.2009.02254.X.

8. Goldstein I, Tseng LJ, Creanga D, Stecher V, Kaminetsky JC. Efficacy and safety of sildenafil by age in men with erectile dysfunction. J Sex Med. 2016;13(5):852–9. https://doi.org/10.1016/J.JSXM.2016.02.166.
9. Gupta M, Kovar A, Meibohm B. The clinical pharmacokinetics of phosphodiesterase-5 inhibitors for erectile dysfunction. J Clin Pharmacol. 2005;45(9):987–1003. https://doi.org/10.1177/0091270005276847.
10. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. 1998. J Urol. 2002;167(2 Pt 2) https://doi.org/10.1016/S0022-5347(02)80386-X.
11. Capogrosso P, et al. Time of onset of vardenafil orodispersible tablet in a real-life setting—looking beyond randomized clinical trials. Expert Rev Clin Pharmacol. 2017;10(3):339–44. https://doi.org/10.1080/17512433.2017.1288567.
12. Chung E, Brock GB. A state of art review on vardenafil in men with erectile dysfunction and associated underlying diseases. Expert Opin Pharmacother. 2011;12(8):1341–8. https://doi.org/10.1517/14656566.2011.584064.
13. Sperling H, Debruyne F, Boermans A, Beneke M, Ulbrich E, Ewald S. The POTENT I randomized trial: efficacy and safety of an orodispersible vardenafil formulation for the treatment of erectile dysfunction. J Sex Med. 2010;7(4 Pt 1):1497–507. https://doi.org/10.1111/J.1743-6109.2010.01806.X.
14. Debruyne FMJ, Gittelman M, Sperling H, Börner M, Beneke M. Time to onset of action of vardenafil: a retrospective analysis of the pivotal trials for the orodispersible and film-coated tablet formulations. J Sex Med. 2011;8(10):2912–23. https://doi.org/10.1111/J.1743-6109.2011.02462.X.
15. Daugan A, et al. The discovery of tadalafil: a novel and highly selective PDE5 inhibitor. 2: 2,3,6,7,12,12a-Hexahydropyrazino[1′,2′ :1,6]pyrido[3,4-b]indole-1,4-dione analogues. J Med Chem. 2003;46(21):4533–42. https://doi.org/10.1021/JM0300577/SUPPL_FILE/JM0300577_S.PDF.
16. Coward RM, Carson CC. Tadalafil in the treatment of erectile dysfunction. Ther Clin Risk Manag. 2008;4(6):1315–29. https://doi.org/10.2147/TCRM.S3336.
17. Wang R, 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(8):2122–9. https://doi.org/10.1111/J.1743-6109.2012.02822.X.
18. Kyle JA, Brown DA, Hill JK. Avanafil for erectile dysfunction. Ann Pharmacother. 2013;47(10):1312–20. https://doi.org/10.1177/1060028013501989.
19. Rajfer J, Aliotta PJ, Steidle CP, Fitch WP, Zhao Y, Yu A. Tadalafil dosed once a day in men with erectile dysfunction: a randomized, double-blind, placebo-controlled study in the US. Int J Impot Res. 2007;19(1):95–103. https://doi.org/10.1038/SJ.IJIR.3901496.
20. Porst H, Padma-Nathan H, Giuliano F, Anglin G, Varanese L, Rosen R. Efficacy of tadalafil for the treatment of erectile dysfunction at 24 and 36 hours after dosing: a randomized controlled trial. Urology. Jul. 2003;62(1):121–5. https://doi.org/10.1016/S0090-4295(03)00359-5.
21. Taylor J, Baldo OB, Storey A, Cartledge J, Eardley I. Differences in side-effect duration and related bother levels between phosphodiesterase type 5 inhibitors. BJU Int. 2009;103(10):1392–5. https://doi.org/10.1111/J.1464-410X.2008.08328.X.
22. Kedia GT, Ückert S, Assadi-Pour F, Kuczyk MA, Albrecht K. Avanafil for the treatment of erectile dysfunction: initial data and clinical key properties. Ther Adv Urol. 2013;5(1):35–41. https://doi.org/10.1177/1756287212466282.
23. Hellstrom WJG, et al. Efficacy of avanafil 15 minutes after dosing in men with erectile dysfunction: a randomized, double-blind, placebo controlled study. J Urol. 2015;194(2):485–92. https://doi.org/10.1016/J.JURO.2014.12.101.
24. Wang H, Yuan J, Hu X, Tao K, Liu J, Hu D. The effectiveness and safety of avanafil for erectile dysfunction: a systematic review and meta-analysis. Curr Med Res Opin. 2014;30(8):1565–71. https://doi.org/10.1185/03007995.2014.909391.
25. Chen L, et al. Phosphodiesterase 5 inhibitors for the treatment of erectile dysfunction: a trade-off network meta-analysis. Eur Urol. 2015;68(4):674–80. https://doi.org/10.1016/J.EURURO.2015.03.031.
26. Swearingen D, Nehra A, Morelos S, Peterson CA. Hemodynamic effect of avanafil and glyceryl trinitrate coadministration. Drugs Context. 2013;2013:212248. https://doi.org/10.7573/DIC.212248.
27. Yuan J, et al. Comparative effectiveness and safety of oral phosphodiesterase type 5 inhibitors for erectile dysfunction: a systematic review and network meta-analysis. Eur Urol. 2013;63(5):902–12. https://doi.org/10.1016/J.EURURO.2013.01.012.
28. Kloner RA, Goldstein I, Kirby MG, Parker JD, Sadovsky R. Cardiovascular safety of phosphodiesterase type 5 inhibitors after nearly 2 decades on the market. Sex Med Rev. 2018;6(4):583–94. https://doi.org/10.1016/J.SXMR.2018.03.008.
29. McCullough AR, Barada JH, Fawzy A, Guay AT, Hatzichristou D. Achieving treatment optimization with sildenafil citrate (Viagra) in patients with erectile dysfunction. Urology. 2002;60(2 Suppl 2):28–38. https://doi.org/10.1016/S0090-4295(02)01688-6.
30. Rosen RC, Padma-Nathan H, Shabsigh R, Saikali K, Watkins V, Pullman W. Determining the earliest time within 30 minutes to erectogenic effect after tadalafil 10 and 20 mg: a multicenter, randomized, double-blind, placebo-controlled, at-home study. J Sex Med. 2004;1(2):193–200. https://doi.org/10.1111/J.1743-6109.2004.04028.X.
31. Padma-Nathan H, Stecher VJ, Sweeney M, Orazem J, Tseng LJ, DeRiesthal H. Minimal time to successful intercourse after sildenafil citrate: results of a

randomized, double-blind, placebo-controlled trial. Urology. 2003;62(3):400–3. https://doi.org/10.1016/S0090-4295(03)00567-3.
32. Marchal-Escalona C, et al. PDE5A polymorphisms influence on sildenafil treatment success. J Sex Med. 2016;13(7):1104–10. https://doi.org/10.1016/J.JSXM.2016.04.075.
33. Costa P, Grivel T, Gehchan N. Tadalafil once daily in the management of erectile dysfunction: patient and partner perspectives. Patient Prefer Adherence. 2009;3:105–11. https://doi.org/10.2147/PPA.S3937.
34. Dean J, et al. Psychosocial outcomes and drug attributes affecting treatment choice in men receiving sildenafil citrate and tadalafil for the treatment of erectile dysfunction: results of a multicenter, randomized, open-label, crossover study. J Sex Med. 2006;3(4):650–61. https://doi.org/10.1111/J.1743-6109.2006.00261.X.
35. Hatzimouratidis K, et al. Psychosocial outcomes after initial treatment of erectile dysfunction with tadalafil once daily, tadalafil on demand or sildenafil citrate on demand: results from a randomized, open-label study. Int J Impot Res. 2014;26(6):223–9. https://doi.org/10.1038/IJIR.2014.15.
36. Lin G, et al. Up and down-regulation of phosphodiesterase-5 as related to tachyphylaxis and priapism. J Urol. 2003;170(2 Pt 2):S15–8. https://doi.org/10.1097/01.JU.0000075500.11519.E8.
37. Vernet D, Magee T, Qian A, Nolazco G, Rajfer J, Gonzalez-Cadavid N. Phosphodiesterase type 5 is not upregulated by tadalafil in cultures of human penile cells. J Sex Med. 2006;3(1):84–95. https://doi.org/10.1111/J.1743-6109.2005.00197.X.
38. Washington SL, Shindel AW. A once-daily dose of tadalafil for erectile dysfunction: compliance and efficacy. Drug Des Devel Ther. 2010;4:159–71. https://doi.org/10.2147/DDDT.S9067.
39. Mirone V, et al. An evaluation of an alternative dosing regimen with tadalafil, 3 times/week, for men with erectile dysfunction: SURE study in 14 European countries. Eur Urol. 2005;47(6):846–54. https://doi.org/10.1016/J.EURURO.2005.02.019.
40. Conaglen HM, Conaglen JV. Investigating women's preference for sildenafil or tadalafil use by their partners with erectile dysfunction: the partners' preference study. J Sex Med. 2008;5(5):1198–207. https://doi.org/10.1111/J.1743-6109.2008.00774.X.
41. Salonia A, et al. Prevention and management of postprostatectomy sexual dysfunctions. Part 1: choosing the right patient at the right time for the right surgery. Eur Urol. Aug. 2012;62(2):261–72. https://doi.org/10.1016/J.EURURO.2012.04.046.
42. Montorsi F, et al. Tadalafil in the treatment of erectile dysfunction following bilateral nerve sparing radical retropubic prostatectomy: a randomized, double-blind, placebo controlled trial. J Urol. 2004;172(3):1036–41. https://doi.org/10.1097/01.JU.0000136448.71773.2B.
43. Salonia A, et al. Sexual and reproductive health EAU guidelines. 2021. p. 282. https://uroweb.org/guideline/sexual-and-reproductive-health/#10.
44. Kim DJ, et al. A prospective, randomized, placebo-controlled trial of on-Demand vs. nightly sildenafil citrate as assessed by Rigiscan and the international index of erectile function. Andrology. 2016;4(1):27–32. https://doi.org/10.1111/ANDR.12118.
45. Nehra A, Grantmyre J, Nadel A, Thibonnier M, Brock G. Vardenafil improved patient satisfaction with erectile hardness, orgasmic function and sexual experience in men with erectile dysfunction following nerve sparing radical prostatectomy. J Urol. 2005;173(6):2067–71. https://doi.org/10.1097/01.JU.0000158456.41788.93.
46. Moncada I, et al. Effects of tadalafil once daily or on demand versus placebo on time to recovery of erectile function in patients after bilateral nerve-sparing radical prostatectomy. World J Urol. 2015;33(7):1031–8. https://doi.org/10.1007/S00345-014-1377-3.
47. Montorsi F, et al. Effects of tadalafil treatment on erectile function recovery following bilateral nerve-sparing radical prostatectomy: a randomised placebo-controlled study (REACTT). Eur Urol. 2014;65(3):587–96. https://doi.org/10.1016/J.EURURO.2013.09.051.
48. Montague DK, et al. Clinical guidelines panel on erectile dysfunction: summary report on the treatment of organic erectile dysfunction. The American Urological Association. J Urol. 1996;156(6):2007–11. https://doi.org/10.1016/S0022-5347(01)65419-3.
49. Yuan J, Hoang AN, Romero CA, Lin H, Dai Y, Wang R. Vacuum therapy in erectile dysfunction—science and clinical evidence. Int J Impot Res. 2010;22(4):211–9. https://doi.org/10.1038/IJIR.2010.4.
50. Levine LA, Dimitriou RJ. Vacuum constriction and external erection devices in erectile dysfunction. Urol Clin North Am. 2001;28(2):335–42. https://doi.org/10.1016/S0094-0143(05)70142-7.
51. Cookson MS, Nadig PW, Moul J. Long-term results with vacuum constriction device. J Urol. 1993;149(2):290–4. https://doi.org/10.1016/S0022-5347(17)36059-7.
52. Pajovic B, Dimitrovski A, Fatic N, Malidzan M, Vukovic M. Vacuum erection device in treatment of organic erectile dysfunction and penile vascular differences between patients with DM type I and DM type II. Aging Male. 2017;20(1):49–53. https://doi.org/10.1080/13685538.2016.1230601.
53. Hanchanale V, Eardley I. Alprostadil for the treatment of impotence. Expert Opin Pharmacother. 2014;15(3):421–8. https://doi.org/10.1517/14656566.2014.873789.
54. Cai T, et al. The intra-meatal application of alprostadil cream (Vitaros®) improves drug efficacy and patient's satisfaction: results from a randomized, two-administration route, cross-over clinical trial.

Int J Impot Res. 2019;31(2):119–25. https://doi.org/10.1038/s41443-018-0087-6.
55. Anaissie J, Hellstrom WJG. Clinical use of alprostadil topical cream in patients with erectile dysfunction: a review. Res Rep Urol. 2016;8:123–31. https://doi.org/10.2147/RRU.S68560.
56. Rooney M, Pfister W, Mahoney M, Nelson M, Yeager J, Steidle C. Long-term, multicenter study of the safety and efficacy of topical alprostadil cream in male patients with erectile dysfunction. J Sex Med. 2009;6(2):520–34. https://doi.org/10.1111/J.1743-6109.2008.01118.X.
57. Mulhall JP, Jahoda AE, Ahmed A, Parker M. Analysis of the consistency of intraurethral prostaglandin E(1) (MUSE) during at-home use. Urology. 2001;58(2):262–6. https://doi.org/10.1016/S0090-4295(01)01164-5.
58. Garrido Abad P, Sinués Ojas B, Martínez Blázquez L, Conde Caturla P, Fernández Arjona M. Safety and efficacy of intraurethral alprostadil in patients with erectile dysfunction refractory to treatment using phosphodiesterase-5 inhibitors. Actas Urol Esp. 2015;39(10):635–40. https://doi.org/10.1016/J.ACURO.2015.04.007.
59. Costa P, Potempa AJ. Intraurethral alprostadil for erectile dysfunction: a review of the literature. Drugs. 2012;72(17):2243–54. https://doi.org/10.2165/11641380-000000000-00000.
60. Kongkanand A, et al. Evaluation of transurethal alprostadil for safety and efficacy in men with erectile dysfunction. J Med Assoc Thai. 2002;85(2):223–8. https://pubmed.ncbi.nlm.nih.gov/12081123/. Accessed 5 Feb 2022.
61. Nagai A, et al. Intracavernous injection of prostaglandin E1 is effective in patients with erectile dysfunction not responding to phosphodiseterase 5 inhibitors. Acta Med Okayama. 2005;59(6):279–80. https://doi.org/10.18926/AMO/31956.
62. Alexandre B, Lemaire A, Desvaux P, Amar E. Intracavernous injections of prostaglandin E1 for erectile dysfunction: patient satisfaction and quality of sex life on long-term treatment. J Sex Med. 2007;4(2):426–31. https://doi.org/10.1111/J.1743-6109.2006.00260.X.
63. Rajpurkar A, Dhabuwala CB. Comparison of satisfaction rates and erectile function in patients treated with sildenafil, intracavernous prostaglandin E1 and penile implant surgery for erectile dysfunction in urology practice. J Urol. 2003;170(1):159–63. https://doi.org/10.1097/01.JU.0000072524.82345.6D.
64. Earle CM, Stuckey BGA, Ching HL, Wisniewski ZS. The incidence and management of priapism in Western Australia: a 16 year audit. Int J Impot Res. 2003;15(4):272–6. https://doi.org/10.1038/SJ.IJIR.3901018.
65. Chew KK, Stuckey BGA, Earle CM, Dhaliwal SS, Keogh EJ, Porst H. Penile fibrosis in intracavernosal prostaglandin E1 injection therapy for erectile dysfunction. Int J Impot Res. 1997;9(4):225–30. https://doi.org/10.1038/SJ.IJIR.3900296.
66. Zhao JC, Zhang BR, Hong L, Shi K, Wu WW, Yu JA. Extracorporeal shock wave therapy with low-energy flux density inhibits hypertrophic scar formation in an animal model. Int J Mol Med. 2018;41(4):1931–8. https://doi.org/10.3892/IJMM.2018.3434.
67. Qiu X, et al. Effects of low-energy shockwave therapy on the erectile function and tissue of a diabetic rat model. J Sex Med. 2013;10(3):738–46. https://doi.org/10.1111/JSM.12024.
68. Lee M-C, El-Sakka AI, Graziottin TM, Ho H-C, Lin C-S, Lue TF. The effect of vascular endothelial growth factor on a rat model of traumatic arteriogenic erectile dysfunction. J Urol. 2002;167(2 Pt 1):761–9. https://doi.org/10.1097/00005392-200202000-00080.
69. Apfel RE. Acoustic cavitation: a possible consequence of biomedical uses of ultrasound. Br J Cancer Suppl. Mar. 1982;5:140–6.
70. Ogden JA, Tóth-Kischkat A, Schultheiss R. Principles of shock wave therapy. Clin Orthop Relat Res. 2001;(387):8–17. https://doi.org/10.1097/00003086-200106000-00003.
71. Gotte G, Amelio E, Russo S, Marlinghaus E, Musci G, Suzuki H. Short-time non-enzymatic nitric oxide synthesis from L-arginine and hydrogen peroxide induced by shock waves treatment. FEBS Lett. 2002;520(1–3):153–5. https://doi.org/10.1016/S0014-5793(02)02807-7.
72. Mariotto S, de Prati A, Cavalieri E, Amelio E, Marlinghaus E, Suzuki H. Extracorporeal shock wave therapy in inflammatory diseases: molecular mechanism that triggers anti-inflammatory action. Curr Med Chem. 2009;16(19):2366–72. https://doi.org/10.2174/092986709788682119.
73. Hatanaka K, et al. Molecular mechanisms of the angiogenic effects of low-energy shock wave therapy: roles of mechanotransduction. Am J Physiol Cell Physiol. 2016;311(3):C378–85. https://doi.org/10.1152/AJPCELL.00152.2016.
74. Aicher A, Heeschen C, Sasaki KI, Urbich C, Zeiher AM, Dimmeler S. Low-energy shock wave for enhancing recruitment of endothelial progenitor cells: a new modality to increase efficacy of cell therapy in chronic hind limb ischemia. Circulation. 2006;114(25):2823–30. https://doi.org/10.1161/CIRCULATIONAHA.106.628623.
75. Chen YJ, et al. Recruitment of mesenchymal stem cells and expression of TGF-beta 1 and VEGF in the early stage of shock wave-promoted bone regeneration of segmental defect in rats. J Orthop Res. 2004;22(3):526–34. https://doi.org/10.1016/J.ORTHRES.2003.10.005.
76. Nurzynska D, et al. Shock waves activate in vitro cultured progenitors and precursors of cardiac cell lineages from the human heart. Ultrasound Med Biol. 2008;34(2):334–42. https://doi.org/10.1016/J.ULTRASMEDBIO.2007.07.017.
77. Jeong HC, et al. Effects of next-generation low-energy extracorporeal shockwave therapy on erectile dysfunction in an animal model of diabetes.

World J Mens Health. 2017;35(3):186. https://doi.org/10.5534/WJMH.17024.
78. Rosen RC, Allen KR, Ni X, Araujo AB. Minimal clinically important differences in the erectile function domain of the International Index of Erectile Function scale. Eur Urol. 2011;60(5):1010–6. https://doi.org/10.1016/J.EURURO.2011.07.053.
79. Reisman Y, Hind A, Varaneckas A, Motil I. Initial experience with linear focused shockwave treatment for erectile dysfunction: a 6-month follow-up pilot study. Int J Impot Res. 2015;27(3):108–12. https://doi.org/10.1038/IJIR.2014.41.
80. Kitrey ND, Gruenwald I, Appel B, Shechter A, Massarwa O, Vardi Y. Penile low intensity shock wave treatment is able to shift PDE5i nonresponders to responders: a double-blind, sham controlled study. J Urol. 2016;195(5):1550–5. https://doi.org/10.1016/J.JURO.2015.12.049.
81. Feldman R, Denes B, Appel B, Vasan SS, Shultz T, Burnett A. PD45-10 the safety and efficacy of LI-ESWT in 604 patients for erectile dysfunction: summary of current and evolving evidence. J Urol. 2015;193(4S):e905–6. https://doi.org/10.1016/J.JURO.2015.02.2582.
82. Nishida T, et al. Extracorporeal cardiac shock wave therapy markedly ameliorates ischemia-induced myocardial dysfunction in pigs in vivo. Circulation. 2004;110(19):3055–61. https://doi.org/10.1161/01.CIR.0000148849.51177.97.